Agnogenic Myeloid Metaplasia With Extramedullary Hematopoiesis and Fibrosis in the Lung*

Report of Two Cases

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Agnogenic myeloid metaplasia (AMM) is a chronic hematologic disorder with a long clinical course, characteristically accompanied by extramedullary hematopoiesis (EMH) in various organs, most commonly the spleen and liver. We describe two cases of AMM with clinically significant and ultimately fatal EMH and associated fibrosis in the lung and pleura. The literature on AMM and EMH involving the lung and pleura is reviewed. Three similar cases were found.

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Agnogenic myeloid metaplasia (AMM), also called myelofibrosis with myeloid metaplasia, is one of the myeloproliferative syndromes thought to be caused by a clonal proliferation of pluripotent hematopoietic stem cells.1,2 This disease pursues a slowly progressive course, and death is most often due to intercurrent infection, hemorrhage, cardiovascular disease, or acute leukemia.2,3 In AMM, the bone marrow typically becomes extensively fibrotic (myelofibrosis), and extramedullary hematopoiesis (EMH) develops in a variety of sites: splenomegaly and hepatomegaly due to EMH are extremely common, but EMH with or without associated fibrosis can be found in many other organs.4,5 Agnogenic myeloid metaplasia with EMH and fibrosis in the lung, causing interstitial lung disease, is quite rare; and we could find only three previous reports. Two additional cases of AMM with EMH and extensive associated fibrosis involving the lung are herein described.

Case Reports

Case 1

A 69-year-old white woman was admitted with a chief complaint of extreme shortness of breath in December 1986. She had a history of bradycardia requiring pacemaker placement in March 1986. Physical examination revealed hepatomegaly and bibasilar rales in the chest. A chest x-ray film was interpreted as showing cardiomegaly and pulmonary edema. The hemoglobin level on admission was 11.8 g/dl; the hematocrit was 37 percent; and the leukocyte count was 13,900/mm³, with a normal differential cell count. Arterial blood gas analysis showed a PaO₂ of 68 mm Hg and a PaCO₂ of 26 mm Hg. A diagnosis of congestive heart failure with pulmonary edema was made, and the patient’s condition improved with diuretic therapy. A similar episode of suspected congestive heart failure occurred in April 1988.

In April 1989, the patient was admitted for evaluation of splenomegaly, with the spleen palpable 15 to 16 cm below the costal margin. No adenopathy was identified. The hemoglobin level was 9.8 g/dl; the WBC count was 10,300/mm³ (80 percent neutrophils; 20 percent lymphocytes); and the platelet count was 646,000/mm³. Splenomegaly due to EMH associated with AMM was suspected, and a bone marrow biopsy confirmed the diagnosis of AMM with myelofibrosis.

In July 1989, the patient was admitted with severe dyspnea. Her chest x-ray film showed cardiomegaly and bilateral interstitial infiltrates. Arterial blood gas analysis with oxygen therapy at (5 L/min) revealed a PaO₂ of 70 mm Hg and PaCO₂ of 37 mm Hg. Transbronchial lung biopsy showed perivascular and peribronchiolar fibrosis and a heterogenous cellular infiltrate of myeloid and erythroid precursors and megakaryocytes (Fig 1). The findings were indicative of pulmonary involvement by AMM with associated interstitial fibrosis, and the patient’s interstitial lung disease was ascribed to AMM with EMH, rather than heart disease.

Therapy was started with steroids and diuretics, with slight transient subjective improvement of her dyspnea. Her lung status remained stable for 6 months. In February 1990, the patient was admitted with acute worsening of dyspnea. She died 12 days later of progressive respiratory failure.

Case 2

A 68-year-old white woman had been diagnosed with AMM by bone marrow biopsy in 1977, at the age of 56 years. She had been found to be anemic on a routine blood screen. Over the next 12 years, she was treated symptomatically with transfusions.

In January 1989, the patient complained of fatigue and dyspnea. In March 1989, she was evaluated for interstitial and pleural disease that had been noted on chest radiographs since 1981. Bilateral crackles were present on physical examination, and evidence of right ventricular failure was noted. Hepatosplenomegaly was found. The patient’s hemocrit value was 23.9 percent; the platelet count was 95,000/mm³, and the WBC count was 6,000/mm³. A chest x-ray film showed bilateral interstitial infiltrates, which were confirmed by a biopsy of the right lung. The patient was diagnosed with EMM and AMM, with splenomegaly and hepatomegaly.

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Figure 1. Chest x-ray film from July of 1989 shows bilateral interstitial infiltrates that are somewhat worse on right than on left (case 1).
6,500/mm³, with a normal differential cell count. Abnormal RBCs, including teardrop forms, were seen on the peripheral smear. Pulmonary function testing revealed a total lung capacity of 45 percent of predicted, a vital capacity of 32 percent of predicted, and severe hypoxemia (PaO₂ of 33 mm Hg on room air). Open lung and pleural biopsies were performed. The pleura was thickened by extensive fibrous tissue, within which occasional megakaryocytes and myeloid and erythroid precursors could be found. The lung parenchyma showed a patchy paucicellular fibrotic process, particularly around bronchioles in which EMH was identifiable as small clusters of myeloid and erythroid precursors and occasional megakaryocytes (Fig 2). The patient became progressively hypoxic and died at home in April 1990 (13 months after the biopsies.)

**DISCUSSION**

Agnogenic myeloid metaplasia is a myeloproliferative disorder thought to be caused by a clonal abnormality in pluripotential stem cells.\(^1,3\) The marrow fibrosis is not clonal and appears to be a secondary phenomenon.\(^1,3,4,6,7\)

The average age at diagnosis of AMM is 60 years, and there is a slight male predominance.\(^2,8,9\) Splenomegaly is the most common physical finding at presentation, seen in nearly 95 percent of patients; hepatomegaly is also frequent (65 percent).\(^2,3\) The peripheral blood of patients with AMM reveals anemia, classically with a leukoerythroblastosis and anisopoikilocytosis of RBCs.\(^2,3,5,8\)

Extramedullary hematopoiesis associated with AMM usually affects the liver and spleen as diffuse enlargement with EMH in the sinusoids. Less commonly, EMH presents as fibrous masses complicating long-standing cases of AMM.\(^4\) The masses are composed predominantly of fibrous tissue, with only scattered megakaryocytes and hematopoietic precursors; the masses are usually found in the spleen, liver, or lymph nodes and less frequently in the kidney and adrenal glands. The fibrous masses may attain considerable proportions, over 9 cm in diameter in a case

**Table 1—Agnogenic Myeloid Metaplasia With EMH in the Lung or Pleura**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Age, yr</th>
<th>Sex</th>
<th>Sites of EMH</th>
<th>Interstitial Pulmonary Disease Clinically</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lieberman et al</td>
<td>1965</td>
<td>54</td>
<td>F</td>
<td>Spleen; lungs; pleura; lymph nodes</td>
<td>No</td>
</tr>
<tr>
<td>Glew et al</td>
<td>1973</td>
<td>62</td>
<td>F</td>
<td>Spleen; kidney; gastrointestinal tract; lungs; pleura; liver; diaphragm; cervix; lymph nodes</td>
<td>No</td>
</tr>
<tr>
<td>Glew et al</td>
<td>1973</td>
<td>54</td>
<td>F</td>
<td>Liver; spleen; lymph nodes; lungs (alveolar walls); retroperitoneum; skin; breast; uterus; ovary; choroid</td>
<td>No</td>
</tr>
<tr>
<td>Glew et al</td>
<td>1973</td>
<td>60</td>
<td>F</td>
<td>Spleen; lungs</td>
<td>Yes</td>
</tr>
<tr>
<td>Glew et al</td>
<td>1973</td>
<td>52</td>
<td>M</td>
<td>Lungs; liver; kidneys; gastrointestinal tract; meninges; retroperitoneum; testis; pericardial fat, lymph nodes</td>
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</tr>
<tr>
<td>Hino and Fukui</td>
<td>1973</td>
<td>59</td>
<td>F</td>
<td>Spleen; liver; lungs; lymph nodes</td>
<td>Yes</td>
</tr>
<tr>
<td>Kataoka et al</td>
<td>1985</td>
<td>65</td>
<td>M</td>
<td>Spleen; liver; lungs; lymph nodes; kidney; adrenal gland</td>
<td>Yes</td>
</tr>
</tbody>
</table>
described by Beckman and Oehrle. The production of fibroblast growth factors in AMM is thought to stimulate the production of the fibrous tissue. Agnogenic myeloid metaplasia with EMH and fibrous tissue in the lung and pleura has only rarely been described; and in the two cases described, pulmonary and pleural fibrosis manifested as a diffuse interstitial process, ultimately fatal in both of our cases.

As shown in Table 1, pulmonary EMH in AMM is very uncommon, and we found only three other cases similar to ours. Lieberman et al. reported the findings in a 54-year-old woman with multiple bilateral pulmonary nodules (up to 1.5 cm) showing EMH. Glew et al. described four cases with EMH in the lung or pleura: a 62-year-old woman with EMH in the lung and pleura, a 54-year-old woman with EMH in the alveolar walls, a 60-year-old woman with marked interstitial fibrosis and nests of EMH in pulmonary vessels, and a 52-year-old man with repeated episodes of pulmonary infarction secondary to thromboemboli of hematopoietic tissues, as well as parenchymal masses of EMH. Hino and Fukui reported the findings in a 59-year-old woman with AMM and prominent interstitial pulmonary fibrosis with EMH. There was marked fibrosis and EMH in a perivascular distribution, particularly near the hilum. The pleura and pericardium were also affected. Kataoka et al. described a 65-year-old man with marked interstitial infiltrates on the chest x-ray film and fibrosis of alveolar walls and EMH histologically. The patient developed acute leukemia with a terminal course. Pitcock et al. mentioned two cases of AMM with EMH in the lungs, but details were not provided.

Glew et al. suggested two mechanisms to explain the occurrence of EMH in the lung: (1) occlusive vascular lesions in the lung could arise from emboli of EMH from other organs, and (2) in situ development of EMH in the lungs. We favor the latter mechanism, because our cases did not show intravascular emboli of EMH. The pulmonary involvement in our two cases probably arose from cells that proliferated in situ in the lung, leading secondarily to pulmonary fibrosis. Hematolymphoid infiltrates in the lung typically follow the lymphatic routes along bronchovascular bundles, in the septa, and in the pleura. In the two cases described, a similar distribution of EMH was seen. An embolic cause for EMH in the lung would not show such a distribution.

The pattern of involvement by EMH was helpful in the differential diagnosis in separating the fibrosis from other types of pulmonary fibrosis, such as idiopathic pulmonary fibrosis. Because of the marked fibrosis in our two cases, the cellular infiltrates of EMH could easily have been overlooked, but with knowledge of the clinical history of AMM and the distribution of lesions along lymphatic routes, the identification of the focal heterogenous cell infiltrates of EMH was facilitated. Transbronchial biopsies tend to sample peribronchial tissue, and thus, it is not surprising that a lesion that follows bronchovascular structures could be identified on a transbronchial biopsy, as in case 1.

The extensive fibrosis associated with pulmonary AMM has implications for therapy. The EMH itself is only a minor component in this tissue, and the vast majority of the lesion is irreversible fibrosis.

Agnogenic myeloid metaplasia is a chronic disorder, and death usually results from medical complications or the development of acute leukemia. Of 55 fatal cases of AMM studied by Bouroncle and Doun, the average length of survival from the diagnosis of AMM to death was 2 years 3 months; a median survival of 3.5 to 5 years is now seen, and survival as long as 16 years is known. Our case 2 had a 12-year course from the time of initial diagnosis of AMM to the time of pulmonary death. Once pulmonary involvement was confirmed, the time to death was only 23 months in case 1 and 13 months in case 2, although the pulmonary disease had been present for some time, at least 2.5 years in case 1 and 8 years in case 2. Among patients with AMM in general, infection is the most frequent cause of death, but acute leukemia, cerebrovascular accidents, hemorrhage, and cardiovascular disease are also common. Death due to pulmonary involvement is very unusual.

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