CHEST

A 58-Year-Old Woman With Lung Nodules and Chronic Cough

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CASE PRESENTATION: A 58-year-old woman was referred to our department with a cough of 1 year duration; her condition was unresponsive to the administration of inhaled steroid and beta-2 agonists. She denied the presence of dyspnea, chest pain, or other extrapulmonary symptoms. She was a never-smoker with a negative medical history and no occupational or domestic exposures. There was no history of cancer, gastroesophageal reflux disease, asthma, allergic rhinitis, or other allergies. CHEST 2021; 160(3):e285-e288

Physical Examination Findings

At presentation, the patient was afebrile with a heart rate of 64 beats/min, BP of 110/60 mm Hg, respiratory rate of 16 breaths/min, and oxygen saturation of 99% on ambient air. Chest auscultation revealed no abnormal findings, and the rest of the physical examination was unremarkable.

Diagnostic Studies

Pulmonary function test results, which had been performed before the initiation of inhaled medications, were within normal limits (FEV_1, 2.47 L, 100% predicted; FVC, 3.22 L, 111% predicted; FEV_1/FVC, 0.77; FEV_1 after bronchodilation, -6%; TLC, 90% predicted; D_{LCO}, 89% predicted). Chest radiography was normal. Because of the persistence of chronic cough in the absence of an obvious cause, high resolution CT (HRCT) exhibited numerous nodules, with some exhibiting a central hyperlucent area (Fig 1). Subsequent bronchoscopy revealed no visible airway abnormalities. Gram and Ziehl-Neelsen staining of bronchial washings were negative for bacterial, mycobacterial, and fungal organisms; cytologic examination revealed no malignant cells. The patient underwent surgical lung biopsy that revealed interstitial nests of epithelioid cells that were positive for epithelial membrane antigen and vimentin with a low Ki-67 positivity of 1% to 2% (Fig 2).

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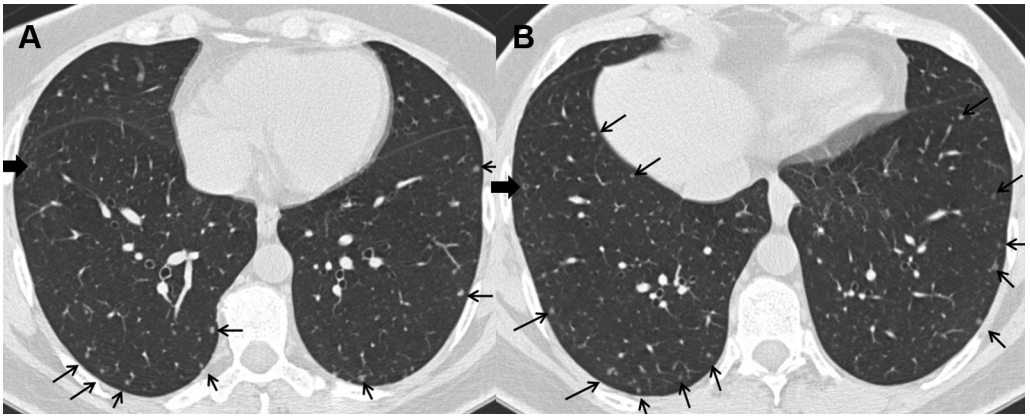

Figure 1 – *A-B, Numerous centrilobular micronodules (small arrows) that mainly involve the periphery of the lung. A central hyperlucent area can be recognized in the center of several nodules (big arrow).*

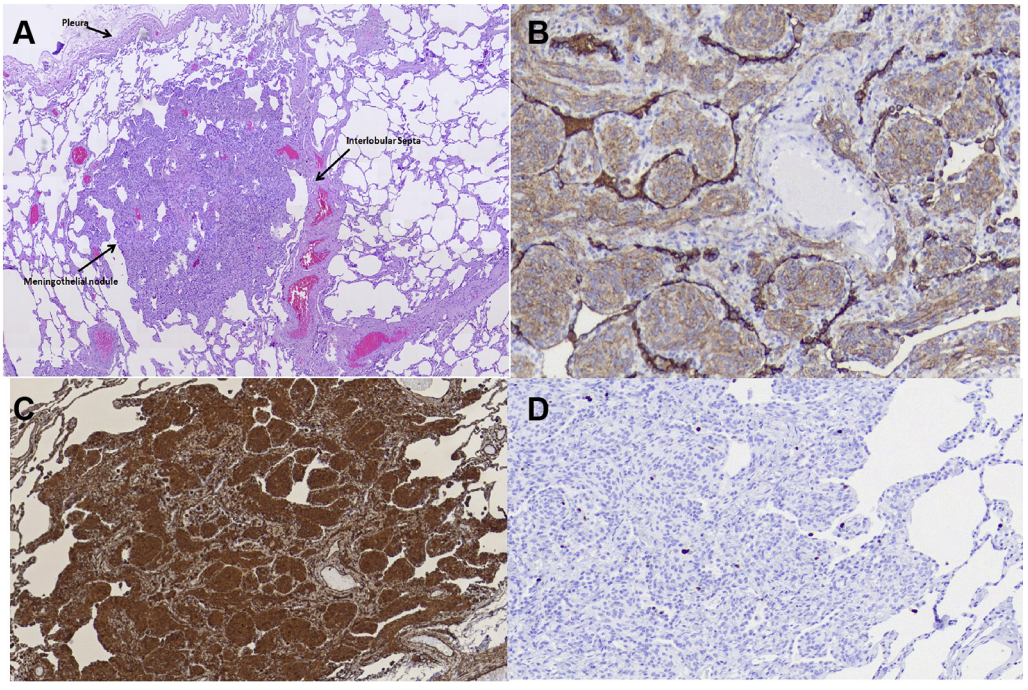

Figure 2 – *A-D, Interstitial nest of spindle cells with meningothelial features that comprise a meningothelial nodule. A, Adjacent lung parenchyma is normal with preserved architecture. B, Meningothelial nodules are positive for epithelial membrane antigen. C, Vimentin. D, Vimentin with low Ki-67 positivity of 1% to 2%. (Hematoxylin and eosin stain; original magnification, × 100.)*

What is the diagnosis?

Diagnosis: Diffuse pulmonary meningotheliomatosis

Discussion

Diffuse pulmonary meningotheliomatosis (DPM) is an extremely rare condition characterized by the presence of multiple minute meningothelial nodules throughout the lungs. The characteristic pathologic lesions were first described by Korn et al in 1960. They described rounded polyhedral or spindle-shaped cells that were arranged in nests (zellballen) and initially were considered to be pulmonary tumors resembling chemodectomas. A characteristic feature was their interstitial location and their relationship to blood vessels because they were always centered on pulmonary venules, especially where the interlobular septa inserted on the pleura. However, later studies showed that meningothelial nodules are located randomly along alveolar septa. Subsequent immunohistochemical studies were positive for epithelial membrane antigen and vimentin, which strongly suggests their meningothelial origin. This led Gaffey et al to coin the term "minute pulmonary meningothelial nodules" in 1988. Despite the advancement in their characterization from a pathologic point of view, their exact cause and clinical significance remain unclear.

Pulmonary meningothelial-like nodules have been found in patients who range in age from 22 to 84 years, with a peak during the sixth decade (median, 62 years). They are rarely observed under the age of 40 years. Their absence in infants and children argues against a congenital origin. There is a female predominance with a female-to-male ratio of 2.2:1. Most patients with DPM are asymptomatic and are discovered incidentally. Some patients report shortness of breath and cough. However, it is unclear whether these symptoms are causally related to DPM.

Imaging is characterized by the presence of multiple, diffuse bilateral nodules that are depicted better on HRCT. These nodules are typically small (approximately 5 mm; smaller than 10 mm), usually centrilobular, and tend to be peripheral involving the outer third of the lung parenchyma. In some cases, there is a diffuse distribution in line with a military pattern. A characteristic finding is that some of the nodules depict the "cheerio sign" (pulmonary nodules with a central lucent area). It is frequently reported as "central cavitation," but this is a misnomer because it does not always correspond to histologic necrosis, depending on the underlying disease.

Because most patients are asymptomatic or present with no specific symptoms and clinical examination is unremarkable, differential diagnosis is based on imaging findings. The "cheerio sign" is characteristic of DPM but is by no means pathognomonic because it has been described in several infectious diseases (mainly mycobacterial and fungal), neoplastic diseases (mainly adenocarcinoma both primary and metastatic), granulomatosis with polyangiitis, rheumatoid arthritis (corresponding to necrobiotic nodules) and pulmonary Langerhans cell histiocytosis. In the latter Case, nodules with the "cheerio sign" is also characteristic, but the upper/mid lung distribution of findings with sparing of the costophrenic angles points to the correct diagnosis. When a miliary pattern is present, the differential diagnosis includes hematogenous spread of an infectious or neoplastic process to the lungs. Typically, in all the aforementioned cases, there are clinical symptoms and associated imaging findings pointing to the correct diagnosis. Particular attention is needed when there is a history or concomitant malignancy. In such cases, it is of utmost importance not to miss a diagnosis of underlying malignancy but, at the same time, not to consider DPM erroneously as metastatic disease. For a definitive diagnosis, tissue confirmation is required, usually by surgical lung biopsy, although there are cases in which diagnosis was made by transbronchial biopsy.

The clinical course of DPM is benign, and no therapeutic intervention is required. It is worth noting that pulmonary minute meningothelial-like nodules are found significantly more often in patients with malignant pulmonary tumors than in those with benign diseases. Furthermore, they might represent the transition between a reactive and neoplastic proliferation, although this has been challenged because they have been described in the context of various diseases that include infections, neoplasms, and pulmonary embolism. Nevertheless, in cases of DPM, a workup for unidentified malignancy can be a reasonable choice on an individualized basis.

Clinical Course

The patient was informed about the benign nature of the disease, and no treatment was given. A follow-up HRCT, 14 months after diagnosis, was unchanged. The patient is in excellent clinical status and reports spontaneous improvement of her cough.

Clinical Pearls

1. *DPM is a rare disease characterized by the presence of multiple minute meningothelial nodules.*

2. *Cheerio sign is a helpful imaging sign that can help to narrow the differential diagnosis (Pulmonary Langerhans Cell Histiocytosis, adenocarcinoma, DPM).*
3. *Patients are usually asymptomatic; diagnosis is suspected based on HRCT findings that exhibit numerous micronodules with a predominant peripheral distribution.*
4. *DPM follows a benign course, and no therapeutic intervention is required.*
5. *A workup for underlying malignancy can be a reasonable choice for patients with a high pretest probability.*

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Suggested Readings

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