Well-Differentiated Squamous Cell Carcinoma Arising in a Ciliated Muconodular Papillary Tumor of the Lung

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An 80-year-old woman with a 0.5 pack per day, 20-year smoking history, who had quit 40 years earlier presented for evaluation of shortness of breath and pneumonia. She had a known nodule in her peripheral right lower lung that was discovered 5 years earlier, followed for 3 years, and considered stable. Current imaging showed the lesion had grown to 3.6 cm and cavitated. On biopsy, the nodule consisted of an abnormal ciliated and mucinous glandular proliferation with an underlying bland squamous proliferation. The lesion was favored to represent a ciliated muconodular papillary tumor (CMPT). A wedge resection was subsequently performed and most of the lesion showed similar morphology to the biopsy with papillary glandular elements, all demonstrating cilia without any cytologic atypia (Figure 1, A and B) and abundant mucin production (Figure 1, C). There were, however, focal areas with marked squamous atypia significant enough to be classified as a well-differentiated squamous cell carcinoma (Figure 1, D). Immunohistochemistry for cytokeratin 7 and thyroid transcription factor 1 predominantly highlighted the glandular elements, with p40, p63, and cytokeratin 5/6 highlighting the presence of basal cells. To our knowledge, a carcinoma arising in a CMPT of the lung has not been described in the literature. Although the currently described case reports indicate CMPTs behave in a benign fashion, we report here an example of a well-differentiated squamous cell carcinoma arising in a CMPT, highlighting the importance of complete excision of these lesions. We propose the name carcinoma ex ciliated muconodular papillary tumor for this lesion.

Human Pulmonary Dirofilariasis Mimicking Malignancy

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Dirofilariasis is a zoonotic infection inadvertently affecting humans, specifically the lungs. It is rare, but cases are being increasingly described as an emerging zoonosis in many parts of the world. We report a case of a 67-year-old man from Goiás State, inner Brazil. He was admitted for diagnostic evaluation of cough, weight loss, and hemoptysis 2 months earlier. On thin-section computed tomography, he had several nodules with well-defined smooth margins distributed in the lower lobes attached to the pleura and interlobar fissure (Figure 2, A). Lung function tests were within reference range. Screening results for infectious diseases were negatives. There was no history of cancer or thrombosis. The computed-tomography–guided percutaneous core needle biopsy showed an extensive venous infarction composed of central, coagulative necrosis (Figure 2, B), surrounded by granulation tissue (Figure 2, C). The identification of the fully matured, adult worm was performed for a diagnosis of human pulmonary dirofilariasis (Figure 2, D). In conclusion, clinicians, radiologists, and pathologists should consider dirofilariasis in the differential diagnosis of patients with pleural and interlobar nodules. Coagulative necrosis and granulation tissue may be the only diagnostic clues for pathologists. The histopathologic identification of worms is critical for final diagnosis and correct treatment.
Light-chain deposition disease is a systemic disorder caused by overproduction and deposition of the immunoglobulin light chain secreted by a B-lymphocyte clone, usually associated with lymphoproliferative and autoimmune diseases. However, a lung form of the disease is rarely seen. In this case, a 38-year-old, male, asymptomatic physician had a computed tomography scan that showed scattered cysts throughout the lungs, but with discrete inferior lung lobes predominance (Figure 3, A), found incidentally during medical monitoring of ankylosing spondylitis. The surgical lung biopsy revealed, at low-power, a well-defined, constrictive bronchiolitis related to several cystic dilations of various dimensions, some incomplete, others divided by delicate alveolar septa within a small vessel (Figure 3, B). At high magnification, their walls were thin because of compression of lung parenchyma with some luminal vascular protuberances (Figure 3, C). Furthermore, a prominent, intimal hyalinization of some small vessels and small hyaline masses in bronchovascular axis, both Congo-red staining negative, were observed (Figure 3, D). Moreover, HMB-45, CD1a, S100, α-SMA, and D2-40 immunomarkers were all negative. Measurement of free κ and λ chains and immunoglobulin (Ig) G, IgA, and IgE in the serum were observed (Figure 3, D). Light-chain deposition disease is in process. In conclusion, a diagnosis of light-chain deposition is in process. In conclusion, a multidisciplinary discussion was critical to clinicoradiologic-pathologic analysis for ruling out differential diagnoses and favoring pulmonary light-chain deposition disease.

Diffuse Pulmonary Lymphangiomatosis

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Pneumocystis jirovecii pneumonia is a rare pulmonary disorder affecting children and young adults with a variable outcome. In this case, a 29-year-old, previously healthy man was referred for dyspnea on mild exertion for more than 12 months. The high-resolution computed tomography scan showed patchy, bilateral, lung parenchymal abnormalities with interlobular septal thickening, ground-glass opacities predominantly in the upper lobes (Figure 4, D), and thickening of the pleura bilaterally with small pleural effusion. He presented with an oxygen saturation of 79% on room air and chronic hypoxia (PaO2 = 49.2). Lung function recorded over the same interval also indicated deterioration of restrictive impairment. Total lung capacity was 2.84 L (43% of predicted). Measurements of forced expiratory volume in first second of expiration (FEV1 = 1.01 L; 25% of predicted) and forced vital capacity (FVC = 0.6 L; 21% of predicted) showed severe restriction (FEV1/FVC, 96%). The diffusing capacity of lung for CO was 3.11 (10% of predicted). A surgical lung biopsy revealed proliferation and dilatation of benign-appearing lymphatic vessels in the pulmonary peribronchovascular axis and interlobular septae (Figure 4, A) with a nonelastic layer (Figure 4, B). These lymphatic channels were D2-40 positive by immunohistochemistry (Figure 4, C). He received interferon α-2b therapy; however, he died after 1 year. An effective treatment is not yet known. The correct diagnosis is very important toward improving treatment.

Pneumocystis jirovecii pneumonia was originally described as a powerful liver carcinogenic agent, and PVC dust was subsequently determined to be an etiologic agent of pulmonary fibrosis. A 59-year-old man was admitted with a 60-month history of exertional dyspnea and fatigue. He had smoked 10 pack-years. During the preceding 20 years, he had worked with PVC pipes. The chest radiograph showed a nodular pattern in the superior zones. High-resolution computed tomography showed a pattern of nodules with increased density and predominance in the right lobes (Figure 5, A) and thickened, interlobular septal lines (“parenchymal bands”); subpleural cysts; and traction bronchiectasis in the lower lobes. Lung function recorded over the same period also indicated deterioration of restrictive impairment. Total lung capacity was 3.44 L (52% of predicted). Measurements of forced expiratory volume in the first second of respiration (FEV1 = 1.27 L; 40% of predicted) and forced vital capacity (FVC = 63 L; 37% of predicted) showed severe restriction (FEV1/FVC = 78%). Surgical lung biopsy demonstrated an intense architectural distortion by fibrosis of periaxial, septal, and subpleural interstitium with diffuse bronchiolectasis and honeycombing, filled by prominent, amorphous, mucoid impaction. The cystic spaces were lined by squamous metaplasia and contained foreign-body granulomas with cholesterol clefts and Langerhans-type giant cells (Figure 5, B). Within the granulomas, the macrophages contained refringent and other inclusions. The Sudan IV stain demonstrated positive deposits within some of those granulomas previously reported for PVC exposure. Chemical analysis by chromatography will be performed. It was concluded that exposure to PVC dust may cause pneumocystis and foreign-body granulomas with cholesterol clefts and Langerhans-type giant cells, an important diagnostic clue for pathology practice.

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Reemergence of Yellow Fever in Brazil: Report of 2 Autopsy Cases

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Yellow fever (YF) is an acute, infectious disease caused by an arbovirus of the genus Flavivirus, which occurs in South America and Africa. In 2017, new cases of the disease were diagnosed and referred to our clinical hospital for treatment. We report 2 cases, a 52-year-old man and a 38-year-old man, with 5-day fevers (38.8–39°C), who showed intense jaundice and diffuse myalgia, which rapidly evolved to skin rash, gingival bleeding, enterorrhagia, acute renal failure, and death. The patients lived in a rural area near an environmental reserve in which there were infected monkeys. The necropsies showed intense jaundice with massive liver necrosis and heavy lungs, weighing more than 1 kg each, which were dark and airless; on slicing of the lung, the cut surfaces exuded blood or heavily blood-stained watery fluid. The pathophysiologic sequence of lung injury included diffuse neutrophil recruitment to the lungs (Figure 6, A), capillaritis with bleeding from the pulmonary microvasculature into the alveoli, and diffuse alveolar hemorrhage (Figure 6, B), with hemosiderin-laden alveolar macrophages as shown with Perls stain (Figure 6, C). The polymerase chain reaction and immunohistochemistry for YF produced positive results (Figure 6, D). Neither patient had received a YF vaccine, and they presented with previous myocardiopathy as a comorbidity. The lack of a vaccine inoculation and heart disease seem to be important risk factors for the fatal form of YF. The main mechanism is an inflammatory process by YF-infected macrophages, triggering a diffuse alveolar hemorrhage and death by respiratory failure.

Adipose-Derived Mesenchymal Stem Cells and Their Conditioned Medium Modulate Parenchyma Remodeling Through Collagen V and Interleukin-17 Pathway in Experimental Pulmonary Fibrosis

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Context: The outcome of many long-term lung diseases may be pulmonary fibrosis, an excessive extracellular matrix deposition without effective treatment. Our aim was to study how adipose-derived mesenchymal stem cells (AD-MSCs) and their conditioned medium (CM) as therapy would act on a bleomycin (BLM) model of pulmonary lung injury.

Design: Pulmonary fibrosis was intratracheally induced by BLM (1.5 U, single dose). After 10 days, animals with BLM lung injury were further randomized into subgroups receiving saline (0.05 mL), AD-MSC immunophenotypically characterized by flow cytometry (1 × 106 cells in 0.2 mL saline), or CM (0.05 mL) intravenously. On days 14 and...
21, MSC and CM mice were sacrificed to be analyzed by immunohistochemistry, immunofluorescence, electronic microscopy, and ELISA assay.

**Results:** The AD-MSC and CM mice had dramatic reduced deposition of type-I collagen fibrils, which were frequently seen around myofibroblasts, compared with that of the BLM mice. Similarly, proinflammatory cytokines were decreased (NOS2, fibrinogen). Reduced transforming growth factor-β, platelet-derived growth factor, and vascular endothelial growth factor and von Willebrand contribute to endothelial and epithelial repair, respectively. Abnormal and disrupted collagen V expression in a bundle manner among groups increased (Figure 7, A through C) by morphometry (Figure 7, D) and was related to a highlighted Th17 response expression.

**Conclusions:** Therapy with AD-MSCs and CM were effective at modulating the inflammatory and fibrogenic processes in BLM injury, which was attributed to paracrine-effects balancing. A negative modulation of myofibroblasts to produce collagen I, related to an exacerbated collagen V-induced Th17 response, may be a future therapeutic target in treatment of pulmonary fibrosis.

### A Common Tumor With Uncommon Histology: Tracheal Chondro-osseous Inflammatory Myofibroblastic Tumor

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Primary tracheal tumors are rare and mostly malignant. Inflammatory myofibroblastic tumors (IMTs) of the trachea are described in children and adults. We present a rare case of a 15-year-old boy who had a tracheal mass occluding 90% of the tracheal lumen on bronchoscopy. The tumor was 2 × 1.8 cm, tan-brown, and lobulated, which, upon cutting, had a bony-hard consistency. Histology showed a well-circumscribed tumor with overlying respiratory epithelium. The tumor displayed a peculiar zonation from periphery to the center. The peripheral thinnest rim of the tumor was composed of plump spindle-to-oval cells with myxoid stroma and intermixed lymphocytes and plasma cells. Most of the tumor in the center was chondro-osseous with patchy areas of calcification. There was no atypia, necrosis, or increased mitotic activity. SMA was diffusely positive, whereas desmin was variable. Because of an admixture of plasma cells with lesional spindle cells, immunohistochemistry for anaplastic lymphoma kinase (ALK) SP144 and D5F3, Ventana Medical Systems, Inc, Oro Valley, Arizona) showed marked chondro-osseous differentiation. Presumably chondroid differentiation was established (Figure 8, A) and cytologically bland, keratin- and PAX8-positive tumor cells forming vague rosettelike structures. Subsequent computed tomography (CT) demonstrated a 2.7-cm anterior mediastinal mass (Figure 10, B, large arrow) from which a tortuous, prominent vessel (Figure 10, B, thin arrow) extended toward the left brachiocephalic vein (Figure 10, B, asterisk). Bilateral lung nodules were also seen. Median sternotomy, anterior mediastinal tumor resection, excision of a portion of the azygos vein, and pulmonary wedge resections were performed. A thymectomy demonstrated a 6.7-cm, 2015 World Health Organization (WHO) 2015 classification.

**Morphologic Spectrum of Thymomas: A Review of 145 Cases Using World Health Organization 2015 Classification**

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**Context:** Histologic diagnosis of thymomas is associated with poor interobserver reproducibility and inconsistencies in the routine diagnosis. The aim of this study was to determine the morphologic spectrum of thymic tumors and to classify thymomas by the World Health Organization (WHO) 2015 classification.

**Design:** The study was performed as a retrospective analysis in a tertiary care center. All cases of morphologically confirmed, surgically resected specimens and small biopsies since 2009 were included. Pathology reports and diagnostic microscopy slides were retrieved for reevaluation. The WHO 2015 classification and the Modified Masaoka staging system were followed. In addition, immunohistochemistry (IHC) for TdT, pan CK, and CK 20 was performed.

**Results:** A total of 145 cases of thymoma (105 resections and 40 biopsies) were identified. There was a male preponderance. The average age was 44 years. The mean weight of the tumor was 97.5 g, and maximum dimension was 18 cm. The histologic distribution, according to WHO 2015, revealed prominence of B2 thymomas (34 cases), predominantly stage I. Type A and AB thymomas were diagnosed with WHO criteria and appropriate IHC; those thymomas showed glandular differentiation, rosetting, meningeal whorls, and microcystic change besides spindle cell fascicles. Type B1 thymomas had medullary islands and some B3 types possessed nuclear atypia. Atypical features, such as mitosis, bizarre nuclei, and clear cell changes, were noticed in 7 cases (Figure 9).

**Conclusions:** Thymomas can possess varied histomorphologic features, which are, therefore, a major diagnostic challenge. Difficult and heterogeneous cases can be diagnosed by the WHO criteria.

### An Unusual Presentation of a Type A Thymoma

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A 73-year-old man presented with progressive, left hip pain and a 7.5-cm, fluorodeoxyglucose (FDG)-avid, left supracapectal lytic lesion. Biopsies showed an epithelioid and spindle cell neoplasm with dense fibrous stroma (Figure 10, A) and cytologically bland, keratin- and PAX8-positive tumor cells forming vague rosettelike structures. Subsequent computed tomography (CT) demonstrated a 2.7-cm anterior mediastinal mass (Figure 10, B, large arrow) from which a tortuous, prominent vessel (Figure 10, B, thin arrow) extended toward the left brachiocephalic vein (Figure 10, B, asterisk). Bilateral lung nodules were also seen. Median sternotomy, anterior mediastinal tumor resection, excision of a portion of the azygos vein, and pulmonary wedge resections were performed. A thymectomy demonstrated a 6.7-cm, 2015 World Health Organization type A thymoma (TAT) (Figure 10, C). The lack of atypia was against atypical TAT and thymic carcinoma. Sections of azygos vein showed a luminal tumor thrombus (Figure 10, D), suggesting hematogenous spread via the superior vena cava, precipitating presentation of bone metastasis. Lung sections revealed metastatic TAT. Next-generation sequencing identified an HRAS exon3 p.Q61R mutation (not previously reported, to our knowledge, in metastatic TAT). A left periacetabular complete tumor excision, cryoablation, and complex reconstruction was then performed, followed by postoperative radiation. Follow-up imaging (3 months) revealed no progressive disease. In summary, we report a TAT presenting as a distant bone metastasis, which, to our knowledge,
has not been previously reported. Lack of atypia, mitoses, and necrosis in this case suggest that histologic features may not predict aggressive behavior in TAT.

Inflammatory Myofibroblastic Tumor of the Trachea: A Rare Occurrence

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We describe a case of a 28-year-old female nonsmoker presenting with cough and shortness of breath. A chest x-ray, performed as part of the initial investigations, was within reference range, but computerized tomography (CT) showed the presence of a tracheal mass partially obstructing her airways. Bronchoscopy showed a large, exophytic, and partially obstructing mass in the midtrachea, which was removed by surgical debulking. Histopathologic examination of the mass demonstrated interlacing fascicles of spindle cells of low cytologic grade (Figure 11, A), along with a peripheral lymphocyte infiltrate, including conspicuous populations of polytypic plasma cells. The spindle cells demonstrated positive immunoreactivity for the anaplastic lymphoma kinase (ALK-1) (Figure 11, B), smooth muscle actin (Figure 11, C), and vimentin (Figure 11, D). Negative immunostaining was observed for S100, anticytokeratins, CD21, CD23, and CD57. The morphologic features and immunohistochemical stains were consistent with that of inflammatory myofibroblastic tumor (IMT). A fluorescence in situ hybridization (FISH) assay for ALK (2p23) rearrangement was also positive, further confirming the diagnosis of IMT. IMTs are rare neoplasms with a low to intermediate malignant potential, usually encountered in children younger than 16 years. Histologically, IMTs are composed of a myofibroblastic spindle cell population accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils. Although some studies suggest that IMTs are reactive, more recent findings of chromosomal rearrangements involving the anaplastic lymphoma kinase (ALK) gene indicate a neoplastic pathogenesis. Moreover, IMTs have been described in the lungs, abdomen, pelvis, and retroperitoneum, but primary tracheal IMT is exceedingly rare.

An Unusual Lung Tumor With Squamous and Mucinous Differentiation: Adenosquamous or Mucoepidermoid Carcinoma?

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We report the case of an 83-year-old male nonsmoker who presented with an incidental right upper-lobe lung mass. Initial transbronchial lung biopsy was reported as squamous cell carcinoma. The patient subsequently underwent right upper lobectomy. The resection specimen showed a 3.5-cm, firm, grayish nodule. Histologic examination revealed an infiltrative tumor arising focally in peribronchial glands without apparent involvement of the bronchial mucosa or the presence of an in situ component. It effaced the parenchyma with a centrifugal pattern of extension. The tumor was composed of branching trabeculae of squamoid cells surrounded by desmoplastic stroma. No overt keratinization was evident. Interspersed among these squamoid cells were some mucinous cells with occasional glandular lumina (Figure 12). The unusual peribronchial growth pattern, in conjunction with a dual population of squamous and mucinous cells, raised the differential diagnoses of adenosquamous carcinoma and mucoepidermoid carcinoma. The squamoid cells were strongly positive for squamous markers CK5/6, p63, and p40. Those markers were focally absent in some cells lining the glandular lumina, which were TTF1istance; TF1 showed a gradated pattern of weak positive to negative staining in squamoid cells and was most intense around native bronchi and residual peribronchial glands, and progressively weaker to negative in the peripheral tumor trabeculae. The mucinous cells were also positive for TTF1. Both cell populations were negative for ALK, EGFR L858R, and EGFR E746-A750del on immunohistochemistry. Fluorescence in situ hybridization for MAML2 rearrangement was negative. Based on histomorphology, immunophenotype, and cytogenetics, we proposed a diagnosis of adenosquamous carcinoma.

Lymphomatoid Granulomatosis in Transbronchial Biopsy—Polymorphous Necroinflammatory Exudates Obliterate Angiitis: Two Case Studies

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Lymphomatoid granulomatosis is a rare lymphoproliferative disorder characterized by angiocentric Epstein-Barr virus–positive, large B cells in a polymorphous lymphoid background. We describe 2 cases of this rare entity, highlighting the need to be vigilant when examining transbronchial biopsies from immunocompromised patients. A 53-year-old Chinese man with a long history of polymyositis treated with
mycophenolate mofetil and prednisolone with recurrent perianal abscesses and bilateral nodular opacities on chest x-ray. Chest computed tomography (CT) scans showed bilateral pulmonary nodules with cavitation. Transbronchial lung biopsies revealed mixed inflammatory infiltrates with extensive necrosis, which were negative for fungal and mycobacterial organisms, and were initially thought to be nonspecific necrotizing inflammation. Careful examination disclosed a few atypical cells reactive for Epstein-Barr virus by in situ hybridization (Figure 13, A and C). Retrospective study of the perianal abscess biopsies revealed similar features. These findings were consistent with lymphomatoid granulomatosis grade 3. A 71-year-old Chinese woman with a history of recurrent high-grade glioma and sigmoid adenocarcinoma on chemotherapy, presented with cough and bicytopenia. The CT of the thorax showed numerous mediastinal and hilar lymphadenopathy as well as bilateral lung nodules. Transbronchial lung biopsy showed polymorphous lymphohistiocytic infiltrates with scattered, enlarged, atypical CD20+ B lymphocytes in a fibrinious hemorrhagic background. The atypical cells were positive for Epstein-Barr virus by in situ hybridization. No angioinvasion was identified on the initial background. The atypical cells were positive for Epstein-Barr virus by in situ hybridization. No angioinvasion was identified on the initial background.

Conclusions: Because SP is an uncommon and challenging intraoperative and cytologic diagnosis, it requires appropriate clinical, radiologic, and gross pathologic correlation.

Next-Generation Sequencing of Non–Small Cell Lung Cancer With a Customized, Targeted Sequencing Panel: Focus on the Epithelial-Mesenchymal Transition

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Context: Despite therapeutic advances, lung cancer is the leading cause of cancer death worldwide. Lung cancer cells often show mesenchymal phenotypes; however, a causative genetic alteration for the induction of epithelial-mesenchymal transition (EMT) in lung cancer cells remains unknown. We aimed to investigate a pattern of genomic variant associated EMT genes.

Design: We performed a targeted next-generation sequencing (NGS) on 92 non–small cell lung cancer (NSCLC) tumors, employing custom Illumina (San Diego, California) panel with coding and noncoding regions of 38 genes and 764 amplicons and coverage of x96 on MiSeq (Illumina) with 2 x 150-base pair, paired-end reads according to the manufacturer’s instructions (Illumina). Resulting data sets were analyzed with Variant Studio software (Illumina) and correlated with clinicopathologic data.

Results: Of the 92 specimens tested, 80 (87%) were adequate for full sequencing and yielded a total of 7362 genomic variants with 78% of single-nucleotide variants and 22% of small insertions and deletions. Seventy-seven samples presented nonsynonymous variants (174 variants with 123 damaging variants) in 25 genes. Genomic alterations were found most commonly in the TP53, PTEN, EGFR, KRAS, EBB2, PIK3CA, MMP2, SNAI, VEGFA, VIM, ZEB1, ZEB2, AXL, CD44, CD276, and CDH1 genes.

Conclusions: The results suggest that genomic variants in NSCLC tissues are complex and show that NGS is an effective way to detect novel mutations in lung cancer. We detected different damaging variants in EMT genes, such as AXL, ZEB1, ZEB2, CDH1, and CD44 suggesting that targeting those genes will be benefit as anticancer treatment.

Liquid-Biopsy Acute Pulmonary Thromboembolism: Plasma-Based Circulating microRNA Profile by Next-Generation Sequencing

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Intraoperative and Cytologic Diagnosis of Sclerosing Pneumocytoma (Hemangioma): A Case Series

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Context: Sclerosing pneumocytoma (SP) of the lung is an uncommon and indolent neoplasm with various growth patterns consisting of epithelial and stromal cells. Preoperative cytology or intraoperative frozen section recognition of SP can prevent unnecessary lobectomies. However, limited material or lack of knowledge of SP can present a diagnostic challenge.

Design: Cases from 2012 to 2016 diagnosed as SP were retrieved. Slides, clinical history, radiology, and pathology reports were reviewed. Results: Five cases of SP were identified, all of which occurred in middle-aged females (48–69 years) with peripheral lung nodules ranging from 0.3 to 2.3 cm. The smallest SP was an incidental finding in a lobectomy for adenocarcinoma. Of the remaining cases, 1 was misinterpreted as adenocarcinoma during intraoperative consultation given the patient’s history of papillary thyroid carcinoma. 1 diagnosis was misled by preoperative diagnosis of adenocarcinoma from an outside hospital; and 2 cases were rendered as unspecified low-grade neoplasms on frozen-section diagnoses. On review, frozen-section artifacts reduced the differences between the stromal and surface cells. The solid component, consisting of sheets of stromal cells with interspersed surface cells, can resemble the invasive component of an adenocarcinoma on frozen section (Figure 14). Cytologic findings in 4 available cases demonstrated bland epithelial cells forming sheets or focal vague papillary structures. The nuclear size was moderately increased, and the chromatin was fine to coarsely granular. Occasional intranuclear inclusions were identified. No necrosis or mitosis was seen.
Although interstitial lung disease (ILD) is a well-recognized complication of some drug treatments for psoriatic arthritis and may also develop when patients harbor other concomitant autoimmune disorders, it remains unclear whether psoriatic arthritis itself is associated with development of ILD, and if so, what pathologic features may be encountered. We report a case of ILD in a 38-year-old, nonsmoking man with untreated, isolated psoriatic arthritis with migratory polyarthritis, erythematous scaly plaques, and hyperkeratosis of the skin on his hands. He presented with progressive shortness of breath, tachypnea, fatigue, and a 40-pound unintentional weight loss. He was using no medications or illicit drugs. Imaging studies showed bilateral consolidation in the lower lobes and ground-glass opacities elsewhere. Serologic and infectious workup was negative, as were studies for Lyme disease and HIV, and his CD4 count was within reference range, but his CD8 was low. Wedge biopsies were obtained. Histologic sections showed patchy organizing pneumonia, superimposed on a background of chronic interstitial pneumonia in a pattern most consistent with fibrotic nonspecific interstitial pneumonia (NSIP), with diffuse alveolar thickening from mild lymphoplasmacytic inflammation and moderate fibrosis. Special stains for microorganisms were negative. Although numerous connective tissue diseases are associated with ILD, psoriatic arthritis is generally not recognized as being directly associated with ILD, unless its course is complicated by a drug reaction or when another autoimmune disorder is also present. This case illustrates that psoriatic arthritis may itself be associated with ILD in rare cases, presenting histologically as organizing pneumonia and/or fibrotic NSIP.

Analysis of p16 Deletion and Loss of BAP1 in Peritoneal Mesothelioma in Japan and in China

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Context: We recently reported that there are many peritoneal mesotheliomas in women related to asbestos textile production in China. The aim of this study was to compare the difference in the proportion of homozygous deletions (HDs) of p16 and BAP1 loss in mesotheliomas between Japan and China.

Design: We collected 29 cases with peritoneal mesothelioma from Japan diagnosed between 2008 and 2016. Twenty-two were men, and seven were women. Twenty-five were epithelioid mesotheliomas, 1 was biphasic, and 3 were sarcomatoid. We also collected 15 cases with peritoneal mesothelioma from China diagnosed between 2005 and 2010. All of the Chinese cases were women and had been exposed to textile chrysotile. Twelve were epithelioid mesothelioma, and 3 were biphasic. Fluorescence in situ hybridization analysis of p16 and immunohistochemistry of BAP1 was performed.

Results: Peritoneal mesotheliomas harbored HDs of p16 in 14% (1 of 7) of the Japanese women, 64% (14 of 22) of the Japanese men, and 93% (14 of 15) of the Chinese women (P < .001). Peritoneal epithelioid mesotheliomas harbored HDs of p16 in 14% (1 of 7) of the Japanese women, 67% (12 of 18) of the Japanese men, and 92% (11 of 12) of the Chinese women (P = .002). Mesotheliomas in Japanese men and women showed BAP1 loss in 57% (4 of 7) and 28% (1 of 4) of cases, respectively, and those of Chinese women showed BAP1 loss in 33% (4 of 12) of the cases (P = .48).

Conclusions: The proportion of HDs of p16 in peritoneal mesotheliomas was high in Japanese men and in Chinese women but was low in Japanese women. There was no difference in BAP1 expression among these groups. Peritoneal mesotheliomas may have a different pathogenesis depending on gender and asbestos exposure.

Performance of TTF1 and p40 Immunohistochemistry in the Subclassification of Poorly Differentiated Non–Small Cell Lung Carcinoma on Small Lung Biopsies

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Context: TTF1 and p40 are the recommended immunomarkers in subclassifying poorly differentiated non–small cell lung carcinoma (PD NSCLC) on small lung biopsies (LB). We observed rare cases of unequivocal dual positivity in the same tumor areas, a finding that may cause diagnostic dilemma.
Design: We identified LBs with both TTF1 (SP24) and p40 (BC28) immunostains performed to subclassify PD NSCLC (2013–2016). Subsequent resection specimens, where available, were used to adjudicate difficult interpretations. In other cases, additional immunostaining, including CK5/6 (D5/16B4) and TTF1 (8G7G3/1) were performed on the LBs to aid in further subclassification.

Results: Fifty-three of PD NSCLC diagnosed on LBs with interpretable TTF1 and p40 were included. In 29 cases (55%), interpretation was straightforward (TTF1+/p40− or TTF1−/p40+). Seven (13%) cases were diagnosed as PD NSCLC, not otherwise specified (TTF1+/p40+). Three cases (6%) showed strong expressions of both TTF1 and p40 in the same tumor area, one of which was misclassified as adenocarcinoma when subsequent resection showed pure squamous cell carcinoma. The other 2 cases required additional immunostains on the LB materials, which showed positive CK5/6 and negative TTF1 (8G7G3/1) to confirm squamous differentiation.

Conclusions: Misclassification of PD NSCLC on LBs might occur if both TTF1 and p40 are expressed in the same tumor area. Awareness of the potential pitfalls of different TTF1 clones and a possibly superior specificity of p40 for squamous cell carcinoma might help favor the correct diagnosis on LBs. Furthermore, using the more-specific, but less-sensitive, TTF1 clone 8G7G3/1 might be a better choice in this scenario. Larger studies are necessary to validate our observations.

**KRAS and EGFR Mutation Coexistence in Pulmonary Adenocarcinomas**

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**Context:** Mutations in EGFR and KRAS were initially thought to be mutually exclusive in lung adenocarcinoma (ADC). Because of that, the KRAS mutation was considered a predictor of EGFR mutations. However, recently reported co-occurrence of EGFR and KRAS may not be completely characterized. This case illustrates a primary adenocarcinoma in situ arising in a squamous papilloma or papillary variant of squamous cell carcinoma in situ arising in a squamous papilloma or papillary variant of squamous cell carcinoma. The NMC histology is characteristically composed of nests or sheets of small to medium, undifferentiated cells with varying degrees of squamous differentiation. Papillomatosis is a recently recognized entity, the full spectrum of histologic findings is a clinically important in deciding treatment options for patients with lung cancer.

**PD-L1 and Immune Microenvironment Analysis in Malignant Pleural Mesothelioma:**

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**Context:** Malignant pleural mesothelioma (MPM) is an aggressive tumor with a poor prognosis; novel therapeutic strategies are urgently required. The immune system seems to have a protective role against MPM; thus, characterization of the tumor immune microenvironment (TME) and immune checkpints are under investigation. We aimed to characterize TME and PD-L1 expression, using 2 different clones, in MPM samples before and after chemotherapy (CT). The samples after CT were obtained after surgery.

**Design:** PD-L1 expression was assessed in 31 epithelioid MPMs by immunohistochemistry with both Leica E1L3N (Cell Signaling Technology, Danvers, Massachusetts) and Ventana SP263 (Roche, Basel, Switzerland) clones. Specimens from 14 of them were analyzed before and after immuno-phytochemistry of TME with anti-CD20, CD3, CD4, CD8, and CD68 antibodies. All markers were quantified as the percentage of positive tumor and inflammatory cells.

**Results:** Forty-five percent of patients showed PD-L1+ immuno-staining before CT without any significant difference between the 2 clones. After CT, PD-L1 expression was greater (P = 0.03), as well as PT CD3+ lymphocytes (P = 0.008). CD4+ and CD8+ lymphocytes were lacking in naive samples, and CD8+ lymphocytes significantly increased after CT (PT, P = 0.02; IT, P = 0.007). The CD8+/CD68+ ratio increased after CT but without statistical significance. No IT B lymphocytes were observed either before or after CT.

**Conclusions:** PD-L1 E1L3N and SP263 clones can be used indifferently in MPM samples. CT significantly increased cytotoxic T lymphocytes at PT and IT levels as well as PD-L1 expression. These data confirm the strong rationale for the combination of checkpoint inhibitors and CT as a promising treatment in MPM.

**Variant Histology in a Pulmonary Nuclear Protein in Tissues Midline Carcinoma**

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A 20-year-old Marine presented with rib pain, productive cough, wheezing, and dyspnea for 8 months after unsuccessful antibiotic therapy. Chest imaging identified a left lower lobe endobronchial lesion. Bronchoscopy revealed a left lower lobe endobronchial lesion, localized to the posterior segment. Histology showed carcinoma with a papillomatous growth pattern, lined by varying numbers of small to medium, undifferentiated cells, with extensive squamous differentiation. Initially, the undifferentiated cellular component was interpreted as poorly differentiated squamous cell carcinoma or squamous carcinoma in situ arising in a squamous papilloma or papillary variant of squamous cell carcinoma. Nuclear protein in tests (NUT) immunohistochemical stain used by expert consultants highlighted 50% of cells, establishing the diagnosis of NUT midline carcinoma (NMC). The NMC is an uncommon, aggressive malignancy, primarily affecting the mediastium and upper aerodigestive tract, characterized by a specific chromosomal translocation of the NUTM1 gene, and it is confirmed with NUT immunohistochemistry. The NMC histology is characteristically composed of nests or sheets of small to medium, undifferentiated cells with varying degrees of squamous differentiation. Papillomatosis in a NUT+ carcinoma has not been previously described. Because NMC is a recently recognized entity, the full spectrum of histologic findings may not be completely characterized. This case illustrates a primary pulmonary NMC with a variant papillomatous histology, not previously described, to our knowledge, in the literature. The variant papilloma-
Pre-enrichment of Tumor Cells in Malignant Pleural Effusion With Inertial Focusing Platform for Histologic and Molecular Diagnosis: A Pilot Study

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Context: Approximately 50% of patients with advanced-stage lung cancer present with malignant pleural effusion, which is, in many cases, the only specimen available for diagnosis and molecular analysis. Although cytologic diagnosis and immunophenotyping on cell block are generally possible, low tumor content and high inflammatory cell background may limit the possibility for molecular analysis. In 2016, at Singapore General Hospital, 10% (7 of 74) of the malignant pleural effusions sent for molecular analysis were insufficient or inconclusive. We assessed the potential for improvement of tumor cell yield from malignant pleural effusions with enrichment before analysis.

Design: Pleural fluid samples from 14 patients with metastatic lung adenocarcinoma were included in this pilot study. A commercially available platform—ClearCell FX (Clearbridge Biomedics, Singapore)—was used to perform size-based tumor-cell enrichment. Cytologic examination, immunocytochemistry, and epidermal growth factor receptor mutation testing were performed as usual. The diagnostic concordance between normal and enriched samples was determined.

Results: Enriched pleural fluid showed intact tumor cells with reduced inflammatory cell background. Increased tumor-cell content facilitated immunocytochemical and molecular analysis, without apparent degradation in sample quality. Epidermal growth factor receptor mutations were observed in 42.9% (6 of 14) of nonenriched samples. Corresponding enriched samples evaluated showed high levels of concordance for both immunocytochemistry and mutational analysis.

Conclusions: Our study showed evidence that enriched tumor cells from pleural effusion via inertial focusing preserved diagnostic quality. Depletion of inflammatory cells from the samples improved the tumor content, which could potentially improve diagnostic yield of samples that have been deemed insufficient for immunocytochemistry and/or mutational analysis.

Pulmonary Capillary Hemangiomatosis

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Pulmonary capillary hemangiomatosis (PCH) is a rare, upper lobe–predominant, chronic pulmonary disease. It is characterized by multifocal, red-brown, mottled nodules that were caused by PCH. It is important to recognize this rare disorder as a cause of pulmonary hypertension because the only definitive treatment is lung transplantation. Moreover, treatment of PCH with prostacyclin analogues (as would be done for idiopathic pulmonary arterial hypertension) may cause severe and even fatal pulmonary edema. Similar Case of Pulmonary Placental Transmogrification

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Pulmonary placental transmogrification, also known as placental bullous lesion of the lung, an extremely rare, benign condition that usually manifest as large bullae in young to middle-aged patients, was first described by T. McChesney (Lab Invest. 1979:40:245–246). Microscopically, it resembles immature placental tissue, although it does not bear any biologic and biochemical properties of a placenta. Here, we describe a similar case of pulmonary placental transmogrification. A nodular, homogeneous, and solid shadow was pointed out in the diaphragmatic side of the right lower lobe on imaging studies in a 76-year-old man. Emphysematous change was seen in the background of the lung, but large bullae were not detected. Partial resection by video-assisted thoracoscopic surgery was performed. The specimen included a 1.2-cm nodule, which consisted of soft yellow-white tissue with indistinct demarcation from healthy tissue. Microscopically, scarring with bronchiolization of alveoli (peribronchiolar metaplasia, lamberto-sis) merged into the surrounding lung tissue. A striking feature was the formation of papillae clothed in hyperplastic alveolar cells, looking like a villous and papillary projection (Figure 16). The fibrous core consisted of collagen bundles and smooth muscle cells and lacked hydropic villous structure, adipose tissue, and immature interstitial cells. However, at first glance, the histologic appearance bore a strong resemblance to that described by McChesney and others as pulmonary placental transmogrification. Pseudoplacental transmogrification may lie on a spectrum with pulmonary placental transmogrification.
sis. Microscopically, the combination of intra-alveolar fibrosis and septal elastosis was most prominent in the subpleural area and in areas adjacent to interlobular septa and bronchovascular bundles. The background lung showed diffuse nonspecific interstitial pneumonia (NSIP)-like changes of a mild degree, with a characteristic increase of elastic fibers in the alveolar septa. In the image analysis, the elastic fiber thickness (EF score) was greater in the NSIP-like change than it was in the NSIP-like lesion; however, a statistically significant difference was observed in the EF scores of NSIP-like lesions among upper, middle, or lower lobes. In this case, the diffuse and evenly distributed, elastic-fiber-rich NSIP-like change, possibly caused by the preceding chemotherapy, may have predisposed the subsequent development of PPFE. Hypothetically, some unknown vulnerability of the upper lobe may exist, with various primary lesions converging to the characteristic upper-lobe predominance of PPFE.

**Plasma-Based Circulating MicroRNA Biomarkers as Liquid Biopsy for Chronic Thromboembolism Pulmonary Hypertension**

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**Context:** Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by thrombus organization, pulmonary remodeling, and increased pulmonary vascular resistance. Our aim was to determine a plasma-circulating microRNA profile as a diagnostic and prognostic biomarker for CTEPH.

**Design:** The study included 12 patients with CTEPH, 10 patients with pulmonary hypertension from other causes, and 10 healthy volunteers, who were sequentially studied in 2016. All relevant clinical data from medical records, the scintigraphy and/or angiotomography, and right heart catheterization results were analyzed. An optimized protocol for RNA extraction from plasma samples with the MiRNeasy Serum/Plasma Kit (Qiagen, Hilden, Germany) in combination with the Vac-Man Vacuum Manifold (Promega, Madison, Wisconsin) was used. The Illumina TruSeq Small RNA-Seq Sample Prep Kit (Illumina, San Diego, California) was used to generate a small RNA library directly from total RNA. Clustering and sequencing was accomplished with the Illumina NextSeq500. Further databases and software used for analysis included the DIANA-Tools software (DIANA FE. Delft, the Netherlands).

**Results:** The New York Heart Association Functional Classification (NYHAF) was used for evaluation of disease severity. The variation between biopsy samples and resection, as well as the correlation between these entities may lead to significant reduction in the morbidity and mortality associated with these deadly diseases. We aimed to investigate the molecular profile of lung adenocarcinoma samples from smokers with and without COPD with a next-generation sequencing (NGS) approach.

**Results:** Thirty-seven surgical specimens of lung adenocarcinoma (11 patients with COPD and 26 from patients without COPD), already genotyped for EGRF and KRAS mutations by conventional methods (Sanger sequencing, Thermo Fisher Scientific, Waltham, Massachusetts), were analyzed with a 30-gene NGS panel on MiSeq platform (Illumina, San Diego, California). Six clinical samples of adenocarcinoma from nonsmokers were also included in the study. All adenocarcinoma samples showed homogeneous demographic characteristics and smoking history, as well as tumor staging.

**Results:** The NGS approach confirmed 100% of mutations detected with Sanger sequencing. Moreover, it identified additional mutations not covered by the routine molecular tests, and their potential clinical impact is not well defined. In particular, when considering all 30 investigated genes, mutations were detected in 5 of 11 smokers with COPD (4 KRAS and 1 TP53), in 13 of 26 smokers without COPD (9 KRAS, 2 TP53, 2 PIK3CA, 1 STK11, and 1 EGRF), and 5 of 6 nonsmokers (3 EGRF, 1 KRAS, and 1 BRAF).

**Conclusions:** An NGS analysis revealed a partially different molecular profile in lung adenocarcinoma of smokers with and without COPD. These results should be confirmed by larger-scale studies to understand their translational value.

**Histologic Patterns in Malignant Mesothelioma of the Pleura: Comparison of Biopsy Versus Pleurectomy, and Primary Versus Metastatic Sites**

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**Context:** The variation between biopsy samples and resection, as well as between primary and metastatic lesions, in pleural mesothelioma is poorly studied.

**Design:** We retrospectively studied 56 patients, comprising 58 biopsies and 27 pleurectomies.

**Results:** There were 41 men (age mean [SD] = 65 [12] years) and 15 women (68 [10] years). Fifty-one of 85 mesotheliomas were epithelioid (59%), were biphasic (31%), and 8 were sarcomatoid (9%). There were 22 paired samples; 18 (82%) showed concordant histology (8 biphasic and 10 epithelioid), and 4 (18%) showed discordant histology between initial and subsequent sampling (2 epithelioid/biphasic, 1 epithelioid/sarcomatoid, and 1 biphasic/sarcomatoid). Lymph node...
sampling was performed in 23 cases and was positive in 13 (57%); 8 of 16 (50%) were epithelioid, and 5 of 7 (71%) were biphasic. All lymph node metastases of epithelioid type were epithelioid; metastasis in biphasic types were biphasic (1 case), epithelioid (2 cases), epithelioid and sarcomatoid in different nodes (1 case), and epithelioid and biphasic (1 case). Rates of positivity were 4 of 7 intramammary (57%), 4 of 8 posterior intercostal (50%), 20 of 20 pleural (100%), 2 of 5 lobar (40%), and 28 of 83 mediastinal (34%). A micropapillary growth pattern was present in 4 of 4 of tumors with lymph node metastasis versus 5 of 12 of those cases without a micropapillary pattern (P = .02, χ² test).

Conclusions: There is a high concordance rate of histologic types between biopsies and resections. Nodal metastases are common. Tumors that lack a micropapillary component have a relatively high rate of metastasis to the lymph nodes.

Comprehensive Assessment of PD-L1 Staining Heterogeneity and Expression by Histologic Pattern in Pulmonary Adenocarcinomas: Clinical Implications

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Context: Molecules directed against programmed death receptor-1 (PD-1) and its ligand (PD-L1) have shown promising results in the treatment of advanced pulmonary non–small cell carcinomas. Their efficiency correlates with PD-L1 expression, but it is unclear why some patients with low PD-L1 expression respond well, whereas others with high expression do not respond. Here, we aimed to determine whether PD-L1 expression heterogeneity may account for some of that discordance.

Results: Thirty-nine percent of patients were positive for PD-L1, whereas 22.9% showed staining heterogeneity (50% cutoff). Among patients with one negative core, 27.3% also had a positive core and could have been considered as false-negatives on a single biopsy. Mean staining rates of PD-L1 were higher in solid (47.2%) and micropapillary (24.9%) patterns and were lower in acinar (15.9%), papillary (1.1%), and lepidic (7.2%) architectures.

Conclusions: A significant proportion of patients present with heterogeneous staining for PD-L1. More than 25% of patients who have negative results on one core turned out to have positive results in another core, which raises a consideration of rebiopsy, in particular, when lepidic, acinar, or papillary patterns are seen on a small biopsy.

Biomarkers of Phenotypic Plasticity Associate With Outcome in Lung Adenocarcinoma

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Context: The aim of this study was to contrast the prognostic value of biomarkers of phenotypic plasticity between primary tumors and patient-matched lymph node metastases in a series of resected lung adenocarcinoma cases.

Results: Twenty-two (91%) of the 24 cases reviewed illustrate the difficulty of correctly diagnosing the relatively uncommon, but benign, sclerosing pneumocytoma.

Conclusions: This study has limitations; however, it does illustrate a proposed method to test the concept of “anchor bias.” Additionally, the cases reviewed illustrate the difficulty of correctly diagnosing the relatively uncommon, but benign, sclerosing pneumocytoma.

Primary Pulmonary Nuclear Protein in Testis Carcinoma

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Nuclear protein in testis (NU1) carcinoma (NC) is a rare, aggressive cancer with an estimated 2-year progression-free survival of 9%. Typically, NC arises from centrally located parts of the body, the upper aerodigestive tract, and the mediastinum. Typically, NC consists of sheets and nests of small to intermediate, undifferentiated cells with monomorphic appearance and commonly showing abrupt foci of keratinization. However, the origin of NC remains unclear. Here, we report on a Japanese patient who showed a pulmonary mass with endobronchial polypoid growth and was diagnosed as having NC. The patient was a 37-year-old man, who initially showed a 91 × 81-mm mass in the right lung detected by chest computed tomography. Transbronchial biopsy specimens showed a solid growth of medium to large undifferentiated round cells beneath bronchial epithelium and marked necrosis. Squamous differentiation or keratinization was not obvious. Immunohistochemical staining demonstrated diffuse positivity for p63 and TTF1. Focal positive staining results were obtained for AE1/
Malignant Mesothelioma With Heterologous Elements

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Context: Malignant mesothelioma (MM) with heterologous elements, such as osseous, cartilaginous, or rhabdomyoblastic differentiation, is very rare, and it is also very difficult to differentiate from extraskeletal osteosarcoma of the pleura. We examined such MM cases and pleural osteosarcomas (POs) using clinicopathologic and immunohistochemical methods.

Design: Using formalin-fixed, paraffin-embedded blocks from each case, we compared 7 malignant pleural mesotheliomas (3 biphasic type and 4 sarcomatoid type) with 2 pleural osteosarcomas.

Results: The median age was 69 years for mesotheliomas, (range, 64–78 years), and 69 years for osteosarcoma (range, 67–70 years). For both diseases, all patients were men. All cases of MM exhibited a diffuse growth pattern, as did 2 cases (cases 2 and 3) of localized PO. Among MM cases, 86% (6 of 7) displayed osteosarcomatous and chondrosarcomatous elements, whereas 14% (1 of 7) exhibited rhabdomyoblastic elements. Immunohistochemical labeling for both AE1/AE3 and calretinin was present in 5 of 7 MM cases, but in only 1 (with focal staining) case of PO. Exposure to asbestos was identified in 5 of 7 MM cases, but in only 1 with focal staining) case of PO. Median survival was 8.1 months after biopsy or surgery for MM, and 18 months for PO after surgery. A patient with localized PO (case 1) died 24 months after surgery.

Conclusions: Although median survival was longer for patients with PO than for those with MM, we could not differentiate MM from PO in the pleura based on clinicopathologic and immunohistochemical data.

Dust Exposure Triggering Sarcoidosis and Silicosis: A Report of 2 Cases

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Despite decades of research, the etiology of sarcoidosis remains unclear. However, there is accumulating evidence for occupational causes of sarcoidosis. Here, we present 2 cases of occupational sarcoidosis. A 30-year-old man, with a long-term occupational history as a stonemason, received a checkup when he was asymptomatic. Chest x-ray (Figure 17, A) and computed tomography (CT) scan showed diffuse bilateral nodules, as well as mediastinal and symmetrical hilar lymphadenopathy. Histologic examination of transbronchial biopsies revealed the presence of nonnecrotizing granulomas compatible with sarcoidosis and silicosis. Because the patient had no response to corticosteroids, the diagnosis of sarcoidosis was questioned, and a silicosis-type pneumoniosis was suspected. Therefore, an open lung biopsy was performed. Histologic examination of the biopsy confirmed the presence of nonnecrotizing granulomas as well as numerous silica nodules and endobronchial ultrasound of the subcarinal lymph node was performed. Histologic examination showed nonnecrotizing granulomas, peribronchial fibrosis, and deposition of birefringent, needle-shaped material. The findings in these 2 patients support the concept that occupational factors may trigger a granulomatous reaction in genetically susceptible individuals.