

WHAT'S YOUR DIAGNOSIS?

Patient With Leukocytosis and Persistent Dry Cough

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An 83-year-old man who was a non-smoker with no history of systemic disease was transferred to the Veterans Affairs Caribbean Healthcare System from an outside hospital due to marked leukocytosis (white blood cell [WBC] count, $22.5 \times 10^3/\mu\text{L}$). He reported a 3-month history of persistent dry cough, which required several primary care physician (PCP) evaluations. He was initially treated for an upper respiratory tract infection without adequate response. Instead, his symptoms progressed, and he presented with associated hoarseness and unintentional 26-pound weight loss.

The patient's physical examination was

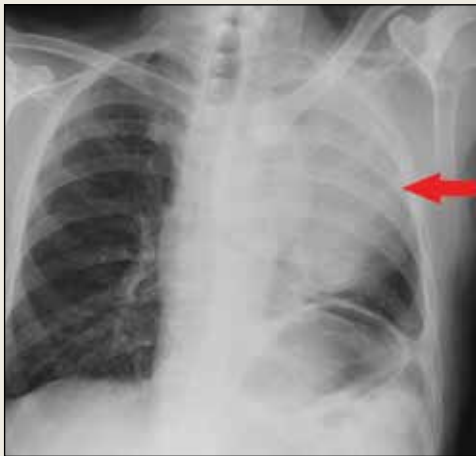
remarkable for left-sided decreased breath sounds. Laboratory tests confirmed leukocytosis (WBC, $20.0 \times 10^3/\mu\text{L}$), and his radiographic chest X-ray (Figure 1) showed a left upper lobe mass, confirmed by computed tomography (CT) (Figure 2) in which mediastinal lymphadenopathy also was seen. The abdominal/pelvic CT showed renal and bilateral adrenal lesions suggestive of metastatic disease. A core needle biopsy from the anterior component of the mediastinal mass showed pleomorphic cells with hyperchromatic nuclei, spindle configuration, and mitotic figures (Figure 3). Immunohistochemistry was positive for pancytokeratin, CK7, and vimentin.

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FIGURE 1 Chest X-ray



A left upper lobe mass (red arrow) can be seen.

FIGURE 2 Computed Tomography



Left upper lobe mass and mediastinal lymphadenopathy (red arrows) can be seen.

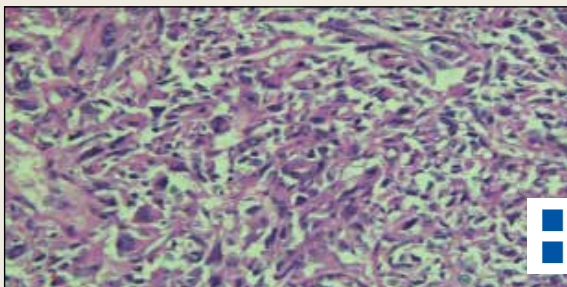


FIGURE 3 Left Upper Lobe Mass Core Needle Biopsy

Hematoxylin and eosin stain demonstrating pleomorphic cells with hyperchromatic nuclei, spindle configuration, and mitotic figures (original magnification $\times 40$).

- What is your diagnosis?
- How would you treat this patient?

TABLE Morphologic Characteristics of Pulmonary Sarcomatoid Carcinomas^a

Classifications	Characteristics
Pleomorphic	Spindle and giant cell only carcinoma or poorly differentiated NSCLC that contains at least 10% of these cells
Spindle cell	No differentiated carcinomatous elements and composed almost exclusively of epithelial spindle cells
Giant cell	No differentiated carcinomatous elements and composed almost exclusively of tumor giant cells
Carcinosarcoma	A combination of NSCLC and sarcoma
Biphasic pulmonary blastoma	A biphasic pattern characterized by the presence of fetal adenocarcinoma and primitive mesenchymal stroma

Abbreviation: NSCLC, non–small cell lung cancer.

^aAdapted from: The 2015 World Health Organization Classifications of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification.²

DISCUSSION

An interdisciplinary discussion regarding the diagnosis considered the clinical features of the patient along with the imaging characteristics. The histological examination demonstrating sarcomatoid features with the supporting immunohistochemistry that confirmed both mesenchymal and epithelioid presence and was used to make the diagnosis of pulmonary sarcomatoid carcinoma (PSC).

PSC is a very rare aggressive subtype of poorly differentiated non–small cell lung carcinoma (NSCLC). This tumor is clinically characterized by tumor cells with molecular, histological, and cytological properties of epithelial and mesenchymal tumors, distinguishing it from other types of NSCLC. PSC has a sarcoma-like differentiation (spindle and/or giant cell) or a component of sarcoma (malignant bone, cartilage, or skeletal muscle).¹⁻⁵ The World Health Organization (WHO) has classified PSC based on morphological characteristics (Table).

The incidence of PSC ranges between 0.1% and 0.4% of all lung malignancies.^{1,4-7} PSC usually occurs in older men whose weight is moderate to heavy and who smoke. PSC appears to have an upper lobe predilection; also, these tumors tend to be bulky with invasive tendency, early recurrence, and systemic metastases. PSC frequently involves the adjacent lung, chest wall, diaphragm, pericardium, and other tissues.¹⁻⁵ The source of the sarcoma component of the PSC re-

mains uncertain. However, prior research suggests that it is associated with a clonal evolution that induces epidermal and mesenchymal tumor histological characteristics.^{1,8,9} The tumor cell epithelial-mesenchymal transition may induce transformation of the carcinoma component of PSC to into a sarcoma component. The epithelial-mesenchymal transition is associated with the PSC high risk for invasiveness and induces metastasis sites, such as the esophagus, colon, rectum, kidneys, and the common sites of NSCLC.

The most common symptoms include productive cough, chest congestion, and chest pain.^{1,7} In view of PSC's clinical presentation and imaging, numerous differential diagnoses should be considered, such as sarcomatoid carcinomas, primary or secondary metastatic sarcomas, malignant melanoma, and pleural mesothelioma.^{6,10}

The tumor is initially identified by a chest CT, confirmed by histology and immunohistochemistry. Several biomarkers are useful for diagnosis and classification of an undifferentiated neoplasm/tumor of uncertain origin. Those biomarkers help to understand the tumor pathobiology, to select the therapeutic regimen, and to predict the patient's outcome. Although immunohistochemical staining of epithelial and mesenchymal markers can be helpful, a reliable diagnosis requires a precise histopathological examination. This is often difficult on small biopsy samples, such as fine-needle aspiration, as all the histological elements of PSC required to make the correct evaluation may not be present. Adequate sampling to generate a considerable number of histological slides is essential for an accurate diagnosis, which can be reached only with surgical resection.⁵

Due to rarity, rapid progression, short survival, and heterogeneous pathological qualities, PSC has been difficult to formulate treatment recommendations. Compared with other histological subtypes of NSCLC, PSC is more aggressive and has a poor prognosis. Survival time on average is about 13.3 months due to early metastasis, lower than other types of NSCLC. The greatest overall survival (OS) benefit has been shown with surgery in early-stage operable PSC, which remains the standard of care. Because most patients with PSC present in the advanced stage, they lose their

opportunity for curative surgery. Auxiliary methods of treatment include radiotherapy and chemotherapy. Prior studies have shown that systemic chemotherapy efficacy has varied, some showing no OS benefit; others showing a modest benefit. It has also been noted that advanced-stage PSC has minimal response to chemotherapy. Further larger prospective studies are needed to outline the efficacy and role of systemic chemotherapy and other therapeutic agents, including targeted therapies and immunotherapy.^{1,4,11-13} However, two-thirds of patients are not sensitive to conventional chemotherapy. In comparison with other types of NSCLC, PSC carries a poor prognosis even in early-stage disease or if tumor metastasis is present. Therefore, further research on novel treatment options is needed to improve long-term survival.^{1,3-8}

CONCLUSIONS

PSC is diagnostically challenging because it is rare and has an aggressive progression. Identification of this tumor requires knowledge of histological criteria to identify their subtypes. Immunohistochemistry has an important role in the classification and to rule out differential diagnoses, including metastatic spread. Nevertheless, a reliable diagnosis requires precise histopathological examination, reached with surgical resection. Therefore, a detailed history, physical examination, systematic investigation, and correlation with chest imaging are needed to avoid misdiagnosis.

Our case highlights the importance of keeping this rare, aggressive tumor as part of the differential diagnosis. In view of its natural history, heterogeneity, and low incidence, published cases of PSC are limited. Thus, further investigation could optimize rapid identification and treatment options.

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Ethics and consent

The patient died before he could provide written consent and relatives were unavailable despite attempts. No personal identifiers were used to maintain the patient's privacy.

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