Pulmonary Hyalinizing Granuloma
Electron Microscopic and Immunologic Studies

John G. Guccion, M.D.*, Prashant K. Rohatgi, M.D.,† and Nirmal Saini, M.D.*

We present a case of pulmonary hyalinizing granuloma (PHG). On light microscopy, the pulmonary nodular lesions consisted of extracellular, eosinophilic hyaline lamellae. Histochemical stains of the hyaline lamellae for amyloid were focally positive and the diagnosis of amyloidosis was seriously considered; however, on electron microscopic examination, the hyaline lamellae consisted of electron-dense, compact, amorphous material quite unlike fibrillar amyloid. Although circulating immune complexes containing IgA were detected in our patient, immunoperoxidase stains did not reveal immunoglobulins in the hyaline lamellae. This case illustrates the value of electron microscopy in differentiating PHG from amyloidosis and supports the hypothesis that PHG represents an exaggerated immune response.

Pulmonary hyalinizing granuloma (PHG) was described by Engleman et al1 in 1977. It is characterized by multiple, bilateral pulmonary nodules consisting of extracellular, eosinophilic hyaline lamellae. Recently, several additional cases without ultrastructural studies have been reported.2-4 The etiology and pathogenesis of PHG remain obscure. An exaggerated chronic immune response possibly to a number of etiologic agents has been postulated.5-6 We present a case of PHG with electron microscopic and immunologic studies.

CASE REPORT

A 58-year-old Negro man was admitted to the Veterans Administration Medical Center, Washington, D.C., in 1982 for removal of Singer’s nodes from his vocal cords. Chest roentgenograms (Fig 1) revealed diffuse, bilateral pulmonary nodules measuring 2-4 mm in diameter. Retrospectively, the infiltrates had been present and progressive for four years. Radiographic evidence of pulmonary tuberculosis was not present. The patient had recently noted increased, non-debilitatory shortness of breath, morning cough, and white sputum production. He had a 20-pack-year history of cigarette smoking. He had systemic hypertension for five years controlled with methyldopa and hydrochlorothiazide. He had a long-standing history of post-traumatic degenerative arthritis of the left knee which ultimately required total knee replacement after a variety of medical and surgical treatments. He had allergies to the penicillins and sulindac (Clinoril).

Physical examination, routine blood studies, urinalysis, and routine blood chemistries were normal. The sedimentation rate and serum C-reactive protein lead were normal. Rheumatoid factor, cryoglobulins, and fluorescent antinuclear antibody were not present. Serum protein electrophoresis was normal with total protein of 5.9 g/dl and albumin of 3.7 g/dl. Quantitation of serum immunoglobulins by nephelometry showed IgG of 646 mg/dl (normal 650 to 1650 mg/dl), IgM, 43.7 mg/dl (normal 35 to 275 mg/dl); and IgA, 34.9 mg/dl (normal 50 to 400 mg/dl). Serum levels of C3 and C4 were normal. Pulmonary function testing revealed mild restrictive disease with normal single breath diffusing capacity for carbon monoxide. Arterial blood gases at room air were pH 7.44, Pco2 41 mm Hg, and Po2 77 mm Hg. Gallium-67 citrate scan was normal with no evidence of abnormal accumulation of the tracer within the lungs. The patient underwent left anterior thoracotomy and an open lung biopsy was performed.

Materials and Methods

For light microscopy, a portion of the lung biopsy was fixed in 10 percent formalin, processed routinely, and embedded in paraffin. Sections were stained with hematoxylin and eosin, Congo red, crystal violet, Ziehl-Neelsen acid-fast, and Gomori methenamine silver stains.

For electron microscopy, a minced portion of the lung biopsy was fixed in phosphate-buffered 2.5 percent glutaraldehyde, post-fixed with 1 percent osmium tetroxide, dehydrated, and embedded in EMBed-812 (Electron Microscope Sciences, Fort Washington, PA). Ultrathin sections were stained with lead citrate and uranyl acetate and examined with an AEI 810 electron microscope.

Immunohistochemical stains for IgA, IgG, and IgM (Immunol, Carpenteria, CA) were performed on paraffin-embedded tissue sections using the indirect peroxidase-antiperoxidase method of Sternberger.5

Results

Gross Examination

The cut surface of the biopsied lung contained numerous, oval, well-circumscribed, firm, white nodules measuring up to 1 cm in greatest dimension.

Light Microscopy

The pulmonary nodules consisted of extracellular, largely acellular, eosinophilic hyaline lamellae which were arranged haphazardly and also concentrically about blood vessels (Fig 2). Macrophages and multinucleated giant cells often in association with lymphocytes and plasma cells were present.

Figure 1. Chest radiograph showing a bilateral pulmonary nodular infiltrate.
Pulmonary Hyalinizing Granuloma (Guccione, Rohatgi, Saini)

In 1977, Engleman et al. described a rare and unusual pulmonary disease called pulmonary hyalinizing granuloma (PHG). The disease affected adults (mean age of 45 years) who were asymptomatic or presented with mild symptoms of cough, hemoptysis, fatigue, fever, and pleuritic chest pain. Chest radiographs typically revealed multiple, bilateral, well-circumscribed pulmonary nodules. Histologically, the pulmonary nodules consisted of extracellular, eosinophilic hyaline lamellae. Although multinucleated histiocytic giant cells, plasma cells, and lymphocytes were typically present within the nodular lesions, well-formed granulomas were not present and special stains for acid-fast bacilli and fungi were negative.

In their original description of PHG, Engleman et al. reported that the pulmonary nodules frequently showed the histochemical staining characteristics of amyloid and postulated that ultrastructural examination would be helpful in distinguishing PHG from nodular pulmonary amyloidosis. To our knowledge, ultrastructural features of the extracellular hyaline lamellae in PHG have not been described. In our case, the Congo red stain with polarization and crystal violet stain were focally positive for amyloid and the diagnosis of amyloidosis was seriously considered. Electron microscopic study of the extracellular hyaline lamellae did not confirm this diagnosis, however. Rather, the hyaline lamellae consisted of electron-dense, compact, homogeneous, amorphous material quite unlike the loosely and haphazardly arranged fibrillar amyloid. This case illustrates the value of

**DISCUSSION**

FIGURE 2. Microphotograph of a pulmonary nodule showing the characteristic, haphazardly arranged hyaline lamellae (original magnification, ×150).

FIGURE 3. Electron micrograph of a hyaline lamella showing electron-dense, compact, amorphous material devoid of amyloid fibrils (original magnification, ×20,000).

Electron Microscopy

The hyaline lamellae consisted of electron-dense, compact, homogeneous, amorphous material (Fig 3). Swollen collagen fibrils were scattered throughout the lamellae. Amyloid fibrils were not present.

Immunologic Studies

The serum analysis for presence of immune complexes showed one precipitin band with polyethylene glycol precipitation assay, 9 percent by Clq binding (normal <6 percent), and 106.3 μg/ml by Raji cell assay (normal <65 μg/ml). Analysis of immune complexes present showed the antibody to be IgG1 IgA and the antigen to be a protein. The immune complexes had alternate pathway complement binding capacity, a positive charge on isoelectric focusing, ability to aggregate platelets, and Fe binding ability, but were not found to cryoprecipitate. Immunoperoxidase stains failed to reveal the presence of IgA, IgG, and IgM in the pulmonary nodules. Granulomas were absent and special stains for acid-fast bacilli and fungi were negative. Birefringent sericites and other particles consistent with pneumocociosis were not seen.

The hyaline lamellae appeared focally metachromatic with the crystal violet stain. They also stained focally positive with the Congo red stain and showed slight, focal apple-green birefringence with polarized light. Necrotizing vasculitis, tissue necrosis, calcification, and mature cartilage and bone were not present in the pulmonary nodules.

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**Figure 2.** Microphotograph of a pulmonary nodule showing the characteristic, haphazardly arranged hyaline lamellae (original magnification, ×150). Within and bordering the nodules. Perivascular accumulations of lymphocytes and plasma cells were also present within the nodules. Granulomas were absent and special stains for acid-fast bacilli and fungi were negative. Birefringent sericites and other particles consistent with pneumocociosis were not seen.

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electron microscopy in differentiating PHG from amyloidosis.

Katzenstein and Askin prefer to consider those cases which histologically resemble PHG, but stain positive for amyloid to be nodular pulmonary amyloidosis. We believe that the light and electron microscopic features of PHG are sufficiently distinctive to warrant separation from nodular pulmonary amyloidosis, despite the fact that the histochimical stains for amyloid are focally positive in some cases of PHG.

The etiology and pathogenesis of PHG are unknown. Engleman et al. postulated that PHG represents an exaggerated immune response, possibly due to chronic granulomatous infections such as tuberculosis or histoplasmosis. This exaggerated immune response may result in deposition of immunoglobulins, fragments of immunoglobulins, or immune complexes in the lung. In support of this hypothesis, Schlosnagle et al. demonstrated autoantibodies (antinuclear antibody, rheumatoid factor, and positive antitabolin tests), as well as circulating immune complexes in two patients with PHG. Autoantibodies were not present in our patient. Circulating immune complexes containing IgA were demonstrated in our patient. The perivascular arrangement of the hyaline lamellae and their electron-dense, compact, homogeneous, amorphous ultrastructural appearance also give support to the hypothesis that the hyaline lamellae consist mainly of immune complexes. Immunoperoxidase stains failed to reveal the presence of immunoglobulins in the hyaline lamellae in our patient. It may be that the antigenic determinants of the immunoglobulin were masked when the immune complexes were deposited in the lung.

The clinical course of PHG in most patients is benign, although there may be gradual enlargement of the pulmonary nodules over several to many years. Three patients with PHG developed sclerosing mediastinitis (which closely resembles PHG histologically) and one patient developed sclerosing mediastinitis and then sclerosing retroperitonitis. During the one year following the diagnosis of PHG, our patient has remained relatively well, his pulmonary nodules have enlarged, and there is no evidence of sclerosing mediastinitis.

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REFERENCES

Successful Treatment of Fetal Supraventricular Tachycardia with Maternal Digoxin Therapy*

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In a fetus with supraventricular tachycardia (SVT) and cardiac failure, normal sinus rhythm (NSR) was restored with maternal digoxin therapy at 26 weeks’ gestation. The diagnosis of cardiac failure was based on ultrasound evidence of ascites and scalp edema. Cardiac failure was attributed to the persistent SVT. The infant remained in NSR and was delivered at 36 weeks’ gestation because of persistent ascites. Intracardiac anatomy was normal. This case confirms the usefulness of prenatal ultrasound examinations in the diagnosis of fetal SVT and cardiac failure and illustrates the effectiveness and safety of transplacental digoxin therapy in the management of fetal SVT.

Sustained fetal SVT is now a well-recognized cause of cardiac failure in utero and of nonimmune hydrops fetalis. In a series of 13 cases of nonimmune hydrops fetalis, three fetuses had SVT as a sole cause. Transplacental pharmacologic treatment of fetal SVT has been attempted without success with digoxin and with digoxin and propranolol. Successful treatment of fetal SVT has been reported with digoxin, digoxin and verapamil, and propranolol.

We describe an infant with intrauterine cardiac failure due to SVT in whom normal sinus rhythm was restored by maternal oral digitalis therapy. The infant was delivered by cesarean section at 36 weeks’ gestation because of ascites. The heart was structurally normal at birth, and normal sinus rhythm has been maintained with therapy digoxin at 11 months of age.

CASE REPORT

In a 24-year-old, primigravida, a fetal heart rate of 190 to 220 beats per minute (bpm) was first observed at 20 weeks’ gestation. At 26 weeks, when the patient was first referred for evaluation, the initial fetal heart rate was 228 bpm, and sonographic evidence of scalp edema, polyhydramnios, and ascites was observed. Within 60 hours of initiation of oral digoxin therapy (0.125 mg/day), the fetal heart rate had normalized. Weekly tests of fetal well-being, ie, nonstress tests, were performed beginning at 28 weeks’ gestation. All of these studies were reactive. In addition, on three occasions, contraction stress tests were performed, and results were negative. Assessment of fetal growth by sonography revealed a normal interval growth between 26 weeks and 29 weeks, when the biparietal diameter was 7.3 cm. Subsequent interval growth at 31 and 34 weeks was normal, with a biparietal diameter of 8.8 cm at 34 weeks. Immediately preceding delivery, the ultrasound evaluation showed a gestational age of 36 to 37 weeks with appropriate interval growth. In addition, there was evidence of decreased fetal scalp edema and normal cardiac anatomy, but persistence of ascites. This was thought to be an ominous sign, which prompted the delivery by cesarean section. Amniocentesis for fetal lung maturity was not obtained. Results of examinations

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