DIAGNOSTIC DILEMMA
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# Getting the Whole Picture: Lymphangitic Carcinomatosis

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## PRESENTATION

Pulmonologists often rely heavily on lung imaging when formulating the differential diagnosis. We present a classic example of this strategy, though the cause of the woman's diagnosis was not at all typical. A 53-year-old woman with a 30 pack-year history of smoking was admitted with severe shortness of breath and a cough that produced frothy whitish sputum. She had been coughing for a month but had experienced progressive worsening over the previous 3-4 days. Upon questioning, she denied fevers, chills, hemoptysis, or chest pain. Further, she had not traveled recently or been exposed to toxic fumes, she did not use illicit drugs, and she did not have new pets or sick contacts. Her past medical history was significant for malignant melanoma of the left foot, which had been excised 2 years earlier. On evaluation, she was hypoxic on 6 L of oxygen and was given 50% oxygen through a face mask.

## ASSESSMENT

The patient was alert, afebrile, and dyspneic. Her blood pressure was 114/72 mmHg. She had a regular tachycardia of 110 beats/min and a respiratory rate of 30 breaths/min. Auscultation of the lungs revealed vesicular breath sounds with coarse crepitation; these were more pronounced at the bases. The rest of the examination was normal.

A chest x-ray disclosed diffuse accentuation of the interstitial markings, bibasal pleuroparenchymal opacities, and small bilateral effusions (**Figure 1**). Laboratory studies demonstrated a leucocyte count of 11.08 $\times$ $10^3$ cells/μL with 94% granulocytes, hemoglobin of 10.7 gm/dL, and a normal metabolic panel. A blood sample was drawn for an arterial blood gas test while the patient was receiving 50% oxygen through the face mask, and the results were as follows: pH, 7.43; partial pressure of oxygen, 58 mmHg; partial pressure of carbon dioxide, 42 mmHg; and bicarbonate, 28 meq/L.

Blood, sputum, and urine were obtained for culture. While awaiting results, the patient was treated with intravenous broad-spectrum antibiotics; specifically, vancomycin and piperacillin-tazobactam. Computed tomography of the chest (**Figure 2A**) revealed extensive smooth interstitial thickening with bilateral small pleural effusions. A pattern of interstitial thickening along with alveolar opacity—so-called crazy paving—was noted in both lower lobes (**Figure 2B**). Mediastinal adenopathy was also seen on the CT scan.

## DIAGNOSIS

Based on imaging results, the differential diagnosis included lymphangitic carcinomatosis, pulmonary alveolar proteinosis, sarcoidosis, *Pneumocystis jirovecii* pneumonia, bronchiolitis obliterans organizing pneumonia (also known as cryptogenic organizing pneumonia), and organizing pneumonia.

Bronchoscopy performed with bronchoalveolar lavage produced cloudy fluid. A trans-bronchial lung biopsy was planned but abandoned because of the patient's tenuous respiratory status. Cytology from bronchoalveolar lavage displayed atypical cells with large nuclei. Immunohistochemistry showed diffuse cytoplasmic staining for HMB-45 in these cells, consistent with melanoma (**Figure 3**).

The predominant radiological pattern in this patient's case, a septal pattern, is characterized by marked thickening of the interlobular septa between the individual secondary pulmonary lobules. A broad but well-defined group of conditions can generate this finding. Determining whether the interstitial thickening is mainly smooth or nodular generally narrows the differential diagnosis. Other factors

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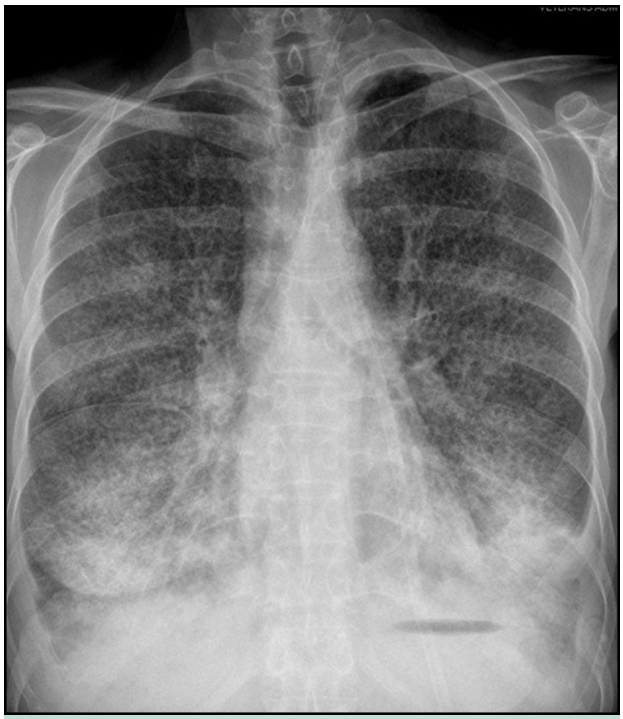

**Figure 1** A chest x-ray revealed increased reticular markings.

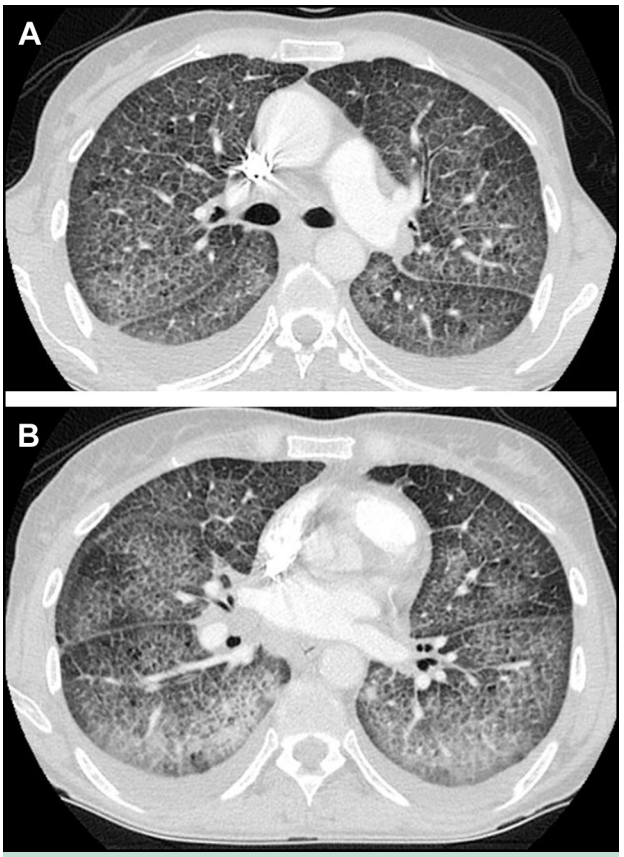


**Figure 2** The patient had computed tomography (CT) of the chest. **A**, Increased reticular markings were more visible on a CT scan. **B**, An alveolar filling pattern was combined with reticular prominence.

that help pinpoint a cause are the distribution of septal thickening, associated lymphadenopathy, alveolar opacities, and pericardial or pleural effusions. However, none of these features are specific for any particular disease.

Usually, a smooth pattern is associated with venous, lymphatic, or infiltrative diseases of the lung.[1] Common causes include pulmonary edema, hemorrhage, or veno-occlusive diseases, lymphangitic carcinomatosis, Erdheim-Chester disease, lymphoma and other lymphoproliferative diseases, lymphangiomatosis, interstitial pneumonias such as *Pneumocystis jirovecii* pneumonia, and acute or chronic eosinophilic pneumonia.[2-6] The nodular pattern is seen frequently in patients with sarcoidosis, asbestosis and other types of pneumoconiosis, lymphatic tumors and other lymphoproliferative diseases, and chronic hypersensitivity pneumonitis.[7-9] However, a degree of overlap can complicate diagnosis. For example, aside from lymphoproliferative diseases, other diseases, such as sarcoidosis, lymphoid interstitial pneumonia, pneumoconiosis, or occasionally, amyloidosis, can be associated with a smooth or nodular pattern. Both forms of thickening may be seen in the same patient.

While the presence of pericardial and pleural effusions with cardiomegaly indicates congestive heart failure, the mediastinal lymphadenopathy identified in our patient pointed towards lymphoma, sarcoidosis, or amyloidosis. Another prominent feature on our patient's images was the crazy paving or combination of alveolar ground-glass opacity and smooth septal thickening. Although initially identified in relation to alveolar proteinosis, this radiological feature is common in hypersensitivity pneumonitis and has been noted in a number of other disorders, such as interstitial pneumonia, lymphangitic carcinomatosis, pulmonary edema, pulmonary hemorrhage, *Pneumocystis Jirovecii* pneumonia, acute and chronic eosinophilic pneumonia, organizing pneumonia, radiation pneumonitis, Churg-Strauss syndrome, and mucinous and nonmucinous adenocarcinoma.[10]

Furthermore, a disease-specific zonal predominance of septal thickening is often helpful in diagnosis. For example, signs of sarcoidosis or chronic hypersensitivity pneumonitis tend to be seen in the upper lobes. In contrast, evidence of asbestosis, silicosis, coal workers' pneumoconiosis, interstitial pneumonia, and nonspecific interstitial pneumonia is generally found in the lower lobes. Location within the lobe is also of diagnostic value. Typically, diseases such as sarcoidosis, pneumoconiosis, lymphangitic carcinomatosis, and hypersensitivity pneumonitis lead to changes that are centrally prominent, sparing the lung periphery, whereas usual interstitial pneumonia, nonspecific interstitial pneumonia, and interstitial lung diseases related to collagen disease produce changes that are peripheral in distribution.

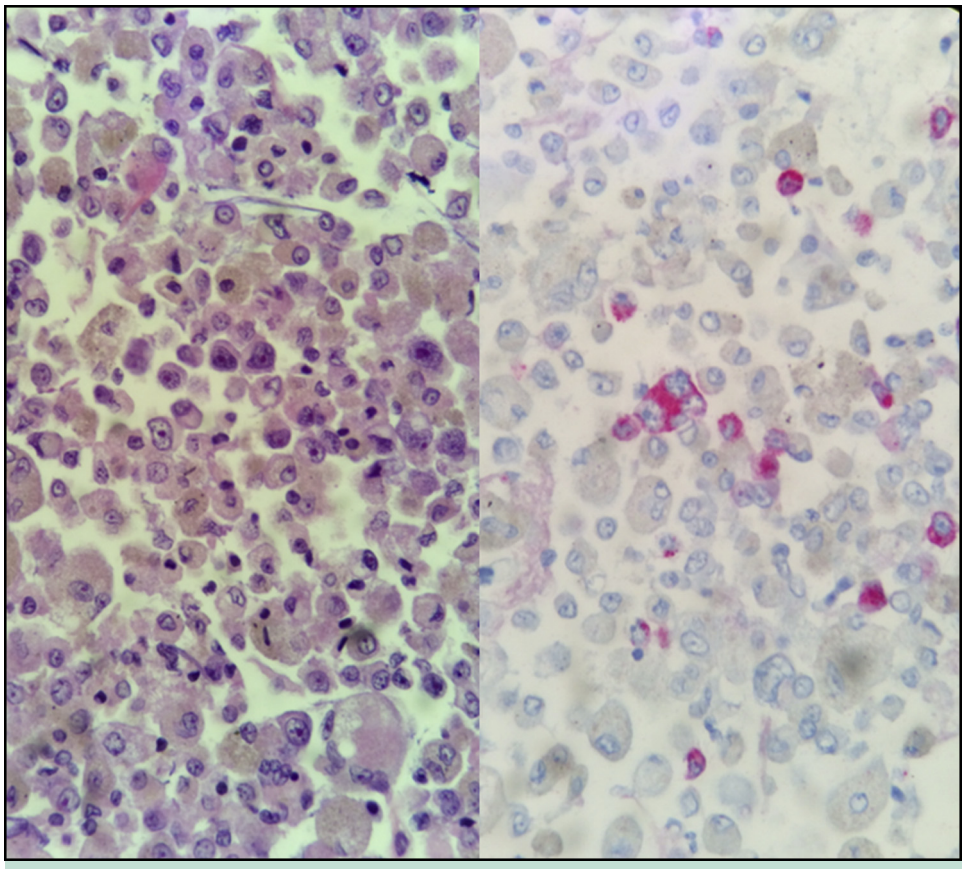

**Figure 3** Atypical cells showed diffuse staining for HMB-45, a marker for melanoma.

A possible diagnosis of lymphangitic carcinomatosis was based on the smooth pattern of interstitial thickening, the diffuse lung involvement, and the presence of significant mediastinal adenopathy. This was confirmed by the results of the bronchoalveolar fluid cytology, which to our surprise, revealed melanoma cells. Commonly, adenocarcinomas and cancers of the breast, lung, colon, pancreas, thyroid, cervix, prostate, larynx, and stomach are associated with such a presentation.[11,12] Rarely has malignant melanoma been described to be a cause of lymphangitic carcinomatosis. Webb and Gamsu reported 5 cases of spread to the lymph vessels of the lung among 65 patients with metastasis to the thorax.[13] Others have reported even rarer occurrence of this type of metastasis (1.5-2.4%) with malignant melanoma.[14,15] Possibly, melanoma spreads through the lymphatic system after blood-borne emboli lodge in smaller pulmonary arteries, later moving through the vessel walls into the perivascular interstitium and lymphatic vessels.

## MANAGEMENT

The patient's melanoma cells were found to have the BRAF V600E gene mutation. As a result, she began treatment with vemurafenib, which is monotherapy for patients with unresectable or metastatic melanoma proven to have that particular genetic alteration.[16]

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