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Ogni anno il carcinoma polmonare colpisce 1.3 milioni di persone e causa 1.18 milioni di decessi. Il tumore polmonare non a piccole cellule (NSCLC) è la forma più diffusa di questo carcinoma.

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Subscription information
Pathologica publishes six issues per year. The annual subscription rates for non-members are as follows:
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This issue € 20,00 for Italy, € 25,00 abroad.

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Journal printed with total chlorine free paper and water varnishing

Printed by Pacini Editore, Pisa, Italy - October 2012
The importance of clinical findings and the limitations of primary intestinal tumour. Histologically defined as a metastatic lesion from an occult primary.

Challenge in differential diagnosis of a liver mass:

- **Background**: The accurate diagnosis of lung carcinoma has become compulsory, especially after the introduction of new targeted therapies. The majority of these patients are non-operable, highlighting the importance of the cytology specimen. Our aim was to assess the diagnostic efficacy of bronchial washings in low income countries where this low cost technique is widely performed.

- **Material and methods**: We conducted a study of 118 bronchial washings collected in the Department of Pathology. Bronchial washings were smeared on 5-6 clean slides. These were fixed in 95% ethyl alcohol for haematoxylin and eosin staining. Cases were retrospectively reviewed by two pathologists (FM and MM) together with the corresponding biopsies. False negative cases were reviewed twice, and the diagnosis was reassessed in one case.

- **Conclusions**: Our study showed a sensitivity of 56%, specificity of 90%, PPV of 55%, NPV of 76% and a Yoden index of 0.45. These results emphasise the diagnostic efficacy of bronchial washings and the possibility of performing molecular tests on cytology specimens.

**CASE REPORTS**

**Challenge in differential diagnosis of a liver mass histologically defined as a metastatic lesion from an occult primary intestinal tumour.**

**The importance of clinical findings and the limitations of histology and molecular profiles.**

**A case report**


Differential diagnosis of liver lesion in the absence of proven primary tumor is still a challenge. We experienced a case of an asymptomatic 14 cm lesion of right hemiliver in a 67-year-old man submitted to right hepatectomy in December 2010. One year before the patient underwent endoscopic removal of a tubular adenoma of the right colon. Preoperative diagnosis was supported by ultrasound, CT scan, PET and liver biopsy. The patient received 6 cycles of preoperative chemotherapy (FOLFOX) with down-staging of the lesion diameter. Immunohistochemistry on the surgical specimen showed positivity for cytokeratins 19 and 20, CEA, MUC-2, negativity for cytokeratin 7 and a-fetoprotein. Moreover, the neoplastic cells showed a focal positivity with lower intensity for MUC-1 and MUC-5AC. The immunohistochemical profile suggested the possibility of a metastatic tumour from the large bowel, without excluding a primitive mucinous cholangiocarcinoma withintestinal phenotype. At 6 months after intervention, the patient was submitted to chemotherapy (FOLFOX). At present he is in good condition, without radiological signs of recurrence. Oncologists must evaluate the possible benefits of further adjuvant treatments based on the differential diagnosis between a primitive or metastatic liver tumour. In conclusion, correct diagnosis of liver masses is mandatory and remains a challenge that can differentiate either follow-up or surgical and adjuvant treatment. Histology and immunohistochemistry must be related to clinical findings as they may not always be sufficient to reach a correct final diagnosis, and can even be confusing. At present, molecular biology cannot be considered a helpful for diagnosis in these cases.

Ancient schwannoma of the orbit

I. Pecorella, J. Toth, O. Lukats

Schwannoma, also referred to as neurilemmoma or peripheral neurinoma, is an unusual orbital benign tumour that may pose diagnostic challenges. Awareness of the clinical features that may be associated with the tumour and prompt surgical excision with histopathologic examination enable correct diagnosis. The authors describe a progressively increasing inferolateral orbital mass in a 32-year-old patient that was demonstrated to be an orbital ancient schwannoma.

Biphasic large cell neuroendocrine carcinoma – pure mucinous carcinoma of the gallbladder (MANEC): a unique combination

S. Russo, F. Russo, F.M. Maiello, B. Paolini, A. Carrabba, A. De Gregorio

**Introduction**: We report a case of primary combined large cell neuroendocrine carcinoma (LCNEC) – pure mucinous carcinoma of the gallbladder (MANEC) – which represents the first description of this entity.

**Methods**: The patient is a 59-year-old Italian male who underwent cholecystectomy under a preoperative diagnosis of cholecystitis with gallstones and gallbladder tumour. During laparotomy, cholecystectomy, liver wedge resection and regional lymph node dissection were performed. The resected gallbladder showed a thickened wall, gallstones and a 4 cm gelatinous, cauliflower-like soft tissue mass.

**Results**: Following surgery, the gallbladder tumour was diagnosed as a mixed endocrine-exocrine carcinoma. There was evidence of lymph node metastasis or direct liver invasion. The mucin-producing carcinoma was composed of poorly differentiated glandular cells with mucin lakes. The LCNEC was characterized by large cells with prominent nucleoli, coarse chromatin and a high mitotic rate. The cells showed an “organoid” growth pattern with rosette formation and frequent areas of necrosis. Chromogranin A, synaptophysin and CD56 were diffusely and strongly expressed.

**Discussion**: This case may provide helpful insights regarding the histogenesis of this unusual combination of tumors: the concept of a collision tumor between two neoplasms that have arisen in adjacent areas may be the best explanation for its pathogenesis.

Primary cutaneous cribriform carcinoma of the neck: a case report

S. Innocenti, L. Fancelli, R. Cecchi

Primary cutaneous cribriform carcinoma is an unusual apocrine tumour that mainly occurs on the limbs of middle-aged females. We herein report a case of a 32-year-old woman who underwent surgical excision of a nodular lesion on her neck that had been present for 10 months. Histopathology showed a dermal tumour composed of interconnected aggregations of neoplastic cells and round spaces of various size and shape, resulting in a cribriform pattern. A diagnosis of cutaneous cribriform carcinoma was made. No peripheral lymphadenopathy was evident, and investigations for internal malignancies gave negative results. The patient was tumour-free 2 years after surgery. Although primary cutaneous cribriform carcinomas have up to now shown an
indolent course, the number of reported cases is too limited for definitive prognostic conclusions. Therefore, surgical excision with clear margins and adequate follow-up are recommended.

Combined uterine smooth muscle tumour: a challenging case

P. Viola, A. Colasante

Uterine smooth muscle tumours that cannot be diagnosed unequivocally as benign or malignant should be termed ‘smooth muscle tumours of uncertain malignant potential’ (STUMP). Since there are no unequivocal morphological and ancillary criteria to differentiate this group of tumours, we present a case of a 49-year-old woman with a combined, benign and borderline lesion, which could have different clinical management strategies, and discuss the diagnostic issues.

Localized ileal giant pseudopolyposis in Crohn’s disease: a case report

F. Limaiem, S. Ben Slama, S. Jedidi, S. Aloui, A. Lahmar, S. Bouraoui, S. Mzabi

Localized giant pseudopolyposis is a rare complication in inflammatory bowel disease defined as a pseudopolyp (isolated or clustered) larger than 1.5 cm in size. Giant pseudopolyps are more commonly found in ulcerative colitis compared to Crohn’s disease and mainly involve the left colon. A 26-year-old male patient with a two-year history of Crohn’s disease was admitted with increasing abdominal pain, vomiting, anorexia, weight loss and fever. On physical examination, the abdomen was diffusely tender. Computed tomography showed diffuse irregular thickening of the ileal wall and stenosis of the terminal ileum. The patient underwent ileo-cecal resection with re-anastomosis. The ileal portion of the resected specimen harboured multiple finger-like pedunculated polyps, with the smallest measuring 0.5 cm and the largest measuring 1.8 cm. Histologically, the polyps were consistent with granulation tissue. No evidence of dysplasia or malignancy was found. The post-operative course was uneventful considering one month follow-up. This report illustrates an unusual case of giant pseudopolyposis involving the ileum in a patient with Crohn’s disease. The natural history of these lesions, as well as their optimal management, remain uncertain.
The efficacy of bronchial washings in diagnosis of lung carcinoma

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Key words
Bronchial washing • Sensitivity • Specificity • Non small cell carcinoma

Summary
Background. The accurate diagnosis of lung carcinoma has become compulsory, especially after the introduction of new targeted therapies. The majority of these patients are non-operable, highlighting the importance of the cytology specimen. Our aim was to assess the diagnostic efficacy of bronchial washings in low income countries where this low cost technique is widely performed.

Material and methods. We conducted a study of 118 bronchial washings collected in the Department of Pathology. Bronchial washings were smeared on 5-6 clean slides. These were fixed in 95% ethyl alcohol for haematoxylin and eosin staining. Cases were retrospectively reviewed by two pathologists (FM and MM) together with the corresponding biopsies. False negative cases were reviewed twice, and the diagnosis was reassessed in one case.

We calculated the sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and Yoden index.

Conclusions. Our study showed a sensitivity of 56%, specificity of 90%, PPV of 55%, NPV of 76% and a Yoden index of 0.45. These results emphasise the diagnostic efficacy of bronchial washings and the possibility of performing molecular tests on cytology specimens.

Background
Lung cancer represents a major health problem, although its diagnosis and management have improved in the last decade. In 2011, a new classification of the lung cancer was established that defined new terminologies, and was the first classification destined not only for pathologists but also for pulmonologists, surgeons and radiologists. This A new classification system was necessary due to the emergence of new targeted therapies implicating new diagnostic criteria, based on both morphologic and molecular characteristics. Diagnosis of lung cancer is mainly made on biopsies, but as these patients rarely present with resecable cancer, cytology specimens are easy and feasible mean of diagnosis. Many authors have advocated the feasibility to perform molecular studies on cytology specimens 1. We assessed the diagnostic efficacy of bronchial washings in a low income country in order to predict the feasibility of further immunocytochemical and molecular studies.

Material and methods
We conducted a study of 118 bronchial washings collected at the Department of Pathology. Bronchial washings were smeared on 5-6 clean slides and fixed in 95% ethyl alcohol for haematoxylin and eosin staining. Cases were retrospectively reviewed by 2 pathologists (FM and MM) together with the corresponding biopsies. False negative cases were reviewed twice and the diagnosis was reevaluated in one case.

We calculated the sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and Yoden index.

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Results

118 bronchial washings, collected during flexible bronchoscopy, were reviewed and correlated with histologic findings. All false negative cases were reviewed twice and the diagnosis was reassessed in one case of small cell carcinoma.

In this study, three were 24 false negative cases, 8 false positive cases, 76 true negative cases and 10 true positive cases.

Accordingly, the sensitivity was 56%, the specificity was 90%, PPV was 55%, NPV was 76% and the Yoden index was 0.45.

Among the 10 true positive cases, 40% were accurately subclassified as squamous cell carcinoma in 2 cases, adenocarcinoma in 1 case and small cell carcinoma in 1 case.

These results are shown in Table I.

Discussion

An accurate diagnosis of lung carcinoma, and especially an accurate subclassification of non small cell lung carcinoma, has become compulsory after the introduction of almost exclusively adenocarcinoma-targetable molecular characteristics, and in relation to the dangerous side-effects of bevacizumab and pemetrexed in patients with squamous cell carcinoma. The majority of patients with non small cell carcinoma present with inoperable advanced disease and often with low performance status; thus, the only available pathological material is a cytology specimen. As cytology examination is easy and low cost, especially in low income countries, we investigated its efficacy in diagnosis of lung carcinoma.

The flexible fibre optic bronchoscope enables several investigations to be carried out, including bronchial brushing, bronchial washings and fine needle aspiration.

Many authors have compared all these techniques, and highlighted their different accuracies. We investigated the diagnostic value of bronchial washing because of its low cost, which is especially relevant in low income countries in order to predict the feasibility of further molecular studies in bronchial washings. Our study showed the actual diagnostic value of this technique has a specificity of 90% and a positive predictive value of 55%. Moreover, the Youden index of 0.45 indicates its diagnostic reliability. In fact, the Youden indicates the inefficacy of a test when it approaches zero. These results may be improved by the use of cytoblocks.

This result encourage performing further molecular studies. In fact, Pang B and colleagues showed that utilizing cytology samples for EGFR testing avoids unnecessary patient re-biopsying, and yields a clinically superior satisfactory rate to the overall satisfactory rate of tissue biopsies of non small cell lung carcinoma.

Conclusions

Considering these results, we attempted to confirm the concept that bronchial washing has reached a sensitivity that is high enough to justify its use as a diagnostic tool in non-operable patients. Moreover, this fact should enable further molecular tests on cytologic specimens, especially in low income countries where the low cost of this technique may be encouraging.

References

Case report

Challenge in differential diagnosis of a liver mass histologically defined as a metastatic lesion from an occult primary intestinal tumour. The importance of clinical findings and the limitations of histology and molecular profiles.

A case report


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Key words

Cholangiocarcinoma • Liver metastasis • Immunohistochemistry

Summary

Differential diagnosis of liver lesion in the absence of proven primary tumor is still a challenge. We experienced a case of an asymptomatic 14 cm lesion of right hemiliver in a 67 year-old man submitted to right hepatectomy in December 2010. One year before the patient underwent to endoscopic removal of a tubular adenoma of the right colon. Preoperative diagnosis was supported by ultrasound, CT scan, PET and liver biopsy. The patient received 6 cycles of preoperative chemotherapy (FOLFOX) with down-staging of the lesion diameter. Immunohistochemistry on the surgical specimen showed positivity for cytokeratins 19 and 20, CEA, MUC-2, negativity for cytokeratin 7 and α-fetoprotein. Moreover, the neoplastic cells showed a focal positivity with lower intensity for MUC-1 and MUC-5AC. The immunohistochemical profile suggested the possibility of a metastatic tumour from the large bowel, without excluding a primitive mucinous cholangiocarcinoma with intestinal phenotype. At 6 months after intervention, the patient was submitted to chemotherapy (FOLFOX). At present he is in good condition, without radiological signs of recurrence. Oncologists must evaluate the possible benefits of further adjuvant treatments based on the differential diagnosis between a primitive or metastatic liver tumour. In conclusion, correct diagnosis of liver masses is mandatory and remains a challenge that can differentiate either follow-up or surgical and adjuvant treatment. Histology and immunohistochemistry must be related to clinical findings as they may not always be sufficient to reach a correct final diagnosis, and can even be confusing. At present, molecular biology cannot be considered a helpful for diagnosis in these cases.

Introduction

Differential diagnosis of liver masses is still challenging whether the clinical history of patients is unclear or if well defined markers (serological or tissue) are missing. Intrahepatic cholangiocarcinomas are neoplasms (largely adenocarcinomas) arising from cholangiocytes, the epithelial cells of intra-hepatic and extra-hepatic bile ducts. These tumours show a specific immunophenotypic pattern characterized by the expression of cytokeratins 7, 8, 18 and 19 that is typical of bile duct epithelia cells. Intra-hepatic cholangiocarcinoma is a malignant epithelial tumour characterized by an infiltrating growth of liver parenchyma. It may show morphologic features mimicking either the hepatocarcinoma or metastases from solid tumours, especially in the mucinous variants; at immunohistochemistry they can express cytokeratins 8 and 18 and α-fetoprotein which is typical of...
hepatocytes. Intra-hepatic cholangiocarcinoma may also present bio-molecular characteristics such as transcriptional peptides of albumin gene, which suggests a common pathogenesis of this tumour and hepatocellular cancers.

Cholangiocarcinoma is the second most common primary liver tumour and its incidence, higher in the past years in Eastern countries (mainly Japan), has slightly increased over the past decades in Western world, partly due to better diagnostic options and a general increase in the life expectancy of citizens in industrialized countries. Furthermore, cholangiocarcinoma is an aggressive disease with a poor prognosis, and an overall 5-year survival rate of about 20-30% can be obtained when a surgical curative approach is possible. About 60% of patients with cholangiocarcinoma patients present with resectable tumors at the time of diagnosis. It has been shown that chemotherapy may influence survival in advanced patients, although there is currently no evidence to support postsurgical adjuvant therapy outside a trial setting. This underlines the importance of definitive diagnosis.

Case report

We report a case of an asymptomatic 14 cm lesion of the right hemiliver in a 67-year-old man. In September 2010, the mass was detected by abdominal ultrasound; former CT (Fig. 1) and PET CT scans suggested a malignant nature of the mass due to FDG positivity in the liver nodule and slightly in peri-renal area. A percutaneous biopsy reported a diagnosis of adenocarcinoma. Serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were normal. One year before the discovery of the liver mass the patient had been submitted to pancolonoscopy with curative intent and complete removal of a polypoid lesion of the right colon histologically diagnosed as tubular adenoma with low grade dysplasia (Fig. 2). A more recent colonoscopy was negative. At the time of clinical diagnosis, the lesion was operable but would have required right hepatectomy enlarged to segment IV due to its extension to middle supraepatic vein (Fig. 1). Therefore, the patient received 6 cycles of preoperative chemotherapy (FOLFOX); CT scan post-chemotherapy showed down-staging of the lesion diameter (8 cm), allowing a less extended liver resection (Fig. 3). In December 2010, 40 days after discontinuation of chemotherapy, the patient underwent right hepatectomy. Intraoperative frozen section showed free resection margins from disease and hypothesized a me-
tastasis from intestinal adenocarcinoma. No masses were grossly detected during surgical intervention either to the gut or colon-rectum. Mild ascites was observed within the first 7 postoperative days and was controlled by diuretics. Postoperative course was characterized by mild monolateral pneumonia, successfully treated by antibiotics. The patient was discharged after 12 postoperative days.

The initial pathological report suggested the possibility of a metastatic lesion from an intestinal occult neoplasm, such as poorly differentiated mucinous adenocarcinoma. Immunohistochemical and molecular analyses were performed and reported in the pathological findings section. Twenty days after discharge, adjuvant therapy was initiated based on FOLFOX, without relevant toxicity events. On January 2012, the patient was submitted to a total body CT scan for re-staging. No signs of recurrence were detected.

**Pathological and molecular findings**

Resection margins were R0 and pathological report defined the lesion as a poorly differentiated mucinous adenocarcinoma more compatible with an intestinal primitive tumour (Fig. 4, 5). At immunohistochemistry, the neoplastic cells showed positivity for cytokeratin 19, MUC-2 and CEA (Fig. 6, 7, 8), and negativity for cytokeratin 7 and α-fetoprotein. Moreover, focal positivity with cytokeratin 20, MUC-1 and MUC-5AC was observed. The immunohistochemical findings could not exclude the possibility of a primitive mucinous cholangiocarcinoma with intestinal phenotype. Mutation analysis of the k-ras and b-raf genes were performed on paraffin-embedded sections of primary tumour. An area containing at least 50% of tumor cells was selected in haematoxylin-eosin-stained sections, and contiguous area on 5 µM section were macrodissected and DNA extracted. Exon 2 of k-ras and exon 15 of b-raf genes were amplified by PCR and sequenced using a BigDye Terminator 3.1 Reaction CycleSequencing kit (Applied Biosystems). Sequence reactions were then separated by capillary electrophoresis with laser-induced fluorescence detection (3100 Genetic Analyzer, Applied Biosystems).

**Fig. 4.** The neoplastic epithelial tubular and solid aggregates are represented on the right and infiltrate the liver, which is shown on the left.

**Fig. 5.** The neoplastic glands are associated with extra-cellular mucous lakes.

**Fig. 6.** CK19 positivity at immunohistochemistry.

**Fig. 7.** MUC-2 positivity at immunohistochemistry.
systems, Foster City, CA, USA). No k-ras or b-raf mutations were detected in paraffin embedded tumour tissue. Clinicopathological features are summarized in Table I. Therefore, the final diagnosis of a primitive mucinous cholangiocarcinoma was based on clinical information, which demonstrated the absence of other tumours.

Discussion

Intrahepatic cholangiocarcinoma is the second commonest primary malignant neoplasm of the liver, originating from cholangiocytes of small intrahepatic bile ducts or bile ductules.

Although radiological findings may be helpful in differential diagnosis in the presence of isolated liver mass without a sure primitive neoplasm, even an invasive procedure involving biopsy may not be conclusive to distinguish intrahepatic cholangiocarcinoma and colorectal carcinoma metastasis. The expression of cytokeratins 7, 8, 18, 19 and 20 and of mucin glycoproteins is generally useful in differential diagnosis between a primary and a metastatic carcinoma of the liver. However, some subtypes of cholangiocarcinoma may be particularly difficult to distinguish from a metastatic colorectal carcinoma by histology and even immunohistochemistry. In particular, non-peripheral cholangiocarcinomas show a CK20-positive immunophenotype in almost cases. Moreover, a smaller percentage of peripheral cholangiocarcinomas can express CK20 by immunohistochemistry. Herein, we report a case where adjuvant chemotherapy has been administered to the patient for a neoplasm of uncertain origin. Clinical history of the patient was unclear and specific immunohistochemical findings could not be obtained to define the correct nature of the tumour. Cholangiocarcinoma is one of the best known mimicking lesion of the liver and, it is difficult to achieve correct diagnosis. Thus, a high level of knowledge is mandatory to perform important diagnostic procedures in order to avoid incorrect diagnosis. Therefore, we believe that this kind of tumour must be treated in centralized centres with a high level of skill and volume. A complete surgical resection with microscopically negative resection margins is the only cure for cholangiocarcinoma. Unfortunately, unresectable tumours represent the majority of cases. Adjuvant chemotherapy has not been shown to improve survival in patients with resected cholangiocarcinoma, and the role of neoadjuvant therapy has not yet been determined. In our case, the hepatic cancer showed high sensitivity to FOLFOX neoadjuvant chemotherapy. This underlines that further investigations are needed to better understand the chemosensitivity of the cholangiocarcinoma based on tumour biology and histopathology.
References


A 32-year-old woman with an uneventful medical history presented with a 1-year history of painless, progressively increasing, swelling under her left eye. A palpable firm, rounded, freely mobile lump in her inferolateral left orbit was clinically noticed. The mass was non-pulsatile and the size did not vary with Valsalva manoeuvre, ocular movements or posture. The left globe was proptosed 3 mm and displaced upwards by 2 mm (Fig. 1). Ocular motility was reduced in down gaze on the left. Pupillary reactions, facial and corneal sensation were normal. Slit-lamp and fundus examination of the left eye showed normal anterior and posterior segments. The right eye and general physical examination were unremarkable. Systemic evaluation including physical examination for any skin lesions and brain MRI was negative for NF1, NF2, and schwannomatosis.

CT scan showed a 1 cm localised homogeneous oval mass below the globe at the level of the inferior orbital rim (Figs. 2a, b). TI-weighted MRI demonstrated moderate signal intensity in the lesion (Fig. 2c). The patient underwent anterior orbitotomy via the lower eyelid. A rubbery lump with a whitish aspect was completely excised with intact capsule and showed no obvious nerve of origin. A pathological diagnosis of orbital ancient schwannoma was made (Fig. 3 a, b). Postoperatively, the patient had an uneventful recovery and was subsequently lost to follow-up.

Discussion

Schwannoma is a benign, slowly growing, painless, peripheral nerve sheath tumour. It has a predilection for the head and neck, especially the eighth cranial nerve in the cerebellopontine angle. It is uncommon in the orbit, representing only 1-4% of orbital tumours. Other possible sites of involvement in the ocular region include the choroid, eyelid, and conjunctiva. Schwannoma can be solitary or associated with neurofibromatosis types 1 (NF1) and 2 (NF2) or schwannomatosis. Schwannomatosis is a recently described entity that is characterized by 2 or more non-intradermal biopsy-proven schwannomas in the absence of vestibular schwannoma and NF2 mutation. Schwannoma may occur at any age with no gender predilection and
ANCIENT SCHWANNOMA OF THE ORBIT

is localised, well-encapsulated and rarely malignant. In the orbit, schwannomas are usually unilateral and may occur anywhere. They usually arise from branches of the supraorbital or supratrochlear nerves, and less commonly from the infraorbital, ciliary, oculomotor, trochlear, abducens or optic nerves. In about 50% of cases its origin remains obscure. Clinically, it possesses no single diagnostic feature and is difficult to ascertain when not associated with von Recklinghausen disease. The average time between symptoms and intervention is 3 years. The size of the tumour ranges from 2.5 to 9 cm in maximum diameter. Schwannomas arising from the infraorbital nerve produce upward displacement of globe (Tab. I). Characteristically, on CT a schwanna is well circumscribed with a smooth contour, displacing normal structures. It tends to be rounded or fusiform. It may extend through the superior orbital fissure into the cavernous sinus. There may be areas of inhomogeneity with lower density areas representing cystic degeneration. The CT appearances of schwannomas are not sufficiently unique to differentiate them from other well circumscribed orbital lesions such as cavernous haemangioma. Other lesions within the differential diagnosis would include fibrous histiocytoma (benign or malignant), neurofibroma and haemangiopericytoma, all being rare lesions within the orbit. Often, diagnosis can only be made on histopathologic examination. MRI appearances are again not diagnostic in orbital schwannoma, with a similar differential diagnosis to that for CT. Intraorbital schwannoma commonly gives low signal intensity in
Tab. I. Benign infraorbital schwannomas described in the literature

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Gender</th>
<th>Age</th>
<th>Eye</th>
<th>Tumour max diam (cm)</th>
<th>Tumour site</th>
<th>Symptoms/signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F</td>
<td>75</td>
<td>L</td>
<td>2.2</td>
<td>Inferior oblique</td>
<td>Vertical diplopia</td>
<td></td>
</tr>
<tr>
<td>1 F</td>
<td>59</td>
<td>R</td>
<td>nr</td>
<td>No obvious nerve of origin</td>
<td>Vertical diplopia when reading in bed</td>
<td></td>
</tr>
<tr>
<td>1 F</td>
<td>60</td>
<td>L</td>
<td>nr</td>
<td>Anterior surface of the inferior oblique muscle</td>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>1 F</td>
<td>28</td>
<td>R</td>
<td>nr</td>
<td>Infraorbital nerve</td>
<td>Vertical diplopia</td>
<td></td>
</tr>
<tr>
<td>2 F</td>
<td>45</td>
<td>L</td>
<td>nr</td>
<td>Infraorbital canal</td>
<td>Proptosis</td>
<td></td>
</tr>
<tr>
<td>3 F</td>
<td>35</td>
<td>R</td>
<td>2</td>
<td>Attached to the infraorbital nerve</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>4 F</td>
<td>18</td>
<td>R</td>
<td>nr</td>
<td>No obvious nerve of origin</td>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td>5 F</td>
<td>16</td>
<td>L</td>
<td>4</td>
<td>No obvious nerve of origin</td>
<td>Pain, upward gaze, bulging, colour change and tenderness in left inferior eyelid</td>
<td></td>
</tr>
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T1 and high signal intensity in T2-weighted images on MRI. It also demonstrates homogeneous contrast enhancement and generally appears as a well-defined lesion with mixed components. Surgical excision as a definitive procedure is indicated to prevent progressive damage to vision, and it is also important, according to Schatz, to remove the tumour before possible malignancy develops (less than 0.5% of tumours), particularly in the setting of neurofibromatosis type 1. 28% of benign peripheral nerve sheath tumours (neurilemmomas/neurofibromas) within the orbit were found to extend into the superior orbital fissure, limiting the extent of resection. In a follow-up ranging from 6 months to 23 years, there has been no recurrence, regardless of whether the surgical approach has been complete or incomplete. The tumour is surrounded by true capsule consisting of the epineurium, though tumours arising in a small nerve resemble a neurofibroma and often obliterate the nerve of origin.

Ancient schwannoma, a histological variant of schwannoma, is a benign tumour with degenerative changes such as perivascular hyalinization, haemorrhage, cystic necrosis, and calcification. These degenerative changes are thought to be the result of the long-term progression of this tumour.

References

CASE REPORT

Biphasic large cell neuroendocrine carcinoma – pure mucinous carcinoma of the gallbladder (MANEC): a unique combination

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Key words
Mucinous • Large cell neuroendocrine carcinoma • Gallbladder • MANEC

Summary

Introduction. We report a case of primary combined large cell neuroendocrine carcinoma (LCNEC) – pure mucinous carcinoma of the gallbladder (MANEC) – which represents the first description of this entity.

Methods. The patient is a 59-year-old Italian male who underwent cholecystectomy under a preoperative diagnosis of cholecystitis with gallstones and gallbladder tumour. During laparotomy, cholecystectomy, liver wedge resection and regional lymph node dissection were performed. The resected gallbladder showed a thickened wall, gallstones and a 4 cm gelatinous, cauliflower-like soft tissue mass.

Results. Following surgery, the gallbladder tumour was diagnosed as a mixed endocrine–exocrine carcinoma. There was evidence of lymph node metastasis or direct liver invasion. The mucin-producing carcinoma was composed of poorly differentiated glandular cells with mucin lakes. The LCNEC was characterized by large cells with prominent nucleoli, coarse chromatin and a high mitotic rate. The cells showed an “organoid” growth pattern with rosette formation and frequent areas of necrosis. Chromogranin A, synaptophysin and CD56 were diffusely and strongly expressed.

Discussion. This case may provide helpful insights regarding the histogenesis of this unusual combination of tumors: the concept of a collision tumor between two neoplasms that have arisen in adjacent areas may be the best explanation for its pathogenesis.

Introduction

Mixed adenocarcinoma-neuroendocrine carcinomas (MANEC) of the gallbladder are rare composite tumours in which areas of adenocarcinoma intermingle with areas of endocrine cell carcinoma formed by solid and/or trabecular structures with cells that are immunoreactive for endocrine markers 1. Because these tumours are uncommon, no prognostic difference from ordinary gallbladder carcinoma has been documented. They can spread early by lymphatic metastasis, hematogenous metastasis and direct invasion into the liver 2. Several factors associated with the disease include porcelain gallbladder, size of gallstone, ethnic differences, and duration of harbourcd stones. The 5-year survival rate in most series reported thus far is less than 5% 3, which is due to the delay in diagnosis and a low resectability rate; by the time of diagnosis, most cases have liver involvement (by direct extension or metastasis). Appropriate therapy for local disease includes en-bloc resection with liver segments IVb and V. For advanced disease, the role of adjuvant chemotherapy and radiotherapy is not clear, but some reports support evidence of prolonged survival. To date, there are seven reports on large cell neuroendocrine carcinoma (LCNEC) in the gallbladder in the English-language literature, comprising four cases combined with another tumour and three pure LCNEC, whereas a combined colloid carcinoma-LCNEC has never been reported 4-6. In 2000, Papotti et al. first described LCNEC in the gallbladder saying that it is morphologically similar to its pulmonary counterpart 7. LCNEC shares some features of a well-differentiated neuroendo-

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crine tumor, such as the “organoid” growth pattern and rosette formation, while also manifesting characteristics of poorly differentiated small cell carcinomas, including necrosis, high mitotic rate and salt-and-pepper chromatin. However, the cells of LCNEC are generally two or three times the size of those in small cell carcinoma. Mucinous adenocarcinomas of the gallbladder are extremely uncommon: only 29 cases have been reported in the literature. They are morphologically similar to those that arise in other anatomic sites. By definition, more than 50% of the tumour contains extracellular mucin. They have a gelatinous appearance on macroscopic examination. There are two histological variants of mucinous adenocarcinomas of the gallbladder: one is characterized by neoplastic glands distended with mucin and lined by columnar cells with mild to moderate nuclear atypia, and the second is characterized by small groups of cells surrounded by abundant mucin (colloid, pure mucinous). This pattern is usually admixed with conventional adenocarcinoma.

**Case report**

A 59-year-old man underwent cholecystectomy for symptomatic cholelithiasis of long duration (gallbladder stones had been found 10 years previously). Laboratory studies on admission revealed prolonged prothrombin time (PT: 51%), with the occurrence of a defibrination syndrome, mild liver dysfunction. An abdominal ultrasound echogram revealed a tumour-like shadow in the gallbladder. Enhanced computed tomography showed an enlarged gallbladder associated with wall thickening and a diffuse papillary protrusion. Magnetic resonance disclosed a soft tissue mass with laminated streaks of fluid inside the gallbladder cavity. The patient received cholecystectomy and liver bed resection 10 days after admission. Liver metastases were detected (IV segment) and removed. The postoperative course was uneventful. The patient received further chemotherapy (octreotide) and remains free of disease 2 years after cholecystectomy. The resected gallbladder was dilated (cm. 7.5 x 3.5) and filled with thick adhesive mucus. The mucus was washed out: a 2 cm gallstone and a 4.5 x 4.0-cm yellowish polypoid indurated mass were found occupying the neck and body of the gallbladder. The cut surface of the tumour was glistening and solid, diffusely infiltrative. The gallbladder was examined on histology involving total segmentation at 5 mm. Tissue sections were fixed in 10% formalin, embedded in paraffin and cut into 4 µm sections and stained with haematoxylin-eosin. Sections parallel to those used for conventional histopathologic examination were stained and processed for automated immunohistochemistry using a standard avidin-biotin-peroxidase complex technique, performed with a Ventana BenchMark XT system (Ventana Medical System, Tucson, Arizona). The following primary antibodies were used: high molecular weight cytokeratin (clone 34betaE12, Ventana), neuron-specific enolase (NSE, clone BBS/NC/V1-H14, Ventana), synaptophysin (polyclonal 760-2668, Ventana), chromogranin A (CGA, MAB, Ventana, clone LK2H10), CD56 (clone 1B6, Ventana). Proliferative activity was determined by counting Ki-67/MIB-1 positive nuclei. Type 2 somatostatin receptors (sst2) were analyzed by means of a specific antibody (polyclonal 760-2667, Ventana) against a synthetic peptide corresponding to a sequence of the N-terminal portion of sst2. Appropriate positive and negative controls were introduced for each immunoperoxidase stain.

**Discussion**

The gallbladder tumour was histopathologically diagnosed as a MANEC. The two elements were distributed through the gallbladder wall, closely juxtaposed (Fig. 1), with no transitions between them in all areas and sharp-cut boundary. The mucinous adenocarcinoma was composed of poorly differentiated, scant, small irregular neoplastic cell clusters floating freely in slightly basophilic mucinous lakes. The LCNEC was characterized by large cells with prominent nucleoli, coarse chromatin and a high mitotic rate (about 40 mitotic figures were observed per 10 high-power fields, but without atypical forms). The cells showed an “organoid” growth pattern with rosette formation and frequent areas of necrosis (Fig. 2). There was evidence of regional lymph node (along the bile duct) metastasis and liver invasion displayed only by the LCNEC component (Fig. 3). According to the American Joint Committee on Cancer staging system, stage IVA (T4N1M0) disease was diagnosed. The tumour was surrounded by a dysplastic and metaplastic mucosa. The Ki-67 labeling indexes were approximately 60% and 80% for LCNEC and colloid carcinoma cells, respectively. Immunohistochemical examination of the LCNC cells revealed that pan-cytokeratin was diffusely positive and high molecular weight cytokeratin was completely nonre-
active, a staining pattern characteristic of neuroendocrine cells. Panendocrine markers were expressed in a variable proportion of tumour cells: NSE was focal (30%); synaptophysin, chromogranin A (Fig. 4) and CD56 (Fig. 5) stains were diffusely and strongly immunoreactive (> 80% of the tumour cells). Stains for somatostatin 2 were nonreactive. No immunoreactive cells for endocrine markers were observed in the pure mucinous portion. The origin of neuroendocrine tumours in the gallbladder is poorly understood 15. Neuroendocrine cells have been identified in the gallbladder, most commonly in association with foci of intestinal metaplasia 16. Neuroendocrine carcinomas are frequently combined with other histological carcinoma elements 17. In the gallbladder, many neuroendocrine carcinomas, excluding small cell carcinomas, have been described as carcinoids (well-differentiated endocrine tumours) or endocrine cell carcinomas (well-differentiated endocrine carcinomas) 18. Many previously reported cases of carcinoids of the gallbladder exhibited regional or distant metastases, suggesting their malignant nature 19 20. Sato et al. 21 have recently suggested that LCNEC is a new tumour classification with characteristic structure similar to that of carcinoids and endocrine cell carcinomas. The only difference between them is the mitotic figure count: LCNEC is defined as tumour presenting with > 20 mitotic figures per 10 high-power fields. A metaplastic event may be the initial step in the development of neuroendocrine tumours of the gallbladder. An alternative explanation is that neuroendocrine gene expression may be activated by divergent differentiation in a common precursor cell and may occur in isolation, yielding pure neuroendocrine tumours, or in combination with the expression of an exocrine phenotype, resulting in mixed adenocarcinoma – neuroendocrine carcinoma. The alternative hypothesis of coincidental neoplastic change in two different cell types (collision tumour) in adjacent areas cannot be excluded. This is the first report on the occurrence of a pure mucinous carcinoma associated with a LCNC in the gallbladder 22 23.
Tab. I. Publications describing an association of tumours in the gallbladder.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title and Subtitle</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Wada A et al.</td>
<td>Carcinoid tumour of the gallbladder associated with adenocarcinoma</td>
<td>Cancer 1983; 51: 1911-1917</td>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Fish DE et al.</td>
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<td>Histopathology 1990; 17: 471-472</td>
</tr>
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</tr>
</tbody>
</table>

References


Primary cutaneous cribriform carcinoma of the neck: a case report

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Key words
Primary cutaneous cribriform carcinoma • Adnexal tumour • Surgical excision • Neck

Summary
Primary cutaneous cribriform carcinoma is an unusual apocrine tumour that mainly occurs on the limbs of middle-aged females. We herein report a case of a 32-year-old woman who underwent surgical excision of a nodular lesion on her neck that had been present for 10 months. Histopathology showed a dermal tumour composed of interconnected aggregations of neoplastic cells and round spaces of various size and shape, resulting in a cribriform pattern. A diagnosis of cutaneous cribriform carcinoma was made. No peripheral lymphadenopathy was evident, and investigations for internal malignancies gave negative results. The patient was tumour-free 2 years after surgery. Although primary cutaneous cribriform carcinomas have up to now shown an indolent course, the number of reported cases is too limited for definitive prognostic conclusions. Therefore, surgical excision with clear margins and adequate follow-up are recommended.

Introduction
Primary cutaneous cribriform carcinoma (PCCC) is a rare and distinct variant of apocrine carcinoma, firstly described in the literature in 1998. Since then, a series of 26 cases and three additional case reports have been reported. The clinical aspect of PCCC is non-specific. The tumour can occur as a small nodule simulating a histiocytoma, epidermal cyst or even a basal cell carcinoma, with a predilection for the trunk and limbs in middle-aged females. The neoplasm generally discloses an indolent behaviour similar to basal cell carcinoma or other low-grade cutaneous carcinomas. We present an additional case of PCCC located on the neck of a 32-year-old woman. To our knowledge, this unusual location has been reported in only one other case.

Case report
A 32-year-old woman was examined for an asymptomatic nodular lesion on her neck, which had been present for approximately 10 months. Her past medical history was unremarkable. Clinical examination revealed a 1.0 cm roundish nodule, covered by normal appearing skin on the posterior aspect of the neck (Fig. 1). The clinical diagnosis of epidermal cyst was made, and local excision was performed. Histological examination revealed a non-encapsulated dermal nodule composed of tubular structures and solid interconnected aggregates of basophilic epithelial cells. Tumour nests were punctuated by small round spaces of various size and shape, arranged in a cribriform pattern (Fig. 2). The ductal formations were lined by cuboidal or cylindrical cells showing decapitation secretion (Fig. 3). Neoplastic cells had large, round, and occasionally pleomorphic nuclei. No mitoses, intra-vascular or perineural infiltration were observed. On immunohistochemistry, the tumour cells stained positively for AE1-AE3, cytokeratin 7, carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA), without any expression for cytokeratin 20 and S-100 protein (Fig. 4). These pathological features were in agreement with a diagnosis of cutaneous cribriform carcinoma. The surgical margins appeared uninvolved. No peripheral lymphadenopathy was apparent, and investigations for internal malignancies, including chest X-ray, sonography of the neck and parotid gland, and abdomen/pelvic computed tomography gave negative results. There was
no evidence for local recurrence or metastasis at 2 years after surgery.

Discussion

In 2009, Rutten et al. 2 reported the largest series of PCCC, focusing on the main clinicopathological and immunohistochemical characteristics and differential diagnosis of this unusual adnexal carcinoma. Microscopically, tumours were composed of dermal or dermal-hypodermal interconnected aggregations of neoplastic cells, dotted by small round spaces, resulting in a cribriform pattern. Cell aggregations, tubular structures and round spaces varied typically in size and shape in the entire neoplasm 2. The indolent biological behaviour of PCCC raised doubts about whether this tumour was a true carcinoma or an adenoma. Furthermore, the presence of variable cell nests, nuclear pleomorphism and hyperchromasia, occasional atypical mitotic figures, cell necrosis, and DNA aneuploidy in some of the observed cases supported a carcinomatous nature for this entity 2.

More recently, Kazarov et al. 7 expressed further considerations on the histology and differential diagnosis of PCCC. Since in certain tumours the solid component prevailed over the cribriform areas, these authors suggested that the term ‘solid cribriform carcinoma’ would be more suitable for this neoplasm. In addition, the presence of thin thread-like bridging strands into the luminal structures, as described in all adenomatoid tumours of the uro-genital tract, seemed to be another distinctive feature of PCCC 7. Moreover, the presence of focal aspects of decapitation secretion and small papillary projections of neoplastic cells in some tubular structures may favour an apocrine rather than an eccrine differentiation for this tumour 2.

Differential diagnosis of PCCC should mainly include adenoid cystic basal cell carcinoma (BCC), primary cutaneous adenoid cystic carcinoma (PCACC), and cutaneous metastasis from cribriform visceral carcinoma. Adenoid
cystic BCC may disclose a cribriform growth pattern and areas of cystic degeneration similar to PCCC. However, adenoid cystic features are generally expressed focally and in combination with typical solid basalioid areas. In addition, adenoid cystic BCC generally presents connections with the overlying epidermis or hair follicles.

PCACC is a rare adnexal skin tumour of uncertain origin, which arises predominantly on the face, head and neck of both males and females. Although this neoplasm is characterized by an indolent course with a reported overall 5-year survival rate of 96.1%, local recurrences are frequently observed (44% of cases). In addition, lymph node and pulmonary metastases have been rarely described in some of these patients. PCACC does not show a cribriform pattern on the entire neoplasm, and cell aggregates and spaces are rather uniform in size and shape. Moreover, deposits of basement membrane material, nuclear monomorphism, and perineural involvement are often reported.

Finally, it is imperative to rule out skin metastasis from other visceral malignancies with histological features of adenoid cystic carcinoma (i.e. from colon or salivary gland carcinomas). Cytokeratin 20 is generally expressed in neoplastic cells of cribriform carcinomas of the prostate and salivary glands. Our patient showed a CK7+/CK20- immunophenotype profile, and the existence of a concurrent cancer was excluded through extensive work-up.

Wide surgical excisions have been made in most patients with PCCC. Moreover, sentinel lymph node biopsy has also been performed in a patient with PCCC of the knee. Although these tumours have shown an indolent course, with no recurrences or metastases, the number of reported cases is still limited for definitive prognostic conclusions. Therefore, surgical excision with clear margins and adequate follow-up, as we performed in our patient, appear appropriate management options.

References


Combined uterine smooth muscle tumour: a challenging case

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Key words
Uterine smooth muscle tumors • Bizarre leiomyoma • STUMP

Summary
Uterine smooth muscle tumours that cannot be diagnosed unequivocally as benign or malignant should be termed ‘smooth muscle tumours of uncertain malignant potential’ (STUMP). Since there are no unequivocal morphological and ancillary criteria to differentiate this group of tumours, we present a case of a 49-year-old woman with a combined, benign and borderline lesion, which could have different clinical management strategies, and discuss the diagnostic issues.

Introduction
Smooth muscle tumours of uterine origin encompass a broad family of lesions: they are classifiable as benign or malignant using morphologic criteria such as nuclear atypia, coagulative tumour cell necrosis and mitotic activity. The World Health Organization classification indicates that a uterine smooth muscle tumour that cannot be diagnosed unequivocally as benign or malignant should be termed smooth muscle tumour of uncertain malignant potential (STUMP) 1. These STUMPs are a controversial entity and present serious diagnostic problems with unpredictable clinical behaviour. Obviously, it is important to differentiate these lesions from the more aggressive LMS, bizarre LM and sometimes cellular LM due to different management strategies and therapies. Since they share many clinical and pathologic features, ancillary studies such as immunohistochemistry with CD44, p16, p53 and Ki67 can be helpful, in addition to well established morphologic criteria. We present the case of a single leiomyoma in which two distinct subtypes coexist and discuss the role of immunohistochemistry in differential diagnosis.

Case report
A 49-year-old woman was admitted to the Gynaecological Department for intermenstrual bleeding. After radiological examination of the pelvic region, an intramural leiomyoma was found in the uterus. The patient underwent hysterectomy and the specimen was sent for histological examination. Grossly, the uterus measured 11 x 9 x 7.2 cm, and the cut surface showed a single intramural yellowish nodule deforming the organ profile. Multiple sections (Kempson recommends at least 10 sections or one section for each cm of diameter 2) were fixed in formalin, embedded in paraffin and stained with haematoxylin-eosin.
Microscopically, the nodule within the uterine wall was well circumscribed and composed of leiomyomatous cells and occasional bizarre elements with dysmorphic and hyperchromatic nuclei. An area of hyaline necrosis, in which there was a distinct zonal pattern reminiscent of an evolving infarct was present. Very rare mitoses were observed and no vascular invasion was seen. Moreover, within this nodule, we found an area of 0.7 cm in maximum diameter composed of multinucleated atypical...
elements with high mitotic activity: 10 mitotic figures (MFs) were counted in 10 high power field (HPF).

On the base of morphological criteria, the former nodule was classified as bizarre leiomyoma, but for a more precise characterization we performed immunohistochemistry: smooth muscle actin (SMA) was strongly positive in the main nodule with weaker colouration in the smaller area; CD44 and p16 showed a strong and diffuse pattern in both lesions, while p53, CD31, CKAE1-3 and S100 were all negative. MIB1 was differently expressed: < 5% in the nodule and > 30 % in the smaller area. A final diagnosis of a STUMP nodule within a bizarre leiomyoma was made and confirmed by another pathologist.

**Discussion**

Uterine smooth muscle tumours are classified according to their pathological features including architecture, growth pattern and cellular morphology. However, the distinction between different types of tumours may sometimes be problematic and challenging for pathologists and clinicians, especially for “borderline” tumours. In our case there was an admixture of two different lesions with different morphological and immunohistochemical features. As a result, additional characterization was necessary because the differentiation between benign and malignant smooth muscle tumours have obvious clinical implications.

The malignant form of smooth muscle neoplasia is uterine leiomyosarcoma (LMS) which has a propensity for local recurrence and metastasis; uterine leiomyoma (LM) is the most common benign smooth muscle tumour in women in a reproductive age.

STUMP is a smooth muscle tumour that cannot be classified as benign or malignant based on the usual and established histopathological criteria.

The main morphologic criteria upon which a tumour is classifiable as benign or malignant are:

- **Necrosis**: two pattern of necrosis have been identified: “Coagulative necrosis” in which there is an abrupt transition between necrotic and the viable cells. The typical appearance is that of a cuff of preserved tumour cells around large vessels surrounded by large expanses of necrotic tumour; pyknosis and karyorrhexis, features of death by apoptosis, are evident. Coagulative necrosis is currently regarded as the most important prognostic predictor in these tumours. “Hyaline necrosis” in which there is a distinct zonal pattern reminiscent of an evolving infarct: a necrotic centre in which nuclear debris is difficult to see, a periphery of granulation tissue and a layer of hyalinised collagen in between. The smooth muscle cells are replaced by collagen with a uniform, pale, eosinophilic, ground glass appearance. The blood vessels within an area of hyaline necrosis undergo the same changes, and can be seen as pale outlines, a point of distinction from the coagulative tumour cell necrosis where the vessels are often preserved (Fig. 1).

- **Mitotic activity**: number of mitotic figures / 10 high power fields (Fig. 2).

- **Atypia**: combination of marked differences in size and shape (pleomorphism) and nuclear hyperchromasia, evident at low power examination. It is classified as focal or extensive, and graded as mild, moderate or severe (Fig. 3).

Other factors to consider are cellularity (even if it is highly subjective) and the relationship of the tumour with surrounding myometrium (tumour borders); the grading system used for sarcomas of the somatic soft tissues is not applicable.

The current approach to diagnosis is derived by Stanford investigators: they delineated four histological subgroups of uterine smooth muscle tumours that had low or uncertain malignant potential:

1. “atypical leiomyoma with limited experience”, if the tumour shows focal or multifocal moderate-to-severe atypia, ≤ 10 MFs/10 HPF and no tumour cell necrosis;
2. “smooth muscle tumour with low malignant potential”, if the tumour shows tumour cell necrosis, but absent-to-mild atypia and < 10 MFs/10 HPF;
3. “atypical leiomyoma with low risk of recurrence”, if there was diffuse moderate-to-severe atypia, < 10 MFs/10 HPFs, and no tumour cell necrosis; and
4. “mitotically active leiomyoma with limited experience”, if the only worrisome feature is a mitotic count of ≥ 20/10 HPFs. If a tumour shows any unusual combinations of the 3 features that do not satisfy the Stanford criteria for LMS, a diagnosis of STUMP is appropriate.

Due to the overlapping features between malignant and benign smooth muscle tumours, efforts in searching for reliable biomarkers have been made: several studies have been conducted using immunohistochemical analyses with the result that a panel composed of p16, p53 and MIB-1 may help in making correct diagnosis. Our lesions were strongly and diffusely CD44 and p16 reactive, SMA positive, while p53, CD31, CKAE1-3 and S100 were negative. Only MIB1 was differently expressed: < 5% in the main nodule and > 30% in the smaller area. It is known that CD44 is present in normal myometrium and in LM, while LMS loses this cell adhesion molecule. Thus, according with this finding, we could exclude a LMS. In LMS, p16 was found to be more frequently and more strongly expressed than in STUMP and bizarre LM, and therefore a possible role in sarcomagenesis has been postulated. In one of the above-mentioned studies, p16 immunoreactivity in LMS was significantly higher than in LM and STUMPs. Unfortunately, both in the present and in a recent study, almost 50% cases of STUMP showed > 75% cells positive for p16 with diffuse and strong immunoreactivity. Due to a limited number of cases, it is difficult to draw conclusions regarding the p16 immunoprofile in STUMP. However, it suggests that in at least in 50% of cases STUMP is closely related to LMS based on the staining pattern of p16. It is conceivable that some tumours considered to be STUMPs are actually under-diagnosed LMS. Our case had strong and diffuse p16 reactivity that was not consistent with a benign lesion. Both mutation and overexpression of p53 have been described in uterine LMS. Although immunohistochemical overexpression of p53 protein was found in up to 70% of LMS, only 40% of LMS has detectable p53 missense mutation. The frequency of
p53 protein overexpression has been reported to range from approximately 30% to 66% in uterine LMS based on different cut-off points \(^{17,18}\). Chen et al. reported that 50% of STUMP and approximately 60% of bizarre LM showed overexpression of p53 protein, similar to the p16 immunoprofile: p16 and p53 were present in the majority of LMS, bizarre LM and cellular LM \(^9\). In contrast, the lack of both markers were seen in 86% of LM and cellular LM \(^9\). Eventually, the absence of p53 staining along with the presence of p16 suggested a borderline lesion.

MIB-1 is associated with cell proliferation and is found throughout the cell cycle of G1, S, G2, and M phases \(^{19}\). Several studies have found that uterine LMS had a significant higher MIB-1 index than benign smooth muscle neoplasms \(^{12,19}\). In contrast to previous reports, there is a large overlapping MIB-1 labelling index between bizarre LM and LMS, although a higher labelling index tends to be seen in LMS. Chen et al. reported that 83% of LMS had more than 10% of tumour cells labelled with MIB-1, compared to 48% of bizarre LM and 50% (1 of 2) of STUMP \(^9\). The different MIB1 expression in the two lesions, along with other data, suggested the possibility of a combined lesion. Ip et al. reported that the most important feature in distinguishing an atypical leiomyoma with low risk of recurrence (or STUMP) from a bizarre LM is mitotic count. The use of a marker to differentiate a true mitosis from degenerating nuclei undergoing apoptosis, which could mimic mitotic figure, may be helpful. On this purpose, studies on phosphohistone H3 have been conducted \(^{20}\).

In conclusion, there is difference for p16, p53 and MIB-1 expression among LMS, LM and cellular LM, but an overlapping staining distribution and staining intensity of these markers between LMS, STUMP and bizarre LM.

These criteria, along with morphological and immunohistochemical features, may be even more helpful in fragmented biopsy samples. In our case, we identified a proliferating nodule STUMP-like within a bizarre leiomyoma and attempted to correctly define both lesions since the first has uncertain behaviour, while the second is a benign tumour. To date, the patient, without further therapies, is in follow-up and free of disease.

Although for well established malignant neoplasia bilateral hysterectomy is standard treatment, for patient with a diagnosis of STUMP there are several proposed follow-up plans. For STUMPs diagnosed in myomectomy specimens, hysterectomy should be the treatment of choice for women who have no desire for childbearing, as recurrent uterine tumours have been reported. These patients should be followed-up postoperatively. For patients who have STUMP diagnosed in hysterectomy specimens, such as in the present case, follow-up should probably be a minimum of every 6 months until the 5th year and, thereafter, annual surveillance for a further 5 years \(^{14}\). If STUMPs recur, the treatment of choice is surgical excision followed by additional therapy such as pelvic irradiation, chemotherapy and medroxyprogesterone \(^{21}\).

**Conclusions**

We describe a case of a patient with the coexistence of a benign and borderline tumour within the same nodule and attempted to provide the optimal therapy and follow up. STUMP is a group of challenging smooth muscle neoplasms with unpredictable clinical behaviour, presenting a serious diagnostic problem, but luckily it is a rare entity. According to most authors, immunostaining alone does not allow absolute distinction between benign and malignant categories, which for now remains dependent on classic morphologic criteria. Obviously only the combination of clinical data, morphologic criteria and ancillary immunostaining will help the pathologist in achieving the correct diagnosis. However, complete and accurate sampling of specimens is required to avoid under- or over-diagnosis.
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Localized ileal giant pseudopolyposis in Crohn’s disease: a case report

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Key words
Giant pseudopolyposis • Crohn’s disease • Ileum • Inflammatory bowel disease

Summary
Localized giant pseudopolyposis is a rare complication in inflammatory bowel disease defined as a pseudopolyp (isolated or clustered) larger than 1.5 cm in size. Giant pseudopolyps are more commonly found in ulcerative colitis compared to Crohn’s disease and mainly involve the left colon. A 26-year-old male patient with a two-year history of Crohn’s disease was admitted with increasing abdominal pain, vomiting, anorexia, weight loss and fever. On physical examination, the abdomen was diffusely tender. Computed tomography showed diffuse irregular thickening of the ileal wall and stenosis of the terminal ileum. The patient underwent ileo-cecal resection with re-anastomosis. The ileal portion of the resected specimen harboured multiple finger-like pedunculated polyps, with the smallest measuring 0.5 cm and the largest measuring 1.8 cm. Histologically, the polyps were consistent with granulation tissue. No evidence of dysplasia or malignancy was found. The post-operative course was uneventful considering one month follow-up. This report illustrates an unusual case of giant pseudopolyposis involving the ileum in a patient with Crohn’s disease. The natural history of these lesions, as well as their optimal management, remain uncertain.

Introduction
Inflammatory pseudopolyps result from a regenerative and healing process that leaves inflamed mucosa in a polypoid configuration. They macroscopically appear as small lesions and very rarely appear as giant protruding masses larger than 1.5 cm that can be confused with a malignant lesion. Giant pseudopolyps associated with inflammatory bowel disease (IBD) is a rare presentation in both ulcerative colitis and Crohn’s disease with more than 75 cases reported in literature to date. Herein, we report a new case of localized giant pseudopolyposis within the stricture of the terminal ileum in a patient with a past medical history for Crohn’s disease. Our aim was to highlight the clinicopathological features of this rare lesion and review the current literature.

Case report
A 26-year-old male patient with a two-year history of Crohn’s disease was admitted with increasing abdominal pain, vomiting, anorexia, weight loss and fever within the context of altered general health. On physical examination, the abdomen was diffusely tender mainly in the right iliac fossa. Computed tomography demonstrated diffuse thickening of the ileal wall that was uniform and homogeneous in density (Fig. 1). Cir-
cumferential stenosis of the terminal ileum and multiple celio-mesenteric and ileo-cecal adenopathies were also identified. The patient underwent ileo-cecal resection with re-anastomosis. The surgical specimen contained a narrow ileal segment measuring 31 cm in length. On gross examination, areas of denuded mucosa surrounding multifocal islands of edematous mucosa were noted. There were multiple pedunculated polyps with the smallest measuring 0.5 and the largest measuring 1.8 cm (Fig. 2). Under microscopic examination, all of the sampled finger-like polyps were either composed of granulation tissue alone, partially covered by regenerating surface epithelium or showed ulceration with a cap of fibrin (Fig. 3). In the non-polypoid areas of the ileum, transmural inflammation with knife-like fissuring ulcerations, together with granulomas and giant cells typical of Crohn’s disease were present (Figs. 4, 5). No evidence of dysplasia or malignancy was found. The post-operative course was unremarkable after one month of follow-up.

**Discussion**

Formation of inflammatory polyps (pseudopolyps) is a recognized sequela of IBD and may involve the small bowel as well as the colon. Pseudopolyps are more commonly found in ulcerative colitis compared to Crohn’s disease. In the latter, the mucosal projections tend to be larger and less symmetric than those seen in ulcerative colitis. When a pseudopolyp is larger than 1.5 cm, which is rare, it is called a giant pseudopolyp, and these are subdivided as follows: 1) localized multiple pseudopolyposis, 2) localized giant pseudopolyposis, 3) generalized pseudopolyposis and 4) long finger-like pseudopolyps. The presence of pseudopolyps in itself does not reflect the severity of the underlying IBD and may be found in both active and quiescent phases of inflammatory bowel disease. Most reports cite the occurrence of giant pseudopolyps in the left side of the colon. Our case is unusual in that giant pseudopolyps involved the ileum. Giant pseudopolyps have no specific symp-
toms, but they may occasionally cause intussusceptions or luminal obstructions that require emergency surgical resection. In patients with a long history of IBD, giant pseudopolyps can be confused with a dysplasia-associated lesion or mass (DALM); in patients without a past history of IBD, they may also be mistaken for adenocarcinoma that requires surgery. However, carcinoma rarely occurs within the first 10 years of IBD, although patients with IBD are at an increased risk for developing dysplasia and carcinoma. Two previous reports demonstrated occult dysplasia arising in a giant pseudopolyp in Crohn’s colitis and malignancy in ulcerative colitis. It remains unclear whether specific factors such as patient age, size of the lesion or duration of disease render a localized giant pseudopolyp more likely to harbour dysplasia. The natural history of these lesions, as well as their optimal management, remain uncertain. Although data about the clinical course and medical therapy of giant pseudopolyposis is lacking, it has been reported that they rarely regress with medical management alone and sometimes require surgical or endoscopic resection. Surgical resection is inevitable when giant pseudopolyps present with obstructive symptoms as was the case in our patient. Follow-up endoscopic evaluation of giant pseudoploys should be considered because regression of these pseudopolyps might be expected and their presence is a potential risk for carcinoma in IBD.

In conclusion, this report illustrates an unusual case of localized ileal giant pseudopolyposis associated with Crohn’s disease that raised suspicion of malignancy. Clinically, endoscopically and radiologically, these masses have commonly been mistaken for neoplastic lesions. The dilemma resolves around confidently differentiating a giant pseudopolyp from DALM or polypoid carcinoma. Radiological investigations can define the location and extent, but not the nature, of these lesions. The literature on giant pseudopolyposis is relatively limited, and although the risk of malignancy is low, extensive sampling of giant pseudopolyps is highly recommended to exclude malignancy.

References

ZytoLight® SPEC ALK/EML4 TriCheck™ Probe Signal Interpretation Guide

An inv(2)(p21p23) is indicated when a green/orange fusion signal, specific for ALK, splits into separate green and orange signals and simultaneously the EML4 specific blue signal splits, resulting in an extra blue signal. The separate green and orange signals each co-localize with a blue signal.

BCR indicates the ALK and EML4 breakpoint cluster regions.

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ALK-EML4 Inversion
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