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GIPP (Gruppo Italiano di Studio di Patologia Pleuropolmonare) • Review

The 2015 World Health Organization Classification of lung tumors: new entities since the 2004 Classification

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Key words

NUT carcinoma • Angiomatoid fibrous histiocytoma • Myxoid sarcoma • PEComatous tumors • Epithelial-myoepithelial carcinoma

Summary

In the last few years different new pulmonary neoplastic lesions have been recognised and some of them, namely NUT carcinoma, PEComatous tumors, pneumocytic adenomyoepithelioma, pulmonary myxoid sarcoma, myoepithelial tumors/carcinomas entered in the last 2015-WHO classification of lung tumors. In addition angiomatoid fibrous histiocytoma and ciliated muconodular papillary tumor have been morphologically and genetically characterized albeit not yet included in the 2015-WHO classification.

In the present paper we summarised the clinical, morphological, immunohistochemical and molecular features of these new entities. The knowledge of key histologic and molecular characteristics may help pathologists in achieving a correct diagnosis thus leading to an adequate therapeutic approach.

Abbreviations:

ADC = adenocarcinoma
ALK = anaplastic lymphoma kinase
AFH = angiomatoid fibrous histiocytoma
CK = cytokeratin
CT = computed tomography
CMPT = ciliated muconodular papillary tumor
EMA = epithelial membrane antigen
ER = estrogen receptor
FDG = (18)F-fluorodeoxyglucose
FISH = fluorescence in situ hybridization
GFAP = glial fibrillary acid protein
HPF = high power of view
IHC = immunohistochemistry
LAM = lymphangioleiomyomatosis
LCC = large cell carcinoma
MT/C = myoepithelial tumor/carcinoma
NC = NUT carcinoma
NE = neuroendocrine markers (chromogranin A, CD56 and synaptophysin)
NSCLC = non-small cell lung cancer
PAS = periodic-acid Schiff
PAME = pneumocytic adenomyoepithelioma
PEC = perivascular epithelioid cell
PET = positron emission tomography
PMS = pulmonary myxoid sarcoma
PR = progesterone receptor
RT-PCR = reverse transcriptase-polymerase chain reaction
SCC = squamous cell carcinoma
SMA = smooth muscle actin
SUV = standardized uptake value
TTF-1 = thyroid transcription factor 1
TS = tuberous sclerosis
WHO = World Health Organization

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Introduction

The 2015 World Health Organization (WHO) Classification of Tumors of the Lung, Pleura, Thymus and Heart [1] introduces some new entities (Fig. 1) compared to those present in the 2004-WHO Classifications of Tumors of the Lung, Pleura, Thymus and Heart [2]. More in detail:

1. NUT carcinoma has been added under the chapter of "*Other and unclassified carcinomas*";
2. pneumocytic adenomyoepithelioma is described as a peculiar variant of epithelial-myoepithelial carcinoma;
3. a group of PEComatous tumors including lymphangioleiomyomatosis, benign PEComa and malignant PEComa has been created;
4. pulmonary myxoid sarcoma with EWSR1-CREB1 translocation has been added;
5. the entities myoepithelioma and myoepithelial carcinomas have been recognized [1].

We summarized the key clinical, morphological, immunohistochemical and molecular features of these entities together with a description of angiomatoid fibrous histiocytoma and ciliated muconodular papillary tumor of the lung, two recently described neoplastic pulmonary lesion carrying distinct molecular alterations.

NUT Carcinoma

WHO-2015 chapter of *"Other and unclassified carcinomas"*

NUT carcinoma (NC) is an aggressive subtype of poorly differentiated carcinoma genetically defined by the presence of NUT gene rearrangement, t (15; 19) [3 4]. Being already present in the thymus section of the 2004-WHO Classification, [2] it has been now recognised also in the lung section of the 2015-WHO as "*NUT carcinoma*" [1].

NC is a rare (1% of lung tumors [1], 3-4% of mediastinal/thymic carcinomas) [2] highly aggressive tumor affecting children and young adults (< 30 years) of both genders [3], although cases of elderly patients (up to 78 years) are also on record [5]. NC commonly involves the midline, supradiaphragmatic structures (nasal cavity, paranasal sinuses, mediastinum and thymus), however it may be found outside the midline including lung, parotid gland, bladder, pancreas, kidney and adrenal glands [3-5]. NC is an extremely aggressive tumor with a fulminant and lethal clinical course (median survival of 6.9 months). Haematogenous and lymphatic spread are common leading to early bone metastases and multiorgan dissemination of disease (ovaries, liver, and brain) [5]. No specific chemotherapeutic regimen has demonstrated efficacy in treating NUT carcinoma [4].

NC of the lung usually presents with symptoms related to the advanced stage and rapid onset of disease including cough, pleuritic chest pain, shortness of breath and weight loss [1 6-8]. Ipsilateral pleural disease is consistently present with pleural effusion and partial or complete opacification of the hemithorax occurring within 2-8 weeks from initial presentation [9 10]. NC and secondary sites of tumors are characteristically intensely (18)F-fluorodeoxyglucose (FDG)-avid (standardized uptake value (SUV) max > 10), thus PET-CT is the modality of choice to determine disease burden and is also helpful in monitoring response to treatment [1 9 10]. NC often presents as an advanced-stage, inoperable disease [4 5]. The sporadic surgically resected NC is a brown and white mass with central necrotic foci extending into hilar structures of the lung [11].

On cytology, NC has not distinctive features besides the typical aspects of undifferentiated carcinoma. Cytologic smears are highly cellular and enclosing loosely cohesive and/or isolated cells of intermediate size (2-2.5 times greater the diameter of a small lymphocyte) with irregular nuclear contours and one or more prominent nucleoli. The cytoplasm varies from pale to densely eosinophilic and may be vacuolated. Necrotic background, crush artefacts and mitotic figure are constant. A clear-cut squamous cell differentiation is not always visible, however the identification of overt pearl formation, dyskeratocytes or intercellular desmosomes in the context of cytological features suggestive of a poorly differentiated carcinoma, strongly suggest a diagnosis of NC [12]. Histologically, NC shows sheets and nests of small-to-intermediate sized undifferentiated cells with a monomorphic appearance. Tumor cells have round-to-oval nuclei with irregular outlines and conspicuous nucleoli. The cytoplasm varies from clear, eosinophilic to basophilic and there is always brisk mitotic activity and necrosis. The key pathologic feature is the presence of neoplastic cells with overt squamous differentiation (squamous pearls, desmosomes, orangiophilic cytoplasm) with abrupt transition from the poorly differentiated area. An acute, neutrophilic granulocytes-based inflammatory infiltrates is frequent [1 6-10]. At immunohistochemistry (IHC), NC is consistently positive for NUT with a clear-cut strong and diffuse nuclear immunoreactivity. Because NUT expression is restricted to testis and ovary, immunohistochemical stain for NUT (specific rabbit monoclonal antibody, clone C52) is a useful diagnostic tool in NC with 100% of specificity and 87% of sensitivity [1 13]. In addition, most cases (> 90%), show nuclear staining with p63/p40 indicating squamous cell differentiation. [1] Occasional staining with CD56, synaptophysin, CD99, CK5/6, epithelial membrane antigen (EMA), FLI1 and even TTF-1 are reported [14]. A potential immunohistochemical pitfall is the positivity for CD34, often found in NC, which may lead to a misdiagnosis of acute leukemia. Germ cell, lymphoid and myeloid markers are negative [1 14]. NC is characterized by the t (15; 19) translocation, leading to the fusion of NUT gene to BRD4 in > 70% of cases. Molecular demonstration of NUT rearrangement either by fluorescence in situ hybridization (FISH), reverse transcriptase-polymerase chain reaction (RT-PCR) or direct sequencing is diagnostic of NC [1 3 4]. Differential diagnosis includes any poorly differentiated malignant neoplasms (small cell lung cancer (SCLC), poorly dif-

Fig. 1. New tumoral entities (marked with highlighter) of the last 2015-WHO Classification of tumors of the lung.

WHO classification of tumours of the lung[a,b]

Epithelial tumours	
Adenocarcinoma	8140/3
Lepidic adenocarcinoma	8250/3*
Acinar adenocarcinoma	8551/3*
Papillary adenocarcinoma	8260/3
Micropapillary adenocarcinoma	8265/3
Solid adenocarcinoma	8230/3
Invasive mucinous adenocarcinoma	8253/3*
Mixed invasive mucinous and non-mucinous adenocarcinoma	8254/3*
Colloid adenocarcinoma	8480/3
Fetal adenocarcinoma	8333/3
Enteric adenocarcinoma	8144/3
Minimally invasive adenocarcinoma	
Non-mucinous	8250/2*
Mucinous	8257/3*
Preinvasive lesions	
Atypical adenomatous hyperplasia	8250/0*
Adenocarcinoma in situ	8140/2
Non-mucinous	8410/2
Mucinous	8253/2
Squamous cell carcinoma	8070/3
Keratinizing squamous cell carcinoma	8071/3
Non-keratinizing squamous cell carcinoma	8072/3
Basaloid squamous cell carcinoma	8083/3
Preinvasive lesion	
Squamous cell carcinoma in situ	8070/2
Neuroendocrine tumours	
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Carcinoid tumours	
Typical carcinoid	8240/3
Atypical carcinoid	8249/3
Preinvasive lesion	
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	8040/0*
Large cell carcinoma	8012/3
Adenosquamous carcinoma	8560/3
Pleomorphic carcinoma	8022/3
Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
Other and unclassified carcinomas	
Lymphoepithelioma-like carcinoma	8082/3
NUT carcinoma	8023/3*
Salivary gland-type tumours	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Epithelial-myoepithelial carcinoma	8562/3
Pleomorphic adenoma	8940/0
Papillomas	
Squamous cell papilloma	8052/0
Exophytic	8052/0
Inverted	8053/0
Glandular papilloma	8260/0
Mixed squamous cell and glandular papilloma	8560/0
Adenomas	
Sclerosing pneumocytoma	8832/0
Alveolar adenoma	8251/0
Papillary adenoma	8260/0
Mucinous cystadenoma	8470/0
Mucous gland adenoma	8480/0
Mesenchymal tumours	
Pulmonary hamartoma	8992/0
Chondroma	9220/0
PEComatous tumours	
Lymphangioleiomyomatosis	9174/1
PEComa, benign	8714/0
Clear cell tumour	8005/0
PEComa, malignant	8714/3
Congenital peribronchial myofibroblastic tumour	8827/1
Diffuse pulmonary lymphangiomatosis	
Inflammatory myofibroblastic tumour	8825/1
Epithelioid haemangioendothelioma	9133/3
Pleuropulmonary blastoma	8973/3
Synovial sarcoma	9040/3
Pulmonary artery intimal sarcoma	9137/3
Pulmonary myxoid sarcoma with *EWSR1-CREB1* translocation	8842/3*
Myoepithelial tumours	
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Lymphohistiocytic tumours	
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	9699/3
Diffuse large B-cell lymphoma	9680/3
Lymphomatoid granulomatosis	9766/1
Intravascular large B-cell lymphoma	9712/3
Pulmonary Langerhans cell histiocytosis	9751/1
Erdheim-Chester disease	9750/1
Tumours of ectopic origin	
Germ cell tumours	
Teratoma, mature	9080/0
Teratoma, immature	9080/1
Intrapulmonary thymoma	8580/3
Melanoma	8720/3
Meningioma, NOS	9530/0
Metastatic tumours	

IARC Lyon, 2015

ferentiated non-small cell lung cancer (NSCLC), undifferentiated or squamous cell thymic carcinomas, round cell sarcomas, high grade lymphomas or leukemia), as a consequence the general recommendation is to test NUT expression by IHC in all poorly differentiated carcinoma lacking glandular differentiation [1 4]. In addition every young and never-smoking patient with a diagnosis of SCLC should be tested for NUT, since 25% may represent truly a NC [15]. For practical purpose, it might be useful to underline that none of the other histotype of lung cancer (adenocarcinoma (ADC), squamous cell carcinoma (SCC), SCLC, large cell carcinoma (LCC) and carcinoid tumors) disclose any NUT expression at IHC [16]. Because of the rarity of NC in the lung, the standard therapeutic approach is a moot point. Recently, two ongoing trials investigating small-molecule BET inhibitors targeting BRD4, showed rapid impressive response with temporary regression of disease, but the disease invariably progressed after a relatively short interruptions (11-5 months) suggesting a development of a secondary resistance mechanisms [17].

Key pathologic features of NUT midline carcinomas

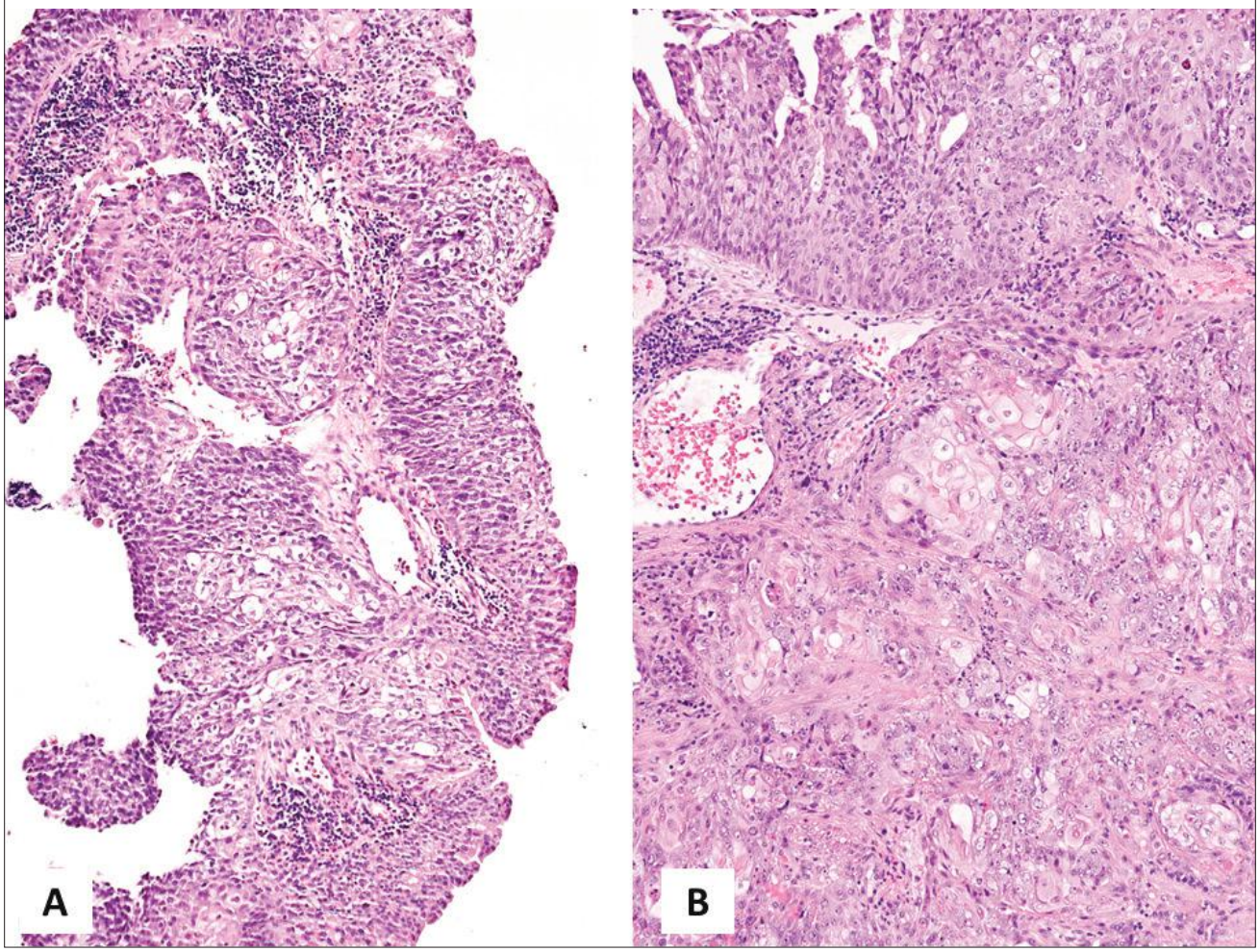
- Typically centrally located and often contiguous to bronchial epithelium (Fig. 2);
- sheets and nests of small blue undifferentiated cells with abrupt transition to large eosinophilic squamous cells (Fig. 3);
- foci of keratinization and desmosomes (Fig. 4);
- positivity for squamous markers: p63/p40;
- diagnostic nuclear positivity (> 50% of tumor cells) with the specific monoclonal NUT antibody (Fig. 5).

Pneumocytic adenomyoepithelioma

WHO-2015 chapter of "*Salivary Gland-type tumors*"/"*Epithelial-myoepithelial carcinoma*"

Pneumocytic adenomyoepithelioma (PAME) is a distinctive subtype of pulmonary low-grade tumor showing epithelial and myoepithelial differentiation with further pneumocytic specialization [18 19]. Since the bi-

Fig. 2. Bronchial biopsy of NUT carcinoma (NC) with prominent inflammatory infiltrates of lymphocytes and neutrophilic granulocytes (A). NC contiguous to and infiltrating the hyperplastic bronchial mucosa, which shows reactive changes (B).



phasic morphology and the absence of chondroid or myxochondroid matrix, it is considered as part of the "*Epithelial-myoepithelial carcinoma*" entity in the last WHO-Classification [1]. PAME affects adults, with a mean age of 51 (range, 52-74 years) and a strong female prevalence [18]. Only one case referred to a man has been described [19]. Usually the detection of PAME is incidental, but a case with chest pain and shortness of breath has been reported. On chest CT, PAME is a peripherally located, well-circumscribed mass without calcifications or association with bronchi or vessels. On macroscopic examination, PAME is a solid tan-withe lesion, measuring from 0.8 to 2.6 cm (mean, 1.5 cm) with an homogenous fascicular cut surface. At histology PAME exhibits epithelial and myoepithelial cells mainly arranged in double-layered glandular structures. The epithelial cells are cuboidal or columnar forming duct-like, tubular or glandular structures surrounded by myoepithelial cells with frequently clear cytoplasm. Glands are usually filled by dense, eosinophilic colloid-like secretions, which is a key pathologic feature of PAME. Myoepithelial cells sometimes are arranged in solid sheets of spindle-shaped cells with abundant eosinophilic cytoplasm. Although a mild nuclear atypia is acceptable, usually cellular pleomorphism, necrosis and high mitotic rate are absent and Ki-67 is < 5%. Chondroid or myxochondroid matrix is always absent. Immunohistochemistry highlights the double cells component showing immunoreactivity for cytokeratin (CK), EMA, surfactant A and TTF-1 in the epithelial component and positivity for smooth muscle actin (SMA), S100, p63 and calponin in myoepithelial spindle cells. Differential diagnosis mainly includes pulmonary pleomorphic adenoma (chondromyxoid stroma, cartilage formation and bronchocentric location), epithelial-myoepithelial carcinoma (lack of pneumocytic differentiation, TTF-1- and surfactant A-), sclerosing pneumocytoma (papillary, solid, hemorragic and sclerotic pattern of growth; CK +, EMA +, surfactant A + and TTF-1 + of surface type cells and TTF-1 +, EMA + and CK -, surfactant A - of round stromal cells are), mucus gland adenoma (central localization, mucin-filled cysts lined by columnar mucus secreting

Fig. 3. Abrupt transition from squamous cell carcinoma to small blue undifferentiated carcinoma characterizes NC.

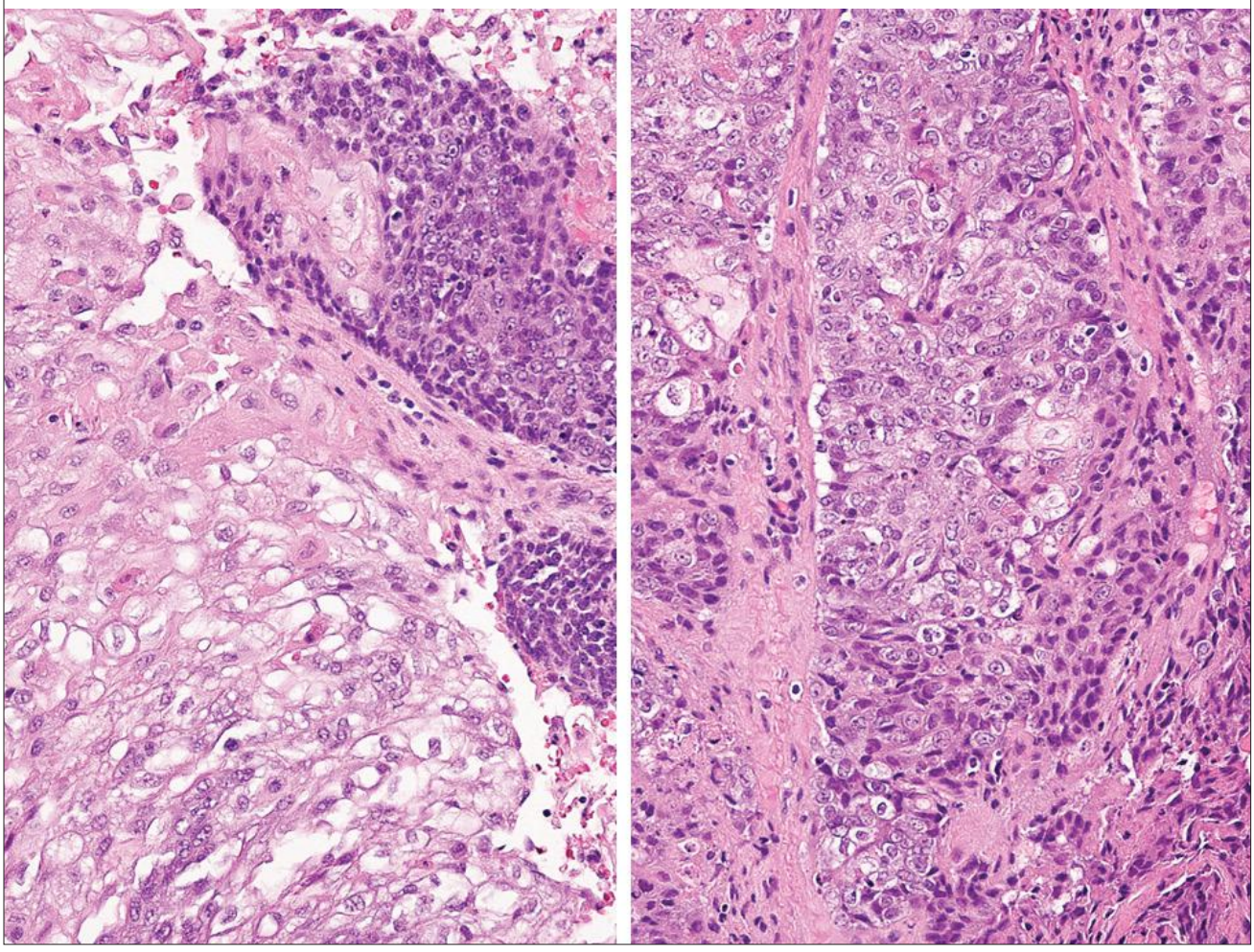
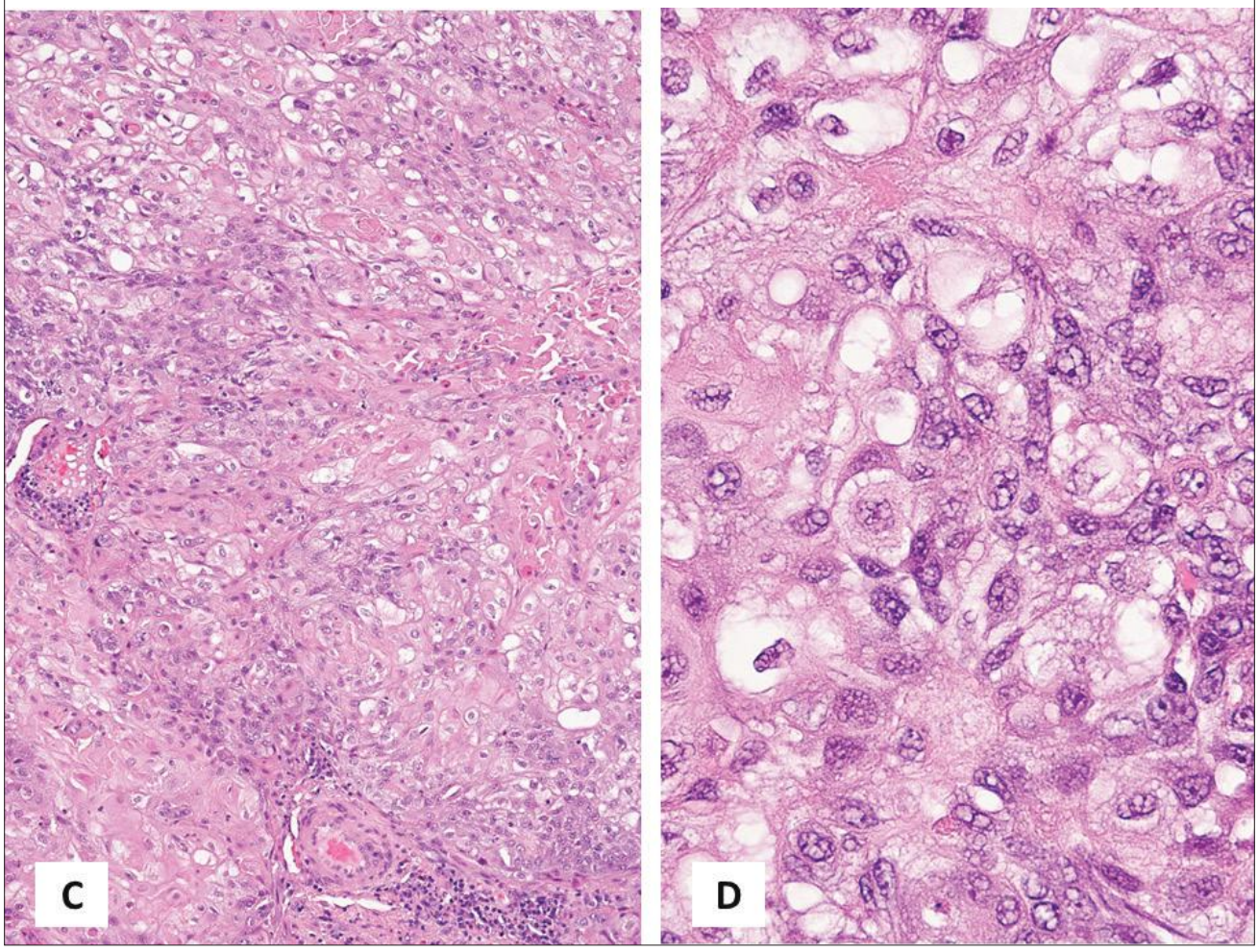


Fig. 4. Foci of keratinization represented by squamous pearls (C), intercellular bridges (D) and clear cell spaces between cells are typical of NC, which is basically a poorly differentiated squamous cell carcinoma carrying translocation of NUT gene.



cells, absence of spindle cell component), neuroendocrine tumors (neuroendocrine (NE) makers +) and metastatic papillary thyroid (thyroglobulin +) and salivary-gland carcinomas (absence of pneumocytic differentiation and clinical/instrumental correlation). PAME has a benign clinical outcome once surgically resected [18].

Key pathologic features of pneumocytic adenomyoepithelioma

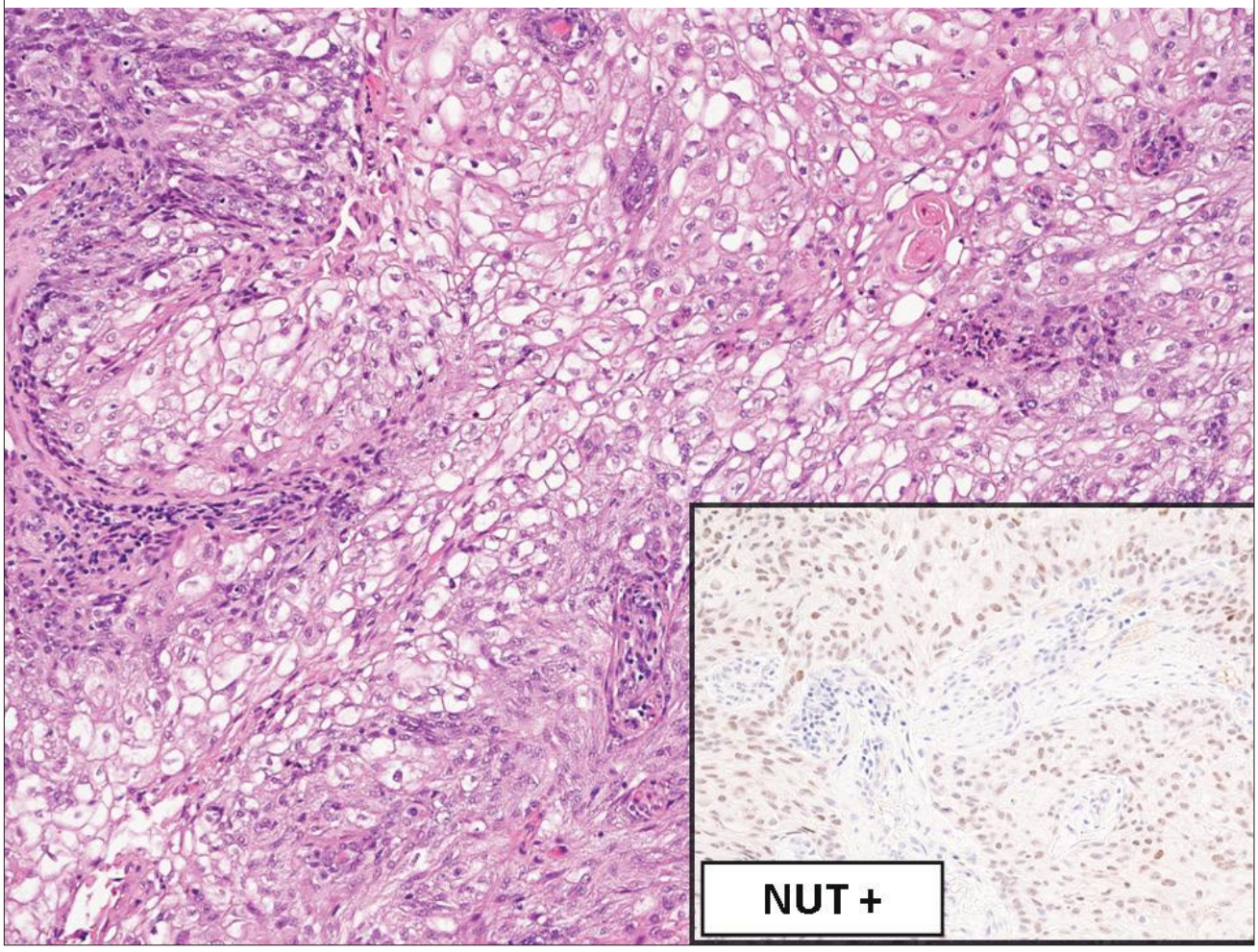
- Well-circumscribed, biphasic neoplasm with epithelial, myoepithelial and pneumocytic differentiation;
- glands filled with colloid-like secretions (Fig. 7), composed of an inner cuboidal epithelial layer surrounded by an outer myoepithelial one merging with foci of spindle cells (Fig. 8);
- expression of CK, EMA, TTF-1 and surfactant A in epithelial cells and S100, SMA, calponin, caldesmon and p63 reactivity in myoepithelial cells (Fig. 9).

PEComatous tumors: lymphangioleiomyomatosis, beningn PEComa, clear cell tumor and malignant PEComa

WHO-2015 chapter of "*Mesenchymal tumors*"/"*PEComatous tumors*"

Perivascular epithelioid cell tumors (PEComa) are mesenchymal neoplasms composed of distinctive epithelioid and/or spindle cells, which are immunoreactive for both smooth muscle and melanocytic markers. The chapter "*PEComatous tumors*" of the last WHO classification of lung tumours includes different entities namely lymphangioleiomyomatosis (LAM), benign PEComa including clear cell tumor and malignant PEComa [1]. The last one is a new entry into the WHO Classifications of tumours since the other entities were already listed under the paragraphs of "*Mesenchymal tumors*" (LAM) and "*Miscellaneous tumors*" (clear cell tumor/ benign PEComa) in the 2004-WHO Classification [2].

Fig. 5. NC with the typical abrupt transition to small blue cell areas and large clear squamous cell sheets shows nuclear immunoreactivity (insert) for the specific NUT antibody.



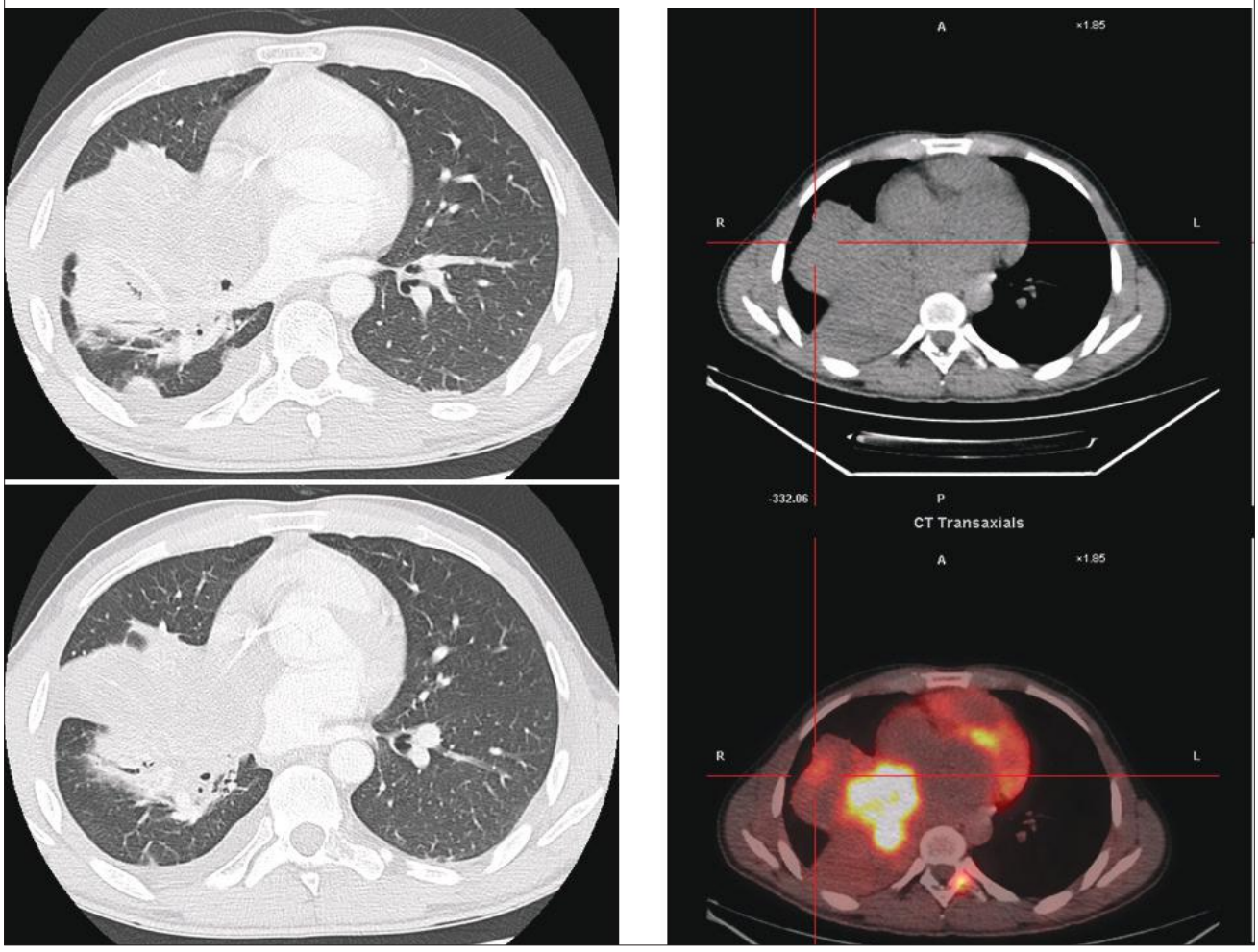
PEComatous tumors are supposed to arise from perivascular epithelioid cells and in the lung they may manifest as:

1. diffuse cystic interstitial lung disease termed LAM [20];
2. a benign localized neoplasm called PEComa, of which clear cell "sugar" tumor is the more frequent variant [21 25];
3. a malignant PEComatous mass [26 27];
4. or a diffuse proliferation with overlapping features between LAM and clear cell tumor [28].

LAM is a well-known and studied condition in the lung. It may be sporadic or tuberous sclerosis (TS)-related disorder occurring almost exclusively in women. Previously considered a non-neoplastic interstitial lung disease, LAM has been recognised as a low-grade mesenchymal metastasizing neoplasm either in the 2004 [2] and 2015 [1] Classifications because of the recognition of clonal origin, growth-promoting DNA mutation and aggressive behaviour (invasive and metastatic potential, recurrence after transplant). LAM shows usual biallelic mutations of TSC2 resulting in abnormal signalling of the mTOR pathway. Dyspnoea, pneumothorax and chylous effusion are common manifestations of LAM and about 60% of patients show elevated serum levels of VEGF-D. Thoracic CT presents thin-walled cysts secondary to a multifocal proliferation of peculiar plum spindle-shaped myoid cells, which show co-expression of melanocytic and muscle markers at immunohistochemistry (HMB45 +, Melan A +, Mart-1 +, MiTF + SMA +). Treatment strategies include lung transplantation and treatment with mTOR inhibitors [1 20].

PEComas of the lung encompass different lesions including clear cell "sugar" tumor, angiomyolipoma, benign and malignant PEComa. PEComa affects adults with a wide age range (8-73 years, mean age of 57), showing a predominant incidence in middle-age and elderly people and a slight male predominance [1 21 22]. No relationship with smoking history has been identified. Opposite to LAM, PEComatous tumor are rarely associated with TS, with a more striking association between the rare angiomyolipoma of the lung and TS [23 24]. Usually PEComas are asymptomatic and incidentally detected, but some patients experience symptoms such as

Fig. 6. Thoracic CT scans of a NC shows a central mass occluding the right main broncus and infiltrating the pulmonary vein, associated with atelectasis and pleural effusion. NC is also extremely avid of FDG at PET-CT (SUVmax = 20).

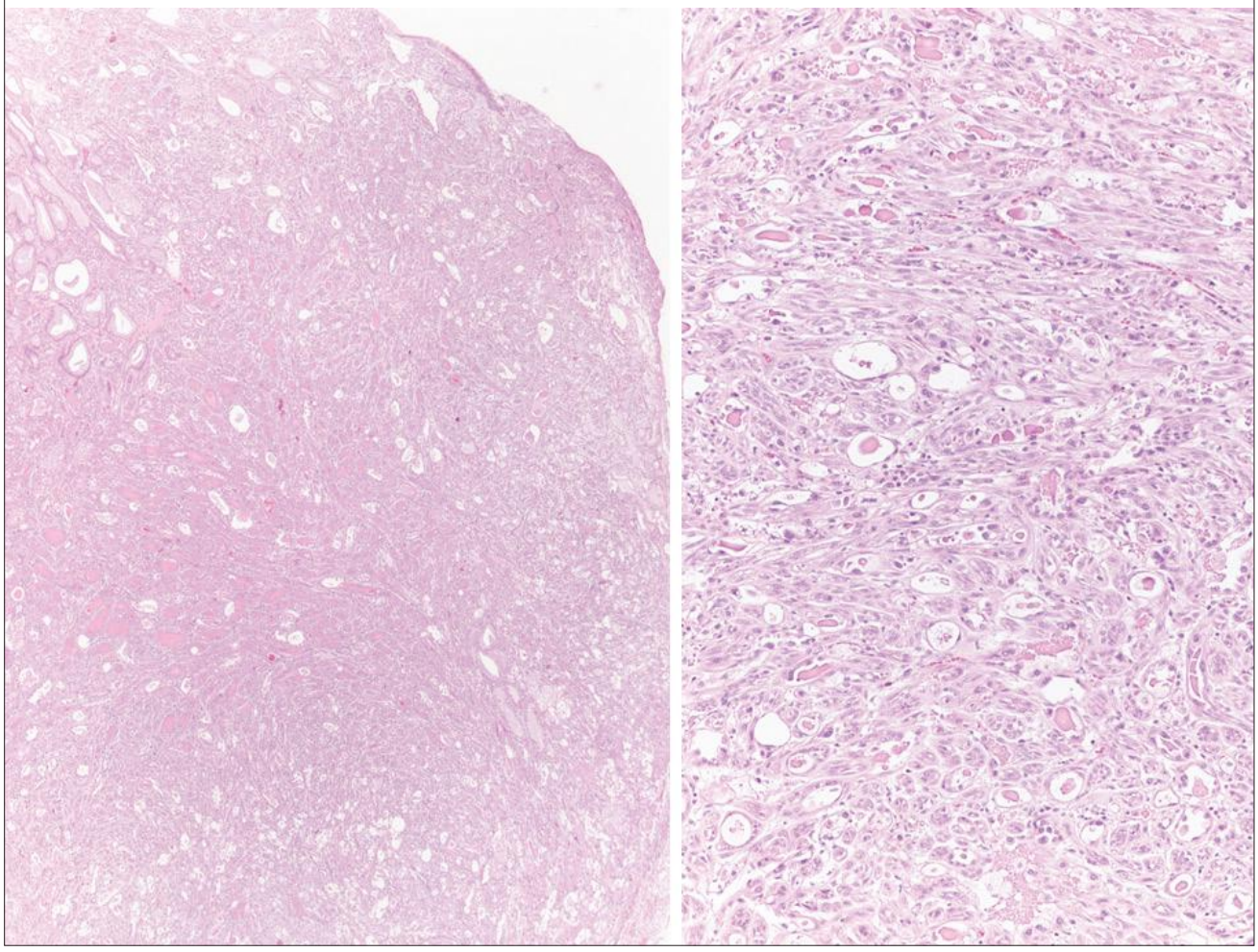


headaches, weakeness, cough, blood sputum, chest pain, thrombocytosis or unexplained fever [1 21-24 26 27]. Imaging features of PEComa can be distinctive. Clear cell sugar tumor of the lung appears on thoracic CT scan as a "coin lesion" [21 22], whereas angiomyolipoma is characterized by heterogeneous enhancement with areas of fat attenuation [24]. Malignant PEComa shows areas of necrosis, haemorrhage and/or cystic changes at imaging with an extensive uptake of FDG by PET-CT [26]. Macroscopic examination of these entities parallel the imaging findings since clear cell tumors reveal a well-demarcated nodule with homogenous red-tan cut surface (0.1-15 cm), [21 22] angiomyolipomas (1.5-9.5 cm) usually show yellow-fatty and fascicular areas in a well-defined nodule [24] and malignant PEComa shows cystic changes and necrotic or haemorrhagic areas of an ill-defined mass, by definition > 5 cm [26 27]. Histologically clear cell tumor is composed of sheets and cords of polygonal and occasionally spindled cells, with distinct cell borders and clear, granular or eosinophilic cytoplasm, arranged around numerous hyalinazed, or "stag's horn", thin-walled vessels. Pleomorphism and nucleoli may be prominent, but mitoses are usually absent. Due to the glycogen-rich cytoplasm there is strong PAS positivity, sensitive to diastase [1 21-23]. Cases of a diffuse interstitial growth of clear cells, showing features overlapping between LAM and clear cell tumor have been rarely described as diffuse PEComatosis [1 28]. Malignant PEComa has to display 2 or more of the following features: large size (> 5 cm), infiltrative growth, high nuclear grade, hypercellularity, mitoses > 1/50 HPF, necrosis or vascular invasion [25].

Angiomyolipoma, rarely occurs in the lung and as well as its renal counterpart, is composed of thick-walled vessels, sheets of smooth muscle spindle cells and mature adipose component in variable proportion [24].

PEComatous tumors are caracterized by a distinctive immunophenotype with a co-expression of both myogenic (SMA, calponin, caldesmon and desmin) and melanocytic markers (HMB45, Melan A, tyrosinase, MiTF) with spindled features associated with a stronger expression of SMA and epithelioid morphology with a stronger expression of HMB45. Although a third of PEComa shows a focal expression of S100, the most sensitive marker for its diagnosis is HMB45 (80%), with a granu-

Fig. 7. Pneumocytic Adenomyoepithelioma (PAME) is a well-circumscribed neoplasm characterized by epithelial glands and myoepithelial spindle cells with characteristic double-layered structures containing colloid-like secretions.



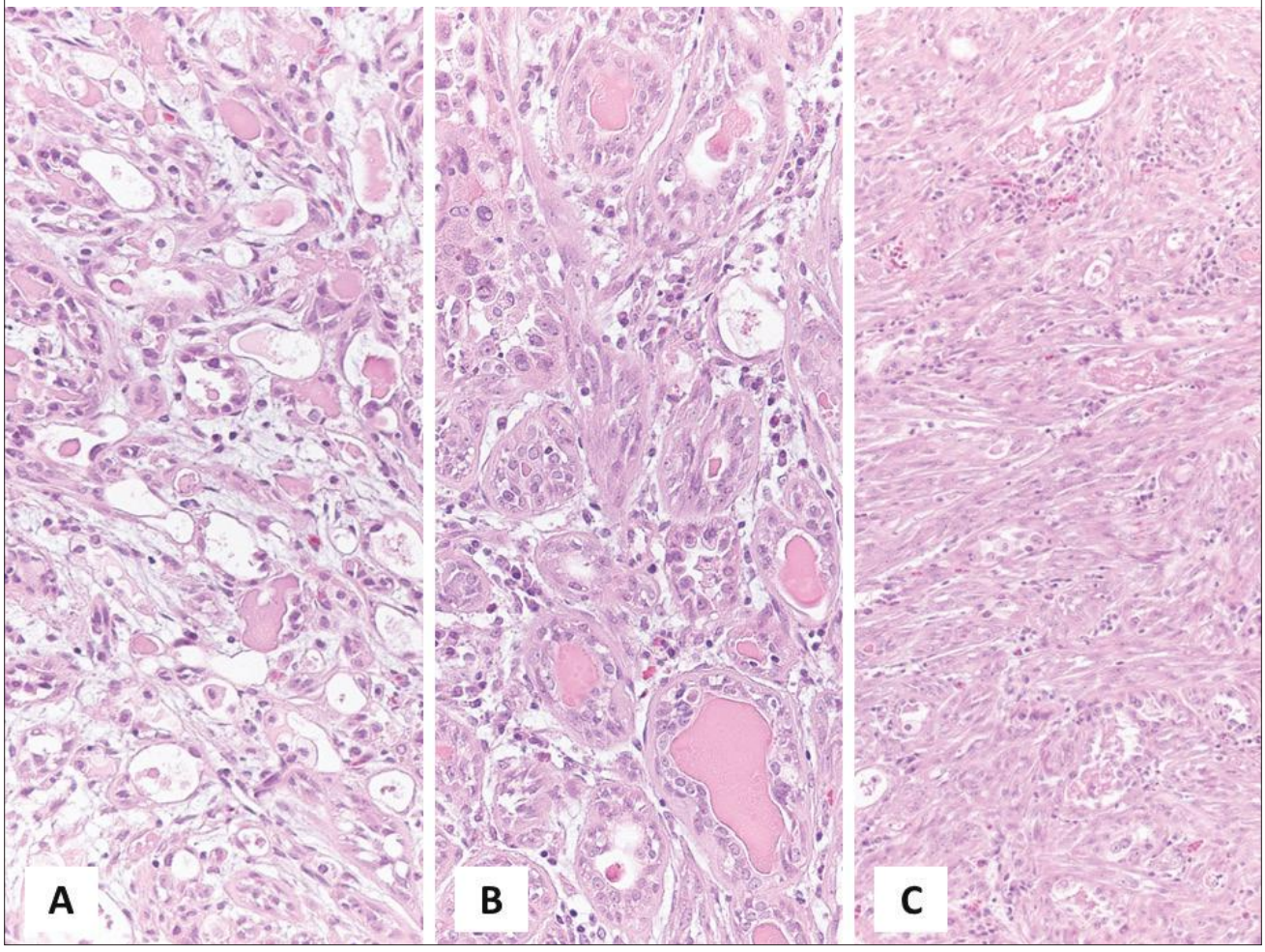
lar cytoplasmic pattern of positivity. CK positivity is occasionally seen [1 21-27].

Nuclear expression of TFE3 is also present in a distinct subgroup of PEComa with TFE3 rearrangement, extrarenal onset, young age, absence of TS, minimal immunoreactivity for muscle markers and frequent melanin pigmentation [27 29]. The development of PEComatous tumors, including LAM, is related to inactivating mutations of TSC1 or TSC2 either sporadic or in the context of TS. TSC mutations lead to dysregulation in mTOR signalling pathway, a potential therapeutic target possibly highlight by IHC for mTOR [1 20 23]. Instead, a distinctive subgroup of PEComas, harbour TFE3 gene rearrangements leading to TFE3 immunopositivity [29]. Differential diagnosis include metastatic renal cell carcinoma (CK +, PAX8 +, CD10 +), granular cell tumor (S100 +), metastatic melanoma and clear cell sarcoma (clinical correlates and overtly malignant features) for clear cell tumor [1 21-23]. Angiomyolipoma has to be differentiated from hamartoma (lobulated architecture and frequent presence of cartilaginous tissue), well-differentiated liposarcoma (MDM2 +, CDK4 +) and benign metastasizing leyomioma (estrogen receptor (ER) +, progesterone receptor (PR) +, absence of fat). Malignant PEComa may pose a challenging differential diagnosis with metastatic or primary melanoma of the lung, in such cases TFE3 positivity, if present, may be helpful together with clinical and instrumental examination [27]. Surgery is the best therapeutic approach for PEComatous tumors of the lung, apart from LAM [1]. Recent therapeutic choices for LAM include mTOR inhibitor, everolimus and sirolimus, as valid alternative to lung transplantation [1 20]. Also a case of diffuse PEComatosis of the lung has been successfully treated with sirolimus [28].

Key pathologic features of PEComatous tumors

- LAM (sporadic or TS-related): cystic interstitial lung disease at CT-scan of females;
- multiple thin-walled cysts showing nodular or diffuse proliferation of spindle myoid cells in the walls (Fig. 10);
- benign PEComa, clear cell "sugar" tumor: small peripheral nodule composed of rounded to oval cells

Fig. 8. Peculiar morphologic features of PAME are: glands spaces with dense eosinophilic secretions (A), double-layered structures with outer myoepithelial layer characterizes by basement-membrane-like pink material (B) and spindle cells with abundant eosinophilic cytoplasm (C).



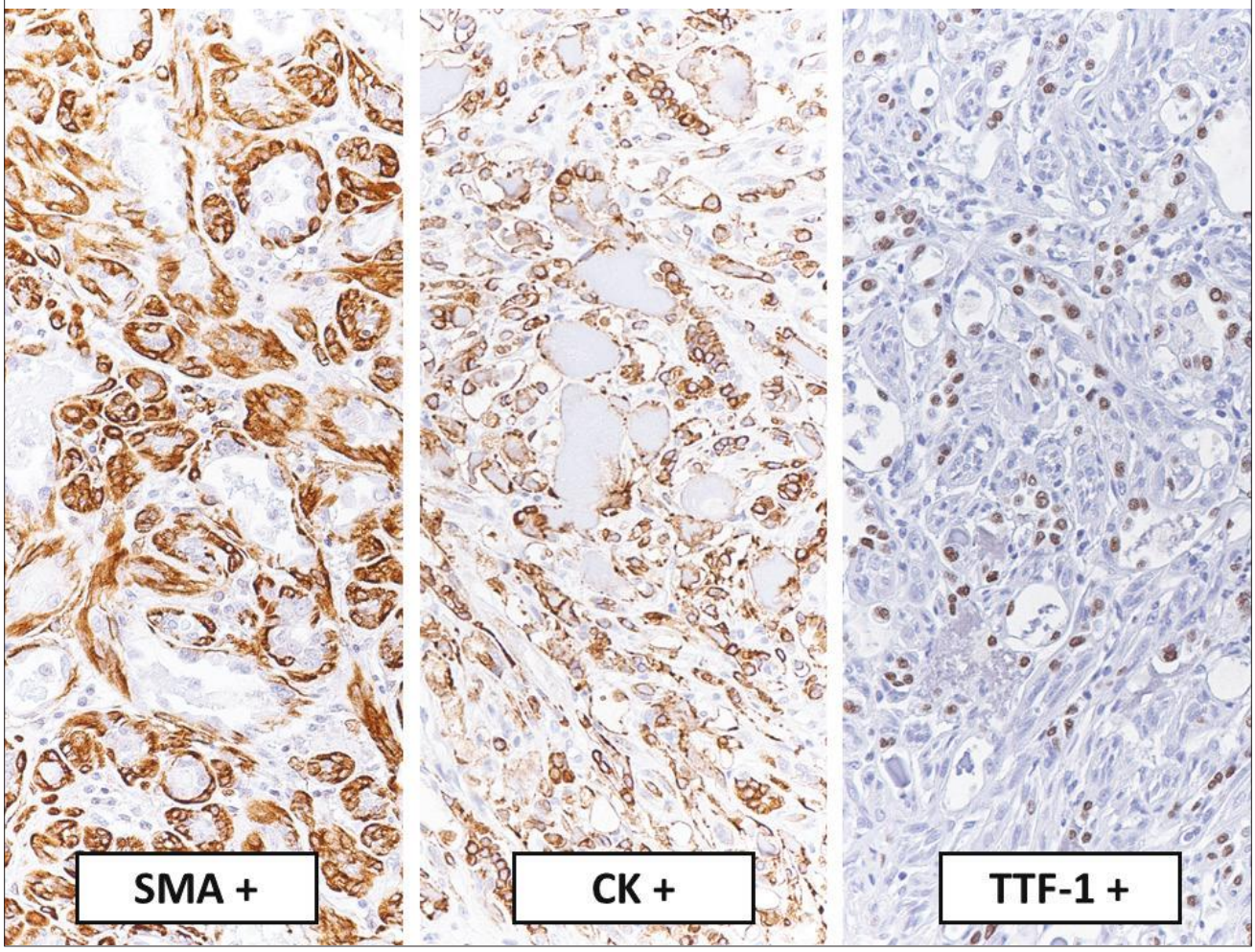
with distinct cell borders, clear granular PAS + cytoplasm and prominent vascularization (Fig. 11);
- benign PEComa, angiomyolipoma: lesion constitutes of fat, smooth muscle and vessels in variable proportion (Fig. 12);
- malignant PEComa: large size (> 5 cm), infiltrative growth, high nuclear grade, hypercellularity, mitoses > 1/50 HPF, necrosis or vascular invasion (Fig. 13);
- combined positivity for melanocytic markers (HMB45) and muscle markers (SMA) is distinctive of PEComatous tumors.

Pulmonary myxoid sarcoma with EWSR1-CREB1 translocation

WHO-2015 chapter of "*Mesenchymal tumors*"

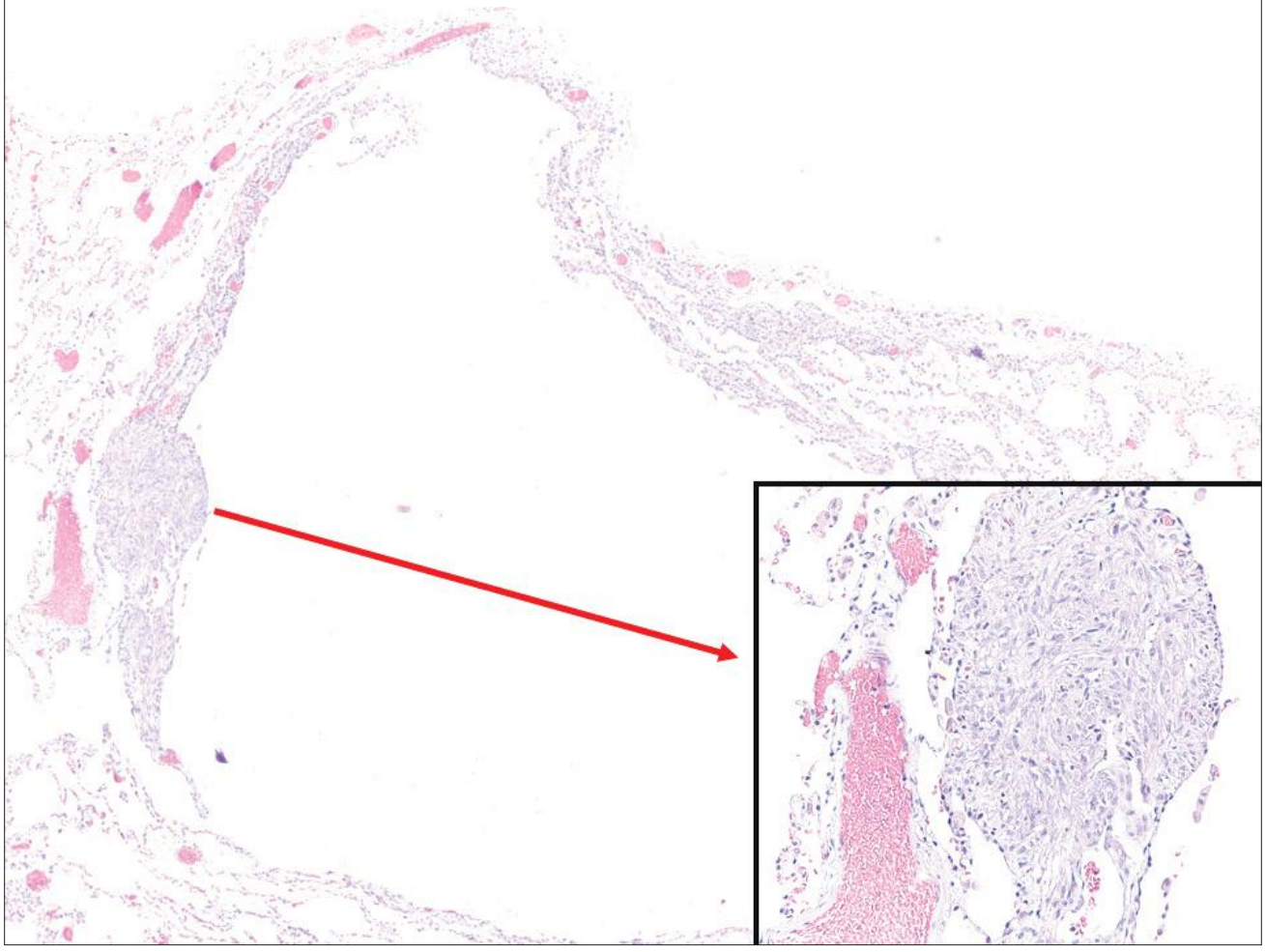
Primary pulmonary myxoid sarcoma (PMS) is a low-grade malignant, recently recognized tumor, usually arising in the central airways and carrying the EWSR1-CREB1 fusion gene [1 31 32]. This new entity of the 2015-WHO Classification [1] encompasses cases previously described as "*malignant myxoid endobronchial tumor*" [33] and cases already reported as "*primary pulmonary extraskelatal myxoid chondrosarcoma*" [34]. PMS affects patients with a wide age range (27-67 years, mean 45.5), showing a slight female predominance (M:F, 1:1.4). Most patients are smokers presenting with cough, haemoptysis and obstructive pneumonia due to the endobronchial site of tumor [1 31 33]. Slight anemia (a constant symptom in the last series and in cases previously reported as "*primary pulmonary extraskeletal myxoid chondrosarcoma*") [34] together with fever, weight loss and symptoms related to metastases may be also detected [1 31-33]. PMS is nearly always (> 80%) near to or arising within a bronchus. On Chest CT a polycyclic bronchocentric "coin lesion", eventually associated with obstructive signs is usually detected [1 31-34]. However, peripheral PMSs have been also described [31-32 34]. Grossly, PMS is a well-circumscribed tumor, measuring 1.5 cm to 13 cm (usually < 4 cm) with a glistering or gelatinous cut surface, ranging from white-grey to yellow in colour. Microscopic findings reveal a characteristic lobulated ar-

Fig. 9. PAME shows the outer layer of glands and spindle cells staining for SMA and the inner layer staining for CK and TTF-1 at IHC.



chitecture and a fibrous pseudocapsule showing a prominent inflammatory infiltrates with lymphoid aggregates. PMS is composed of spindle and stellate-to-polygonal cells within a prominent myxoid stroma, often lightly basophilic, displaying a reticular network with delicate lace-like strands and cords. More solid areas could also be detected and occasionally represent the predominant pattern. Cellular atypia is variable, ranging from absent to moderate in the vast majority of tumors, with occasional cases showing marked atypia. Mitotic index is also variable, with fewer than 5 mitoses/10 HPF usually detected. Necrosis, typically focal, is present in 50% of neoplasms. No chondroid differentiation or lipoblasts have to be seen. Focal hemosiderin deposition may be observed [1 31-34]. Ultrastructural features may suggest a possible fibroblastic or myofibroblastic origin of PMS tumor cells [35]. Neoplasitc cells lack specific immunohistochemical phenotype: expression of vimentin and weak and focal staining for EMA is reported in 60% of cases. Negativity for S100, CK, CD34, SMA, desmin and NE markers is a usual feature. CD68 may reveal the coexistence of histiocytes. The negativity for desmin may help in the differential diagnosis with angiomatoid fibrous histiocytoma (AFH). Histochemistry with Alcian blue stains the myxoid stroma, but is sensitive to treatment with hyaluronidase. Tumor cells may show cytoplasmic reactivity to periodic-acid Schiff (PAS) [1 31-33]. The great majority of PMS harbors a specific EWSR1-CREB1 fusion by RT-PCR and by direct sequencing and/or EWSR1 rearrangements by FISH [1 31 32 35 36]. The characteristic fusion transcripts EWSR1-NR4A3 and TAF15-NR4A3, detected in extraskeletal myxoid chondrosarcoma, are never detected in PMS. The main differential diagnosis includes extraskeletal myxoid chondrosarcoma, which is morphologically very similar, but carry the diagnostic recurrent chromosomal translocation that fuse NR4A3 with variable partners, particularly NR4A3-EWSR1 and NR4A3-TAF15 [34 36]. Other differentials includes epithelial-myoepithelial carcinoma (CK + in the epithelial and myoepithelial markers + in the spindle cell components, respectively), metastatic parachordoma (CK +, S100 +), pulmonary myxoma, myxoid liposarcoma (presence of lipoblasts and t(12; 16) (q13; p11) resulting in DDIT3-FUS fusion gene), aggressive angiomyxoma (desmin +, SMA +, ER +, PR +) [37], microcystic fibromyxoma (microcystic pattern of growth) [38] and other metastatic myx-

Fig. 10. Lymphangioleiomyomatosis (LAM). A cystic space is visible within lesional PEComatous cells form a nodule in the wall and diffusely infiltrate the edges of cystic spaces. High power (insert) show the pathognomonic myoid spindle-shaped cells with abundant eosinophilic and finely vacuolated cytoplasm



oid sarcoma (obvious features of malignancy: increased cellularity, nuclear atypia, hyperchromasia and high mitotic activity). AFH of the lung is also a possible differential diagnosis, since PMS and AFH share the same EWSR1-CREB1 fusion and may display morphological overlap [1 36]. Surgical resection represents the treatment of choice for PMS that usually shows a benign course of disease. However, just three reported cases are associated with brain, kidney and lung metastases, respectively. No histological prognostic features were detected at yet [1 31-33]. In dealing with a myxoid sarcoma of the lung, a meticulous exclusion of a possible source of metastases is mandatory; once excluded such eventuality, the possibility of primary PMS may be supported by the specific and pathognomonic EWSR1-CREB1 rearrangements.

Key pathologic features of pulmonary myxoid sarcoma with EWSR1-CREB1 translocation

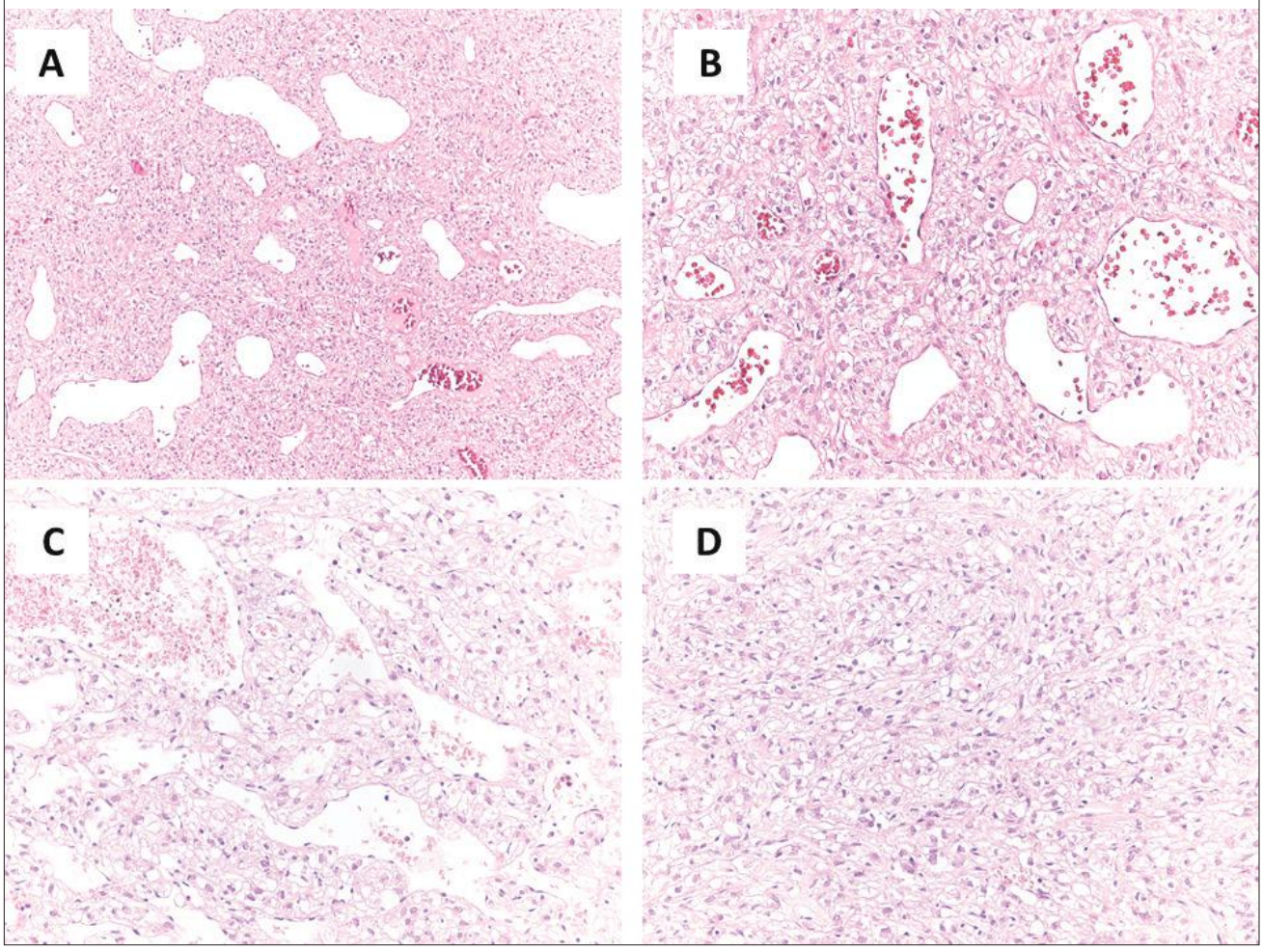
- Typically centrally located and often contiguous to bronchial epithelium with a lobulated architecture (Fig. 14);
- spindle, stellate and polygonal cells with lace-like or reticular architecture and prominent myxoid stroma morphologically similar to extraskelatal myxoid chondrosarcoma (Fig. 15);
- focal necrosis in about half of tumors, usually low mitotic activity (< 5 mitosis/HPF);
- absence of chondroid and fatty differentiation;
- expression of vimentin and weak, focal staining for EMA in 60% of tumors;
- myxoid stroma positive for Alcian blue, sensitive to treatment with hyaluronidase;
- FISH detection of EWSR1 rearrangements and/or RT-PCR demonstration of EWSR1-CREB1 fusion transcripts.

Myoepithelial tumors/myoepithelial carcinoma

WHO-2015 chapter of "*Mesenchymal tumors*"

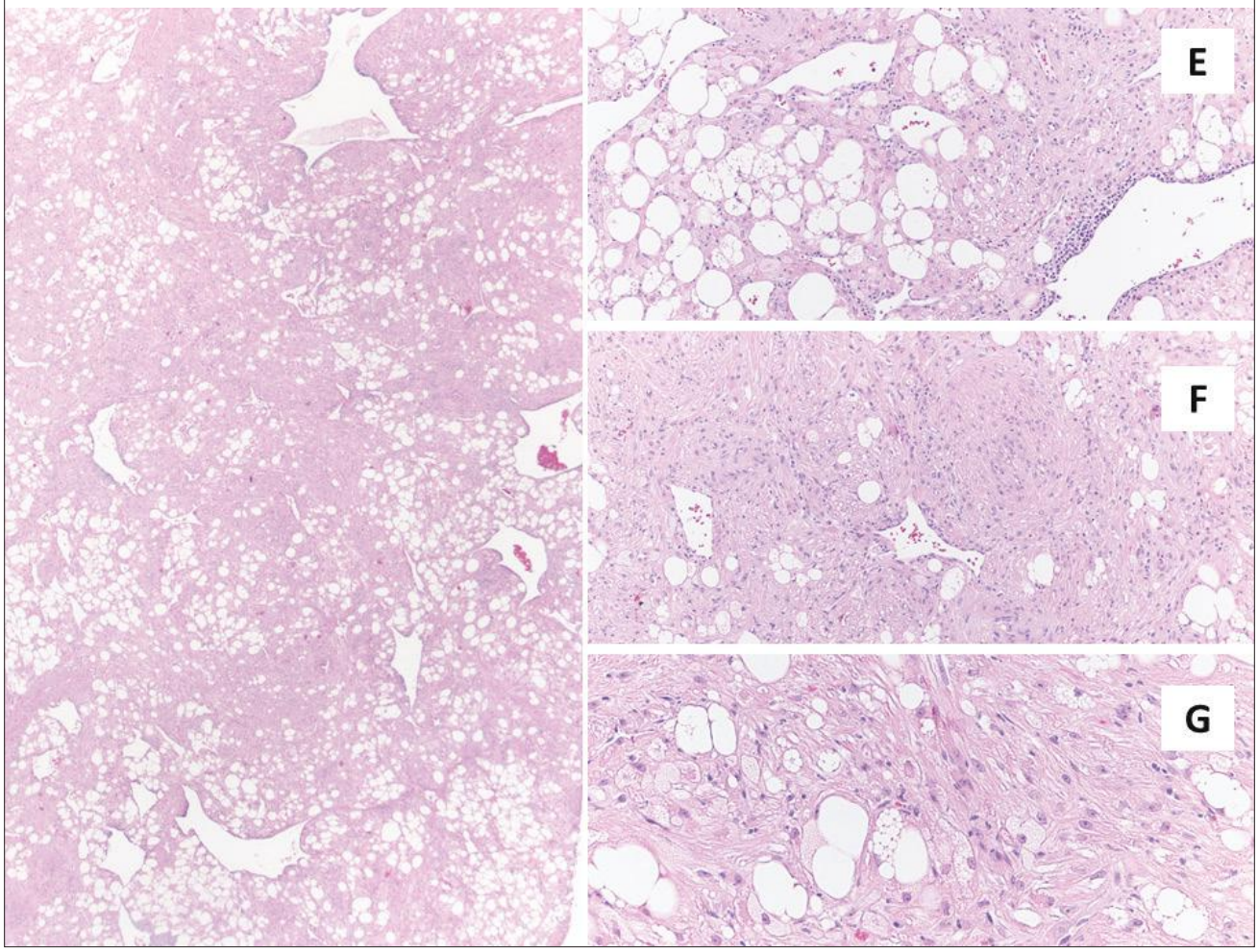
Myoepithelial tumor (myoepithelioma) and myoepithe-

Fig. 11. Different morphologic features of clear cell "sugar" tumor of the lung are illustrated: the prominent vascularization of thin-walled hemangiopericytoma-like vessels (A, B), the interstitial pattern of growth defining: "diffuse PEComatosis" (C) and the clear epithelioid and spindled cells constituting the lesion (D).



lial carcinoma of the lung are neoplasm histologically analogous to those arising in salivary glands, breast and soft tissue [1]. Primary myoepithelial tumor/carcinoma (MTC) of the lung are extremely rare neoplasms showing a predominant or exclusive myoepithelial differentiation [1 39-46]. The last WHO Classification enclosed MTC as a newly separate entity differentiating it from epithelial-myoepithelial carcinoma and pleomorphic adenoma in consideration of the lack of ductal/glandular component. [1] Primary pulmonary myoepithelial lesions are thought to arise from submucosal bronchial glands of the lower respiratory tract [43] and recently EWSR1 rearrangements have been identified as possible molecular alteration in MTC [36]. MTC in the lung is a rare neoplasm occurring in adults with a wide age range (18-76 years) with most benign cases affecting females and most malignant cases affecting males. The majority of patients (71%) have a smoking history. Symptoms of airway obstruction (cough, dyspnoea) or blood sputum may be present in patient with endobronchial or endotracheal lesions [1 39-46]. Chest pain and respiratory distress characterize the rare mediastinal location of MTC [42]. Patients with peripheral tumors may be asymptomatic [39-41]. MTC can arise as endobronchial central mass or as a peripheral nodule. Thoracic CT can evidence circumscribed nodule, spiculated mass or nodular shadow with irregular margins [40 45]. MT is negative at PET-CT [40], whereas MC can be hypermetabolic [46]. Gross examination usually reveals a well-circumscribed mass ranging from 1.5 to 20 cm, with a yellow-tan, sometimes glistering cut surface [1 39-41]. Invasive growth, necrosis and haemorrhage may be present in MC [43-46]. Microscopic examination reveal a lobulated, multinodular neoplasm composed of cords and nests of epithelioid, spindle, clear and plasmacytoid cells with a variable reticular architecture and a myxoid, chondromyxoid or collagenous/hyalinised stroma [1 39-46]. The absence of ductal differentiation, distinguishes MTC from epithelial-myoepithelial carcinoma and pleomorphic adenoma [1]. Neoplastic cells are variably epithelioid (round-to-polygonal with abundant eosinophilic cytoplasm), spindled (short-to-elongated with eosinophilic-to-clear cytoplasm and tapered nuclei), plasmacytoid (plump with abundant eccentrically placed hyaline cytoplasmic inclusions) or clear [1 39-46]. Helpful

Fig. 12. Angiomyolipomas is characterized by fat tissue with dispersed lipoblasts (E), prominent thick-walled vessels (F) and bundles of spindle eosinophilic muscle cells somewhat arranged around vessels (G).

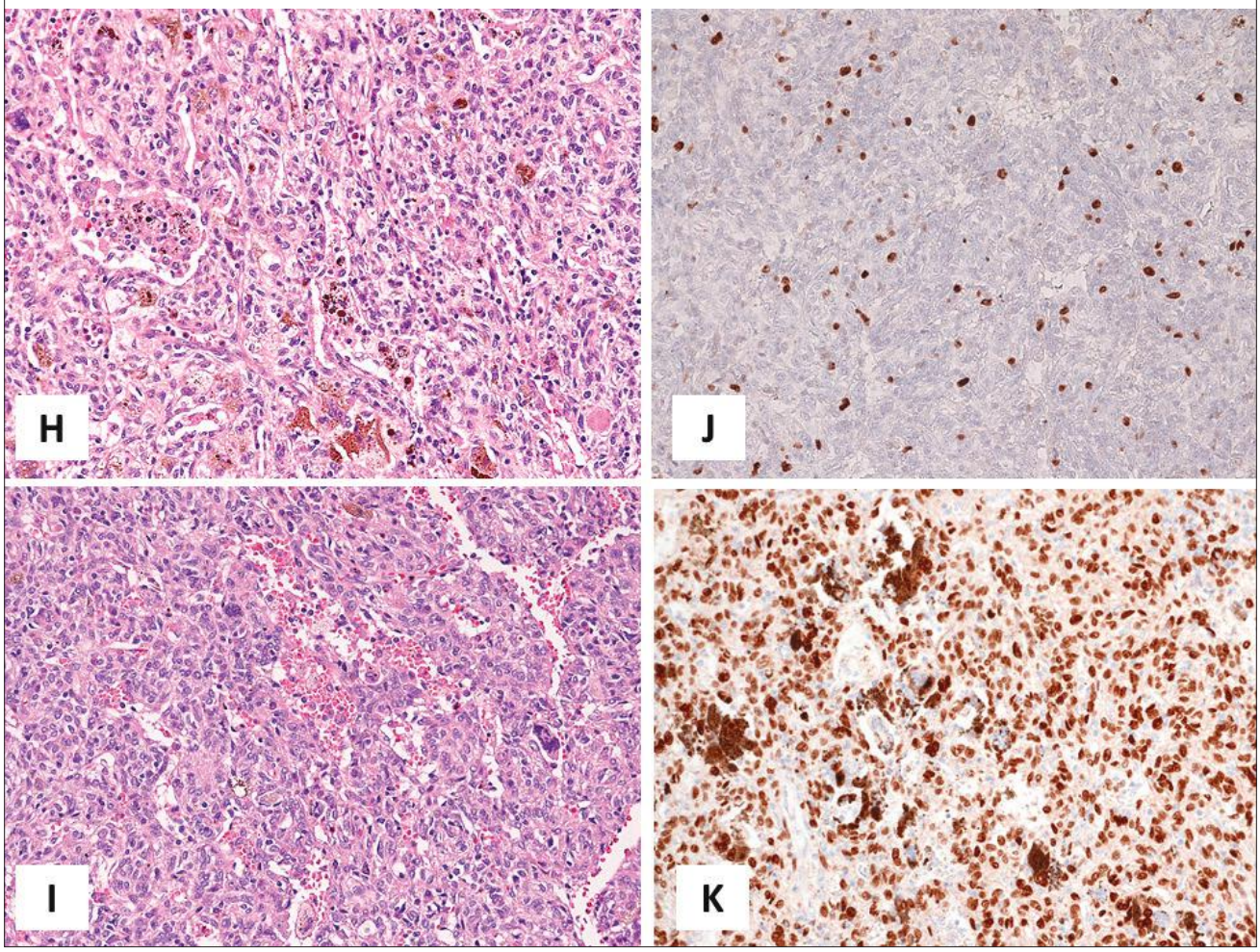


criteria to differentiate benign MT from malignant MC include high mitotic rate (mean 13/10 HPF), necrosis, nuclear atypia with hyperchromasia, multinucleation and prominent nucleoli [43-46]. MTC consistently express epithelial markers (CK, EMA) and is also immunoreactive for at least one myoepithelial marker (S100, calponin, SMA, glial fibrillary acid protein (GFAP), caldesmon, p63). Desmin and CD34 are usually negative. Genetically, MTC are often characterized by EWSR1 gene rearrangements with a variety of different fusion partners including ZNF444 in a MC with clear cell and FUS in a MC with spindle cell morphology. However, the majority of MTC lack an identifiable fusion partner at yet [1]. The differential diagnosis include other salivary gland-type tumors of lung such as pleomorphic adenoma/mixed tumor (presence of glandular/ductal component in a chondromyxoid stroma, lack of EWSR1 rearrangements), epithelial-myoepithelial carcinoma (presence of ductal component, lack of EWSR1 rearrangements), adenoid cystic carcinoma (biphasic neoplasm composed of epithelial and myoepithelial cells with cribriform pattern of growth, CD117 +) and metastatic lesions from salivary glands, breast or soft tissue (clinical, anemnestical and radiological correlations, multiple lung nodules) [1 39 43 46]. When benign, localized to the lung and completely surgically resected, MT is cured [39-41]. MC can metastasize to liver, brain, contralateral lung and soft tissue, but rarely show lymphnode dissemination [1 43-46]. Once excluded the hypothesis of metastases, the possibility of primary MTC may be advanced and also supported by EWSR1 rearrangements.

Key pathologic features of myoepithelial tumors/myoepithelial carcinoma

- Typically centrally located with most benign cases (MT) occurring in females and most malignant cases (MC) occurring in males;
- multinodular, lobulated architecture (Fig. 17A) and a spectrum of trabecular, reticular or solid pattern of growth with variably myxoid, chondromyxoid or collagenous/hyalinized stroma;
- epithelioid (Fig. 17B), spindled (Fig. 17C), plasmacytoid (Fig. 17D) or clear (Fig. 17B) tumoral cells;
- malignant features defining MC are: necrosis

Fig. 13. Malignant and pigmented PEComa of the lung is illustrated, showing prominent melanin deposition (H), atypical nuclear features with multinucleation, hyperchromatic nuclei (I), increased mitotic index with Ki-67/MIB-1 (J) and nuclear strong and diffuse positivity with TFE3 at IHC.



(Fig. 18E), high mitotic rate (Fig. 18F) and/or nuclear atypia (multinucleated cells, hyperchromatic nuclei, prominent nucleoli) (Fig. 18G);
- positivity for CK, S100, GFAP and calponin (SMA and p63 may also be positive);
- negativity for desmin and CD34;
- frequent EWSR1 rearrangements.

Angiomatoid fibrous histiocytoma

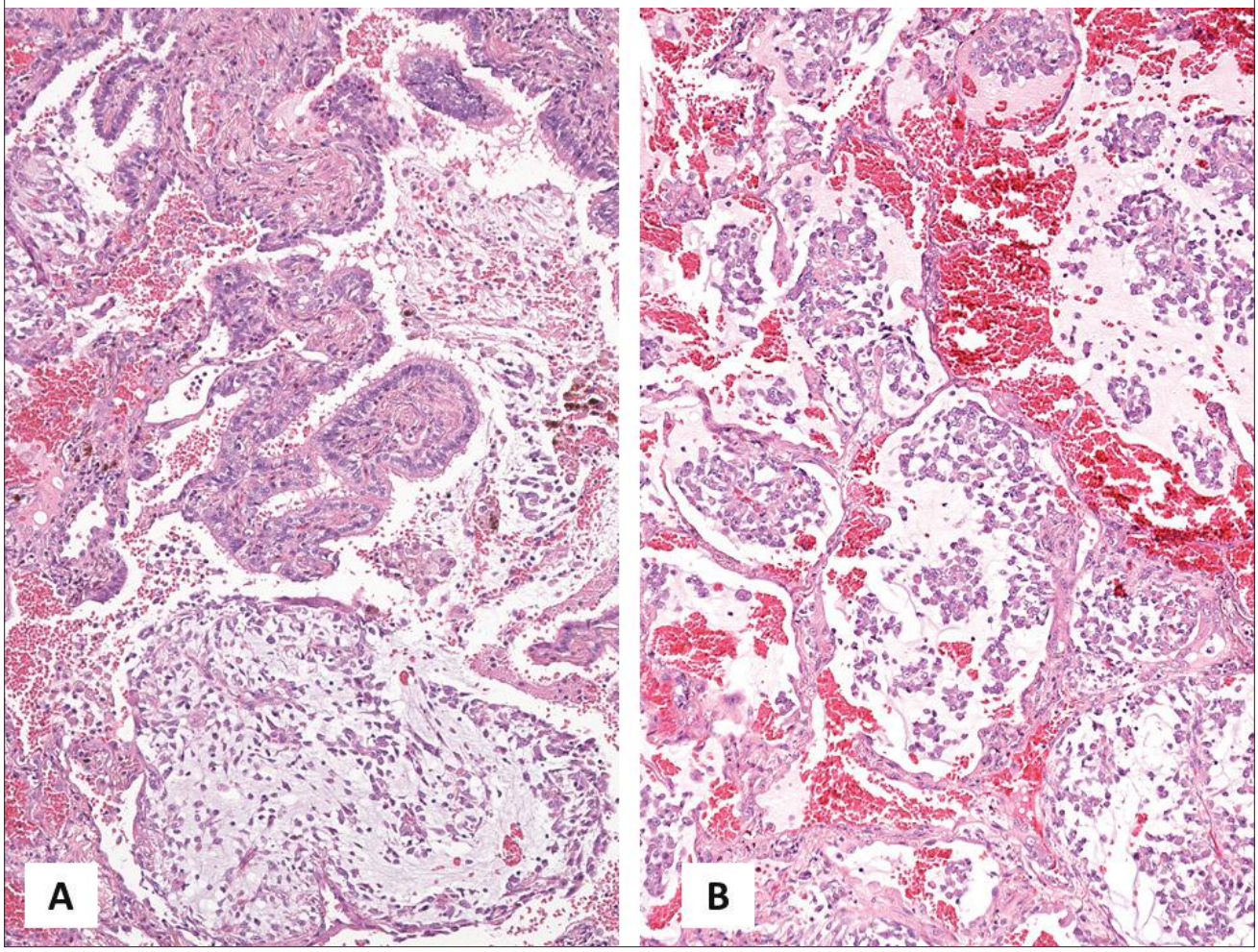
Not yet received a WHO Classification

Angiomatoid fibrous histiocytoma (AFH) is an uncommon soft tissue neoplasm of intermediate (borderline) malignancy and uncertain histogenesis, rarely affecting the lung [47-50]. Primary AFH of the lung affects adults with a mean age of 53 (range 28-70 years) with a slight male prevalence (M:F, 2.5:1). Symptoms are nonspecific and some AFH are incidentally detected. At chest CT, lung AFH appears as a peripherally-located, well-demarcated, homogeneous parenchymal mass with moderate PET uptake. Grossly, AFH is a solid, red, yellow-tan or white mass, measuring from 1.5 to 8.5 cm (mean, 2.7 cm) [47 48]. Endobronchial cases have been described [49] and cut-surface may reveal blood-filled cystic spaces. Histologically, AFH shows four key morphologic features in varying proportions:

1. multinodular pattern of growth of short spindled myoid cells or ovoid histiocyte-like cells with a distinctive syncytial growth;
2. pseudoangiomatous spaces filled with extravasated erythrocytes and foci of haemorrhage forming large blood-filled spaces lined by flattened tumor cells rather than endothelial cells;
3. thick incomplete fibrous pseudocapsule and intratumoral fibrous septa leading to a lobulated appearance at low-power magnification;
4. pericapsular cuffing of lymphoplasmacytic cells with occasional germinal centres, mimicking a lymph node infiltrated by a metastatic tumor [47-50].

The main diagnostic clue of AFH is represented by peritumoral shells of lymphocytes and plasma cells.
The neoplastic population consists of uniform, bland,

Fig. 14. Pulmonary myxoid sarcoma (PMS) near to a focus of peribronchiolar metaplasia with ciliated bronchiolar epithelium (A), shows the typical multilobulated pattern of growth within alveolar spaces (B).



spindly, oval or mixed spindly and oval cells with abundant palely eosinophilic cytoplasm and indistinct cell borders forming sheets and nodular aggregates sometimes showing whorled or storiform growth pattern. Cellular pleomorphism, mitotic activity, hyperchromatic giant cells, myxoid stroma, and a small blue-cell phenotype may be observed [48]. At IHC, about half of cases express desmin and EMA. SMA is positive in 40% and myogenin, CK, S100, CD34 and follicular dendritic cell markers (CD21, CD23, CD35, D2-40, clusterin) are negative. A non-specific staining with CD99, CD68 and CD163 was also detected [47-50]. In about 75% of AFHs the characteristic chromosomal translocations t(2; 22) EWSR1-CREB1 is observed. In a subset of AFHs chromosomal rearrangements resulting in the EWSR1-ATF1, and FUS-ATF1 gene fusions have been described [51].

EWSR1-ATF1 or EWSR1-CREB1 gene fusion also characterize clear cell sarcoma, hyalinizing clear cell sarcoma of the salivary gland, myoepithelial tumor of soft tissue (EWSR1-ATF1) and pulmonary myxoid sarcoma [36 51].

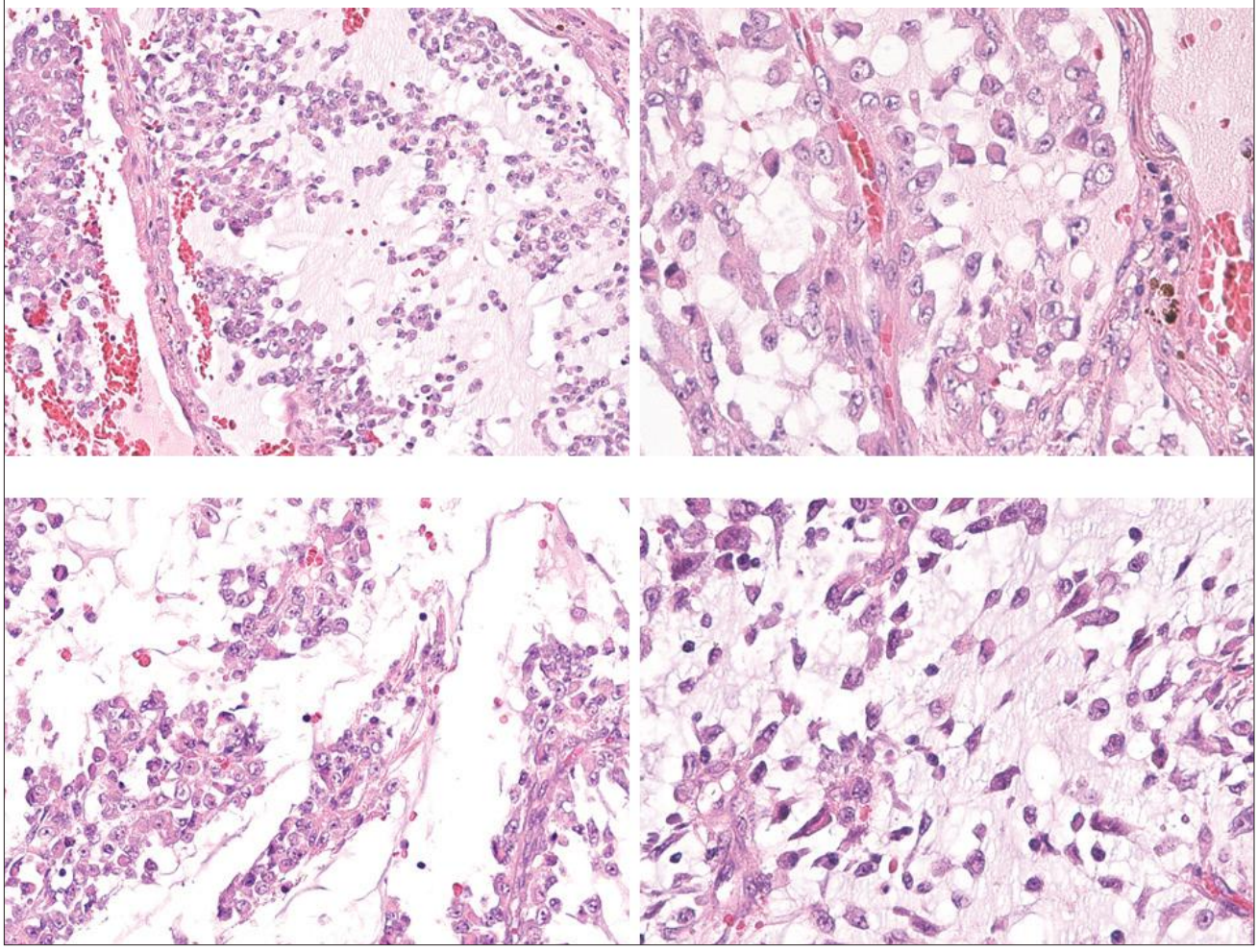
Differential diagnosis mainly includes inflammatory myofibroblastic tumor (SMA +, ALK +/-), follicular dendritic cell sarcoma (CD21+, CD23+ and/or CD35+), spindle-cell sarcomatoid carcinoma (CK +) and Kaposi's sarcoma (HHV8+) [1 47].

Once completely resected, pulmonary AFH shows a benign clinical behavior, even if metastasis to the kidney and the brain has been recently reported [50].

Key pathologic features of angiomatoid fibrous histiocytoma

- Multinodular pattern of growth of spindle myoid and histiocytoid cells (Fig. 20);
- peripheral thick fibrous pseudocapsule with prominent hemosiderin deposits and pericapsular cuffing of lymphoplasmacytic cells (Fig. 21);
- pseudoangiomatous spaces filled with blood and surrounded by tumoral cells (Fig. 22);
- positivity for desmin and EMA in 50% of cases (Fig. 23).

Fig. 15. PMS displays the specific myxoid background in which sparse spindle, stellate and polygonal cells are arranged in a reticular network.



Ciliated muconodular papillary tumor of the lung

Not yet received a WHO Classification

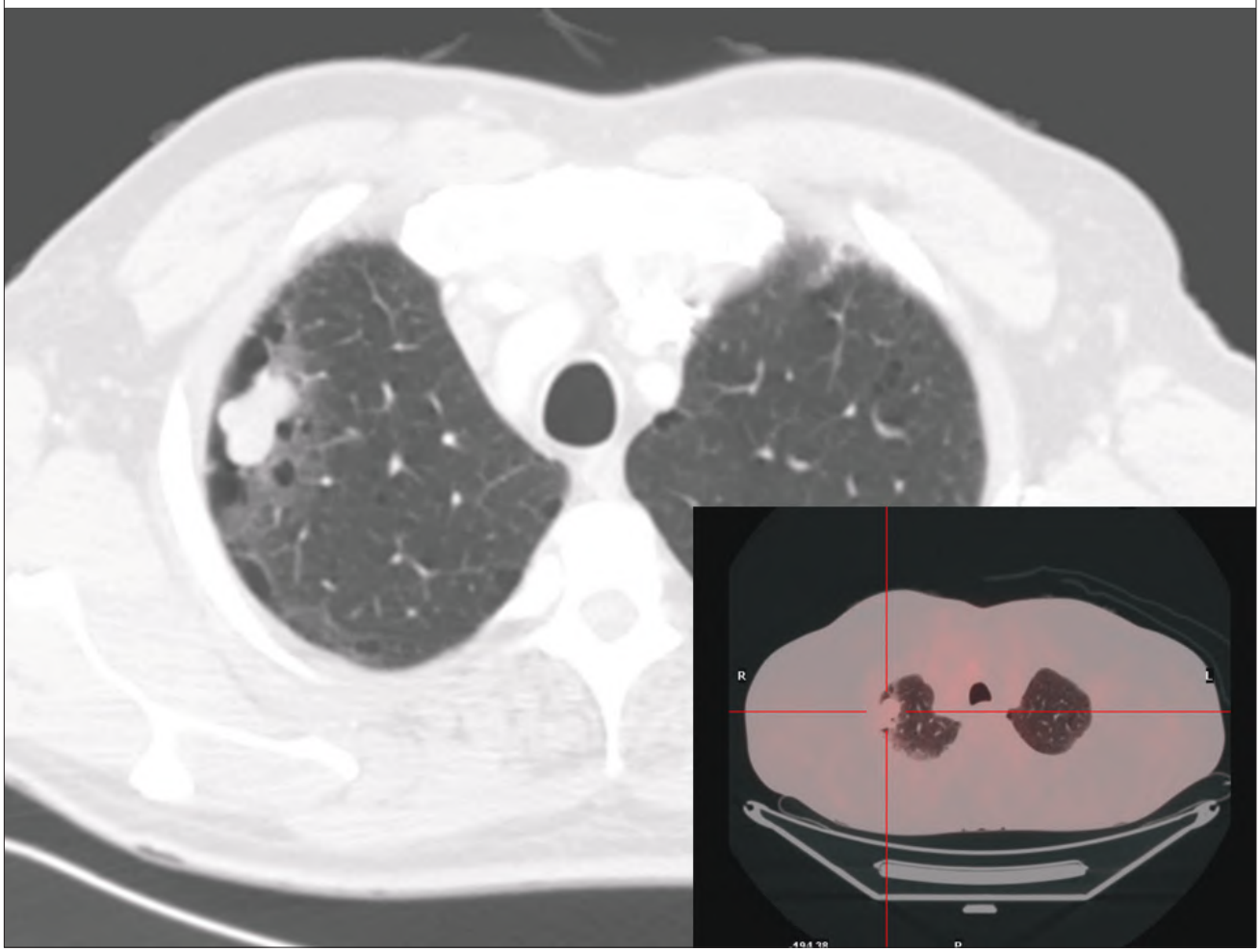
Ciliated Muconodular Papillary Tumor of the Lung (CMPT) is a low-grade malignant tumor with ciliated, goblet and basal cells, typically presenting as a peripheral lung nodule in adults [53-60]. CMPT is not yet included in the WHO Classification, but its peculiar morphology and molecular characterization might recognize it as a distinct new lung entity in the very next future [54-57]. CMPT is a rare low-grade, peripheral pulmonary tumor showing a benign course after complete surgical resection. CMPT affects adults with a wide age range (19-83 years), but mainly occurs in elderly (> 60 years), smoker patients. CMPT affects patients of both genders, with a female predominance. Usually CMPT is asymptomatic and incidentally detected during follow-up or staging for different malignancy. Imaging features of CMPT are variable: well-circumscribed nodules, mass with irregular margins or cystic cavitations, ground-glass opacities, with a constant peripheral location. PET-CT can either show a slight-to-moderately increased uptake of FDG or be completely negative [55 57].

Grossly, CMPT is a small nodule (0.8 to 4.5 cm, usually < 1.5 cm) white-to gray in colour, with a gelatinous cut surface [57]. Endobronchial growth has not been reported. Histologically, CMPT display a papillary and glandular architecture with cystic change. There is abundant extracellular mucin surrounding the tumor and within cystic spaces. A tripartite cellular component is pathognomonic and characterized by:

1. ciliated columnar epithelial cells;
2. mucinous goblet cells;
3. and basal cells.

The outer layer of papillae shows an admixture of ciliated and goblet cells and the inner one consists of a continuous layer of basal cells. The key diagnostic pathologic feature, also helping in differentials, is the presence of ciliated columnar cells [53 56 57 59]. Nuclear atypia, mitoses and necrosis are not observed. At IHC, CMPT is reactive for TTF-1 and CK7 in all the three cellular

Fig. 16. Thoracic CT of a PMS shows a bilobated nodule of the right upper lobe with peripheral ground glass opacities likely due to the growth within alveolar spaces of the tumor, near to emphysematous bullae. PET-CT scan discloses a mild uptake of FDG. Although PMS are more frequently detected near the main bronchi, as centrally located nodules, rare cases manifest as peripheral lesion.

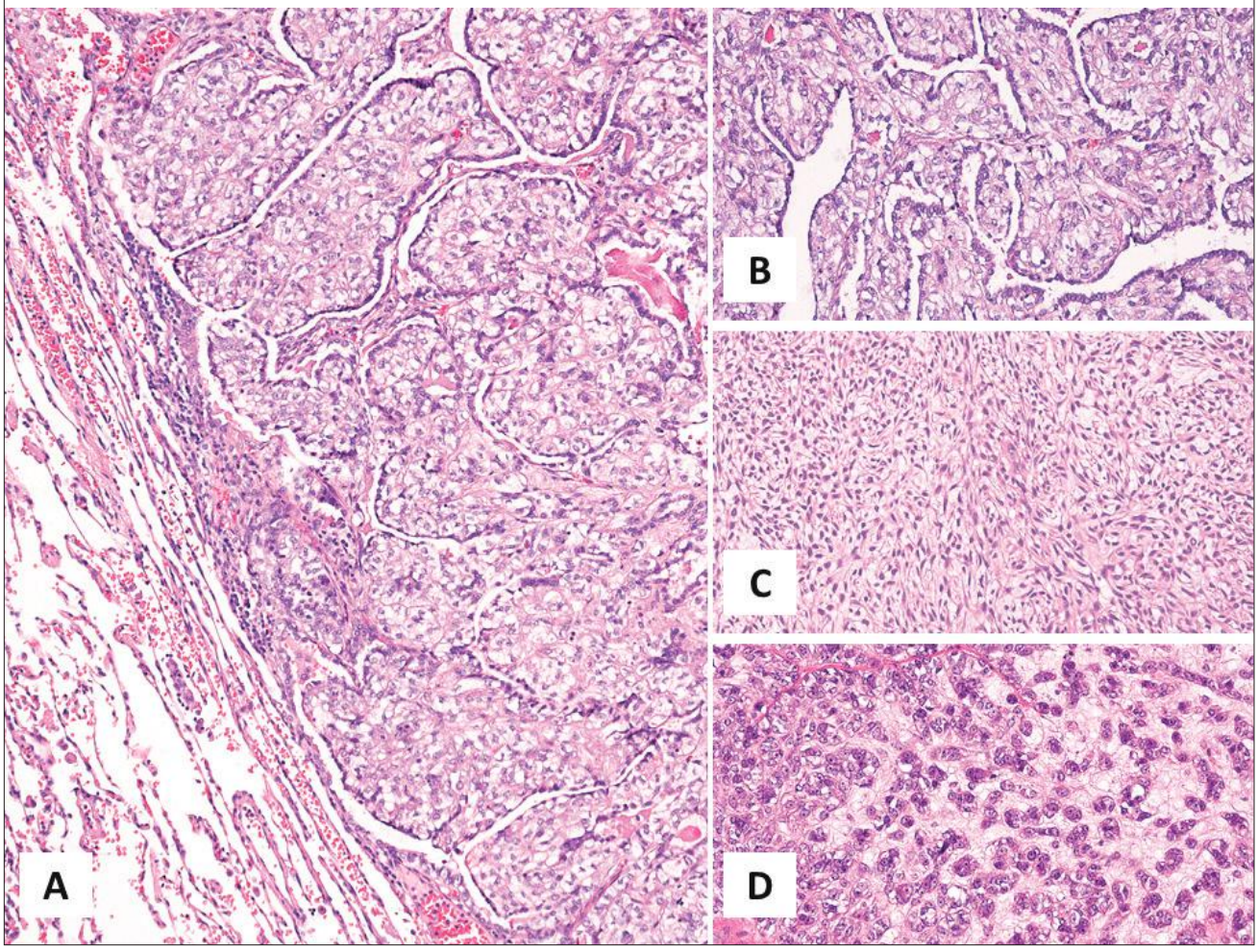


component. CEA shows a patchy positivity. CK20 is always negative. Recent molecular studies have identified BRAF V600E mutations in 40%, exon 19 deletions of EGFR in 30%, PTPN11 in 20% of CMPT and other sporadic mutations (AKT E17K, BRAF G606R, CTNNB1, IDH1 and TP53) were detected. CMPT harbouring V600E BRAF mutation might also show cytoplasmic positivity for BRAF (clone VE1) at IHC [60]. Differential diagnosis may be challenging on small biopsies or frozen section [55 56]. However, the recognition of a ciliated cellular population in a small peripheral lung nodule, should suggest a conservative surgical approach by wedge resection with free margins rather than lobectomy. Several benign, low-grade and malignant entities enter in the differential diagnosis of CMPT, as well as the peribronchiolar metaplasia (lack of goblet cells, mucin pools and of a distinctive nodule at imaging), mixed squamous and glandular papilloma (similar morphology, but central, endobronchial location), primary or metastatic mucoepidermoid carcinoma (primary: centrally located, metastatic: multiple nodules, overt atypia, absence of ciliated cells), invasive mucinous ADC (lack of cilia with the exception of rare and debatable entity such as: "*mucinous adenocarcinoma with cilia formation*" or "*well-differntiated papillary adenocarcinoma with cilia formation*" that possibly represent CMPT, absence of the tripartite components, evident nuclear atypia and mitotic activity) [1 53-60]. Awareness of the existence of CMPT is of paramount importance in order to do not mistake this low-grade lesion with malignant invasive ADC, which require aggressive surgical approach [55 56].

Key pathologic features of ciliated muconodular papillary tumor of the lung

- Peripherally located;
- variable imaging features on CT: well-circumscribed nodules (Fig. 24), nodules with irregular margins or ground glass opacities;
- papillary and/or glandular architecture with prominent surrounding alveolar mucin (Fig. 25A);
- papillae lined by a combination of mucinous cells re-

Fig. 17. Pulmonary myoepithelial tumor (MT) shows a lobulated architecture and interstitial pattern of growth (A). Epithelioid and clear (B), spindle (C) and plasmacytoid cells (D) variably characterize MT.



sembling goblet cells and columnar cells with cilia;
- continuous basal inner layer immunoreactive for p63/p40 and CK 5/6;
- variable positivity for TTF-1, CK7 and CEA in all tumoral cell populations;
- negativity for CK20;
- 40% BRAF (V600E), 30% EGFR (del 19) mutated.

Conclusion

Pathologists have to be conscious about the existence of new rare entities recognized in the last WHO Classification of Tumors of the Lung [1], together with angiomatoid fibrous histiocytoma [47] and ciliated muconodular papillary tumor [57] not yet included into the 2015-WHO.
The knowledge of their peculiar morphological, immunohistochemical, molecular features is mandatory for pulmonary pathologists to achieve a correct and precise diagnosis leading to an adequate surgical and/or oncological approach.

Fig. 18. The main pathological features defining myoepithelial carcinoma (MC) of the lung are necrosis (E), high mitotic rate (F) and nuclear atypia with multinucleated cells (G), hyperchromatic nuclei and prominent nucleoli.

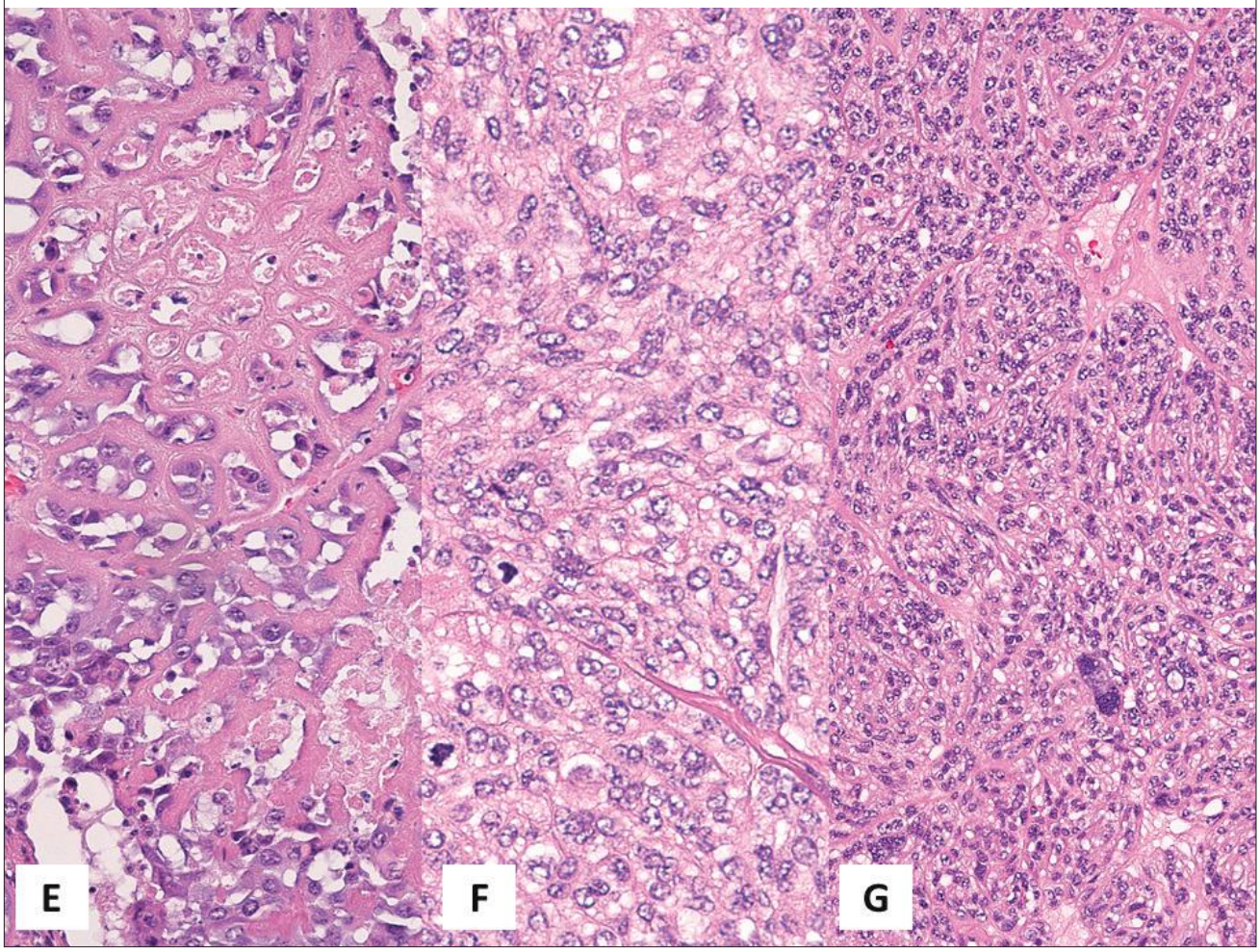


Fig. 19. Most MT express cytokeratin and calponin and about one third are positive for p63.

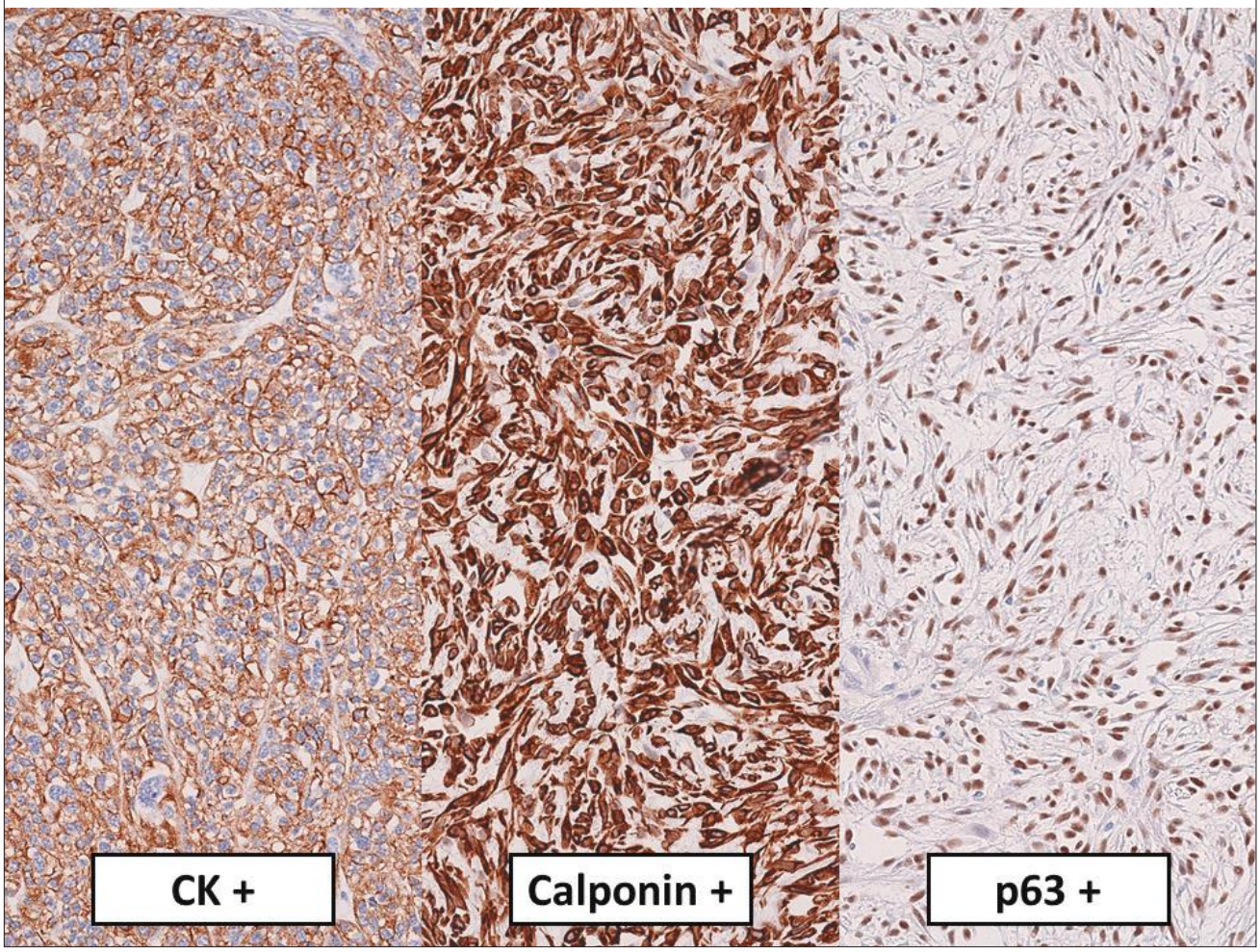


Fig. 20. Angiomatoid Fibrous Histiocytoma (AFH) shows multinodular pattern of growth with fibrous septa and lymphoplasmacytic cuffing (A). Uniform, bland spindle myoid cells (B) and ovoid histiocytoid cells with abundant palely eosinophilic cytoplasm and indistinct cell borders, imparting a syncytial appearance (C), characterize the lesion.

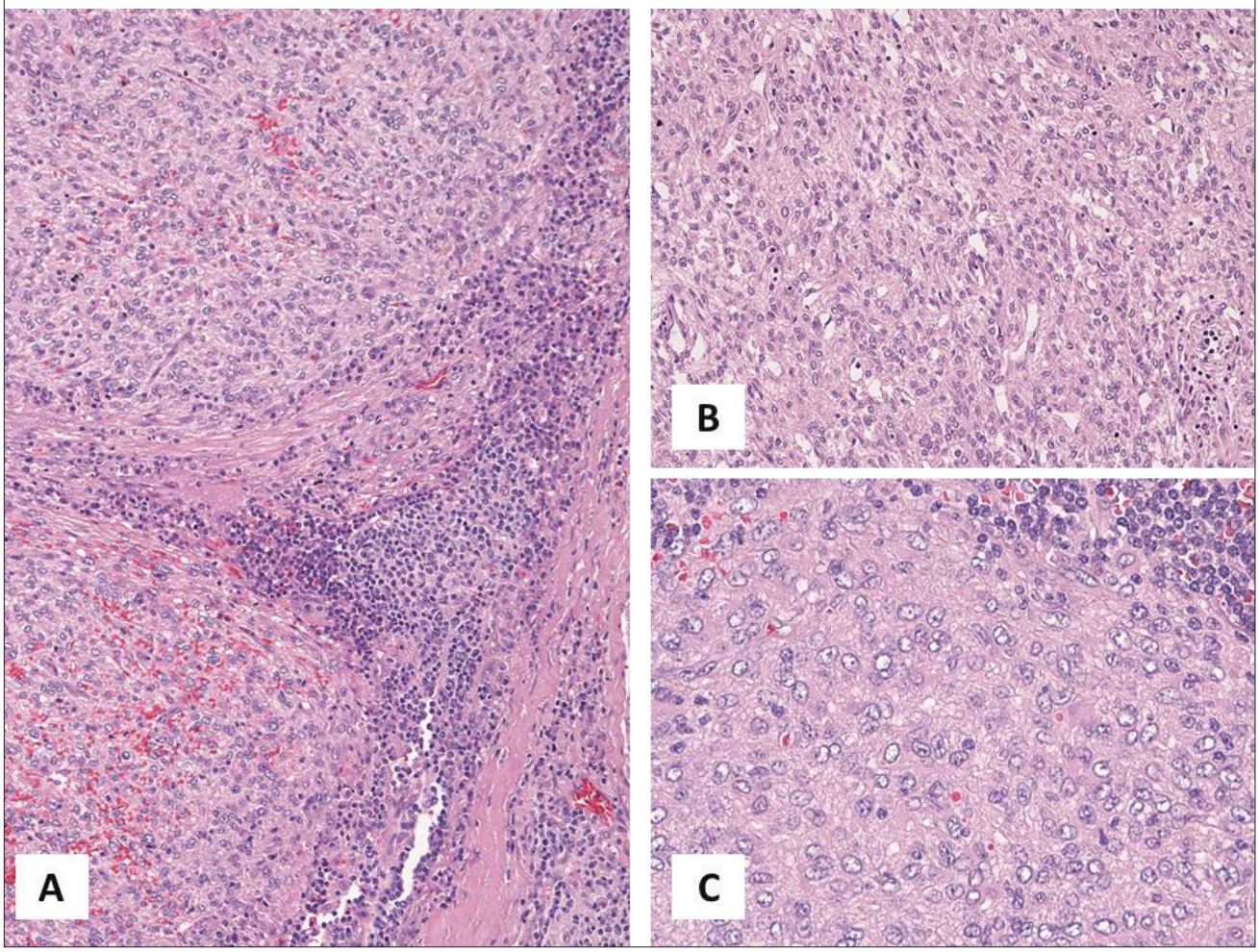


Fig. 21. Thick fibrous hyaline pseudocapsule with hemosiderin deposition (D) and pericapsular aggregates of lymphocytes with abundant admixed plasma cells (E) are typical of AFH.

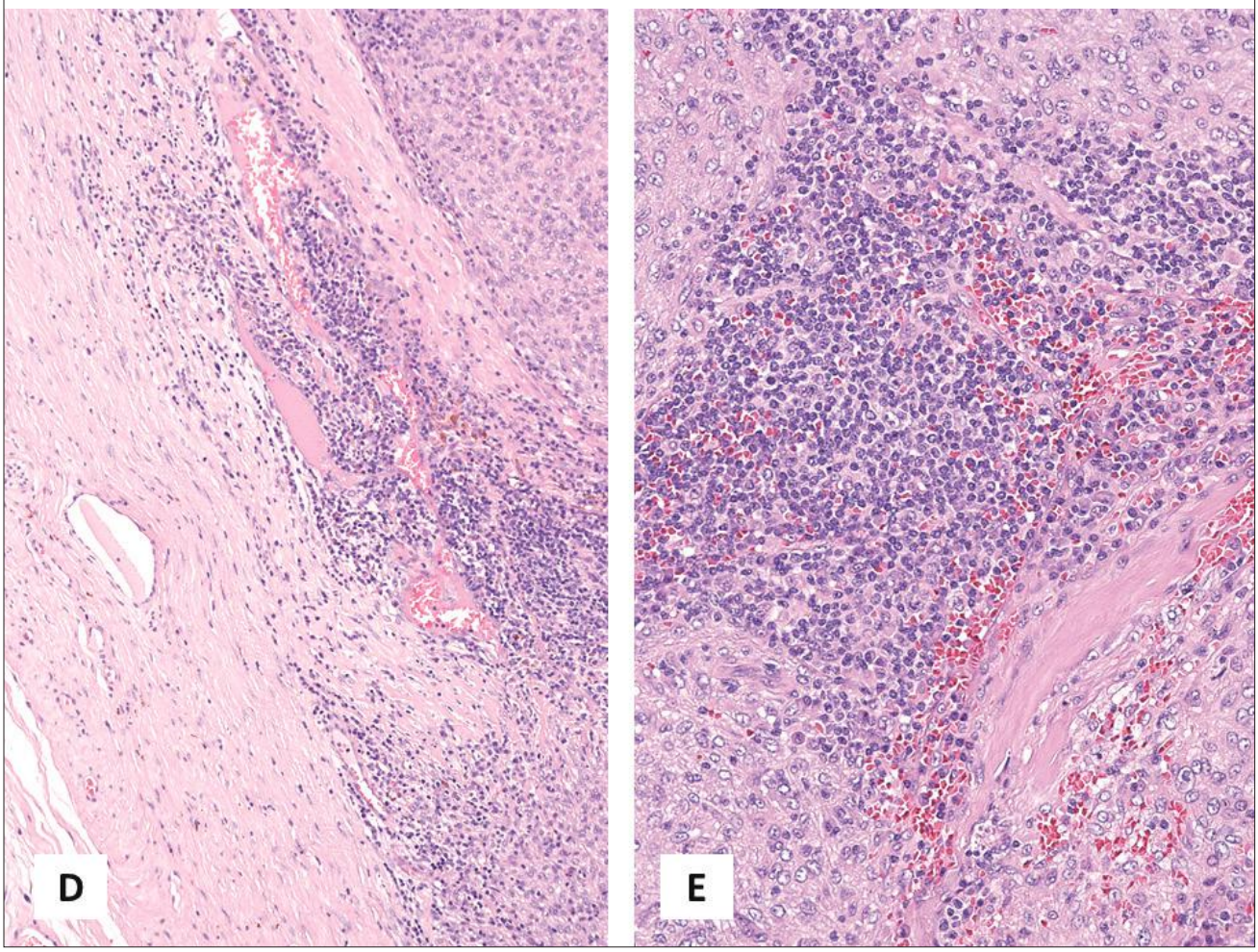


Fig. 22. Foci of intralesional haemorrhage are often present in the centre of the tumor, leading to a formation of large blood-filled spaces (F). Pseudoangiomatous spaces with extravasated red blood cells surrounded by tumor cells (G) are a key morphologic feature of AFH.

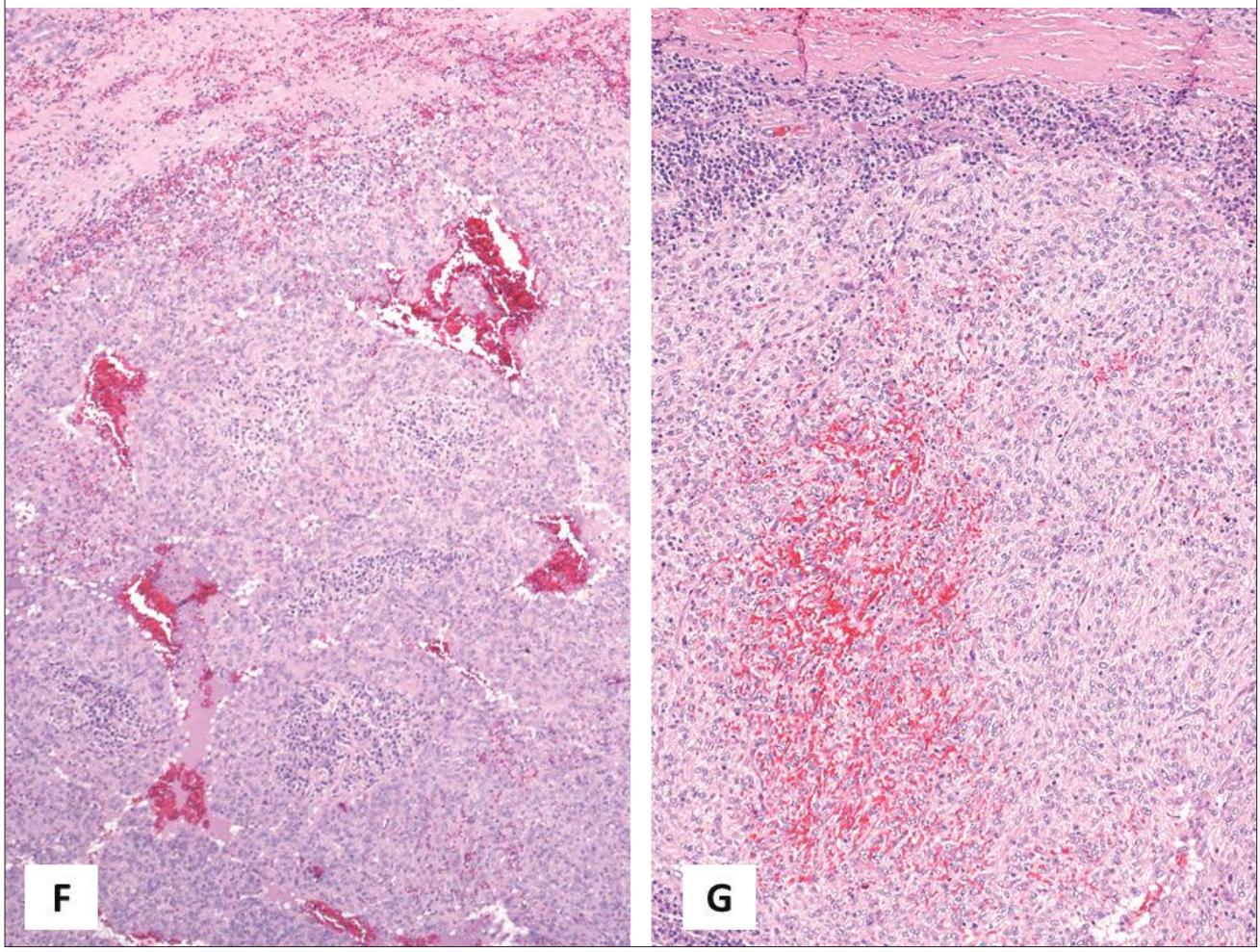


Fig. 23. AFH expresses both desmin with dendritic cell processes and EMA. The expression of EMA is usually of weaker quality than that of desmin.

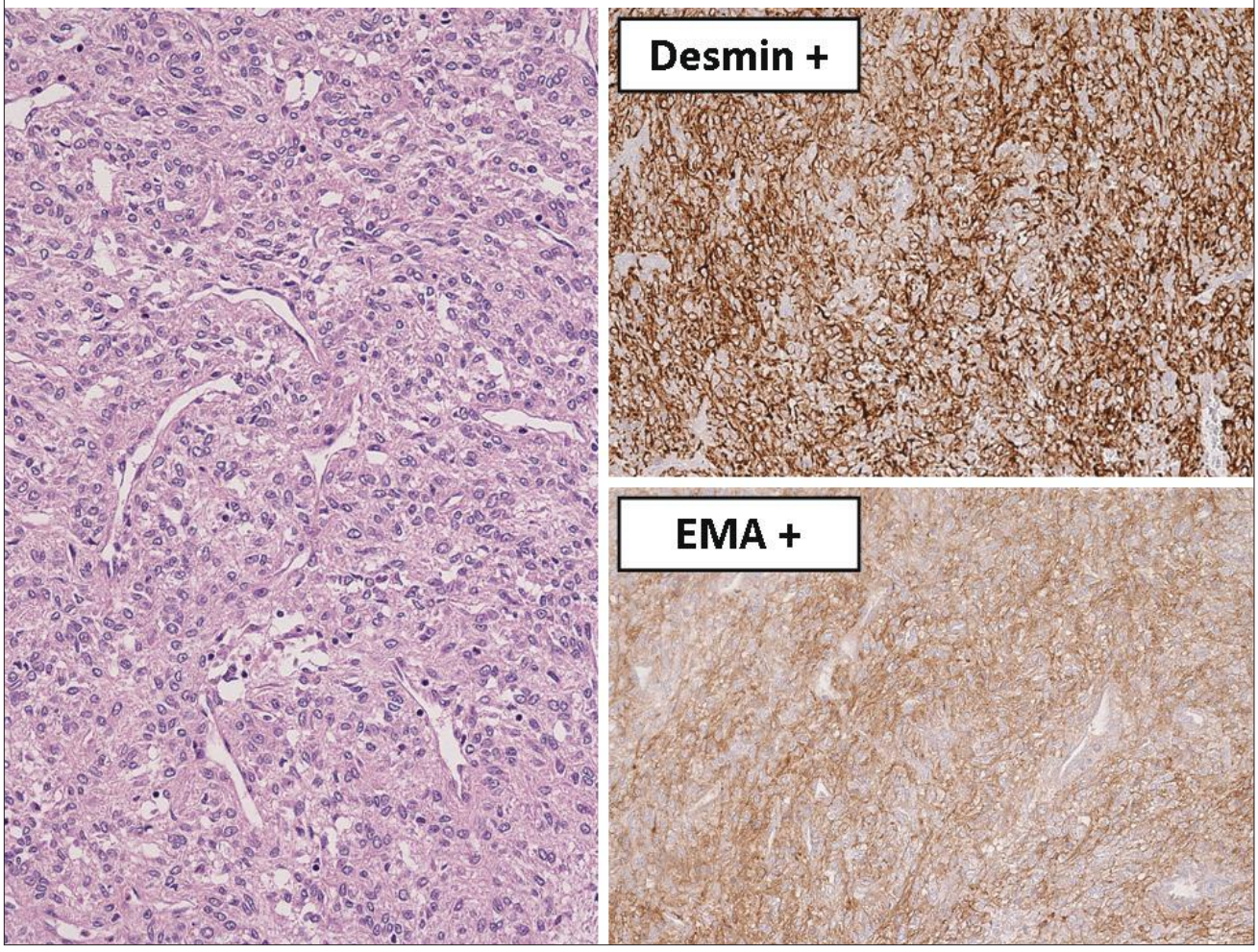


Fig. 24. Chest CT of Ciliated Muconodular Papillary Tumor (CMPT) disclose a peripheral nodule with well defined margins. Different radiologic pattern of CMPT have been also described, including nodules with ill-defined/irregular margin, cystic/cavitated nodules, ground-glass opacities with a constant and peculiar peripheral location.

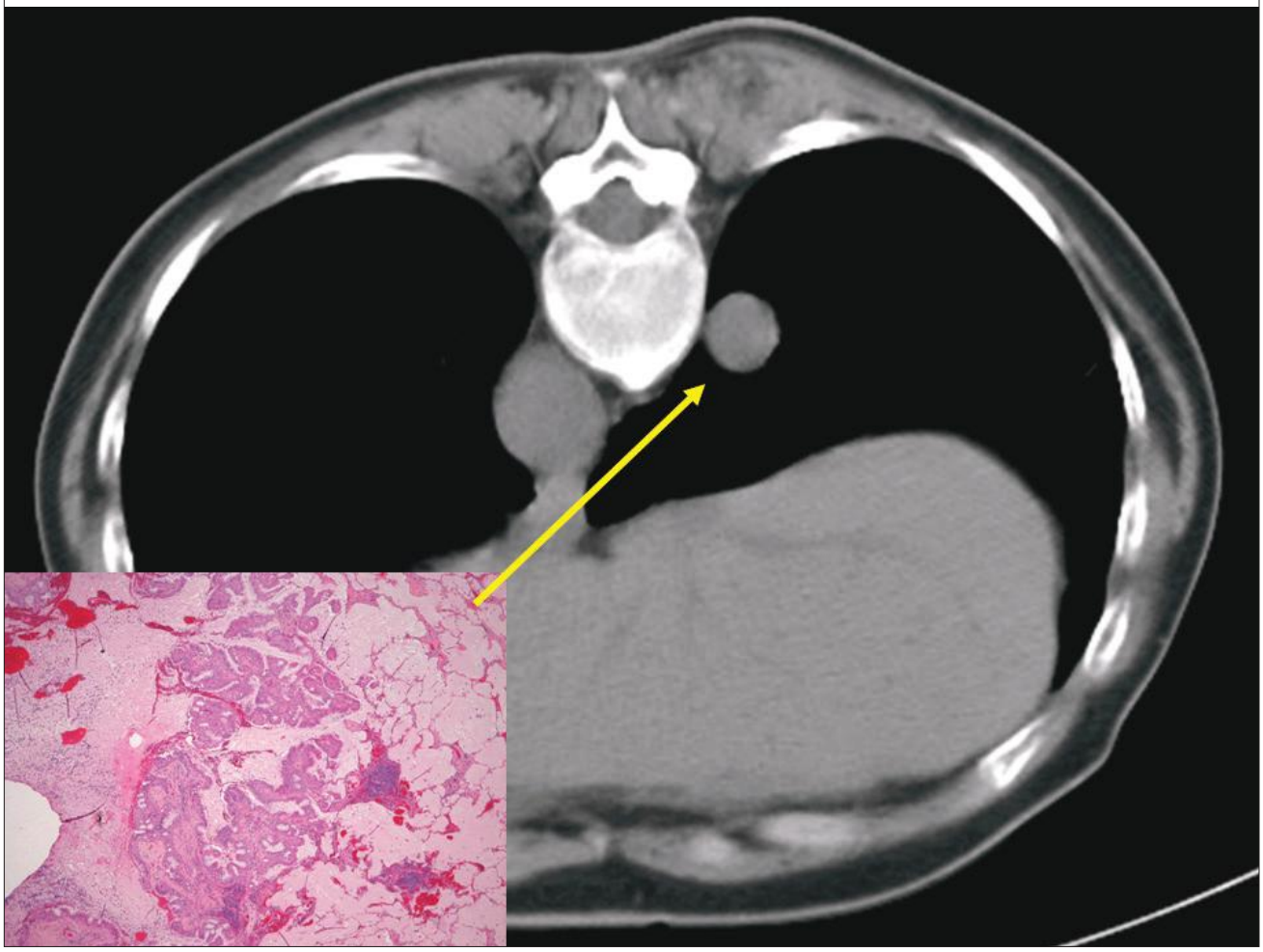
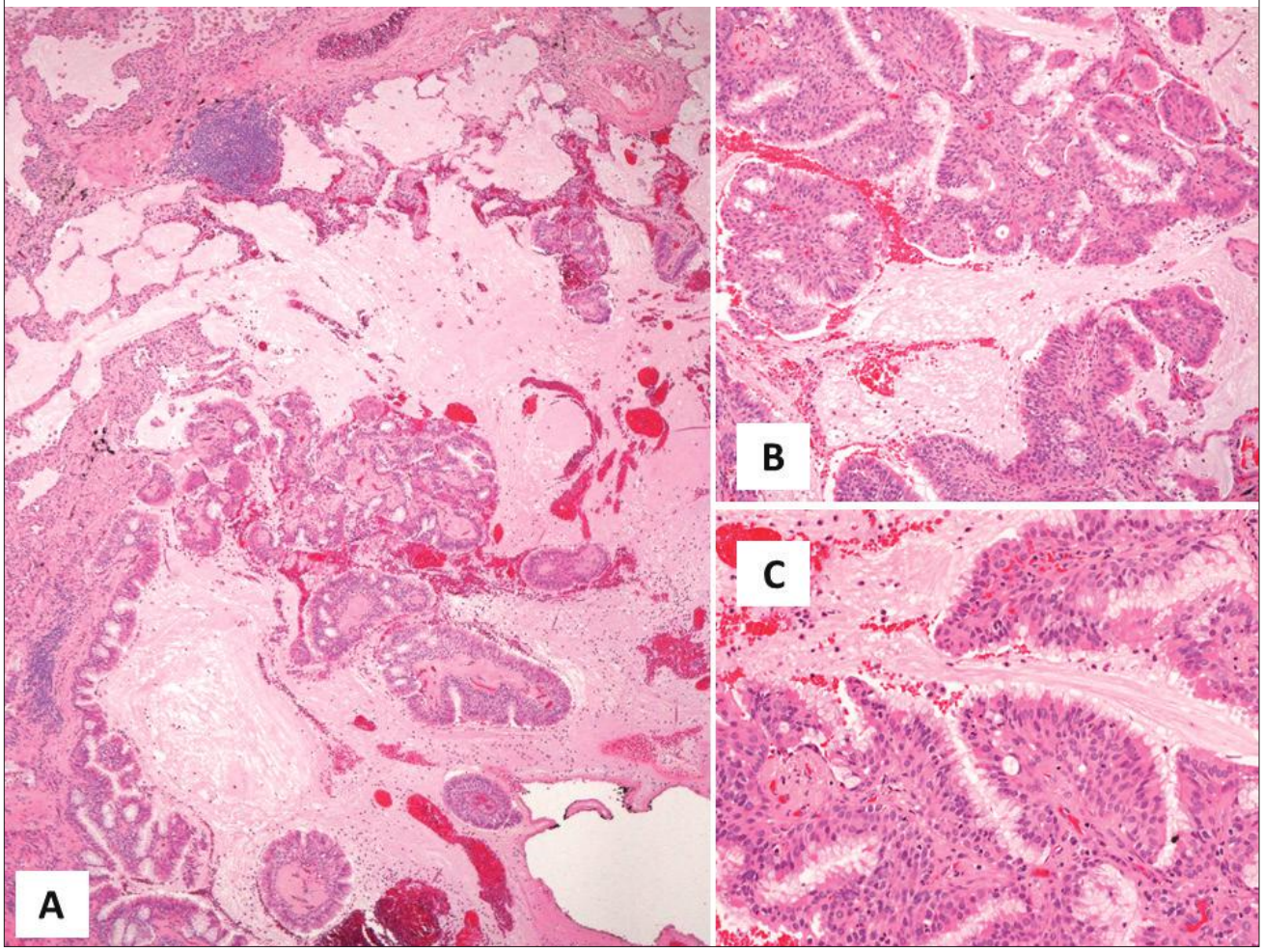


Fig. 25. CMPT of the lung shows a papillary pattern of growth with copious amounts of mucus (A). At higher magnification, the typical tripartite cellular component is visible: ciliated columnar cells and goblet cells lining the papillary structures and basal cells constituting the inner layer (B, C).



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