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Original articles
Current usefulness of aspiration cytology (FNAC) in the head and neck diagnosis
An outbreak of cutaneous leishmaniasis in Modena province (Northern Italy): report of 35 cases

Case reports

Proceedings
III Meeting Nazionale 2017,
Gruppo Italiano di Paleopatologia
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Do not send the text in PDF.

Text and individual tables must be stored in separate files.

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(1) a title (in English);
(2) an abstract (in English);
(3) a set of key words (in English);
(4) titles and legends for all of the tables and figures.

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The second page should contain the abstract. At the end of the text should appear the bibliography, the legends to the tables and figures, and specification (where applicable) of the congress at which all or part of the data in the paper may have already been presented.

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Must be limited in number (the same data should not be presented twice, in both the text and tables), typewritten one to a page, and numbered consecutively with Roman numbers. In the text and legend of the tables, Authors must use, in the exact order, the following symbols: * , †, ‡, §, **, ††, ‡‡ …

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Mathematical terms, formulae, abbreviations, units and measures should conform to the standards set out in Science 1954;120:1078.

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Front cover: The biopsy of pituitary mass revealed a metastatic adenocarcinoma (A, H&E stain) expressing TTF-1 (B), Napsin (C), synaptophysin (D) and ALK (E), page 409.
Current usefulness of aspiration cytology (FNAC) in the head and neck diagnosis

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Key words

Cytology • FNAC and histology • Diagnostic oncology

Summary

Background. Fine Needle Aspiration Cytology (FNAC) is a well established and widely used method for both a preliminary and sometime final non-invasive pathologic diagnosis. FNAC is a simple and inexpensive diagnostic tool and should represent the standard of care in developing and resource-poor countries while maintaining its diagnostic usefulness in developed and advanced ones.

Methods. The concordance between preoperative FNAC and final histology was evaluated in 168 patients operated on at the Otorhinolaryngology Unit, “A. Murri” Hospital, Fermo (Italy), from January 2012 to October 2016, including thyroid cases, salivary glands and cervical masses.

Results. The percentages of correct diagnosis provided by FNAC were good in all groups of pathologies and in accordance with the mean data of the literature. In particular the kappa statistic for the degree of agreement between FNAC and definitive histology (good > 0.6 and excellent > 0.8) was 0.74 for the thyroid, 0.83 for the parotid and 0.71 for both the submandibular and the cervical masses.

Discussion. Thy 3 group is still the most challenging for a successful FNAC diagnostic prediction. Especially in the developed and advanced countries, both the immediate review of the smear with its repetition, if needed, and the aspiration performed under CT/MRI guidance, when necessary, seem to further empower FNAC diagnostic resolution and should be pursued. Being routinely used for more than 40 years, FNAC is still a valuable and cost-effective tool to distinguish between cases that don’t need any treatment, cases to be treated medically and those that require surgical excision. In the Authors’ opinion every institution should periodically review its data in order to monitor and assess the accuracy of its diagnostic activity.

Introduction

Fine Needle Aspiration Cytology (FNAC), introduced ninety years ago, has been routinely used for the last 40 years as the gold standard in the diagnosis of head and neck masses. All along several reports have highlighted the diagnostic power, reliability, tolerability and cost effectiveness of this exam.

The samples may be obtained directly by the specialist involved or by the cytopathologist, freehand under palpation or with an ultrasonographic guide. Besides depending on the skill of the ultrasonographer, the ability of the pathologist to take the sample in the most representative area of the target organ and the good interplay between the two operators, FNAC is mainly conditioned by the experience of the cytopathologist. For this reason every institution should regularly assess the reliability of its cytology service and try to improve it if it is poor.

In November 2011 our institution enrolled a well referenced cytopathologist (PMG) and since then we had a close and fruitful cooperation. Before that time our cytopathological facility was suboptimal and we accepted external reports, whereas nowadays we prefer that patients undergoing surgery are examined by our own cytology facility. After five years of such activity we decided to analyse the collected data in order to monitor the epidemiology of the diseases and to confirm the impression of a steadily increasing quality of our FNAC.

Methods

From January 2012 to October 2016, 206 consecutive patients were operated on at the Otorhinolaryngology Unit, “A. Murri” Hospital, Fermo (Italy) (Tab. I). Nearly all the parotid patients and the vast majority of
the thyroid patients had a previous FNAC performed under ultrasonographic control. Few thyroid patients were operated on without previous cytology, due to a clear history of thyroid dysfunction or chronic enlargement without any sign of malignancy.

For other head and neck masses (cervical masses) the request of a FNAC in the pre-operative work-up relied on the clinical history and the diagnostic question of the referring specialist (haematologist, infectious disease specialist, etc.).

The cases available for our review were 168. In most of the cases the patients were referred to us by our endocrinologists and had already a cytologic report. When necessary we repeated the exam, mainly when there was a doubtful diagnosis. Our cytologist collects himself the samples in the radiology outpatient office working together with the ultrasonographer. Aspiration is performed through a 22 gauge needle connected to a 20 cc syringe mounted on a Cam-eco-like handle. The material is smeared on glass, fixed

---

**Tab. I. Composition of the series (January 2012-December 2016).**

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Previous cytology available</th>
<th>Cytology done by us</th>
<th>Cytology done elsewhere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Male</td>
<td>Female</td>
<td>Total</td>
</tr>
<tr>
<td>Thyroid</td>
<td>108</td>
<td>32</td>
<td>76</td>
<td>88</td>
</tr>
<tr>
<td>Salivary glands</td>
<td>64</td>
<td>38</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Parotid</td>
<td>51</td>
<td>32</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Submandibular</td>
<td>13</td>
<td>6</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Cervical masses</td>
<td>34</td>
<td>12</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>Total cases</td>
<td>206</td>
<td>82</td>
<td>124</td>
<td>168</td>
</tr>
</tbody>
</table>

**Tab. II. Concordance FNA–HISTOLOGY: Thyroid.**

<table>
<thead>
<tr>
<th>Class</th>
<th>Series</th>
<th>FNAC</th>
<th>Histopathology</th>
<th>Statistics</th>
</tr>
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<tbody>
<tr>
<td>Thy 2</td>
<td>Our data</td>
<td>23 0</td>
<td>21 2</td>
<td>8.7%</td>
</tr>
<tr>
<td></td>
<td>23 (m. 6 - f. 17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Done elsewhere</td>
<td>6 0</td>
<td>6 0</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>6 (m. 1 - f. 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thy 3*</td>
<td>Our data</td>
<td>28 0</td>
<td>23 5</td>
<td>17.9%</td>
</tr>
<tr>
<td></td>
<td>28 (m. 9 - f. 19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Done elsewhere</td>
<td>5 0</td>
<td>3 2</td>
<td>40.0%</td>
</tr>
<tr>
<td></td>
<td>5 (m. 1 - f. 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thy 4</td>
<td>Our data</td>
<td>0 7</td>
<td>2 5</td>
<td>28.6%</td>
</tr>
<tr>
<td></td>
<td>7 (m. 2 - f. 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Done elsewhere</td>
<td>0 1</td>
<td>0 1</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td>1 (m. 1 - f. 0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thy 5</td>
<td>Our data</td>
<td>0 17</td>
<td>0 17</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>17 (m. 4 - f. 13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Done elsewhere</td>
<td>0 1</td>
<td>1 0</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>1 (m. 0 - f. 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Thy 3 and oxiphilic component “o”* | Benign | Malignant | %
---|---|---|---|
| without “o” (18 pts) | 15 | 3 | 16.6% |
| with “o” (10 pts) | 8 | 2 | 20.0% |

*Thy 3a and Thy 3b* | Benign | Malignant | %
---|---|---|---|
| Thy 3a (9 pts) | 8 | 1 | 11.1% |
| Thy 3b (19 pts) | 15 | 4 | 21.0% |
in ethanol and stained with Papanicolaou solution. The slides are then examined on a different day.
In this study we compared the diagnostic response given by the FNAC to the final pathologic diagnosis, pointing out the percentage of agreement and analysing what went wrong with the cytologic analysis (Tabs. II-III-IV). The cytologic diagnosis was done according to the C1-C5 reporting scheme, which is validated only for breast but it is routinely used for several other organs; non-diagnostic (C1), benign (C2), indeterminate (C3), suspicious (C4), and malignant (C5).
As regards the thyroid group we used the Thy (1 to 5) nomenclature.
The statistical analysis was carried out only on the cases where the cytology was performed and read by our cytologist. Eventually 148 cases were then compared (Tab. V).
Statistical study included sensitivity, specificity, positive and negative predictive values (PPV, NPV), likelihood ratio for positive and negative test results (a good test has LR + > 10 and LR- < 0.1), the area under the ROC curve (AUC > 0.7 good; > 0.8. very good; > 0.9 excellent), Youden’s index (Y = 0, poor; Y = 1, perfect) and diagnostic odds ratio (DOR: values from 0 to infinity. DOR < 0.05, high negative association; DOR = 1, no association; DOR > 20, high positive association), according to STARD statement.
We also calculated the overall accuracy (OA) and kappa statistic for the degree of agreement between FNAC and

<table>
<thead>
<tr>
<th>PAROTID</th>
<th>HISTOPATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNAC</td>
<td>Benign Correct Other benign Malignant (false negative)</td>
</tr>
<tr>
<td>Pleomorphic Adenoma (Pl.A)</td>
<td></td>
</tr>
<tr>
<td>Our data: 19 (9 m-10 f)</td>
<td>19</td>
</tr>
<tr>
<td>Done elsewhere: 3 (2 m-1 f)</td>
<td>3</td>
</tr>
<tr>
<td>Adenolymphoma (Alph) (Warthin’s)</td>
<td></td>
</tr>
<tr>
<td>Our data: 12 (11 m-1 f)</td>
<td>9</td>
</tr>
<tr>
<td>Done elsewhere: 1 m</td>
<td>1</td>
</tr>
<tr>
<td>Oxyphilic Adenoma</td>
<td></td>
</tr>
<tr>
<td>Our data: 1 m</td>
<td>1</td>
</tr>
<tr>
<td>Done elsewhere: 1 m</td>
<td>1</td>
</tr>
<tr>
<td>? inflam/Adenolymph</td>
<td></td>
</tr>
<tr>
<td>Our data: 1 f</td>
<td>1 (inflam)</td>
</tr>
<tr>
<td>Malignant Correct Other malign Benign (false positive)</td>
<td></td>
</tr>
<tr>
<td>Our data: 8 (7 m-1 f)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUBMANDIBULAR</th>
<th>HISTOPATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNAC</td>
<td>Benign Correct Other benign Malignant (false negative)</td>
</tr>
<tr>
<td>Pleomorphic Adenoma (Pl.A)</td>
<td></td>
</tr>
<tr>
<td>Our data: 2 f</td>
<td>2</td>
</tr>
<tr>
<td>Adenolymphoma (Warthin’s)</td>
<td></td>
</tr>
<tr>
<td>Our data: 1 m</td>
<td>1</td>
</tr>
<tr>
<td>? Inflammation</td>
<td></td>
</tr>
<tr>
<td>Our data: 2 (1 m-1 f)</td>
<td>2</td>
</tr>
<tr>
<td>? Adenolymph/nH-lymph</td>
<td></td>
</tr>
<tr>
<td>Our data: 1 m</td>
<td>1 (nH-L)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CERVICAL MASSES</th>
<th>HISTOPATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNAC</td>
<td>Benign Correct Other benign Malignant (false negative)</td>
</tr>
<tr>
<td>Our data: 9 (4 m-5 f)</td>
<td>6</td>
</tr>
<tr>
<td>MALIGNANT Correct Other malign Benign (false positive)</td>
<td></td>
</tr>
<tr>
<td>Our data: 3 (1 m-2 f)</td>
<td>3</td>
</tr>
<tr>
<td>Done elsewhere: 2 f</td>
<td>2</td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Our data: 12 (6 m-6 f)</td>
<td>12</td>
</tr>
</tbody>
</table>
conclusive histology (> 0.4 moderate, > 0.6 good, > 0.8 excellent), as reported in the literature.

Results

THYROID (TAB. II)

In the 29 patients where the FNAC diagnosis was Thy 2, the basic report of benignity (colloid plus hypertrophic thyrocytes) was histologically confirmed in 20/21 cases. In one case (female) foci of papillary carcinoma (PK) ≥ 1 cm were detected by histology. In this patient FNAC was performed on another nodule where the diagnosis of Thy 2 was indeed correct.

Specific FNAC diagnosis of goiter (G) was confirmed in 4/4 cases, in one of which final histology also detected a chronic thyroiditis (cT), while in another one a follicular adenoma (FA) was also present.

One case with oxyphilic component at FNAC resulted in a FA + G + cT.

FNAC suggestion of FA was histologically confirmed in 2/3 patients (one done by us, the other done elsewhere). In the third case (FNAC done elsewhere) the histologic result was G + cT. In a patient (male) with a FNAC diagnosis of FA done by our cytologist, the histology showed a PK in another nodule (1.4 cm) which hadn’t been aspirated.

Thus, a missed diagnosis of malignity at FNAC (false negative) occurred in 2/23 our cases (8.5%), where the malignant nodule had not been aspirate. The cytology done elsewhere was correct in all the 6 cases.

In Thy 3 group we consider the so-called follicular lesion of undetermined significance (FLUS).

Among the 28 patients who had the cytology performed at our facility the definitive histology showed five malignancies (false negative: 17.8%).

In one female a FA plus a papillary cancer, follicular variant (PKF), was detected.

Another female turned out to be affected by a FA plus a PK. Again, cancer was detected in a not FNAC-sampled nodule.

Two further cases (females) with a FNAC diagnosis of no more specified FLUS turned out to be G with a microfocus (0.3 and 0.35 cm, respectively) of PK. The fifth case, a young man with FLUS at the cytology, had a final histology of minimally angioinvasive Follicular Carcinoma (FK).

We operated on five patients with the cytology done elsewhere. Two of these had a malignancy histologically detected: one PK in FA and two medullary carcinomas (MK).

In Thy 4 group, for three patients (all males) with query malignant FNAC, the diagnosis was histologically confirmed: one PK in FA and two medullary carcinomas (MK).

In the four cases (all females) where a PKF was suspected at FNAC, definitive histology was benign in two cases. In the third a 0.5 cm PK in FA was spotted at
As regards Warthin’s Tumour (Alph), FNAC was cytology done elsewhere. The same happened for the three patients with the cytology done elsewhere.

In our series we observed 19 pleomorphic adenomas (Pl.A) and the FNAC diagnosis was correct in every case. The same happened for the three patients with the cytology done elsewhere.

As regards Warthin’s Tumour (Alph), FNAC was correct in 9/12 patients. In 3/12 cases the definitive histology showed a different diagnosis of benignity (two Pl.A and one Oxyphilic Adenoma (oA)), still correct for the statistical analysis. In the patient with the FNAC done elsewhere the cytologic diagnosis of Alph was confirmed by histology.

Two oxyphilic (Hurtle’s cell) adenomas (oA) diagnosed at FNAC (one done by us, another done elsewhere) were confirmed by histology.

One patient whose FNAC was in doubt between inflammation and Alph turned out to be simple inflammation. Six out of 8 malignancies suspected by FNAC were confirmed at definitive histology. Two false positives (25%) were detected: one query malignant cytology resulted in inflammation, whereas one FNAC suspected for adenocystic carcinoma (Adenocystic C) turned out to be a basal cell adenoma (BCA). No lymphoma was observed.

Submandibular

In the 8 patients of this group FNAC reports matched the following histology in all but two cases. One (female) diagnosed by FNAC as Alph turned out to be an inflammation; another (male) with FNAC uncertain between Alph and non-Hodgkin lymphoma (nH-L) was detected as nH-L by definitive histology.

For the statistical analysis (Tab. V) only this second case is relevant and was considered as a false negative (12.5%).

Cervical Masses (Tab. IV)

In this group there was correspondence between FNAC and histology in 21/24 of our patients (87.5%) and in the two patients with the cytology done elsewhere. 2/24 of our cases had a wrong FNAC diagnosis of benignity, C2.

A 56 year-old male with clinical, indolent, left neck adenopathy, FNAC diagnosed as inflammation, at definitive histology (after several slide reviews and consultations) turned out to be a centrofollicular, nodular and diffuse, “floral” variant of grade 2 B lymphoma.

A 41 year-old female, with a 1.5 cm right supraclavicular mass, had a FNAC diagnosis compatible with lymphadenitis, but she was operated for breast cancer five years before. Due to this clinical history we proceeded directly to surgery and the histology showed a fibrofatty tissue with big nervous structures infiltrated by epithelial cancer cells, predominantly organized in solid nodules and occasionally in glandular structures. No lymphatic structures were recognizable. Consistent with metastasis from breast cancer.

One (female) of the two patients with dubious/query malignant FNAC (C3: query lymphoadenitis/granuloma/lymphoma), resulted as nH-L at the histologic examination and we accounted it as another false negative, while the other patient (male) with a possible mesenchymal disease vs. pleomorphic adenoma was Pl.A at histology. In two of our cases and in one with FNAC done elsewhere we had a diagnosis of “necrosis”. All three had a final histology of malignancy. Due to our attitude in such cases to both repeat the FNAC and go on to surgery we considered them as correct (Tab. III).

Discussion

The majority of papers reports a statistical appraisal of the overall cases. Following this criterion, our series sensitivity is 80.36%, specificity 95.65%, overall accuracy 89.86%, PPV 91.84% and NPV 88.89% (Tab. V).

These figures are substantially in agreement with the ones reported by Tandon and Co. and Suryawanshi and Co. In this latter Authors’ series, as in nearly all the series of the far east, FNAC is mostly adopted for lymph node lesions, while in western countries the thyroid cytodiagnosis is generally the most frequent indication.

From our experience it is more useful and meaningful to study the diagnostic power of FNAC for the different categories of sampling.

Thyroid

In the Thy 2 group FNAC diagnosis did not match the final histology in 2/23 cases.

Remarkably, in both cases the malignant cells were located in a nodule which had not been sampled. This drawback reinforces the discussion about how many nodules have to be sampled. In fact, besides mastering a meticulous sampling technique, a multiple node aspiration and an immediate analysis of the smear would be advisable too and an improved resolution of the US imaging should be pursued.

Thy 3 group represents 37% of all our thyroid FNAC cases and is the class that sets the most challenging decisional tasks.

In our series we registered 5 false negative cases, that is a 17.8% risk of missing a patient with malignant disease if we choose not to operate on. This is a better percentage than the 28.2% reported by Lakhani and coworkers. and slightly less than the range between 20% and 50% of the literature. Based on these results we might probably suggest our endocrinologists to reduce their indications to surgery in Thy 3 cases, as the trustability of our cytologist seems to be good.
In order to improve the therapeutic decision we used to subdivide the cases as without and with oxyphilic component (o), (Fig. 1), based on the opinion that the presence of oxyphilic cells might increase the risk of malignancy at the final histology.

According to this criterion of grouping, (Tab. II) Thy 3 without o (18 patients) showed 3/15 malignancies (false negative: 16.6%) while in Thy 3 with o subgroup (10 patients) the false negative were two (20%). Unfortunately the numerosity is not enough for getting a reliable statistical feed-back, even if the trend doesn’t seem significant.

Moreover our data point to another pitfall, besides the better detection of the nodule to be sampled or the necessity of sampling more or even all the nodules: the dimension of the malignancy.

In fact 2/5 of our patients showed malignant nodules of less than 0.5 cm and these cases might not account for a wrong diagnosis, as stated by Singh et al., 2011. Another patient had a minimal angioinvasion of the capsule of a typical FA and again his prognosis seems to be considered the same as of a simple FA.

In 2014 the ‘Indeterminate for malignancy’ (Tir3/Thy3 in the Italian and British systems for classification) was suggested and the Italian Thyroid Association together with the Italian Society of Pathology and Cytology adopted the sub-classification in Thy 3a and Thy 3b. Thy 3a is characterized by increased cellularity with scattered microfollicular structures (< 60% of the whole cellularity) and exclusively mild cytologic atypia (Fig. 2).

Thy 3b presents high cellularity in a predominant microfollicular/trabecular arrangement (> 60% of the cell component), with focal cytologic atypia (mostly moderate, rarely severe) suggestive of a “follicular neoplasm” (FN), (see Fig. 3).

Samples composed almost exclusively of Hurtle cells (“Hurtle cell neoplasm”) are included in the Thy 3b sub-category, too (Fig. 4).

We classified our Thy 3 material also in the light of these
further recommendations and the results are as follows (Tab. II).

Thy 3a cases where 9 with one malignancy (11,1%), while we had 19 Thy 3b patients with 4 malignant cases (21%). Such results seem to confirm that subdividing the Thy 3 class in these two subgroups is helpful in selecting patients to address to surgery, even if the percentage of risk remains low. This decision should, in our opinion, be complemented by other factors like the volume of the lesion, its US characteristics, the tendency to size increasing over the time, the presence of infoldings and microcalcifications.

In Thy 4 series 2/5 malignancies correctly diagnosed at FNAC were ≤ 0.5 cm in size while the malignancy was overestimated in 2/6 cases. No false negative was present. In Thy 5 group 100/100 of malignancies were detected and the histotype was correct. No false negative was present.

The statistical analysis took into consideration only the 75 patients whose FNAC was performed and read by our cytologist. We grouped the patients as follows:

• non malignant: Thy 2 and Thy 3
• malignant: Thy 4 and Thy 5

The results are showed in Tab. III.

Sensitivity is 75.86%, specificity 95.65% and overall accuracy 88%. The kappa statistic for the degree of agreement between FNAC and definitive histology is 0.74, being good > 0.6 and excellent > 0.8.

These figures are in accordance with the mean data of the literature as reported by Gharib 14.

**Salivary Glands**

Statistical analysis of our cases is in accordance with the data available in the literature 4-8.

While considering parotid and submandibular lesions separately, the figures appear better for the parotid.

**Parotid**

In our series the FNAC diagnosis of Pl.A was confirmed at definitive histology in every case, both ours and done elsewhere.

Such results agree with Atanda’s report 15 but not with Singh and coworkers 16 who highlighted the difficulty in differentiating between Pl.A and Adenocystic Carcinoma (AdenocysticC), with FNAC underestimating the disease.

Naz and Co. (2015) 4 reported both underestimation (Mucopidermoid Carcinoma and AdenocysticC diagnosed at FNAC as Pl.A) and overdiagnosing (FNAC uncertain between Metastatic Squamous Cell Carcinoma and Mucoepidermoid Carcinoma and histology consistent with Pl.A).

As far as Alph and oA no overestimation has been reported.

Six out of eight malignancies suspected by FNAC were confirmed at definitive histology. Two false positives were detected: one possibly malignant turned out to be inflammation, another suspected AdenocysticC resulted in a Basal Cell Adenoma (BCA).

Misdiagnosis between AdenocysticC and BCA may happen because the former is a close differential of BCA and Pl.A 17.

In our experience this overestimation was worrisome for the patient but safe for his prognosis.

No lymphoma was observed. Sensitivity is 100%, specificity 94.29% and overall accuracy 95.12%, with all the other parameters between good to excellent.

**Submandibular**

For the sole false positive no substantial overestimation of the pathology took place because the indication for surgery existed for both the diagnoses (Alymph-Hlymph).

Despite the sensitivity is 66.67% the specificity reaches 100%, the overall accuracy is 87.50% and the kappa statistic 0.71.

**Cervical Masses**

As far as the two missed diagnoses of lymphoma (one FNAC diagnosed as C2-inflammation, the other FNAC classified as C3) the difficulties in differentiating between non-Hodgkin lymphoma and non-specific lymphadenitis or reactive follicular hyperplasia were already mentioned in the literature 18.

At least for the C3 case nothing changed in terms of treatment because in our hands nearly all C3 diagnoses undergo both a repetition of the FNAC or direct surgery. The same happens for the FNAC diagnosis of necrosis. We consider such cases as malignant until proved otherwise and always go back to the patient’s history and clinical examination and either repeat the aspiration or proceed directly to surgical excision.

Finally, for the case of supraclavicular metastasis of breast cancer, the story of the patient was too strong to let us trust on the FNAC report. We proceeded surgically and the correct diagnosis was achieved.

FNAC on head and neck masses is routinely done in the far east countries, where tubercular lymphadenitis is the most common pathological finding, while in our experience the case load is smaller.

We tried to contrast our data with an European study 19 and the results appear comparable and good.

**Conclusions**

As already mentioned the history of FNAC dates back to nearly ninety years ago, when it was firstly introduced in Europe 1 and in the United States 20. Since then it has quickly become the gold standard in the diagnosis of palpable masses of the body.

Taking samples is, per se, an easy procedure that the specialist can perform himself, under palpation, even though in the majority of cases it is done by an ultrasonographer in cooperation with a pathologist. It has been also advised to have an immediate cytologic review, in order to increase the number of significant smears with a time saving for both the institution and the patients 21.

In recent years, due to its coupling with imaging techniques as CT and MRI, cytologic diagnosis has been extended to
non-palpable and deep masses, too, and even core needle biopsies can be performed where FNCA diagnostic resolution is supposed to be lower like for parotid lesions. Because FNAC is a quick, easy to perform, safe, reliable and cost-effective technique, it is widely used and represents a powerful diagnostic tool, especially in the developing and resource-challenging countries. Due to its significant diagnostic capability, in most cases a FNAC result enables the physician to choose between clinical follow up and surgery, and in the latter case it helps to plan the extension of the operation and to adequately prepare the patient.

When dealing with poor-risk (aged) people, FNAC diagnosis of a non-malignant disease may be a solid argument for avoiding surgery.

As we pointed out in the introduction, what is crucial is the expertise of the cytologist and this is particularly true for the parotid.

For this reason we strongly recommend that every institution periodically reviews its results, in order to compare and contrast them with a universal standard of care.

References

An outbreak of cutaneous leishmaniasis in Modena province (Northern Italy): report of 35 cases

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Key words
Leishmania • Skin • Epidemiology • Histopathology • PCR

Summary

Canine Leishmaniasis is a disease endemic in many parts of Europe, carried by insects of phlebotomous species. Humans are occasional hosts of the parasites. Cases of human leishmaniasis have been registered in Italy, particularly in the southern and coastal regions. In the period 1997-2016, we collected a series of 35 patients affected by cutaneous leishmaniasis, uncovered by skin biopsy and histological examination, 21 of them found in last 3 years. The patients, 28 males and 7 female, aged between 19 and 91, resided in a restricted area of Northern Italy, and none, but two, had travelled abroad. Lesions presented clinically mostly as single nodule or plaque, often ulcerated, and involved predominantly head-neck and upper extremities. Histology showed a diffuse, granulomatous inflammation including numerous plasma cells. Variable numbers of amastigotes were visible, usually in the superficial part of the dermis, in all cases but two. In these two cases, highly suspicious by clinico-pathologic features, PCR analysis allowed to achieve the correct diagnosis. Our attention was then focused on the geographical residence of the patients, that turned out to be mostly in the piedmont area, whereas only one lived in the alluvial area corresponding to Padana plain. These data underline the diffusion of phlebotomus in northern areas of Italy, and particularly on the hills, characterized by a type of soil more favorable to vector survival; also, they indicate the adaptation of leishmania to hosts other than dogs, such as foxes and small rodents. Histology alone resulted sufficient to make diagnosis in most cases, but PCR analysis is recommended in those cases showing a suspicious background, in absence of amastigotes.

Introduction

Leishmaniasis is a disease caused by an intracellular parasite of the genus Leishmania, transmitted by different species of phlebotomine sandflies. In Europe, leishmaniasis is endemic in the Mediterranean basin, it is caused mainly by Leishmania Infantum, and dogs represent the main reservoirs of parasites. In recent years, an increased number of imported cases has been registered, due to immigration, tourism or military operations. Cutaneous involvement is the most common clinical manifestation of leishmaniasis. A positive trend in reporting the disease has been observed, because of better awareness and consequent diagnosis, although probably many cases are still misdiagnosed or underdiagnosed.

In Italy, canine leishmaniasis is endemic in central and southern regions, mainly in the Tyrrhenian coasts and the islands, but a spreading toward the northern regions has been registered, and a focus of infection in the hills has been reported in 2011 in Emilia Romagna region.

In the present study, we describe 35 cases of cutaneous leishmaniasis, histologically diagnosed in patients resident in the province of Modena, Emilia Romagna region, Northern Italy, most of them living in the hills, or so-called piedmont area. The majority of cases were discovered in the last three years, suggesting an outbreak of the disease in this area.

Materials and methods

Thirty-five cases of cutaneous leishmaniasis were consecutively diagnosed at the department of Anatomic Pathology of our tertiary-care hospital, in the period 1997-2016, 21 of them (60%) in the years 2014-2016 (Fig. 1). Patients were 28 males and 7...
females, all Italian but one young man of Moroccan origin; the age ranged between 19 and 91 years. The most involved anatomical sites were head/neck and upper arm. Clinically, the lesions presented mostly as solitary nodule, or plaque, sometimes ulcerated. Complete clinical data are listed in Table I. Skin biopsies were sent for histological examination by clinicians with different diagnoses, including “epithelioma” (Fig. 2A), chronic ulcer, or “tumor”. In two cases, only, leishmaniasis was among the clinical suspects. Biopsies were routinely processed and hematoxylin-eosin (H&E) staining was performed, together with special stains, including PAS, Grocott methenamine and Giemsa.

![Fig. 1. Incidence of cutaneous leishmaniasis cases in the period 1997-2016.](image)

Tab. I. Clinical data of 35 patients with cutaneous Leishmaniasis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)/gender</th>
<th>Anatomic location</th>
<th>Clinical features</th>
<th>Type of biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56/F</td>
<td>Left leg</td>
<td>NA</td>
<td>Incisional</td>
</tr>
<tr>
<td>2</td>
<td>24/M</td>
<td>Left arm</td>
<td>Centrally ulcerated nodule</td>
<td>Excisional</td>
</tr>
<tr>
<td>3</td>
<td>29/M</td>
<td>Nasolabial fold</td>
<td>NA</td>
<td>Incisional</td>
</tr>
<tr>
<td>4</td>
<td>38/M</td>
<td>Right hand</td>
<td>Centrally ulcerated nodule</td>
<td>Excisional</td>
</tr>
<tr>
<td>5</td>
<td>32/F</td>
<td>Forehead</td>
<td>NA</td>
<td>Incisional</td>
</tr>
<tr>
<td>6</td>
<td>29/M</td>
<td>Right elbow</td>
<td>Crusted erythematous papule</td>
<td>Incisional + radical excision</td>
</tr>
<tr>
<td>7</td>
<td>25/M</td>
<td>Lumbosacral region</td>
<td>NA</td>
<td>Incisional</td>
</tr>
<tr>
<td>8</td>
<td>19/F</td>
<td>Back</td>
<td>Itching papule</td>
<td>Incisional</td>
</tr>
<tr>
<td>9</td>
<td>38/M</td>
<td>Right arm</td>
<td>Ulcerated nodule</td>
<td>Incisional</td>
</tr>
<tr>
<td>10</td>
<td>72/M</td>
<td>NA</td>
<td>Exudative squamous patch</td>
<td>Incisional</td>
</tr>
<tr>
<td>11</td>
<td>50/F</td>
<td>Nose</td>
<td>Infiltrated erythematous plaque</td>
<td>Incisional</td>
</tr>
<tr>
<td>12</td>
<td>71/M</td>
<td>Neck (tracheostomy)</td>
<td>NA</td>
<td>Incisional</td>
</tr>
<tr>
<td>13</td>
<td>76/M</td>
<td>Forehead</td>
<td>Desquamative ulcerated lesion</td>
<td>Excisional</td>
</tr>
<tr>
<td>14</td>
<td>68/M</td>
<td>Neck</td>
<td>Erythematous-edematous crusted nodule, with previous suppuration</td>
<td>Incisional + radical excision</td>
</tr>
<tr>
<td>15</td>
<td>75/M</td>
<td>Forehead</td>
<td>Fixed erythema-pomphoid lesion</td>
<td>Incisional</td>
</tr>
<tr>
<td>16</td>
<td>36/M</td>
<td>Right hand (back)</td>
<td>NA</td>
<td>Incisional</td>
</tr>
<tr>
<td>17</td>
<td>48/M</td>
<td>Scalp</td>
<td>Ulcerated lesion</td>
<td>Incisional</td>
</tr>
<tr>
<td>18</td>
<td>71/M</td>
<td>Left shoulder</td>
<td>Ulcerated lesion</td>
<td>Incisional</td>
</tr>
<tr>
<td>19</td>
<td>63/M</td>
<td>Right forearm</td>
<td>Ulcerated nodule</td>
<td>Incisional + radical excision</td>
</tr>
<tr>
<td>20</td>
<td>19/M</td>
<td>Left arm</td>
<td>Grouped reddish papules</td>
<td>Incisional + radical excision</td>
</tr>
<tr>
<td>21</td>
<td>62/M</td>
<td>Right arm</td>
<td>NA</td>
<td>Incisional</td>
</tr>
<tr>
<td>22</td>
<td>56/M</td>
<td>Nose</td>
<td>NA</td>
<td>Incisional</td>
</tr>
<tr>
<td>23</td>
<td>91/F</td>
<td>Nose</td>
<td>Erythematous-edematous plaque with central ulcer</td>
<td>Incisional</td>
</tr>
<tr>
<td>24</td>
<td>68/M</td>
<td>Left arm</td>
<td>Extensively inflamed nodule</td>
<td>Incisional + radical excision</td>
</tr>
<tr>
<td>25</td>
<td>55/M</td>
<td>Right leg</td>
<td>Non itching, crusted plaque</td>
<td>Incisional (*)</td>
</tr>
<tr>
<td>26</td>
<td>53/M</td>
<td>Nasal mucosa</td>
<td>NA</td>
<td>Incisional</td>
</tr>
<tr>
<td>27</td>
<td>72/M</td>
<td>Right arm</td>
<td>Non itching, reddish nodules</td>
<td>Incisional + radical excision</td>
</tr>
<tr>
<td>28</td>
<td>29/F</td>
<td>Forehead</td>
<td>NA</td>
<td>Incisional</td>
</tr>
<tr>
<td>29</td>
<td>61/M</td>
<td>Right hand</td>
<td>Ulcer</td>
<td>Incisional</td>
</tr>
<tr>
<td>30</td>
<td>71/M</td>
<td>Scalp</td>
<td>Nodule</td>
<td>Incisional + radical excision</td>
</tr>
<tr>
<td>31</td>
<td>27/F</td>
<td>Right leg</td>
<td>NA</td>
<td>Incisional + radical excision</td>
</tr>
<tr>
<td>32</td>
<td>65/M</td>
<td>Nose</td>
<td>Persistent, edematous plaque</td>
<td>Incisional</td>
</tr>
<tr>
<td>33</td>
<td>42/M</td>
<td>Right leg</td>
<td>Erythematous nodule</td>
<td>Incisional (*)</td>
</tr>
<tr>
<td>34</td>
<td>79/M</td>
<td>Scalp</td>
<td>Ulcerated lesion</td>
<td>Incisional</td>
</tr>
<tr>
<td>35</td>
<td>87/M</td>
<td>Scalp</td>
<td>Hyperkeratotic plaque</td>
<td>Incisional</td>
</tr>
</tbody>
</table>

(*) cases diagnosed by PCR

NA: not available
PCR analysis was performed on paraffin embedded tissue in two cases, characterized by a clinico-pathological background highly suspicious, but devoid of unequivocal amastigotes at H&E examination and after Giemsa staining. Briefly, DNA’s from formalin-fixed, paraffin-embedded samples were purified by MasterPure™ Compete DNA and RNA Purification Kit (Epicentre, Madison, WI, USA) according to the manufacturer’s protocol. For the first round PCR, 1.5 µg of each DNA was used. External and nested-PCR primers used were CSB2XF/CSB1XR and 13Z/LiR respectively, as previously described 9.

Results

With the exception of a patient of Moroccan and one of Italian origin, all others had never travelled abroad in endemic areas; moreover, all patients were immunocompetent. Histologic examination showed in all cases a diffuse pattern of inflammation, characterized by granulomas, lymphocytes and several plasma cells. Ulceration was observed in 16 cases. In all cases, but two, amastigotes were visible inside the cytoplasm of macrophages, predominantly in the papillary dermis (Fig. 2B, C), and were highlighted by Giemsa stain (Fig. 2D). According to the modified Ridley’s index 10, 2 cases were classified as 0, 5 as 1+, 23 as 2+ and 5 as 3+. PCR analysis confirmed the presence of Leishmania DNA in the two cases with parasite index 0. PAS and Grocott methenamine stains resulted negative for fungi. Interestingly, one patient had a previous biopsy with a diagnosis of lymphoproliferative disease, because of massive lymphoid infiltrate; the diagnosis was revised and amended after a second biopsy.

Focusing on the geographical distribution of cases throughout the territory of the province, we found out that patients lived in places at altitudes that ranged between 28 and 682 meters (Fig. 3A); interestingly, 18 of them resided on the hills, between 100 and 200 meters, corresponding to the southern part of the province, the so-called piedmont area; 5 patients lived in areas less than 50 meters in altitude, and only one resided in the northern part of the province, corresponding to the Padana plain, the so-called alluvial area (Fig. 3B).
Discussion

Leishmaniasis is a zoonosis endemic in many regions of old world, including the coastal zones of Italy. In Italy it constitutes an emerging problem also for humans, partly as a consequence of imported cases, partly because of the diffusion of canine leishmaniasis, particularly in Northern Italy. We observed a dramatically increased number of cases of cutaneous leishmaniasis diagnosed in our department of Anatomic Pathology in last three years, accounting for 60% of all cases diagnosed in a 20 years period. Interestingly, all patients were Italian, but one Moroccan, and none but two had travelled abroad in endemic places. The infection was unsuspected in the large majority of cases, the patients were immunocompetent and developed mostly a single cutaneous lesion. Our data are in contrast with those reported in a recent paper by Giavedoni et al., in which roughly the same number of cases of cutaneous leishmaniasis has been reported in a tertiary-care hospital in Spain in two consecutive decades, between 1992 and 2012. Moreover, 35% of cases were imported, and immunocompromised patients accounted for almost 30% of total number, being particularly numerous in the native group; finally, in 59% of cases multiple lesions were observed, particularly in immunocompromised patients. A previous study, performed in another tertiary-care hospital in Emilia Romagna region, Northern Italy, evaluated the number of visceral and cutaneous leishmaniasis in the period 1992-2013. Fifteen out of 134 patients analyzed were found to be affected by leishmaniasis; 8 had cutaneous leishmaniasis, three of them came from endemic area of Northern Africa and one had worked as missionary in Africa; only four patients did not have travelled abroad.

The cases of cutaneous leishmaniasis reported in the present study were diagnosed by histologic examination, and the large majority were unsuspected by the clinicians. All skin biopsies were characterized by a granulomatous infiltrate with lymphocytes and several plasma cells. The presence of amastigotes was documented in all cases but two. Although immunostaining with anti-CD1a has been proposed as a useful ancillary technique to enhance amastigotes in cases without unequivocal parasites, we performed PCR analysis that allowed to confirm the diagnosis of leishmaniasis in both cases with parasitic index 0. Of note, another case showed a massive lymphoid infiltrate, that was misinterpreted in a first biopsy as lymphoproliferative disease, a potential pitfall reported in the literature.

Given the high number of cutaneous leishmaniasis registered among the native population of our province in last three years, we sought to explain the reason of this outbreak. The great majority of our patients resulted to live in the so-called piedmont area. In this area the soil is characterized by a lesser degree of humidity, since it is constituted by a higher percentage of sand and gravel and a lower percentage of clay, as compared to the so-called alluvial plane. These geological properties of the soil make the piedmont area more suitable for the survival and proliferation of phlebotomus, whose diffusion seems to be inversely correlated to the level of ambient humidity. In fact, a recent study carried out in Iran revealed that cases of cutaneous leishmaniasis were more frequent in regions with desert and dry climate. The prevalence of our cases of cutaneous leishmaniasis in the hilly region can be correlated, also, to a study conducted on canine population in Emilia Romagna region. This study demonstrated the diffusion of canine leishmaniasis in last decade, due to increasing number of vectors of phlebotomous genre, mainly restricted to the piedmont area. Analogously, another study performed in north-western Italy documented the presence of Phlebotomous perniciosus, the main...
vector of leishmaniasis in dogs, particularly in hilly zones, between 100 and 300 meters of altitude. All these data could justify the outbreak registered also in our province. On the other hand, the sanitary surveillance and prevention of vectors’ diffusion made in last years by Emilia Romagna region in kennels, has lowered the risk of infection in dogs 11, therefore it is plausible that wild mammals, such as foxes, as documented in southern Italy 19, or even small rodents 20, have become new hosts of parasites also in this area.

In conclusion, cutaneous leishmaniasis is an emerging problem also in immunocompetent and non-travelers patients, resident in certain areas of Northern Italy. The observation of a granulomatous infiltrate with numerous plasma cells in a skin biopsy should prompt the search of amastigotes, also with PCR techniques in cases without visible parasites.

References

CASE REPORT

Angiomyofibroblastoma of the spermatic cord: a case report

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Key words
Angiomyofibroblastoma • Male genital tract • Paratesticular • Immunohistochemistry

Summary

Introduction

Angiomyofibroblastoma (AMF) is a rare benign mesenchymal tumor with tendency to arise in the lower genital tract of middle-aged women, predominately in the vulva. A few cases of AMF in males have been reported involving the scrotum, perineum or spermatic cord. We report a new case of AMF arising in the right inguinal region of a 27-year-old man. The tumor was well-circumscribed, myxoid and measured 30 mm in maximum dimension. On microscopic examination, the tumor was composed of spindle cells without atypia and with less than one mitosis figure per 10 high-power fields. Multinucleated cells and mast cells were observed. The stroma was myxoid and edematous with abundant capillary-sized blood vessels. Immunohistochemical staining showed a strong immunoreactivity for desmin and smooth muscle actin. The tumor cells were negative for estrogen receptors and focally positive for progesterone receptors with a low proliferative index of Ki67 (< 5%). This unusual neoplasm should be distinguished from aggressive angiomyxoma and other myxoid malignant tumors.

Case report

A 27-year-old man presented with right inguinal hernia. The patient underwent a surgery, a tumoral nodule of the spermatic cord was found associated to the hernia. The testis and the epididymis were not involved. Surgical excision was performed. Macroscopically, it was a 3 cm, myxoid and well-circumscribed nodule. Microscopic examination revealed a fusocellular proliferation encapsulated by a thick fibrous capsule with alternating hypercellular and hypocellular edematous areas (Fig. 1). The cells were spindle shaped with eosinophilic cytoplasm and elongated nuclei without atypia and with less than one mitosis figure per 10 high-power fields. Cell borders were often indistinct. Multinucleated cells and mast cells were observed within the myxoid and edematous stroma (Fig. 2) intermingled with abundant capillary-sized blood vessels. Immunohistochemical stains showed a strong immunoreactivity for desmin and smooth muscle actin (Fig. 3). The tumor cells were negative for estrogen receptors and focally positive for progesterone receptors with a low proliferative index of Ki67 (< 5%).

Discussion

AMF is a rare tumor first described in the vulva by Fletcher et al. in 1992. To date 26 cases of male AMF have been reported. Male genital tract AMF involves scrotum, perineum or spermatic cord. Grossly, it is mostly well circumscribed, round, ovoid, nodular mass sometimes gelatinous with a soft to rubbery consistency. The cut surface has a grayish-brown homogeneous appearance with no hemorrhage or necrosis. Most cases of AMF measure less than 5 cm, and previously reported cases ranged from 0.5 cm to 13.0 cm in greatest diameter. On microscopic examination, AMF is well de-
ANGIOMYOFIBROBLASTOMA OF THE SPERMATIC CORD: A CASE REPORT

Fig. 1. H. Ex 100: Alternating hypercellular and hypocellular edematous areas. Myxoid stroma with abundant thick-walled blood vessels.

Fig. 2. H.E x200: Multinucleated cells within the mesenchymal proliferation.

Fig. 3. Positive staining of tumoral cells for smooth muscle actin.

The most important differential diagnosis of AMF is aggressive angiomyxoma (AAM), which is locally invasive with a high risk of local recurrence and occurs predominately in the pelvic-perineal region. AAM differs from AMF in its infiltrative growth pattern, lower cellularity and a less conspicuous vascular component. It has been suggested that AMF and AAM are related neoplasms, both included in a wide spectrum of angiomyxoid tumors, which exhibit some overlapping features and various combinations of myofibroblastic, fibroblastic and lipomatous differentiation. The differential diagnosis of AMF also includes smooth muscle tumors, peripheral nerve sheath tumors, glomus tumor, chondroid syringoma, myxoid malignant fibrous histiocytoma, angiomylipoma, spindle cell lipoma and myxoid liposarcoma. It has been proposed that AMF might arise from perivascular stem cells, which are capable of differentiating into fatty and myofibroblastic differentiation.

This tumor has no local recurrence or metastatic potential. Local excision with clear margins appears sufficient for the surgical management of AMF. In conclusion, AMF is a rare benign tumor which occurs rarely in male and must be known by the urologists and pathologists. It should be distinguished from aggressive angiomyxoma and other myxoid malignant tumors. The treatment of choice for AMF is simple total excision. There are almost no incidences of recurrences or metastasis after complete excision.

References


Iatrogenic colorectal Kaposi’s sarcoma complicating a refractory ulcerative colitis in a human immunodeficiency negative-virus patient

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Key words
Kaposi’s Sarcoma • Ulcerative colitis • Human Herpes Virus-8 • Iatrogenic • Immunosuppression • Corticosteroids

Summary
Kaposi sarcoma is an unusual tumor associated to a human herpes virus-8 infection involving the skin or internal organs. Iatrogenic Kaposi’s sarcoma often occurs in patients receiving immunosuppressive therapy. So far, a few Kaposi’s sarcoma cases have been reported in the literature associated with inflammatory bowel diseases. We report a 53-year-old male diagnosed with a severe refractory ulcerative colitis who was treated with corticosteroids and azathioprine. The patient underwent a colectomy after the failure of medical treatment. Histological examination of the colon showed findings suggestive of Kaposi’s sarcoma. Immunohistochemistry for human herpes virus-8 was positive in the colonic lesions.

Introduction
Kaposi’s sarcoma (KS), first described by Moritz Kaposi in 1872, is commonly known as an unusual vascular tumor principally involving the skin. However, in some cases, it can also affect any organ system. It is strongly associated to human herpes virus-8 (HHV-8) infection ¹⁻⁷. Iatrogenic form of Kaposi’s sarcoma often occurs in patients receiving immunosuppressive therapy. Although the association between Kaposi’s sarcoma and renal transplant has been well documented, there are less Kaposi’s sarcoma cases in the literature associated with ulcerative colitis (UC) or other inflammatory bowel diseases (IBD) ¹⁻²². We report a case of a human immunodeficiency virus (HIV) negative man, with refractory ulcerative colitis who developed Kaposi’s sarcoma, associated with HHV-8, following treatment with azathioprine and additional corticosteroids. This patient underwent a colectomy.

With the present case, we wish to draw the interaction of immunosuppressive therapy used in ulcerative colitis patients with the development of colonic Kaposi’s sarcoma.

Case report
A 53-year-old heterosexual man, without personal or familial medical history, was diagnosed with ulcerative colitis for three months ago revealed by chronic bloody diarrhea (6-8 stools daily) with abdominal pain, rectal syndrome and weight loss of 2 kg. He had no smoking or alcohol drinking history. Initially, before admission in our center, oral steroid and local mesalamine was prescribed without a complete relief of rectal bleeding. Upon physical exam, blood pressure was 130/80 mmHg and his body mass index was 18.7 kg/m². Abdominal exam proved to be normal. Mucus and blood soiled finger at DRE. Besides, there was no skin lesion or lymph node swelling. Laboratory investigations showed iron deficiency anemia (10.3 g/dL) and signs of inflammation: white blood cell count of 9,800/mm³, erythrocyte sedimentation rate (ESR) of 60 mm and C - reactive protein (CRP) of 84 mg/L were noted. Albumin level was 28 g/L. Copro-parasitological examinations were negative.

Ileocolonoscopy showed pancolitis with mucosal fragility, large superficial ulcerations and pseudo-polyps, without severe endoscopic signs and with normal ileum. Histology found clear signs of active ulcerative colitis with no malignancy signs.
He was initially treated with intravenous steroids (1 mg/kg/day of prednisone), local mesalamine and parenteral nutrition for a severely active disease with a partial relief of diarrhea relayed by oral corticosteroids. At week 4 of corticosteroid therapy decreasing, relapse occurred (6 stools daily, anemia 8.6 g/dL, ESR 40 mm). Dose escalation of steroid was prescribed in association with Azathioprine (2.5 mg/kg/day). After 4 weeks of free steroid treatment, and while patient with Azathioprine (at month 6) another severe relapse occurred (8 stools daily, anemia 6.5 g/dL, ESR 40 mm, CRP 89 mg/L). Copro-parasitological examinations were always negative. Cytomegalovirus and HIV testing was negative too. Detection of Clostridium difficile toxins was not conducted. We had considered that it was a refractory severe ulcerative colitis and we suggested a surgical treatment for the patient. A subtotal colectomy with double stoma of the ileum and of the sigmoid colon was performed. Colon macroscopic examination revealed multiple mucosal and submucosal hemorrhagic polyoid lesions that coalesce, associated with large ulcerations. Histologic examination of polyoid lesions (Figs. 1-2) showed sheets of spindle cells interspersed by clusters of extravasated erythrocytes. The spindle cells often run parallel to the mucosae. Many spindle cells show mitoses. Endothelial cells lining the spaces are flattened or more oval, with little atypia, deposits of hemosiderin surrounded the vascular structures. Slit-like spaces, lymphocyte and plasma cell infiltration and extravasated erythrocytes are also observed. There was a partial infiltration of the appendix. No lymph node metastasis was demonstrated. Equally important, histology also found clear signs of active ulcerative colitis. On immunohistochemistry, the spindle cells were positive for vascular markers (CD31, CD34) and HHV-8 (Fig. 3) and were negative for factor VIII, actin, desmin and c-kit. These results were consistent with the diagnosis of Kaposi’s sarcoma, associated with typical features of ulcerative colitis. Once again, the patient underwent a total proctocolectomy and ileoanal anastomosis. The patient tolerated the surgery therapy well and recovered after operation.

**Discussion**

This paper report a case of iatrogenic colonic KS, associated to HHV-8, in an HIV-negative heterosexual man who had suffered ulcerative colitis. Kaposi’s sarcoma developed after starting steroid or immunosuppressive therapy, supporting the theory that colorectal Kaposi’s sarcoma associated with ulcerative colitis is iatrogenic. Table I summarizes the main data in literature of KS in association with IBD with or without HIV or HHV-8 infections.

Kaposi sarcoma-associated herpes virus (KSHV) occurs in four distinct clinical forms: classic or sporadic KS, endemic KS, HIV-associated epidemic KS and iatrogenic KS associated with immunosuppressor therapy. Predominantly, Kaposi’s sarcoma is seen in the case of homosexual males suffering from AIDS.
The association of iatrogenic KS and immunosuppressive therapy in renal or liver transplant patients has been frequently reported. In much less cases in the literature, iatrogenic KS were associated with UC on immunosuppressor or immunomodulator therapy. Our patient has received steroids and immunosuppressor therapy. The link between steroid-therapy and KS is well documented. However, there was no evident correlation between the development of KS and dose or duration of steroid therapy. Reduction or withdrawal of immunosuppressor therapy often leads to improvement in KS lesions. The diagnosis of colorectal KS may be difficult to establish in the absence of skin lesions, as in the case of our patient. At endoscopy, nodules on the bowel mucosa and polyloid lesions have been reported, as well as some cases of diffuse bowel involvement. In the case of intraluminal polypoids forms, polyposis red or blue, due to high vascular and conjunctive tissue proliferation. They can be confused with inflammatory pseudo-polyps in inflammatory bowel diseases. In accordance with the data provided, our patient has intraluminal pseudo-polyps associated with ulcerations. Biopsies may fail to sample diagnostic tissue before tumor infiltration of the mucosa. Large polyloid lesions may frequently undergo ulceration. Thus, superficial biopsies of such lesions may be diagnostically challenging to the histopathologist, and may, therefore, be misinterpreted as an inflammatory polyp. Upon histological exam, the tumor is made of cellular proliferation of neoplastic spindled cells arranged in fascicles. The tumor cells are relatively monomorph with some mitoses. Erythrocytes are contained within slit-like channels between the individual spindled cells. Hyaline globules may be seen. The periphery of the tumor may show dilated vascular spaces. Kaposi's sarcoma lesion may be mistaken for several other spindle cell mesenchymal neoplasms such as stromal tumor (GIST) or inflammatory fibroid polyp. The diagnosis is confirmed by positive immunohistochemical staining of the tumor cells for HHV-8. This HHV-8 is the major cause in the development of all epidemiologic variants of KS. Rezza et al. have reported a 30% risk of developing KS within 10 years in patients co infected with HHV-8 and HIV. The therapeutic approach is challenging. Conservative therapy with immunosuppressive drugs withdrawal has been successfully described. Proctocolectomy associated to immunosuppressive drugs discontinuation is usually effective to treat both tumor and coli-
After initial subtotal colectomy, the patient would undergo proctectomy when Kaposi’s sarcoma associated with ulcerative colitis is confirmed.

Conclusion

This report has illustrated that it is important to consider a concomitant colorectal Kaposi’s sarcoma in patients with refractory ulcerative colitis receiving immunosuppressive drugs. This tumor may be related to immunosuppressor therapy and opportunistic infection with HHV-8, independently of HIV status. Subsequently, in our practice, immunosuppressor therapy should be carefully planned and HHV-8 should be recognized as a possible underlying opportunistic infection in immunocompromised patients with IBD. Surgery and immunosuppressive drugs discontinuation may be indicated to treat both Kaposi’s sarcoma and refractory colitis.

References

Collision tumors represent a coexistence of two adjacent but histologically distinct tumors without histologic admixture in a organ. Primary well differentiated neuroendocrine tumor of ovary is rare and coexistent borderline mucinous tumor makes this association extremely rare. Although these tumors have been reported in other organs, its occurrence in ovary is rare. Collision tumor comprising primary neuroendocrine tumor of ovary and mucinous borderline tumor is an extremely rare occurrence. Here we report a case of this collision tumor in a postmenopausal female. H&E and immunohistochemical stains for chromogranin, synaptophysin, CDX-2, CK20, CK7 and Ki-67 were performed to confirm the diagnosis of collision tumor. Extensive search of literature revealed only a couple of cases report so far with this association. Our case is unique for a reason that we have reported trabecular variant of neuroendocrine tumor while the previously reported cases were insular variant. Management depends on patient’s age, desire for fertility and disease distribution.

Introduction
Collision tumor represents a coexistence of two adjacent but histologically different neoplasms occurring in the same organ without histological admixture with both tumors displaying a different histogenesis and different tumorogenesis pathway. Primary well differentiated neuroendocrine tumor of ovary is in itself rare and coexisting Mucinous borderline tumor, intestinal type makes this association even rarer. Primary neuroendocrine tumor of ovary constitute less than 0.5-1.7% of all neuroendocrine tumor and less than 0.1% of all ovarian cancer. Four histologic subtypes include insular, trabecular, strumal and mucinous and these types resemble their counterpart in gastrointestinal tract. Insular type is most common followed by strumal, trabecular, and mucinous and may occur in pure form or within a dermoid cyst, a mucinous cystic tumour or a Brenner tumor. Insular type is midgut derived and commonly observed in western countries and presents with classical carcinoid syndrome caused by serotonin and its precursors. In contrast, trabecular and strumal types are foregut or hindguts derived and are primarily reported in Japan and presents with constipation induced by the production of peptide YY, an inhibitor of intestinal mobility. Ovarian neuroendocrine tumors are derived from germ cells, and other teratomatous elements may be present in up to 90% of tumors.

Case report
A 55-year-old G1P0 woman presented with abdominal distension for 8 months. Her past medical history was unremarkable. Physical examination revealed was a large mass in pelvis measuring 25 cm, and extending above umbilicus and displacing cervix posteriorly. Large volume ascites was also noted. A chest radiograph showed no metastatic disease. She had an elevated CEA 259 ng/ml and normal CA 125 U/ml. Computerized tomography of the abdomen and pelvis confirmed 20.2 cm x 16.4 cm x 16.2 cm ovarian mass with internal cystic change...
with massive ascites with soft tissue nodularity in anterior peritoneum. A paracentesis was performed and cytological findings were reactive mesothelial cells without evidence of malignancy. She underwent exploratory laparotomy with unilateral salpingoophorectomy. Per operative findings were large ovarian mass, large volume mucinous ascites, and yellow necrotic material within peritoneal cavity with extensive adhesive disease of small bowel, large bowel and peritoneum. The liver, stomach, bowel, gallbladder and appendix were normal. There was no evidence of intraluminal gastric or intestinal tumors. Grossly tumor measured 20 cm in greatest dimension with irregular outer surface. Cut surface was partially solid and cystic with mucoid material and papillary projections. (Fig. 1) Microscopically the tumor consists of well differentiated neuroendocrine tumor with coexisting borderline mucinous tumor, intestinal type. Neuroendocrine tumor is composed of monomorphic cells with round nucleus, stippled chromatin, arranged in a wavy and anastomosing ribbons and cords depicting trabecular pattern. Borderline mucinous tumor is composed of the cysts lined by stratified mucinous epithelial cells which resemble dysplastic intestinal epithelial cell and contains goblet cells, neuroendocrine cells and Paneth cells. (Figs. 2-3). The neuroendocrine cells are diffusely positive for synaptophysin and chromogranin with a low Ki-67 labeling index supporting the diagnosis of well differentiated neuroendocrine tumor. (Figs. 4-5-6). The intestinal epithelial cells are positive for CDX-2 and CK20 immunostains.

Discussion

Primary well differentiated neuroendocrine tumors of ovary are very rare and a co-existing borderline mucinous tumor is even rarer and only few cases has been reported. Robboy has described two cases of insular carcinoid with mucinous borderline tumor and mucinous cystadenocarcinoma respectively 6, our case is unique in a respect that we encountered trabecular variant of neuroendocrine tumor. Review of literature reveals cases of large cell neuroendocrine carcinomas of ovary and associated serous carcinoma 8 and mucinous borderline tumor of the ovary 9. Primary and metastatic neuroendocrine tumor of ovary is difficult to differentiate specially in absence of teratomatous component. Appendix is the most common primary site for metastatic ovarian neuroendocrine tumor 4. Appendix, stomach, large and small intestine was normal in our case. Primary neuroendocrine tumor of ovary constitute less than 0.5-1.7% of all neuroendocrine tumor and less than 0.1% of all ovarian cancer 23. The median age of diagnosis is 53 years of age (range 14-79 years) 3. Primary neuroendocrine tumor may occur as a pure form or within a dermoid cyst, mu-
Primary Well Differentiated Neuroendocrine Tumor of Ovary Collides with Mucinous Borderline Tumor in a Postmenopausal Female: A Report of Case and Review of Literature

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Cinetic cystic neoplasm or Brenner tumor. Clinical sign of carcinoid syndrome can be present in 30% of insular carcinoid, rare in trabecular (13%) and strumal carcinoid (3.2%)\(^3\). Trabecular carcinoid may causes severe constipation and pain in defecation in about 15% of cases due to peptide YY production\(^3\). Functioning thyroid symptoms can be found in 8% of the strumal carcinoid\(^3\). Our case didn’t present with any carcinoid syndrome. Primary neuroendocrine tumor of ovary are found incidentally on cross section or ultrasound imaging and rarely presents with abdominal pain, constipation, hirsutism and a pelvic mass\(^10\). This tumors is considered to originate from germ cell, and other teratomatous elements, usually a dermoid cyst, are present in up to 90% of tumors\(^5\). Grossly the tumor presents as a tan yellow solid nodule adjacent to or protruding from a cyst, while in others as a mural thickening. Neuroendocrine tumor whether pure or associated with a teratoma usually presents as a solid mass while infrequently cut section is cystic\(^5\). The most common variant of primary ovarian neuroendocrine tumor is insular, followed by strumal trabecular and mucinous\(^3\). Histologically insular variants are characterized by nests and islands of round cells with monomorphic nuclei with abundant eosinophilic cytoplasm surrounded by an abundant fibromatous stroma. Strumal variants are characterized by variable admixture of neoplastic thyroid tissue with neuroendocrine component which in most cases is trabecular or mixed trabecular and insular. Trabecular variants are characterized by growth of the tumor cells in wavy ribbons and anastomosing cord with oblong nuclei with prominent nucleoli. Mucinous variant consists of columnar or cuboidal cells forming small glands with occasional intracytoplasmic mucin or with a goblet cell appearance\(^3\).\(^11\). Management of ovarian neuroendocrine tumor depends on the age of patient, disease distribution and fertility. In younger patient fertility sparing surgery is usually recommended as in most case these tumors are unilateral and associated with a good prognosis. Radical debulking is done when tumor has spread to adjacent organ. Metastasis is common in regional lymph nodes, liver, bones and lungs. Neuroendocrine tumor has a strong affinity for liver metastasis and unresected tumor should be considered for cryotherapy, radiofrequency ablation or regional embolization\(^9\).
Our patient was managed by unilateral salpingooophorectomy with lysis of adhesion and remains disease free after surgery.
In summary primary neuroendocrine tumor of ovary is rare and a coexistent mucinous borderline tumor makes this association an interesting case to report. Clinical awareness and recognition of such tumors are important as they will dictate appropriate treatment strategies depending on the individual biological aggressiveness of each of the tumor components.

References

Adenomatoid odontogenic tumor (AOT) is always benign. Given the very rare recurrence rate and the zero potential of malignant transformation, authors have considered it a hamartoma. Accordingly, ‘AOT’ is no more than a misnomer. This report, however, describes the first recognition of cellular atypia and pleomorphism in a peripheral oropharyngeal AOT which embraces an ameloblastic component. The overall picture was diagnosed, after careful histological and immunohistochemical assessment, as a peripheral adenoid ameloblastoma. This find may promote a new pathogenetic scenario to the nosology of this debatable lesion.

Background

Philipsen and Birn proposed the designation of AOT which was two years later, promoted by the World Health Organization. Adenomatoid odontogenic tumor (AOT), both in nature and designation, is now questioned. Based on clinical and immunohistochemical findings, it was suggested to be hamartomatous with histogenesis from the reduced enamel epithelium. Owing to its benign behavior, slow growth and clear delineation, as well as its low tendency to recur (0.2%), the treatment of choice is conservative surgical enucleation and simple curettage. Later, AOT has eschewed the very usual pathway to appear in combination with ameloblastic elements and exhibit new features. This paper reports one of the rarest findings in this domain.

Case report

A 38-year-old female manifested a small swelling at the retromolar pad of the right mandible. The asymptomatic exophytic swelling measured 1 x 1.5 cm. It was incidentally discovered during a routine examination. The overlying mucosa displayed normal color and texture. The radiological picture, moreover, showed no bony involvement. The lesion was surgically excised 8 months ago with no evidence of recurrence so far.

Histologically, atypical AOT areas with rosettes and duct-like structures were intervening the salivary tissue in conjunction with peripheral ameloblastic elements, both in a mass (Fig. 1) and intermittent configurations (Fig. 2). The classical eosinophilic materials were inconspicuous. Dentinoid materials were surprisingly remarkable. Intriguingly, the lesion evinced nuclear atypia, even some mitotic figures, and hyperchromatic tumor cells (Figs. 3-4). No necrosis was obvious. The cellular atypia could not prove to promote a malignancy. Immunohistochemically, the lesion was strongly positive for p53 (Fig. 5). CD-31 and S-100 expression were negative. The specimen margins were negative for any micro-invasions. The diagnosis was established as a peripheral adenoid ameloblastoma.

Discussion

Adenomatoid odontogenic tumor (AOT) is an uncommon, progressively growing, and asymptomatic benign non-invasive lesion, which occurs twice as often in females and usually in the second decade of life. The three variants of AOT are characteristic – a follicular, extrafollicular, and peripheral – endorsing the hamartomatous nature of this lesion, rather than being a true neoplasm. A low neoplasticity of AOT is also proposed. The peripheral variant is, among all, the rarest comprising only
14 reported cases in the medical literature. Nevertheless, AOT can be traced in association with other pathologies as well as *per se*. A hybridization of ameloblastoma and AOT was reported, evident. Complicating matters, AOT was homogenously observed in cases where it intermingles with native ameloblastic components. This rarity was designated “adenoid” ameloblastoma (AA) specifies those tumors which reveal impressive occurrence of AOT-like areas.

Histologically, AOT is a multi-nodular proliferation of spindle, cuboidal, and columnar cells in a variety of patterns comprising of scattered duct-like structures. Characteristically, eosinophilic materials are observed along with dystrophic calcifications in several forms; delimited by a fibrous capsule of varying thickness. Pertinently, between the epithelial cells of the nodules and in the center of the rosette-like configuration, pools of amorphous amyloid-like material, hyaline, dysplastic...
ones, and even, in very rare cases, dentin-like material may exist in both lesional tissue and stromal cells. Given the rare cases of unequivocal recurrent AOT \(^8\), a malignant AOT is unlikely to be expected. Accordingly, the rarity of this previously unreported may open a strong debate regarding the potential transformation. Immunohistochemically, AOT is strongly positive for amelogenin, ameoblastin and amelotin which can explain the milder aggression, comparable to other odontogenic tumors. AOT is also positive for podoplanin; accounting for the proliferative activity which is, again, the mildest. However, AOT do not usually stains positively for p53 \(^4\).

In our reported case, there appeared, for the first time, some clear-cut tumoral features which could prompt deeper speculations about the nature of this confusing disease. Cellular atypia was not abundant enough to support a frank malignancy. The strong expression of p53 was another striking caveat which warranted close follow up for atypical peripheral AOT.

**Conclusion**

Adenomatoid odontogenic tumor can represent more than a hamartomatous nature. Clinicians and pathologists need to reconsider the benign nature of atypical cases.

**References**


Vaginal rhabdomyoma: a case report of an uncommon and misleading neoplasm

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Key words
Rhabdomyoma • Vagina • Genital • Vaginal polyp

Summary
Vaginal rhabdomyoma is an extremely rare tumor which presents as a vaginal polypoid masses. It is essential to differentiate it from benign and malignant mimickers so that appropriate therapy may be provided. The present report describes a vaginal wall nodule of a symptomatic 24-year-old woman. Local excision and subsequent pathological examination were performed. The final diagnosis was vaginal rhabdomyoma. The literature is reviewed and differential diagnosis are discussed.

Introduction
Rhabdomyoma is a benign mesenchymal tumor originating from striated muscle tissue. It is rare, representing less than 2% of all striated muscle tumors and is classified into cardiac and extracardiac types. Among the extracardiac rhabdomyomas, three categories can be individualized: adult, fetal and genital rhabdomyoma. The vaginal rhabdomyoma belongs to this last category and is extremely rare with less than 30 cases reported in the literature. The distinction from the other varieties of rhabdomyomas is based on its different clinical and histological features. The diagnosis of rhabdomyoma should be taken into consideration in front of a vaginal polypoid mass.

We report below a case of a genital rhabdomyoma arising in the vagina of a 24-year-old woman. The clinicopathological features of this entity and its differential diagnosis will be discussed.

Case report
A 24 year-old nulliparous and nulligeste woman, consulted on gynecology for feeling of genital heaviness without menstrual disorders. There were no associated urinary or gastrointestinal symptoms. The patient’s past medical history was not significant. Physical examination revealed a vaginal wall nodule. A local excision was performed. Gross examination found polypoid, firm, mucosacovered formation which measured 1.5 x 0.8 x 0.5 cm. Microscopic examination revealed polypoid lesion covered by a normal, squamous, non-keratinized epithelium consistent with vaginal mucosa (Fig. 1). Within a loose connective stroma, we find a spindle-shaped tumor cells with abundant eosinophilic cytoplasm containing a cross-striation (Fig. 2). The nucleus was vesicular, regular, with visible nucleolus. Cellular atypia and mitotic activity were absent. The diagnosis of vaginal rhabdomyoma was retained.

Discussion
The vaginal rhabdomyoma is extremely rare. Less than 30 cases were reported in the literature. As all genital rhabdomyomas, it is characterized by an advanced skeletal muscle differentiation. Its etiopathogenesis still unknown. This tumor arises almost exclusively in middle-aged women with a mean age of 42 years. Clinically, this lesion is often asymptomatic, found incidentally on routine physical examination. In some cases, patients can present dyspareunia, vaginal bleeding or signs of compression of the urinary tract. On physical examination, the tumor presents as a polypoid or cyst-like mass, reddish-brown or grayish with a mean size of 2 cm.

The diagnosis is purely made by histological examination which shows a mass covered by a non-keratinizing squamous epithelium. It consists of scattered muscle

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fibers showing advanced maturation with abundant eosinophilic cytoplasm containing distinct cross-striations. The nuclei are vesicular and round with prominent nucleoli. The tumour cells are arranged haphazardly within a fibrous stroma containing varying amounts of collagen, mucoid material and dilated vessels. As with other rhabdomyomas, the immunohistochemical staining shows a positivity of tumor cells for desmin, myogenin and muscle-specific actin.

The differential diagnosis includes benign vaginal polyps and botryoid embryonal rhabdomyosarcoma. Unlike vaginal rhabdomyoma, the botryoid embryonal rhabdomyosarcoma is a rapidly growing lesion which usually occurs in young children aged less than 5 years. It often ulcerates the overlying epithelium in contrast of vaginal rhabdomyoma where the epithelium is intact. Furthermore, the “cambium layer” characteristic of botryoid embryonal rhabdomyosarcoma is absent in vaginal rhabdomyomas. Atypia and mitoses are more frequent in rhabdomyosarcomas than in rhabdomyoma.

Regarding the benign vaginal polyps, they lack striated muscle cells found in vaginal rhabdomyoma.

The behavior of rhabdomyoma is benign. Thus, the complete excision of the lesion is curative. Local recurrences are rare and no metastases have been reported.

References

Malignancies of the parotid gland are relatively uncommon, accounting for only 3-6% of all head and neck cancers. Most of them are primary neoplasms, metastases are uncommon. Renal cell carcinoma (RCC) represents 3% of adult malignancies, the clear cell type comprises up to 70% of all RCC. RCC has an unpredictable behavior and the unique potential to metastasize to nearly every organ in the body. Though not as frequent, metastatic RCC to the head and neck has been identified in the thyroid, salivary glands, skull base, sinuses, pharynx, tonsils, tongue, lip and skin. Metastasis to the parotid gland is very rare. Here, we report the case of a clear cell type RCC metastatic to the parotid gland and mimicking a primary clear cell oncocytoma. Differential diagnoses and a brief review of the literature are added.

Case report

A 60 year-old woman was referred to our Hospital for the management of a right parotid mass that lasted since two months. The patient denied any significant change in size of the lesion, paresthesia, or facial weakness. She had a past medical history of mono-kidney. On physical examination, there was a non-tender, soft nodule in the tail of the right parotid without associated lymphadenopathy. Both contrasted computed tomography (CT) scan and magnetic resonance imaging of the neck
showed an isolated right-sided lobular parotid mass that measured 3.5 x 2.4 x 2.5 cm, with an intense contrast uptake. Intraoperative examination of frozen sections revealed a clear cell neoplasm. The patient underwent a total parotidectomy with facial nerve preservation. Macroscopically, the parotid harbored a soft, well-encapsulated, orange-tan, homogenous and well-circumscribed lesion. The tumor appeared to be confined within a thin capsule. The remainder of the specimen demonstrated normal parotid tissue. Histological evaluation identified a non-encapsulated tumor. The mass was totally composed of solid clusters of polygonal-to-round cells with abundant clear cytoplasm, large slightly basophilic nuclei and small nucleoli. Pleomorphism was limited and no mitoses were found (Fig. 1A-B). There was also a prominent vascularization and an expansive pattern of growth with isolated solid nests infiltrating the capsule. Differential diagnosis between clear cell oncocytoma of parotid gland and metastasis from clear cell RCC was posed. Immunohistochemistry detected positive staining for CD10, vimentin, EMA (Fig. 2A-C), and negativity of CK7 and CK20; therefore, the final diagnosis
was renal cell carcinoma metastatic to the parotid gland. Following this diagnosis, the patient underwent a whole body CT-scan demonstrating 3 small lesions in the right lung and a 9-cm lesion of the kidney with renal vein invasion. Although the renal lesion had a large diameter, the patient underwent only a partial nephrectomy due to her clinical condition. Grossly, the surgical specimen was entirely replaced by a 9.5 x 6 x 6 cm yellow-white mass, with focal extension through the renal capsule. Microscopically the mass consisted of nests of medium-sized polygonal cells with abundant clear cytoplasm, surrounded by a network of thin-walled blood vessels, with pleomorphic nuclei, variably vesicular chromatin and prominent nucleoli (Fig. 3). There was infiltration of surgical margins but not adipose invasion. The final diagnosis was RCC, clear cell type, grading 2 according to ISUP 2013 5.

**Discussion**

Metastasis from RCC to the parotid gland is a rare finding 11,12; however, it should be considered in the differential diagnosis of clear cell neoplasms. RCC poses a particular diagnostic challenge because metastases can present synchronous with the primary tumor; otherwise, a metachronous distant presentation may occur many years after therapy for the primary. In addition it may alert the clinician to an undiagnosed primary renal tumor as in our case, and/or more widespread metastases and, depending on the patient’s symptomatology and overall clinical picture, guide the decision making for surgical resection. To date, 46 cases of RCC metastatic to the parotid gland have been described so far 8,11-13. However, the lack of a complete radiological and immunohistochemical work-up in 14 cases, renders these diagnoses

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<th>Age</th>
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<th>Location</th>
<th>Size (cm)</th>
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<td>Mass</td>
<td>L 3</td>
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<td>Pulsatile mass</td>
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<td>Masses</td>
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<td>7 years</td>
<td>/</td>
<td>Superficial parotidectomy with facial nerve preservation</td>
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Tab. I. Summary of case reports of RCC metastatic to the parotid gland.
The mean age of onset was 63 years (range: 40–83 ys) with a male predilection. All the patients had a palpable mass on presentation, mostly right; only in three cases the lesion was bilateral. Nine-teen patients were asymptomatic. The mean size of the metastatic lesion was 2.5 cm (ranging from 0.8 cm to 8 cm). Just less than half of the cases presented as syn-
chronous metastases, while 19 cases were discovered metachronously. Fourteen patients had been diagnosed and treated for RCC prior to parotid metastasis with an interval time spanning from 5 months to 19 years. In 16 cases, staging work-up demonstrated metastatic dis-
ease beyond the parotid. The other sites of metastasis included lungs, liver and peripheral lymph nodes. The treatment consisted of surgery in about all cases, with only three cases treated with radiotherapy plus surgery. Interestingly, only in one case, parotid metastasis was the first sign of RCC. For all these reasons, metastatic parotid clear cell RCC can be a challenging diagnosis. Differential diagnosis includes both primary and sec-

<p>| Tab. I. Summary of case reports of RCC metastatic to the parotid gland (follows). |
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<td>Stanley et al.</td>
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<td>2</td>
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<td>Li et al.</td>
<td>63 M</td>
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<td>B</td>
<td>3/2.5</td>
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<td>Park et al.</td>
<td>83 F</td>
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<td>/</td>
<td>R</td>
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<td>L</td>
<td>2</td>
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<td>R adrenal, lungs, retroperitoneal lymph nodes</td>
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<td>Newton et al.</td>
<td>74 F</td>
<td>/</td>
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<td>76 F</td>
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<td>R</td>
<td>/</td>
<td>Meta</td>
<td>RCC</td>
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<td>62 M</td>
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<td>L</td>
<td>3</td>
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<td>Laco et al.</td>
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<td>Deeb et al.</td>
<td>82 M</td>
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<td>4</td>
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<td>Lau et al.</td>
<td>79 F</td>
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<td>1.4</td>
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<td>Lawlor et al.</td>
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<td>Pancreas</td>
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<tr>
<td>Our case</td>
<td>60 F</td>
<td>Mass</td>
<td>R</td>
<td>3.5</td>
<td>Syn</td>
<td>RCC R</td>
<td>Lungs</td>
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M: male; F: female; R: right; L: left; B: bilateral; RCC: renal cell carcinoma; Syn: synchronous; Meta: metachronous
ondary clear cell tumors (myoepithelioma, clear cell oncocytoma, clear cell acinic cell carcinoma, myoepithelial carcinoma, epithelial-myoeipithelial carcinoma, mucoepidermoid carcinoma, primary clear cell carcinoma, clear cell thyroid carcinoma, RCC clear cell type and sometimes melanoma) \(^1\). A panel of immunohistochemical stains (according to the algorithm by Udager et al.) \(^1\) including cytokeratin AE1/AE3, CK7, CK20, p63, vimentin, CD10, EMA, PAX8, HMB45 is mandatory to achieve the correct diagnosis. In our case, the differential diagnosis between clear cell oncocytoma of the parotid gland and metastatic RCC, clear cell type, was resolved by a limited panel of antibodies (CK7, CK20, EMA, CD10). At the last follow-up (10 months after the initial diagnosis) the patient was alive. However, prognosis as well as the appropriate management options for patients with parotid metastasis from RCC is difficult to predict due to the limited number of cases reported in the literature. A thorough metastatic work-up and a collaborative team approach is advantageous to achieve the better clinical response.

References


Ovarian leiomyoma with myxoid stroma

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Key words
Myxoid leiomyoma • Ovary • Stromal tumors

Summary
Ovarian smooth muscle tumours are rare. Notable myxoid change in smooth muscle tumours is uncommon, and raises diagnostic issues that need to be considered on evaluating a spindle cell lesion with notable myxoid change. There is only one case of myxoid leiomyoma of the ovary previously reported. We here report a case of ovarian leiomyoma with areas of myxoid stroma and discuss the relevant differential diagnosis and histological features to be assessed in such a lesion.

Introduction
Ovarian smooth muscle tumors, both benign and malignant, are rare, based on our experience and that in the literature, even allowing for the fact that sporadically encountered benign examples would not warrant reporting. There are fewer than 150 cases reported over a wide age range, from 3 to 103 years-old, mean 43 years-old. Most are unilateral. Rarely bilateral leiomyomas have been reported in young women 16 to 38 years of age 1, 2. There is only one sizable series 1. In that report it was documented that histologically ovarian leiomyomas demonstrate a similar spectrum to their uterine counterparts, including leiomyoma with bizarre nuclei, mitotically active leiomyoma, cellular leiomyoma, epithelioid leiomyoma and lipoleiomyomas 1. Myxoid leiomyoma of the ovary is a very rare entity with only one case described in the literature to date 1. We have recently encountered an additional case of ovarian leiomyoma with myxoid stroma and report it herein along with a brief consideration of myxoid ovarian tumors, which, like myxoid tumors elsewhere may cause diagnostic difficulty.

Case report
A 23 years-old woman presented with abdominal pain and investigation revealed a right ovarian cyst that was suspicious for malignancy with MRI imaging. The patient underwent right salpingo-oophorectomy.

Macroscopically. The ovary was replaced by a well circumscribed mass with a smooth outer surface measuring 60 x 45 x 35 mm. The cut surface was mainly solid, pale brown with firm gritty white areas. An adjacent small cyst was seen, measuring 18 mm.

Microscopically. The majority of the tumour consisted of bundles of smooth muscle fibres with delicate spindle cells dispersed in an amorphous, pale, blue matrix (Figs. 1A-D). No notable nuclear atypia and no necrosis were seen and the mitotic count was < 1/50 HPF. On immunostaining the tumour cells expressed vimentin, smooth muscle markers (SMA, desmin, h-Caldesmon, and calponin, CD56 (Figs. 1E-J), being negative for inhibin, cytokeratin, S100, WT-1 and CD34. The macroscopically described cyst adjacent to the lesion is a mature cystic teratoma.

Discussion
Myxoid degeneration is seen in 3% to 13% of leiomyomas. The myxoid stroma in a leiomyoma arises from myxoid degeneration of collagen surrounding smooth muscle nodules. Myxoid leiomyoma was first emphasised in female genital tract neoplasia by Tavassoli and Norris in 1979 in vulval cases 3, 4. Myxoid leiomyomas are composed of anastomosing fas-
cicles of fusiform smooth muscle cells. There is abundant cellular material rich in acid mucins. The tumour tends to have large vessels. There is no cytological atypia. Mitotic figures are usually < 2/10 HPF.

It is most important to distinguish myxoid leiomyoma from myxoid leiomyosarcoma, which can be challenging in some cases. Myxoid leiomyosarcoma shows abundant myxoid stroma that separates the smooth muscle fibres with nuclear enlargement, pleomorphism, infiltrative growth, high mitotic count, higher ki67 and p53 expression. The myxoid leiomyosarcomas are either hypercellular or variably cellular. The hypocellular foci contain mucin pools or have myxoid matrix that imparts a reticular appearance. Sometimes the stroma is myxohyaline which is alcin blue positive. The neoplastic cells are arranged in bundles or fascicles or even individually within the myxoid matrix. The tumour cells have eosinophilic cytoplasm and elongated cigar-shaped hyperchromatic nuclei. Geographic tumour cell necrosis is observed in 48% of cases and lymphovascular invasion in 36% of cases. Myxoid leiomyosarcoma diagnosis is established if the tumour border is infiltrative and there is at least one of the following criteria:

- ≥ 2 mitoses /10 HPF;
- moderate or severe atypia;
- coagulative tumour necrosis.

As recommended by Lerwill et al. in the ovary, 2 or more of the following criteria in a smooth muscle tumour should raise the diagnosis of leiomyosarcoma:

- significant nuclear atypia;
- mitotic index 10 or more mitoses/10 HPF;
- necrosis.

In the uterus the presence of tumour cell necrosis would preclude placing a smooth muscle tumour with significant atypia and mitotic activity in a benign category. In the absence of tumour cell necrosis mitotic count of ≥ 5 mitoses/10 HPF in a cytologically atypical ovarian tumour warrants a diagnosis of leiomyosarcoma, a threshold lower than applied by Bell et al (10 mitoses/10 HPF) in uterine smooth muscle tumors, although others diagnose sarcoma in the uterus when mitotic counts are below 10 mitoses/10 HPF provided there is significant atypia. Another very characteristic feature in leiomyosarcoma is the absence of large thick walled blood vessels, which are usually present in myxoid leiomyoma.

Another lesion to be considered in the differential diagnosis is myxoma of the ovary, which appears with loose myxomatous stroma, scattered spindle cells without pleomorphism and without mitotic activity. The tumour cells express vimentin but are negative for desmin, cytokeratin and S100.

Ovarian leiomyomata are frequently confused with the more common fibroma, which often shows edema, but rarely myxoid change. The tumour cells are positive for CD56, SMA, WT1, occasionally S100 and CD34. We should consider in differential diagnosis the apoplectic leiomyoma which consists of stellate to ovoid stroma with hypercellular periphery and central haemorrhage, necrosis and hyalinization. The hypercellular areas can sometimes show increased mitoses ~ 14/10 HPF but no cytological atypia. There is edema and cyst formation in 95% and 42% of cases respectively. The hypercellular areas show spindle cells with nuclear pyknosis and mitoses are distributed only at the periphery and are not diffusely distributed as in leiomyosarcoma cases.

Sclerosing stromal tumor of ovary is another lesion which appears with a pseudolobular pattern of growth and widespread areas of sclerosis with myxoid-fibrotic stroma and focal cystic spaces. There are two cell populations, spindle and round cells and hemangio-pericytoma like vessels. The immunohistochemistry shows positivity of tumour cells for vimentin, inhibin and SMA.

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Fig. 1. Myxoid leiomyoma. A and B; Interlacing bundles of smooth muscle fibres in a background of myxoid stroma (A and B: X100, C: X 200, D: X400), E; h-caldesmon, F; SMA, G; Desmin, H; Calponin, I; vimentin and J; CD56 (E-J X200).
Finally we should consider the inflammatory myofibroblastic tumour where there are myofibroblastic and fibroblastic spindle cells with an inflammatory infiltrate of lymphocytes, plasma cells, eosinophils, and histiocytes. The background has abundant blood vessels. Immunohistochemically the tumour cells are positive for Vimentin, SMA, and calponin and in 1/3 of cases for desmin and keratin. ALK overexpression by immunohistochemistry may assist in distinguishing between myofibroblastic tumour and myxoid leiomyosarcoma as it is present in the former and negative in 85% of myxoid leiomyosarcomas.

ALK rearrangements may be helpful in confirming the diagnosis. Although documented in several other tumors like PNST and rhabdomyosarcomas, distinction from these entities is possible both on the basis of morphology and immunoprofile. In molecular studies 40% of uterine leiomyomas have detectable chromosomal abnormalities as t12,14 (q15, q23-24) rearrangements involving the short arm of chromosome 6 and chromosome 7. Specific mutations of the MED12 protein have been noted in 70% of uterine leiomyomas. Genetic changes in ovarian leiomyomas have not been studied.

In conclusion, we report the second case of leiomyoma with myxoid stroma encountered in the ovary, and discuss the differential diagnosis and approach to distinguish this benign entity from other neoplasms, which would significantly influence patient management.

References

Mixed malignant mullerian tumor with neuroendocrine features in an irradiated uterus for cervical carcinoma. A unique association? A morphological, immunohistochemistry and ultrastructural study

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Key words
MMMT • Neuroendocrine tumor • Radio-chemotherapy • Ultrastructure • Immunohistochemistry

Summary

Chemo-radiation represents an effective therapy for carcinoma of the uterine cervix. The endometrium may however receive a consistent dose of mutagenic radiations and patients may have an increased risk of secondary malignancies. Endometrial mixed malignant mullerian tumor (MMMT) is a rare, highly aggressive disease, and neuroendocrine features are even rarer. A 68 years old woman underwent radio-chemotherapy for a squamous cell carcinoma of the cervix. Follow up was uneventful until, eight years after radio-chemotherapy, imaging exams detected a diffuse enlargement of the uterine body. Radical hysterectomy revealed a multiphasic lesion with both sarcomatous and mixed carcinomatous components. The carcinomatous, component presented neuroendocrine histologic and ultrastructural features and an intense expression of neuroendocrine immunohistochemistry markers. No residual cervical carcinoma was documented (pR0). The patient died of disease after 9 months. Reported cases further demonstrate how the irradiation of the uterus for cervical cancer carries a not negligible risk of developing a second endometrial cancer. The second cancer may develop years after initial therapy and may have aggressive histologic and clinical features. This case underlines the importance for a long follow-up in women having received radio-chemotherapy alone.

Introduction

Endometrial mixed malignant mullerian tumor (MMMT) or carcinosarcoma is a rare, highly aggressive disease, accounting for approximately 3% of all uterine neoplasms typically occurring in elderly postmenopausal women with a median age of 65 years. By definition, these are neoplasms composed of an admixture of malignant epithelial and mesenchymal components. Both the components may show a wide pattern of differentiation: the carcinomatous component may have endometrioid, serous, undifferentiated or clear cell morphology while the sarcomatous component may show diverse histotypes resembling both typical uterine sarcomas (homologous) and other soft tissues tumors (heterologous). Neuroendocrine features are infrequently observed in the lower female genital tract and predominantly in the cervix.

Radiation therapy is the standard treatment for most patients with stage IIb–IVA cervical cancer. Recent randomized trials demonstrating improved survival when concurrent chemotherapy is added to radiation have led to the adoption of chemo-radiotherapy as the standard treatment for advanced cervical cancer with or without subsequent surgery. While chemo-radiotherapy is often curative, the radiation used can damage normal tissues, including the uterine corpus, and, if surgery is not performed, patients may survive long enough to be at risk of developing second uterine malignancies.

Neuroendocrine features are considered an extremely rare event in MMMT. In particular, no reports exist up till now of MMMT with neuroendocrine features in a
MIXED MALIGNANT MULLERIAN TUMOR WITH NEUROENDOCRINE FEATURES IN AN IRRADIATED UTERUS FOR CERVICAL CARCINOMA. A UNIQUE ASSOCIATION?

A 68 year old post-menopausal woman, without significant medical history, presented with meno-metrorrhagia and intermittent pelvic pain. Subsequent colposcopy revealed a mass deforming the uterine cervix. Biopsic samples revealed a moderately differentiated (G2), invasive, squamous cell carcinoma. Staging magnetic resonance imaging (MRI) demonstrated a 6 cm mass located in the uterine cervix infiltrating the right paracervical connective tissue. The tumour was thus assigned a IIB FIGO stage and the patient was treated with chemotheraphy (cisplastin and taxol) and radio (brachi)therapy, according to validated international protocols of treatment. Although chemio-radiotherapy was complicated by significant morbidity (actinic colitis and endometritis), the gynecological follow up, performed regularly, showed no evidence of residual disease.

Eight years later follow up computed tomography and MRI detected a diffuse enlargement of the uterine body within which 43 x 32 x 49 mm mass was seen. Clinical and radiological suspicion of a new, different primitive neoplasm of the uterine corpus was raised and the patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy.

PATHOLOGIC FINDINGS
At macroscopy, the neoplasm measured 40 x 30 x 50 mm and was solid and polypoid in nature, friable and necrotic. It occupied a large part of the uterine cavity with ulceration of the endometrial mucosa and deep infiltration throughout the myometrium with focal involvement of the serosa. Ovaries and salpinges were unremarkable. Microscopically, a carcinosarcoma (Mixed Mullerian Malignant Tumor) composed of different intermingled cancer cell populations was diagnosed.
The carcinomatous component was mixed, consisting of three different histotypes: moderately differentiated endometrioid carcinoma (70%) (Fig. 1A) neuroendocrine carcinoma (20%) (Fig. 1B); serous carcinoma (10%) (Fig. 1C).

The sarcomatous component consisted of spindle cells with marked cytological atypia and high mitotic count (Fig. 1D), immunopositive for vimentin (Fig. 2B) and negative for cytokeratins (Ck AE/AE3, CAM 5.2, Ck MNF-116) (Fig. 2A), smooth muscle actin (SMA), desmin and caldesmon, CD68 and CD10.

The neuroendocrine carcinomatous component was characterized by typical architectural and cytological features such as solid and insulo-trabecular growth and presence of wide areas of confluent necrosis. Cells showed irregular nuclei with vesicular chromatin and with incospicious nucleoli and amphophilic granular cytoplasms. The mitotic count was high (more than 20 mitosis/10HPF) with an high ki67 staining index (90%). Immunohistochemistry displayed strong and intense expression of neuroendocrine markers Chromogranin, Synaptophysin and CD56 only in the carcinomatous component. (Fig. 2C-E).

Complete evaluation of the surgical specimen showed total regression of the cervical cancer and evidence of actinic cervicitis along with other radio-induced alterations such as vascular sclerosis and stromal fibrosis. No residual tumor was documented (pR0) 12.

Electronic microscopy confirmed the multiphasic nature of the neoplasm. Epithelial looking polygonal cells arranged in chords and nests, rarely forming glandular lumens (Fig. 3A), with tights junctions and cytoplasmic small electron dense neurosecretive were seen. Furthermore sarcomatoid spindle cells with irregular nuclear outlines (Fig. 3B) were also documented.

The neoplasm infiltrated the myometrium and metastatic deposits were documented on the uterine serosa; no other metastases were evident at surgery (FIGO stage IIIA).

The patient received three courses of platinum-based chemotherapy but died of metastatic disease after 9 months.

Discussion

MMMT are relatively rare diseases and show an extremely aggressive clinical course. In the past, four different pathogenetic theories have been proposed for this disease: the collision theory suggests that the carcinoma and sarcoma are two independent neoplasms; the combination theory suggests that both components are derived from a single stem cell which undergoes divergent differentiation early in the evolution of the tumour; the conversion theory suggests that the sarcomatous element derives from the carcinoma during the evolution of the tumour; the composition theory suggests that the spindle cell component is a pseudosarcomatous stromal reaction to the presence of the carcinoma 13.
Recent studies have shown that uterine carcinosarcoma should be regarded as a metaplastic carcinoma: indeed, the carcinomatous component is considered the “driving force” of the disease, being the most frequently found element in tumor-involved lymph-vascular spaces, metastatic lesions, and representing, above all, the major determinant of clinical outcome. The emergence of sarcomatous elements would therefore represent the evolution of subclones arising within an aggressive, poorly differentiated endometrial carcinoma with endometrioid, serous or clear cell histology. Even in metastases, endometrial carcinoma can progress to carcinosarcoma. All these findings seem to support the conversion theory which considers MMMT a particular subtype of endometrial carcinoma rather than a sarcoma. MMMT should therefore be included in the Type II subgroup having a p53-mediated pathogenesis, an aggressive behavior and adverse prognosis.

Aside from anecdotal reports, neuroendocrine differentiation in mixed mesodermal (Müllerian) tumors of the female genital tract have accounted for up to 17% in a relatively large series of 47 cases. This percentage, based on a rather old study, seems to be high. It may be possible that the neuroendocrine pattern is underestimated in routine pathology practice, and interpreted merely as undifferentiated carcinoma. Though some published data suggest an aggressive course and poorer prognosis for carcinosarcomas with neuroendocrine or neuroectodermal differentiation, it remains to be clarified whether the neuroendocrine pattern bears clinical significance, both for diagnosis and therapeutic approaches. The present case confirmed an aggressive behavior and resistance to therapy leading to patient death despite prompt surgery and adjuvant chemotherapy.

Cervical cancer remains the second most common female malignancy worldwide. Women treated with radiation for cervical carcinoma are usually young and often survive for many years. The addition of concurrent chemotherapy may further improve survival rates for those with loco-regional advanced disease.

Previous studies have been carried out on radiation-induced second cancers. There are some epidemiologic surveys for second cancers following radiation treatment for cervical cancer. A study from Czesnin et al. found the risk of uterine sarcomas, including carcinosarcoma, to be 5.4 times that of the control population. Fehr et al. observed 2294 patients who were irradiated for cervical carcinomas, and found 12 patients with proven endometrial cancer. This was more than double the expected annual spontaneous incidence of endometrial cancer. More recently, Pothuti et al. reporting the experience of two large US Cancer Centres, described 23 post irradiation endometrial cancers, 7 of which with combined carcinomatous and sarcomatous features. Radiation-associated endometrial cancers carry a poor prognosis because they are more likely to be non-endometrioid, poorly differentiated and advanced stage cancers. The longer latency, in general more than a decade, of radiation-associated endometrial cancers may suggest a possible delay in clinical presentation and diagnosis.

In the presented case the patient had scrupulously adhered to follow-up, however she came to surgery in an advanced stage confirming the aggressive behavior of the disease.

The mechanism for tumorigenesis of post radiation carcinoma is still unclear. Parkash et al. have pointed out that it is possible that the obliteration of the cervical os by previous radiation therapy favors the development of an inflammatory process in the uterine cavity, which might lead to necrosis and cancer. It should be underlined that the endometrial cavity is very close to the cervix and during radiotherapy, it receives a considerable dose of irradiation. The relationship between radiation and carcinogenesis is complex. Radiation-induced DNA damage is most commonly found in the form of double strand breaks, which may result in mutation when the normal mechanisms for DNA repair or apoptosis fail.
Endometrial tissue can persist after radiation therapy for cervical cancer and undergo neoplastic transformation. Furthermore, young women treated with radiation for cervical cancer receiving hormone replacement therapy with estrogen may have an increased risk of endometrial cancer. In our experience on surgically removed uteri after neo-adjuvant radio-chemotherapy for uterine cervix carcinoma, the endometrial lining is often modified by treatment and, in general, shows atrophic features sometimes associated with nuclear enlargement, mild hyperchromasia with irregular nuclear outlines and rarely, nuclear p53 accumulation can be observed with immunohistochemistry. These latter "atypical" cases, in an intriguing hypothesis to be verified by further studies, may represent a very early radiation induced pre-neoplastic lesion may result in a second endometrial cancer in time. In a recent, interesting in vitro study, Tsukamoto et al. experimentally demonstrated a radiation induced epithelial-mesenchymal transition on cultured endometrial cells, explaining the unexpectedly high rates of MMMT in patients with irradiated uteri. In conclusion all these observations demonstrate how the irradiation of the uterus for cervical cancer carries a not negligible risk of developing a second endometrial cancer, in those patients were the uterus not surgically removed after completion of radio-chemotherapy. The second cancer may develop many years after therapy and can have aggressive histologic features such as sarcomatoid and neuroendocrine morphology, rapidly carrying these patients to exitus. Patients where the uterus is left in its anatomic site after the completion of the curative-intention radio-chemotherapy, probably require a longer and more thorough follow-up for the risk of a second malignancy. This latter observation should be taken into account when curative-intention radio-chemotherapy protocols are comparatively evaluated with neo-adjuvant treatments followed by radical surgery.

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**CASE REPORT**

**Gastric metastasis from cervix cancer: a case report**


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**Key words**

Cervix cancer • Cervix metastases • Gastric metastases • Gastric ulcer • Gastric bleeding

**Summary**

Gastric metastasis by solid tumor cancer is a rare event. Concomitant metastases to other organs are frequent, so that this condition is often associated to a poor prognosis. Upper gastrointestinal bleeding and anemia are the most common presenting symptoms. We present the case of a 81 years old women previously treated for cervix carcinoma showing later a stomach metastasis. The patient is alive and disease free 39 months after salvage gastrectomy. A radical surgery in selected patients could be useful for symptom palliation and prolonged survival.

**Introduction**

Gastric metastasis by solid tumors is a rare event. The most common primary sites are the lung, breast, skin (melanoma) and esophagus. The most frequent presenting symptoms are upper gastrointestinal bleeding and anemia. We present the case of a patient previously treated for cervix carcinoma showing a stomach metastasis, with symptoms and disease control improved by total gastrectomy.

**Case report**

A 81 years old women underwent in January 2012 to radical hysterectomy for poor differentiated carcinoma of cervix uteri (Fig. 1), pathological stage according to International Federation of Gynecology and Obstetrics (FIGO) IIA2, with vascular invasion and vaginal surgical margin involved. Pre-operative chest x-ray was normal; post-operative abdomen computerized tomography (TC) detected a right pelvic 2.5 cm lymph node metastasis. The patient was treated with daily pelvic external beam radiotherapy, 5 fractions per week, up to 50.4 Gy to the pelvis and residual vagina, and up to 54 Gy to the pelvic lymph node metastasis, 1.8 Gy per fraction.

The residual vagina was also later treated with endocavitary high dose rate brachytherapy boost up to 12 Gy in 3 fraction of 4 Gy delivered in a week. The treatment was completed on June 2012. In September 2012 chest and abdominal TC and clinical evaluation showed no disease evidence. In November she came to the our Radiation Department for planned control showing marked pallor and strong fatigue, without other symptoms. Hematological count detected a marked anemia: hemoglobin was 4.5 g/dl. After blood transfusion, diagnostic work-up (esophagogastroduodenoscopy and colonoscopy) detected a gastric ulcerate lesion, 6 x 5 centimeter. Endoscopic biopsies showed squamous carcinoma. On 11 December 2012, under general anesthesia, a total gastrectomy with a standardized D2 lymph node dissection was performed. Neither intra- nor post-operative complication occurred. Then, the patient started to eat without any functional disorder. The histological examination showed gastric localization of poor differentiated squamous cervix carcinoma (Fig. 2); the examined 37 lymph nodes were uninvolved. Follow up consisted of regular clinical examinations, blood tests, chest x-ray, abdominal TC or 18-FDG total body positron emission tomography. At 50 months from primary surgery and 39 months from salvage surgery the patient is alive with good health and disease free.
Fig. 1. Histological pictures of cervical cancer carcinoma. (1a) Squamous cells carcinoma of the cervix infiltrating sub-epithelial tissues. Scanning image (Hem-eos 4x). (1b) Squamous cells carcinoma of the cervix infiltrating sub-epithelial tissues. Scanning image (Hem-eos 10x). (1b) Same specimen as 1a. Detail of the cytological features (Hem-eos 20x). (1c) Same specimen. High power view of the tumour (Hem-eos 40x).

Fig. 2. Histological pictures of gastric localization of cervix squamous carcinoma. (2a-2b) Scanning image of gastric localization of the cervix squamous cells tumor (Hem-eos 4x). (2c) Same specimen. Detail of cytology of the squamous cells very similar to those of the cervix (Hem-eos 10x).
Discussion

According to our knowledge, only 5 cases \(^1\) of gastric metastases by cervical cancer had been previously reported. Oda et al. \(^3\) described 19 cases of gastric metastases from uterus without distinguishing body from cervical cancers. As in most other reported cases, upper gastrointestinal bleeding and anemia were the presenting symptoms \(^1\) \(^6\) \(^9\), and the time elapsed between the diagnosis of the primary tumor \(^1\) or relapse to the primary site \(^6\), and diagnosis of metachronous gastric metastasis was less than 1 year. The macroscopic features observed by esophagogastroduodenoscopy are not specific of metastatic disease \(^1\) \(^3\), so that an histological diagnosis is mandatory.

A surgical treatment, such as a partial gastrectomy, was performed in 2 previous cases by Journey et al. \(^6\) with a follow-up limited to 6 months, and by Campoli et al. \(^1\) without data reported on the outcome of the specific patient, even if no patient survived longer than 14 months. The presence of concomitant metastases to other organs is frequent, so that this condition is often associated to a poor prognosis \(^1\) \(^6\).

In our patient, the clinical evidence of a single site of disease led to an aggressive approach with a total gastrectomy despite advanced age, resulting in a symptoms palliation and a prolonged survival. In this uncommon scenario there is not an evidence based recommended treatment due to a very limited number of previously reported cases.

Even if the conclusions getting from a single case reported have a poor evidence, data from also only one experiences could be helpful to know.

References

Dedifferentiated primary mediastinal liposarcoma mimicking a thymic tumor

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Key words
Liposarcoma • Mediastinal liposarcoma • Thymic tumor

Summary
Mediastinal tumors are heterogeneous and the diagnosis depends on their location in the mediastinum. The most frequent tumors are germinal tumor, lymphoma and thymoma. The clinical and radiological aspects are often not sufficient to orient the diagnosis and biopsy is necessary to confirmed it. Here, we present a rare case of an anterior mediastinal mass incidentally detected in a 63 years old man during assessment for asthma. The lesion was presumptively diagnosed as a thymic epithelial tumor based on location and radiological characteristics. Surgical biopsy revealed a primary dedifferentiated mediastinal liposarcoma with multiple lung metastases.

Introduction
Mediastinal tumors are rare and most of them occur in the anterior mediastinum corresponding to thymomas, lymphomas or germ cell tumors. Otherwise, primary liposarcoma of the mediastinum is an extremely rare tumor, accounting for 0.13% to 0.75% of all mediastinal tumors1. On the other side, these neoplasms usually arise from the lower extremities and the retroperitoneum, while the mediastinal localization is very rarely reported in clinical practice (about 1% to 2% of all liposarcomas) and usually at the level of the posterior mediastinum2. 3. According to the most recent classification by the World Health Organization, liposarcomas are classified histologically into well-differentiated liposarcoma (accounting for 40% to 45% of liposarcomas); myxoid liposarcoma (accounting for 15% to 20%); dedifferentiated liposarcoma (arising de novo and occurring in up to 10% of well-differentiated liposarcomas); and pleomorphic liposarcomas (rarest, accounting for 5%)4. Here, we report and discuss an unusual dedifferentiated liposarcoma presenting as an anterior mediastinal mass and mimicking a thymic epithelial tumor.

Clinical case
An anterior mediastinal mass was discovered in a 63 years old man during assessment for asthma. The patient had no relevant clinical history and complained about dyspnea and weight loss (10% over the last 6 months). Thoracic Computerized Tomography (CT) scan revealed a left anterior mediastinal mass with a large central calcified area (Fig. 1). The tumor measured 11 cm in the main axis and had an aggressive and infiltrant behavior (lung parenchyma, phrenic nerve). It was associated to multiple pleural nodules and a moderate pleural effusion. No nodal enlargement was seen, but there were several centro-lateral lung micronodules, consistent with metastatic spreading (Fig. 1). These radiologic findings suggested a thymic tumor. Clinical examination revealed no sign of myasthenia. Serum markers of germinal tumors were not elevated (Human Chorionic Gonadotropin or Alpha Foetoprotein). During video-assisted thoracoscopy, we confirmed diffuse pleural extension. The biopsy of a pleural nodule and talc poudrage were performed. Histologic examination showed a malignant tumor with two different parts. The most abundant
component was an undifferentiated high-grade spindle-cell proliferation organized in storiform pattern, with moderate mitotic activity (10 mitoses/10 HPF). Another component consisted of bone-forming tumor (Fig. 2). Tumor cells were negative for immunostains with smooth muscle actin, desmin, CD34, S100 protein, AE1/AE3 and EMA antibodies. MDM2 antibody revealed nuclear staining in both tumor areas (Fig. 2). Chromogenic In Situ Hybridization (CISH) performed with a MDM2 probe on formalin-fixed paraffin-embedded tissue sample showed amplification of MDM2 gene (Fig. 2). Although no well-differentiated liposarcoma component was found in the biopsy samples, dedifferentiated liposarcoma was final diagnosis according to histological features and molecular pattern. Because of metastatic disease at presentation, the tumor was not considered as resectable and chemotherapy based on doxorubicin and ifosfamide was started.

Discussion

We report an unusual case of large anterior mediastinal mass corresponding to dedifferentiated liposarcoma. The most common tumors of the anterior mediastinum include thymic tumor, lymphoma and germ cell tumors. As remarked by Grobmyer and co-workers, fewer than 150 cases have been reported in the medical literature. In our case, these diagnoses were rapidly infirmed on the basis of clinical, laboratory and pathologic grounds. The hypothesis of dedifferentiated liposarcoma was not suggested by radiologic findings, because of the absence of fatty component. Moreover, mediastinal liposarcomas are rarely encountered in clinical practice representing 1% to 2% of all liposarcomas; anyway they are the most common sarcomas of the mediastinum, particularly in the anterior location. As primary mediastinal liposarcomas are rare, it is mandatory to exclude a metastatic disease from a primary liposarcoma of the retroperitoneum or soft tissues.
Three main histologic types with different prognostic behavior are described: well-differentiated/dedifferentiated liposarcoma, myxoid liposarcoma, and pleomorphic liposarcoma. In anterior mediastinum, the most frequent type is well-differentiated/dedifferentiated liposarcoma, whereas pleomorphic liposarcomas are uncommon, and myxoid liposarcomas are exceptional. Liposarcoma classification has been improved by advances in the molecular characterization of soft tissue tumors. Less than 200 primary mediastinal liposarcomas have been reported to date, either in case reports or in series, but in the majority of these reports, molecular analysis was not used to confirm diagnosis. A recent series of 24 cases of intrathoracic liposarcomas showed that mediastinal liposarcomas present a preponderance of uncommon subtypes and unusual morphologic variants, including, for example, myxoid well-differentiated liposarcoma mimicking myxoid liposarcoma, as well as differentiated myxoid liposarcoma mimicking well-differentiated liposarcoma. In these cases, diagnosis was confirmed by molecular genetic testing. Thus, accurate histopathologic and molecular classification is essential to distinguish relatively indolent well-differentiated and dedifferentiated liposarcomas from much more rapidly progressive histotypes, such as myxoid and pleomorphic liposarcoma.

**Conclusion**

Although infrequent, primary mediastinal liposarcoma should be considered in differential diagnosis of anterior mediastinal masses. Molecular characterization should be made, as different subtype of liposarcoma have different prognosis. Exhaustive clinical and pathological work-up are necessary to best characterize and manage this unusual tumor.

**References**

Inflammatory lesions of the breast encompass primary reactive processes and local manifestation of systemic diseases. They are very rare and they are generally treated without resort to biopsy. Nevertheless they could be clinically challenge mimicking malignant process and needing surgery to reach a correct diagnosis. Here we describe a rare case of breast granulomatosis with polyangiitis, which presented with radiological and clinical alarming features that immediately raised the suspicious of malignancy leading to breast-conserving surgery.

**Key words**

Breast • Granulomatosis with polyangiitis • C-ANCA • Giant cell arteritis • Wegener’s granulomatosis

**Summary**

Inflammatory lesions of the breast encompass primary reactive processes and local manifestation of systemic diseases. They are very rare and they are generally treated without resort to biopsy. Nevertheless they could be clinically challenge mimicking malignant process and needing surgery to reach a correct diagnosis.
sarcomatoid carcinoma or triple-negative breast cancer. No other significant abnormalities were detected in other organs. In April 2010, nipple-sparing central quadrantectomy was performed. Grossly, the surgical specimen showed a cystic lesion containing necrotic grayish material. Histological examination revealed a necrotic cavitated mass lined by a chronic inflammatory process (Fig. 2). No neoplastic or sarcomatoid cells were observed. The inflammatory process included a necrotizing small-vessel vasculitis, scattered “wrinkled” multinucleated giant cells and serpiginous neutrophilic microabscesses (Figs. 3-4). Even on surgical specimen, no microorganisms were identified on special stains. A diagnosis of chronic granulomatous inflammation with necrosis suggesting a vasculitic disease, mainly granulomatosis with polyangiitis (formerly Wegener’s granulomatosis) was performed. In May 2010, based on pathologic report, a PR3-ANCA (anti-neutrophil cytoplasmic antibody...
against proteinase-3, C-ANCA) test was ordered with negative result. No further therapy was performed. In the subsequent months, the patient developed systemic symptoms (fever, malaise and weight loss), involvement of the respiratory tract (tracheo-bronchial stenosis, sinusitis), scleritis, and bilateral otitis media leading to hearing loss. In September 2010, a biopsy of crusted nasal lesions revealed a necrotizing process characterized by neutrophilic microabscesses, darkly giant cells and chondritis consistent of granulomatosis with polyangiitis involving the upper respiratory tract. Specific serum laboratory tests were repeated one month later revealing C-ANCA positivity by ELISA. Thus, a diagnosis of systemic granulomatosis with polyangiitis was made. The patient started the induction therapy with cyclophosphamide (2 mg/Kg/day) and prednisone (1 mg/kg/day) with prompt clinical response. She continued with cyclophosphamide and prednisone in the maintenance therapy for 12 months achieving a complete remission of the disease.

**Commentary**

Granulomatosis with polyangiitis and giant cell arteritis represent the most common systemic vasculitis manifesting as tumor-like mass even in the breast parenchyma. Imaging features of a mammary ill-defined cavitated mass should then rise suspicious for vasculitis, particularly in patients experiencing constitutional symptoms such as fever, weight loss, malaise or fatigue, arthralgia and myalgia and bilateral involvement. Although histology of granulomatosis with polyangiitis is mainly characterized by vasculitis, necrosis and inflammatory background, some of these features are lacking and the diagnosis requires a close clinico-pathologic and laboratoristic correlation. Furthermore, localized granulomatosis with polyangiitis is not infrequently associated with a negative C-ANCA serum test. Nevertheless, cases of granulomatosis with polyangiitis with negative serum test and localized disease in the breast does exist and are the most difficult cases to diagnose. Indeed, the differential diagnosis includes several infections and many other inflammatory diseases (e.g., diabetic mastopathy, sarcoidosis, granulomatous mastitis, IgG4-related syndrome).

As showed here, this condition may remain silent and underscored for several months until systemic involvement with conversion to serum C-ANCA positivity occur. Awareness of atypical manifestation of granulomatosis with polyangiitis coupled to meticulous clinico-pathologic correlation may prevent unnecessary surgery.

**References**

We report an ALK-rearranged adenocarcinoma of the lung presenting as a pituitary metastasis, clinically simulating a pituitary adenoma. The patient, a 50 year-old, former-smoker woman was admitted with a Parinaud’s syndrome characterized by progressive oculomotor impairment of visual verticality, bitemporal hemianopsia and nystagmus. Imaging studies showed a sellar tumor and the biopsy revealed a TTF-1 and napsin positive lung adenocarcinoma strongly expressing synaptophysin and CD56, also harboring ALK rearrangement. A subsequent CT scan disclosed the primary lung mass of the left upper lobe. The patient progressed after 4 cycles of cisplatin/pemetrexed as first line treatment, but showed a partial response and a significant clinical benefit from the combination of ceritinib and nivolumab in a phase Ib trial. Despite its central nervous system tropism, ALK-rearranged adenocarcinoma manifesting with pituitary gland involvement was never reported. Second generation ALK inhibitors seem the best therapeutic strategy.

### Case report

**ALK-positive adenocarcinoma of the lung expressing neuroendocrine markers and presenting as a “pituitary adenoma”**

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**Key words**

Lung • Adenocarcinoma • Immunohistochemistry • Neuroendocrine • ALK • Pituitary gland • Metastasis

**Summary**

We report an ALK-rearranged adenocarcinoma of the lung presenting as a pituitary metastasis, clinically simulating a pituitary adenoma. The patient, a 50 year-old, former-smoker woman was admitted with a Parinaud’s syndrome characterized by progressive oculomotor impairment of visual verticality, bitemporal hemianopsia and nystagmus. Imaging studies showed a sellar tumor and the biopsy revealed a TTF-1 and napsin positive lung adenocarcinoma strongly expressing synaptophysin and CD56, also harboring ALK rearrangement. A subsequent CT scan disclosed the primary lung mass of the left upper lobe. The patient progressed after 4 cycles of cisplatin/pemetrexed as first line treatment, but showed a partial response and a significant clinical benefit from the combination of ceritinib and nivolumab in a phase Ib trial. Despite its central nervous system tropism, ALK-rearranged adenocarcinoma manifesting with pituitary gland involvement was never reported. Second generation ALK inhibitors seem the best therapeutic strategy.

### Introduction

Primary lung carcinoma presenting as a metastasis to the pituitary gland is exceedingly rare and generally represents a diagnostic challenge for pathologists. In addition, immunohistochemical stains may be misleading since TTF-1 expression is observed in some primary pituitary tumors. We describe here the case of a 50-year-old, former smoker woman presenting with neurologic symptoms due to a sellar mass clinically suggestive of a pituitary adenoma. The tumor biopsy revealed an adenocarcinoma with acinar pattern expressing TTF-1 and napsin, but also neuroendocrine markers (synaptophysin, CD56) and ALK protein. ALK gene rearrangement was confirmed at FISH testing and a pulmonary mass was subsequently identified at chest CT-scan. To our knowledge, this is the first ALK-positive lung adenocarcinoma manifesting with pituitary gland metastasis. The concurrent neuroendocrine differentiation at immunostains and the site-related therapeutic strategies were discussed.

### Case report

A 50 year-old women, former smoker, was admitted to the Neurology Unit with polydipsia and progressive ocular impairment in visual verticality. Ophthalmologic examination revealed bitemporal hemianopsia and nystagmus. A magnetic resonance imaging (MRI) with gadolinium (Fig. 1) showed a 2.2 cm sellar lesion, clinically suggesting a pituitary adenoma with compression of the optic chiasm.

Routine laboratory test were unremarkable. The tumor was, then, partially removed through a trans-sphenoidal approach. Histological examination (Fig. 2) showed an adenocarcinoma with an acinar pattern expressing TTF-1 (clone 8G7G3/1), napsin (clone MRQ60), synaptophysin (clone SP11) and CD56 (clone 123C3). Chromogranin (clone LK2H19) was negative. All primary antibodies were tested using an automated immunostainer (UltraView, Ventana Medical system, Tucson, AZ, USA). A diagnosis of pituitary metastasis from an adenocarcinoma consistent with lung primary was made.

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ALK-POSITIVE ADENOCARCINOMA OF THE LUNG EXPRESSING NEUROENDOCRINE MARKERS AND PRESENTING AS A “PITUITARY ADENOMA”

and predictive biomarkers were ordered as reflex test. Tumor cells were strongly positive (score 3+) for ALK protein (clone D5F3) and ALK rearrangement was further confirmed by fluorescence in-situ hybridization (FISH) technique (46% of tumor cells with classic split signals). Extractive molecular analysis by MALDI-TOF method ((Sequenom, LungCarta Panel v1.0, Agena Bioscience, San Diego, CA) did not evidence gene alterations of EGFR, KRAS, BRAF, HER2, PI3KCA, NRAS.

A left upper lobe nodular opacity was noted and chest X-rays and computed-tomography (CT) (Fig. 3) confirmed a mass of 3.5 cm of maximum diameter with ipsilateral hilar lymphadenopathies. The patient started first-line chemotherapy with cisplatin (75 mg per square meter) and pemetrexed (500 mg per square meter of body-surface area). After 4 cycles, CT scan showed a progression of residual sellar lesion and disease stability of the primary site.

Given the CNS involvement at the diagnosis, the patient was enrolled in a phase Ib study with a second generation ALK inhibitor (ceritinib, 750 mg taken orally once daily) plus the anti-PD-1 nivolumab (240 mg IV every two weeks) until disease progression or intolerable toxicity.

Fig. 1. Contrast-enhanced magnetic resonance (sagittal-T1-weighted images) shows a 2.2 cm lesion of the pituitary region suggestive of pituitary macroadenoma.

Fig. 2. The biopsy of pituitary mass revealed a metastatic adenocarcinoma (A, H&E stain) expressing TTF-1 (B), Napsin (C), synaptophysin (D) and ALK (E).
The high risk of iatrogenic blindness and long-term neurocognitive toxicity precluded a radiotherapy treatment of the metastatic site. The patient promptly experienced a clinical benefit and an improvement of visual acuity. Imaging studies showed a partial response of the lung adenocarcinoma (1.1 cm of maximum diameter) and a stability of the pituitary metastasis. After 6 months, the patient presented with neural symptoms and MRI documented a multifocal brain progression. The experimental treatment was stopped and the patient underwent whole-brain irradiation and started a third line treatment with crizotinib (250 mg orally twice daily). She is alive with disease after 14 months from the diagnosis.

Discussion

The case described here had different interesting points. First, although lung and breast cancers are the most common metastatic tumors to the pituitary gland, a lung adenocarcinoma presenting with neurologic symptoms and simulating pituitary adenoma at imaging studies is exceedingly rare. Since presenting symptoms of a pituitary lesion, either primary or metastatic, are related to the involvement of optic chiasm (visual impairment, bitemporal hemianopsia and occasionally development of dorsal midbrain syndrome/Parinaud’s syndrome), the correct diagnosis substantially relies on pathologic findings. Histologic recognition of a pituitary gland metastatic tumor in absence a medical history of a known primary elsewhere may be very challenging. Apart from the morphologic features overtly revealing an adenocarcinoma, then favouring a metastasis, the immunohistochemical coordinated expression of TTF-1 and neuroendocrine markers was somehow controversial. Indeed, although generally considered a specific markers of pulmonary tumors (among others), TTF-1 is also expressed in pituitary tumors. By contrast, the finding of strong positivity for synaptophysin and CD56 is extremely uncommon in lung adenocarcinoma, rather supporting a pituitary adenoma.

However, the set of morphology and immunostains, reinforced by the reactivity of tumor cells with napsin A, were more consistent with a sellar metastasis from lung adenocarcinoma. It is noteworthy that pioneering gene expression profiling studies on lung adenocarcinoma have correlated the presence of neuroendocrine differentiation to significant poor prognosis and acquisition of a neuroendocrine phenotype seems to characterize ALK-positive lung adenocarcinomas resistant to crizotinib. Again, pulmonary neuroendocrine carcinomas harbouring ALK rearrangement do not respond to crizotinib, then suggesting the presence of neuroendocrine differentiation in ALK-positive carcinomas as a mechanism of primary or secondary resistance to ALK inhibitors.

ALK-positive adenocarcinomas account for about 5% of all NSCLC and are associated with a peculiar tropism for central nervous system (CNS) metastases (approximately 35-50%). However, it is not clear if patients with ALK-rearranged adenocarcinoma have per se more probability to develop CNS metastases independently from the received therapy or to the poor diffusion capacity of crizotinib through the brain-blood barriers.

The case here seems to support a peculiar metastatic potential of ALK-positive adenocarcinoma to neural involvement, including the pituitary gland. The best therapeutic strategy when dealing with a metastatic ALK-rearranged adenocarcinoma metastatic to the pituitary gland may be quite problematic. Indeed, stereotactic radiotherapy may provoke significant vision alterations leading to a poor quality-of-life, especially in an active young patient. Promising results were reported using second-generation ALK-inhibitors in light of their higher diffusion capacity through the brain.

In summary, we report the first case of ALK-positive pulmonary adenocarcinoma with neuroendocrine differentiation presenting as a pituitary gland metastasis. Exceedingly rare occurrence, as here, may result very challenging on a diagnostic and therapeutic levels requiring a close cooperation between pathologist and clinician.

References

ALK-POSITIVE ADENOCARCINOMA OF THE LUNG EXPRESSING NEUROENDOCRINE MARKERS AND PRESENTING AS A “PITUITARY ADENOMA”


Adenoid cystic carcinoma: a rare breast carcinoma

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Key words
Adenoid cystic carcinoma • Breast • Excellent prognosis • Rare neoplasm

Summary
Adenoid cystic carcinoma is a rare neoplasm accounting for <0.1% of breast carcinomas. The mean age of presentation is fifth to sixth decade of life and it generally presents as a painful breast lump. The histological features are characteristic with cribriform and acinar pattern of basaloid cells. It is triple negative tumor with CD117 and p63 positivity and excellent prognosis.

Introduction
Adenoid cystic carcinoma (ACC) of breast is a rare neoplasm comprising of <0.1% of breast carcinomas. The mean age of presentation is fifth to sixth decade of life. Commonly it presents as a painful breast mass. The mammographic findings are not specific. Histologically, it is similar to its analogue in the salivary gland and composed of biphasic population of cells arranged in cribriform pattern. It is a carcinoma of low malignant potential and can be cured by simple mastectomy. ACC of breast is associated with excellent prognosis and regional lymph node or distant metastases seldom occur.

Case report
A 50 year old female presented with a small tender lump in left breast in subareolar region with a clinical diagnosis of fibroadenoma. No erythema, ecchymosis, skin ulceration or dimpling was noted. The patient was a non smoker and non alcoholic. Mammography revealed a well defined mass 2.8 cm in size and located in retroareolar region. Family history of the patient was negative for breast cancer. It was graded as M3 on Breast Imaging Reporting and Data System scale. Initially the excision biopsy was performed and evaluated at an outside laboratory. Grossly, a globular tissue bit measuring 3 x 2.7 x 1.2 cm with cut section showing grey-white areas was received. Histopathological diagnosis of Invasive Lobular Carcinoma was given. The slides were reviewed in our hospital and diagnosis of adenoid cystic carcinoma was made. Sections studied show basaloid cells and myoepithelial cells arranged in cribriform pattern (Fig. 1 A, B). Nottingham’s histological score of 4 was given based on tubular differentiation, nuclear pleomorphism and mitotic count. Foci of lymph vascular invasion seen. On IHC the tumor cells were positive for CD117 (Biogenix;YR145) (Fig. 1C) and p63 (Biogenix;4A4) and negative for ER,PR and HERCEPT (Fig. 1 D, E, F respectively).

Discussion
Adenoid cystic carcinoma has a special importance because of its rarity as a primary neoplasm of the breast and also because of its excellent prognosis. Its mean age of presentation is 6th decade and it usually presents as a lump in the breast which is painful on palpation. The radiological findings are generally non-contributory. On histology biphasic population of cells arranged in cribriform pattern are seen. The neoplastic cells form two types of patterns, true acini and pseudolaminate. The true acini are lined by luminal cells and are filled with PAS positive mucin. The myoepithelial cells line the...
pseudolaminate and are filled with alcian blue positive acidic mucin. A third type of cells with sebaceous differentiation can also be identified. ACC has been classified into three grades of tumor on the basis of the solid component as: grade 1, completely glandular and cystic; grade 2, < 30% solid component; grade 3, > 30% of solid components. All grade 3 tumors appear to behave like high grade ductal breast cancer.

On IHC, the cells around acini are positive for CD117 and CK5/6 while pseudoluminar cells are positive for p63. Adenoid cystic carcinomas are triple negative tumors and should be differentiated from collagenous spherulosis and invasive cribriform carcinoma on histology, staining with alcian blue, PAS and by IHC.

Conclusions

Diagnosis of Adenoid Cystic Carcinoma is important not only because it is a rare neoplasm in primary site breast but also because clinically and radiologically it mimicks well circumscribed benign lesions. Since it is associated with excellent patient survival, precise diagnosis is essential.

References

Brunner’s gland hyperplasia is a rare benign lesion arising from the duodenum. It is often an incidental finding on endoscopy with the majority of patients being asymptomatic. It may also present with various symptoms depending on location and tumor size, such as gastrointestinal bleeding, obstruction and abdominal pain. We report an unusual case of large Brunner’s gland hyperplasia in a 72-years old man, admitted to hospital for epigastric pain, recurrent vomiting and significantly weight loss. Upper endoscopy showed an obstructive submucous tumour of the bulb. Abdominal computed tomography scan revealed a circumferential thickening and stenosing mass of the first part of the duodenum leading to severe obstruction. Though pre-operative biopsies were negative, imaging studies and endoscopy were strongly suggestive of malignancy and the patient underwent duodenocephalopancreatectomy. Brunner’s gland hyperplasia may have unusual presentation, mimicking malignancy. Therefore, extensive pre-operative evaluation, including repetitive tumor biopsies, is necessary to avoid radical surgical procedure.

Introduction

Brunner’s glands are branched acinotubular glands normally found in the deep mucosal or submucosal layers of proximal duodenum and secrete alkaline-based mucus to protect the duodenal lining from gastric acid 1. Brunner’s gland hyperplasia, also known as Brunner’s adenoma is a rare, benign, proliferative lesion characterized by lobules of Brunner’s glands that are increased in both size and number 2. We report an unusual case of Brunner’s gland hyperplasia leading to severe duodenal obstruction mimicking a malignancy and requiring therefore radical surgical procedure.

Case report

A 72 year old male with no history, presented with epigastric pain and recurrent vomiting occurring tardively after meals during 12 months, associated with significantly weight loss. Physical exam revealed abdominal distension and epigastric pain in palpation. Esophagogastroduodenoscopy showed an obstructive submucosal tumour of the bulb. Biopsies were small and negative for malignancy. Abdominal computed tomography scan showed a slightly enhanced, circumferential thickening and stenosing 3 cm mass of the first part of the duodenum, abutting gallbladder and head of pancreas without loss of fat planes (Fig. 1).

Laboratory data showed low hemoglobin (9 g/dl) and albumin (31 g/l) levels. Tumor markers (Carcino-embryonic antigen and CA19-9) were within normal limits.

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Patient underwent cephalic duodenopancreatectomy (Whipple’s procedure) in our institute with clinical diagnosis of duodenal carcinoma and the specimen was sent for histopathological examination.

Gross examination noted circumferential thickening of the first part of the duodenum. When opened, mucosal surface exhibited 2.5 x 2 cm polypoid mass that was 1 cm from the ampulla. It was grey white on section with few cystic areas.

Histologically, tumor showed proliferating Brunner’s glands in a lobular pattern, constituting about 75% of the thickness of the duodenal wall. They extend focally through the muscularis mucosae and are separated by delicate fibrous septa (Fig. 2). Some glands were dilated (Fig. 3). Cells were columnar with basally located round nuclei and bland neutral mucin-containing cytoplasm. No mitosis, necrosis or atypia were observed (Fig. 4).

Patient recovered well and remained symptom free at 12 months follow up.

Discussion

Brunner’s gland hyperplasia is a benign lesion which most commonly encountered in the duodenal bulb 2. There is no sex predilection and patients present in the fifth to sixth decades of life 3.

It is often an incidental finding on endoscopy with the majority of patients being asymptomatic, but it may be seen as one of the constellation of changes typical of peptic duodenitis or associated with end-stage renal disease and uremia. Depending on location and tumor size, Brunner’s gland hyperplasia can result in dyspepsia, vomiting, gastrointestinal bleeding, obstruction and abdominal pain 3 4.

The etiology of Brunner’s gland hyperplasia is not known. It is hypothesized that excess gastric acid secretion or increased inflammation may lead to hyperplasia 2. Polyps resulting from Brunner’s gland hyperplasia are typically small (< 1 cm). Occasionally, they may be large in size with clinical manifestations of hemorrhage or obstruction, as in our case 5.

Imaging studies are of little help in the diagnosis 1. Endoscopically, Brunner’s gland hyperplasia can be nodular or polypoid mimicking gastrointestinal stromal tumor, lymphoma, carcinoid or Peutz Jeghers polyp 7. It can also be diffuse with thickening of the duodenal wall and hence can be misdiagnosed as malignancy.

Even if endoscopy and endoscopic ultrasound can sometimes be helpful, definitive diagnosis requires pathologic examination 8.

Histologically, proliferating glands extend into the lamina propria and are separated by delicate fibrous septa. Cystically dilated glands have been reported, but this finding is relatively uncommon. The cells constituting the glands are cytologically bland with abundant neutral mucin cytoplasm and small, basally located nuclei with minimal or absent mitotic activity 2.
sia. Furthermore, diagnosis in small biopsy specimens is difficult, as in our case, and a deeper samples would be more contributive. Exceptional cases of malignant transformation of Brunner’s gland hyperplasia were reported. These cases do not unequivocally demonstrate de novo neoplasia within Brunner’s glands, as opposed to secondary involvement of Brunner’s glands by dysplasia or carcinoma arising in the surface mucosa.

When Brunner’s gland hyperplasia is symptomatic or leads to complications or when definite diagnosis is necessary, the treatment of choice is mass removal by endoscopic or surgical procedure. Strategies of resection suggest that size and pedunculation were important characteristics in determining amenability for endoscopic removal. This approach is less invasive and safer than surgery, but it can be limited by difficult anatomical sites.

Surgery is usually discussed for polyps 5 cm or larger. Even in these cases, cephalic duodeno-pancreatectomy is exceptionally made since it leads to high morbidity and mortality rates. Usually, surgical polypectomy, duodenal wedge resection, or partial gastrectomy extending to the duodenal bulb are proposed for Brunner’s hyperplasia.

As in our case, when the tumor is discovered during an obstructive syndrome, radical surgery is often performed especially to eliminate malignancy (Tab. I). Some authors justified this attitude by the fact that consequences of leaving an undiagnosed pancreatic cancer are worse than the risk of undergoing duodenopancreatectomy.

In all cases, repeated and deeper duodenal biopsies could be useful to avoid “overtreatment”.

<table>
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<tr>
<th>Authors</th>
<th>Sex/age (years)</th>
<th>Symptoms</th>
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<th>Esophagogastro duodenoscopy (EGD)</th>
<th>Initial Biopsy</th>
<th>Treatment</th>
<th>Macroscopic features</th>
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<tr>
<td>Duminda BS</td>
<td>F/59</td>
<td>Acutely worsening oral intolerance + weight loss</td>
<td>Distended stomach with retention of contrast material</td>
<td>Pyloric channel narrowing + a clean-based antral ulcer</td>
<td>Negative for malignancy</td>
<td>Distal gastrectomy with gastrojejunostomy</td>
<td>2 cm × 2 cm polypoid mass</td>
</tr>
<tr>
<td>Sen R</td>
<td>M/42</td>
<td>Epigastric pain + recurrent vomiting</td>
<td>Circumferential thickening of the 2nd DD</td>
<td>Nodular stricture at D1/D2 junction</td>
<td>Well differentiated adenocarcinoma.</td>
<td>Cephalic duodeno-pancreatectomy</td>
<td>Diffuse grey white area of 4 x 4 cm with cystic and hemorrhagic zones</td>
</tr>
<tr>
<td>Cheung, TT</td>
<td>M/70</td>
<td>Repeated vomiting + melena</td>
<td>Large tumour occupying the 1st and 2nd DD</td>
<td>ND</td>
<td>ND</td>
<td>Cephalic duodeno-pancreatectomy</td>
<td>Well-encapsulated submucosal tumour of 10 x 8 x 6 cm</td>
</tr>
<tr>
<td>Lee WC</td>
<td>M/64</td>
<td>Dyspepsia, vomiting + weight loss</td>
<td>2.5 cm mass of the 2nd DD with loss of fat plane beside the pancreas</td>
<td>Infiltrating and obstructive mass of the 2nd DD</td>
<td>Chronically active duodenitis.</td>
<td>Cephalic duodeno-pancreatectomy</td>
<td>2.5 cm-sized mass in the 2nd DD</td>
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<td>Lusco D</td>
<td>M/60</td>
<td>Belt-like upper abdominal pain</td>
<td>5.5 cm bulky mass of the 1st and 2nd DD + Ectasia of Wirsung duct</td>
<td>Large mass of the 1st and 2nd DD + imposible cannulation of the papilla</td>
<td>Aspecific duodenitis.</td>
<td>Cephalic duodeno-pancreatectomy</td>
<td>A hard mass, vegetating in the 1st and 2nd DD lumen + intense peri-duodenitis</td>
</tr>
<tr>
<td>Hwang IT</td>
<td>M/44</td>
<td>Recurrent vomiting + epigastric pain</td>
<td>Dilatation of the CBD and the main pancreatic duct + wall thickening of proximal DD</td>
<td>Polypoid mass with mucosal swelling and nearly complete obstruction of the bulb</td>
<td>Non-specific duodenitis.</td>
<td>Cephalic duodeno-pancreatectomy</td>
<td>Circumferential enlargement of the duodenal mucosa in the proximal DD</td>
</tr>
<tr>
<td>Our case</td>
<td>M/72</td>
<td>Epigastric pain, recurrent vomiting + weight loss</td>
<td>Circumferential thickening and stenosing 3 cm mass of the 1st DD</td>
<td>Obstructive submucosal tumour of the bulb</td>
<td>Negative for malignancy</td>
<td>Cephalic duodeno-pancreatectomy</td>
<td>2.5 x 2 cm polypoid mass with cystic areas causing circumferential thickening of the 1st DD</td>
</tr>
</tbody>
</table>

M: Male; F: Female; ND: Not done; DD: Duodenum; CBD: common bile duct.
Conclusion

Brunner’s gland hyperplasia is a rare benign lesion arising from the duodenum. It may have an unusual presentation, mimicking malignancy. Thus, extensive pre-operative evaluation including repetitive and deep tumor specimen is necessary to avoid radical surgical procedure.

References

Sarcoidosis is a multisystemic granulomatous disease characterized by the presence of noncaseating granulomas, the exact etiology of which is yet to be determined. Most of patients show granulomas located in the lungs or in the related lymph nodes. However, lesions can affect any organ. Noncaseating granulomas are not a pathognomonic sign of sarcoidosis, being observed also in other diseases, therefore the diagnosis is often of exclusion.

We report a case of sarcoidosis with parotid gland involvement in the context of a Heerfordt syndrome, discussing about its clinical presentation, pathogenesis, pathology and differential diagnosis with other granulomatous diseases.

**Case report**

Parotid gland involvement in Heerfordt syndrome: a case report

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**Key words**

Sarcoidosis • Granuloma • Parotid • Heerfordt syndrome

**Summary**

Sarcoidosis is a multisystemic granulomatous disease characterized by the presence of noncaseating granulomas, the exact etiology of which is yet to be determined. Most of patients show granulomas located in the lungs or in the related lymph nodes. However, lesions can affect any organ. Noncaseating granulomas are not a pathognomonic sign of sarcoidosis, being observed also in other diseases, therefore the diagnosis is often of exclusion.

We report a case of sarcoidosis with parotid gland involvement in the context of a Heerfordt syndrome, discussing about its clinical presentation, pathogenesis, pathology and differential diagnosis with other granulomatous diseases.

**Introduction**

Sarcoidosis is a systemic disorder of unknown cause, pathologically characterized by the accumulation of inflammatory cells forming non-caseating granulomas. Lesions can be localized in any organ but in about 90% of patients, granulomas affect the lungs or the related lymph nodes. Extra-pulmonary sarcoidosis has been described in 30% of patients with the disease¹. The most common sites are liver, spleen, biliary tree, peritoneum, and abdominal lymphonodes². A cutaneous and ocular involvement is reported in 25% of patients.

Heerfordt syndrome, first described in 1909³ as part of the spectrum of sarcoidosis, occurs in approximately 0.3% of all sarcoidosis cases⁴. It is defined as a combination of uveitis, parotid gland enlargement, fever and facial nerve palsy⁵. Dr. Jan Waldenström made the observation that this syndrome was associated with sarcoidosis in 1937⁶. Cases presenting all the abovementioned features are defined as "complete Heerfordt syndrome", nevertheless this syndrome manifests in various forms, and cases of complete Heerfordt syndrome are extremely rare¹⁷. We herein report a case of parotid gland involvement of sarcoidosis in a woman with Heerfordt syndrome presenting with the entire constellation of symptoms.

**Case report**

A 60 years old woman was admitted to the neurological clinic of our department for the sudden appearance of blurred vision, headache and mouth deviation to the left, since a week, after a febrile episode. The day after fever appearance, she showed a complete facial palsy and a bilateral enlargement of the cheeks. Physical examination revealed unpainful enlargement of the left parotid gland and bilateral facial palsy. She also presented left abducent nerve palsy with limitation of the lateral movements of the eye, and deviation of the tongue to the left. No skin rashes were noted. The remaining neurological examination was normal. Infectivological screening, anti-neuronal, anti-ganglioside and anti-myelin antibodies were all negative. The cerebrospinal fluid examination excluded the presence of inflammatory or infective diseases. An ophthalmologic evaluation revealed bilateral vascular sclerosis and alterations compatible with the diagnosis of uveitis. Brain Magnetic Resonance Imaging (MRI) with gadolinium showed the presence of contrast enhancement of both the internal auditory canals with bilateral involvement of VII cranial nerve (Fig. 1A) and impregnation of the cisternal portion of the left abducent nerve (Fig. 1B). The MRI of the parotid glands (Fig. 2) showed three nodular lesions in the left parotid gland.
and an area of altered signal in the right parotid gland. Chest CT scan revealed diffuse areas of parenchymal consolidation with “frosted glass” areas in both lungs (Fig. 3A) and mediastinal lymph nodes of increased dimensions (Fig. 3B). Serum ACE enzyme levels were within the normal range. Nevertheless, a fibrobronchoscopy was performed with bronchoalveolar lavage. The cytological analysis showed lymphocytosis (lymphocytes: 16%; normal value: 2-12%). Lymphocyte typing revealed an increased CD4/CD8 ratio with a value greater than 3.6 (positive predictive value of 76% with 94% specificity) suggesting the diagnosis of sarcoidosis. In order to confirm the diagnosis, a biopsy of the left parotid gland was performed. Histological examination of hematoxylin and eosin-stained sections (4-5 micron thick) revealed, within the context of normal salivary gland, an area of chronic granulomatous inflammation with marginalized, non-necrotizing, epithelioid cell nodules (Fig. 4). Granulomas showed epithelioid histiocytes, foreign body-type multinucleated giant cells and some lymphocytes (A); immunostaining for pan-CK (B) and CD68 (C) confirmed the presence of residual glandular ducts and the histiocytic phenotype of epithelioid cells.
confirmed the histiocytic phenotype of epithelioid cells (Fig 5C). Finally, the morphological and immunohistochemical findings of the lesions were consistent with the parotid gland localization of sarcoidosis leading to the diagnosis of Heerfordt syndrome. Treatment with oral prednisolone at the dose of 60 mg per day, after a three months follow up, led to a moderate clinical and radiological improvement.

Discussion

Heerfordt syndrome is a rare disease, not common in the Western countries, therefore clinical and pathological diagnosis could be missed. The classical clinical tetrad of facial nerve palsy, parotid gland enlargement, anterior uveitis and fever can be partially present with one symptom missing or prevailing on others. The incidence of cranial nerve palsy in sarcoidosis is about 5-6% with the facial nerve followed by the optic nerve being the most common nerves involved. Both the etiology and the pathogenesis of this syndrome are still ambiguous. Nerve root and cranial nerve involvement can be either caused by the compressive effect of an adjacent granuloma or due to perivascular and intraneural lymphocytic infiltration. In cases of a granulomatous sialadenitis, particular care should be taken to distinguish the diagnosis of sarcoidosis from other diseases such as tuberculosis, atypical mycobacterial infections, protozoan and fungal infections, no immune-mediated granulomas (typically represented by foreign-body granulomas), granulomatous reactions linked to neoplasms, lymphomas, Wegener’s Granulomatosis, Sjögren’s syndrome, cat-scratch disease, calculus or carcinomatous duct obstructions or orofacial granuloma. In a clinicopathological study of 57 cases of granulomatous sialadenitis of the major salivary glands, the authors reported that tuberculosis, sarcoidosis, calculus duct obstruction and carcinomatous duct obstruction were the most frequent causes of granulomatous sialadenitis; in particular, this study referred calculus sialadenopathy as a major cause of granulomatous sialadenitis. Histologically, tuberculosis as well as fungal infections, differs from sarcoidosis for the presence of a central caseating-necrosis area within the granuloma; however, tuberculosis, especially in the early stages of the disease, can show the presence of small non-caseating epithelioid cell granulomas. Sarcoid granulomas can also contain focal central necrosis areas, so histochemical staining and molecular biology techniques can be very useful in the differential diagnosis, allowing the identification of etiologic agents within the inflammatory tissue. Furthermore, it needs to be pointed out the presence of the so-called “Necrotizing sarcoid granulomatosis (NSG)”, a rare systemic disease, characterized by sarcoid-like granulomas, vasculitis and variable degrees of necrosis. Cases of gland duct obstruction often show single to multiple small granulomas which contain mucin and are related to ruptured ducts. In cat-scratch disease, as well as in atypical mycobacterial infections, granulomas show suppurative necrosis central areas and the evidence of etiological agent can be obtained through histochemical staining and molecular biology. Wegener’s granulomatosis is generally characterized by less demarcated granulomas than sarcoid or tubercular ones. In conclusion, since the histological presence of non-caseating epithelioid cell granuloma is not a pathognomonic sign of the disease, histological diagnosis of sarcoidosis is often made based on the integration of morphological, immunohistochemical, histochemical, clinical and radiological data. In our case, the evidence of sarcoid granulomas on parotid gland biopsies, together with classical clinical tetrad of facial nerve palsy, parotid gland enlargement, anterior uveitis and fever, helped us to make a diagnosis of parotid gland localization of sarcoidosis as part of Heerfordt syndrome.

References

Renal cell carcinoma is one of the most common tumours to spread by extranodal metastases to the head and neck. Metastatic renal cell carcinoma to the head and neck area has been demonstrated mostly in the paranasal sinuses, parotid gland, the mandible, larynx and hypopharynx. Renal cell carcinoma should be excluded whenever a metastatic lesion is encountered in the head and neck area, even if the metastatic lesion is the first clinical presentation. The diagnosis of metastatic RCC should be suspected in any patient with even a remote history of renal cell carcinoma. We report a case of 79 year old woman with recurrent episodes of rhinorrhea, headache, hyposmia and monolateral right epistaxis, with a history of RCC. We describe RCC nasal metastases in a metachronous bilateral neoplasm, in which a second occult lesion debuted with a homolateral nasal metastases, ten years after left nephrectomy.

**Case Report**

**Nasal metastasis as the first manifestation of a metachronous bilateral renal cell carcinoma**

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**Key words**

Metastasis • Nasopharynx • Renal cell carcinoma

**Summary**

Renal cell carcinoma is one of the most common tumours to spread by extranodal metastases to the head and neck. Metastatic renal cell carcinoma to the head and neck area has been demonstrated mostly in the paranasal sinuses, parotid gland, the mandible, larynx and hypopharynx. Renal cell carcinoma should be excluded whenever a metastatic lesion is encountered in the head and neck area, even if the metastatic lesion is the first clinical presentation. The diagnosis of metastatic RCC should be suspected in any patient with even a remote history of renal cell carcinoma. We report a case of 79 year old woman with recurrent episodes of rhinorrhea, headache, hyposmia and monolateral right epistaxis, with a history of RCC. We describe RCC nasal metastases in a metachronous bilateral neoplasm, in which a second occult lesion debuted with a homolateral nasal metastases, ten years after left nephrectomy.

**Introduction**

Nasal malignant tumors, usually primary, are 0.3% of all neoplasms and 3% of all head and neck neoplasms¹. Occasionally metastatic sinonasal tumors from infracavitary sites, mainly the kidneys and, to a lesser degree, the lungs and breast, may manifest with nasal symptoms². In particular, after lung and breast carcinomas, renal cell carcinoma (RCC) is the third most common neoplasm to metastasize to the head and neck region, but metastasis to the nasal cavity is an extremely rare occurrence. Several cases are reported in the literature to localization maxillary, ethmoid and in the nasal cavity³. The peculiarity of the case report described is metachronous bilateral renal neoplasm, in which a second occult lesion debuted with a homolateral nasal metastases.

**Case report**

A 79-year-old Caucasian woman presented to ENT Department of University of Catania with a eight months history of recurrent episodes of rhinorrhea, headache, hyposmia and monolateral right epistaxis. Her medical history was positive for hypertension, thyroid and RCC, reason why she underwent a left nephrectomy ten years previously. The histological diagnosis revealed clear cell renal carcinoma, staged as pT1bN0M0. The oncologic follow-up, run for the next five years has brought to light a complete remission of the neoplastic disease, it therefore did not need concomitant and/or additional treatments.

Laboratory tests showed normal haemoglobin levels (14 mg/dl), liver function, coagulation profile, serum calcium level, and other routine blood test results were all normal. On nasal endoscopy the examination showed a highly vascular reddish mass, readily bleeding in the right nasal cavity with complete obstruction of the nasal fossa (Fig. 1). Rather peculiar was the finding of like polypoid evidence in the contralateral nasal fossa. Presurgical computed tomography (CT) of the nose and paranasal sinuses revealed a soft-tissue mass including, maxillary sinus, ethmoid sinus and right nasal cavity, extending into the roof of nasopharynx. The mass was strongly enhanced on contrast enhanced viewing and lytic bone lesions of the right maxillary sinus were observed (Fig. 2). Magnetic resonance imaging (MRI) confirmed a nasal lesion, seen as a low signal area on...
T2-weighted, the lesion appeared hyperintense on T2-weighted imaging (T2WI) and isointense on T1WI, with strong enhancement (Fig. 3). Trans nasal endoscopic surgery under general anesthesia was performed, using monopolar electrocautery, to biopsy. Histological examination of the specimen revealed clear cell carcinoma of renal origin, clear-cell type RCC. The tumor was composed of cells interspersed with abundant thin walled vessels that result in a sinusoidal vascular pattern, characterized by a clear cytoplasm surrounded by a distinct cell membrane. Nuclei were round and uniform, with finely granular chromatin, with inconspicuous nucleoli at 10x objective (Furhman nuclear grade 2) (Fig. 4). Immunohistochemically, the tumour cells were strongly positive for vimentin (Fig. 5A), CD10 (Fig. 5B), and pancytokeratin (Fig. 5C), but negative for CK20, CK7 and S100. Abdomen CT, performed later, found a solid mass at the lower pole of the right kidney and urinalysis revealed microscopic haematuria. In relation to old age and in order to low extension of the lesion that did not reach cribra lamina, if only with a perilesional oedema, the tumors was resected by an entirely extra cranial approach through a paralateral rhinotomy incision, with partial right maxillectomy. The margin of resection were free of the tumor. The surgical approach has been characterized by a profuse bleeding intraoperative, which required a blood transfusion of three bags of packed red blood cells and an anterior and posterior nasal packing. Patient maintained full bed rest in a 30-degree upright position until the third postoperative day. Nasal packing was gradually removed within 48 hours. Intravenous third-generation cephalosporin therapy was started the day before surgery and continued for at least 5 days. The patient was therefore staged as T1aN0M1 and she has been started to biological treatment for RCC.
Discussion

RCC represents 3% of all adult malignancies and occurs more frequently in the fifth and sixth decades of life. It’s the most frequent infraclavicular tumor to metastasize to the nasal cavity and paranasal sinuses and it may metastasize when the diameter of the primary tumor exceeds 3 cm. Choong et al., analyzed 301 cases of metastatic RCC treated over a period of 20 years, and found only 4 cases of nasal metastases (1.3%). In two of these four cases, nasal lesion was the first presenting feature of RCC. In another large series of 1785 patients of surgically treated RCC, incidence of atypical metastases was 1.88% (37 cases). Among these 37, only 3 patients had metastases to the nasopharynx region. A review of 98 paranasal sinus metastases revealed that RCC comprised 54% of the primary tumors with a predilection for the maxillary antrum (36%), ethmoidal sinuses (25%), frontal sinus (17%), and nasal cavity (11%). There are two routes for renal cancer to metastasize to the nasal and paranasal sinuses. One is the caval route in which tumor cells travel through the inferior vena cava, the right heart, and finally the lungs, the left heart and the maxillary artery to reach the nasal and paranasal sinuses. The other is the vertebral plexus route, less commonly followed, in which tumor cells do not flow into the inferior vena cava, but via Batson paravertebral plexus of azygous veins, which surrounds the vertebrae and communicates with pelvic veins caudally, intercostal veins cranially, and IVC in the abdomen (through azygous veins). Through this route, the tumor cells may bypass the lungs. Emboli can enter the cranial vault through a combination of anterograde and retrograde flow in the intracranial vascular sinuses, arriving at the internal jugular vein, where further unusual flow patterns would allow the emboli to seed structures and develop metastasis in the paranasal sinuses. Thirty percent of patients present a distant metastasis and only 10% exhibit the classical presentation of the tumor with flank pain, palpable mass and gross haematuria. Intermittent haematuria, however, may be present in 90% of patients. Symptoms of metastatic tumors to the paranasal sinuses include epistaxis, nasal mass or swelling, nasal obstruction and pain, in decreasing order of frequency. The vascular stroma of these metastatic deposits accounts for the fact that the most common symptom of these sinonasal lesions is epistaxis. RCC comprises a histologically diverse group of solid tumors but the most common histological variant being the clear cell RCC (85%). This variant is associated with loss of function of the von Hippel Lindau gene, which leads to up-regulation of the hypoxia inducible factor (HIF) and, finally, increased function of the vascular endothelial growth factor (VEGF). Therefore, sinonasal metastases of RCC origin are characterized by a propensity for severe bleeding, like in the case described by us. A differential diagnosis of nasal bleeding lesions should include angiofibromas, hemangiopericytomas, hemangiomas, and other less vascular benign lesions and/or malignant such as adenocarcinomas, melanomas and metastatic tumors from the breast and lungs have to be differentiated. A paranasal sinus CT scan may provide some hints about the benign or malignant nature of the lesion, such as bone erosion and remodeling (signs of malignant and metastatic lesions), hypervascularity, expansion of the sphenopalatine foramen and pterygopalatine fossa (angiofibromas). Magnetic resonance imaging (MRI) shows the true extent of the lesion, infiltration of the skull base and leptomeningeal metastases. Biopsy of a suspicious nasal lesion is imperative to guide further workup, but severe hemorrhage may occur. Some authors advocate selective embolization prior to tumor biopsy particularly if there is a known history of nephrectomy. Biopsy of RCC nasal metastasis may prove non-diagnostic due to diffuse necrosis of the lesion so several attempts are sometimes necessary. Its histopathologic characteristics include the presence of encapsulating connective tissue, clear cell borders, round or oval nuclei, and abundant clear cytoplasm that contains cholesterol, phospho-lipids, and glycogen. Approximately 50% of specimens express vimentin, with most also staining positive for CD10, EMA, and...
pancytokeratin. However, the histologic subtype is not a recognized prognostic factor in RCC. If the histological specimen shows clear cells, the abdomen should be investigated with ultrasonography and CT. Other sites prone to RCC metastasis, such as the lungs, brain and bone, should be screened with CT and bone scintigraphy, respectively. The 5-year survival rates are 81%, 74%, 53%, and 8% in stages I to IV, respectively, according to the National Cancer Database. Also, the presence of vascular invasion and capsular infiltration, microvessel density and tumor necrosis are important clinic-histological prognostic factors. However, low performance status (70 or less in Karnofski’s scale), thrombocytosis, and neutrophilia, one and a half times higher than normal levels of serum LDH, low hemoglobin, corrected serum calcium levels higher than 10 mg/dL are poor prognostic indicators. Treatment options of RCC are variable and prognosis depends on clinical, radiological, serological and histological factors. According to the The National Comprehensive Cancer Network practice guidelines for kidney cancer, patients with a resectable primary tumor and a single metastasis or post-nephrectomy patients who develop a metastatic renal cell carcinoma may benefit from nephrectomy and metastasectomy or metastasectomy respectively. Patients with a single resectable metastatic lesion should be treated aggressively, since they have an excellent chance for extended survival before further progression of this disease. Excision of solitary metastatic lesions after nephrectomy results in a 41% survival at 2 years and 13% at 5 years, regardless of the interval between nephrectomy and diagnosis of metastases, and so it provides some survival advantage in select patients. At the sinonasal level, this option must take into account the choice of surgical approach. The lateral rhinotomic approaches offer excellent exposure of the maxillary ethmoidal region with a degree of 5-year survival ranging from 25% to 65%. Also more control than the upper limits of the disease was achieved with the association to cranio-facial approaches that saw the prognosis of malignant lesions involving the skull base significantly improve front. However, it is known that transfacial approaches may be followed by sequelae such as facial aesthetic deformities, strictures of the nasal vestibule, anesthesia or pain in the infraorbital and lacrimal dysfunction. The transcranial approaches may be associated with persistent symptoms such as headache, diplopia and anosmia. Moreover, the intraoperative blood loss is often considerable and the postoperative course is characterized by a long period of hospitalization. Some surgical schools, in an attempt to reduce postoperative morbidity, have applied to this disease micro-invasive techniques such as micro-endoscopic intranasal. More recently, endoscopic resection seems to be the best treatment for small localized paranasal and nasal metastases. The choice of a laser surgery does not appear applicable. Nasal surgery will be also effective in preventing epistaxis and subsequent anemia. It is important to note the fact that owing to the vascularity of the tumor, surgery must be undertaken with caution. If the primary tumor is potentially resectable but multiple metastases coexist, nephrectomy and systematic cytoreductive therapy is likely to benefit. If the primary tumor is unresectable and the nasal metastasis causes epistaxis and visual disturbances, the patient may receive systemic therapy or resection or radiotherapy of the metastasis. Sabo et al., have even reported complete regression of nasopharyngeal metastasis of RCC with radiotherapy and brachytherapy. A reasonable options to employ radiotherapy followed by surgical resection of any residual metastatic lesion. This strategy can also be helpful even if the primary tumor is unresectable.

Conclusions

The case treated by us is interesting, especially in relation to the development of a small tumor metachronous controlateral, to the previous appeared ten years before, which made its debut with ipsilateral nasal metastases. It is important to recognize metastases from renal cell carcinoma, especially if they were in unusual sites, such as the nasopharynx, nasal cavity, and paranasal sinuses, because they can be misdiagnosed as primary malignant or benign diseases, particularly for those patients without a clinical history and in relation to nonspecific symptoms of the lesion. Nasal metastases are associated with poor prognosis. The surgical management is recommended for isolated metastasis, but patient can be selected for targeted therapy or radiotherapy.

References

Nasal Metastasis as the First Manifestation of a Metachronous Bilateral Renal Cell Carcinoma


BRAF mutations occur in about 3% of all lung adenocarcinomas and V600E missense mutation characterizes about half of BRAF-mutated lung adenocarcinomas and is significantly associated with micropapillary pattern and shorter disease-free and overall survival rates. In this report, we report a challenging case of a patient with a metastatic micropapillary adenocarcinoma of the lung harbouring V600E BRAF mutation who experienced a surprising protracted clinical response to metronomic vinorelbine. The possible association between the V600E BRAF mutation pathway and the effective use of vinca alkaloid is discussed.

**Introduction**

BRAF mutations occur in about 3% of all lung adenocarcinomas and V600E missense mutation characterizes about half of BRAF-mutated lung adenocarcinomas and is significantly associated with the female gender, micropapillary pattern at histology and shorter disease-free and overall survival rates. According to the new WHO classification, invasive adenocarcinoma with micropapillary pattern tends to spread through airspaces with a greater capacity for local and lymphangitic infiltration. Together with solid type, micropapillary pattern is independently associated with patients survival in surgically-resected adenocarcinomas and seems to better respond to chemotherapy in adjuvant setting.

Most interestingly, a recent work by Vecchione et al. demonstrated that “in vitro” and “in vivo” V600E BRAF mutant colon cancer cells demonstrate a significant sensitivity to vinorelbine, possibly through inhibition of a defective activity of RANBP2, a small GTP-binding protein belonging to the RAS superfamily regulating the nucleo-cytoplasmic transport and stabilizing the kinetochore function during mitotic activity.

Vinorelbine is a semisynthetic vinca alkaloid that binds to tubulin, thus inhibiting mitotic microtubule polymerization and demonstrating a radioenhancer cell cycle-dependent activity on tumor cells, exerting its widest efficacy in cell killing during the G2/M phase of the cell cycle. Oral administration of vinorelbine has shown a good clinical safety profile, but no biomarker has been identified in predicting vinorelbine efficacy.

Nevertheless, previous works have observed a major clinical response of some chemotherapeutic agents in small subsets of molecular-driven adenocarcinomas, namely pemetrexed in ALK and ROS1 rearranged tumors possibly related to high content of thymidylate synthase, one of the subcellular target of pemetrexed.

In this report, we describe a metastatic micropapillary adenocarcinoma of the lung simulating an inflammatory cancer of the breast, harbouring V600E BRAF mutation and lacking RANBP2 expression. The patient experienced a surprising protracted clinical response to metronomic vinorelbine. The possible association between the V600E BRAF mutation pathway and the effective use of vinca alkaloid is discussed.
**Case report**

A 80 year-old woman, current smoker, presented with a diffuse swelling of the left breast associated with skin reddening and pain from several weeks. She had a previous history of primary lung adenocarcinoma resected 4 years before (left lower lobe, stage IIA; pT1N1). She also suffered from autoimmune thyroiditis and vascular hypertension.

Clinical examination of the breast showed erythematous, thickened and edematous skin suggesting carcinomatous mastitis. No palpable nodules were noted. No axillary lymphadenopathy was observed and the right breast looked entirely normal.

Routine laboratory tests were unremarkable, while CEA was significantly increased (1366 ug/L). CA15.3 and CA19.9 serum tumor markers showed normal levels. Ultrasound echography of the left breast revealed diffuse tissue edema with hypertrophy of the mammary parenchyma. Mammography showed diffuse increase of the breast density associated with scattered microcalcifications and marked thickening of the skin (Fig. 1A). No alterations were noted in the right breast. A core-biopsy using a 14G needle was performed. Histologic examination showed fragments of adipose tissue with lymphatic vessels engulfed by an adenocarcinoma with micropapillary pattern associated with psammomatous microcalcifications (Fig. 1B).

At immunohistochemistry, the neoplastic cells expressed TTF-1 (clone 8G7G3/1, Ventana Medical Biosystem, Tucson, AZ, USA) and napsin A (clone MRQ60, Ventana), whereas estrogen (clone SP1, Ventana) and progesterone (clone 1E2, Ventana) receptors were negative (Fig. 1C).

The comparison of morphology and immunoprofile between the primary lung adenocarcinoma and the breast tumor revealed an identical phenotype (Fig. 1D-E). Thus, a diagnosis of breast metastasis from lung adenocarcinoma with micropapillary pattern was made.

At molecular analysis, neither **EGFR** mutations nor **ALK** rearrangement were detected. However, the presence of the micropapillary pattern prompted us to investigate **BRAF** gene alterations and the missense V600E mutation was identified either in primary lung cancer and breast metastasis (Fig. 2A).

Tumor cells also expressed BRAF V600E mutation-specific antibody (clone VE1, Ventana) at immunohistochemistry (Fig. 2B), while immunostaining with RANPB2 (mAb58385, Abcam, Cambridge, UK) was negative (Fig. 2C).

A 18-FDG PET scan revealed the presence of hypermetabolic uptake in the left breast, mediastinal lymph nodes, pleura, ribs and humerus. Given the poor conditions of the patient (ECOG PS:2) and the impossibility to use specific BRAF inhibitors in routine practice, chemotherapy with metronomic oral vinorelbine at the dose of 50 mg (one capsule of 20 mg plus one of 30 mg) three times weekly on Monday, Wednesday and Friday was started continuously until disease progression, patient refusal or excessive toxicity. At the same time, radiotherapy was performed to relieve bone pain. The patient promptly experienced general improvement of both mammary (Fig. 2D) and bone symptoms and she is still alive with disease in good conditions (ECOG PS:1) at 9 month’s follow up from chemotherapy starting.

**Discussion**

There are two interesting clues characterizing the case here described. Firstly, the clinical presentation of a metastatic lung adenocarcinoma with micropapillary pattern involving the breast and strikingly mimicking an inflam-
Inflammatory carcinoma. Our case is very similar to that described by Jeong et al. reporting a 47-year-old woman with a pulmonary metastatic micropapillary adenocarcinoma to the breast after 3 years from the lung resection. Since micropapillary growth pattern is observed even in primary breast carcinoma, the differential diagnosis may be challenging, requiring the knowledge of the patient’s clinical history, results of imaging and laboratory studies and comparison of morphology, immunoprofile and molecular features between primary and metastatic tumors. Although lung cancer metastatic to the breast generally pursues a dismal outcome, a correct diagnosis is mandatory to prevent unnecessary breast surgery and properly leading to investigate predictive biomarkers, then permitting alternative effective therapies using targeted molecules with a low-toxicity profile. In their case, Jeong et al. evidenced the presence of EGFR mutation in exon 19 (L747-E749del) and the patient experienced a long-lasting survival (disease-free after 23 months from the diagnosis of breast metastasis) under gefitinib. Similarly to EGFR mutations, Marchetti et al. evidenced that micropapillary component is a characteristic growth pattern (80%) also in pulmonary adenocarcinoma harbouring V600E BRAF mutation. Indeed, the second point of discussion emerging from the case herein concerns the good clinical response to vinorelbine correlated to the presence of V600E BRAF mutation. Although no biomarkers have been identified in predicting vinorelbine efficacy in lung cancer, an interesting study by Vecchione et al. elegantly demonstrated in preclinical models that V600E BRAF-mutated colon cancer cells were significantly inhibited by vinorelbine through depletion of RANBP2, an essential tumor suppressor gene responsible of the interaction of kinetochores with the microtubule bundles that extend from the centrosomes to the kinetochores during mitosis and maintaining chromosome stability. Depletion of RANBP2 leads to abnormal mitotic progression, and abnormal chromosome segregation and seems to characterize V600E BRAF mutated colon cancer, then representing a vulnerability point for microtubule disrupting agents, as vinca alkaloid. Although only at immunohistochemistry level, according to these latter observations, we found that tumor cells of the primary lung and metastatic adenocarcinomas were negative for RANBP2. In lung cancer, RANBP2 expression has been poorly investigated, but the great majority of NSCLC cell lines show up-regulation of this protein. In summary, we reported a metastatic micropapillary pulmonary adenocarcinoma clinically mimicking an inflammatory breast cancer after 4 years from surgery. A significant clinical response to metronomic vinorelbine was observed and the tumor cells evidenced V600E BRAF mutation coupled to defective RANBP2 protein. Whether these molecular alterations could predict vinorelbine efficacy in lung cancer, as recently demonstrated in preclinical models of colon cancer, clearly require further investigations.

Waiting for the official approval of effective V600E BRAF mutation-specific inhibitors, patients with lung adenocarcinoma harboring V600E BRAF mutation could receive a clinical benefit from a vinorelbine-based chemotherapy regimen.

References

III MEETING NAZIONALE

Gruppo Italiano di Paleopatologia

12 Maggio 2017 ore 9

Pisa, Aula Magna della Scuola Medica, via Roma 55

Inaugurazione dell’esposizione dei preparati anatomici del Museo di Anatomia Patologica dell’Università di Pisa con il contributo della Fondazione Pisa

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Info: www.paleopatologia.it
Restoration and preservation of the anatomical specimens of the Museum of Pathological Anatomy at the University of Pisa

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The aim of the recently established system of the University Museum of Pisa is to promote and develop the University collections, and to encourage the reorganization of the Museum of Pathological Anatomy, whose precious pieces are provisionally stored in a nearby warehouse. In the last year, the economic support of the “Fondazione Pisa” has allowed to start the process of recovery and restoration of a part of the specimens. The collection comprises 1500 human and animal pathological specimens of great scientific relevance, some of which dating back to the Granducal period. The remains consist in pathological changes and congenital anomalies detected on human and animal bodies and organs, either dry or preserved in formaldehyde. In particular, the Museum houses a collection of 50 human bladder stones going back to the first half of the 19th century; a collection of malformed human newborns documenting 25 rare congenital malformations of the end of 19th and beginning of 20th century; a collection of animal teratology; a collection of helminthic parasitology. Over the last 30 years, the Museum has been enriched with a collection of pieces from pathological autopsies, such as lung, cardiovascular, renal, and brain diseases. The recovery was initially aimed at restoring the wet formaldehyde-preserved preparations requiring urgent emergency intervention. In fact, in many cases the evaporation of the liquid has determined the deterioration of the specimens; moreover, alcohol has replaced formalin, formally declared toxic by the new Museum dispositions that require the substitution of dangerous preserving liquids. A selection of over 100 restored artifacts will be exhibited in the next 2017 GiPaleo Meeting.

Paleopathological study and facial reconstruction of a mummy of Borgo Cerreto, central Italy (XVII century)

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The subject under study is one of the twenty-three natural mummies of Borgo Cerreto (Perugia, central Italy). The burials took place between the second half of the 17th and the half of 19th century. According to the historical and archaeological data, the individual was one of the first burials that took place. Indeed the style of the garment is typical of a member of the upper class of the Umbrian rural population of the XVII century. The mummy is well preserved. Macroscopic, radiological and CT examination were performed. The anthropological study revealed that the subject was an adult male with a stature of 1.69 cm. The macroscopic study had not evidenced any skin lesions or pathological alterations. Tooth examination evidenced an osteolytic lesion of the first upper left molar compatible with a cyst can also be observed. CT examination evidenced calcified lamina tectoria and neo articulation with clivus. The spine showed diffuse spondylosis and osteophytosis with intersomatic bridge. Light lumbar arthrosis, irregularities and sclerosis of pubic symphysis and bilateral gonarthrosis are observable too. CT examination revealed the fracture of 4th right and 10th left ribs, probably as a result of post-mortem effects. A comparison between the cranial structure of the subject and a portrait of Baronio Vincenti (XVII century), Physicus et Medicus, the commissioner of the funerary chapel, was performed. Amira System, Programme Face Gen (Singular Inversion) and Photoshop with form 3 D were applied. The results of the anthropological and paleopathological study suggest that the individual was a mature male, as confirmed by the generalized osteoarthrosis framework. The good condition of the dental apparatus, in relation to the age of the subject, suggests that he was a member of the upper class. The results of the facial reconstruction and the overlay on the portrait make the identification of the subject with Baronio Vincenzi very likely.

References

A pathographic profile of the composer Antonio Zacara da Teramo (ante 1365-1416)

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Antonius Berardi Andree, commonly known as “Zacara”, was born in Teramo (northern Abruzzo region) shortly before 1365. He was a scribe, illuminator, poet, singer and composer, being in Rome since 1380s. During the next two decades, as a married layman, he worked as a scripure litteratum apostolica and Papal Chapel singer under Boniface IX, Innocent VII and Gregory XII. Before the Council of Pisa, in the most turbulent phase of the Great Schism, he left Gregory, and stayed in Florence until 1410. Subsequently, he became Chapel Master to the antipope John XXIII, but when the latter, in June 1413, left the Holy See, Zacara went back in Teramo and probably died here in 1416.

The nickname “Zacara” (scrawl) indicates a thing of little value. An illustration from the XV century Squircialupi Codex held in Florence, Biblioteca Medicea Laurenziana, displays with merciless realism his physical ailments. Additional information on his health status may be obtained by the analysis of some of his verses dealing with Fortune (Dime Fortuna, Spesso Fortuna cridote) and an entry in the Necrologio Aprutino (the obituary of the Cathedral of Teramo).
Behind Castrato’s voice. Paleopathological analysis of the singer Gaspare Pacchierotti

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Up until the end of the 1800s, a gruesome practice was performed on male opera singers to preserve their mezzo-soprano voices. The growing up of modern opera in Italy caused a demand for these particular voices, so the singers were castrated before reaching puberty, allowing their young voices to carry on through adulthood.

Among the castrati, Gaspare Pacchierotti (Fabriano, 1740 - Padua, 1821) was probably one of the most famous. The remains of Pacchierotti were exhumed for the first time in 2013 to reconstruct his biological profile and understand the secret of his sublime voice. The remains were studied in the laboratory of the Museum of Pathological Anatomy at the University of Padua, where CT scans and X-rays were conducted on the bones.

The castrati were often much taller than their unaltered peers, Pacchierotti stood more than 190 cm, with a large barrel-shaped chest, infante larynx, long, spindly legs. The analysis showed the presence of epiphyseal lines on Pacchierotti’s iliac crests, which are typically fused at 23 years old and disappear by the time a man is older than 35. CT scans revealed vertebral fractures and a decrease in bone density, because the hormonal effects of castration led the singer to develop osteoporosis and disorders of the spine. The dental condition was very interesting: there was an extremely advanced dental erosion due to bruxism, that was probably caused by psychic distress from compulsion as it happens in prisoners or people forced to do something.

However, the singer’s skeletal anomalies were not only attributed to castration. Pacchierotti’s cervical vertebrae were all strongly eroded with signs of osteophytic lipping in the body, because of osteoporosis and of continuous movements of head and neck during singing exercises. There were also other changes in his body and bones, including modifications in the insertion of three respiratory muscles, which work to elevate certain ribs and assist in breathing. Despite his castration and bone conditions, Pacchierotti died at the age of 81 due to dropsy.

References


The survival of an amputated limb without antibiotics: a case study from a Longobard necropolis (VI-VIII centuries AD)

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The Longobard necropolis of Poveglia Veronese located in Veneto, Northern Italy was discovered in 1985. Archaeological evidence tells us the necropolis was used during the VI-VIII centuries AD. Over 240 skeletons have been recovered from the necropolis. Age and sex for each burial has been previously reported. The skeleton of an older Longobard male (aged 40-50 years), an individual of the first generation of Longobards arrived at Poveglia Veronese, shows a unique well-healed amputated right forearm. The focus of this presentation is to discuss the trauma and healing of his right forearm. The orientation of the forearm fracture suggests an angled cut to the ulna and radius by a single blow. There are several reasons why a forearm from this cultural period might be amputated, loss due to fighting and/or loss due to judicial punishment. As with other amputation cases cited in the bio-archaeological literature, this example exhibits both healing of the fracture and osteophytic growth specific to biomechanical loading. We argue that the osteophytes of this individual comes from the use of a prosthesis. The healing includes a semi-fusion (ankyloses) of the forearm bones and well-healed end-caps for both bones. Additionally, dental modification of right upper second incisor tooth shows considerable wear and smoothing of the occlusal surface. We suggest that this dental defect is the result of tying down a prosthetic device used to protect the forearm stump. Other indications of how this individual adjusted to his amputated condition includes a slight change in the orientation of the right glenoid fossa surface, and the thinning of cortical bone of the right humerus.

In conclusion, this case shows us a remarkable situation by which an older male not only survived an amputated limb in a
pre-antibiotic era, but also adjusted very well to his condition with the use of a culturally derived device.

References

Infectious diseases: possible divergence in mortality trend and in pre- and post-antibiotic era
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The study of past infectious diseases increases our knowledge of the presence, impact and spread of pathogens within ancient populations. Many diseases involve the skeleton, but paleopathology occurs in a low percentage of cases. For example in both tuberculosis (TB) and leprosy, the percentage of bone involvement is only about 3-5% of untreated cases. In other pathologies as well the plague the involvement of the skeleton is null. The only approach useful to find ancient individuals with plague are the immunodetection and the biomolecular analysis with high cost for the research. There are other instruments to verify the presence of an epidemic situation in an old population. The first is a good excavation of the cemetery. The contemporary inhumation of many people is an indicators of a catastrophic event. The second (when possible) are the historical sources. The third is the analysis of the mortality curves. This last indicators at this moment shows good information because the mortality trend results different between some infectious diseases. Furthermore this analysis permit us to evaluate the impact of the diseases both in pre- that post-antibiotic era. This last point is an important topic of reflection.

Anatomo-Surgical Practice in 17th and 18th century: the case of the old hospital cemetery in Forlì
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Surgical practices have an enormous importance in the history of medicine; in particular, during the 17th and 18th centuries, medical investigations and demonstrations on cadavers became the most important mean for teaching and learning. In this study, we analysed the remains of four individuals dated from the 17th and 18th centuries, from the old hospital cemetery of Forli. Archaeologically excavated during 2014, the cemetery is located near the ancient city hospital. Biological and pathological profiles of the subjects were analysed, and then forensic methods were applied for the observation of the sectioned surfaces. In the attempt to reconstruct the actions made by surgeons and to deduce technical characteristic of the instruments, we made macro and microscopic observations by taking high definition photographs and using stereomicroscope and SEM. In this way, creating a comparison to the treatises of the time, the execution of a craniotomy and three limbs amputations on adults were described. Without damaging the occipital, the craniotomy (individual 2, burial 68) was executed probably from the left to the right side of a male cranium by using a linear hand powered saw with the set of the blade circa 1,3 mm wide. The individual 2, burial 1, a male, shows a bilateral amputation which was probably made by an alternated push saw having a 2 mm distance between the teeth; the operator stood on the lateral side of the limbs. For the other cases of the left femur and humerus amputations, respectively of the individual 1, burial 121 (male) and of the individual 4, burial 24 (indeterminable), we hypothesize that both incisions were made by a pull saw from the medial side of the limbs. Excluding the individual 4, burial 24 which exhibits a sharp force lesion on the ulna, none of the other individuals show bone diseases which could justify surgical practices. In conclusion, we discuss a possible case of post-traumatic intervention and three probable cases of post-mortem incisions.

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Klippel-Feil syndrome in a Sardinian population of the 16th century
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During the 2009 archaeological excavations conducted in the Alghero cemetery (Sardinia) dating back to the 1582-1583 plague outbreak, sixteen long and narrow graves (trenches), and ten multiple graves were uncovered. A total of 198 skeletons were examined, including the skeletons of two adult males and two subadults, for which the fusion of two cervical vertebrae was identified.
The Bottaro: when the study of acromegaly went beyond the osteology

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Acromegaly is an endocrine-metabolic disease caused by a pituitary gland tumour producing a surplus of growth hormone. Although the etiology has been described in 1909, since the 16th century physicians have been interested in the study of this disease. The “Luigi Cattaneo” Museum of Bologna exhibits the skull, the wax bust and the dry stomach preparation once belonging to Luigi Marchetti, known as il Bottaro (i.e. the barrel maker, after his profession). The case is known in literature on acromegaly thanks to a publication of the pathologist Cesare Taruffi in 1877. Mistakenly, however, we could think that this case report was contemporary to Taruffi. In fact, Taruffi’s studies are the result of the observation of anatomical specimens made certainly at the beginning of the 19th century at the request of the anatomist Alessandro Moretti’s. Currently, also because of the change of the venue of the museum and some inaccurate cataloging of the anatomical specimens, many questions remain open. First of all, there was no certainty about Bottaro’s precise date of death: Taruffi noted 1808, while on the wax bust it is marked 1811; secondly a giant stomach is also exhibited in the museum but unexpectedly placed in a room distant from the one the skull and the bust of Bottaro are preserved. Our study was born a museumological one, to later expand into a full palaeopathological and historico-medical one owing to a careful analysis of Taruffi’s writing. The investigations, besides clarifying Bottaro’s year of death in 1808, confirmed the retrospective diagnosis of acromegaly. On the basis of the gathered information a review of the scientific literature was conducted: it revealed that cases of acromegaly chronologically preceding the Bottaro’s were primarily osteological studies, and Moreschi was actually the first to observe the internal organs and to study them.

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About some cases of vascular pathology belonging to the collection of the “Regio Museo dell’Università di Torino”

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Among the old pathology specimens belonging to the collection of the “Regio Museum dell’Università di Torino” there are many interesting cases of vascular pathology dating back to the beginning of the XX century, notably there are cases of aortic aneurisms and luetic aortitis.

The cases of aortic aneurisms are both dry preparations and fluid-preserved specimens. whereas the cases of aortitis are all fluid-preserved specimens.

The most significant dry preparations of vascular lesions are two cases of “true” aortic aneurisms of luetic origin whose clinical and autopsy data were reported by Dr. G. Gallo in 1821 (Repertorio Medico-Chirurgico 1821;1:241-7).

Other cases were reported by Dr. Ferruccio Vanzetti (Trattato di Anatomia Patologica). The restoration of the dry specimens was recently performed following historical records (cleaning with lye water and with a decoction of Saponaria Officinalis and final application of shellac over the surface). The chemical analysis has showed that the dry preparations were fixed with very good result, showing the perfect preservation of the histological details after more than a century.

The aspect of this condition is characteristic, because not only the vertebral bodies, but also all the other parts of the two vertebrae can be involved, including neural arches, spinous processes and zygoapophyseal joints, with absence of osteophytes: the two fused cervical vertebrae appear not only structurally as one, but also function as one. In medical and palaeopathological literature, similar features have been attributed to congenital fusion of cervical vertebrae, a congenital synostosis of one or more continuous segments of the cervical spine, resulting from an embryological failure in the normal spinal segmentation. Furthermore, besides this condition, if the fusion of two vertebrae is accompanied by other anomalies, affecting above all the spinal column, a diagnosis of Klippel-Feil syndrome, a rare type of complex congenital condition, can be considered.

Individual 2291, a subadult aged 7-8 years, showed alteration in the morphology of the pars basilaris, a posterior defect of the atlas, fusion of C2-C3, thoracic and lumbar supernumerary vertebrae, lumbar posterior arch defect of L6, spina bifida occulta, and bifurcation of the sternal end of one fragmented rib. The association of these anomalies suggests that the individual was affected by the Klippel-Feil syndrome. Individuals 2284, 2309, 2890, showed fusion of two cervical vertebrae, but no other abnormalities, in part as a consequence of the poor state of preservation of the skeletal remains. In these cases, a diagnosis of Klippel-Feil syndrome is dubious, and a simple congenital fusion of cervical vertebrae is more likely.

The references

Isotopic signatures and stress markers: evaluation in bone remains from ancient Rome

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Molecular evaluation of bone remains could provide a huge amount of information about health conditions and lifestyle of past populations. Although carbon and nitrogen stable isotope analysis on human skeletal remains is widely performed to investigate dietary patterns 1, proper interpretations could aid in the definition of the individual biological status related to homeostatic/metabolic alterations 2,3.

The present research aims to evaluate the isotopic signatures of ancient bone remains pertaining to more than 150 individuals from the Roman territory where specific metabolic disorders and/or non-specific stress indicators have been identified. In particular, the dental and skeletal physiological dysfunctions related signs that have been taken into account are porotic hyperostosis, periositis, enamel hypoplasia and caries.

Our evaluation pointed out that the alteration in isotopic values due to the presence of non specific stress markers could be primarily ascribed to nitrogen fractionation. However, the non specificity of the etiological causes involved in the development of the alterations makes not straightforward to ascribe the phenotypic expression of such markers to a sole nutritional reason.

Nevertheless, pathological conditions can significantly alter the isotopic compositions of human tissues and these isotope values could mirror both altered metabolic processes and variations in the diet. These evidence suggest that stable isotope analysis should be carefully applied at all to make inferences about diet, especially to avoid erroneous reconstruction of the nutritional habits of ancient people exposed to nutritional stresses or affected by metabolic diseases.

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References

MSCT study of ancient bone remains: investigative protocols

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Aim of the study is evaluate the image optimization in MSCT for studying ancient bones. Despite the experience of many years to the study of small anatomical images such as the auditory ossicles of the middle ear in children. The biggest obstacle for antiquities bones was that all protocols did not consider the absence of soft tissues.

We used for our study two archaeological finds made available by the Soprintendenza Speciale per il Colosseo and l’Area Archeologica Centrale di Roma, pertaining to the imperial necropolis of Castel Malnome and medieval cemetery of San Pancrazio, that have undergone various displays with Toshiba Aquilion 16 layers CT equipment. 5 types of exposure was carried out in order to identify the protocols with variation of acquisition parameters starting proper centering of the find, the FOV, the kV and mA, exposure time, pitch and filter selection.

The reference table of results rather articulate showed that despite having the technical constraints due to the machine you can perform high quality low dose examinations for all equipment MSCT.

The technological approach with CT to skeleton bones requires special parameters to obtain increased spatial resolution and contrast resolution which allows to highlight the details that help to identify the pathologies of the find. Avoiding the use of standard parameters that are not useful to the study.

References

Anthropological and paleopathological investigations of human remains from medieval cemeterial area of San Biagio, Cittiglio (Varese)

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In 2006, the restoration works of the medieval church of San Biagio in Cittiglio (Varese-Northern Italy) brought to light several archaeological findings. Near the current presbytery, excavations allowed to show a very interesting sequence of tombs, probably those of the ruling family members. In particular, two of these tombs are remarkable under the pa-
leopathological point of view. A tomb containing the skeletal remains of a young male showed three important perimortem cuts on the skull. The other tomb contained the bones of a woman with a spearhead at the level of the ribs. We believe that these subjects were killed during a battle; however, other hypotheses regarding the young man, suggested a death for justice. Several elements, from our point of view, let us to assume a “battle theory”, but we must verify the presence or absence of other violent deaths.

Another important aspect recorded during this archaeological phase is the conspicuous presence of childhood graves, especially for those younger than three years.

In order to better investigate the paleodemography and paleopathology we needed more bioarchaeological data. Therefore, we focused our attention on the funerary area immediately outside the church. The archaeological excavation started in March 2016 and brought to light several other burials. At the end of the excavation phase, anthropological investigations of skeletal remains were performed. These data confirmed the high infant mortality; we have also recorded the presence of skeletal remains belonging to three fetuses, two of which buried inside of a tile. Moreover, we found other traumatic injuries, in particular on a skull of an adult man presenting, on the parietal bone, the remodeling of an ancient sharp trauma, and an isolated femur with an important post trauma callus. Although, it is difficult to speculate about these last violent deaths we could be able to verify the “battle theory” with the next archaeological investigation, planned for the month of May 2017.

Acknowledgments

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References


Archeology: a little clay head dating back to the IV-III century b. C. Bell’s paralysis

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The finance guard intercepted a clandestine archaeological excavation related to a votive deposit in the locality called Pantanacci, in the year 2012 during the reconnaissance of Lanuvio territory (Rome). The retrieval of judicial police investigations of the archaeological material at the home of abusive excavators has allowed the Archaeological Superintendence to highlight one of the most interesting votive deposits of the last twenty years in central Italy. This finding has been well described from an archeological view point, but far less in the history of medicine (given the amount of medical objects) in an article that appeared on multiple names on Archeologia Viva in 2013. Between the medical-pathological material found there is a small terracotta sculpture dating back to the IV-III sec. a.C. It is a head depicting an adult man with a significant grimace on his face. The small head (6x3 cm) made with a rough dough appears harsh in its execution, but a careful examination of the artifact indicates with great precision the pathology known as Bell’s paralysis. This pathology is manifested by the crushing of the nerve of the emi-face, the closure of the omlateral eye, and asymmetries, the deviation of the nose to the right, and the upper lip lowering at the lower right, the bending of the mouth.

Bell’s paralysis affects the facial nerve, seventh pair of the cranial nerves. The cause seems to be attributed to a viral agent, but traumas, tumors, degenerative nerve diseases and infections should also be considered. This paralysis seems to be triggered by a sudden drop in temperature. Generally, those that can be healed regress in a short time.

From a comparative point of view, some evidence has been taken into consideration but do not allow an authoritative confirmation of this pathology.

The influence of the Etruscan medical school is evident, however, which since the 7th century b.C. gives us many examples of anatomical and pathological knowledge attested in different parts of central Italy.

A case of therapeutic trepanation from 13th century Tuscany

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During the archaeological excavations carried out in 2007 in the Medieval cemetery of the Church of S. Agostino in Poggibonsi, Tuscany (Italy), a collective tomb was investigated. The large funerary structure, which contained the skeletal remains of 24 individuals, is dated back to the 13th century. A skull, belonging to an adult male, was found among the skeletal remains showing evidences of two head lesions produced by bladed instruments.

The first consists in a linear wound that involved only the outer cranial table of parietal bones; bone remodeling indicates that the individual survived the injury for a long time. The second is located on the right portion of the frontal squama and involves all the thickness of the bone with clean and well-defined margins; the absence of any traces of reparative processes and signs of healing allows a diagnosis of peri mortem lesion. Only the triangular extremities of this injury can be recognized because the central portion of the wound

References


is obliterated by an oval bone loss, 3x2 cm, characterized by clean cutting-edges along the outer cranial table, whereas the margins of the inner cranial table are irregulars. In order to treat this lesion, the patient was submitted to a surgical intervention, probably performed to clean the wound and remove any bone splinters. Trepanation performed to treat cranial traumas was described in detail by several medical classic and medieval Authors, whose texts were available in the 13th century. In particular, the surgeon from Poggibonsi had access to the medical literature and he probably followed the prescriptions of the surgical texts, such as that of Albacasis, which was one of the most famous during the Middle Ages. Despite he was skilful in the management of head wounds, the surgical intervention failed and the patient dead in surgery or soon afterwards. This case represents a rare direct Middle Ages evidence of neurosurgery practised to treat a bone injury.

References


The Gout of Duke Frederick of Montefeltro (1422 - 1482): historical sources and osteological evidence

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Frederick of Montefeltro (1422-1482), Duke of Urbino, is one of the foremost warlords and patron of the arts of the whole Italian Renaissance. He died in Ferrara in the autumn of 1482 after contracting an infectious disease during his last military campaign in Northern Italy. His body was taken to Urbino and after solemn funerals it was embalmed. The corpse remained in a wooden coffin hung to the wall, to the right of the main altar, in the church of San Bernardino until 1620, when it was placed in a burial chamber under the floor of the church. The remains were exhumed twice: in 1824 and in 1938. On both occasions they were found in a rather poor state of preservation. The last exhumation in 2000 confirmed the extremely poor preservation status of his skeletal remains. However it was possible to note a marked development of the muscular attachments of the upper limbs and of the pelvic bone, especially of the iliac crest, that are the result of considerable physical activity, unmistakably linked to his extensive practice of horse riding. The most remarkable find is the first metatarsal bone of the right foot, fortunately still well preserved. The metatarsal, showing a deep erosion at the medial side, has subsequently undergone radiological analysis (conventional X-ray and CT scan) which clearly demonstrated the typical morphology of a gouty lesion, exhibiting a periarticular lytic lesion with an excavated appearance and foci of reactive bone deposition and sclerosis around the margins. Various historical sources report that Federico of Montefeltro suffered from a severe form of gout, but an outstanding primary source is a handwritten private letter sent by the Duke to his physician Battiderro da Mercatello in 1461, that clarifies the gouty nature of his ailments. The study shows how an alliance between historical, documental and paleopathological methods may increase the precision of retrospective diagnoses, thus helping to shed clearer light onto the antiquity and evolution of diseases.

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References


A case of multiple osteochondromatosis from the Nunnery of Montescudaio (Pisa, XII-XIV century)

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Osteochondroma is a relatively common benign cartilaginous tumor (35% to 40% of all benign bone tumors) characterized by a cartilage-capped bony projections or outgrowth on the surface of bones. When there is the development of two or more bony outgrowths, the disorder is called Multiple Osteochondromas (MO), a hereditary autosomal dominant disease. Paleopathological researches have demonstrated the presence of MO in a very broad geographical and chronological distribution, from the Middle Bronze Age (1700 B.C.) to the 19th century, even if only 18 cases are reported in the previous literature. The archaeological survey in Montescudaio, Cecina Valley (Pisa), between 2005 and 2010, discovered the Nunnery of Santa Maria, founded in the late 11th century by the Counts of Gherardesca. The archaeologists investigated many burials from 10th to 16th century. One of the skeletons, a 35-40-year-old male dated between the 12-14th centuries, showed two voluminous multiple exostoses, located on the lateral part of the left clavicle and on the proximal left femur metaphysis. Anthropological observations and radiographic analysis of affected bones suggested a diagnosis of MO. The differential diagnosis of multiple osteochondromatosis includes malignant (osteosarcoma, chondrosarcoma) and benign diseases (e.g. multiple enchondromas, metaphysochondromatosis, chondroblastoma, and ossifying myositis), so radiographic analysis are needed. The symptomatic presentation of MO
A monostotic form of Paget from a Northern Italy Medieval Necropolis

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An excavation conducted in 2002 by the Lombardy Archaeological Heritage in the St. Giulio Church (Cassano Magnago-Northern Italy) brought to light a burial dated between VIII-IXth century, presenting a complete skeleton in anatomical position, belonged to a male, near 50 years old and 177 cm tall. The left femur presents an important alteration: it is longer than the contralateral and exhibits a swelling of the entire diaphysis; the surface is coarsened and porous. In cross section, all the cortical bone has been converted into cancellous bone, with porosity alternating with calcified areas (porotic hyperostosis). Radiological investigations (X-ray and CT scan) were performed and revealed a cotton-wool appearance, with thinned cortical bone because of an expanded and subverted structure of lamellar bone.

Microscopic slides were performed by a resin embedding technique and a stain with Haematoxilin and Eosin and Goldner’s Trichrome. Microscopic analysis revealed a cortical constituted by a more compact external part and an internal section characterized by incomplete osteons, narrowing of the bone marrow and a thickened and disorganized trabecular pattern with thick cement lines, an appearance referred to a mosaic pattern. These characteristics are typical of the mixed phase (osteoblast and osteoclast activity) of Paget’s disease. Macroscopic, radiographic and microscopic alterations are suggestive of monostotic form of Paget’s disease, a chronic disorder, characterized by focal areas of excessive osteoclastic bone resorption followed by secondary increase in osteoblastic bone formation. This pathology can involve one bone (monostotic form) or more bones (polyostotic form): the most commonly affected sites are pelvis, vertebral spine, femur, skull and tibia.

Moreover, other pathological conditions were evaluated in differential diagnosis: fibrous dysplasia, sclerosis osteomyelitis of Garré, osteitis illi condensans, lymphoma.
Supracondylar process of the humerus in children.
Cases from the 15th-18th century in Settimo Vittone (Piedmont)

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Six single burials and several dislocated bones dated to the period between the 15th and the 18th century were discovered under the floor of the Baptistery of San Giovanni Battista (Settimo Vittone, Turin) during an archaeological excavation undertaken by the Soprintendenza Archeologica, Belle Arti e Paesaggio per la Città Metropolitana di Torino in 2014. The minimum number of individuals recovered is 81 (55 non adults, 26 adults).

In the present study we describe and discuss 5 cases of supracondylar process in infant and perinatal humeri. The supracondylar processes, either prominent (5 mm long) or extremely rudimentary (1 mm long) appear as a hook-like bony spine of variable size that project distally from the anteromedial surface of the humerus. The outgrowth of bone is oriented towards the distal end above the medial epicondyle. Only in one case the process occurs bilaterally.

In the scientific literature this lesion, also called supra-epitrochlear process, epicondylar process, epicondylic process or supratrochlear spur, is considered a normal anatomical variation.

The high occurrence of the process is striking and it may suggest a family relationship among the individuals buried.

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