PATHOLOGICA

Journal of the Italian Society of Anatomic Pathology and Diagnostic Cytopathology, Italian Division of the International Academy of Pathology

REVIEW

329 Computed tomography-histologic correlations in lung cancer
I. Ariozzi, I. Paladini, L. Gnetti, M. Silva, D. Colombi, M. De Filippo, N. Sverzellati

ORIGINAL ARTICLES

337 Tumours of the skin adnexa: a case series with focus on multiple segmental forms

342 Role of on-site microscopic evaluation of kidney biopsy for adequacy and allocation of glomeruli: comparison of renal biopsies with and without on-site microscopic evaluation
S.M. Gilani, D. Ockner, H. Qu

CASE REPORTS

346 Adenocarcinoma arising in a tailgut cyst: a case report
S. Rammeh, S. Ben Abdelkrim, M.H. Ben Hadji Khalita, R. Letaief, M. Mokni

349 Breast cholesterol granuloma: a report of two cases with discussion on potential pathogenesis
J. Bezić, M. Piljić-Burazer

353 Synchronous occurrence of pulmonary adenocarcinoma and pleural diffuse malignant mesothelioma

357 Coexistence of lobular granulomatous mastitis and ductal carcinoma: a fortuitous association?
F. Limaierm, A. Khadhar, F. Hassan, S. Bouraoui, A. Lahmar, S. Mzabi

361 Letter to the Editor
V. Eusebi
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RESULTS

The multidisciplinary approach is ideal in the management of patients with lung cancer. Multidisciplinary evaluation strengthens the differential diagnosis of aspecific radiological findings, indeed. Notably, the differential diagnosis of early stage lung cancer is a current challenge of CT imaging because the earlier the detection, the lower the accuracy of radiological features. This is particularly true for the most common subtype of lung cancer, adenocarcinoma, because it shows various radiological features. Such variability is also reflected by the 2011 classification of lung cancer, that likely affected the diagnostic agreement between radiologist and clinician.

This review discusses the common issues of lung cancer diagnosis by paired radiological-histologic interpretation of CT findings.

ORIGINAL ARTICLES

Tumours of the skin adnexa: a case series with focus on multiple segmental forms


Objective. Skin adnexal tumours (SAT) as a whole are rare tumours, and most of our current knowledge on SAT is from single case reports or small series focused on single histotypes. The purpose of this paper is to review a series of benign and malignant SAT diagnosed in a 20-year period.

Methods. All consecutive cases of SAT diagnosed between January 1992 and December 2011 were retrieved. All slides were reviewed and diagnosed according to currently accepted criteria.

Results. 281 consecutive cases of SAT were found. The majority of cases (94.3%) were benign, the most frequent histotypes were eccrine spiradenoma, hidrocystoma, eccrine poroma, syringoma, sebaceous adenoma and trichofolliculoma. Benign SAT affected adult males more frequently (M/F = 153/112) (mean age 59 years). Recurrences were rare (2/265). Three cases of multiple segmental spiradenoma were observed. Malignant SAT constituted only 5.7% of all cases comprising sebaceous carcinoma, extramammary Paget disease and apocrine carcinoma. There was a slight female predilection (M/F = 79/151) (mean age 72 years), although patients were older than those affected by benign SAT. All neoplasms were small and no recurrences were recorded.

Conclusion. SAT are rare and most frequently benign. Correct diagnosis and complete surgical removal are important.

Role of on-site microscopic evaluation of kidney biopsy for adequacy and allocation of glomeruli: comparison of renal biopsies with and without on-site microscopic evaluation

S.M. Gilani, D. Ockner, H. Qu

Evaluation of kidney core biopsies ideally begins with on-site microscopic examination for adequacy and allocation of tissue for light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM). However, some renal biopsies are not microscopically evaluated by a pathologist at the time of procedure, and are allocated without on-site evaluation. This study compares the actual outcome of these two techniques. We reviewed the reports of patients who underwent kidney biopsy for medical causes in the past two years. Eighty-eight biopsies had on-site microscopic evaluation by pathologists, and 70 biopsies did not undergo on-site evaluation.

For biopsies without on-site evaluation, no glomeruli were seen in 5 (7.14%) cases for LM, 11 (15.71%) cases for IF and 6 (8.57%) cases for EM. In cases with on-site evaluation, the absence of glomeruli was identified in 1 (1.13%) case for LM, 3 (3.4%) for IF and 3 (3.4%) for EM. The biopsies with on-site microscopic evaluation had 5.68% of the cases considered as inadequate, while 22% of biopsies without on-site evaluation were considered inadequate. The biopsies with on-site evaluation tended to have more glomeruli obtained during the procedure (p < 0.0005).

Without on-site evaluation, the likelihood of getting an inadequate specimen compared to on-site evaluation is nearly four times greater.
Computed tomography-histologic correlations in lung cancer

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Key words
Lung cancer • CT • Histology • Differential diagnosis

Summary
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The multidisciplinary approach is ideal in the management of patients with lung cancer. Multidisciplinary evaluation strengthens the differential diagnosis of aspecific radiological findings, indeed. Notably, the differential diagnosis of early stage lung cancer is a current challenge of CT imaging because the earlier the detection, the lower the accuracy of radiological features. This is particularly true for the most common subtype of lung cancer, adenocarcinoma, because it shows various radiological features. Such variety is also reflected by the 2011 classification of lung cancer, that likely affected the diagnostic agreement between radiologist and clinician. This review discusses the common issues of lung cancer diagnosis by paired radiological-histologic interpretation of CT findings.

Introduction
Primary cancers of the lung encompass several histological entities that arise from various pulmonary components. A multidisciplinary approach is now recommended for diagnosis and treatment planning because it integrates radiologic and histologic data. Since its inception, imaging has been included in the management of patients with lung cancer. Currently, computed tomography (CT) is the radiological gold standard because it grants very high sensitivity for detection of lung cancer. Of note, the increasing use of thin-section collimation allows the identification of very small and subsolid nodules that were previously undetectable. The advantage of early detection, however, is weakened by a decrease in specificity that raised concerns about differential diagnosis and management of these findings. In this scenario, comprehensive and multidisciplinary approach is ideal. In particular, such a synergy is made easier by the increasing familiarity of non-radiologist specialists with imaging features.

The aim of this review is to summarize the main CT features and histologic correlation of the most common lung cancers arising from the epithelial surface of bronchi and alveoli.

Basic computed tomography signs of lung cancer
Primary lung cancer usually appears on computed tomography (CT) as a subsolid nodule, solid nodule or mass. A pulmonary nodule is defined as a sharply-defined circular opacity that is 2 to 30 mm in diameter. Solid nodules are those composed of soft tissue that completely obscures the lung parenchyma. In distinction, subsolid nodules (SSNs) are defined as areas of increased lung attenuation through which normal parenchymal structures such as pulmonary vessels can be seen. A pulmonary mass is any pulmonary, pleural, or mediastinal lesion seen as an opacity greater than 3 cm in diameter (without considering contour, border, or density characteristics). A pulmonary mass usually implies a solid or partly solid opacity.
Benign versus malignant CT features of pulmonary nodules

Pulmonary nodules may have various etiologies, including neoplasm, infection and inflammation, vascular, and congenital abnormalities. Still, the overall likelihood of malignancy for a pulmonary nodule is low. First, it is essential to establish if nodules are multiple with specific distribution within the pulmonary secondary lobule (e.g. perilymphatic or centrilobular). Multiple small incidental nodules are considered independently when lacking a distinctive relationship to structures within the secondary lobule. Otherwise, the description of correlation between nodule distribution and non-neoplastic etiology is beyond the scope of this article.

Accepted predictors of malignancy for a lung nodule are as follows: upper-lobe location, size > 20 mm, ill-defined or spiculated margins, air bronchograms, inhomogeneous central attenuation, cavitation with nodular wall thicker than 15 mm. Moreover, round nodules are more likely to be malignant than triangular or flat-shaped nodules. The latters may be intrapulmonary lymph nodes or granulomas. Of note, intrapulmonary lymph nodes are increasingly recognized as a benign cause of solitary pulmonary nodule on CT. Notably, lymph node has generally perifissural or subpleural location (< 15 mm from pleural surface), usually with coffee-bean shape and thin, linear opacity of connection to pleural surface.

Calcification and fat tissue can both be detected on CT. Completely calcified nodules are almost invariably benign. Otherwise, malignant calcification is rare and is usually stippled or eccentric. The detection of fat density in a pulmonary nodule strongly suggests hamartoma.

Subsolid nodules (SSNs) include both pure ground glass nodules (pure GGNs) and part-solid ground-glass nodules (part-solid GGNs). Of note, the likelihood of malignancy is greater in SSN than solid nodule. In a lung cancer screening setting, 63% incidence of malignancy was reported for part-solid GGNs, whereas it was lower for pure GGNs and solid nodules (18% and 7%, respectively). Hence, the solid component of SSN is the radiological feature with the strongest association with malignancy.

Both pure GGNs and part-solid GGNs may be transient because they may reflect infectious or inflammatory process. Therefore, a conservative approach with initial follow-up is recommended. On the other hand, persistence is a malignant feature for SSN. Moreover, features suggesting malignancy of larger SSNs also include lobulated margins, pleural tags, air bronchograms, and internal lucencies. However, it was demonstrated that CT features cannot reliably differentiate benign versus malignant persistent SSNs.

Interval change in size and density of SSN should be thoroughly assessed before surgical approach. Of note, in a lung cancer screening setting, the progression rate of SSN toward clinically relevant disease was extreme-
ly low. These data support active surveillance of small SSN, indeed. However, the optimal balance between prompt resection and the need to limit overtreatment is still a matter of debate.

Cautiously, pulmonary nodule is classified as an indeterminate, possibly malignant lesion if no definite benign morphologic finding is seen. Then, the management depends on size and density, namely: i) if solid and larger than 8 mm, the nodule should be evaluated by other non-invasive (e.g. PET) or invasive procedures; if solid and smaller than 8 mm, it should be followed-up according to predetermined time intervals as suggested by major international guidelines; ii) SSNs could also be followed-up, but surgery is generally suggested for persistent ones because of their high likelihood of malignancy (Tab. I).

**CT-histologic correlations of subsolid nodules and invasive mucinous adenocarcinoma**

SSNs may represent a variety of disorders ranging from inflammatory abnormalities to lung neoplasm. Evolution of the SSN over time is the most accurate feature for differential diagnosis between benign and malignant finding (Figs. 2, 3). Otherwise, other CT features of SSN may allow narrowing the differential diagnosis. Neoplastic pure GGN reflects focal incomplete obliteration of airspace. Notably, pure GGN may associate either to haemorrhagic tumor or to “lepidic” growth pattern of neoplastic cells lining over alveolar wall (Fig. 2). Nevertheless, these pure GGNs may be caused by benign abnormalities, such as inflammation, edema, fibrosis, partial collapse of alveoli, focal benign haemorrhage, infectious load (macrophages, pus, debris, colonization from bacteria, virus, and fungi).

Neoplastic part-solid GGN is seen in minimally-invasive (MIA) or invasive adenocarcinoma. Notably, the solid component is usually central and represents the invasive portion of the neoplasm, whereas, the ground glass opacity is usually peripheral and reflects areas of lepidic growth (Fig. 2). Contributors to solid component may be various, namely: alveolar collapse, deposition of inflammatory cells and fibroblast, fibrosis and fibrotic scar. Furthermore, the amount of ground glass component directly correlates with the likelihood of mutation of epidermal growth factor receptor (EGFR). Accordingly, the 2011 Multidisciplinary Classification of Adenocarcinoma focused on the strong relation between CT findings and histology. Non-mucinous adenocarcinoma shows indeed a direct correlation between size of the solid component on CT and tumoral invasion on histology. According to radiologic-histologic correlation, the 2011 classification implies T staging to be calculated on the diameter of solid component, whereas in previous classification the whole nodule was measured, including the ground glass component. Hence, two main thresholds were suggested for the size of solid component: diameter < 3 mm defines adenocarcinoma in situ (AIS), diameter 3-5 mm defines minimally invasive adenocarcinoma (MIA), and diameter > 5 mm defines invasive non-mucinous adenocarcinoma (Tab. II). However, this correlation is less strong in mucinous adenocarci-

<table>
<thead>
<tr>
<th>Tab. I.</th>
<th>Management of pulmonary nodule (adapted from reference 25).</th>
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<tbody>
<tr>
<td><strong>Nodule Type</strong></td>
<td><strong>Management Recommendation</strong></td>
</tr>
<tr>
<td>Solitary Pure GGN</td>
<td></td>
</tr>
<tr>
<td>&lt; 5 mm</td>
<td>No additional follow up required</td>
</tr>
<tr>
<td>≥ 5 mm</td>
<td>Initial follow-up at 3 months to confirm persistence, then annual CT surveillance for a minimum of 3 years</td>
</tr>
<tr>
<td>Solitary part-solid nodules</td>
<td>Initial follow-up at 3 months to confirm persistence. If persistent and solid component &lt; 5 mm, yearly CT surveillance for a minimum of 3 years. If persistent and solid component ≥ 5 mm, biopsy or surgical resection</td>
</tr>
<tr>
<td>Multiple subsolid nodules</td>
<td></td>
</tr>
<tr>
<td>Pure GGNs ≤ 5 mm</td>
<td>Follow-up CT at 2 and 4 years</td>
</tr>
<tr>
<td>Pure GGNs &gt; 5 mm without dominant lesion</td>
<td>Initial follow-up CT at 3 months. If persistent, yearly CT surveillance for a minimum of 3 years</td>
</tr>
<tr>
<td>Dominant nodule with part-solid or solid component</td>
<td>Initial follow-up at 3 month to confirm persistence. If persistent biopsy or surgical resection is recommended especially for lesions with &gt; 6 mm solid component</td>
</tr>
</tbody>
</table>
noma because the solid component may represent both the neoplastic invasion and the alveolar collapse related to mucinous obstruction.  

Multiple SSNs are more likely preinvasive lesions, whereas invasive adenocarcinoma more commonly looks like a solitary SSN. A number of molecular studies have demonstrated that multifocal SSNs are more likely synchronous primary cancers rather than intrapulmonary spread of disease. Furthermore, non-malignant multiple SSNs are also seen in pulmonary infections (e.g. viral), eosinophilic lung diseases, drug toxicity, radiation-induced pulmonary disease, and inhalational pulmonary disease from cigarette smoke or organic and inorganic dust.

The main CT features of invasive adenocarcinoma with predominant lepidic growth can be related to the histologic abnormalities as follows: 1) ground glass opacity caused by replacement, tumoral growth or lepidic growth of either cuboidal or columnar cells, without invasion of the stroma; 2) consolidation related to active fibroblasts and tumor cells proliferation evolving into areas of retained mucus and alveolar collapse (consolidation can even evolve to a lobar swelling and a bulging of the interlobar fissure); 3) crazy paving pattern described as diffuse ground-glass attenuation with superimposed interlobular septal thickening and intralobular lines related to interstitial infiltration by tumor cells or inflammatory component (more frequently observed in the mucinous multifocal disease); 4) tree-in-bud opacities (uncommon feature) representing bronchiolar dilatation and filling of mucus or fluid, resembling a branching or a budding tree. Besides, invasive adenocarcinoma may associate with CT features, such as: bubble-like radiolucencies, the angiogram sign (seen as enhancing branching pulmonary vessels in a homogeneous low-attenuating large consolidation of lung parenchyma). The histological type of invasive adenocarcinoma can be roughly predicted by CT. In particular, the mucinous type commonly appears as areas of extensive consolidation, ground glass or crazy paving representing the tumour growth along alveolar wall or alveolar space filled with mucin. On the other hand, the non-mucinous type manifests as a solitary SSN, reflecting a tumoural growth along alveolar wall with preserved underlying framework. Mihara et al. also found a correlation between three bronchioloalveolar subtypes (globet cells, Clara cells and type 2 pneumocyte subtype) and their CT patterns, but an attempt of such a distinction in clinical practice is likely unreliable.

A number of lung abnormalities have been associated with the adenocarcinoma, such as: tuberculous scarring, lung fibrosis, congenital pulmonary airway malformation (CPAM). Because they may represent precursor lesions of adenocarcinoma, the prompt recognition of these findings should grant timely histologic diagnosis. Moreover, it has been suggested that an unstable epithelial component within the wall of congenital cyst may be responsible for the development of adenocarcinoma. Also, areas of metaplasia within fibrosis or malformation may evolve to dysplastic lesions.

CT features of the other main histological subtypes of lung cancer

The four major histological types of lung cancer (e.g. squamous cell carcinoma, adenocarcinoma, small cell carcinoma and large cell carcinoma) commonly show different CT features. Squamous cell carcinoma usually grows in the main, lobar or segmental bronchi as an endobronchial mass that...
spreads by infiltration of the bronchial wall and rapid invasion into lymphatic system \(^\text{41,42}\). At the first CT diagnosis, squamous cell adenocarcinoma appears as a large, rounded solid mass that may cavitate and invade hilar and mediastinal structures, typically with lymph node involvement \(^\text{43}\). Only about 30% of squamous cell carcinoma occur as solitary nodule or mass at the lung periphery. Secondary signs of bronchial obstruction (e.g. atelectasis, obstructive pneumonia, mucous plugs, etc.) are frequently associated to squamous cell carcinoma that is often indistinguishable from the surrounding collapsed parenchyma. Adenocarcinoma appears as a peripheral solitary nodule or mass in 75% of cases, more commonly in the upper lobes. Yet, adenocarcinoma may also grow on main airways as a central mass with mediastinal lymph node enlargement, thus mimicking squamous cell carcinoma \(^\text{41-44}\). Small cell carcinoma mostly originates from the main or lobar bronchi as a voluminous hilar or para-hilar mass associated with parenchymal invasion and massive mediastinal lymph node enlargement \(^\text{41,45}\). Therefore, CT features of small cell carcinoma may overlap findings of squamous cell carcinoma \(^\text{46}\).

Large cell carcinoma occurs as a voluminous peripheral mass (> 40 mm) with irregular margins, in more than 60% of cases. It is generally larger in size than adenocarcinoma at the time of diagnosis. Cavitation and calcification are rare. Of note, early extrapulmonary metastases are frequently observed at first diagnosis \(^\text{41,47}\).

<table>
<thead>
<tr>
<th>Histopathologic findings small biopsy/citology: IASLC/ATS/ERS 2011 Classification of Lung Adenocarcinoma</th>
<th>CT findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinvasive lesions</td>
<td></td>
</tr>
<tr>
<td>Atypical adenomatous hyperplasia (AAH)</td>
<td>Pure ground-glass nodule, typically &lt;5 mm in diameter, although these lesions can be as large as 1 to 2 cm.</td>
</tr>
<tr>
<td>Adenocarcinoma in situ (AIS)</td>
<td>Mostly nonsolid nodule, slightly more opaque than AAH.</td>
</tr>
<tr>
<td>Nonmucinous AIS</td>
<td>Pure ground glass nodule &gt;5 mm in diameter. It may also appear as part-solid GGN for the presence of alveolar collapse.</td>
</tr>
<tr>
<td>Mucinous AIS</td>
<td>Solitary solid nodule.</td>
</tr>
<tr>
<td>Mixed mucinous/nonmucinous</td>
<td>Overlap CT features of mucinous and non-mucinous</td>
</tr>
<tr>
<td>Minimally invasive adenocarcinoma (MIA)</td>
<td>The lepidic growth portion is seen as hazy ground glass component, whereas the invasive portion is solid and usually with diameter &lt;5 mm. Alveolar collapse, inflammatory cells, fibroblast, fibrosis, and fibrotic scar appear as solid area.</td>
</tr>
<tr>
<td>Nonmucinous MIA (usually)</td>
<td>Either pure GGN or part-solid GGN with a small solid component ≤ 5mm.</td>
</tr>
<tr>
<td>Mucinous MIA (rare)</td>
<td>Mucin may contribute to a solid, part-solid or predominantly solid appearance of the tumor at CT.</td>
</tr>
<tr>
<td>Mixed mucinous/nonmucinous MIA</td>
<td>Overlap CT features mucinous/nonmucinous.</td>
</tr>
<tr>
<td>Invasive adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Morphologic adenocarcinoma pattern clearly present</td>
<td></td>
</tr>
<tr>
<td>Lepidic predominant pattern</td>
<td>Usually manifest as a solid or part solid nodule, only rarely appears as pure GGNs.</td>
</tr>
<tr>
<td>Acinar predominant pattern</td>
<td></td>
</tr>
<tr>
<td>Papillary predominant pattern</td>
<td></td>
</tr>
<tr>
<td>Micropapillary predominant pattern</td>
<td></td>
</tr>
<tr>
<td>Solid predominant pattern</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma with (describe pattern present) and clear cell features</td>
<td>Solid or predominantly solid nodule or mass with a small non solid component.</td>
</tr>
<tr>
<td>Adenocarcinoma with (describe pattern present) and signet ring features</td>
<td></td>
</tr>
<tr>
<td>Morphologic adenocarcinoma pattern not present: non small cell carcinoma, favor adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Variants of invasive adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Invasive mucinous adenocarcinoma</td>
<td>Aspecific appearance: single or multifocal (sometimes multilobar) solid, part-solid or ground glass nodules or masses, frequently centrilobular or bronchocentric. Consolidation and air bronchogram are also seen.</td>
</tr>
<tr>
<td>Colloid</td>
<td>Typically seen as solid or predominantly solid.</td>
</tr>
<tr>
<td>Fetal (low and high grade)</td>
<td></td>
</tr>
<tr>
<td>Enteric</td>
<td></td>
</tr>
</tbody>
</table>
Bronchial carcinoid

Bronchial carcinoids may be typical or atypical. Both types of carcinoid appear as a spherical or ovoid nodule or mass with a well-defined and slightly lobulated border. However, atypical carcinoids have been reported to be larger than typical carcinoids, with mean diameter of 3.6 cm and 2.3 cm, respectively. Calcifications occur in up to 30% of lesions showing punctate or diffuse pattern. Both typical and atypical carcinoids show high contrast enhancement due to the abundant vascular stroma and the numerous thin-walled blood vessels. The majority of carcinoids belongs to the typical subtype (80-90% of cases). Notably, typical carcinoid is usually seen as an endobronchial nodule in the main, lobar, or segmental airways or as a hilar-perihilar mass associated with bronchial narrowing, deformation, obstruction, and even secondary signs of airway obstruction such as atelectasis or obstructive pneumonia (Fig. 5). Peripheral lesions are more likely associated with the atypical subtype.

Mimickers of lung cancer on CT

Many diseases may appear as pulmonary nodule, mass or irregular consolidation on CT. Thus, these CT abnormalities may be non-specific of malignancy when other signs of neoplastic lesion are lacking (e.g. contiguous organs invasion, metastases etc.). Irregular consolidation or masses resembling lung tumors may also occur in infections, autoimmune diseases, and inflammatory disorders. Differential diagnosis is made even more difficult by aspecific and overlapping clinical findings. Consolidation without obvious cavitation, as well as few large nodules may be all forms of radiological presentation of granulomatosis with polyangiitis, previously known as Wegener disease (Fig. 6). Such a vasculitis may

Fig. 5. Typical carcinoid in a 43-year-old individual. CT scan shows a nodule obstructing the right lower lobe bronchus and atelectasis in the right upper lobe.

Fig. 4. Mucinous adenocarcinoma (formerly bronchioloalveolar carcinoma) in a 54-year-old woman. (a) Thin-section CT image shows patchy consolidation with air bronchogram, ground glass opacity, crazy paving pattern (arrow), and scant nodules. (b,c) Photomicrographs (original magnification, X10, X4; hematoxylin-eosin stain) show mucin-containing tumor cells along the alveolar walls. The alveolar spaces are filled with mucin, as well.
also cause airway involvement, with stenosis of large airways that might be misinterpreted as lung cancer. Occasionally, a large solitary nodule or mass with irregular margins may be seen in organizing pneumonia, prompting invasive investigations for lung cancer. Also exogenous lipoid pneumonia can manifest with irregular mass-like opacities. In this case, superimposed fibrosis on CT can make differential diagnosis with lung cancer more difficult. A striking diagnostic CT clue for lipoid pneumonia is fat attenuation within the pulmonary lesion.

Pulmonary infections such as cryptococcosis, actinomycosis, histoplasmosis or nocardiosis may present as large masses or nodules mimicking lung cancer. In the presence of specific anamnestic data, the radiologist may suggest infectious differential diagnosis. IgG4-related lung disease may also cause misdiagnosis of pulmonary findings because it may appear as large solid or subsolid nodules, with ground glass opacity (Fig. 7). Such a spectrum of appearance may particularly overlap adenocarcinoma with lepidic growth pattern.

References

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Tumours of the skin adnexa: a case series with focus on multiple segmental forms

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Key words
Skin adnexa • Eccrine spiradenoma • Multiple segmental eccrine spiradenoma

Objective. Skin adnexal tumours (SAT) as a whole are rare tumours, and most of our current knowledge on SAT is from single case reports or small series focused on single histotypes. The purpose of this paper is to review a series of benign and malignant SAT diagnosed in a 20-year period.

Methods. All consecutive cases of SAT diagnosed between January 1992 and December 2011 were retrieved. All slides were reviewed and diagnosed according to currently accepted criteria.

Results. 281 consecutive cases of SAT were found. The majority of cases (94.3%) were benign, the most frequent histotypes were eccrine spiradenoma, hidrocystoma, eccrine poroma, syringoma, sebaceous adenoma and trichofolliculoma. Benign SAT affected adult males more frequently (M/F = 153/112) (mean age 59 years). Recurrences were rare (2/265). Three cases of multiple segmental spiradenoma were observed. Malignant SAT constituted only 5.7% of all cases comprising sebaceous carcinoma, extramammary Paget disease and apocrine carcinoma. There was a slight female predilection (M/F = 7/9) (mean age 72 years), although patients were older than those affected by benign SAT. All neoplasms were small and no recurrences were recorded.

Conclusion. SAT are rare and most frequently benign. Correct diagnosis and complete surgical removal are important.

Introduction
Skin adnexal tumours (SAT) constitute a wide spectrum of lesions differentiating towards epithelial adnexal structures. SAT are classified according to their presumed origin into those with apocrine, eccrine, follicular and sebaceous differentiation. Almost all of these types of tumours can have benign and malignant counterparts. Even though the histopathological criteria to define the biological behaviour are well established, SAT form a wide morphological spectrum of lesions, that can sometimes cause difficult histological diagnosis. Only a few recently published papers in the literature considered appendageal tumours as a single group, while most of our current knowledge on SAT is derived from single case reports or small series focusing on a simple histotype.

The purpose of this paper is to review a series of benign and malignant SAT diagnosed over a 20-year period.

Methods
All cases of skin adnexal tumours diagnosed between 1 January 1992 and 31 December 2011 at the Section of Anatomic Pathology of the Department of Biomedical Sciences and Neuromuscular Disorders at Bellaria Hospital were retrieved.

The medical and surgical records of the cases were analyzed, and all original slides were reviewed and diagnosed according to current criteria. To establish the incidence of SAT, the number of cases retrieved was compared with the total number of non-melanocytic skin epithelial tumours, including squa-
mous and basal cell carcinomas, diagnosed in the same time interval.

Results

281 cases were retrieved and constituted the basis of the present study. Patients consisted of 160 males (56.93%) and 121 females (43.07%), with an age from 12 to 99 years (mean age 62.82 years). The incidence of SAT was evaluated among non-melanocytic epithelial tumours of the skin. In the same time interval, besides the 281 SAT cases, 7567 basal cell carcinomas and 1459 squamous cell carcinomas were diagnosed. Therefore, SAT constituted 3.01% of a total of 9026 cases of epithelial tumours of the skin. Clinical data are summarized in Tables I and II.

The vast majority of SAT cases were benign (265 cases, 94.3%), while only 16 (5.7%) malignant cases were observed.

Tab. I. Clinical data of benign SAT.

<table>
<thead>
<tr>
<th>Histotype</th>
<th>No. cases</th>
<th>M\F</th>
<th>Age range (mean±SD)</th>
<th>Diameter range (mean±SD)</th>
<th>Recurrences &amp; multiple nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiradenoma</td>
<td>55</td>
<td>32/23</td>
<td>21-90 (52.5±16.1)</td>
<td>0.2-3 cm (1.2±1.08 cm)</td>
<td>1 recurrence after 6 years 3 multiple nodules</td>
</tr>
<tr>
<td>Hidrocystoma</td>
<td>52</td>
<td>30/22</td>
<td>22-84 (58.02±16.0)</td>
<td>0.2-2.5 cm (0.81±0.47 cm)</td>
<td>-</td>
</tr>
<tr>
<td>Eccrine Poroma</td>
<td>45</td>
<td>21/24</td>
<td>31-80 (60.02±13.3)</td>
<td>0.3-3.7 cm (0.90±0.65 cm)</td>
<td>1 recurrence after 7 months</td>
</tr>
<tr>
<td>Syringoma</td>
<td>41</td>
<td>21/20</td>
<td>32-93 (55.62±15.9)</td>
<td>0.2-3.2 cm (0.95±0.70 cm)</td>
<td>-</td>
</tr>
<tr>
<td>Sebaceous adenoma</td>
<td>24</td>
<td>21/3</td>
<td>32-84 (68.29±13.9)</td>
<td>0.4-3.2 cm (0.64±0.57 cm)</td>
<td>-</td>
</tr>
<tr>
<td>Trichofolliculoma</td>
<td>21</td>
<td>14/7</td>
<td>21-89 (59.47±21.2)</td>
<td>0.3-1.5 cm (0.54±0.34 cm)</td>
<td>-</td>
</tr>
<tr>
<td>Trichoblastoma</td>
<td>17</td>
<td>9/8</td>
<td>12-82 (62.82±19.1)</td>
<td>0.3-3.5 cm (1.1±0.86 cm)</td>
<td>-</td>
</tr>
<tr>
<td>Trichilemmoma</td>
<td>10</td>
<td>5/5</td>
<td>24-79 (55.4±18.7)</td>
<td>0.4-2.2 cm (0.85±0.54 cm)</td>
<td>-</td>
</tr>
</tbody>
</table>

Tab. II. Clinical data of malignant SAT.

<table>
<thead>
<tr>
<th>Histotype</th>
<th>No. cases</th>
<th>M/F</th>
<th>Age range (median±SD)</th>
<th>Diameter range (median±SD)</th>
<th>Recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sebaceous carcinoma</td>
<td>6</td>
<td>2/4</td>
<td>39-86 (65.83±18.1)</td>
<td>1.3-2.4 cm (1.74±0.56 cm)</td>
<td>-</td>
</tr>
<tr>
<td>EMPD</td>
<td>6</td>
<td>1/5</td>
<td>62-99 (78.33±14.8)</td>
<td>0.2-1.5 cm (01.06±0.58 cm)</td>
<td>-</td>
</tr>
<tr>
<td>Apocrine carcinoma</td>
<td>4</td>
<td>4/0</td>
<td>61-86 (73.33±12.5)</td>
<td>1-1.7 cm (1.35±0.49 cm)</td>
<td>-</td>
</tr>
</tbody>
</table>

Legend: No. cases=number of cases; M=male; F=female.
EMPD=extra-mammary Paget disease.

Tab. III. Sites of benign lesions.

<table>
<thead>
<tr>
<th></th>
<th>Torso</th>
<th>Scalp</th>
<th>Face</th>
<th>Axilla</th>
<th>Back</th>
<th>Limbs</th>
<th>Periocular</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hidroc.</td>
<td>-</td>
<td>7</td>
<td>23</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Syring.</td>
<td>2</td>
<td>2</td>
<td>21</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Poroma</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>21</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Spirad.</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td>-</td>
<td>14</td>
<td>17</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Trichob.</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Trichil.</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Trico.</td>
<td>-</td>
<td>2</td>
<td>15</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Seb. Ad.</td>
<td>-</td>
<td>1</td>
<td>15</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>30</td>
<td>96</td>
<td>7</td>
<td>26</td>
<td>54</td>
<td>20</td>
<td>13</td>
</tr>
</tbody>
</table>

Legend: Ad=adenoma; Ca=carcinoma; Seb=sebaceous; Apo=apocrine; Trico=trichofolliculoma; Trichil=trichilemmoma; Tricobl=trichoblastoma; Spirad=spiradenoma; Syring=syringoma; Hidroc=hidrocystoma.
**Benign SAT**

The most frequent histotypes of benign SAT (94.3%), in descending order were: spiradenoma (55 cases), hidrocystoma (52 cases), eccrine poroma (45 cases), syringoma (41 cases), sebaceous adenoma (24 cases) and trichofolliculoma (21 cases).

Most cases of benign SAT affected adult patients, the mean age being 59.20 years, ranging from 12 to 99 years. Only one case was observed in a patient younger than 18, specifically a 12-year-old girl presenting with a trichoblastoma.

In almost all cases there was a slightly greater incidence in males (M/F = 153/112). Only eccrine poroma (M/F = 21/24) affected female patients more frequently than males.

**Malignant SAT**

All cases had been diagnosed and removed when they were small in size. Mean diameter was 0.9 cm, with a range from 0.2 cm to 3.7 cm. The largest diameter observed was in a case of eccrine poroma, while the smallest cases were of eccrine spiradenoma, hidrocystoma and syringoma.

Sites of lesions are summarized in Table III and Figure 1. Cases of benign SAT were localized as follows: head and neck (146 cases, 51.9%), limbs (54 cases, 19.2%) and back (26 cases, 9.3%).

Recurrences appeared in only two cases (0.71%). One case, a male with eccrine spiradenoma, presented a local recurrence 6 years after the first surgery. The neoplasm was in close proximity to surgical margins at the time of first presentation. The second case was a male patient with an eccrine poroma who presented a recurrence 7 months after first surgery, and in this case also the margins were involved by the neoplasm after first removal.

**Multiple segmental forms**

Three of 55 cases of eccrine spiradenoma (1.06% of all SAT and 5.5% of eccrine spiradenoma) presented as multiple segmental forms, appearing as multiple nodules affecting one region. Multiple segmental eccrine spiradenoma (MSES) affected two females (aged 32 and 73) and one male (aged 22). The two female patients presented multiple nodules located, respectively, in the right arm and scalp, thus presenting a zosteriform appearance. On the contrary, the male patient developed multiple nodules located in the torso and back, thus developing a dermatomal presentation. On histology all lesions were composed of multiple dermal nodules, had well defined borders and were constituted by clusters of small, basophilic cells, intermingled with lymphocytes (Fig. 2). The nodules ranged in greatest axis from 146 microns to 15 mm.

In the female patient presenting nodules in the right arm, the nodules appeared over a two year period.

**Malignant SAT**

The malignant SAT observed herein were composed of, in descending order: sebaceous carcinoma (SC) (6 cases), extra-mammary Paget disease (EMPD) (6 cases) and apocrine carcinoma (AC) (4 cases). Patients presenting malignant SAT were older than those affected by the benign forms, with a mean age of 72.58 years (range 39 to 99 years). In SC and EMPD, a slightly greater incidence in female patients (M/F = 3/9) was observed. On the contrary, AC affected male patients only (M/F = 4/0). All cases of malignant SATs were small in size and radical surgical excision was achieved. The mean diam-
eter was 1.33 cm (range 0.2 cm to 2.74 cm). The largest diameter was seen in sebaceous carcinoma and the smallest in EMPD. Malignant SATs were located (Tab. IV and Fig. 1) as follows: head and neck region (7 cases, 43.7%), torso (5 cases, 31.3%), axilla (3 cases, 18.7%) and limbs (1 cases, 6.3%). No recurrences were recorded among the cases of malignant SATs.

**Discussion**

The appendageal tumours constitute a small percentage of all tumours of the skin. The present series observed during a period of 20 years consists of 281 cases, corresponding to 3.01% of non-melanocytic lesions of skin. Samalia analyzed adnexal skin tumours in Zaria (Niger), and found only 52 cases of SAT among 5642 cutaneous tumours (0.92%) (melanocytic and non-melanocytic tumours of skin) during a period of 15 years. Holtherhues et al. in the Netherlands evaluated the incidence of SAT during a 16 year period (from 1989 to 2005) and observed an incidence of 0.35% among all cutaneous neoplasms. The higher incidence of SAT in the present series is, most probably, a consequence of the fact that we considered only non-melanocytic (basal cell carcinoma and squamous cell carcinoma).

In the present series, the majority of SAT were benign (94%) and the most frequent forms were those arising from the sweat glands, and specifically: spiradenoma, hidrocystoma, eccrine poroma, syringoma, sebaceous adenoma and trichofolliculoma. This is consistent with the data in the literature.

According to previously published data, the most frequent sites affected by benign SAT were the head and neck area and limbs. Accordingly, in present series more than half of the benign SAT were located to head and neck area (face, periorcular area and scalp), while other frequent localizations were the limbs, back and torso.

Tab. IV. Sites of malignant lesions.

<table>
<thead>
<tr>
<th>Torso</th>
<th>Scalp</th>
<th>Face</th>
<th>Axilla</th>
<th>Back</th>
<th>Limbs</th>
<th>Periocular</th>
<th>Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo Ca.</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EMPD</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Seb. Ca</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Legend: Ca: carcinoma; Apo: apocrina; Seb: sebaceous; EMPD: Extra Mammary Paget Disease

Three cases of MSES were observed. Since the original description appeared in 1956, less than 40 cases of MSES have been described, and therefore their incidence remains unknown. In the present series, they constituted only 1.11% of all SAT and 5.5% of eccrine spiradenoma.

MSES present as multiple cutaneous nodules, having a zosteriform or dermatomal appearance. They affect mainly adult patients, but paediatric cases have been recorded. In addition, rare forms of familial cases have been documented. In the present cases, no family history was available. The two female patients presented a zosteriform type of distribution, while the male patient presented a dermatomal type of distribution. In one of the present cases, the nodules appeared over a period of two years. The appearing lesions were considered multiple forms and not true recurrences, as in all the samples small nodules were present very close to the surgical margins. None of the present cases presented malignant transformation.

Malignant SAT were rare and constituted only 6% of the present series. They were composed of SC, EMPD and AC. According to previously published data, the most frequent sites affected by malignant SAT were the torso and head and neck region. They affected patients with a higher mean age than benign SAT (72 vs 59 years, respectively), with a slight female predominance. In none of the 15 cases herein observed were recurrences and/or metastasis recorded. This is most probably a consequence of the small dimension of tumours at presentation combined with radical surgical excision.

**Conclusions**

SAT are rare cutaneous tumours, constitute only about 3% of non-melanocytic tumours of the skin and have a wide spectrum of morphological features. The majority of SATs are benign, although complete surgical excision is of utmost importance to avoid local recurrences. MSES are rare variant of SAT, appearing in about 1% of cases. Knowledge of these rare forms is important to achieve correct surgical treatment. Malignant SATs are rare, and, if correctly diagnosed and completely removed surgically, can have a good prognosis.
References


Role of on-site microscopic evaluation of kidney biopsy for adequacy and allocation of glomeruli: comparison of renal biopsies with and without on-site microscopic evaluation

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St. John Hospital & Medical Center, Detroit MI, USA

Key words
Kidney biopsy • Onsite evaluation • Glomeruli • Adequacy

Summary
For biopsies without on-site evaluation, no glomeruli were seen in 5 (7.14%) cases for LM, 11 (15.71%) cases for IF and 6 (8.57%) cases for EM. In cases with on-site evaluation, the absence of glomeruli was identified in 1 (1.13%) case for LM, 3 (3.4%) for IF and 3 (3.4%) for EM. The biopsies with on-site microscopic evaluation had 5.68% of the cases considered as inadequate, while 22% of biopsies without on-site evaluation were considered inadequate. The biopsies with on-site evaluation tended to have more glomeruli obtained during the procedure (p < 0.0005). Without on-site evaluation, the likelihood of getting an inadequate specimen compared to on-site evaluation is nearly four times greater.

Introduction
Kidney biopsy is the gold standard in the evaluation of renal diseases. It plays an indispensable role in the definitive diagnosis and guidance of treatment of renal disease. Light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM) are the most important tools for this process. Ideally, the evaluation should start with an on-site microscopic examination for adequacy and proper distribution of the specimen for light microscopy, immunofluorescence and electron microscopy, followed by the systemic evaluation of glomeruli, tubules, interstitium and vasculature. To obtain an adequate specimen is the first step in this complex process. Adequacy of the specimen is determined by the number of glomeruli present in the core. However, this invasive procedure carries rare but genuine risks of serious complications. The adequacy should be obtained with minimal passes in order to minimize risk. On-site evaluation provides real-time guidance to the biopsy operator. Without onsite microscopic examination, the adequacy is determined solely based on number of the cores. The purpose of this study is to assess the efficacy of on-site microscopic evaluation of medical kidney biopsies for adequacy and allocation of glomeruli and comparison of both techniques.

Materials and methods
This study was started after the approval of the Institution Review Board (IRB). We retrospectively reviewed the data of the adult patients who underwent native kidney biopsies from 2009 to 2010 for medical causes. Transplant kidney biopsies were excluded. Pathology reports of 158 kidney biopsies were examined and data was compared between patients with and without on-site microscopic evaluation. At one facility, kidney core
biopsies are evaluated at the site of procedure by pathologist, using a dissecting or standard light microscope. At the other facility, kidney biopsies did not undergo on-site microscopic evaluation and were allocated by the radiologist. Eighty-eight (55.69%) patients had on-site microscopic evaluations performed by a pathologist, and 70 (44.30%) did not receive any microscopic evaluation at the time of the procedure. At the time of the procedure, specimens were evaluated under the microscope by the pathologist and it was then allocated accordingly for LM, IF and EM. On average, the large portion of the specimen (predominantly cortex) was submitted in formalin for subsequent light microscopic evaluation, while a small portion of cortex was placed in the Michel’s media for immunofluorescence analysis. A very small portion of the cortex was allocated in the glutaraldehyde fixative for EM. On contrary, the specimen in the cases with no on-site microscopic evaluation was divided for LM, IF and EM and transported in formalin, Michel’s media and glutaraldehyde fixative, respectively. However, the allocation of the specimen was done randomly without microscopic evaluation. We divided the patients into two groups (with and without microscopic evaluation). We collected the following data including age, gender, light microscopy, immunofluorescence and electron microscopy reports.

For the adequacy of the sample there are no definitive criteria. We defined the sample as adequate if at least one non-sclerotic or partially sclerotic glomerulus was present in the sample for light microscopy, immunofluorescence and electron microscopy. The sample was defined as inadequate if there was absence glomerulus or the presence of only completely sclerotic glomeruli. After collecting the data we have compared the adequacy of the sample between the above-mentioned groups. The data was also compared between LM, IF and EM of both groups. Statistical analysis was performed by using Chi-square analysis and Student’s T-test or ANOVA when appropriate. P-values <0.05 were considered statistically significant.

**Results**

A total of 88 patients (48 females and 40 males) with on-site microscopic evaluation were analyzed. Only 1 (1.13%) case for light microscopy which was female was classified in the category of inadequate due to absence of glomeruli. Three (3.4%) cases for immunofluorescence and 3 (3.4%) of electron microscopy had no glomeruli. In all 88 cases, approximately 37 glomeruli per case were obtained after on-site microscopic evaluation.

<p>| Tab. I. Comparison of both groups for the inadequacy of glomeruli. |
|-----------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Groups</th>
<th>Total cases</th>
<th>LM (Absent/ Inadequate)</th>
<th>IF (Absent / Inadequate)</th>
<th>EM (Absent / Inadequate)</th>
<th>Total number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with on-site microscopic evaluation</td>
<td>88</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Cases without on-site evaluation</td>
<td>70</td>
<td>5</td>
<td>11</td>
<td>6</td>
<td>22</td>
</tr>
</tbody>
</table>

LM, light microscopy; IF, immunofluorescence and EM, electron microscopy

<p>| Tab. II. Overall comparison of both groups &amp; EM; electron microscopy. |
|-----------------|----------------|-----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Groups</th>
<th>Total cases</th>
<th>Total number of cases with absent glomeruli Even if absent in either LM or IF or EM</th>
<th>Total percentage of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with on-site microscopic evaluation</td>
<td>88</td>
<td>n = 5</td>
<td>5.68%</td>
</tr>
<tr>
<td>Cases without microscopic evaluation</td>
<td>70</td>
<td>n = 16</td>
<td>22.85%</td>
</tr>
</tbody>
</table>

(LM, light microscopy; IF; immunofluorescence & EM; electron microscopy)

<p>| Tab. III. Comparison of inadequacy between light microscopy cases with and without on-site evaluation. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th>% of inadequate cases (if adequacy is one glomerulus)</th>
<th>% of inadequate cases (if adequacy is 5 glomeruli)</th>
<th>% of inadequate cases (if adequacy is 10 glomeruli)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with on-site microscopic evaluation</td>
<td>5.68%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Cases without on-site microscopic evaluation</td>
<td>22.85%</td>
<td>28.57%</td>
</tr>
</tbody>
</table>
On the other hand, 70 patients (39 females and 31 males) without on-site microscopic evaluation were examined, and approximately 23 glomeruli per case were obtained. Five (7.14%) cases for light microscopy, 11 (15.71%) cases for immunofluorescence and 6 (8.57%) cases for electron microscopy were classified as inadequate with no glomerulus (Tab. I). The mean number of non-sclerotic glomeruli observed was 26.88 ± 15.56 (mean ± SD, n = 88) for the on-site microscopic evaluation group, and 17.99 ± 12.35 for the group without on-site evaluation (n = 70, p < 0.0005).

If we define the absence of glomerulus in any sample for either light or immunofluorescence or electron microscopy as an inadequate sample, the differences were more striking on the overall comparison of both groups. The group with on-site microscopic evaluation had only 5.68% cases with no glomeruli and the group without on-site microscopic evaluation had 22% of cases absent non-sclerotic glomeruli (Tab. II).

By increasing the cut-off for adequacy of glomeruli for light microscopy to 5 glomeruli, we found 5.6% cases with on-site evaluation were inadequate compared to 28.5% for cases without on-site microscopic evaluation. Similarly, by increasing the cut-off value for adequacy up to 10 glomeruli, we observed that 25.0% cases with on-site microscopic evaluation were inadequate versus 52.8% cases without on-site evaluation (Tab. III). No significant differences were found considering gender or age.

**Discussion**

Kidney core needle biopsy is an important method to diagnose medical and transplant diseases pertaining to the kidney. In our study, we found that on-site microscopic evaluation of kidney biopsies was helpful in getting an adequate number of glomeruli for the LM, IF and EM compared to cases with no on-site microscopic evaluation. For light microscopy there is no definitive criteria for adequacy of glomeruli. In the literature, different numbers for adequacy have been suggested. To overcome this issue, we have also compared the adequacy of glomeruli for light microscopy between both above-mentioned groups by increasing the adequacy to 5 and then 10 glomeruli. By increasing the cut-off for adequacy of glomeruli for light microscopy to 5 glomeruli, 5.6% cases with on-site evaluation were inadequate compared to 28.5% for cases without on-site microscopic evaluation. If adequacy of glomeruli is increased up to 10 glomeruli as described by a few authors in the literature, then the difference is even more striking. The cases with on-site evaluation (25%) were categorized as inadequate in comparison to 52.85% cases without on-site evaluation.

We emphasized the onsite evaluation of the needle core because it is more likely to obtain an adequate specimen. On-site evaluation is more likely to keep the core intact, which is essential in observing the disease distribution pattern, such as subcapillary or paramedullary distribution. This helps in the proper and adequate distribution of the specimen for LM, IF and EM, increasing the overall diagnostic yield. Many investigators have in-
vestigated the efficacy of image-guided biopsies and the adequacy of specimens. The majority of medical kidney diseases require EM evaluation, and proper allocation of the glomeruli for EM is very essential to establish a diagnosis \(^5\-\(^6\), which can be achieved through on-site evaluation of kidney core biopsies. Mahoney et al. noted that image guided percutaneous biopsies in transplant patients are useful \(^7\). Patel et al. also emphasized the relevance of ultrasound-guided kidney biopsies \(^8\). In our experience, teamed with radiologists, on-site evaluation of the specimen by the pathologist improves the rate of adequacy.

**Conclusions**

Without onsite evaluation of the kidney core biopsies at the time of procedure the chances of getting an inadequate sample is four times greater compared to the specimen with on-site evaluation. On-site microscopic evaluation plays a key role in assessment of adequacy and proper allocation of the glomeruli for further evaluation. Based on our study, we recommend evaluation of the kidney biopsy specimens by the pathologist under microscope at the time of procedure.

**References**

Adenocarcinoma arising in a tailgut cyst: a case report

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Key words
Tailgut cyst • Retrorectal hamartoma • Developmental cyst • Malignant transformation

Summary
We report herein the clinicopathologic features and the follow-up of a new case of a TGC with adenocarcinomatous transformation occurring in a 61 year-old woman.

Introduction
Tailgut cyst (TGC), also called retrorectal hamartoma, is a rare congenital lesion arising from persistent remnants of the postanal gut. Complications of TGCs include benign reactive lesions associated with infection and inflammation, and malignant transformation 1 2. We describe here the clinicopathologic features of a new case of TGC associated with focal malignant transformation.

Case report
A 61-year-old woman with uneventful past medical and surgical history presented with pelvic and perineal pain of 3 months’ duration. Digital rectal examination showed a tender, extrinsic, well defined presacral mass compressing the rectum. On the remainder of physical examination, there was no abnormality. Sigmoidoscopy was normal. Abdominal computed tomography (CT) scan demonstrated a well-demarcated hypodense, cystic lesion, measuring 7x5 cm (Fig. 1). On MRI, the mass repressed the rectum without invading the rectal wall and the other locoregional structures (Fig. 2). Exploratory laparotomy revealed a cystic mass affixed to the sacrum. The lesion was partially resected. The surgical specimen showed a cystic mass with haemorrhagic content. Microscopic examination revealed that the wall of the cyst was lined by benign stratified squamous, stratified ciliated columnar epithelium (Fig. 3) and transitional cells. Interrupted bundles and wisps of smooth muscle were present, separated from the epithelium by a thin layer of inflammatory fibrous tissue. There was no distinct nerve plexus. Focal areas of adenocarcinomatous changes in the cyst wall consisting of small foci of carcinomatous glands were noted (Fig. 4). The patient’s postoperative recovery was uncomplicated. The patient was lost to follow-up and did not receive any further therapy. Ten months later, she presented with perineal pain and a relapse confirmed by CT scan was detected. The mass, measuring 7 cm, was adherent to the posterior wall of the rectum (Fig. 5) and to the anal sphincter muscles. The resection was partial and complicated by a rectal fistula. The patient refused abdominoperineal amputation and underwent adjuvant radiation [50 Gy]. She died 18 months later for local recurrence.

Discussion
TGCs are unusual lesions arising in the retrorectal, presacral space and considered to be of developmental origin arising from remnants of the tail gut 1. Various names have been used to describe this entity, such as retrorectal cyst-hamartoma, cyst of the postanal intestine, mucin-secreting developmental cyst, tailgut vestige and rectal cyst 2. Hjermstad and Helwig 3 suggested the term tailgut cyst because of its unambiguity. TGCs occur in all age groups and are three times more common in women than in men. Nearly half of patients are as-
Fig. 1. CT showing a retrorectal mass of liquidian density.

Fig. 2. T2-weighted MRI of the perineal region showing an encapsulated retrorectal mass with a heterogeneous liquidian hypersignal. New formations are seen in the lower part of the mass.

Fig. 3. Cystic wall lined by benign stratified ciliated columnar cells (haematoxylin and eosin staining, original magnification x 40).

Fig. 4. Focal area of carcinomatous transformation in the cyst wall which is lined by normal columnar cells (haematoxylin and eosin staining, original magnification x 40). Below and to the right: detail of carcinomatous glands (haematoxylin and eosin staining, original magnification x 200).

Fig. 5. CT shows the mass invading the posterior wall of the rectum.

ymptomatic, and the other half present with symptoms resulting from local mass effects (constipation, rectal fullness, lower abdominal pain, dysuria, etc.), with a palpable retrorectal mass at digital rectal examination, or a complication. Loco-regional inflammatory processes frequently complicate this lesion and can cause perirectal fistulae, bleeding and malignant degeneration, which are the major complications of developmental cysts 1-3. TGCs have specific radiological and histopathological features that distinguish them from other similar formations 4. Radiologically, differential diagnoses include dermoid cyst, epidermoid cyst, teratoma, rectal duplication cyst and anal gland cyst. The presence of calcification is suggestive of a dermoid cyst or teratoma. Rectal duplication cysts often communicate with the rectal lumen and
are anterior to the rectum. Anal gland cysts have a lower location than TGCs and are typically close to the anal sphincter. Histologically, various epithelial cell types line the cyst, but identification of transitional or glandular-type epithelium with or without stratified squamous components is essential for diagnosis. The other histologic requisites for the diagnosis are absence of a well-defined muscular coat containing a myenteric plexus and serosa. These criteria differentiate retrorectal cysts from epidermoid (stratified squamous epithelium only), dermoid (stratified squamous epithelium with skin adnexal structures) and duplication cysts which are lined by epithelium similar to that of the gastrointestinal and respiratory tracts and which have a distinctive feature consisting in two layers of muscular bundles containing a nerve plexus.

Malignant transformation is rare. The largest series of 53 cases was reported by Hjermsted and Helwig; they found only 1 case associated with malignant transformation. A recent report of a large series of the Mayo Clinic including 31 patients showed a 13% risk of malignant transformation (adenocarcinoma in three cases and carcinoid in one case). In an extensive review of the world literature, Tampi and colleagues reported 2 cases of TGCs with neuroendocrine malignant transformation and found 14 other cases of carcinoid tumors arising in TGCs in the literature. Malignant transformation mainly involves the neuroendocrine or glandular epithelium; recently, a transitional cell carcinoma that arose in a tailgut cyst was reported for the first time. Table I details the cases of malignant transformation of TGC reported to date. Differential diagnosis of such cases includes extension of a locoregional carcinoma, and metastatic disease.

Prognosis of malignant TGC varies from case to case, but depends on the status of the surgical margins and tumour histology. There is no standardized postoperative chemotherapy protocol because of the few reported cases. Further reports and studies are required to better define the management of this entity.

### References

CASE REPORT

Breast cholesterol granuloma: a report of two cases with discussion on potential pathogenesis

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Key words
Breast • Cholesterol granuloma • Duct ectasia • Macrocyst

Summary
Breast cholesterol granuloma is a very rare lesion that can clinically and radiologically mimic breast carcinoma. Herein, we report two cases of breast cholesterol granulomas along with clinical, radiological, cytological and histological findings. We also discuss the potential pathogenesis of this rare breast nodular lesion, suggesting its relation not only to mammary duct ectasia but also to the rupture of a breast macrocyst.

Introduction
Breast cholesterol granuloma is an uncommon nodular breast lesion that can be encountered in pathohistological evaluation of screening-detected abnormalities suspicious for malignancies. Its pathogenesis is still unclear. In the literature, breast cholesterol granuloma is commonly related to mammary duct ectasia accompanied with the rupture of ectatic ducts. However, in the majority of cases with duct ectasia, rupture of the ectatic ducts generates only an inflammatory reaction known as periductal mastitis. The tumorous mass containing inflammatory cells and cholesterol crystals, known as cholesterol granuloma, is rarely found. Herein, we present two typical cases of breast cholesterol granuloma along with clinical, radiological, cytological, and pathohistological imaging findings. We also discuss a potential pathogenesis of this rare tumorous breast lesion, proposing its relation not only to mammary duct ectasia, but also to the rupture of breast macrocysts.

Case report

CLINICAL AND RADIOLOGICAL FINDINGS

Case 1
A 55-year-old asymptomatic woman presented with a suspicious nodular lesion in the right breast discovered on routine ultrasonographic examination, with no palpable abnormality on physical examination. The lesion was nodular and hypoechoic, with a maximum diameter of 7 mm, and located peripherally on the border of lateral breast quadrants (Fig. 1). A mammogram, performed a few months before ultrasonographic examination, showed no visible abnormality except a large cyst on the site of the subsequently discovered ultrasonographic abnormality of the right breast. The patient denied any significant traumatic event of the breast tissue after previous mammography. Fine needle aspiration cytology (FNAC) was recommended.

Case 2
Routine ultrasonographic examination of the breasts of a 57-year-old asymptomatic woman showed round hypoechoic lesion with slight acoustic shadow, located centrally on the border of lateral quadrants of the right breast. The maximum diameter of the lesion was 6 mm.
A mammogram performed one month before the ultrasonographic examination showed numerous cysts in the parenchyma of the both breasts measuring 5-10 mm in the greatest diameter. FNAC was recommended.

**CYTOLOGICAL findings**

The FNA specimens of nodules were obtained using 21-gauge needles. Brownish viscous content was yielded in both cases. The contents were immediately smeared onto glass slides, air-dried and May-Grünwald-Giemsa stained. The cytological smears in both cases showed numerous giant multinuclear cells with occasional histiocytes and ductal epithelium (Fig. 2). Extirpation followed by pathohistological evaluation of the nodules was recommended.

**PATHOHISTOLOGICAL findings**

Excisional biopsies of the detected lesions were performed. On gross examination, both lesions were presented as well circumscribed brownish nodules, of soft consistency, with maximum diameters of 6 mm (Fig. 3). The surrounding breast tissue was grossly unremarkable in both cases. The tissues were fixed in neutral buffered formalin and embedded in paraffin for routine histological examination. The slides were stained with haematoxylin and eosin. Histologically, the nodules were composed of sheets of histiocytes with ample eosinophilic cytoplasm. Some of the histiocytes were giant and multinuclear, while at the periphery of the nodules mild lymphocytic infiltrate was noticed. Additionally, massive cholesterol deposition in the form of cholesterol crystals arranged in irregular arrays was observed in both cases (Figs. 4 and 5). The granuloma in case 1 addi-
Breast cholesterol granuloma tionally contained numerous siderophages accompanied with marked fibrous proliferation. The residual epithelial component was not recognizable in either nodule. Based on these findings, a pathohistological diagnosis of cholesterol granuloma was made for both cases. In case 1, the surrounding breast tissue was histologically unremarkable, while in case 2 mildly dilated ducts surrounded by fibrous proliferation and both lymphocytic and histiocytic infiltration was observed. This finding was consistent with duct ectasia and periductal mastitis (Fig. 6).

Discussion

Breast cholesterol granuloma is a very rare finding in the spectrum of benign breast nodular lesions, with only dozen of cases so far reported in the English literature. Döring and Wedemeier were the first who described this entity in the female breast in 1974. Cholesterol granuloma is a common disorder in the middle ear and mastoid process, with exceptionally reported cases in the testis, kidney, parotid gland, lymph nodes, thyroglossal duct and peritoneum. Typically, pathohistological characteristics of mammary cases do not differ from those of extramammary cases, with some exceptions as is the case with extensive osseous metaplasia and a case accompanied by breast cancer. The main significance of this entity in breast tissue is that it may be clinically and radiologically indistinguishable from breast carcinoma. Proper diagnosis usually requires excisional biopsy and pathohistological confirmation of the benign nature of this disease.

The pathogenesis of the breast cholesterol granuloma is still controversial. This entity is traditionally related to duct ectasia accompanied by the rupture of ectatic ducts. The lipid-rich material from the damaged lumina of ectatic ducts escapes into the periductal parenchyma causing the formation of cholesterol crystals surrounded by massive foreign body inflammatory reaction. According to this scenario, Wilhelmus et al. postulated that the cholesterol granuloma formation is “an unusual development in the advanced stage of mammary duct ectasia”. Osada and coworkers, in their work with literature review of 8 breast cholesterol granuloma cases, found adjacent mammary duct ectasia in 5 cases. Our findings in case 2 confirmed that the origin of the cholesterol granuloma was ruptured ectatic duct. We easily identified a mild duct ectasia with periductal inflammation in surrounding breast parenchyma. However, some of the reported cases of breast cholesterol granuloma were without histologically confirmed duct ectasia in surrounding breast tissue. Furthermore, many of the reported cases were situated on the periphery of breast parenchyma, while the duct ectasia is centrally located. Taking this into consideration, our case 1 is particularly interesting. In this patient, the granuloma was located on the periphery of breast parenchyma, with no histological finding of inflammatory reaction around surrounding breast ducts. Previous mammography showed a large cyst on the same site where the subsequent granuloma had been found. We speculate that a spontaneous rupture of the breast macrocyst into surrounding breast parenchyma elicited the cholesterol granuloma formation. In cases of duct ectasia, periductal inflammation is probably a primary lesion, causing the damage of the duct wall with consequent periductal fibrosis. Only in the minority of cases the leakage of lipid rich luminal material cause the formation of small histiocyte aggregates with resulting xanthogranulomatous mastitis, or exceptionally, the formation of large histiocyte aggregates with “macrogranuloma” formation. Alternatively, we propose that in some rare cases with ruptured, peripherally located breast macrocyst the inflammatory response is cellular rather than fibrotic, which facilitates the aggregation of histiocytes on the site of the rupture, with...
formation of granuloma around precipitated cholesterol crystals.
In conclusion, we confirm that centrally located cases of this rare benign nodular breast lesion represent late stage of mammary duct ectasia. We believe that in cases of peripherally located nodules cholesterol granuloma formation may be an unusual result of the rupture of a breast macrocyst.

References
Synchronous occurrence of pulmonary adenocarcinoma and pleural diffuse malignant mesothelioma

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Key words
Synchronous pulmonary neoplasias • Adenocarcinoma • Pleural malignant mesothelioma

Summary
We report a rare case of diffuse malignant pleural mesothelioma synchronous with a localized adenocarcinoma of lung in a 68-year-old man with a suspicious history of asbestos exposure. Computed tomography revealed a sub-pleural mass in the lower lobe and an irregular dense area of medium lobe of right lung with thickening of pleura encasing the lung parenchyma and homolateral pleural effusion 1 cm thick. The patient underwent surgery and a right medium and lower lobectomy was performed. Upon frozen sections, intraoperative diagnosis was adenocarcinoma with a poorly differentiated component of lung infiltrating the pleura. The postoperative histological definitive diagnosis with an important contribution of immunostaining was synchronous pulmonary adenocarcinoma and pleural diffuse malignant epithelioid mesothelioma.

Case report
A 68-year-old male was admitted to the Pneumology department for fever, pain and discomfort at right hypochondrium. The patient was a non-smoke, retired customs agent, with suspicious contact with asbestos, who referred several episodes of pleuritis, the first time at 20 years old and the last two years ago. He had never undergone a clinical search for asbestos bodies. Thoracic standard X ray revealed hyperdensity of the inferior lobe of right lung. A CT scan with contrast showed, in the right lung, a nodule in the parenchyma at the posterior region of the basal inferior lobe of 12 mm, an irregular dense parenchymal area of medium lobe with thickening of pleura and effusion of about 1 cm thick in the same hemithorax (Figs. 1, 2). Blood workup showed an increase in inflammatory indices with a D-Dimer of 300.

Introduction
The simultaneous occurrence of various primary pleuropulmonary tumours is a rare condition. This might be differentiated from histologic heterogeneity of multiple localization of the same tumour that occurs frequently in the lung. There are criteria to confirm the multiplicity of primary malignant neoplasms described by Warren and Gates 1. The co-existence of malignant mesothelioma and pulmonary adenocarcinoma is very rare 2. Whereas the association of asbestos with malignant mesothelioma is definite, the development of concurrent malignant pleural mesothelioma and lung carcinoma has been infrequently reported in asbestos-exposed individuals 3-6; only in 1.8% of 500 malignant mesotheliomas in the series of Attanoos 7.

In this report, we describe a rare case of synchronous diffuse malignant pleural mesothelioma and adenocarcinoma in a case of suspicious asbestos exposure, but no clinical and pathological confirmation of evidence of asbestosis.

Acknowledgements
The authors wish to thank Dr Cavazza (Reggio Emilia) for consultancy along with our laboratory staff.

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tion examinations on margins of bronchial resection and the nodulectomy specimen. The bronchial margin was clean, and the nodule of inferior lobe was an adenocarcinomatous infiltration in the sub-pleural parenchyma with prevalently tubulopapillary growth pattern associated with histologically different solid epitheliomatous malignant infiltration of the above visceral pleura, encasing the lung parenchyma and intimately mixed and formed collision tumours. This was interpreted as a less differentiated component of the adenocarcinoma by the pathologist at frozen section examination. The next two frozen section examinations of another sub-pleural segment of inferior lobe and one segment of medium lobe demonstrated similar solid neoplastic infiltrations of the pleura.

Gross examination showed a nodule of 1 cm diameter with a grey cut surface in the first frozen specimen with thickening of the above pleura and in other frozen sections thickening of pleura with thick septa and small nodules penetrated in the parenchyma. Formalin-fixed tissue was processed routinely, and 5 micron thick paraffin sections were cut and stained with haematoxilin and eosin (Figs. 3-5). These tissue blocks reflected the same aspects of frozen sections with more detail about the solid epithelioid pleural components. No diffuse interstitial fibrosis and no asbestos bodies were seen on light microscopy. No lymph node metastasis was seen.

By immunostaining, neoplastic cells of the first nodule showed diffuse nuclear positivity for thyroid transcription factor-1 TTF1 (Clone 8G7G3/1 DAKO) (Figs. 7, 8) and were negative for calretinin (Clone DAH/calret1DAKO) (Figs. 9, 10), while the pleural lesions with the relative septal and nodular coinfiltrating components was positive for calretinin and negative for TTF1.

The patient was uneventfully discharged on the 12th day after surgery and had 6 cycles of chemotherapy with carboplatin and pemetrexed, and has had no recurrence after 7 months of follow-up and CT.

**Discussion**

In the literature, cases with different histologically-different malignancies in the same lung are only rarely reported. Historically, there is a case of squamous cell and oat cell carcinoma appearing in different lobes of the right lung 8, a case of squamous cell carcinoma, adenocarcinoma and anaplastic carcinoma, three separate primary tumours in the right lung in autopsy 9 and 53 double primary lung tumours 10. There is also case of synchronous occurrence of an intermediate small cell and a bronchiolo-alveolar carcinoma 11. Co-existing granular cell tumour and adenocarcinoma of the lung has also been documented 12. Successively, another authors have reported the cases of synchronous pleural diffuse malignant mesothelioma and pulmonary carcinoma, sometimes with significant histories of asbestos exposure 11-13, three cases of synchronous pulmonary carci-

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**Figs. 1, 2.** CT scans of the chest show a nodule in the basal inferior lobe of the right lung and effusion and thickening of pleura encasing the lung parenchyma.

**Figs. 3-5.** Histopathology shows the synchronous presence of pulmonary adenocarcinoma and pleural malignant mesothelioma (H&E, x100).
Synchronous occurrence of Pulmonary adenocarcinoma and Pleural diffuse malignant mesothelioma from 16,000 pleuropulmonary cases of three referral centres, often with history of smoking or asbestos exposure reported 3. 9 cases of synchronous diffuse malignant mesothelioma and carcinomas in asbestos-exposed individuals 7, minute localized malignant pleural mesothelioma coexisting with multiple adenocarcinoma 14 and 1 case of metachronous malignant mesothelioma and pulmonary adenocarcinoma 15 (Tab. I). However, a history of asbestos is not required for diagnosis, and patients tend to be older than those with a single tumour 14. More rarely, there is simultaneous pulmonary carcinoma and pleural malignant mesothelioma with nodular lung parenchyma coinvolvement. In these cases, patients underwent sur-

Tab. I. Literature review.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year of publication</th>
<th>Diagnostic indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanbury W.J.</td>
<td>1961</td>
<td>1 case of squamous cell and oat cell carcinoma in different lobes of the right lung</td>
</tr>
<tr>
<td>Onuigbo W.I.</td>
<td>1962</td>
<td>1 case of squamous cell carcinoma, adenocarcinoma and anaplastic carcinoma in autopsy</td>
</tr>
<tr>
<td>Shields T.W.</td>
<td>1964</td>
<td>53 double primary lung tumours</td>
</tr>
<tr>
<td>Verska J.J.</td>
<td>1968</td>
<td>1 case of simultaneous bronchial adenoma and bronchiolo-alveolar carcinoma</td>
</tr>
<tr>
<td>Dohner V.A.</td>
<td>1975</td>
<td>1 case of simultaneous pulmonary adenocarcinoma and pleural diffuse malignant mesothelioma</td>
</tr>
<tr>
<td>Okumara T.</td>
<td>1980</td>
<td>2 cases of mesothelioma with lung cancer</td>
</tr>
<tr>
<td>Wong K.</td>
<td>1993</td>
<td>1 case of co-existing granular cell tumour and adenocarcinoma of the lung</td>
</tr>
<tr>
<td>Cagle P.T.</td>
<td>1994</td>
<td>1 case of concurrent mesothelioma and adenocarcinoma of the lung</td>
</tr>
<tr>
<td>Suzuki Y.</td>
<td>1994</td>
<td>1 case of concurrent mesothelioma and adenocarcinoma of the lung with asbestosis</td>
</tr>
<tr>
<td>French C.A.</td>
<td>1999</td>
<td>1 case of synchronous pleural mesothelioma and primary lung carcinoma</td>
</tr>
<tr>
<td>Attanoos R.L.</td>
<td>2003</td>
<td>9 cases of synchronous diffuse malignant mesothelioma and carcinomas in asbestos-exposed individuals</td>
</tr>
<tr>
<td>Allen T.C.</td>
<td>2006</td>
<td>3 cases of synchronous pulmonary carcinoma and pleural diffuse malignant mesothelioma</td>
</tr>
<tr>
<td>Maeda R.</td>
<td>2009</td>
<td>1 case of minute localised malignant pleural mesothelioma coexisting with multiple adenocarcinomas</td>
</tr>
<tr>
<td>Ozbudak I.H.</td>
<td>2013</td>
<td>1 case of metachronous malignant mesothelioma and pulmonary adenocarcinoma</td>
</tr>
</tbody>
</table>
gery for treatment of carcinoma; non-malignant mesothelioma was identified preoperatively. It is of interest that upon frozen section examination the mesothelioma can simulate a less differentiated carcinoma, but immunostaining supports definitive diagnosis. Such synchronous neoplasms occur rarely in patients with asbestos risk factors.

Conclusion

Pleural diffuse malignant mesothelioma coexisting with lung adenocarcinoma is rare. Knowledge of the clinical features and patient history is crucial. Immunohistochemical staining techniques are necessary to confirm diagnosis of a mesotheliomatous component of synchronous tumours.

References

Coexistence of lobular granulomatous mastitis and ductal carcinoma: a fortuitous association?

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Key words
Granulomatous lobular mastitis • Breast carcinoma • Surgery

Summary
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A 77-year-old female patient with a medical history significant for hypertension and epilepsy presented with right breast pain of 6-months duration. Examination revealed a hard sub-areola tender mass with irregular borders associated with mild right nipple retraction. Mammography showed a 2.2 x 2.4 cm stellate mass of the right breast. Ultrasound-guided core biopsies of the tumour were performed. Pathological examination revealed a grade II infiltrating ductal carcinoma. The patient underwent right radical mastectomy with homolateral axillary lymphadenectomy. Histological examination of the surgical specimen revealed grade II infiltrating ductal carcinoma concomitant with granulomatous lobular mastitis. To the best of our knowledge, the coexistence of granulomatous lobular mastitis and ductal carcinoma has been described only twice in the English language literature. The theory that chronic inflammation leads to cancer is well documented. Whether our patient had developed cancer from granulomatous lobular mastitis or otherwise is a matter of debate until more cases are encountered and more research is done in the area of breast cancer pathogenesis with regards to it arising from granulomatous lobular mastitis.

Introduction
Granulomatous mastitis (GM), also called granulomatous lobular mastitis, is an uncommon chronic inflammatory disease of the breast. The aetiology of this disorder is unknown, but its clinical and radiological features can mimic breast carcinoma. To the best of our knowledge, the coexistence of GM and ductal carcinoma has been described only twice in the English language literature. In this paper, the authors report a new case of breast infiltrating ductal carcinoma coexisting with GM and discuss the pathophysiological mechanism of this rare association.

Clinical history
A 77-year-old female patient with a medical history significant for hypertension and epilepsy presented with right breast pain of 6-months duration. Examination revealed a hard sub-areola tender mass with irregular borders almost fixed to underlying structure. This was associated with mild right nipple retraction and a 0.7 cm non-tender right axillary node. The mammography report noted a 2.2 x 2.4 cm stellate mass of the right breast. Results of standard laboratory analyses were within normal range. Ultrasound-guided core biopsies of the tumour were performed. Pathologic examination revealed a Grade II infiltrating ductal carcinoma. The patient underwent right radical mastectomy with homolateral axillary lymphadenectomy. Histopathological examination showed destruction of lobular architecture by granulomatous inflammation and a moderately differentiated infiltrating ductal carcinoma (Grade II according to Modified Scarff-Bloom-Richardson grading system) (Figs. 1, 2). The granulomatous inflammatory reaction was centred on lobules. Granulomas were composed of epithelioid histiocytes, Langhans giant cells accompanied by lymphocytes, and plasma cells (Figs. 3, 4). Axillary lymph nodes were not metastatic. Immunohistochemical staining of tumour cells showed strongly positive nuclear staining for oestrogen and progesterone receptors and negative staining for HER-2neu protein overexpression. The final pathological diagnosis was grade II infiltrating ductal carcinoma concomitant with granulomatous lobular mastitis. During her hospitalization, work-up for me-
tastases was negative. The patient’s course two months after the operation remained uneventful and she refused to receive adjuvant chemotherapy.

**Discussion**

Granulomatous mastitis is a rare, chronic, non-caseating, granulomatous lobulitis of uncertain aetiology that usually affects women of a child-bearing age. Since its initial description by Kessler and Wolloch in 1972, more than 120 cases of GM have been reported in the English language literature to date. Most case series regarding GM are less than 20 patients and from developing countries or countries with predominantly Caucasian populations. GM is, pathologically, a diagnosis of exclusion: other granulomatous inflammatory breast diseases must be first ruled out, including plasma cell mastitis, Wegener’s granulomatosis and granulomatous reaction secondary to sarcoidosis, ruptured cyst, duct ectasia, fat necrosis, foreign body reaction, tuberculosis, brucellosis or other fungal or parasitic infections. Some authors have speculated that the increasing incidence of GM coming from developing countries, in particular from the Mediterranean region and Asia, may be due to underdiagnosed breast tuberculosis. No consistent association has been observed with smoking, contrary to periductal mastitis, or with trauma to the breast, foreign material, feeding-breast-feeding or oral contraception. Thus, an autoimmune disease process is thought to be most likely. The autoimmune hypothesis is supported by the fact that the condition...
often improves with the administration of steroids. Furthermore, erythema nodosum has been reported as an extramammary manifestation of GM. On the other hand, classic serologic tests of autoimmune disorders, such as antinuclear antibodies and rheumatoid factors, are usually to be negative. The suggested pathophysiology for this autoimmune hypothesis is through damage to ductal epithelium producing a leak of luminal protein-rich secretions and fat into the lobular connective tissue, eliciting a granulomatous reaction with lymphocyte and macrophage migration. Extravasated lactational secretions occurring in women with recent pregnancy and lactation may elicit such a local granulomatous response, with local trauma or other infections as other possible triggers. The most common clinical presentation of GM is a unilateral firm-to-hard extra-areolar mass ranging from 0.5 to 9 cm in size. The lump may involve the overlying skin or penetrate the underlying pectoralis muscle with nipple retraction, sinus formation and axillary lymphadenopathy clinically mimicking breast carcinoma. With its retro-areolar or central location, features of inflammation and its common occurrence in recent pregnancy and lactation, the breast mass can also be mistaken clinically for a lactating breast abscess. Routine radiological examination including ultrasonography and mammography cannot differentiate idiopathic GM from carcinoma. Ultrasonography usually reveals inhomogeneous, irregular hypoechoic lesions with focal posterior shadowing or multiple relatively circumscribed heterogeneous hypoechoic lesions associated with a large mass. Doppler examination reveals increased vascularity of the lesions and surrounding tissues. On MRI, it is not possible to differentiate an active inflammatory process from a tumoral process. With the exception of two cases, no additional reported cases have suggested the possibility of an association between GM and malignancy. A literature search of any infection leading to breast cancer has only revealed that the cross species viral infection by the Mouse Mammary Tumour Virus can lead to the pathogenesis of breast cancer, although this remains at a very early stage of research. The theory that chronic inflammation leads to cancer is well documented. It is postulated that as a result of infection from an offending microorganism the host’s defense mechanisms produce free radicals which lead to oxidative damage and nitration of DNA bases which increases the risk of DNA damage. This would eventually lead to cell dysplasia and subsequently the development of cancer. It has been reported that nearly 15% of worldwide cancer is associated with microbial infection. However, breast cancer is not associated with such infections. The difficulty in differentiating breast carcinoma and GM and the possibility that GM could have led to cancer prompts us to raise the question whether current management with regard to monitoring and surgical therapy is adequate and appropriate. Current practice indicates that following careful confirmation of the diagnosis of GM, initial treatment should be non-operative and that in patients with more severe symptoms, a course of prednisolone may be started. In more persistent cases, either further immunosuppressive therapies like methotrexate or azothioprine may be used or the patient can be offered surgical management such as wide surgical excision or mastectomy. Surgical excision has the advantage of fewer recurrences. It was reported that only 3 recurrences occurred after excision of 18 cases diagnosed with GM. Whether the need for more radical surgery is needed remains a matter of debate until it can be demonstrated that GM can lead to cancer. In summary, two different hypotheses are possible in our patient. Firstly, that the patient has developed breast carcinoma as a second separate pathology in the same breast. Secondly, she developed breast carcinoma as a result of chronic inflammation leading to dysplasia and subsequent malignant change. Whether the patient had developed cancer from GM or otherwise is a matter of debate until more cases are encountered and more research is done in the area of breast cancer pathogenesis with regard to it arising from GM. The result of future research can affect the diagnosis and treatment of GM, and will certainly alter the course of its management.

References
Sir,
I enjoyed very much reading the paper by Limaiem et al. (Pathologica 2013;105:101-3) in which the first case of hydatic cyst presenting as breast lump in a male patient was described. It is pertinent to remind readers that in this same journal (Gaspa & Eusebi, Pathologica 1973;65:235-7) the first case of hydatic cyst in a breast of a Sardinian female patient was reported. The cyst manifested as a lump that upon excision revealed a minute invasive carcinoma in the cyst capsule. The patient was followed for lengthy period, but no sign of carcinoma was evident. This appeared as the first and unique case of an early diagnosis facilitated by a parassite!
Index Volume 105, No. 1-6

Issue 1
February 2013

ORIGINAL ARTICLE
1 Clinical management of thyroid nodules with indeterminate cytology: our institutional experience using SIAPEC cytological criteria and v600-BRAF test
G. Di Benedetto, A. Fabozzi, C. Rinaldi

CASE REPORTS
5 Role of biopsy in low-grade laryngeal chondrosarcoma: report of two cases
M. Onorati, L. Moneghini, A. Maccari, M. Albertoni, I. Talamo, F. Ferrario, G. Bulfamante, S. Romagnoli, F. Di Nuovo

8 Uterine endometrioid adenocarcinoma with extensive pilomatrixoma-like areas.
A case report
S. Squillaci, R. Marchione, M. Piccolomini, M. Chiodinelli, E. Fiumanò, M. Ungari

11 Recurrent ossifying fibroma of the maxillary sinus in an adult patient
D. Cabibi, R. Speciale, F. Lorusso

15 Intraparenchymal serous papillary cystadenoma of the testis: a case report
L. Olla, N. Di Naro, G. Puliga, G.A. Tolu

18 Pancreatic heterotopia of the small intestine: two case reports
F. Limaiem, I. Haddad, L. Marsaoui, A. Lahmar, S. Bouraoui, S. Mzabi

21 Molecular diagnostics of pulmonary metastasis from cervical cancer
C. Fodero, A. Cavazza, R. Bio, L. Bulgarelli, L. Campioli, T. Rubino, V. Semeraro, S. Prandi

24 Pure uterine lipoma
H. Imenpour, F. Petrogalli, L. Anselmi

LINEE GUIDA
28 Il carcinoma del pancreas esocrino: il referito istologico
C. Capella, L. Albarello, P. Capelli, F. Sessa, G. Zamponi per conto del Gruppo Italiano Patologi Apparato Digerente (GIPAD) e della Società Italiana di Anatomia Patologica e Citopatologia Diagnostica / International Academy of Pathology, Italian Division (SIAPEC/IAP)

39 In memoriam of John G. Azzopardi
V. Eusebi, T. Krausz

Issue 2
April 2013

ORIGINAL ARTICLES
43 On the question of cognitive limits in diagnostic histopathology
E. Cardesi, D. Galliano

51 Histological evaluation of papillary lesions of the breast from needle biopsy to the excised specimen: a single institutional experience
S. Gilani, R. Tashjian, P. Kowalski

CASE REPORTS
56 Pancreatic adenocarcinoma in duodenal ectopic pancreas: a case report and review of the literature
A. Ginori, L. Vassallo, M.A.G.M. Butorano, F. Betterini, G. Di Mare, D. Marrelli

59 Pulse granuloma involving Meckel’s diverticulum: a case report and literature review
J.K. Karp, A. Davis, P.J. Read, A. Mashayekh, A. Bombonati, F. Palazzo

62 Sclerosing stromal tumour of the ovary: two case reports
F. Limaiem, E. Boudabous, S. Ben Slama, B. Chelly, A. Lahmar, S. Bouraoui, F. Gara, S. Mzabi

66 Diagnosis and clinical course of cardiac myxoma
M. Mlika, A. Ben Youssef, R. Hamrouni, A. Ayadi-Kaddour, T. Kilani, F. El Mezni

69 Lung metastasis from TTF-1 positive sigmoid adenocarcinoma. Pitfalls and management

73 Primary tuberculosis of the adenoids in an 11-year-old male presenting with hearing loss: a case report
S. Taghipour-Zahir, M.H. Baradaranfar, A.A. Zolfaghari

76 Memoir of Antoine Zajdela
L. Di Bonito
363

INDEX VOLUME 105, NO. 1-6

363

Issue 3
June 2013

ORIGINAL ARTICLES
77 Giant benign solitary fibrous tumour of the pleura (>15 cm): role of radiological pathological correlations in management. Report of 3 cases and review of the literature
T. Pusiol, I. Piscioli, M. Scialpi, E. Hanspeter

83 The Cancer Screening Monitoring System: indicators for organised programmes and possible extension to spontaneous screening
P. Giorgi Rossi, A. Federici, M. Zappa

CASE REPORTS
86 A complex association between derivatives from the neural crest. A case report
M. Filottico, O. Potì, S. Carluccio

90 Gangliocytic paraganglioma of duodenum metastatic to lymph nodes and liver and extending into the retropancreatic space
S.M. Amin, N. Wewer Albrechtsen, J. Forster, I. Damjanov

94 A case of sclerosing angiomatoid nodular transformation of the spleen
A. Giorlandino, R. Caltabiano, S. Lanzafame

98 Epithelioid fibrous histiocytoma EMA positivity: a case report
C. Floris, N. Di Naro, L. Olla, G. Puliga, D. Altea, G.A. Tolu

101 Hydatid cyst presenting as a breast lump in a male patient
F. Limaiem, S. Bouslama, I. Haddad, S. Bouraoui, A. Lahmar, S. Mzabi

104 About a challenging tumour, elastofibroma dorsi: an eight-case study
M. Mlika, N.B. Abdeljalil, S. Boudaya, A. Ayadi-Kaddour, T. Kilani, F. Mezni

107 Leiomyomatosis peritonealis disseminata: pregnancy, contraception and myometctomy of its pathogenesis

Issue 4
August 2013

ORIGINAL ARTICLES
111 Lymphomatoid granulomatosis: a practical review for pathologists dealing with this rare pulmonary lymphoproliferative process
E. Tagliavini, G. Rossi, R. Valli, M. Zanelli, A. Cadioli, M.C. Mengoli, A. Bisagni, A. Cavazza, G. Gardini

117 About the necessity of improving the current nodal classification of non-small cell lung carcinoma
M. Mlika, A. Ayadi-Kaddour, S. Boudaya, A. Marghli, T. Kilani, F. Mezni

122 Intraparenchymal leiomyoma of the breast: report of a case with emphasis on needle core biopsy-based diagnosis

128 Primary mucinous carcinoma of the thyroid gland: case report with review of the literature
H. Mnif, A. Chakroun, S. Charfi, S. Ellouze, M. Ghorbel, T. Sallemi-Boudawara

CASE REPORTS
132 A solitary polypoid gastric metastasis 20 years after renal cell carcinoma: an event to be considered, and a brief review of the literature

137 Coexistence of xanthogranulomatous cholecystitis and gallbladder adenocarcinoma: a fortuitous association?
F. Limaiem, B. Chelly, F. Hassan, I. Haddad, S. Ben Slama, A. Lahmar, S. Bouraoui, S. Mzabi-Regaya

140 Pinkus tumour: an unusual case
S. Sehli Attafi, M. Jones, B. Fazaa, R. Zermani, S.R. Rommany

142 Mammary myofibroblastoma with leiomyomatous differentiation: case report and literature review
H. Mnif, S. Charfi, N. Abid, T. Sallemi-Boudawara

Issue 5
October 2013

ATTI DI CONGRESSO
147 6° Congresso Triennale SIAPEC-IAP
Roma, 26-30 ottobre 2013
Issue 6
December 2013

REVIEW
329 Computed tomography-histologic correlations in lung cancer
I. Ariozzi, I. Paladini, L. Gnetti, M. Silva, D. Colombi, M. De Filippo, N. Sverzellati

ORIGINAL ARTICLES
337 Tumours of the skin adnexa: a case series with focus on multiple segmental forms

342 Role of on-site microscopic evaluation of kidney biopsy for adequacy and allocation of glomeruli: comparison of renal biopsies with and without on-site microscopic evaluation
S.M. Gilani, D. Ockner, H. Qu

CASE REPORTS
346 Adenocarcinoma arising in a tailgut cyst: a case report
S. Rammeh, S. Ben Abdelkrim, M.H. Ben Hadj Khali-fa, R. Letaief, M. Mokni

349 Breast cholesterol granuloma: a report of two cases with discussion on potential pathogenesis
J. Bezić, M. Piljić-Burazer

353 Synchronous occurrence of pulmonary adenocarcinoma and pleural diffuse malignant mesothelioma

357 Coexistence of lobular granulomatous mastitis and ductal carcinoma: a fortuitous association?
F. Limaïem, A. Khadhar, F. Hassan, S. Bouraoui, A. Lahmar, S. Mzabi

361 Letter to the Editor
V. Eusebi
**Key words index**

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th>Hydatid cyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma cuttale</td>
<td>Hypertrophy</td>
</tr>
<tr>
<td>Adenoids</td>
<td>Ileum</td>
</tr>
<tr>
<td>Adequacy</td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td>Benign tumour of the pleura</td>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>Biopsy</td>
<td>43, 98, 111, 122, 128</td>
</tr>
<tr>
<td>Breast</td>
<td>5, 51, 142</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Kidney biopsy</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>Larynx</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Leiomyoma</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Leiomyomatosis</td>
</tr>
<tr>
<td>Cemento-ossifying fibroma</td>
<td>Lipoma</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Low-grade chondrosarcoma</td>
</tr>
<tr>
<td>Cholesterol granuloma</td>
<td>Lung</td>
</tr>
<tr>
<td>Cognitive process</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>Metastases to liver</td>
</tr>
<tr>
<td>Contraception</td>
<td>Malignant transformation</td>
</tr>
<tr>
<td>CT</td>
<td>Mass screening</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Maxillary sinus</td>
</tr>
<tr>
<td>Developmental cyst</td>
<td>Meckel’s diverticulum</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Mesenchymal tumours</td>
</tr>
<tr>
<td>Diagnostic histopathology</td>
<td>Multiple segmental eccrine spiroadenoma</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>Myeloblastoma</td>
</tr>
<tr>
<td>Duct ectasia</td>
<td>Myxoma</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Neoplasia intraduttale</td>
</tr>
<tr>
<td>EBV</td>
<td>Neurocristopathic complex neoplasia</td>
</tr>
<tr>
<td>Eccrine spiradenoma</td>
<td>Non-small cell lung carcinoma</td>
</tr>
<tr>
<td>Ectopic pancreas</td>
<td>Odontogenic fibro-osseous lesions</td>
</tr>
<tr>
<td>Elastofibroma dorsi</td>
<td>Osteoid osteoma</td>
</tr>
<tr>
<td>EMA</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Endocrine tumour</td>
<td>Osteosarcoma metastasis</td>
</tr>
<tr>
<td>Endometrial adenocarcinoma</td>
<td>Palliative therapy</td>
</tr>
<tr>
<td>Epithelioid fibrous histiocytoma</td>
<td>Papillary fibro-osseous lesions</td>
</tr>
<tr>
<td>Fibro-osseous dysplasias</td>
<td>Papilloma</td>
</tr>
<tr>
<td>Fibroepithelioma</td>
<td>Paracrine hyperplasia</td>
</tr>
<tr>
<td>Fibrous tumour</td>
<td>Performance indicators</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Pilomatrix carcinoma</td>
</tr>
<tr>
<td>Gangliocytic paraganglioma</td>
<td>Pilomatrixoma</td>
</tr>
<tr>
<td>Gastric obstruction</td>
<td>Polypoid gastritis</td>
</tr>
<tr>
<td>Glomeruli</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Granulomatous lobular mastitis</td>
<td>Primary</td>
</tr>
<tr>
<td>H-caldesmon</td>
<td>Pseudotumor</td>
</tr>
<tr>
<td>Histology</td>
<td>Pulse granuloma</td>
</tr>
<tr>
<td>HPV genotyping</td>
<td>Quality assurance</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Radiology of the pleura</td>
</tr>
<tr>
<td>H-caldesmon</td>
<td>Rare tumors</td>
</tr>
<tr>
<td>Hydatid cyst</td>
<td>Ratio of metastatic lymph nodes</td>
</tr>
<tr>
<td>Incisional biopsy</td>
<td>Referto GIPAD</td>
</tr>
<tr>
<td>Intraductal papilloma</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Retrorectal hamartoma</td>
</tr>
<tr>
<td>Inflammatory pseudotumor</td>
<td>SANT</td>
</tr>
<tr>
<td>Intraoperative evaluation</td>
<td>Sclerosing stromal tumour</td>
</tr>
<tr>
<td>Invasive adenocarcinoma</td>
<td>Serous papillary cystadenoma</td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>Serous papillary cystic tumor</td>
</tr>
<tr>
<td>Invasive duct papilloma</td>
<td>Sex cord-stromal tumours</td>
</tr>
<tr>
<td>Invasive duct tumour</td>
<td>Simple cyst</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>Skin adnexa</td>
</tr>
<tr>
<td>Invasive papillary carcinoma</td>
<td>Skin and soft tissue neoplasms</td>
</tr>
<tr>
<td>Invasive pleomorphic adenoma</td>
<td>Skin and soft tissue neoplasms</td>
</tr>
<tr>
<td>Invasive pleomorphic adenoma</td>
<td>Skin and soft tissue neoplasms</td>
</tr>
<tr>
<td>Invasive squamous cell carcinoma</td>
<td>Spindle cell tumors</td>
</tr>
<tr>
<td>Invasive well-differentiated adenocarcinoma</td>
<td>Spleen</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td>Synchronous pulmonary neoplasias</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Tables of truth</td>
</tr>
<tr>
<td>Macrocyst</td>
<td>Tailgut cyst</td>
</tr>
<tr>
<td>Malignant transformation</td>
<td>Testicular neoplasms</td>
</tr>
<tr>
<td>Mass screening</td>
<td>Testis</td>
</tr>
<tr>
<td>Maxillary sinus</td>
<td>Thyroid FNAB</td>
</tr>
<tr>
<td>Metastases to liver</td>
<td>Thyroid gland</td>
</tr>
<tr>
<td>Molecular biology</td>
<td>TNM classification</td>
</tr>
<tr>
<td>Morphology</td>
<td>Ultrasoundography</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>Uterine lipoma</td>
</tr>
<tr>
<td>Multiple segmental eccrine spiroadenoma</td>
<td>V600-Braf</td>
</tr>
<tr>
<td>Myeloblastoma</td>
<td>Xanthogranulomatous cholecystitis</td>
</tr>
</tbody>
</table>