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Gestational diabetes insipidus: a morphological study of the placenta


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Key words
Gestational diabetes insipidus • Morphological study of placenta

Summary
Gestational diabetes insipidus (GDI) refers to the state of excessive water intake and hypotonic polyuria. Those cases manifesting in pregnancy and referred to as GDI may persist thereafter or may be a transient latent form that resolves after delivery. Microscopic examination of affected subjects has not been previously reported. In the literature, there are various case reports and case series on diabetes insipidus in pregnancy. In this study, we present a case that had transient diabetes insipidus during pregnancy in which the placenta was examined.

Introduction
Gestational diabetes insipidus (GDI) is a rare endocrinopathy complicating pregnancy with an incidence of approximately four in every 100,000 pregnancies. Polyuria, polydypsia, excessive thirst and dehydration are the main features of the disease. The aetiology is thought to depend on excessive vasopressinase activity, a placental enzyme that degrades arginine vasopressin (AVP), but not 1-deamino-8-d-arginine vasopressin (dDAVP), which is a synthetic form with a different N-terminal. GDI can be categorized into two groups depending on the response to arginine vasopressin (AVP) and dDAVP: vasopressin-resistant and dDAVP resistant (nephrogenic), and vasopressin and dDAVP-sensitive (central).

Although there is an increase in AVP levels in pregnancy to maintain sufficient antidiuretic activity, decreased renal effect due to its increased catabolism by placental vasopressinase may result in and is the main cause of GDI. Another factor contributing to the pathophysiology is transient liver dysfunction in which vasopressinase degradation in liver is decreased, explaining its association with acute fatty liver during pregnancy and HELLP syndrome. Microscopic examination of the placenta in affected subjected has not been previously reported. In the literature, there are various case reports and case series regarding diabetes insipidus in pregnancy. Herein, we present a case of transient diabetes insipidus in pregnancy in whom placental examination was performed.

Case report
A 36-year-old Caucasian patient was referred in the 33rd week of gestation with symptoms of polyuria, polydypsia, inability to tolerate oral intake, weight loss and fatigue that began in the third trimester and worsened with time. The prenatal course was uncomplicated until 30 weeks; after that time, urination and oral intake progressively increased to the degree that upon presentation, she could not tolerate a sufficient quantity of water to quench her thirst. Her past medical story was unremarkable. The women had 2 previous pregnancies: the first physiological, and the second was a twin pregnancy with foetal intrauterine death in the 20th week. The family history was unremarkable for endocrinopathies and liver disease. No therapy was given during pregnancy, and her symptoms resolved in the third week.

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of puerperium. Ultrasonography at 35th weeks of gestation showed a normal amniotic fluid index and foetal biometry. Physical and gynaecological examinations were unremarkable. Blood pressure was 105/75 mmHg and the pulse rate 90/min. The general condition of the patient was moderate, skin turgor was reduced and her mouth was completely dry. The patient was admitted to the hospital for further assessment. The therapy with dDAVP was begun. The planned caesarean section at 37 weeks of gestation was performed under combined spinal-epidural anaesthesia with oral dDAVP. A female foetus of 2,600 g was delivered after one minute the Apgar score of the fetus was 9. The postoperative course was uneventful. dDAVP treatment was continued until symptoms subsided.

After delivery, the placenta was evaluated macroscopically by the pathologist and then fixed in 10% buffered in formalin and embedded in paraffin. The placenta was 500 g with a placental weight index of 5.2 (foetal weight/placental weight), which is slightly less than normal (6.2). Macroscopic evaluation showed a placenta disc of cm 21 x 19 x 2.6. The umbilical cord inserted eccentrically into the placenta disc. The maternal surface of the placenta was dark red, shiny and coarsely folded into regular lobulations. The foetal surface of the chorionic plate was covered by glistening, transparent amnion. Membranes normally arise from the margin of the disc. Chorionic arteries and veins branched from the umbilical cord. There were three umbilical vessels. The funicle was 27 cm in length and 1.2 cm in diameter. Ten sections of placental tissue, 2 umbilical cord and 2 of the amniotic membrane were processed for microscopic examination after haematoxilin-eosin staining. Microscopic evaluation revealed both old and recent infarcts in 15% of the placenta (Fig. 1). Fibrinoid necrosis was detected in 10% of placent (Figs. 2, 3). Scattered areas of placental “Tenney-Parker” changes were present in 3 of the 10 sections (over 20%) (Fig. 4). Chorioamnionitis and umbilical cord alterations were absent.

**Discussion**

Gestational diabetes insipidus refers to the state of excessive water intake and hypotonic polyuria. Those manifesting in pregnancy and referred to as GDI may persist thereafter or may be a transient latent form that
resolves after delivery. It may be associated with pre-eclampsia, acute fatty liver during pregnancy or HELLP syndrome. There are no descriptions in literature of placental morphology in GDI, perhaps because of the rarity of the disease or to the delay in sample delivery to the pathologist. It is complex to understand the peculiar aspects of this pathology. The placenta examined was a placenta at 37 weeks, presenting focal areas suggesting advanced villous maturation, infarcts and fibrin deposits. These were frequent after 30 week or so, perhaps non-specific in a GDI placenta. The placental infarct was a localized region of villi ischemic necrosis, which is surrounded by coagulated blood. Small infarcts (less than 3 cm) are found in about one-fourth of placentas from uncomplicated pregnancies. Placenta infarcts occur when maternal blood flow through the spiral arteries is insufficient. A small infarct of less than 3 cm in diameter near the placental margin is a common occurrence, and as an isolated finding has no clinical significance. This alteration is often present in placenta after 35 weeks of pregnancy, and is thus not specific of this pathology. We consider placenta exam useful in GDI to determine if these findings are occasional or consistent with similar cases.

References

Simultaneous occurrence of primary diffuse large B-cell lymphoma and extranodal marginal zone (MALT) B-cell lymphoma in the gallbladder: a case report

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Key words
Gallbladder • MALT • Large B-cell lymphoma

Summary
Primary lymphoma of the gallbladder is extremely rare. We present an asymptomatic case of primary combined DLBCL – MALT lymphoma of the gallbladder in a 78-year-old man in whom definitive diagnosis was made with laparotomic cholecystectomy. Preoperative diagnosis was supported by NMR, CT and PET scans. The pathological report identified a polypoid lesion measuring 3.5 cm in diameter. A non-Hodgkin lymphoma with two different coexisting patterns was identified histologically: large diffuse B-cell lymphoma (DLBCL) associated with focal areas of extranodal marginal zone B-cell lymphoma (MALT-type) of the gallbladder. The postoperative course was uneventful and the patient is currently without clinical or radiological signs of disease. Chemotherapy was not indicated due to cardiopathy. In conclusion, a primary gallbladder lymphoma is a rare entity. Radiological findings may be helpful, but cholecystectomy may be necessary for definitive diagnosis. In this report, we describe the possible association between MALT and DLBCL of the gallbladder.

Introduction
Malignant lymphomas usually originate from lymph nodes, although 40% occur in extranodal tissues or organs. Almost all extranodal lymphomas originate from the gastrointestinal tract, and the gallbladder is rarely a primary site of malignant lymphoma. To date, less than 50 cases have been reported in the literature. At present, it is very difficult to differentiate this tumor from adenocarcinoma of the gallbladder. In fact, the presence of a 2-3 cm intramural gallbladder lesion with or without lithiasis, and the absence of regional lymphadenopathy, is often suspected for gallbladder cancer. While tumor markers may be helpful, they are often negative even in the presence of gallbladder carcinoma. There is no well-established method of preoperative diagnosis, and thus most cases reported have been diagnosed after surgery by pathologic examination. In this report, we present the radiological and pathological findings from a case of primary malignant lymphoma of the gallbladder.

Case report
We report an asymptomatic case of primary combined DLBCL – MALT lymphoma of the gallbladder in a 78-year-old man in whom definitive diagnosis was possible using laparotomic cholecystectomy. The patient, followed for rectocolitis, underwent abdominal ultrasonography in August 2008 which revealed a gallbladder lesion of 2 cm. Abdominal computed tomography (CT scan – Fig. 1) confirmed the presence of a 2-cm gallbladder polypoid lesion without signs of regional enlarged lymph nodes. Serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were normal. The patient presented a high operative risk due to severe cardiovascular disease, diabetes and hypertension and initially refused surgery. Two months later, the lesions was controlled by NMR, which revealed an increase in size (3 cm; Fig. 2) and mild splenomegaly. The patient gave consent for surgery, and tomoscintigraphy (PET) was performed before intervention. The PET scan showed pathological positivity (Fig. 3) only on the gallbladder lesion (3 cm). Preoperative blood workup showed reduction of leukocytes (2970/ml) and high level of β2 globulin, with other parameters within nor-

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Simultaneous occurrence of primary diffuse large B-cell lymphoma

Physical examination showed no abnormal findings. Serum levels of tumor markers were negative. Gallbladder carcinoma was suspected clinically, and in January 2009 the patient underwent laparotomic cholecystectomy. The results of intraoperative examination of frozen-sections led to a high suspicion of malignant lymphoma, and thus the surgery was not extended to liver resection.

The final diagnosis was large diffuse B-cell lymphoma (DLBCL) associated with focal areas of extranodal marginal zone MALT-type B-cell lymphoma of the gallbladder. Postoperative course was uneventful. On February 2009, the patient was submitted to a total body CT scan for re-staging. No signs of disease were detected. The oncologists decided to submit the patient to a VNCOP-B chemotherapy regimen based on the administration of vincristine, cyclophosphamide, rituximab, etoposide, and mitoxantrone. The treatment required steroid (methylprednisolone) administration (40 mg/day for 8 weeks) considering the histotype of the lymphoma. Three months after surgery the patient is alive without clinical or radiological signs of disease.

**Pathological findings**

A polypoid lesion measuring 3.5 cm in diameter was observed. The lesion was 1.5 cm from the margin of surgical resection, near the cystic duct. The cut-end was tumor free. A non-Hodgkin lymphoma with two different coexisting patterns was identified histologically: diffuse large B-cell lymphoma was the most represented neoplastic component (90%), while extranodal marginal zone MALT B-cell lymphoma was less prominent (10%).
Histologically, diffuse large B-cell lymphoma (Fig. 4) showed a diffuse growth pattern and was constituted mostly by large, pleomorphic and polylobated cells with more than one confluent nucleoli. Occasionally, the lymphoid blasts showed one central or eccentric nucleoli (immunoblasts and centroblasts). Concomitant foci of necrosis, apoptotic bodies and frequent mitoses were observed. The nuclei of the large cells were vesicular with finely spread chromatin. The cytoplasm was pale and not well defined. The neoplastic cells were positive for CD20 and bcl-6 and negative for CD5 and CD10 by immunohistochemical analysis. The proliferation fraction, as detected by Ki-67 staining, was high (70%).

The MALT-type lymphomatous cells (Fig. 5) were distributed around reactive B-cell follicles and invaded a marginal zone, external to a preserved follicle mantle, spreading out to form larger confluent areas. The characteristic marginal zone B-cells (CD20+) had small to medium-sized, slightly irregular nuclei with moderately dispersed chromatin and inconspicuous nucleoli, resembling those of centrocytes; they had relatively abundant, pale cytoplasm. The accumulation of paler staining cytoplasm led to a monocytoid appearance in some areas. Alternatively, the marginal zone cells more closely resembled small lymphocytes. Concomitant scattered immunoblasts and centroblast-like cells, epitheliod histiocytes and non-neoplastic mature plasma cells were detected. The neoplastic cells typically infiltrated the epithelium, forming lymphoepithelial lesions (Fig. 6).

Moreover, the neoplastic component expressed IgG and showed light chain restriction.

**Discussion**

Based on the recent World Health Organization (WHO) classification (2008)\(^1\), extranodal marginal zone MALT
B-cell and diffuse large B-cell represent the majority of primary gallbladder lymphomas. Only two cases of follicular lymphoma of the gallbladder have been reported. The literature suggests that the radiological features of gallbladder lymphoma depend upon their pathological classifications: high-grade lymphomas, such as diffuse large B cell type, tend to form a solid or polypoid mass in the gallbladder or have marked and irregular wall thickening, whereas most low-grade lymphomas, such as MALTomas or follicular lymphomas, show mild thickening of the gallbladder wall.

Initially, lymphoid tissue does not exist in the gallbladder, and it may be hypothesized that malignant lymphoma of the gallbladder is related to chronic inflammation, such as chronic cholecystitis associated with cholelithiasis. Some of the previously reported cases had gallstones. However, half of the reported cases had no signs of stones or inflammation.

Although in some issues it is reported that radiological findings may be helpful in the case of suspicion of gallbladder lymphoma, and sometimes a laparoscopic approach may be used for a definitive diagnosis, we strongly recommend a conventional approach to avoid the potential risk of tumor cell dissemination. We believe that preoperative diagnosis of primary gallbladder lymphoma is a genuine challenge, and in our case it was hypothesized that the patient was affected by a gallbladder carcinoma. Even if preoperative diagnosis of primary gallbladder lymphoma could be highly suspected, as reported in some pediatric cases (Gravel et al. reported a case of primary non-Hodgkin’s lymphoma of the extrahepatic biliary tract and gallbladder in a child), cholecistectomy would be indicated in order to obtain a final diagnosis. Therefore, taking into account the extreme rarity of this lesion, in our opinion all adult patients with gallbladder carcinoma should be treated surgically.

In conclusion, gallbladder lymphoma should be taken into consideration in the differential diagnosis of gallbladder tumors, especially when imaging findings and clinical presentation are not consistent with the typical signs of gallbladder carcinoma.

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**Tab. I.** Histological and radiological findings of primary malignant lymphoma of the gallbladder.

<table>
<thead>
<tr>
<th>N. of reported cases (Ref)</th>
<th>Year - Author</th>
<th>Age</th>
<th>Sex</th>
<th>Histology</th>
<th>Stone</th>
<th>Radiological findings of the gallbladder</th>
<th>Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 6</td>
<td>2001 Sato</td>
<td>67</td>
<td>F</td>
<td>Diffuse large B cell type</td>
<td>No</td>
<td>Mass forming</td>
<td>CT/US/ERC</td>
</tr>
<tr>
<td>2 7</td>
<td>2001 Tsuchiya</td>
<td>58</td>
<td>F</td>
<td>MALT-oma</td>
<td>No</td>
<td>Polypoid lesions</td>
<td>CT/US</td>
</tr>
<tr>
<td>3 4</td>
<td>2003 Yokoe</td>
<td>76</td>
<td>F</td>
<td>Diffuse large B cell type</td>
<td>Yes</td>
<td>Mass forming</td>
<td>CT/US</td>
</tr>
<tr>
<td>4 8</td>
<td>2003 Ferluga</td>
<td>63</td>
<td>F</td>
<td>Follicular lymphoma</td>
<td>No</td>
<td>Mass forming</td>
<td>US</td>
</tr>
<tr>
<td>5 9</td>
<td>2003 Yanagida</td>
<td>63</td>
<td>F</td>
<td>MALT-oma</td>
<td>Yes</td>
<td>Wall thickening</td>
<td>CT/US</td>
</tr>
<tr>
<td>6 10</td>
<td>2003 Rajesh</td>
<td>31</td>
<td>F</td>
<td>MALT-oma</td>
<td>No</td>
<td>Wall thickening</td>
<td>CT/US</td>
</tr>
<tr>
<td>7 11</td>
<td>2004 Jelic</td>
<td>70</td>
<td>F</td>
<td>Follicular lymphoma</td>
<td>Yes</td>
<td>Wall thickening</td>
<td>ERC</td>
</tr>
<tr>
<td>8 12</td>
<td>2004 Takano</td>
<td>91</td>
<td>F</td>
<td>MALT-oma</td>
<td>Yes</td>
<td>Wall thickening</td>
<td>CT/MRI/US/ERC</td>
</tr>
<tr>
<td>9 5</td>
<td>2005 Yamamoto</td>
<td>1</td>
<td>M</td>
<td>Diffuse large B cell type</td>
<td>No</td>
<td>Mass forming</td>
<td>CT/MRI/US</td>
</tr>
<tr>
<td>10 2</td>
<td>2009 Ono</td>
<td>78</td>
<td>M</td>
<td>MALT - Diffuse large B cell type</td>
<td>No</td>
<td>Wall thickening</td>
<td>CT/MRI/US</td>
</tr>
</tbody>
</table>

Present report | / | 79 | M | MALT - Diffuse large B cell type | No | Polypoid lesion | CT/MRI/US/PET |

MALT: mucosa-associated lymphoid tissue; US, ultrasound; ERC, endoscopic retrograde cholangiography; MRI: magnetic resonance; CT; computed tomography.
References

Case report

Congenital tracheal atresia in newborn: case report and review of the literature

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Key words

Tracheal atresia • Congenital malformation • Tracheal agenesis

Summary

Tracheal atresia is an uncommon congenital malformation with a high mortality rate. Clinical symptoms occur suddenly after birth. The diagnosis is suspected in any infant in whom improved ventilation is obtained despite aggressive attempts at resuscitation. We describe a small gestational week 34 male newborn affected by tracheal atresia without esophageal fistula with associated fetal growth restriction, ascites and polyhydramnios. Post mortem examination revealed a diffuse cyanotic status, abdominal ascites and a low birth weight. A 3 cm tract of trachea was documented that distantly ended in a blind pouch and without tracheoesophageal fistulae and enlarged bulky lungs connected to each other by a common thin-walled bronchus. Histological examination showed a normal conformed larynx and scratchily cartilaginous disks in the proximal tract of the short trachea. Vascular space referred to small arteries and veins, thin bands of fibrous tissue and adipose tissue were detected under the blind pouch. Lung distal airspaces were lined by premature cubic epithelium separated by a broad poorly vascularized interstitium. A striking interstitial and alveolar edema was remarkable.

Background

Tracheal atresia (TA) is an uncommon congenital malformation with a high mortality rate. The first case was described by Payne in 1900, and about 100 cases have been reported in the literature. Its incidence is about 1:50,000 with a male predominance, and the recurrence risk for siblings is 1%. Clinical symptoms occur suddenly after delivery and include aphonia, cyanosis, neonatal respiratory distress and difficulty during endotracheal respiration support. Prenatal ultrasonographic examination may be useful for diagnosis. It may be associated with altered amniotic fluid status such as oligohydramnios or polyhydramnios. Although the majority of TA are related with tracheoesophageal fistula or bronchoesophageal fistula, isolated forms have also been reported.

Case report

The autopsy of a 34 week gestational male (46 XY-caryotype) newborn by preterm vaginal labour complicated by polyhydramnios was performed in the Institute of Anatomia Patologica of Modena. The mother was a 38-year-old Nigerian woman, gravida 1, para 0 with no history of diabetes, hypertension, infection or toxemia. The pregnancy had been uneventful until the 34th week of gestation when the woman was referred to our diagnostic centre for acute vaginal bleeding. Urgent ultrasonographic examination revealed polyhydramnios, intrauterine fetal growth restriction (IUGR) and fetal abdominal ascites. A meticulous ultrasonic morphological evaluation of the fetus revealed a normally positioned short trachea interrupted for a few cm over a dilated unique bronchus connecting enlarged hyperechogenic lungs (images not available) leading to the suspect of tracheal malformation. Previously ultrasound records relative to the status of the fetus were not available. At delivery, the infant showed absence of cry and independent breath, diffuse cyanoses, a hypo-expanded thorax and abdominal distension. The infant was shifted to the neonatal intensive care unit where, despite aggressive attempts at resuscitation, he died 1 hour and 26 minutes after birth.

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A post-mortem examination was performed with parental consensus and revealed diffuse cyanotic status, abdominal ascites and a low birth weight (LBW) of 1510 gm (theoretic weight, 1905 gm; data from Handbook of Paediatric Autopsy Pathology Enid Gilbert-Barness, Diane E. Debich-Spicer, John M. Opitz, 2004 Humana Press). Auxologic parameters obtained from the post-mortem examination were: 29 cm, crown to rump length; 36 cm, crown to heel length; 29.4 cm, head circumference; 27 cm, thorax circumference; 29 cm, abdominal circumference; 4.8 cm, foot length; and 2.7 cm, hand length. A tract of 3 cm of trachea distantly ending in a blind pouch and without tracheoesophageal fistulae (Fig. 1A) and enlarged bulky lungs connected to each other by a common thin-walled bronchus were documented (Fig. 1B). A diagnosis of tracheal atresia was made. No other congenital malformations were detected, and a normal vascularized umbilical cord was observed. Consecutively, 0.3 cm serial sections from the larynx to the dilated unique bronchus were taken. Histological examination showed a normal conformed larynx and scratchily cartilaginous disks only in the proximal tract of the short trachea (Figs. 1C and 1D). Vascular space referred to small arteries and veins, thin bands of fibrous tissue and adipose tissue were detected under the blind pouch (Fig.1D). The esophagus and the larynx were well developed. Histologically, the lung distal airspaces were lined by premature cubic epithelium separated by a broad, poorly vascularized interstitium. A striking interstitial and alveolar edema was remarkable. The placenta was unremarkable.

Discussion

Tracheal atresia (TA) is a rare anomaly that includes varying manifestations of tracheal malformation. Respiratory distress at birth with absence of audible cry, cyanosis and the impossibility of tracheal intubation are the main clinical presentations. Although emergency tracheotomy in delivery room and different attempts of resuscitation can be applied, the mortality rate of TA remains high. Few long-term survivors with surgically reconstructed TA have been reported. The etiology remains unknown and it is likely to be multifactorial. External factors may be implicated in the development of this malformation, such as pathogenic mechanisms causing early distruption of blastogenesis disruption. Experimental studies using mouse models have shown that genes in the Hoxb cluster have an important role during tracheal and esophageal development. In particular, mutations in candidate genes as Sonic hedgehog (Shh), Gli2 and 3, and thyroid transcription factor-1 (TTFI) seem to be involved in its pathogenesis. A variety of congenital anomalies can be found associated with 50% of TA, including cardiovascular, gastrointestinal and genitourinary tract malformations. A case of TA in a patient delivered with mosaIC Turner’s Syndrome was reported by Hirakawa.

Concomitant laryngeal abnormalities and defects of umbilical vessels have also been observed. Even if the inclusion of TA in the presenting malformation of VACTERL associations (vertebral defects, anal atresia, cardiac anomalies, tracheo-esophageal fistula, renal anomalies and limb defects) or TACRD association (laryngeal atresia, complex cardiac abnormalities or ventricular septal defect, radial ray defects and duodenal atresia) is controversial, it has been suggested that about 34% of TA may be considered as a component of these complex anomalies. Morphologically, different classifications of TA have been proposed (see Tab. 1). Floyd et al identified three types of tracheal agenesis based on the development of distal tracheobronchus and its esophageal connection. The Type 1, arising about 10% of cases, consists of a short distal segment of trachea containing a normal carina and communicating with the esophagus through a tracheoesophageal fistula. Type 2 (nearly 59%) represents the most common form of tracheal agenesis and describes the complete agenesis of the trachea with two normal bronchi fused together in the midline of the carina. Type 2 is the only form that can occur without esophageal fistula. Complete tracheal agenesis and two independent bronchi connected separately with the esophagus characterize Type 3.

Faro et al. proposed an alternative practical application in surgical rehearsal. The author divided TA into seven categories representing various types of airway anomalies decreasing in severity and in which the category termed “A” represents the total pulmonary atresia. The last category, referred to as “G”, represents a tracheal stenosis. This system takes into consideration cases of total tracheopulmonary agenesis in addition to forms without esophageal communication. In particular, type F represents a blind bronchial bifurcation with no esophageal fistula and type G includes a short segment of TA with no esophageal communication. The case that we studied is unusual and concerns an incomplete segment of trachea ending in blind pouch with the absence of a tracheoesophageal connection. These findings meet the morphological criteria attributed by Faro to TA-type G. Only a few cases of isolated TA without tracheoesophageal fistula have been described. In a review of 47 cases published in the English literature from 1900 to 1989, Diaz et al. selected only 2 cases of TA without esophageal fistula, while only 1 of the 32 cases reviewed by Bray and Lamb had an isolated TA. Van Veenendaal et al. found the absence of tracheoesophageal fistula in about 6% of an heterogeneous group of tracheal anomalies including 82 cases of tracheal agenesis and 7 cases of tracheal atresia. Thoracic anomalies including distended chest circumference or hypoexpanded thorax and pulmonary malformations, represented by enlarged lungs and incomplete lobulation, were reported to be associated with TA, many of which are detectable during prenatal sonography or MRI imaging. Hyperechoic pulmonary and echogenic areas in the chest profile described in fetuses affected by TA can be distinguished by cystic adenomatoid malformations, se-
Fig. 1. An interrupted tract of trachea ending in a blind pouch and disconnected to the esophagus (1A). The bulky lungs are connected to each other by a common dilated bronchus (1B). Scratchily incomplete cartilaginous disks constitute the short trachea (1C-1E). Small arteries and veins and thin bands of fibrous tissue and adipose tissue were detected under the blind pouch (1F). Hematoxylin and eosin staining, (x10).
questration of the lung, pulmonary lymphangectasis and congenital lobar emphysema. Pulmonary distension can be explained by the accumulation of the fluid secreted by the lungs during fetal life that cannot be expelled because of tracheal and larynx obstruction or atrophy. Mori et al. using immunohistochemical methods (antibodies directed to surfactant proteins) and electron microscopy to evaluate the maturation of pulmonary epithelial cells in hyperplastic lungs and concluded that the differentiation of pulmonary epithelial cells appeared to be more advanced depending on the gestational age. In fetuses affected by TA, additional clinical findings include oligohydramnios and most frequently polyhydramnios and frequently polyhydramnios. Polyhydramnios has been explained as a result of obstruction of the esophageal passage of amniotic fluid by enlarged lungs or compression of the stomach and intestine by abdominal ascitic fluid. Low creatine levels and low lecithin-sphingomyelin ratio in the amniotic fluid have been suggested as possible prenatal markers of tracheal agenesis.

Abdominal ascites have been reported in association with TA and can be explained by the expanding lungs that should cause inversion of the diaphragm and compression of the heart with a consecutive impairment of venous return to the right atrium, resulting in low output congestive heart failure.

Fetal prematurity, including IUGR status suspected at prenatal sonography, have been reported in TA. In the present case, urgent prenatal ultrasonographic examination showed moderate polyhydramnios, uniform hyper-echogenic thorax with expanded lungs, fetal abdominal ascites, and intra-uterine fetal growth restriction (IUGR). A relationship between congenital malformations and IUGR has been largely demonstrated. We interpreted IUGR as probably consequent to the obstruction of the airways, possibly due to inadequate lung development. Additional investigations should be performed to better understand the mechanisms of such an association. Post mortem examination remains an important procedure to morphologically describe these rare anomalies.

**References**


CASE REPORT

Metastasis of high grade renal cell carcinoma, clear cell type, in fibrous dysplasia with superimposed giant cell reparative granuloma

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Key words
Fibrous dysplasia • Giant cell granuloma • Long bones • Metastasis

Summary
A case of monostotic fibrous dysplasia in a 54-year-old male complaining of severe pain in the right hip is presented. Imaging findings demonstrated an extremely aggressive lesion involving bones, liver, lungs, and lymph nodes, and suggested the possibility of sarcomatous transformation. Histological examination established a diagnosis of metastatic high-grade renal carcinoma, clear cell type, and demonstrated the presence of superimposed giant cell reparative granuloma. This latter is a rare example of giant cell reparative granuloma arising in a long bone and in association with fibrous dysplasia. The clinical, radiographic, and histopathologic features of fibrous dysplasia and giant cell reparative granuloma are discussed.

Introduction
Fibrous dysplasia is a dysplastic disorder of bone characterized by solitary or multifocal polyostotic intramedullary lesions composed of proliferations of fibroblast-like spindle cells in which trabeculae of immature woven bone, typically not bordered by palisading osteoblasts, may be present. Fibrous dysplasia may undergo, although very infrequently, malignant transformation.

Giant cell reparative granuloma is an uncommon benign reactive lesion with a predilection for the craniofacial bones, characterized by a prominent fibroblastic stroma containing giant cells, often centred around zones of stromal hemorrhage. It may develop in normal bone or in pre-existing lesions, such as fibrous dysplasia, hyperparathyroid bone disease, or Paget’s disease in rare instances.

This report presents a case of monostotic fibrous dysplasia in which imaging findings were suggestive of the development of secondary sarcoma. Histological examination established a diagnosis of metastatic renal cell carcinoma, and demonstrated the presence of superimposed giant cell reparative granuloma. It is a unique example of giant cell reparative granuloma arising in the pelvis and in association with fibrous dysplasia.

Case report
A 54-year-old male presented to the emergency room complaining of a severe pain in the right hip. He had a medical history significant for a monostotic fibrous dysplasia of the right iliac wing. Initial physical examination revealed sciatic nerve compression and a mass within the right quadriceps muscle. Laboratory findings were within normal limits. CT of the pelvis showed an expansile osteolytic lesion in the right iliac wing, at the site of the pre-existing fibrous dysplasia. In comparison to the preceding examination, the mass appeared enlarged (13 cm in diameter versus 10 cm), with resorption of the perilesional sclerotic rim, and extended upwards in the retroperitoneum (Fig. 1). Segmental polyphasic and whole-body bone scintiscan showed an area of enhanced radiotracer uptake in the medial ileal region that delimited a broad area of decreased uptake occupying the central and lateral ileal regions and a large portion of the neighbouring soft tissues, suggesting a malignant neoplastic process. There were also focal areas of increased radionuclide uptake in the middle third of the diaphysis and in the medial condyle of the right femur, and in the 8th rib. CT of the diaphyseal lesion identified a neoplastic process of 10x6 cm that eroded the bone and displaced the femoral vessels. Total-body CT revealed the presence of about 10 solid lesions in the lungs, neo-
plastic replacement of the left kidney with thrombosis of the renal vein, multiple lesions in the perirenal fat, enlargement of the para-aortic lymph nodes, and about 10 solid lesions in the liver. Suspecting a sarcomatous transformation of fibrous dysplasia, surgical exploration of the iliac lesion was performed. Grossly, the biopsy specimen was composed of several fragments of firm gray-brown tissue. Microscopic examination showed areas typical of fibrous dysplasia with irregularly shaped trabeculae of woven bone lacking osteoblastic rimming in a background of moderately cellular fibrous tissue (Fig. 2). They merged in areas in which numerous multinucleated giant cells were lying in a cellular fibroblastic stroma, with foci of extravasated erythrocytes and granules of hemosiderin pigment (Fig. 3). The giant cells were both scattered throughout the lesion and arranged in focal aggregates, especially along the surface of the trabeculae, which showed signs of resorption (Fig. 4). This tissue was extensively infiltrated by solid sheets of large neoplastic cells with clear cytoplasm surrounded by a distinct cell membrane, and highly pleomorphic nuclei with prominent nucleoli (Fig. 5). Immunohistochemical examination showed co-expression of cytokeratins 8, 18 and 19 (CAM 5.2 antibody) and vimentin, positivity for RCC and negativity for cytokeratin 7 and cytokeratin 20. After consultation with the radiologist, the pathologic diagnosis of metastasis of renal cell carcinoma, clear cell type, in fibrous dysplasia with superimposed giant cell reparative granuloma was established.

An explorative laparotomy was performed, but the neoplastic left kidney was adhered to the descending mesocolon and was not excisable without carrying out a left hemicolectomy. Consequently, in consideration of the advanced stage of the disease, the procedure was suspended. The patient died 4 months later.

Discussion

In the present case, imaging findings demonstrated an extremely aggressive lesion and suggested the possibility of malignant transformation of fibrous dysplasia. Fibrous dysplasia is a common fibro-osseous lesion in which a fibrovascular matrix containing variable amounts of mineralized material replaces the normal bone. Hamartomatous proliferation and localized failure of bone to mature from the woven to the lamellar form may account for fibrous dysplasia. Most cases involve a single bone, but about 20 percent of patients have polyostotic involvement, often with extraskeletal abnormalities. The disease usually becomes manifest during the first three decades of life. It may be asymptomatic, and discovered incidentally on radiographs obtained for other reasons. The most common clinical symptoms are swelling or deformity of the affected site, and pathologic fracture. Most fibrous dysplasias cease to be active after puberty, although a few cases first present later in life, and some lesions are reactivated with pregnancy. In the monocentric form, the most frequent sites of involvement are the ribs, craniofacial bones, proximal femur, and tibia. In patients with polyostotic disease, the lower extremities and pelvis are involved in 75-90% of cases. Small bones of the feet may also be involved, as well as the ribs and skull. Fibrous dysplasia produces widely variable radiographic images, often with a so-called ground glass appearance. The lesion may be sharply defined with a sclerotic rim, or lack perilesional sclerosis and fade into the adjacent normal bone. The affected bone may be expanded with cortical thinning. Histologically, fibrous dysplasia appears as irregularly shaped trabeculae of woven bone devoid of rimming osteoblasts, in a background of moderately cellular fibrous tissue. There is a large variability in the number and distribution of bone trabeculae and their level of maturation. Microscopic foci of cartilaginous differentiation are frequently present. The fibro-osseous tissue infiltrates between trabeculae of normal bone.
at the periphery of the lesion, leading to a mixture of reactive bone with prominent osteoblastic rimming and typical fibrous dysplasia. Secondary changes include hemorrhage with fibrohistiocytic reaction, myxoid or cystic change of stromal tissue, and secondary aneurysmal bone cyst. Differential diagnosis of fibrous dysplasia includes osteofibrous dysplasia, well-differentiated intraosseous osteosarcoma, and desmoplastic fibroma. The management of the disease is complex, depending on the bone(s) involved, symptoms, extent of disease, and age of the patient. Recurrence following curettage or marginal resection is common since fibrous dysplasia extends between trabeculae of normal bone at the periphery of the lesion, and such extensions may not be clinically recognized. The development of secondary sarcoma in fibrous dysplasia is an extremely rare but well-established event. It occurs in less than 1% of long-standing lesions, especially if treated with radiation therapy. The most frequent is osteosarcoma, followed by fibrosarcoma and chondrosarcoma.

In the case presented, the histological features of the pelvic lesion were not consistent with a sarcomatous transformation of fibrous dysplasia. The large neoplastic cells with clear cytoplasm, and highly pleomorphic nuclei with prominent nucleoli, were somewhat reminiscent of a renal cell carcinoma. Imaging findings were consistent with this diagnostic hypothesis. Immunohistochemical examination, demonstrating the co-expression of low molecular weight cytokeratins and vimentin and the expression of the renal cell marker RCC by neoplastic cells, allowed confirmation of the diagnosis of high-grade renal cell carcinoma, clear cell type, with metastases to bones, liver, lungs, and lymph nodes.

In the medical literature, there are only few reported cases of malignant neoplasms arising in patients with fibrous dysplasia, in particular breast and thyroid carcinomas. These reports are focused on the different diagnosis between fibrous dysplasia and bone metastases, and a possible correlation between the two lesions is not taken into consideration. Renal cell carcinoma in fibrous dysplasia has never been described but, to our knowledge, there are no reasons to hypothesize a pathogenetic link in this case, and the lesions can be considered as merely collision lesions.

A further component of the lesion was giant cell reparative granuloma. Giant cell reparative granuloma is a benign intraosseous proliferation characterized by granuloma-like aggregates of giant cells in a background of fibrovascular stroma. It has been suggested that it could be a reaction to some form of hemodynamic disturbance in bone marrow, perhaps associated with trauma or hemorrhage. The peak age of incidence of giant cell reparative granuloma is in the second decade of life. Radiological examination usually shows a radiolucent lesion with occasional fine to coarse trabeculations. It has distinct borders with minimal reactive sclerosis. The contour of bone can be expanded with markedly thinned but usually intact cortex and no periosteal reaction. Histologically, giant cell reparative granuloma is composed
of a prominent, fibroblastic stroma containing multinucleated giant cells. In some areas, the giant cells may be more diffusely distributed, but focal aggregates are usually present. They are particularly evident in zones of stromal hemorrhage, and some contain phagocytized blood cells and hemosiderin. The stromal fibroblasts vary in appearance from spindle to ovoid and form both hypercellular zones and zones of prominent collagenization with few cells. Usually, there are few monocellular inflammatory cells and trabeculae of reactive osteoid and bone. In nearly 30% of giant cell reparative granulomas, foci of aneurymsmal bone cyst are present. Differential diagnosis comprises “brown tumor” of hyperparathyroidism, giant cell tumor, aneurysmal bone cyst, non-ossifying fibroma. Giant cell reparative granuloma usually occurs in the craniofacial bones, such as the mandible and maxilla. A second common location is in the small bones of the hands and feet. It is extremely rare in the long tubular bones and vertebrae. Isolated cases have also been reported in flat bones such as the pelvis. Giant cell reparative granuloma generally develops in normal bone, but has also been described as a secondary lesion in patients with hyperparathyroid bone disease, Paget’s disease or, as in our case, fibrous dysplasia. In fibrous dysplasia, multinucleated giant cells, presumably functioning as osteoclasts, are present focally along the surface of trabeculae. Occasionally, intralesional hemorrhage can provoke extensive giant cell reaction, in a pattern reminiscent of giant cell reparative granuloma. Nevertheless, although the association between fibrous dysplasia and giant cell reparative granuloma is usually taken for granted, only two cases have been previously reported in the literature. The first occurred in the upper end of the left femur, mimicking a neoplastic lesion, while the second arose in the body of the right mandible.

In summary, we report a case of monostotic fibrous dysplasia in which imaging findings were suggestive of the possibility of malignant transformation. Histological examination established a diagnosis of metastasis of renal cell carcinoma, clear cell type, in fibrous dysplasia with superimposed giant cell reparative granuloma. To the best of our knowledge, this is the third reported case of giant cell reparative granuloma arising in fibrous dysplasia, and it is unique since it developed in an uncommon location such as the pelvis.

References

A rare case of primitive neuroectodermal tumor in the soft tissues of the hand

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Key words
Primitive neuroectodermal tumor (PNET) • Hand soft tissues • 11;22 (q24;q12) translocation

Summary
Primitive neuroectodermal tumors of the hand are extremely rare, and only 5 cases have been described to date. Here, we report a case of a 35 year-old male who presented a progressive swelling on the palm of his right hand. Clinical examination showed a solid mass and X-ray revealed a soft tissue mass. Magnetic resonance imaging (MRI) revealed infiltrated interosseous muscles, metacarpal bones and tendons. The patient underwent surgery and the lesion was removed. On the basis of morphological, immunohistochemical and molecular biology findings, a diagnosis of primitive neuroectodermal tumor was made.

Introduction
Following the first reports of peripheral neuroectodermal tumors (PNET) as tumors of the nerves (peripheral neuroepitheliomas, Askin tumors, adult neuroblastomas, peripheral neuroblastomas), many decades passed before they were described as possibly arising in soft tissues independently of nerves, and that their cell of origin is in the primitive neural crest. They are now defined as peripheral primitive neuroectodermal tumors (pPNETS), and may occur at various sites, including the nervous system, visceral sites, soft tissues and bone. Based on histology and immunohistochemistry, PNETS share the same chromosomal translocations (11;22) and (21;22) are now classified in the same group as Ewing’s sarcoma (ES) of bone and soft tissues, under the family ES/PNET. However, while Ewing’s sarcoma tends to be poorly differentiated, PNET often show definite neuroectodermal differentiation. The family of tumors has a peak of incidence in the second decade of life, with a slight prevalence in males. Very few cases have been described of ES/PNET originating in the hand. Here, we report a new case of PNET in the palm of the hand.

Case report
A 35-year-old male presented with a rapidly progressive swelling on the palm of his right hand. It was a tender, slightly movable and moderately painful mass 2x1 cm in size, and not associated with lymphadenopathy. There was no previous trauma. Standard radiographs revealed a mass in the soft tissues, which by MRI was found to infiltrate the interosseous muscles and tendons, and the second, third and fourth metacarpal bones, showing osteolytic activity. A whole body computed tomogram (CT) scan did not detect any metastases. The patient underwent surgical intervention to remove the tumor. The mass was brown, hard, encircled by a dense rim of fibrous tissue, with nodular protrusions on the external surface. It invaded the intraosseous spaces, muscles and metacarpal bones. On the basis of morphological, immunohistochemical and molecular biology findings, a diagnosis of peripheral primitive neuroectodermal tumor (ES/PNET) with desmoplasia was made.

Materials and methods
Representative samples of the surgical material were fixed in 10% buffered formalin and embedded in paraffin according to standard procedures. Tissue

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sections (4 mm thick) were cut and stained with hematoxylin/eosin. Immunohistochemical stains were performed on additional sections of each block employing the Ultravision Detection System anti-polyspecific HRP (LabVision, Fremont, CA, U.S.A.; Bio-Optica) and using diaminobenzidine (DAB; Dako) as a chromogen. After being dewaxed and rehydrated, sections were incubated with 3% H2O2 in TBS (Tris-buffered saline), unmasked with Wcap buffer at pH 6.0 (for 40' at 98°C; Bio-Optica, Milan, Italy) and incubated with antibodies for synaptophysin (clone SY38 (1); dilution 1:100, Dako, Milan, Italy), WT-1 (clone 6E-H2; dilution 1:200; Dako, Milan, Italy), Vimentin (clone V9; dilution 1:200; Dako, Milan, Italy), myogenin (clone F5D; dilution 1:50, Bio-Optica, Milan, Italy), high molecular weight cytokeratins (HMWC) (clone 34βE12; dilution 1:300, Menarini, Florence, Italy), NB84 (clone NB84a; dilution 1:50; Novocastra, Newcastle upon Tyne, UK), and Ki-67 (clone SP6, dilution 1:200; NeoMarkers, Fremont, CA, USA). Some sections were directly incubated with anti-CD 99 (clone HBA-71; dilution 1:40; Dako, Milan, Italy), anti-EMA (clone E29; dilution 1:400; Dako, Milan, Italy), anti-NSE (clone BBS/NCVI-H14 (1); dilution 1:100; Dako, Milan, Italy), anti-LCA (clone 2B11; dilution 1:300; Dako, Milan, Italy), anti-S-100 (polyclonal; dilution 1:300; Dako, Milan, Italy), anti-neurofilaments (clone 2F11; dilution 1:200; Dako, Milan, Italy), anti-smooth-muscle actin (clone 5C5.F8.C7; dilution 1:300; Bio-Optica, Milan, Italy), anti-desmin (clone D33; dilution 1:200; Dako, Milan, Italy). Another section was pre-treated in the microwave for 5 min at 700 watts, and incubated with anti-chromogranin (clone PHE5; dilution 1:200; Dako, Milan, Italy). Negative controls were obtained by replacing the specific antibody with non-immune serum immunoglobulins at the same concentration as the primary antibody. Sections were then counterstained with Harris hematoxylin, dehydrated in alcohol, cleared in xylene and cover-slipped.

Cell proliferation was assessed by counting the percentage of Ki-67-positive tumor cell nuclei of total tumor cell nuclei in at least 10 high power (x400) fields. Fluorescence in situ hybridization (FISH) was performed on sections from formalin-fixed, paraffin-embedded samples, using two oligonucleotide probes for the EWSR1 gene breakpoint (Vysis EWSR Break Apart FISH Probe Kit; Abbot, IL, USA).

**Results**

The pathological specimen consisted of a brownish hard mass, with irregular surface, measuring 2x1x1 cm. Serial sections were cut perpendicularly to the longitudinal axis.

Histological examination demonstrated a lobular and trabecular growth pattern, with a well developed vascular network. Cell aggregates were occasionally separated by dense fibrous tissue. The vast majority of neoplastic cells were small, with round or ovoid nuclei, finely distributed chromatin and small nucleoli, and scanty cytoplasm (Fig. 1). A few areas were populated by larger cells with coarser nuclear chromatin, more evident nucleoli, and more abundant eosinophilic cytoplasm. Cells encircled vessels in a pseudorosette fashion in some of the latter areas, although no true rosettes were found.

Immunohistochemistry showed cell membrane positivity for CD99 (Fig. 2), diffuse cytoplasmatic decoration with vimentin and WT1, and dot-like positivity for NSE. LCA, S-100, neurofilaments, synaptophysin, chromogranin, desmin, myogenin, smooth-muscle actin, EMA, NB84 and cytokeratins were negative. The cytoplasm was negative for PAS. The proliferation index was about 15%. The mitotic index was 2/10 HPF.
Fluorescence in situ hybridization (FISH) on parafin embedded neoplastic tissue revealed the reciprocal translocation 11:22 (q24;q12) (inset of Fig. 2, bottom right). The final histopathological diagnosis was peripheral primitive neuroectodermal tumor (ES/PNET) with desmoplasia.

Discussion

To our knowledge, only five cases of ES/PNET of the hand have been described so far. Erdmann et al. described a case of congenital neuroepithelioma occurring in the soft tissues of the palm of the left hand, at the base of the index and middle fingers; Daw et al. illustrated a congenital PNET of the soft tissues between the thumb and index fingers; Harder et al. reported a case of PNET of the soft tissues and metacarpal bone of the thumb in a 27-year-old woman; the PNET described by Alymlahi et al. in a 21-year-old woman was also in the thumb, but at the distal phalanx, with involvement of soft tissues and bone; the case illustrated by Hapa et al. also originated in the distal phalanx, but on the middle finger and limited to soft tissues; Jayakumar et al. reported a PNET of the tendon sheath of the little finger invading the head of the fifth metacarpal bone and the proximal phalanx of the little finger. Herein, we illustrate another case, which originated in the palm of the right hand and invaded the muscles, tendons and small bones, as in the cases of Harder et al., Alymlahi et al. and Jayakumar et al.

Our case is peculiar not only due to the site of origin, but also because the age of the patient, who is over 30 years, which can be considered very rare. Various histotypes were considered for differential diagnosis. The negativity for muscle-specific markers excluded rhabdomyosarcoma, whereas negativity for LCA excluded lymphoblastic lymphoma. The neoplastic cells were PAS negative, thus eliminating the possibility of Ewing’s sarcoma. Neurofilaments, synaptophysin and NB84 were negative, excluding a neuroblastoma. FISH revealed the 11:22 translocation due to EWSR1 gene rearrangement, as in most previously described cases. The finding of desmoplasia within the tumor mass led us to consider the possibility of a desmoplastic small round cell tumor. However, such tumors are composed of sharply demarcated nests of small round cells embedded in a desmoplastic stroma, and the cell nests are frequently centrally necrotic. Furthermore, this neoplasm exhibited a polyphenotypic profile, usually positive to WT1 (nuclear decoration), cytokeratin, desmin and EMA. In our case, desmoplasia was not very extensive, necrosis was absent, and there was cytoplasmatic positivity for WT1, whereas cytokeratin, desmin and EMA were all negative.

We currently have no follow-up data on our patient. However, based on the description of the surgical intervention, it seems reasonable to assume that complete removal of the tumor was achieved, while no appreciable metastatic spread was present at diagnosis. Considering that tumors of the ES/PNET family comprise only 0.5% of all malignancies, oncology units can only be expected to treat a very limited number of cases, and hence the most effective therapy has yet to be defined. However, since ES/PNETs are very aggressive, the best choice seems to treat these tumors with radiation and multidrug chemotherapy, as was done in the present case. The clinical presentation may be underestimated for a long period. In fact, the neoplastic mass may range from 2 cm in size, as in the case of Hapa et al. and in our case, to a 7 cm mass of the case of Harder et al., reaching up to 15 cm in the case of Alymlahi et al. When it occurs in the hand, the mass is easily noticeable and palpable.

References

A RARE CASE OF PRIMITIVE NEUROECTODERMAL TUMOR


**Ossifying fibromyxoid tumor with atypical histological features: a case report**

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**Key words**

Ossifying fibromyxoid tumor • Immunohistochemistry • Differential diagnosis

**Summary**

Ossifying fibromyxoid tumor of soft tissues (OFMT) is considered a rare mesenchymal neoplasm. Its main histological features are sheets and ill-defined lobules of rounded bland cells within a fibromyxoid background and a thick collagenous capsule with an incomplete rim of lamellar bone. This lesion occurs mostly in the soft tissues of the lower extremities and limb girdles. In this paper, we describe a mesenchymal tumor removed from the right thigh of a 41 year-old-woman. The neoplasm differed histologically from typical forms of OFMT for areas of moderate cellularity and atypia, nuclear enlargement and small nucleoli. Focally, stromal tongues of osteoid were centrally and irregularly located within the lesion with evident spindling of tumor cells around them.

**Introduction**

Ossifying fibromyxoid tumor (OFMT) is a rare neoplasm of the soft tissues recently described by Enzinger et al. in 1989. As its name implies, the tumor is morphologically similar to low-grade fibromyxoid sarcoma and is usually located in the subcutis or deeper tissue of extremities. This distinctive clinicopathologic entity is characterized histologically by a combination of a lobulated growth of rounded or occasionally spindle cells with a fibromyxoid matrix and a well-defined fibrous capsule containing a variable shell of bone. The number of published cases is relatively limited, and there is still disagreement with regard to its exact histogenesis and cell differentiation lineage. The majority of cases are benign, but a small number behave in a malignant fashion. We report herein a new case of OFMT with atypical histological features and present its immunohistochemical and ultrastructural findings.

**Case report**

A 41-year-old woman was admitted to the Department of Surgery of Vallecamonica Hospital, Edolo, Italy, for evaluation of a painless swelling in the right thigh dating to 8 years prior, which had been progressively increasing in size over the previous 12 months. Her past medical history was unremarkable. Exploration revealed a hard, parenchymatous, mobile nodule measuring at least 4 cm that did not adhere to muscle and was completely separate from the femur. No other nodules were present. Laboratory tests were all within normal ranges. The clinical diagnosis was adipose tumor. The mass was excised under local anesthesia and a histologic diagnosis of atypical OFMT reported to be positive for calponin. The patient is currently alive and well with no evidence of disease at 96 months following surgery. In spite of low-grade histology, OFMT has high local recurrence rate and low metastatic potential, primarily in the lungs, even several years after surgical removal. The recognition of this entity is important. In this report the authors address differential diagnosis and enigmatic histogenesis of this neoplasm.

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was performed on paraffin sections using nonavidin biotin-based detection system (EnVision, DakoCytomation, USA). The following monoclonal antibodies were used: cytokeratin (AE1/AE3, Dako), vimentin (Biocare), CD34 (NeoMarkers), desmin (Dako), S-100 protein (Biocare), α-smooth muscle actin (NeoMarkers), CD56 (Dako), CD99 (NeoMarkers), calponin (Dako), glial fibrillary acidic protein (GFAP) (Zymed), CD10 (CellMarque), p63 (Dako) and collagen IV (Dako).

On gross inspection, the tumor was a well-circumscribed, lobulated mass measuring 5.5 x 4.5 x 2.5 cm. The tumor was solid and firm with a glistening, grayish pink cut-surface that contained a peripheral frame of calcified tissue. Histological examination revealed a well-demarcated, partially encapsulated lesion, with pushing rather than infiltrating margins, and a partial shell of mature lamellar bone extending into the inner fibrous septa. Normal fat tissue was seen adjacent to the lesion. Within the capsule, a mesenchymal proliferation with increased cellularity was observed (Fig. 1). The neoplastic cells were uniform and small to medium-sized, with rounded to ovoid vesicular nuclei, clear or eosinophilic cytoplasm and poorly defined cellular outlines. They were often arranged in sheets and ill-defined lobules of varying size formed by indistinct fascicles. A cord-like and trabecular arrangement of elements was focally observed (Fig. 2). Intermingled with the tumor cells were irregular areas of variably abundant paucicellular collagenous and myxoid stroma that showed the presence of alcian blue positive hyaluronidase sensitive material. PAS preparation failed to reveal the presence of intracellular glycogen. The neoplastic lobules commonly contained delicate, curving vessels and a sparse inflammatory cell component made up of lymphocytes, mature plasma cells and mast cells which were often dispersed around them.

Focally, areas of neoplastic osteoid with scattered foci of mineralization were randomly distributed and centrally located. Within this central osteoid, the tumor was composed of spindle cells with slight to moderate pleomorphism, sometimes organized in a herringbone arrangement (Fig. 3).

Varying degrees of cellular density and atypia, with nuclear enlargement and occasional small nucleoli, were observable throughout. High cellularity and high polymorphism were absent; mitotic figures were sparse with up to 19 mitoses per 50 HPF and with atypical forms rarely identified (Fig. 4).

Immunohistochemically, tumor cells demonstrated diffuse positivity for CD10, vimentin and calponin with focal strong reactivity for S-100 protein, smooth muscle actin, CD56 and CD99 (Figs. 5A-C, 6B). Cytokeratin reacted only in rare neoplastic elements (Fig. 6A). Also there was diffuse condensed collagen IV positive staining in and around the neoplastic cells of the ill-defined lobules with compact growth (Fig. 5D). All other stains were negative.
Discussion

OFMT is a rare tumor that presents a wide distribution age (range, 3 weeks to 86 years), but occurs mainly in the fourth to seventh decades, and has a male predominance. It usually presents as a painless, subcutaneous or deep soft tissue lesion, most commonly in the lower extremities or limb girdles, usually in the lower limb. Other primary sites, such as trunk, head and neck region may less frequently be involved, and exceptional examples have been reported arising from mediastinum and retroperitoneal tissue.

Most OFMTs are well circumscribed with a lobulated growth pattern and measure up to 17 cm in diameter. The tumor was initially reported in 1989 as a series of 59 cases collected over 25 years. Classically, the tumors were of low to moderate cellularity and were composed of a fibromyxoid matrix, containing cords, strands, nests of relatively uniform oval cells with a vaguely plexiform growth pattern. This first series portrayed OFMT as a mesenchymal neoplasm with low malignant potential and a recurrence rate of 27%.

Subsequently, several other cases have been reported in the literature, and to date approximately 220 tumors have been published as OFMTs. The majority of these cases have had classic morphology, but recently more emphasis has been placed on the recognition of atypical and clinically malignant variants. These cases with unusual traits were presented in small series or single cases by Kilpatrick et al., Holck et al., Hirose et al., Ekfors et al., Min et al. Owing to their rarity, clear criteria for malignancy in OFMTs are still unclear. In the largest clinicopathologic study of OFMT, Folpe and Weiss have proposed that the histologic features predictive of clinical malignancy include: 1) high nuclear grade or 2) increased cellularity and high mitotic count (> 2/50 HPF). This study revealed local recurrence in 9
of 51 (18%) cases of OFMT and metastasis in 8 (16%) of 51 patients, especially to the lungs 4. Very recently, the largest series of OFMT, 104 cases, was reported by Miettinen et al. 2 which included only examples with conventional morphology, excluding all others. Local recurrences (22%) were not associated with a worse prognosis; none of the patients had metastatic neoplasm or died of disease. The current case was difficult to diagnose on histological grounds alone, and could be initially erroneously classified as a low grade, well differentiated osteosarcoma 2 4. The lobulated neoplastic growth of S-100 positive elements with focal lace-like pattern within a fibromyxoid stroma raised the suggestion of OFMT, but the overall moderate cellularity and significant proliferative index (up to 19 mitoses/50 HPF) were considered to be atypical 4. Based on the previous reports, our case, as with other ‘atypical’ OFMTs, might have high risk of local recurrence, even several years after surgical removal, and a low metastatic potential, not significantly different from conventional forms of the disease 2 4.

Although phenotypically established, OFMT is a histogenetically enigmatic entity. The tumor was thought to be of neuroectodermal origin on the basis of S-100 immunoreactivity and the presence of partial redundant external lamina (EL) at the ultrastructural level 3 4 7-15. Folpe and Weiss 4 and Miettinen et al. 2 reported 60 and 94% positivity for S-100 protein in their series, respectively. Other neural markers including NSE, PGP 9.5, Leu 7, GFAP, neurofilaments, synaptophyisin, CD99 and CD56 were positive in small numbers of cases 3 7 10 12 13. However, similarities between peripheral sheath tumors and OFMTs seem to be limited. Infrequent expression of collagen IV, as observed in the present case and some previous reports, made the possibility of a typical schwannian differentiation unlikely 2 10 11 14 15. In addition, the expression of keratins, smooth muscle actin and CD10, as found in the present case and some previous reports, together with ultrastructural features as incomplete EL seen only along the stromal border of the neoplastic cell clusters could raise the possibility of modified myoepithelial cells being origin of OFMT 2 4 5 10-12.

In our study, we report the immunopositivity for calponin by OFMT cells for the first time. Calponin is a 34kD smooth muscle-specific protein implicated in the regulation of smooth muscle contraction as a result of its ability to inhibit actin-activated Mg-ATPase of smooth muscle myosin. It is expressed in parenchymal and vascular smooth muscle cells of various organs, in myofibroblasts of desmoplastic stroma and in myoepithelial cells. As yet, no analogous of calponin have been found in non-muscle cells. Our findings could further suggest a myoepithelial or adnexal origin of OFMTs; however, all OFMTs including our case, tested negative for p63, a recently introduced myoepithelial marker detected in cutaneous myoepithelial cells and some myoepithelio-mas of skin and soft tissues; also, myofilaments have not been demonstrated in ultrastructural studies of these tumors 2. Although further investigation of OFMT with other myoepithelium-associated markers such as maspin might be of interest, neither marker is specific for myoepithelium, and the significance of their expression in these frequently actin and/or cytokeratin negative tumors would be rather debatable 4.

Very few studies have demonstrated genetic abnormalities in OFMTs. Folpe and Weiss 4 have suggested that they may be related to the expanding family of translocation-associated sarcomas, not all of which recapitulate a normal line of differentiation. However, the cytogenetic findings of three recently reported cases and one unpublished karyotype do not support this view 4 16. A partial rearrangement of chromosomes 6 and 12 was found in two cases of typical OFMT 10. A variety of heterogeneous and complex chromosomal abnormalities has also been detected in three tumors, including atypical and malignant forms 16. Further studies might lead to better understanding of the specific cytogenetic events responsible for the development and growth of OFMTs as well as distinction from other types of epithelioid and spindle cell neoplasms 2.

Several entities should be considered in differential diagnosis. One is low-grade fibromyxoid sarcoma (LGFS) that can occasionally exhibit an arrangement of the tumor cells into rows with epithelioid morphology. Nevertheless, the fibroblast-looking cells of LGFS have a number of other features that set them apart from the glomoid ones of OFMT, including the lack of S-100 protein and the presence of cytoplasmic intranuclear invaginations and occasional hyaline rosettes 2 17.

Atypical OFMT sometimes shows distinct and abundant osteoid deposition, so that they acquire similarity with some variants of low-grade extraskeletal osteosarcoma. The latter is entirely composed of lace-like osteoid-forming spindle malignant cells without the lobulated growth of uniform oval to round neoplastic cells of the former 23. OFMT must be distinguished from extraskeletal myxoid chondrosarcoma, a malignant tumor featuring a similar pattern and a clear ground substance; however, OFMT cells lack PAS-positive intracellular glycogen and have generally a more intricate vasculature and a marginal rim of mature lamellar bone 1 3 6 9 10 13 14 18.

Myoepithelioma shares the S-100 protein and occasionally even actin positivity with OFMT, but the latter is nearly always cytokeratin negative and usually has a more pronounced lobular growth pattern with peripheral metastastic ossification and thin cords of neoplastic cells 2 19.

Our case bears some morphological similarity to sclerosing epithelioid fibrosarcoma (SEF) because both show small epithelioid cells set in a hyalinized stroma, but differs from SEF in other aspects as well: it contains a peripherally located incomplete shell of lamellar bone and is prevalently composed of cells of lower nuclear grade 2 49.

Furthermore, another tumor that needs to be differentiated from OFMT is pleomorphic schwannoma, which generally shows a continuity with peripheral nerves and displays strong and diffuse S-100 protein staining 1 3 9 14 18.
In other conditions, including infiltrating carcinoma, glomus tumor, epithelioid leiomyosarcoma, clear cell sarcoma the use of the strict morphological criteria in the context of the clinical settings, followed by immunohistochemical analysis, and ultrastructural studies in dubious cases, are all helpful to confirm proper diagnosis. The awareness of the existence of this rare entity will prevent eventual misdiagnosis of this neoplasm as a benign lesion, which may be followed by inadequate surgical excision and high rate of local recurrences. Standard therapy is wide surgical excision with long-term follow-up.

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Conclusion

OFMT is a rare, recently-described neoplasm, which spans a spectrum of malignant potential. It is usually asymptomatic and generally manifests as a subcutaneous nodule. Histological diagnosis can be difficult to distinguish from a variety of soft tissue neoplasms, including nerve sheath tumors and extraskeletal myxoid chondrosarcoma. Several fundamental aspects justify its inclusion in future classifications of soft tissue tumors.

Urothelial carcinoma with plasmocytoid component

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Summary
Plasmocytoid urothelial carcinoma is a rare subtype of tumour of the urinary bladder. Its clinical and histopathological features have not been well characterized. There are few reports of this type of tumour. We report a case of 65-year-old man who was operated in our department for bladder tumour. The pathological diagnosis was high-grade urothelial carcinoma with plasmocytoid component. The patient died shortly thereafter from liver and bone metastasis.

Case report
We report the case of 65-year-old man, who was referred to our department with a history of recurrent haematuria, anorexia and weight loss of 20 kg. Physical examination was normal. Ultrasound showed a thickening of the posterior urinary bladder. Cystoscopy revealed a large indurated lesion at the bladder base including the trigone. Biopsy by transurethral resection was performed, and histopathological examination showed dyscohesive tumour cells with dense and eosinophilic cytoplasm and eccentric uniform hyperchromatic nuclei mimicking plasmocytoma (Figs. 1, 2). The stroma was loose and myxoid. The tumour was massive, compact and trabecular with nodular features. Tumour foci were composed of cells variable in size with significant anisokaryotic cytonuclear atypia. These aspects correspond to high-grade urothelial carcinoma. The neoplastic cells extended into the muscularis propria.

At immunohistochemical analysis, tumour cells expressed cytokeratin (CK) CK7, CK 20 and CD 138. Immunostaining for kappa and lambda light chains, CLA (Common Leucocyte Antigen), vimentin, actin and chromogranin were negative. The pathological diagnosis was high-grade urothelial carcinoma with plasmocytoid component. The patient died 1 month later of liver and bone metastasis.

Commentary
Plasmocytoid urothelial carcinoma was described for the first time by Sahin et al. in 1991. 1 Zukerberg et al. 2 reported 5 cases of urothelial carcinoma mimicking lymphoma and 2 had plasmocytoid features. The largest reported series of 17 cases was described by Priya 3. This tumour is rare, and less than 40 cases have been reported in the literature. 3 Histologically, the tumour contains discohesive cells with dense and eosinophilic cytoplasm and eccentric uniform hyperchromatic nuclei. The stroma was lose and myxoid. This type of tumour tends to present at an advanced stage, as in our patient 4.

The contingent proportion of plasmocytoid features is variable, and can be exclusive. This proportion has been reported to vary from 15% to 100%. 3 Cells with plasmocytoid features can be seen in many tumours such as lymphoma, plasmocytoma, melanoma, paraganglioma, neuroendocrine carcinoma and rhabdomyosarcoma. Rhabdoid cell and signet ring cells can have a plasmocytoid appearance because of eccentric nuclei 2 5. These diagnoses can be excluded by the presence of carcinoma in situ in the mucosa or typical urothelial component. Plasmocytoid urothelial carcinoma should not be confused with pseudo-neoplastic urothelial lesions. An immunohistochemical panel such as CK20, CD44, Ki-67 and p53 are useful in the diagnosis of urothelial proliferative lesions 6. Immunostaining shows that both plasmocytoid and conventional tumour cells expressed cytokeratin CK7, CK 20 and lymphoid markers are negative. CD 138 as a marker of plasmocytes can be found, but
light chains are negative. P53 expression was low, and ranged between 5 and 10%. Vimentin, actin, desmin, S100 protein and neuroendocrine markers were negative. Tumour cells of plasmocytoid urothelial carcinoma are Alcian blue negative. The tumour is aggressive, and generally diagnosed at a late stage with extension into adjacent pelvic organs and metastases. The tumour confers poor prognosis. The rare cases reported were treated by surgery combined with chemotherapy. In conclusion, plasmocytoid urothelial carcinoma of the bladder can be confused with signet cell tumours. Immunostaining can aid in diagnosis. It is an aggressive tumour, and treatment is based on surgery and chemotherapy; prognosis is poor.

References

Cystadenocarcinoma of the appendix: an incidental perioperatory finding in a patient with adenocarcinoma of the ascending and sigmoid colon: case report and review of literature

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Key words
Cystadenocarcinoma • Appendix • Colon carcinoma • Imaging

Background. Primary adenocarcinomas of the appendix are uncommon, constituting 1% of all colorectal malignancies. Appendiceal malignancies often present atypically, thus creating diagnostic challenges. Although there are many pathology reports of primary cystadenocarcinoma of the appendix, only a limited number of cases have appeared in the radiological or surgical literature. We present a unique case of primary cystadenocarcinoma of the appendix occurring concurrently with adenocarcinoma of the colon, and overview the clinical and therapeutic difficulties posed by this rare entity.

Case presentation. A mucocele of the appendix, due to mucinous cystadenocarcinoma, was documented as an incidental perioperatory finding in a 68-year-old female. The patient was admitted due to rectal haemorrhage and underwent colonoscopy with biopsy, X-ray, abdominal ultrasonography and CT scan. Degenerated adenomatous polyp of the ascending colon and mucinous adenocarcinoma of the sigmoid colon invading the parietal peritoneum of the uterine and vagina was diagnosed. At laparoscopy, a cystic appendiceal lesion was found, without perforation. The patient underwent right hemicolectomy, sigmoidectomy and hysterectomy associated with salpingo-oophrectomy.

Conclusions. Preoperative diagnosis of an underlying malignancy in a mucocele is important for patient management, but is difficult to reach by imaging studies alone. Synchronous colon cancer may occur in patients with appendiceal mucoceles. In such patients, the colon should be investigated. Surgery is the recommended method of treatment.

Background
Appendiceal carcinoma is a very rare clinical entity, constituting about 1% of all colorectal malignancies and 1% of all appendectomy specimens. Appendiceal malignancies often present atypically, thus creating diagnostic challenges. Although there are many pathology reports of primary cystadenocarcinoma of the appendix, only a limited number of cases have appeared in the radiological or surgical literature. Preoperative diagnosis is difficult, but important for surgical management. Most symptomatic appendiceal tumours present as appendicitis, although other far less common presentations have also been described. These tumours may also be encountered unexpectedly in any acute or elective abdominal operation, and correct diagnosis is rarely made pre- or intraoperatively. Most are identified only after histopathological examination. We present a unique case of primary cystadenocarcinoma of the appendix occurring concurrently with adenocarcinoma of the colon.

Case report
A 68-year-old female was admitted with rectal haemorrhage. Her past medical history included mild hypertension. She complained of malaise and tiredness lasting 6 months and a recent episode of diarrhoea and vomiting followed by an increase in the frequency of bowel movements. Upon examination of the abdomen, the patient had distension with lower abdominal tenderness. Laboratory findings showed only iron-deficiency anaemia. Flexible sigmoidoscopy demonstrated a 6 cm,
circumferential and indurated tumour located 17 cm from the anal verge. Biopsy specimens from the lesion demonstrated a moderately differentiated adenocarcinoma. Ultrasonography also visualized the sigmoid obstructive lesion that invaded the vagina and uterine cervix. In close proximity with the ileocecal valve, CT showed a large tumour mass in the ascending colon, while the terminal ileum was partially invaginated into the caecum. There was no ascites or other abnormalities in the peritoneum. Laboratory tests were unremarkable except for elevated carcino-embryonic antigen (CEA). A laparotomy was performed, during which large bowel obstruction was found to be secondary to a “sigmoid tumour”, with a malignant fistula at the uterus and cervix, as they were abnormal and “fixed” to the upper rectum distal to the tumour. The appendix was noted to be abnormally enlarged with mucocoele. The tumour presented a right urethral impingement leading to urethral obstruction. A sigmoidectomy was performed with en-bloc total hysterectomy and bilateral salpingo-oophorectomy. A separate right hemicolectomy with end ileostomy was also performed. On macroscopic examination, the mucocele measured 60 x 40 mm and was filled with gelatinous material. The ascending colon tumour measured 4 cm. The sigmoid white- indurate stricture of the tumour measured 7 cm; it infiltrated the colonic wall up to the uterine isthmus and cervix, with an endocervical protrusion. Colonic mucosa showed several (about 20) sessile or pedunculated polyloid lesions with stalks of varying length measuring from 5-20 mm. Microscopic examination showed circumferential replacement of the normal appendiceal epithelium by proliferative mucinous epithelium. The tumour had a single layer of neoplastic mucinous cells with occasional small epithelial tufts overlying a fibrotic and atrophic lamina propria and submucosa. Villous projections were covered by a single layer of mucus rich columnar cells on a surface of mucinous neoplastic epithelium. The nuclei of the neoplastic cells were typically elongated, hyperchromatic and lacked prominent nucleoli. Mitotic figures were scarce. Diffuse mucin pools were present on the appendiceal serosa, which contained isolated and islands of epithelial cells. Mucin stains were positive. Mural hyalinization and mucin extravasation were prominent. A diagnosis of appendiceal mucinous cystadenocarcinoma was made. The tumour mass in the ascending colon was a well-differentiated adenocarcinoma arising in an adenomatous polyp with severe epithelial dysplasia. The sigmoid colon tumour was a mucinous infiltrating adenocarcinoma, extending serosa and infiltrating the uterine cervix and isthmus. The endometrium, ovaries and fallopian tubes were free of tumour. The colonic surgical margins were also free of tumour, and there were no involved lymph nodes. Histologically, colonic polyps corresponded to tubulovillous adenomas with mild to severe dysplasia. There were no pseudomyxoma peritonei. Postoperatively, the patient presented hydronephrosis and acute kidney failure due to ureteral obstruction; ureterostomy was performed. The patient underwent intraperitoneal chemotherapy and the patient recovered well during the following 7 months.

Discussion

Adenocarcinoma of the vermiform appendix is a rare neoplasm of the gastrointestinal tract with an incidence of about 0.01-0.2% (4-6). Moreover, carcinoma of the appendix has been identified in only 0.08% of reported appendectomies or autopsies 5. Only about 500 cases of primary adenocarcinoma of appendix have been described since Berger first recognized the neoplasm in 1882. In a review of over 2000 appendectomy specimens, histological confirmation of appendiceal neoplasm included carcinoid (0.27%), adenocarcinoma (0.14%), malignant mucocoele (0.005%) and lymphoma (0.005%) 3. Most symptomatic appendiceal tumours present as appendicitis, while other less common presentations have also been described. These tumours may also be unexpectedly encountered in any acute or elective abdominal operation, although correct diagnosis is rarely made either pre- or intraoperatively. Most of these tumours are identified only after histopathological examination of an appendectomy specimen 57. Appendiceal mucocoele (AM) is not clinically suspected in 50% of cases where it is diagnosed, and 25% of AM patients are asymptomatic at diagnosis 189. The International Classification of Diseases for Oncology (ICD-O) divides tumours of appendix into 5 categories: colonic type adenocarcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, goblet cell carcinoma, and malignant carcinoid/adenocarcinoid 68. These carcinomas arise in pre-existing adenomas, either with a cystic or colonic growth pattern 10. The classification of appendiceal mucinous tumours is controversial, and terminology is inconsistent, particularly when a mucinous tumour lacks overtly malignant features but is associated with extra-appendiceal spread. Morphologically, identical tumours that are associated with appendiceal rupture and peritoneal seeding have been designated as ruptured adenomas. The presence of invasion is required for diagnosis of adenocarcinoma 81011. AM is nearly always present in women diagnosed with ovarian cystadenocarcinoma, and concomitant benign ovarian cystic tumour is sometimes seen in association with AM 12. Preoperative diagnosis is difficult due to the nonspecific nature of the disease. Adenocarcinoma of the colon has been identified in 20% of AM 13. Thus, a finding of AM should always prompt thorough evaluation for the presence of concomitant malignancy. Herein, we present a case of appendiceal adenocarcinoma associated with a double location of colonic cancer. Only one similar case has been reported in the literature 24. In our review of the literature, other unusual presentations of appendiceal tumours have also been reported, including an appendiceal adenocarcinoma...
presenting as a vesical fistula, neck mass and vaginal bleeding, spontaneous skin fistula, inguinal hernia, and disseminated ovarian carcinoma. There is also a reported case of adenocarcinoma of the appendix presenting as a uterine tumour, leading to left-sided large bowel obstruction, and simulating a submucosal tumour of the cecum. Urethral obstruction, caused by an appendiceal carcinoma has been reported. An adenocarcinoma of the appendix presenting as a bladder tumour has also been documented. In one case, the tumour presented as caeco-colic intussusceptions, and in another as a fistula of the mid-rectum that masqueraded as a rectal villous adenoma. A case of primary cystadenocarcinoma of the appendix occurring concurrently with adenocarcinoma of the colon has been described. A unique association of a large appendiceal mucinous cystadenoma and adenocarcinoma of the sigmoid colon with hepatocellular carcinoma of the liver was also reported.

The most common symptom is right lower abdominal pain mimicking appendicitis. Mucocele can also be asymptomatic, as in our patient, found incidentally on surgery. Clinically, most appendiceal tumours present as acute appendicitis (79.1%). Incidental findings, pelvic abscesses with gastrointestinal symptoms and bowel obstruction were also present. Other less common presentations include right iliac fossa mass, inflammatory bowel disease and strangulated hernia. Symptomatic lesions are associated with malignant disease more frequently than asymptomatic ones.

Appendiceal neoplasms are also known to be associated with a significant incidence of synchronous and metachronous colorectal neoplasms. Patients with colorectal cancer have a 3–5% risk of synchronous and a 2.3% risk of metachronous neoplasia. Some authors have suggested that because of the inability to assess the appendiceal mucosa postoperatively, routine removal of the appendix in patients undergoing colorectal cancer resection is justified. As part of formal exploratory laparotomy, in addition to the routine thorough examination of the abdominal viscera, looking for deposits and lymphadenopathy, inspection and palpation of the appendix and mesoappendix as part of the intraoperative examination of any gastrointestinal surgery for malignancy seems to be mandatory.

Laboratory findings are usually non-specific, but the elevation of tumour markers often indicates a neoplastic origin and/or associated tumours, which was seen in our patient. Modern imaging techniques allow visualization of most complications and associated conditions. Sonography usually shows a cystic encapsulated lesion with a liquid content adjacent to the cecum. CT scan shows a low density, encapsulated, thin-walled mass that does not contain contrast medium and communicates directly with the cecum. Other solid or cystic abdominal and peritoneal tumours could also be detected by these methods. Small right lymph nodes or soft tissue in the surrounding fat on CT examination may suggest malignancy. Although there are many pathology reports of primary mucinous cystadenocarcinoma, only a few cases have been reported in the radiological literature. Preoperative diagnosis, although important for proper surgical management, is difficult due to the absence of specific imaging findings. The presence of a cystic mass in the expected area of the appendix with enhancing wall and nodularity on CT examination suggests the possibility of mucinous cystadenocarcinoma. Wall thickness has not been proven to be a reliable differential point between neoplastic and non-neoplastic causes of mucocele. Curvilinear nodular or punctuate wall calcifications have been reported in both malignant and benign mucoceles. Considering that the appendix is a part of the large intestine, adenomatous polyps, papillary adenomas and adenocarcinomas in the appendix are simply an expression of colonic neoplasms in this anatomic location. Thus, the low incidence of...
mucoceles is attributed to the relatively small size of the appendix in comparison to the rest of the large bowel \(^{24}\). In our patient, CT examination revealed small right lymph nodes and soft tissue in the surrounding fat that were misdiagnosed. The lesion may also be identified endoscopically. In one previously reported case, the lesion appeared to be a submucosal tumour of the cecum by endoscopy \(^3\). Appendiceal perforation, leading to acute abdominal infection, has been reported in 6% of cystadenocarcinomas \(^1\) \(^2\) \(^4\). Pseudomyxoma peritonei, or the implantation of mucinous epithelial cells from a ruptured AM onto peritoneal surfaces, leads to mucinous accumulation within the peritoneal cavity and the formation of adhesions that may cause intestinal obstruction or carcinomatosis. It is considered the worst complication of this disease \(^1\) \(^4\) \(^10\) \(^28\) \(^29\).

The type of surgical treatment is related to the size and histology of the lesion. Appendectomy is used for early cystoadenocarcinoma, when the appendiceal base is intact \(^13\) \(^30\). In fact, appendiceal neoplasms can be found at any acute or elective abdominal surgery, and the management plan should then be based on intraoperative findings. Some authors suggested that for tumours found incidentally at surgical intervention, appendicectomy is appropriate if the tumour was confined to the appendix and smaller than 2 cm, without evidence of mesoappendiceal involvement and not involving the base of the appendix. Any neoplasm larger than 2 cm and any involving the base of the appendix or mesoappendix should be considered for immediate right hemicolectomy for an optimal outcome \(^13\) \(^11\). Right hemicolectomy is presently considered to be the treatment of choice for all lesions with invasion beyond the mucosa \(^9\) \(^10\). In our case, right hemicolectomy was done for ascending-colon tumour. For in situ carcinoma, some authors suggest there is no survival advantage in performing a right hemicolectomy over appendectomy alone \(^12\) \(^19\). The role and safety of laparoscopic appendectomy for management of incidentally discovered appendiceal tumours has not yet been established \(^11\) \(^12\) \(^24\). A laparoscopic approach has been reported to have a slightly higher rate of inadequate resection \(^12\). However, it is not associated with a significantly poorer patient prognosis than open appendectomy \(^10\) \(^20\).

The treatment options for metastatic disease include systemic chemotherapy alone, hyperthermic intraoperative intraperitoneal chemotherapy, cytoreductive surgery with peritoneectomy, and a combination of treatments. Of the aforementioned treatment options, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy have recently become the treatment of choice for metastatic diseases at most large centres \(^11\) \(^30\) \(^32\). Aggressive cytoreductive surgery for mucinous-type tumours is known to improve the survival rate and reduce the recurrence rate in patients with generalized pseudomyxoma peritonei compared to simple appendectomy \(^29\) \(^31\). In addition, the most consistent prognostic factor for survival is completeness of cytoreduction \(^12\) \(^33\). Several lines of evidence suggest that routine right hemicolectomy should not be performed in patients with aggressive appendiceal malignancy unless in conjunction with both complete cytoreduction and intraperitoneal chemotherapy. Considering systemic chemotherapy, an alternative option for metastatic appendiceal carcinomas, the available data, although limited, favour integration of systemic chemotherapy, including mitomycin C, fluoropyrimidines and platinum compounds, which have been used as an intraperitoneal chemotherapy \(^24\) \(^33\) \(^34\). In the future, novel targeted therapies, including EGFR inhibitor or anti-angiogenic agents, in combination with regional treatment or systemic chemotherapy, should be evaluated \(^35\). Radiotherapy generally has no role in therapy unless the margins are involved, as for colorectal cancer. Follow-up colonoscopy and pelvic examination are also warranted for the high association with another colon malignancy \(^10\) \(^16\) \(^24\). Recently, the use of CEA and carbohydrate antigen 19-9 (CA 19-9) tu-
mour markers were shown to have practical value in the management and follow-up of patients with mucinous appendiceal malignancies. Depending on the stage and the grade of the tumour, the overall 5-year survival reported for adenocarcinoma of the appendix is between 21% and 45%.

**Conclusion**

Synchronous colon cancer may occur in patients with appendiceal mucocoeles. In such patients, the colon should also be investigated. Surgery is the recommended therapy. During resection of a gastrointestinal tumour, thorough inspection of the abdominal cavity should be undertaken to investigate the possibility of metastatic secondary lesions or a synchronous tumour, as in the present case. Surgical resection alone has been demonstrated to be ineffective for the treatment of peritoneal implant and pseudomyxoma peritonei. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy have been reported to be efficacious in patients with disseminated mucinous tumors of the appendix. An integrative approach is thus required for diagnostic investigation and management of appendiceal malignancies.

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CASE REPORT

A benign cystic mass of the pancreas mimicking a malignant lesion

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Key words

Chronic pancreatitis • Cystic lesions

Summary

Herein, we highlight the diagnostic challenges of cystic pancreatic tumours, and report a case of chronic pancreatitis caused by a cystic tumour, which consisted in a canal dilatation -- and not a pseudocyst. The case thus demonstrates a rare association between a cystic form of chronic pancreatitis and adrenal adenoma. We report the case of a 46-year-old patient with no particular past medical history who presented with long lasting symptoms consisting in an abdominal pain and deterioration in general health. Imaging findings (ultrasound, CT-scan, MRI) showed a 3-cm cystic lesion of the tail of the pancreas associated with a 3-cm adrenal mass. Because of the suspicion of a malignant disease, surgical treatment was performed. Pathological findings consisted in fibrotic chronic pancreatitis with canal dilatation and an adrenal adenoma. Pancreatic cystic lesions are rare tumours. Despite of the multiplicity of imaging techniques, differential techniques lack sensitivity and specificity. Final diagnosis must be based on pathological features.

Cystic lesions of the pancreas are rare lesions posing a diagnostic challenge. They represent 0.7% of all pancreatic neoplasms, and are premalignant or malignant in 65-70% of cases 1.

We report the case of 46-year-old patient without particular past medical history, without documentation of pancreatitis, who presented with a 3-month history of abdominal pain with deterioration of general health. Ultrasound examination and CT-scan revealed a simple lithiasis of the gallbladder with a 3 cm cystic lesion in the tail of the pancreas and an adrenal mass of 3 cm suggestive of adenoma (Fig. 1a). Magnetic resonance cholangiopancreatography was performed, which revealed a 3 cm cystic lesion of the pancreas with a dilatation of Wirsung’s canal. This cyst had a thick capsule. Laboratory findings showed high levels of CRP, while the levels of amylase, SGOT, SGPT and tumour markers (CA 19-9) were normal. Due to suspicion of a malignant lesion, surgical excision was performed. Pathological findings consisted in a fibrotic chronic pancreatitis with a canal dilatation and the presence of necrotic lesions (Fig. 1b). The adrenal tumour consisted in an adenoma. Chronic pancreatitis is a rare pathology that affects from 7 to 10 persons/100,000 per year 2. The disease is rarely caused by a cystic tumour. It generally consists in a pseudocyst, which was not observed in the present case. In fact, the cystic lesion consisted in a canal dilatation and there were no pseudocysts. Diagnosis is challenging because of the clinicopathological similarities with a tumoral lesion. The cystic presentation of the disease in our case led to suspicion of several differential diagnoses. Mucinous cystic neoplasms, intraductal papillary mucinous neoplasm or a serous cystadenoma were suspected but the thickness of the capsule and the dilatation of Wirsung’s canal pointed to the possibility of malignant disease. A cystadenocarcinoma was also suspected despite the absence of vascular invasion. Other rare cystic lesions, including cystic NETs and cystic lymphangioma were also suspected. Multiple diagnostic

Fig. 1. (a) Dilatation of the excretory canal associated with diffuse pancreatic fibrosis; (b) MRI demonstrating a 5-cm cyst in the pancreatic tail associated with an adrenal mass (arrow).

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techniques including ultrasound, CT scan, MRI, endoscopic ultrasound with fine needle aspiration are available, but neither imaging studies nor cyst aspiration has sufficient sensitivity and specificity to provide an accurate diagnosis. Some authors have attempted to define predictors of neoplastic cysts. Kristine and coworkers suggested that pancreatic cysts in patients older than 70 years are likely to be malignant. Tumour markers including CA 19-9 can be falsely increased in both acute and chronic pancreatitis as well as in the presence of jaundice. Surgical treatment as in our case seems to be the best modality of treatment to reach a final diagnosis. The association of cystic lesions with adrenal adenoma has not been previously reported. The presence of this association in our case seems to be casual.

A benign cystic lesion of the pancreas must be distinguished from other malignant lesions. Despite of the multiplicity of radiological techniques, they cannot replace pathological findings, which necessitate surgical treatment and its associated risks.

References

A useful individual protection system for the Gross Room and autopsy activity of the Pathologist

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Key words
Surgical pathology • Biological risk • Chemical risk • Fixation • Formalin • Individual protection device

The chemical risk, due to the employment of toxic substances, and the biological risk, are often present during the pathologist’s activity; in the Gross Room, during description and sampling of surgical specimens, the pathologist is exposed both to potentially biological infective material, and to dangerous chemical substances, especially fixatives. Among the latter, a 10% buffered solution of formaldehyde, commonly known as formalin, is the most widespread fixative employed in pathology, due to its ease of use, low cost, fairly fast fixation, easy processing, and wide variety of histological techniques that can be performed following fixation in formalin; it can also be successfully used for fixation of biological samples of large dimension, such as colorectal specimens, or, in the autopsy field, the brain. It also preserves tissues for extended periods of time. In 1987, the Formaldehyde Standard became law in the United States, alerting laboratory workers to the potential carcinogenicity of formaldehyde. As a result, other fixatives, most of which are alcohol derivatives, are presently employed as a substitute for formalin with good results; nevertheless, none of these alternative fixatives is totally lacking toxic/irritant/allergic activity.

Here, we describe an individual protective system which offers the following advantages:
1) Total protection of the face and respiratory tract from biological and chemical risk.
2) Low cost.

Firms specialised in products for protection at the workplace commercialize individual protection devices that consist of a headtop (Figs. 1A, B) which combines hair, face and respiratory protection; the headtop is connected with a compressed air dispenser system, in combination with an air flow-regulator mounted on a belt (Fig. 1C) and an air filter unit, (Fig. 1D), which supplies high quality air by removing excess water, oil aerosols, particles and odours. Positive air pressure is created inside the headtop, preventing the entrance of external contamination, perfectly isolating the operator. The air flows over the top of the wearer’s head and down in front of the face, and, finally, goes out through small holes located on the mask below the operator’s chin (Fig. 1B). The system is easily utilized also by operators who wear corrective glasses, and is predisposed to be used by a second operator, for example, a technician.

With the exception of the predisposition of medical compressed air supply installation, usually widely available in hospital structures, the described device, costs about €1400, and requires only minimal servicing (the filters should be changed after about 1000 hours of work); the only component subject to wear is the headtop, which however costing inexpensive (about €120).

In our experience over a period of several years, such an individual protection system is well-tolerated by the operator, and does not significantly hamper the activity of macroscopical analysis and sampling of biological specimens. It is also perfectly compatible with the use of chemical hoods. It consents, moreover, good possibilities for movement, since the length of the cable connecting the flow regulator to the filter unit (Fig. 1C) is adaptable according to the necessity of the operator.

In addition, this safety device could also be easily employed in the autopsy room, especially considering biological risk (TBC, HIV, HCV, prion protein contamination) and the odours linked with autoptic activities.

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Fig. 1. A) The headtop combines full face and respiratory protection; it is not uncomfortable and does not hinder the operator’s activities; the headtop is connected to an air flow-regulator by a breathing tube. B) detail of Fig. A. the air goes out through small holes located below the operator’s chin (arrow); C: an air flow-regulator mounted on a belt: the operator can regulate the quantity of air according to personal necessity; the arrow indicates the cable that connects the flow regulator to the filter unit (Fig. D); the length of the cable is established by the operator according to his necessities. D): air filter unit that provides high quality of air.

References
Squamous carcinoma of the lung metastatic to the breast

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Clinical history. A 64-year-old woman, with no relevant prior clinical history, revealed a nodule in the right breast by screening mammography, 10 mm in diameter, with features of malignancy.

Cytological smears showed irregular sheets of epithelial cells with pleomorphic, hyperchromatic nuclei and scarce cytoplasmic cytoplasm. There were also cells with abundant eosinophilic cytoplasm and hyperchromatic nucleus. A diagnosis of malignant cells with features of high grade carcinoma, probably metaplastic, was made. However, a metastatic squamous carcinoma could not be excluded.

An X-ray of the thorax, one month later, revealed a hypo-diaphanous image in the medio-basal right region. A diagnosis of pneumonia was made.

Ten days later, regardless of therapy, a slight improvement of the lesion with pleural effusion at the control X-ray was found. Bronchoscopy showed stenosis of the right inferior bronchial tube. Bronchial aspiration and biopsy showed a squamous carcinoma.

A total body CT scan revealed a solid mass, 5 cm in diameter, in the right inferior bronchial lobe adjacent to the right atrium and near the esophagus. The patient was treated with chemotherapy. In the following months, the CT scan showed a reduction of the pulmonary mass. At mammography, no increase of the nodule was documented. One year after, cutaneous and hepatic metastases were found. The patient died one year later.

Conclusions. Breast metastases are very rare, accounting for about 0.5-3% of patients with extra-mammary malignant neoplasms. In 70% of cases, the primary neoplasm is identifiable and a cytological smear is useful to confirm diagnosis.

Very rarely, breast metastases represent the first sign of neoplastic disease and often simulate clinically and cytologically a primary neoplasm.

Of the tumours metastasizing to the breast, one of the most frequent is small cell carcinoma of the lung. Squamous carcinoma metastasizing to the breast has been described deriving from the oesophagus, oral cavity, pharynx, cervix, vulva and lung.

The differential diagnoses to be considered when malignant squamous cells in a breast FNA are: squamous and adenosquamous metaplastic carcinoma, low grade adenosquamous carcinoma and, finally, metastatic carcinoma.

This case demonstrates the importance of breast cytology for the correct management of rare lesions also avoiding unnecessary surgical intervention whenever possible.

References

Short course: endometrial cytology
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Several diagnostic procedures are available to investigate the endometrium. Among these, endometrial cytology is the less-commonly utilized. Improvements in the diagnostic capacity of endometrial cytology related to the introduction of the liquid-based method suggests that it can be used for endometrial diagnosis.

In contrast to cervico-vaginal cytology, which has been precisely codified in terms of both diagnostic criteria and reporting format, endometrial cytology has not been standardized. Herein, we report on the diagnostic and reporting criteria in liquid-based endometrial cytology used at our Institution as result of the experience matured during 8 years of liquid-based methodology in endometrial cytology.
**Statement on specimen adequacy.** Specimens are considered inadequate for diagnostic evaluation when they contain less than 6 epithelial endometrial cell clusters. Moreover, specimens are also considered unsatisfactory for diagnosis when insufficient clinical information (i.e. age, menopausal state, menstrual state, hormonal therapy, risk factors, symptoms) is provided.

**Diagnostic criteria.** Diagnostic criteria are based on cyto-architectural evaluations and consider the epithelial and stromal endometrial cells and the cellular background. *Proliferative endometrium* is characterized by the presence of three-dimensional cylindrical epithelial endometrial clusters. Cytoplasm is scant. Nuclei are isomorphic with finely granular chromatin. Nucleoli are small or absent. Cellular polarity is preserved. Stromal cells are abundant and spindle-shaped. Background is clean. *Secretory endometrium* shows wide three-dimensional cylindrical epithelial clusters. Two-dimensional placards may be present in the late secretory phase. Cytoplasm is clear and obvious. Nuclei are isomorphic with dispersed chromatin and small or absent nucleoli. Cellular polarity is preserved. Stromal cells are abundant and decidualized (wide cytoplasm, round nuclei, finely granulated chromatin, micro-nucleoli). Background is clean or, in late secretory phase moderately inflammatory. *Endometrial atrophy* is characterized by the presence of small cylindrical three-dimensional epithelial clusters. Epithelial clusters may appear swollen in cystic atrophy. Cytoplasm is scant. Nuclei are isomorphic with dense chromatin and small or absent nucleoli. Cellular polarity is preserved. Stromal cells are abundant and spindle-shaped. Background is clean. Multinucleated histiocytes are often recognizable. *Hormonal administration* determines endometrial morphological modifications mainly depending on the type of the administered hormone, dosage, regimen (combined or sequential estrogen-progestin administration) the duration of the administration and, in fertile women, the menstrual phase in which the hormone is administered. The estrogens, when unopposed by progestins, produce a proliferative input on the endometrium determining a possible hyperplastic and even neoplastic progression. On the contrary, the progestins are responsible for arrest of proliferation, glandular secretion and decidualization of stromal cells. Prolonged progesterone treatment induces progressive arrest of the secretion and glandular atrophy. Cytological features in endometrial specimens reflect such hormonal induced modifications. *Endometrial hyperplasia* appears in cytological samples in form of numerous, wide three-dimensional epithelial endometrial clusters with variable cellular crowding and architectural disorder. In typical endometrial hyperplasia, the cytoplasm is commonly scant and the nuclei are isomorphic with finely granular chromatin and small or absent nucleoli. In atypical endometrial hyperplasia, the cytoplasm becomes evident and nuclei may show a moderate-grade of pleomorphism. Spindle shaped stromal cells are abundant in typical hyperplasia, while they are less represented in atypical hyperplasia. The background may enclose inflammatory cells. Main diagnostic criteria for *endometrial carcinoma* are: 1. architectural (loss of polarity, papillary cell clusters, dyshesive cells); 2. cellular (high nucleus/cytoplasm ratio, anisonucleosis and poikiloneucleosis, coarse and/or margined chromatin, nucleolar prominence, nuclear membrane incisures, cell cannibalism); 3. background (scarcity of stromal cells, necrosis). Cell cannibalism is observed more often in poorly differentiated tumors. Specimens obtained from patient affected by serous carcinomas are hypercellular (small cellular clusters with inconspicuous cellular crowding, single cells, bare nuclei). Psammoma bodies can sometimes be seen.

Endometrial cytology is an efficacious diagnostic procedure. It can be applied alone or in association with other diagnostic procedures to improve diagnostic accuracy.

**Common but remarkable cytologic features in thyroid tumours.**

**Description of two cases**

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**Introduction.** In some conditions, the common cytologic features of neoplastic thyroid lesions may be challenging and require scrupulous diagnostic procedures. Two cases are reported that support this supposition, and illustrate several diagnostic considerations in aspiration cytology, one related to intranuclear inclusions and other to papillary features in thyroid fine needle aspiration (FNA).

**1) Case report**

A 47-year-old woman presented for a nodule in the superior right lobe of the thyroid. Routine blood investigation revealed she was euthyroid with negative antibodies and with a slight increase in calcitonin. The nodule measured 11 mm in diameter, and echographically it was hypoechoic and solid. The
2) Case report

A 66-year-old man was referred to our hospital in 2005 for the appearance of a mass in the left lower neck that had been present for about two months. The lesion measured 2 cm and by ultrasound (US) it was strongly hypoechoic and nonhomogenous with irregular borders. A surgeon promptly performed a US-guided FNA and obtained a core biopsy. The cytological samples revealed strands and solid aggregates of cells with round-oval nuclei with frequent incisures and rare cytoplasmic nuclear inclusions (Fig. 4). Microscopic examination of biopsied tissue sections revealed a carcinoma with papillary architectural pattern, psammoma bodies and nuclear pseudoinclusions. By immunostaining, cells were positive for TTF-1: the final diagnosis was metastatic papillary carcinoma of the thyroid (Fig. 5).

Staging of the thyroid tumor showed evidence by CT of a nodule in the right apical inferior pulmonary lobe: at this point, bronchoscopy with transbronchial lung biopsy, FNA and bronchial washing were performed. The FNA smears showed a bloody background with the presence of neoplastic cells in small pseudopapillary aggregates with frequent nuclear inclusions (Fig. 6). The transbronchial biopsy showed histological findings consistent with a well differentiated adenocarcinoma with papillary features, microcalcifications and rare nuclear inclusions.

Conclusions. Even if the presence of intranuclear inclusions is a useful diagnostic criteria for diagnosis of thyroid papillary carcinoma, they are not pathognomonic for it. Intranuclear inclusions have been described in other pathologic conditions of the thyroid, such as Hurthle cell neoplasia and metastatic renal cell carcinoma as well as in hyalinizing trabecular adenoma. Cytologic diagnosis of papillary carcinoma relies on a series of cytologic features like monolayered, solid or papillary cellular sheets, nuclear incisures and inclusions, multinucleated cells, and thick colloid. Most of these features should be present before a diagnosis of papillary carcinoma is made. Cytological diagnosis of trabecular adenoma may be suspected when large pale cells with nuclear inclusions are radially disposed around metachromatic material in a background without colloid, multinucleated cells, papillary and follicular structures. A surgical excision should be recommended in the presence of such a cellular smear.

References

pseudoinclusions (Fig. 7). Cells were immunoreactive for TTF-1 and CEA, and negative for thyroglobulin (TG) and vimentin. A diagnosis of adenocarcinoma of the lung was made, most probably primary. A bronchial lavage was also positive for non-small cell carcinoma. The histological sections of the metastatic lymph node were reviewed and showed faint immunoreactivity for TG, but not unequivocally. CEA immunostain was negative. The original diagnosis of metastatic papillary carcinoma of the thyroid was nonetheless confirmed. Finally, an 8 mm left thyroid nodule was found at US, and a FNA showed a few neoplastic cells consistent with papillary carcinoma (Fig. 8). Radical dissection of the thyroid with bilateral cervical nodes confirmed a well differentiated papillary thyroid carcinoma with unilateral lymph node metastases. Surgical resection of the upper and medium pulmonary lobes was performed: microscopic examination of the resected tissue revealed a well differentiated adenocarcinoma of the lung with papillary features. The patient died 2 years after the first diagnosis from diffuse bone metastases of pulmonary adenocarcinoma.

Conclusions. The coexistence of papillary thyroid carcinoma and adenocarcinoma of the lung with papillary features may give rise to problematic situations when the first diagnostic step is a FNA cytological diagnosis of a metastatic cervical node. In this case, the morphologic features of the two tumors were similar and other than TG, immunostaining was not useful in defining the primary origin of the metastatic neoplasia. The application of immunostains in cytologic smears is quite useful, but restricted, since the small number of specimens generally reduces the possibility of using a large number of markers. In such situations, the reliability of using FNA to distinguish thyroid and pulmonary papillary tumors in a metastatic setting is questionable, and a precise clinico-pathological correlation is paramount. As in our case, in spite of the location of the nodules, the presence of two distinct tumors was suggested, and a biopsy is needed in order to histologically confirm the diagnosis.

Unusual cytologic aspects of a primary bladder neoplasm


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Bladder cancer is the 7th most common malignant neoplasm worldwide with an incidence of approximately 260,000 new cases per year in men and 76,000 in women, with a male/female ratio of 3.5:1. The incidence of bladder cancer is six times higher in industrialized countries than in the developing world. The most common bladder cancer is urothelial carcinoma, which accounts for up to 90% of all bladder malignancies. Other histotypes such as squamous cell carcinoma and adenocarcinoma are much more infrequent. 70 to 80% of patients with first diagnosis of urothelial bladder carcinoma have a non-invasive or minimally-invasive form. Most patients with infiltrating urothelial carcinoma have microhematuria, but macrohematuria and pain are also frequent. Cystoscopy and histology are considered the gold standard for diagnosis of urothelial carcinoma, but are invasive and traumatic for the patient. It is thus preferable to perform cytology in the first instance, which is highly sensitive for the identification of high-grade tumors. At our laboratory, "UCO Citodiagnostica e Istopatologia" of the University Hospital of Trieste, about 3400 urinary cytology samples are processed per year from over 1000 patients. The first diagnosis of cancer is present in about 50% of all positive urinary cytologies, while the remaining half is related to relapse of patients.
during follow up. The number of urinary samples and the possibility of daily cyto-histological comparison has allowed us to gain expertise in detection and characterization of urothelial lesions. The case we present is in a 80-year-old woman who undergoes regular controls for urinary disorders and intermittent haematuria. In addition to the routine laboratory investigations, she was prescribed three consecutive urinary cytology exams in which small atypical cells were observed. These elements, sometimes arranged in "vertebrae-like" structures, had nuclear hyperchromasia, irregularly distributed chromatin and scanty cytoplasm. In the background, there were some inflammatory elements and red blood cells. After an initial evaluation, which confirmed malignancy, we observed a cellular appearance and arrangement that was reminiscent of the cytological characteristics of small lung cancer. The case was reported as carcinoma with "small-cell aspects". Histology following cytectomy confirmed the diagnosis. In particular, the carcinoma showed immunohistochemical positivity for CK 18, CK 19, CK 8 ("dot-like" positivity), for chromogranin A, synaptophysin and CD 56. This pattern was compatible with neuroendocrine differentiation. The pathological stage on the surgical specimen was pT2b, N0, Mx G3-4. The cancer was a malignant urothelial neoplasm cytologically and histologically similar to the pulmonary histotype. 56% of patients with this rare bladder tumor at the time of diagnosis have regional lymph node, bone, liver and lung metastases. In our case, the bladder showed a large newly-formed button-like mass occupying much of the trigone district with no regional lymph node metastases. Approximately 8 months after surgery, the patient was found to have two nodules in the left breast about 17 and 19 mm diameter. The mammary lesions were aspirated under ultrasound guidance and by rapid cytology many small neoplastic cells were observed. Given the history of the patient and the cytological findings, it was decided to proceed in the same session to obtain a core biopsy of the lesions. The histological diagnosis was of secondary breast localizations of primary bladder cancer diagnosed previously. Metastases to the breast are very rare and most often are due to primary lung cancer. Even rarer are mammary locations from tumors of the genito-urinary tract. Small cell neuroendocrine carcinoma is characterized by an aggressive clinical course, and prognosis is related to the stage of the disease. Micrometastases may be already present at diagnosis in patients with localized lesions. In our case, mammary localization was the first sign of widespread progression of disease.

References


Large B cell lymphoma on pleural effusion

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A case of B large cell lymphoma diagnosed on pleural effusion is presented. A 74-year-old female presented with persistent dyspnea. A chest radiogram revealed a left pleural effusion. The fluid was treated by conventional and liquid-based methods. Cytological analysis showed medium- and large-size lymphoid cells that, also by immunohistochemical and cytofluorimetric studies, suggested a diagnosis of large B cell lymphoma. The differential diagnosis, in presence of a cytological pattern of atypical lymphoid cells in effusions is rather complicated, and includes immunoreactive conditions, malignancies and borderline proliferations. A complete knowledge of clinical setting and a panel of immunohistochemical antibodies are critical for diagnosis, and immunocytofluorimetric analysis can also be useful. Lymphoid proliferations in effusion are relatively uncommon, and a comprehensive analysis is required to make a useful clinical diagnosis.

A case of large cell neuroendocrine carcinoma of the lung: diagnostic challenges and pitfalls

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Introduction. Fine needle aspiration biopsy (FNAB) is used extensively in the clinical work-up of radiologically detected lung lesions. It allows pathologists to achieve a correct diagnosis and direct the patient towards the most appropriate treatment. In particular, it is well known that the pathologic distinction of small cell (SCLC) from non-small cell-lung carcinoma (NSCLC) has considerable therapeutic significance. Unfortunately, the exact definition of histologic types of lung cancer based on cytopathic samples poses several differential diagnostic challenges, due, for example, to scant cellularity and lack of tissue architecture.

Large-cell neuroendocrine carcinomas (LCNECs) are aggressive tumors, with the biological behavior similar to a high-grade neuroendocrine tumor, and with therapeutic strategies that may be different from SLCL. For these reasons, LCNEC must be correctly recognized and distinguished from SCLC, even by FNAB. LCNECs are more frequently suspected by pathologists at FNAB and small biopsies that closely combine cytomorphologic criteria with immunohistochemical markers of neuroendocrine differentiation such as synaptophysin, chromogranin A and CD56. Indeed, neither morphology nor immunohistochemistry alone are sufficient to reach a correct diagnostic assessment.

Case report. We present a case of a 43-year-old woman with a neoplastic mass in the upper lobe of the right lung. Microscopic examination of a single small bronchoscopic biopsy and cytopathic preparations obtained by transbronchial FNAB (Papanicolaou-stained and Giemsa-stained) revealed a tumor composed of large cells characterized by low nuclear/cytoplasmic ratio, abundant cytoplasm and nuclei with coarse chromatin and small to middle-sized nucleoli: on the basis of these features, a diagnosis of LCNEC was made.

A lobectomy with regional lymphadenectomy was performed. Histological examination of the tumor, conducted after extensive sampling and associated to immunohistochemical assays, confirmed the previous diagnosis (tumor stage: pT2/G3/N0/ Mx).
In ricordo di Franco Mollo

Il 29 luglio 2009 ci ha lasciati Franco Mollo, Professore Ordinario di Anatomia Patologica e Professore Emerito presso la Facoltà di Medicina e Chirurgia dell’Università di Torino, dopo una lunga malattia affrontata con serenità e sopportata con stoicismo.

Laureatosi in Medicina e Chirurgia nel 1954 con una tesi sulle cause di ematuria nell’idronefrosi sperimentale nel ratto, ha percorso tutta la carriera accademica nell’Ateneo torinese, come assistente del Prof. Mottura, come Professore Aggregato e infine come Professore Ordinario, lasciando il servizio nel 2002.

Franco Mollo è stato docente lucido e rigoroso per generazioni di medici e di specializzandi, sempre attento a sottolineare il significato e l’utilità clinica dello studio anatomopatologico accurato, soprattutto ai fini prognostici e per scopi terapeutici. Significativi in tal senso già i primi studi della fine degli anni ’50 su casistiche di melanomi o tumori dell’osso che si inserivano nel filone emergente delle indagini di surgical pathology che avrebbero avuto grande sviluppo e rilevanza negli anni successivi.

Aperto al nuovo e curioso di quanto la tecnologia metteva a disposizione della diagnostica e della ricerca, fin dai primi anni ’60 s’interessò alle applicazioni della microscopia elettronica in Anatomia Patologica, condividendo esperienze stimolanti e ricche di speranze con i pochi colleghi italiani interessati alla patologia ultrastrutturale, primo fra tutti il Prof. Vittorino Maritotti, allora punto di riferimento in proposito. Si fece carico della creazione e quindi della direzione del Centro di Microscopia Elettronica dell’Istituto di Anatomia Patologica dove si svolsero, fra le altre, ricerche sulla patologia ultrastrutturale dei linfomi, dei carcinomi polmonari, dei tumori del tessuto nervoso periferico, dell’epatite virale e delle malattie del muscolo striato.

Il suo interesse era soprattutto rivolto ai nuovi campi della diagnostica e della ricerca anatomo-patologica che si andavano aprendo che non di rado attiravano l’attenzione dei clinici, disponibili a cimentarsi in un campo improprio. Uno dei meriti che si debbono riconoscere a Franco Mollo è quello di aver contribuito con un costante impegno con i fatti alla conservazione all’a nostra disciplina di campi della diagnostica, che era la fine degli anni ’60 tendeva a essere appannaggio di nefrologi volonterosi e capaci, ma certo privi di una necessaria visione generale della patologia. Lo studio della biopsia renale anche con tecniche immunoistochechiche e ultrastrutturali ha rappresentato un campo di specifico interesse nel quale ha saputo coinvolgere allievi e collaboratori. In questa, come in altre occasioni, è emersa la capacità di motivare i giovani, di suscitare interesse ed entusiasmo, formando un gruppo che avrebbe continuato il percorso quando i suoi interessi si orientarono altrove.

Era certo una sua caratteristica l’irrequietezza intellettuale e la propensione a scegliere nuovi obiettivi da affrontare con immutato acume e rigore. Gli interessi scientifici si sono voltati, a partire dalla fine degli anni ’70, verso la patologia ambientale polmonare, collegando idealmente la propria ricerca con quella della Scuola, e in particolare del suo maestro Prof. Mottura. I frutti di indagini più che ventennali sono documentate da oltre 50 pubblicazioni su riviste internazionali, prevalentemente relative alla patologia da asbesto (mesoteliomi, asbestosi minima), ma anche al carcinoma polmonare e alla bronchite cronica. Sono questi campi indagati a fondo, in cui la valutazione anatomo-patologica si associa a indagini epidemiologiche e a correlazioni anatomo-cliniche, in cui le procedure spaziano dalla microscopia elettronica, alla immunoistochechica, alla semplice e tradizionale indagine autoptica. I suoi commenti
sugli studi di ampie casistiche autopiche richiamano alla nostra memoria il compiacimento nel sottolineare, con una vena di snobismo intellettuale velata da un tipico understatement sabaudo, la premenza dell’idea sul mezzo e l’identica efficacia scientifica delle sofisticate procedure del biologo molecolare e del coltello del settore. In questo stesso atteggiamento intellettuale anticonvenzionale si collocano anche la sottolineatura e il richiamo alla non univocità del giudizio diagnostico, al comprendere l’esistenza della componente soggettiva della valutazione, soprattutto quando il terreno diventa “fine” ed ultraspecialistico. Lungi dall’essere un cultore del relativismo, seppure tuttavia infondere la consapevolezza di quanto oggi viene riportato sulla variabilità diagnostica inter e intra-osservatore e sul bias che spesso è correlato alla applicazione di tecniche sofisticate di laboratorio. La competenza e l’impegno professionali non si sono esauriti con l’uscita dal mondo accademico, ma hanno continuato a trovare applicazione pratica offrendo il supporto tecnico alla magistratura torinese impegnata a contrastare l’inquinamento dell’ambiente e del mondo del lavoro. Emergiva anche in queste situazioni la capacità di un approccio razionale, di offrire dimostrazioni documentate e rigorose, valutazioni equilibrate, brave di spirito fazioso, qualità riconosciute anche da chi, nel momento più imprevedibili e che, unita a una fine ironia austera, si celasse un’allegria che affiorava nei momenti più imprevedibili, di razionale approccio ai problemi, di capacità di confronto franco, talora anche duro, ma sempre equilibrato, di razionale approccio ai problemi intellettuali e pratici, di disponibilità a farsi carico di competenze e per spiegare le cause dell’evento. In sintesi, egli ha insegnato un metodo di lavoro organizzato, non estemporaneo, non individualistico, e uno stile di direzione pacato, ma fermo, basato sull’analisi dei problemi, sul coinvolgimento degli attori, sull’attuazione finale delle decisioni.

La sua personalità non si esauriva nell’attività professionale, ma era aperta verso la cultura e la politica. Chi gli è stato vicino e ha convissuto gli anni della contestazione, può testimoniarne la relaborazione dei fermenti e delle istanze proprie del tempo che, assolutamente estranea allo spirito barricadiero e talora intelectualmente approssimativo, lo ha portato a considerare l’impegno politico come un dovere civile, vissuto anche con fatica certamente senza vantaggi personali. Ricca è l’eredità lasciata a quanti hanno avuto il privilegio di condividere un lungo periodo di attività professionale, didattica e scientifica e di godere della sua amicizia, ma anche ai tanti allievi, collaboratori e colleghi, non solo anatomopatologi. È stato un esempio di costante impegno nella faticosa attività quotidiana, di capacità di confronto franco, talora anche duro, ma sempre equilibrato, di razionale approccio ai problemi intellettuali e pratici, di disponibilità a farsi carico di compiti magari poco gratificanti. È bello però, alla fine di queste nostre righe ricordare come, fra le pieghe di una personalità seria e forse anche all’apparenza un po’ austera, si celasse un’allegria di fondo che affiorava nei momenti più improveribili e che, unita a una fine ironia (e autoironia) sapeva sdrammatisare le evenienze della vita, sino ad essere in grado di aiutarlo (e aiutare quanti gli erano vicini) ad affrontare le malattia che ha portato alla conclusione della sua presenza tra noi.

Alberto Andrion, Gianna Mazzucco, Guido Monga