Angiosarcoma in the Lung
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Angiosarcoma involving the lung is a rare disorder and its clinical features are not well known. We conducted a retrospective analysis of 15 patients seen at our institution from 1950 to 1990 in an attempt to better characterize the spectrum of clinical and radiographic findings of angiosarcoma in the lung. No documented case of primary angiosarcoma of the lung was seen. The diagnosis of metastatic angiosarcoma to the lung was made antemortem in 12 of 15 cases, either by lung biopsy specimen (5 patients), biopsy evidence of metastatic disease elsewhere with abnormal chest radiograph (4 patients), or a compatible clinical picture in a patient with previously documented angiosarcoma arising in an extrapulmonary site (3 patients). The median age at the time of diagnosis was 45 years with the most common presenting symptom being hemoptysis (7 of 15 patients). Other presenting complaints included weight loss (6 of 15), cough (4 of 15), and chest pain (4 of 15) occurring 6 weeks to 1 year prior to diagnosis. Chest radiographs frequently disclosed multiple pulmonary nodules (11 of 15). Primary origins of the angiosarcoma most commonly included the heart and breast. Metastatic sites other than the lung included the pericardium, liver, spleen, kidney, adrenal gland, bone, and brain. The prognosis is generally poor, with our study population surviving an average of 9 months after diagnosis.

METHODS
The Mayo Clinic Patient Registry was used to extract all patients seen at the Mayo Clinic between 1950 and 1990 with the diagnosis of angiosarcoma involving the lung. Demographic data as well as clinical and laboratory information were collected retrospectively and relevant articles from a Medline search using the MESZ database (1968 to 1992) of BRS Colleague were reviewed.

RESULTS

Patient Population
The Mayo Clinic Patient Registry contained 15 records (1950 to 1990) of angiosarcoma involving the lung. All 15 cases indicated a metastatic origin of the pulmonary lesion, i.e., there were no primary cases seen in the interval searched. There was no sex predilection (8 male and 7 female patients), and the median age of the study group was 45 years (range, 5 to 71 years old). Eight patients had a history of smoking. The diagnosis of metastatic angiosarcoma to the lung was made antemortem in 12 of 15 cases, either by lung biopsy specimen (5 patients), biopsy evidence of metastatic disease elsewhere with abnormal chest roentgenogram (4 patients), or a compatible clinical picture in a patient with previously documented angiosarcoma arising in an extrapulmonary site (3 patients). The diagnosis was made by postmortem examination in the other three cases.

Signs/Symptoms
As depicted in Table 1, the patients' signs and pulmonary symptoms at the time of presentation were variable, but almost half had hemoptysis. The onset

<table>
<thead>
<tr>
<th>Features</th>
<th>No.</th>
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<tbody>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>7</td>
</tr>
<tr>
<td>Weight loss</td>
<td>6</td>
</tr>
<tr>
<td>Cough</td>
<td>4</td>
</tr>
<tr>
<td>Chest pain</td>
<td>4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
</tr>
<tr>
<td>None*</td>
<td>3</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>10</td>
</tr>
<tr>
<td>Crackles</td>
<td>2</td>
</tr>
<tr>
<td>Clubbing</td>
<td>1</td>
</tr>
<tr>
<td>Chest tenderness</td>
<td>1</td>
</tr>
<tr>
<td>Arm swelling</td>
<td>1</td>
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*Previously documented angiosarcoma in an extrapulmonary site with metastatic involvement of the lung noted on a follow-up chest radiograph or chest computed tomographic scan.
Table 2—Radiographic Features of Angiosarcoma in the Lung

<table>
<thead>
<tr>
<th>Features</th>
<th>No.</th>
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</thead>
<tbody>
<tr>
<td>Multiple nodules</td>
<td>11</td>
</tr>
<tr>
<td>Linear infiltrate(s)</td>
<td>3</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>2</td>
</tr>
<tr>
<td>Diffuse &quot;alveolar&quot;*</td>
<td>1</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1</td>
</tr>
<tr>
<td>Normal chest radiograph†</td>
<td>1</td>
</tr>
</tbody>
</table>

*Two additional patients subsequently developed chest radiographic evidence of "alveolar" changes, presumably due to pulmonary hemorrhage.
†Patient had massive hemoptysis (died within 4 h).

of symptoms preceded the diagnosis of metastatic angiosarcoma by an average of 3.8 months (range, 3 weeks to 1 year). Three patients had asymptomatic bilateral pulmonary nodules detected on chest radiographs done as part of a routine oncologic follow-up. Two of these patients had prior modified radical mastectomies for angiosarcoma and one patient had angiosarcoma arising in the scalp. No specific physical signs were consistently present.

**Laboratory Evaluation**

**Chest Radiograph:** Radiographic features of metastatic angiosarcoma to the lung at the time of diagnosis are shown in Table 2. Bilateral pulmonary nodular lesions were seen in 11 of 15 (73 percent) patients at the time of diagnosis of metastatic disease. The nodules were 0.5 cm to 3 cm in diameter, uncalcified, and indistinguishable from those seen in other metastatic malignant neoplasms. Three patients had linear infiltrates in addition to multiple nodular changes, while one patient had a pneumothorax in addition to bilateral pulmonary nodules. One patient presented with massive hemoptysis and died within hours. His initial chest radiograph revealed no lung parenchymal abnormalities. One additional patient disclosed changes consistent with diffuse alveolar hemorrhage, while two additional patients subsequently developed chest radiographic evidence of "alveolar" changes, presumably due to pulmonary hemorrhage. Thus, only 3 of 15 patients with angiosarcoma in the lung had radiologic evidence of pulmonary hemorrhage.

**Bronchoscopy:** Bronchoscopy did not appear to contribute to an earlier diagnosis of this condition. Of the four patients in whom bronchoscopy was performed, evidence of recent bleeding was seen in three patients without any other visible abnormalities. One patient had normal results of a bronchoscopic examination.

**Computed Tomography/Magnetic Resonance Imaging:** Computed tomography (CT) of the chest demonstrated nodules that proved to be metastatic angiosarcoma in all three patients in whom it was performed. In one case, chest CT clarified chest radiograph by demonstrating a 2-cm mass in an area of a nodular apical infiltrate. An abdominal CT was performed in three patients disclosing metastatic spread to the liver, spleen, kidney, and adrenal glands. There was no characteristic appearance that would differentiate these nodules from other types of metastatic disease. Magnetic resonance imaging of the chest (MRI) was obtained in one patient to confirm echocardiographic evidence of a periventricular mass. The MRI demonstrated multiple masses around the right ventricle, but the diagnosis of primary cardiac angiosarcoma metastatic to the lung was not made until the time of autopsy.

**Diagnoses**

Acknowledging that the primary origin of metastatic angiosarcoma is often difficult to establish with certainty, the analysis of our cases revealed the angiosarcoma to arise from the heart (three patients), breast (3 patients), and then one case each from the forearm, skin, scalp, skull (subgaleal), liver, tibia, jugular vein, and chest wall. One case failed to reveal any obvious primary source. As stated previously, the diagnosis of metastatic angiosarcoma to the lung was made postmortem in 3 of 15 cases and antemortem in 12 of 15 cases, either by lung biopsy specimen (5 patients), biopsy evidence of metastatic disease elsewhere with abnormal chest radiograph (4 patients), or compatible clinical picture in a patient with previously documented angiosarcoma arising in another site (3 patients).

**Treatment and Course**

Treatment modalities used varied from none in 6 of 12 patients to lobectomy (2 cases), chemotherapeutic regimens (5 cases), and with or without radiation therapy (4 cases). The effect of treatment on survival was difficult to assess based on very few numbers and the relatively short postdiagnosis survival time.

The clinical course was dismal with 10 of 11 patients with an antemortem diagnosis dying an average of nine months (1 week to 3 years) after recognition of metastatic lung involvement. Follow-up information was not available in one patient with advanced metastatic disease. The remaining three patients had a postmortem diagnosis. The only known survivor was a 19-year-old man who had been diagnosed as having primary angiosarcoma of the jugular vein metastatic to the lung and liver at 5 years of age treated by surgery and chemotherapy.

**DISCUSSION**

Previous reports of angiosarcoma involving the lung have been largely case reports, with the majority describing metastatic disease to the lung. Primary angiosarcoma of the lung is an extremely rare tumor
with eight cases reported thus far.\textsuperscript{1-6} Metastatic angiosarcoma has been associated with pulmonary hemorrhage,\textsuperscript{2,4,6} spontaneous pneumothorax due to subpleural metastases,\textsuperscript{7,8} as well as evidence of cavitation\textsuperscript{9} of the metastatic lesion. Nonspecific respiratory symptoms such as cough and dyspnea, as well as asymptomatic chest radiographic abnormalities, are not uncommon. In our patients, almost half had hemothysis. Chest radiographic evidence of pulmonary hemorrhage was present in only three patients. One patient with angiosarcoma of the scalp metastatic to the lungs had a pneumothorax and bilateral pulmonary nodules in addition to hemothysis. Kitagawa and colleagues\textsuperscript{10} reviewed the Japanese autopsy registry data of 95 angiosarcoma cases and noted the scalp to be the primary site in 33 of 95 cases (34.7 percent). This "scalp-group" also had a significantly higher incidence of pulmonary complications such as pneumothorax and hemothorax.

Virtually any organ has been reported as a primary site for angiosarcomas. Frequent primary sites appeared to involve the heart,\textsuperscript{11-14} liver,\textsuperscript{15,16} and breast,\textsuperscript{17,18} with over 100 cases of each reported. Other primary sites that have been reported, in decreasing order of frequency, include skin (including scalp),\textsuperscript{10,20-23} spleen,\textsuperscript{24,25} lung,\textsuperscript{2,5,26} bronchus, pulmonary artery,\textsuperscript{27} central nervous system,\textsuperscript{27} gastrointestinal tract,\textsuperscript{28} and bone.\textsuperscript{29} Case reports of angiosarcoma arising in adrenal gland,\textsuperscript{30} ovary,\textsuperscript{31} prostate,\textsuperscript{32} vagina,\textsuperscript{33} and maxillary sinus\textsuperscript{34} have also been described. Predisposing factors for angiosarcomas may be polychlorinated and thorium dioxide (Thorotrust)\textsuperscript{35} exposure (hepatic angiosarcoma), as well as postmastectomy\textsuperscript{37} and postirradiation\textsuperscript{38-40} states (cutaneous angiosarcoma). Possible associations with foreign body material,\textsuperscript{41} neurofibromatosis,\textsuperscript{42} tuberous sclerosis,\textsuperscript{43} and meningiomas\textsuperscript{44} have also been reported.

The lung is one of the most common sites of metastatic involvement, along with liver and lymph nodes depending on the primary site of origin of the angiosarcoma. Other reported metastatic sites include bone,\textsuperscript{45,46} adrenal glands,\textsuperscript{30} gallbladder,\textsuperscript{47} choroid plexus,\textsuperscript{5} colon,\textsuperscript{48} and the femoral artery (embolus).\textsuperscript{49} Metastases to the lungs occur in 60 to 80 percent of cutaneous\textsuperscript{40} and cardiac\textsuperscript{14,50,51} angiosarcomas. Many patients with metastatic angiosarcoma of the heart to the lungs present with symptoms ranging from chest pain and dyspnea\textsuperscript{52} to hemothysis.\textsuperscript{12,46,53} Magnetic resonance imaging may be useful for preoperative diagnosis and follow-up of patients with angiosarcoma of the heart,\textsuperscript{54} though this application is still in its infancy.

Early diagnosis is not common because of the rarity of angiosarcoma in the lung and hence, low index of suspicion. Chest radiography may reveal a spectrum of findings ranging from normal to multiple nodular densities with or without pleural effusions to diffuse alveolar infiltrates compatible with pulmonary hemorrhage. The role of echocardiography, CT, and MRI is uncertain in this rare entity, but it appears that MRI of the chest may help confirm the vascular nature of angiosarcoma. Both transbronchial and transthoracic needle biopsy specimens\textsuperscript{9} have been used in establishing the diagnosis with no additional risk of bleeding.

Although the initial histopathologic criteria for angiosarcomas were described by Stout\textsuperscript{55} in the 1940s, distinction between benign and malignant lesions as well as defining the primary origin of the vascular neoplasm may be very difficult. In addition, similar histopathologic findings may be seen with intravascular bronchoalveolar tumor,\textsuperscript{56-58} Kaposi's sarcoma,\textsuperscript{14,60} and other less differentiated vascular tumors.\textsuperscript{51,60} The electron microscopic appearance and positive immunohistochemical staining with Factor VIII-related antigen,\textsuperscript{61} Ulex europaeus,\textsuperscript{62} and vimentin (intermediate filament) seen in angiosarcomatous lesions\textsuperscript{63} have alleviated some of the difficulties previously experienced in confirming the endothelial differentiation of this lesion.

Unfortunately, therapeutic modalities such as radiation therapy, chemotherapy (including doxorubicin [Adriamycin] and methotrexate\textsuperscript{56}), and surgical interventions such as either wedge resection or pneumonectomy have all been described, but none of these have been shown to be dramatically effective. Recent reports concerning angiosarcoma of the breast suggest that prognosis may be influenced by the degree of differentiation of the tumor with the well-differentiated neoplasms having a more indolent course.\textsuperscript{19}

**Conclusions**

Metastatic angiosarcoma to the lung is a rare disorder, with primary angiosarcoma of the lung being extremely rare. The spectrum of clinical and radiographic findings of this condition are not well defined. In our review, the most common presenting symptom was hemothysis. Chest radiographs often disclosed multiple nodules. Cavitation of the lesion, pneumothorax, or hemothorax due to rupture of subpleural metastases have been reported to be more common with angiosarcomas from the scalp. There were no other consistent characteristic physical signs or laboratory tests, though MRI may be useful for following the therapeutic response of patients with metastatic angiosarcoma to the lung. Common primary sites for angiosarcoma include the heart, skin, breast, and scalp. The prognosis is generally poor, with our study population surviving an average of nine months after diagnosis.

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