Pulmonary Lymphangioleiomyomatosis Associated with Pulmonary Parenchymal, Hilar, and Mediastinal Noncaseating Granulomas*

Jeffrey P. Huml, M.D.; Marilyn W. Borkgren, R.N., M.S.; L. Bruce Henley, M.D.; and Patrick J. Fahey, M.D., F.C.C.P.

A young nonsmoking woman presented with severe dyspnea, exercise desaturation, and chest discomfort. Pathologic and histochemical findings revealed pulmonary lymphangioleiomyomatosis (LAM) as the primary abnormality. In addition, there were multiple noncaseating granulomas with special stains and cultures negative for organisms. This highly unusual combination of pathologic findings might suggest the presence of coexistent sarcoidosis in our patient with LAM.

\[ \text{LAM} = \text{lymphangioleiomyomatosis} \]

We report a case of pulmonary lymphangioleiomyomatosis (LAM) confirmed by open lung biopsy specimen with associated noncaseating granulomas in the pulmonary parenchyma, hilum, and mediastinum. To our knowledge, this combination of pathologic findings has not been previously reported. In view of negative fungal stains and cultures, the granulomatous process appeared consistent with sarcoidosis. The initial chest roentgenogram, pulmonary function study, and presenting clinical picture contained features shared by both LAM and sarcoidosis. However, there were no additional distinctive clinical or laboratory data suggestive of active sarcoidosis. The exact etiology and clinical significance of numerous noncaseating granulomas in our patient with LAM remains unclear.

CASE REPORT

A 35-year-old nonsmoking woman, gravida 2, para 2, presented with resting chest discomfort and severe dyspnea on exertion of two months' duration. Walking one half block induced breathlessness and oxygen desaturation from an initial \( \text{SaO}_2 \) of 93 percent at rest to 83 percent at end exercise. Vital signs were normal, and the initial physical examination did not disclose lymphadenopathy, cutaneous abnormalities, or cardiovascular abnormalities. Breath sounds were diminished bilaterally; however, adventitious lung sounds were absent. The patient had no known allergies and no significant medical or occupational history.

The initial chest roentgenogram demonstrated normal-appearing lung volumes with a fine, subtle diffuse interstitial infiltrate. In addition, there was bilateral hilar fullness suggesting the possibility of mediastinal or hilar adenopathy. On computed tomography of the chest (Fig 1), there was diffuse interstitial disease with numerous cystic air spaces, and stretching and attenuation of small pulmonary vessels. The pulmonary function tests revealed airflow obstruction and hyperinflation. Forced vital capacity (FVC) was 2.36 L (62 percent) of predicted, and the FEV, was 1.30 L (43 percent) of predicted, with an FEV/FVC ratio of 55 percent. Total lung capacity was 94 percent of predicted, and the residual volume was 133 percent of predicted. Diffusion capacity was markedly impaired at 9.5 ml/min Hg (42 percent of predicted). Hematologic and biochemical laboratory values were normal, including \( \alpha_1 \)-antitrypsin and angiotensin-converting enzyme levels.

For definitive diagnosis, open lung biopsy was performed and confirmed our suspicion of LAM. Pathologic evaluation (Fig 2) disclosed random proliferation of smooth muscle fibers in the interstitium with dilated air spaces likely secondary to air trapping. Immunophenotyping was positive for the presence of estrogen and progesterone receptors, the latter being more prominent. In addition to the LAM, scattered throughout the pulmonary parenchyma were noncaseating granulomas (Fig 3). The hilar lymph node was almost completely replaced by granulomatous inflammation. Fungal stains and cultures were negative.

While undergoing therapy with medroxyprogesterone, the patient developed acute tension pneumothorax out of hospital with subsequent cardiopulmonary arrest and death. Pertinent autopsy findings include the following: scattered bilateral noncaseating granulomas in pulmonary parenchyma; hilar and mediastinal granulomatous adenopathy; lymphangioma of the right lobe of the liver; and uterine leiomyoma.

DISCUSSION

LAM is a rare, progressive disease afflicting women primarily of child-bearing age. The abdomen, thorax, and

![FIGURE 1. Computed tomographic scan showing diffuse cystic changes characteristic of LAM.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21637/)

![FIGURE 2. Lymphangioleiomyomatosis. Tuft-like proliferation of smooth muscle cells in walls of pulmonary lymphatics (hematoxylin-eosin, original magnification x 100).](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21637/)
Figure 3. Noncaseating microgranuloma in pulmonary septum (hematoxylin-eosin, original magnification ×100).

lungs may be involved singly or in combination in this disease characterized histologically by proliferation of smooth muscle along pulmonary lymphatics. In pulmonary LAM, diffuse hyperplasia of atypical smooth muscle obstructs bronchioles, lymphatics, and venules. Clinical consequences include dyspnea, chylothorax, hemoptysis, and recurrent pneumothorax.

The first 57 reported cases of pulmonary LAM were reviewed by Corrin et al in 1975. Later, Carrington et al thoroughly discussed physiologic, pathologic, and radiologic correlations of this distinctive and debilitating disease. More recent reports indicate increased recognition of pulmonary LAM, as well as further investigation into diagnosis, pathophysiology, and treatment options. The etiology remains unknown, but hormonal influences are suspected.

The patient's initial presentation included several nonspecific subjective and objective pulmonary findings. Dyspnea is the most common initial symptom in pulmonary LAM as it was in our patient, but it occurs in a wide array of other lung diseases, including sarcoidosis. Chest pain is also reported in these conditions. The nonspecific interstitial pattern on the initial chest roentgenogram is consistent with LAM, but it could also reflect roentgenographic findings of sarcoidosis. Physiologic evidence of airflow obstruction is characteristic on pulmonary function tests in LAM, and it may also be observed in sarcoidosis. Finally, both conditions usually present during young adulthood. LAM occurs almost exclusively in women of child-bearing age.

Despite these similarities, the principal pathologic and histochemical findings on lung tissue samples confirmed LAM as the primary abnormality in our patient. The appearance of multiple, scattered noncaseating granulomas raised the possibility of concomitant sarcoidosis. While exact causes of both diseases remain unknown, theories of pathogenesis fail to suggest any link or expected association between sarcoidosis and LAM. Noncaseating granulomas occur in a variety of other lung diseases, including infection and malignancy, as well as in association with foreign body or autoimmune reactions. All of these are ruled out in this patient. Berylliosis remains yet another possible cause of noncaseating granulomas in the lung. However, given the lack of occupational or environmental exposure, coupled with the absence of beryllium obtained in biologic tissues sampled, this diagnosis can virtually be eliminated. It remains possible that the unique combination of pathologic findings described in this report represents coexistent sarcoidosis in our patient with pulmonary LAM.

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REFERENCES

Exercise-Related Atrioventricular Block

Influence of Myocardial Ischemia

Neil L. Coplan, M.D.; Monty C. Morales, M.D.; Raul Romanello, M.D.; James W. Wilentz, M.D.; and Jeffrey W. Moses, M.D.

A 62-year-old woman was noted to have complete heart block immediately following an exercise stress test. Coronary arteriography subsequently revealed a significant lesion in the right coronary artery, which was successfully dilated. Thallium-exercise testing following angioplasty showed no evidence of inducible ischemia and no arrhythmia was seen, supporting the idea that exercise-related heart block may occur secondary to myocardial ischemia.

Exercise-related atrioventricular (AV) block is an uncommon arrhythmia that has recently been attributed to

Exercise-related AV Block (Coplan et al)

Figure 1. Electrocardiogram one minute following peak exercise, revealing acute ST elevation and 2:1 atrioventricular block with a narrow QRS complex.