Diffuse pulmonary meningotheliomatosis: a rare cause of multiple pulmonary nodules

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SUMMARY

This case describes a woman in her 50s who presented with recurrent lower respiratory tract infections. She was an ex-smoker and had worked on a livestock farm for many years. Chest radiograph and CT of the chest revealed multiple bilateral pulmonary nodules. Bronchoalveolar lavage and transbronchial biopsy did not confirm a unifying diagnosis and thus, surgical biopsy was pursued. Video-assisted thoracoscopic surgical guided biopsy of the right upper, middle and lower lobes demonstrated intraparenchymal minute nodules, consisting of bland epithelioid cells without any evidence of malignancy. The nodules stained positive for neural cell adhesion molecule (CD56) and progesterone receptor with weakly positive epithelial membrane antigen and smooth muscle actin. The combination of this characteristic staining pattern, the diffuse subcentimetre nature of the nodules and this clinical presentation fit with a diagnosis of the ultra-rare pulmonary disease, diffuse pulmonary meningotheliomatosis (DPM). This case highlights a rare cause of bilateral diffuse pulmonary nodules and thus, the breadth of differential diagnoses that need to be considered when approaching such a finding. Careful history-taking and thorough workup is often needed, typically requiring input from multiple specialties. DPM, while rare, should not be overlooked when considering the underlying cause of this presentation, especially in female patients. This case reiterates how common clinical presentations can unveil rare conditions and the contributions of physicians, pathologists and radiologists in the diagnosis and management of these complex diseases.

BACKGROUND

Diffuse pulmonary nodules are a common finding on chest imaging. The potential list of causes is exhaustive and range from benign to infectious to malignant disease processes. Despite radiological advances, histopathological sampling is often needed to confirm the diagnosis with confidence and rule out more sinister causes. Given the morbidity of potential causes of bilateral pulmonary nodules such as malignancy and progressive interstitial lung diseases (ILDs), it is pertinent that this diagnosis is achieved in a timely manner.

Diffuse pulmonary meningotheliomatosis (DPM) is a rare diffuse pulmonary disease, which is more common in females and is usually diagnosed in the 5th–7th decades of life. It is characterised by the presence of multiple bilateral (100 µm to a few mm) pulmonary nodules on chest imaging and nests of moderately sized elongated cells with oval nuclei, finely granular chromatin, inconspicuous nucleoli, and abundant granular and eosinophilic cytoplasm on histopathological assessment.[1] While DPM is rare, it's general appearance on radiology; bilateral diffuse pulmonary nodules, is seen more commonly by physicians.[2 3]

CASE PRESENTATION

A female patient in her 50s was referred to the specialist respiratory outpatient clinic by her primary care physician with recurrent lower respiratory chest infections. She reported a chronic cough for 4 months, productive of moderate volumes of green sputum. There were no triggers and no diurnal variation. She reported long-standing dyspnoea on walking up hills only. She had generalised malaise but denied haemoptysis, weight loss and night sweats. She had no recent travel. She received four courses of antibiotics per annum for the last 5 years but had never been hospitalised.

Other medical history was notable for juvenile arthritis, hypothyroidism, hyperlipidaemia and depression. Medications included mirtazapine, rosuvastatin, sertraline, fluticasone furoate nasal spray, brinzolamide eye-drops and levothyroxine. She had been started on salbutamol and budesonide/formoterol inhalers in the community for possible asthma as a cause for her symptoms. She had a 50 pack-year smoking history having stopped 6 years prior. She continued to use e-cigarettes daily. She worked on a livestock farm all her life with significant exposure to poultry and goats. She had no relevant family history of note.

On examination, oxygen saturations were 98% on room air and she was not in respiratory distress. There was no evidence of finger clubbing or connective tissue disease. Respiratory examination revealed normal vesicular breath sounds throughout.

INVESTIGATIONS

Posteroanterior chest radiograph showed numerous small nodules, mainly in the upper lobes bilaterally (figure 1). These had been identified on prior chest radiographs dating back 3 years and were reported as stable. Pulmonary function tests identified a forced expiratory volume in 1 s (FEV1) of 1.96 L (85% of predicted value), forced vital capacity (FVC) of 2.65 L (98% of predicted value), an FEV1/FVC ratio of 74% and a diffusing capacity of the lung for carbon monoxide (DLCO) of 76% of predicted value.

Laboratory workup was pursued and revealed normal inflammatory markers. Antinuclear antibody

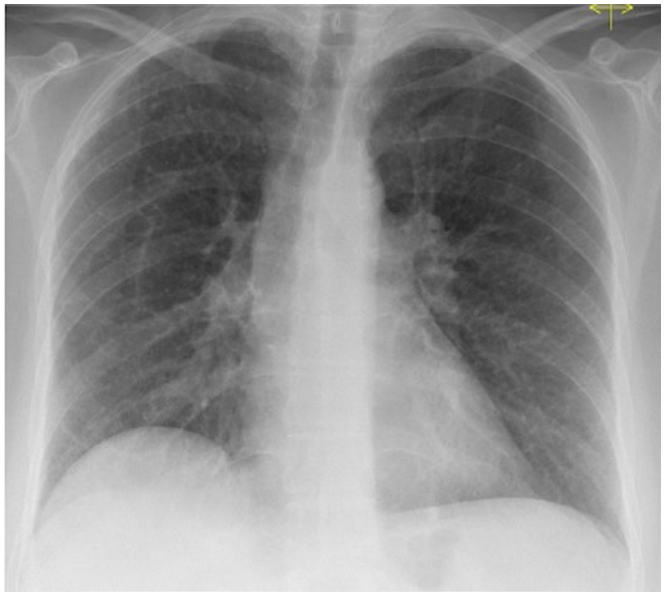

Figure 1 Chest radiograph demonstrates multiple tiny pulmonary parenchymal nodules throughout both lung fields but with an upper lobe predominance.

titre was positive at 400 IU/mL in a homogeneous pattern. The remainder of the connective tissue disease screen was normal. Peak eosinophil count was 0.4 (range: 0.02–0.5×10^9/L) with the total IgE at 100 kU/L (range: 0–100 kU/L). IgE house dust mite, dog dander and grass mix were all negative with IgE to cat dander mildly elevated at 0.42 kU/L (range: 0.0–0.35 kU). High-resolution CT of the chest revealed background fibrotic ILD with predominantly subpleural changes, affecting the lung apices and right lower lobe. One 6 mm left upper lobe nodule was identified and two 5 mm nodules in the right upper lobe. There was no mediastinal adenopathy but several small, calcified granulomata were noted bilaterally (figures 2 and 3).

Microbiological testing on bronchoalveolar lavage (BAL) from the right middle and upper lobes were negative for bacteria and fungi. BAL cell differential demonstrated 75% macrophages, 18% lymphocytes, 2% neutrophils and 5% eosinophils. Transbronchial biopsy revealed findings suggestive of respiratory bronchiolitis with prominent aggregates of intra-alveolar foamy histiocytes and background anthracotic pigmentation. The case was discussed at the respiratory multidisciplinary team (MDT) meeting where it was agreed that respiratory bronchiolitis was unlikely to explain all the radiological findings. Thus, surgical sampling was recommended. Video-assisted thoracoscopic surgical (VATS) guided wedge resection was performed with biopsies taken from the right upper, middle and lower lobe.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for pulmonary nodules is broad and includes infections, sarcoidosis, hypersensitivity pneumonitis, small airways disease, malignancy and other rare lung diseases. The importance of a detailed history and clinical examination to guide investigation cannot be overlooked. The patient we present had a history of recurrent infections which led us to consider an infectious cause or a predisposing underlying small airways disease, especially in the context of a notable eosinophilia. However, the negative microbiology on BAL did not support infectious aetiology. Total IgE titres were normal, with only a mildly elevated cat dander-specific IgE, and there was a preserved FEV1/FVC ratio on spirometry, all going against a diagnosis such as asthma. There was no radiological evidence of mosaic attenuation or air trapping, and the distribution of nodules was not typical for hypersensitivity pneumonitis or sarcoidosis, but remained in the differential diagnosis. Primary lung cancer and metastatic disease were considered in light of the chronicity of symptoms and tobacco history. Rare lung diseases such a pulmonary Langerhans cell histiocytosis (PLCH) and multifocal micronodular pneumocyte hyperplasia as seen in patients with tuberous sclerosis were also considered. PLCH is more common but not exclusively seen in male patients with a smoking history and the history was not suggestive of an underlying diagnosis of tuberous sclerosis.[4]

VATS surgical biopsy of the right upper, middle and lower lobes was pursued to investigate for malignancy and determine the underlying cause. Histopathology revealed small intraparenchymal minute nodules of bland epithelioid cells without any evidence of malignancy. The nodules stained positive for neural cell adhesion molecule (CD56) and progesterone receptor, and epithelial membrane antigen (EMA) and smooth muscle actin (SMA) were weakly positive. Staining was negative for TTF-1, napsin A, chromogranin, HMB45, S100 and desmin. In addition, there were tobacco-related changes of emphysema, small airway disease with bronchiectasis, peribronchial metaplasia, peribronchial inflammation and respiratory bronchiolitis.

TTF-1, napsin A and chromogranin staining ruled out primary lung malignancy and the lack of HMB45, S100 and desmin staining were reassuring from a metastatic disease perspective. While progesterone receptor staining, often seen in rare lung diseases, was weakly positive, HMB45 negativity would go against diagnoses such as lymphangioleoimyomatosis. Furthermore in pulmonary benign metastasising leiomyoma, the nodules usually stain strongly positive for SMA and desmin. As seen in this case, strong expression of EMA and vimentin, and negative S-100 and SMA staining in the presence of small intraparenchymal minute nodules of bland epithelioid cells is in keeping with Minute Pulmonary Meningothelial like Nodules (MPMN). CD56 staining has been reported in the literature in more recent cases of MPMN also.[5] The case was discussed at MDT where it was agreed the nodular change identified on both radiology and histology were in keeping with a unifying diagnosis of DPM. The background fibrotic ILD is likely smoking related.

TREATMENT

There are no specific treatments or recommendations available on how best to approach treatment in the case of DPM. This is likely due to the rarity of this disease and also the benign disease course.

OUTCOME AND FOLLOW-UP

Since diagnosis, she has been followed up closely in the specialist respiratory outpatient clinic. Her symptoms remain stable with an ongoing productive cough. She continues to use an e-cigarette with no further exposure to poultry or livestock. Spirometry has remained stable over a 4-year period with a drop in DLCO from 76% to 67.6% predicted value. Using the Fleischner Society pulmonary nodule guidelines, repeat CT thorax at a 2-year interval showed stable appearances of previously described lung nodules.

DISCUSSION

This case describes DPM as the cause of bilateral pulmonary nodules in a female patient in her 50s. While the reported

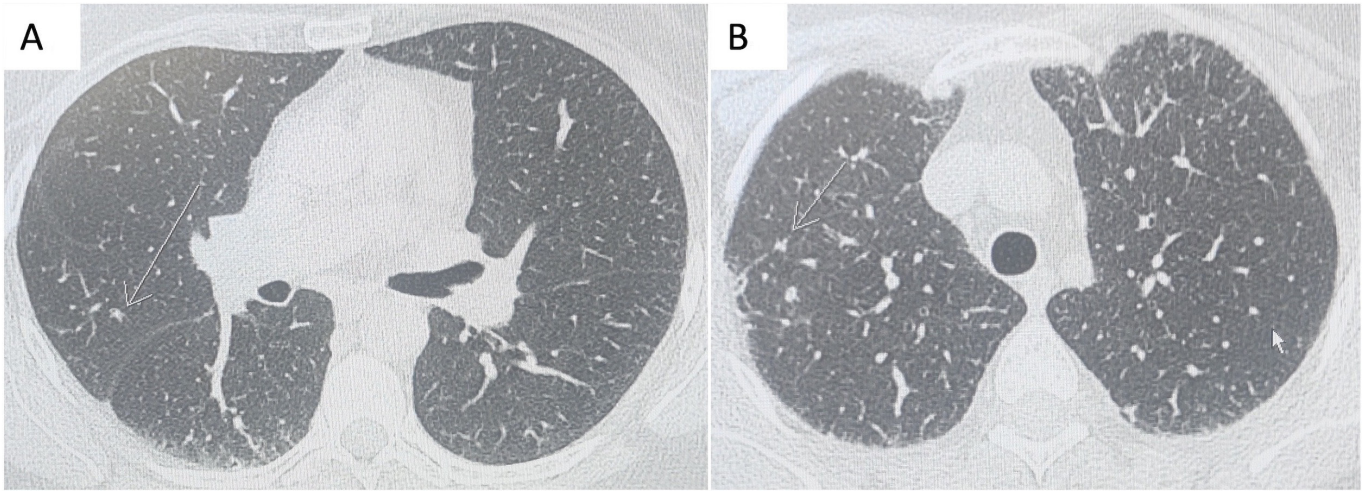

Figure 2 Cross-sectional slices from the high-resolution CT of the chest of our patient demonstrating two distinct nodules in the right upper lobe (see arrows) (A, B).

incidence of DPM is exceedingly rare, there is a growing consensus on the clinical significance it may play.

MPMNs were first discovered in 1960 by Korn *et al*, who described their appearance as distinctive perivascular cellular proliferations suggestive of chemodectomas in cytology and arrangement and arranged in clusters along the intra-alveolar septae, findings supported by Zak and Chabes's observations in 1963.[6 7] Chemodectoma is the term given to a carotid body tumour consisting of non-chromaffin reacting paraganglionic or glomic tissue.[8] Glomic tissue deposition outside of the cervical chain and carotid body distribution has been reported for many years but typically in close proximity to the pulmonary artery and ascending aorta.[7] These were the first cases to describe a chemodectoma within the lung parenchyma, namely a 'pulmonary chemodectoma', although no association with clinical presentation was made at this time but a female preponderance was noted. The nomenclature was subsequently changed to 'so-called chemodectomas' when neurosecretory granules were not detected by electron microscopy.[9] The proposed neuroendocrine descent came further into question when Gaffey *et al* found evidence of meningothelial derivation on immunohistochemistry with reactivity with vimentin and EMA and lack of reactivity with cytokeratin, actin, S-100 and neuron-specific enolase.[10 11] In 1988, based off these histopathological observations, the name MPMN was coined.[12]

While most cases of MPMN are picked up incidentally, small case series and case reports have described patients with multiple MPMNs. The condition was initially called chemodectomatosis and later changed to minute pulmonary meningothelial-like nodulomatosis or MPMN-atosis.[7 12] The relationship between the asymptomatic and symptomatic disease was unclear but led many to question if a neoplastic process might be at play in those who develop MPMN-atosis. With this in mind, Ionescu *et al* explored if there were genotypic and molecular overlap between MPMN and meningiomas, a well-studied and understood benign meningothelial cell neoplastic disease. The surgical lung specimens were collected from 16 patients and yielded 31 MPMNs. All of these cases were investigated for the presence of

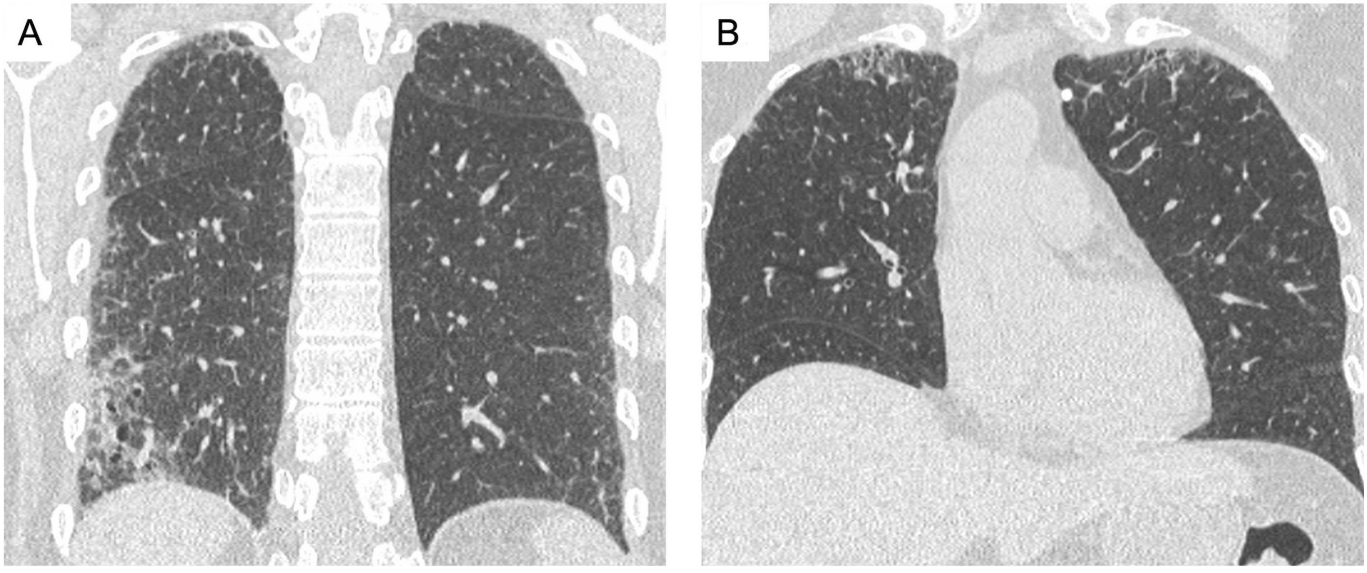

Figure 3 Coronal sections from the high-resolution CT of the chest of our patient demonstrating interstitial fibrosis in the right lower lobe (A) and the lung apices (B).

loss of heterozygosity (LOH) at 20 microsatellite markers from 11 chromosomal loci (1p, 3p, 5q, 9p, 9q, 10q, 14q, 17p, 18q, 19q and 22q). The sporadic presence of LOH was reported in all 12 cases of patients with an isolated MPMN, confirming the reactive nature of MPMN.[12] Greater genetic instability with LOH seen in at least one chromosomal locus per nodule were found in patients with MPMN-omatosis, suggesting that this condition might represent a transition between a reactive and neoplastic process. 22q mutations were identified in both cases of meningiomas and MPMN but were significantly more prevalent in meningiomas (60% vs 10%). Mutations of the TP53 gene on chromosome 17, which has a very low incidence in meningiomas, accounted for the highest rate of LOH in MPMN-omatosis (19.04%) and were also seen in single MPMN (10%).[12 13] This led the authors to conclude that differing genetic pathways were at play, casting further mystery over the exact origin and nature of MPMNs.

A possible link with thromboembolic disease was described in 2009. Mukhopadhyay *et al* systematically examined over 500 surgical specimens for evidence of MPMNs and found an incidence of 13.8%. MPMNs were detected in a staggering 42% of surgical lung biopsies from cases of thromboembolic disease or infarcts and 26% of patients with Respiratory bronchiolitis-ILD/desquamative interstitial pneumonia. Interestingly, MPMNs were not identified in any of the 92 paediatric lung specimens, suggesting that these findings are not congenital in nature.[14] Other case series have found a higher incidence of history of previous or active malignancy in cases where MPMNs are identified.[1 15 16]

The term DPM was introduced by Suster and Moran in 2007 after they encountered five patients with dyspnoea, bilateral interstitial infiltrates on chest imaging and diffuse bilateral MPMN on histopathological assessment. The diffuse bilateral involvement of the lung parenchyma with MPMN led to the appropriate terming DPM.[15] Classically, patients with DPM are asymptomatic (up to 60% of cases) and it is usually an incidental finding on imaging, at autopsy or in a surgical resection for an unrelated cause. When symptomatic, patients will typically report dyspnoea and cough.[1] High-resolution CT of the chest is usually required to further characterise the pulmonary nodules with most patients undergoing surgical lung biopsy for a definitive diagnosis.[1] Diagnosis by transbronchial biopsy and cryobiopsy have also been described.[1 5 17 18] The treatment and prognosis of this condition is not well understood or documented in scientific research. Over the last four decades, there have been a number of case reports and case series describing patients with DPM but there remains a noticeable void in any large database or studies. This is surprising given the high incidence of MPMNs in 13.8% of the surgical lung biopsies performed by Mukhopadhyay *et al* in 2009.

In summary, the significance of MPMNs alone and MPMNs in the context of DPM is unclear. The pathophysiology, clinical course and prognosis of DPM is undetermined. In the fast-paced world that we currently live in, where resourceful use of medical resources is pertinent, defining the significance of conditions such as DPM should be essential. If clarified as a benign or reactive condition, physicians would have the confidence to reduce the need for imaging or further surgical intervention. However, given the possible link of DPM as a transitional state to a neoplastic process, the presentation of multiple pulmonary nodules poses a clinical dilemma. Once a malignant cause is ruled out, should MPMNs be surveyed and followed and if so, for how long? If DPM is a precursor of malignancy, further surveillance and or intervention will be required, however, currently further research is needed to clarify the clinical significance of DPM.

Patient's perspective

From a young age, I always felt I had weak lungs. Over the last few years, I noticed an increase in my attendance to my local doctor for chest infections, which concerned me. I was a heavy smoker and I continue to use my e-cigarette, so I was worried about something serious. After my scan, I was very nervous about going ahead with surgery, but I also felt adamant to get to the cause of my issues. When I spoke to my specialist doctor after the results of the surgery, I felt conflicted. On one hand, I was relieved it wasn't an anything immediately life threatening. However, I have to admit I felt a little disappointed it wasn't something that could be solved overnight, or with medication. I currently feel better, however I still have an occasional cough, perhaps not as frequent as before. I feel a little wheezy at times, but I am not short of breath and I am able to carry on doing my normal activities. I have avoided livestock since, but I still need to stop using my e-cigarette. I am glad I still have follow up with the specialist service.

Learning points

- Despite advances in diagnostic techniques, a detailed history and clinical examination is still fundamental to establishing an accurate differential diagnosis.
- In patients with bilateral pulmonary nodules, diffuse pulmonary meningotheliomatosis should be considered in the differential diagnoses, particularly in women.
- It is pertinent to maintain a broad differential even for the most common clinical presentations, to avoid missing a rare cause.

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