Gaucher's Disease of the Lung Causing Severe Pulmonary Hypertension with Associated Acute Recurrent Pericarditis

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SUMMARY
The clinical and pathological features of a 30-year-old man with Gaucher's disease are described. He had severe pulmonary hypertension resulting from obstruction of pulmonary capillaries by Gaucher cells. Acute recurrent pericarditis of unknown etiology terminally led to hemopericardium and cardiac tamponade.

Additional Indexing Words:
Cerebral involvement Cor pulmonale
Elastic fibers Bronchial constriction

GAUCHER'S DISEASE is a familial disorder characterized by accumulation in reticuloendothelial cells of glucocerebrosides, compounds containing sphingosine, fatty acid, and glucose in equimolar amounts. The storage cells, called Gaucher cells, have a characteristic appearance, and their increasing numbers in the liver, spleen, lymph nodes, and bone marrow are responsible for most of the clinical manifestations of the disorder. Although nearly all patients have hepatosplenomegaly, Gaucher cells in marrow aspirates, and an abnormally high concentration of non-tartrate-inhibitable serum acid phosphatase, at least two forms of Gaucher's disease exist clinically. They probably represent expression of different mutations. In the infantile or acute form, the children have a characteristic stereotyped appearance (strabismus, opisthotonus, retracted lips and often spastic and flexed extremities), and death generally occurs before 2 years of age. The adult or chronic form comprises the majority of cases of Gaucher's disease. It may be detected at any age, usually because of hepatosplenomegaly. Neurological signs rarely if ever occur, osseous lesions are often pronounced, and hematological abnormalities associated with hypersplenism, skin pigmentation, and pingueculae usually develop. It is relatively common among Ashkenazi Jews, in contrast to the infantile form, which is very rarely seen in a Jewish child. Death in the infantile form is usually related to the cerebral involvement and cachexia, and, in the adult form, to anemia or superimposed infection. The present report describes an adult patient with Gaucher's disease followed for 25 years, who developed severe pulmonary hypertension, recurrent acute pericarditis, and finally hemorrhagic cardiac tamponade. Pulmonary hypertension, which has not been documented previously in a patient with Gaucher's disease, resulted from the plugging of alveolar capillaries by Gaucher cells.

Report of Patient
A.K. (02-62-62), a 30-year-old lawyer, died at the National Heart Institute on January 3, 1962. He had been followed from age 5 to age 16 years (1936-1947) by Dr. Siegfried J. Thannhauser, who described this patient's course during this interval in detail in his monograph on the lipidoses (patient 48). This patient was the younger of two male children of parents who were both Ashkenazi Jews. A single bone marrow aspiration in the mother, who came from Palestine, showed no abnormality. The father, who came from Lithuania, died at age 32 of an
acute myocardial infarct. The patient's oldest sibling is normal. Between the ages of 9 and 12 months, the patient was taken to physicians with a question of retarded growth and abdominal enlargement. At age 4 years hepatospleno-megaly was established and Gaucher cells were discovered in the sternal marrow. By age 7 years the spleen had become so large (7 pounds; patient weighed 35 pounds) that abdominal discomfort and dyspnea resulted, and it was therefore removed. For the next 20 years he led an outwardly normal life. He was an excellent student, and was admitted to the bar. Throughout his school life, however, he had repeated episodes of bone pain and fractures, some spontaneous and others associated with minor

Figure 1

Electrocardiograms. Upper. Recorded 29 months before death. Lower. Recorded 1 hour before death at the time of massive hemopericardium.
Figure 2

Figure 3
Exterior of heart (left) and opened right ventricle and pulmonary trunk (right). The right ventricle (R.V.) is markedly hypertrophied; the left ventricle (L.V.) is small. Atheromata are present in the pulmonary trunk (P.T.). R.A. = right atrium.

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trauma, eventually leading to permanent deformities of the left hip and leg.

The patient was first seen by one of us (D.S.F.) in August 1959. His only complaints during the previous 5 years were easy fatigability and rare bone pain. Five days earlier he had fainted while lifting a heavy table. On examination, the liver was enormous, extending to the iliac crest. The skin had a sallow yellow color with duskeness over the tibias, and each eye had small pingueculae. The pulmonic second sound was markedly accentuated, but there was no precordial murmur or rub. The blood pressure was 120/80 mm Hg. The axillary, cervical, supraclavicular and inguinal lymph nodes were not enlarged. No abnormalities were detected on neurological examination.

The electrocardiogram (fig. 1) showed right axis deviation, right atrial and right ventricular hypertrophy, and the chest roentgenogram (fig. 2) showed a large right ventricle and pulmonary trunk. The blood hematocrit was 46%, white blood cell count, 18,000 mm$^3$ with 48 neutrophils, 49 lymphocytes and 3% monocytes; serum acid phosphatase, 3.08 Bessey-Lowry units (upper limit of normal = 0.6), 0.15 being tartrate-inhibitable. Bromsulphalein retention in 45 minutes, 11%; total serum bilirubin, 0.7 mg per 100 ml; total cholesterol, 135 mg per 100 ml with free cholesterol 46; phospholipids 176; and triglycerides, 192 mg per 100 ml (upper limit of normal for triglycerides = 150 mg per 100 ml).

Fifteen months later (November 1960) he had the first episode of acute lower substernal and precordial pain, which worsened with inspiration and movement and lasted 18 hours. Several days later the pain reappeared and a loud precordial friction rub was heard as well as a ventricular gallop. Six similar episodes of anterior chest pain occurred during the next 13 months. A pericardial friction rub was audible on each occasion, sometimes accompanied by a pleural friction rub. Atrial flutter occurred during four of these episodes. He was afebrile and had normal erythrocyte sedimentation rates during each episode. On one occasion the antistreptolysin-O titer was 500 units. His last acute illness began 7 days before death with the onset of a severe, nonproductive, hacking cough. He was brought to the hospital 2 hours before death, and at this time was severely dyspneic, cyanotic, and had tachycardia, distended neck veins, pulsus paradoxus (20 mm Hg), and a white blood cell count of 31,000 mm$^3$. Chest roentgenogram showed an enormous cardiac silhouette, a massive increase in size as compared to his previous x-rays (fig. 2). Pericardiocentesis yielded 150 ml of blood. Shortly thereafter asystole occurred.

At autopsy (A62-4), 600 ml of blood was found in the pericardial sac; the pericardial surfaces were “shaggy” and contained numerous acute and chronic inflammatory cells and vascular channels, but no Gaucher cells. The left pleural space contained 600 ml of serosanguineous fluid, but the pleural surfaces were normal. The heart weighed 500 g; the right ventricle and atrium were markedly hypertrophied (fig. 3) and contained focal fibrous scars. The cardiac valves were normal and coronary arteries were within the range of normal for this age. The lungs together weighed 850 g, and showed evidence of pulmonary edema. The walls of both small and large pulmonary arteries were thickened and contained atheromata. The histological sections of lung disclosed the presence of numerous Gaucher cells plugging the lumina of alveolar capillaries throughout the lung (fig. 4). In addition, Gaucher cells were seen occasionally in the alveolar spaces. The pulmonary arterioles, muscular arteries, and elastic arteries showed changes characteristic of severe (grade V/VI) hypertensive pulmonary vascular disease (classification of Heath and Edwards$^3$) (fig. 5). Plexiform lesions were present throughout all lobes of both lungs (fig. 5). The liver, bone marrow, and lymph nodes contained massive numbers of Gaucher cells. The liver weighed 8.1 kg, and its architecture was disrupted by infiltrates of Gaucher cells, hemopoietic elements, and fibrous tissue. Analysis of the liver revealed 77 mg of chloroform-soluble glycolipids per gm of dry weight (normal <10 mg per g). The

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**Figure 4**

Pulmonary alveolar capillaries occluded by Gaucher cells (arrows). Periodic acid-Schiff stain; $\times$ 780.

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Figure 5

Muscular pulmonary arteries, each demonstrating changes indicative of severe pulmonary hypertension. Left. The muscular artery and its branching arteriole shows extensive intimal proliferation. Numerous large thin-walled dilated vessels surround the obstructed arteriole. Right. Classical plexiform lesion arising from a muscular artery, which has hypertrophied media and intimal fibrous proliferation at the site of origin of the plexiform lesion. Elastic-van Gieson stains; × 150 (left), × 195 (right).

Abdominal lymph nodes were enlarged (up to 3 cm in diameter) and were virtually replaced by Gaucher cells. The thoracic lymph nodes were not enlarged.

Figure 6

Thin-layer chromatography of the chloroform-soluble glycolipids prepared from lung according to the technique of Mårtensson et al. Extracts representing equal amounts of wet lung tissue are chromatographed in lanes 2 (control) and 3 (patient A.K.). Chromatographed in lane 1 is a mixture of galactocerebrosides obtained from beef spinal cord. The arrow designates a dense band of material in the lung of A.K. having an Rf comparable to glucocerebrosides. Note the absence of significant amounts of this material in the control extract. Chromatographs were developed in one dimension in chloroform/methanol/H₂O (65/25/4) and the spots identified by spraying with an acid solution of anisaldehyde and heating 20 minutes for 120.
The glycolipids from a sample of frozen lung from patient A. K. and from a control were extracted and partially purified according to the technique of Martensson and associates.4 The control patient (I. D., A56-217) was a 12-year-old boy who had idiopathic left ventricular hypertrophy. His pulmonary arterial pressure was 16/9 mm Hg, and his left ventricular pressure was 130/10 mm Hg. The cerebroside contents of the lungs were compared qualitatively by thin-layer chromatography (fig. 6). The lung from A. K. contained massive amounts of material having the chromatographic behavior of glucocerebrosides relative to the control.

Comments
In 1933 Merklen and associates reported the finding of Gaucher cells in the sputum of a 51-year-old man with this disease.5 In 1937 Myers described Gaucher cells in the alveolar walls and sacs and in the hilar and mediastinal lymph nodes of an 8-year-old girl who died of Gaucher’s disease.6 In addition to pleurisy this child had signs of bronchial constriction, which were attributed to compression on these structures by the enlarged hilar lymph nodes. In 1948 Groen and Garrer described an “especially accentuated” pulmonic second sound, diffuse crepitant pulmonary rales, bilateral pleural effusions, cardiomegaly, and dilatation of the pulmonary trunk in a 48-year-old woman who died of Gaucher’s disease after repeated attacks of severe dyspnea with extreme cyanosis.7 An autopsy was not performed but these authors speculated that the clinical picture of cor pulmonale and pulmonary hypertension resulted from “obstruction in the smaller circulation . . . due to an accumulation of Gaucher cells in the lungs.” In 1950 Kaiser described a miliary pattern on chest roentgenogram in a patient with Gaucher’s disease.8 Subsequently, this miliary-type appearance had been described in other patients with this disease.9-12 The 3-year-old child (case VII) reported by Levin died from “massive hemoptysis” and necropsy disclosed “numerous Gaucher cells in the lungs.”9 The patient reported by Jackson and Simon was also a 3-year-old girl who died of severe respiratory distress.12 The lungs of this child on chest roentgenogram also demonstrated a miliary pattern, and at autopsy “enormous numbers of Gaucher cells” were present in the alveolar septa and spaces.

Although Gaucher cells have been described in alveolar septa, their location within the alveolar capillaries has not been previously described. In the present patient, obstruction to these capillaries by Gaucher cells appears to have been the cause of his severe pulmonary hypertension. The configuration of the elastic fibers in the pulmonary trunk were of the adult type, indicating that the pulmonary hypertension was acquired and not present at birth.13 There is no mention of the cardiovascular or pulmonary systems in the description of this patient during childhood by Thannhauser.2 When first seen at this clinic 29 months before his death, he demonstrated signs of severe pulmonary hypertension.

The cause of the acute recurrent pericarditis was never determined. Although a wide variety of inflammatory cells were present, no Gaucher cells were identified in the pericardium. Since this patient’s pericardium was exceedingly vascular and since he experienced uncontrollable coughing during his last several days, the terminal hemopericardium and cardiac tamponade may have resulted from rupture of one or several of the pericardial vessels during the coughing episodes. Hemopericardium with cardiac tamponade has been described previously in a patient with Gaucher’s disease.14 This 59-year-old woman, however, also had an adenocarcinoma, probably primary in the lung, and malignant cells were found in the aspirated pericardial and pleural fluids. Zlotnick and Groen in 1961 described massive pericardial calcification in a 46-year-old woman who died of Gaucher’s disease.15 The cause of the pericardial calcification was not determined although “hemorrhagic diathesis . . . secondary to unrecognized hemorrhage into the pericardial cavity, with organization and deposition of calcium” was suggested. No Gaucher cells were described in her pericardium at necropsy, but interestingly these cells were found in her lungs.
This patient had an accentuated pulmonary second sound, but electrocardiogram did not indicate ventricular hypertrophy.

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References


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