Pulmonary Histoplasmosis Producing a Spindle Cell “Pseudotumor”

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Key Words: Histoplasmosis; Spindle cell lesion; Pseudotumor; Lung pseudoneoplasm

Abstract

Pulmonary spindle cell proliferations have been reported in association with a limited group of infectious agents. These lesions are rare and identified most often in the setting of immunosuppression. Because their appearance can simulate a spindle cell neoplasm, they are diagnostically treacherous, sometimes delaying antimicrobial therapy or resulting in unnecessary surgery. We report a case of a spindle pseudotumor of the lung resulting from Histoplasma capsulatum infection, a previously unreported cause of a spindle cell lesion in the lung. The patient was a 67-year-old woman in whom positron emission tomography–positive nodules developed in the left lung and left mediastinum. The patient had undergone renal transplantation and was receiving immunosuppressive therapy with mycophenolate, tacrolimus, and low-dose prednisone. Infection with H capsulatum was confirmed by culture of pleural effusion fluid, DNA probe analysis of the pleural fluid culture isolate, urinary Histoplasma antigen detection, and Grocott methenamine silver stains of tissue sections. To our knowledge, this is the first case of a spindle cell “pseudotumor” of the lung resulting from histoplasmosis. It highlights the importance of performing special stains for organisms when evaluating pulmonary spindle cell lesions in an immunocompromised host.

The modern classification of “inflammatory pseudotumors” encompasses a diverse group of lesions of reactive, reparative, and neoplastic causes. Among the infectious causes of these lesions, most of the reported cases have occurred in the setting of mycobacterial infection in immunocompromised hosts.1-11 These mycobacterial-associated spindle cell lesions have been reported in multiple sites, including brain, lungs, spleen, lymph nodes, skin, and bone marrow. There have also been multiple reports of spindle cell lesions arising from infection with nonmycobacterial agents, including Cryptococcus neoformans,12 Coxiella burnetti,13 Aspergillus fumigatus,14 and Clostridium difficile.15 We describe a case of histoplasmosis causing a spindle cell pseudotumor of the lung in a renal transplant recipient, a previously unreported cause of this entity.

Case Report

The patient was a 67-year-old woman residing in the central United States in an area known to be endemic for histoplasmosis. The patient sought care for the present condition 2 years after receiving a cadaveric renal transplant. She complained of 3 weeks of cough and shortness of breath with fever (temperature, 38.3°C) and chills. Her cough was productive of white to yellow sputum. She also complained of left lower quadrant pain and tenderness of her renal allograft site. She had a history of type 2 diabetes, hypertension, peptic ulcer disease, osteoarthritis, diastolic dysfunction, and bronchial asthma. Her immunosuppressive therapy included mycophenolate (Myfortic), tacrolimus (Prograf), and low-dose prednisone.
Chest radiographs demonstrated a left lower lobe infiltrate and bilateral pleural effusions. Her urine showed pyuria with many bacteria, 2+ leukocytes, and positive nitrites. A computed tomography (CT) scan of her abdomen showed perinephric stranding around her renal allograft consistent with pyelonephritis. Urine cultures were positive for *Klebsiella pneumoniae*, and she was given a diagnosis of pyelonephritis involving the renal allograft. She was treated with multiple antibiotics, including piperacillin and tazobactam (Zosyn), levofloxacin (Levaquin), and doripenem (Doribax).

Repeated urinalysis showed resolution of pyuria; however, dyspnea and fevers persisted, and, thus, a left thoracentesis was performed and yielded 1,400 mL of exudative fluid. Fungal cultures of the pleural fluid were positive for *Histoplasma capsulatum*. Blood cultures were negative. Following thoracentesis, the patient’s dyspnea was significantly improved. A CT scan of the chest showed a left pleural effusion, a left-sided hilar mass, prevascular lymph nodes, vascular engorgement, and bilateral atelectasis.

The patient was discharged to home with levofloxacin, 500 mg orally twice a day for persistent fevers. A positron emission tomography (PET) scan showed abnormal uptake of 15 standardized uptake values (SUVs) involving the left upper lobe lesion and approximately 15 SUVs in the left hilar region. Lymph nodes in the region of the left hilum/mediastinum demonstrated 4 or 5 small foci of abnormal increased uptake. A CT-guided, 20-gauge needle core biopsy was performed on the left lung mass. Additional infectious disease workup included a urine specimen that was weakly positive for *Histoplasma* antigen and identification of *H. capsulatum* by DNA probe analysis performed on the pleural fluid culture isolate.

**Pathologic Findings**

Four white needle core biopsies were received. Histologic examination of H&E-stained sections demonstrated a spindle cell proliferation with associated foci of necrosis and rare multinucleated giant cells. The spindle cells had small, bland, elongated nuclei and moderate amounts of eosinophilic cytoplasm with indistinct cell borders. In the background, occasional lymphocytes and rare plasma cells were present. A histiocytic component was present, and routine H&E staining revealed that the cytoplasm of these cells contained pale, punctate microorganisms, compatible with *Histoplasma*. Grocott methenamine silver and periodic acid–Schiff stains highlighted numerous yeast forms often clustered within a single histiocyte. The spindle cell and histiocytic components of the lesion were immunoreactive for CD68. This lesion was diagnosed as a spindle cell/inflammatory pseudotumor resulting from infection with *Histoplasma*.

**Discussion**

Histoplasmosis is a fungal infection occurring most commonly in endemic areas of North and Central America, including the Ohio and Mississippi River valleys. The
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incidence of disseminated histoplasmosis is highest in immunocompromised people, particularly HIV-infected patients. However, histoplasmosis has rarely been documented in solid organ transplant recipients, occurring in approximately 1/1,000 transplant person years. Histoplasma can produce multiple forms of disease. The most common form of disease among immunocompetent hosts is acute pulmonary histoplasmosis. Acute pulmonary histoplasmosis is a self-limited infection characterized by flu-like symptoms and pulmonary infiltrates. Pulmonary histoplasmosis becomes chronic when symptoms progress for several months. When chronic, pulmonary histoplasmosis can produce well-formed necrotizing granulomas. If the necrotizing granulomas form a mass that is walled off from the surrounding pulmonary tissue, the lesion is referred to as a histoplasmaoma. Disseminated histoplasmosis occurs primarily in immunocompromised hosts and can produce a unique histologic picture characterized by sheets of histiocytes containing large numbers of Histoplasma yeast without granuloma formation. Although acute pulmonary

![Image 1](https://via.placeholder.com/150)

**Image 1** Spindle cells with small bland nuclei and moderate amounts of eosinophilic cytoplasm (A, H&E, ×200) and vaguely visible organisms (arrows) within spindle cells with foamy cytoplasm (B, H&E, ×400).

![Image 2](https://via.placeholder.com/150)

**Image 2** Large numbers of Histoplasma yeast within spindle cells (A, Grocott methenamine silver, ×200) and small, uniform, budding yeasts of Histoplasma capsulatum with intracellular clustering (B, Grocott methenamine silver, ×1,000).
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Histoplasmosis is rarely biopsied, a recently published series of 4 cases describes a unique histologic pattern mimicking lymphomatoid granulomatosis. Histologic features of this pattern included a prominent lymphohistiocytic infiltrate, parenchymal necrosis, vasculitis, palisading necrotizing granulomas, and multinucleated giant cells.

The case reported herein manifested with a pulmonary mass shown on CT scan that was also positive on PET scan, raising clinical concern for a malignant lesion (Image 1). The presence of enlarged mediastinal lymph nodes with increased activity on the PET scan was also suggestive of malignancy. Given these concerns, the clinical team elected to perform a needle core biopsy. H&E-stained sections of the biopsy sample demonstrated a dense spindle cell proliferation accompanied by microscopic foci of fibrin/necrosis and rare multinucleated giant cells (Image 2). Thus, this lesion mimicked a neoplasm in its radiographic and histologic manifestations. However, the identification of numerous yeast forms on silver stains clearly established the cause of the lesion as infectious. Given the multiple lines of evidence identifying the infectious agent as *H capsulatum*, this case is the first reported instance of a spindle cell lesion arising due to infection by *H capsulatum*.

The differential diagnosis of spindle cell lesions of the lung is broad, including inflammatory myofibroblastic tumor, localized fibrous tumor, inflammatory sarcomatoid carcinoma, primary undifferentiated high-grade pleomorphic sarcoma, benign and malignant smooth muscle neoplasms, metastatic low-grade sarcomas, organizing pneumonia, and spindle cell lesions resulting from infection. Spindle cell tumors arising from infection generally are composed of spindle cells growing in a fascicular pattern. The spindle cells may have foamy cytoplasm and frequently stain with histiocytic markers such as CD68 and lysozyme. Significant cytologic atypia is not seen. Scattered lymphocytes and plasma cells may be seen. Organisms may be evident on routinely stained sections but may require special stains for detection. Given the association of these lesions with immune compromise, all spindle cell lesions arising in the setting of infection should raise suspicion of an infectious etiology.

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### Table 1

Differential Diagnosis of Spindle Cell Lesions of the Lung

<table>
<thead>
<tr>
<th>Diagnostic Entity</th>
<th>Morphologic Features</th>
<th>Immunohistochemical Features</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory myofibroblastic tumor</td>
<td>Bland spindle cells arranged in vague fascicles, usually with interspersed plasma cells</td>
<td>Immunoreactive for vimentin, α-smooth muscle actin and muscle-specific actins, negative for desmin, caldesmon, CD34, and pancytokeratin</td>
<td>Coffin et al20; Yamamoto et al21</td>
</tr>
<tr>
<td>Localized fibrous tumor</td>
<td>Uniform spindle cells; may have a diffuse sclerosing pattern</td>
<td>Immunoreactive for CD34, CD99, and bcl-2</td>
<td>Ali et al22</td>
</tr>
<tr>
<td>Inflammatory sarcomatoid carcinoma</td>
<td>Atypical spindle cells arranged in a haphazard or fascicular pattern; sometimes contains lymphocytes and plasma cells, often areas of necrosis; usually obvious cytologic anaplasia but can be bland</td>
<td>Usually positive for keratins, including AE1/3, Cam 5.2, CK18, and CK7</td>
<td>Franks and Galvin23, Travis24</td>
</tr>
<tr>
<td>Primary undifferentiated high-grade pleomorphic sarcoma</td>
<td>Fusiform and pleomorphic spindle cells arranged in a storiform to fascicular pattern; usually significant pleomorphism, including large bizarre, often multinucleated cells and frequent mitosis</td>
<td>Usually positive for vimentin, factor XIIa, CD68, usually negative for keratin, melanoma markers, and CD45</td>
<td>Halyard et al25; McDonnell et al26</td>
</tr>
<tr>
<td>Benign and malignant smooth muscle tumors</td>
<td>Interlacing fascicles of spindle cells; increased cellularity, pleomorphism, necrosis, and mitosis should raise suspicion of malignancy</td>
<td>Positive for vimentin, smooth muscle actin, and desmin; negative for CK</td>
<td>Gal et al27; Mlika et al28</td>
</tr>
<tr>
<td>Metastatic low-grade sarcomas</td>
<td>Variable morphologic appearance between different entities and even within some single lesions</td>
<td>Positive for vimentin; negative for Mart-1, S-100, EMA, CD99, and calretinin; synovial sarcomas variably positive for EMA, CD99, and calretinin</td>
<td>Fisher29</td>
</tr>
<tr>
<td>Organizing pneumonia</td>
<td>Bands of plump, fibrous tissue filling airways; cells have a fibroblastic appearance with plump spindle cells and minimal to no nuclear atypia</td>
<td>Noncontributory</td>
<td>Beasley30; Yi and Aubry21</td>
</tr>
<tr>
<td>Spindle cell lesions resulting from infection</td>
<td>Spindle cells growing in a fascicular pattern; may have foamy cytoplasm; significant cytologic atypia not seen; scattered lymphocytes and plasma cells may be seen</td>
<td>Frequently stain with histiocytic markers such as CD68 and lysozyme</td>
<td>Sing and Ramdial12</td>
</tr>
</tbody>
</table>

CK, cytokeratin; EMA, epithelial membrane antigen.
of immunosuppression, especially in patients with known infection, should initially be stained for organisms. In this setting, special stains for organisms can provide an accurate, cost-effective diagnosis and facilitate timely initiation of therapy. Spindle cell lesions that are negative for organisms can then be worked up with immunohistochemical stains and other relevant techniques to further classify them.

Spindle cell lesions arising from infections are rare lesions that have been associated with multiple infectious agents. These lesions have been observed to occur most frequently in the setting of immunosuppression. The pathogenesis of such lesions is an ongoing area of speculation. It has been suggested that infection-associated lesions could be separated from neoplastic lesions by immunophenotype, with infectious lesions having a histiocytic or follicular dendritic cell phenotype and neoplastic lesions having a myofibroblastic immunophenotype. This picture is clouded by the observation of histiocytic and myofibroblastic cell types within infectious spindle cell lesions resulting from Cryptococcus. The differentiation of neoplastic from reactive processes is further complicated by the observation that persistent inflammation resulting from infection has been linked to malignant transformation in other organ systems, such as gastric mucosa-associated lymphoid tissue lymphomas arising in the setting of Helicobacter pylori infection. Furthermore, many of these lymphomas will regress with resolution of infection, and the regression of these lesions can be predicted based on molecular features of the neoplastic clone. Mass lesions arising in the setting of infection remain an intriguing but poorly understood phenomenon awaiting further molecular and genetic characterization of their reactive vs neoplastic nature.

**Table 2**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Age (y)</th>
<th>Immune Status and/or Risk Factors</th>
<th>Site of Involvement</th>
<th>No. of Cases</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus fumigatus</td>
<td>42</td>
<td>Peripheral stem cell transplantation</td>
<td>Pulmonary</td>
<td>1</td>
<td>Priebe-Richter et al14</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>9 mo</td>
<td>Liver transplantation</td>
<td>Colon</td>
<td>1</td>
<td>Lykaviers et al15</td>
</tr>
<tr>
<td>Coxella burnetti</td>
<td>36</td>
<td>None</td>
<td>Pulmonary</td>
<td>1</td>
<td>Lipton et al13</td>
</tr>
<tr>
<td>Cryptococcus species</td>
<td>19-43</td>
<td>HIV+</td>
<td>Skin, soft tissue</td>
<td>5</td>
<td>Sing and Ramzial12</td>
</tr>
<tr>
<td>Mycobacterium species</td>
<td>25-55</td>
<td>HIV+, CMV+, HSV+</td>
<td>Lymph node, spleen</td>
<td>5</td>
<td>Brandvein et al2; Chen3; Loo et al8; Suster et al9; Lipton et al13</td>
</tr>
<tr>
<td>Mycobacterium avium-intracellulare</td>
<td>27-54</td>
<td>HIV+, cardiac transplantation, Hodgkin lymphoma</td>
<td>Bone marrow, brain, lymph node, pulmonary, skin</td>
<td>10</td>
<td>Apel and Samarantunga1; Brandvein et al2; Chen3; Joshi4; Morrison et al6; Umas et al8; Wood10</td>
</tr>
<tr>
<td>Mycobacterium kansasii</td>
<td>34</td>
<td>HIV+</td>
<td>Skin</td>
<td>1</td>
<td>Brandvein et al2</td>
</tr>
<tr>
<td>Mycobacterium malmoense</td>
<td>27</td>
<td>HIV+</td>
<td>Pulmonary</td>
<td>1</td>
<td>Yoganathan et al11</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>32</td>
<td>Cadaveric renal and pancreas transplantation, tacrolimus</td>
<td>Pulmonary</td>
<td>1</td>
<td>Sekosan et al7</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; HSV, herpes simplex virus.
* Unless otherwise indicated.

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**References**


