beats, and there was also a change in the mean velocity of posterior wall motion (Table 1). The other echocardiographic features were that the mitral valve was essentially normal, with alternation of the opening amplitude D-E and the E-F slope, with the largest values occurring after the strong beats. The left atrium was moderately enlarged, and the aorta and aortic valve were structurally normal. The prejection period and left ventricular ejection time alternated from beat to beat; total electromechanical systole (Q-A_{p}) was constant.

On standing, pulsus alternans increased markedly; the systolic pressure varied from 102 to 78 mm Hg (Table 1). The left ventricle decreased in size, and there was marked beat-to-beat alternation in the ventricular end-diastolic dimension and also in the percentage and velocity of shortening of the left ventricular posterior radius. The heart rate increased to 109 beats per minute. The prejection period and left ventricular ejection time changed markedly from beat to beat, as did total electromechanical systole.

Squatting was associated with a decrease in pulsus alternans to 8 mm Hg (systolic pressure difference), the same as that in the supine position. The size of the ventricular cavity returned to that of the lying position, although a small difference was now measurable in end-diastolic dimension. The beat-to-beat change in percentage of shortening and in the velocity of ventricular ejection was similar to that observed with the patient in the supine position.

**D I S C U S S I O N**

The echocardiographic findings in our patient are similar to those described in the small number of patients with mechanical alternans of the left ventricle who have been studied. There was alternation of the amplitude of systolic shortening of the left ventricle, the extent and velocity of left ventricular posterior wall motion, the mitral D-E amplitude and mitral E-F slope (steeper after a strong beat), and the duration of the left ventricular prejection period and ejection time.

The increase in pulsus alternans which occurred on standing was dramatic. Ventricular volume decreased, and there was an increase in contractility on the strong beats and a decrease on the weak beats. The increased contractility may have been the consequence of the increase in sympathetic tone which occurs on standing after the fall in venous return, stroke output, and arterial blood pressure. The great beat-to-beat differences in end-diastolic dimension and measurements of ventricular contractility were noteworthy and suggest that Starling's mechanism was important. It is also noteworthy that the total electromechanical systole changed markedly from beat to beat while the patient was standing. This is not the usual finding in ventricular alternans, where total electromechanical systole is surprisingly constant, despite the changes in prejection period and left ventricular ejection time; the changes in total electromechanical systole in our patient may have been related to the unusual severity of pulsus alternans at that time.

**REFERENCES**


**Idiopathic Pulmonary Hemosiderosis***

A Report of Familial Occurrence

Robert L. Breckenridge, Jr., M.D., and Jeffrey S. Ross, M.D.

The findings in two siblings with morphologic evidence of idiopathic pulmonary hemosiderosis are reported, along with historical evidence for the disease occurring in their paternal grandmother. This is the first detailed report of the occurrence of this condition in siblings who were not twins. Possible etiologic factors of idiopathic pulmonary hemosiderosis are briefly discussed.

Idiopathic pulmonary hemosiderosis is a rare disease, predominantly occurring in children and young adults, with a markedly variable clinical course characterized by repeated episodes of multifocal pulmonary hemorrhages. The condition occurs in the absence of primary cardiac disease, glomerulonephritis, or other disorders associated with intrapulmonary bleeding and is defined clinically by the triad of hemoptysis, diffuse...

*From the Department of Pathology, University of Massachusetts Medical School at the Berkshire Medical Center, Pittsfield.
Reprint requests: Dr. Ross, Department of Pathology, Berkshire Medical Center, Pittsfield, Massachusetts 01201.
parenchymal infiltrates on the chest roentgenogram, and iron-deficiency anemia. Despite numerous experimental, morphologic, immunologic, and ultrastructural studies, the etiology and pathogenesis of idiopathic pulmonary hemosiderosis are not known. Other than a single report of the condition in probable monozygotic twins, no occurrence in siblings has been described. Recently, idiopathic pulmonary hemosiderosis has been described as occurring in a mother and her adult son. We report a detailed study of a family with morphologic evidence of idiopathic pulmonary hemosiderosis in two sisters and clinical and historical evidence of the disease in their paternal grandmother.

CASE REPORTS

CASE 1

A three-year-old white girl was admitted to the Berkshire Medical Center, Pittsfield, Mass, in April 1973 for evaluation of anemia. There were no significant findings in the medical history. The patient had developed a cough and rhinorrhea three days prior to admission. Physical examination disclosed a grade 2/6 systolic murmur heard along the left sternal border. Significant laboratory values included the following: hematocrit reading, 14.7 percent; hemoglobin level, 4.5 gm/100 ml; red blood cell count, 2,160,000/cu mm; normal leukocyte count and differential cell count; serum level of iron, 25 mg/100 ml; and iron saturation, 5 percent. No chest roentgenogram was taken. The patient was treated with oral administration of ferrous sulfate.

Five months after discharge, the patient was rehospitalized with dyspnea, tachypnea, cough, rhinorrhea, fever, and hematemesis. A chest roentgenogram taken at that time showed bilateral pulmonary infiltrates (Fig 1). Significant physical findings included a respiratory rate of 44/min and rales heard in the superior pulmonary fields anteriorly. The hematocrit reading was 27.2 percent, the hemoglobin level was 8.3 gm/100 ml, the red blood cell count was 3,450,000/cu mm, and the leukocyte count was 10,800/cu mm, with 74 percent neutrophils, 24 percent lymphocytes, and 2 percent monocytes. The reticulocyte count was 2.6 percent. The results of studies of coagulation were normal. Despite therapy, the patient suffered a massive pulmonary hemorrhage, from which she died 72 hours later.

At autopsy, the trachea and main-stem bronchi were filled with large quantities of fresh blood. The lungs were red-brown, with a solid consistency. On histologic sections, the blood clot extended into the peripheral bronchi, and the parenchyma had an alternating pattern of brown induration and recent hemorrhage. Microscopically, typical features of idiopathic pulmonary hemosiderosis that were seen included recent intra-alveolar hemorrhage, intrabronchial accumulation of blood, large numbers of intra-alveolar hemosiderin-laden macrophages, and mild diffuse interstitial fibrosis. All other organ systems, including the heart and kidneys, were normal.

CASE 2

The five-year-old sister of patient 1 was admitted at the time of the final admission of her sister; the five-year-old girl had a fever and cough of two days' duration and a chest roentgenogram that showed an extensive bilateral pulmonary infiltration. The findings from physical examination were unremarkable. The serum level of hemoglobin was 7.1 gm/100 ml, and the reticulocyte count was 5.0 percent. Occult blood was detected in the stool on two occasions. There was no growth in the cultures of blood, sputum, and nasopharyngeal material. A small amount of blood was coughed up on the first day of hospitalization. The infiltrate on the chest roentgenogram cleared, and the patient was discharged on the eighth day of hospitalization after treatment with prednisone and clindamycin.

After one month, the patient was rehospitalized for malaise, cough, anemia, and reappearance of the characteristic bilateral infiltrates on the chest roentgenogram. The serum level of hemoglobin was 9.7 gm/100 ml. Viral cultures were negative. Samples of serum obtained during the acute and convalescent phases of the illness were negative when tested against a battery of viral antigens. A tracheal aspirate demonstrated large numbers of hemosiderin-laden macrophages, and a diagnosis of idiopathic pulmonary hemosiderosis was made.

Two isolated episodes of microscopic hematuria were evaluated by a closed renal biopsy, which showed morphologically unremarkable glomeruli on which nonspecific granular accumulations of IgM and the C3 portion of complement were noted in the mesangium. No other immunoglobulins were demonstrated, and there has been no recurrence of the hematuria. Despite several additional episodes of hemoptysis requiring transfusions of blood, the patient has most recently done well while receiving therapy with prednisone, azathioprine, and an orally administered iron supplement. She is currently in a clinical remission of one year's duration.

PATERNAL GRANDMOTHER

The 66-year-old paternal grandmother of the two sisters was hospitalized in Europe at the age of three years for coughing up blood. The records of that hospitalization were destroyed, and although the patient is clinically and radiographically asymptomatic, the possibility of idiopathic pulmonary hemosiderosis with long-term spontaneous remission must be considered.

DISCUSSION

The etiology of idiopathic pulmonary hemosiderosis remains obscure, largely because of the inconsistency of the ultrastructural data and the lack of immunologic evidence. Early theories of defects in the elastic fibers,
abnormal acid mucopolysaccharides, neoplastic alveolar capillaries, and impaired vasomotor control have not been substantiated. An allergic basis for the condition has been proposed, largely as a result of the demonstration of precipitating antibodies to cow’s milk in patients with idiopathic pulmonary hemosiderosis; however, the milk precipitins have not been present consistently, and they were absent in case 2 of this report. Furthermore, a diverse group of pulmonary inflammatory conditions, none of which is associated with hemorrhage, has been linked with the presence of milk precipitins. Moreover, eosinophilia of the peripheral blood is not typical of idiopathic pulmonary hemosiderosis. Autoimmunity is an attractive hypothesis, but the normal serum levels of complement, the negative tests for serum antinuclear and antipulmonary antibodies, and the failure to find localized immunoglobulin or complement in pulmonary tissue by immunofluorescent techniques rule strongly against this. Although serum levels of immunoglobulin are usually normal, nonspecific increases in the serum level of IgA have been reported in children with idiopathic pulmonary hemosiderosis.

Viral infection has been suggested as the underlying cause of idiopathic pulmonary hemosiderosis and increased titers of cold agglutinin antibodies have been reported. Although the clinical course of cough, dyspnea, fever, and tachycardia is typical of pulmonary infectious disease, no viral agents have been isolated from patients with idiopathic pulmonary hemosiderosis. It is interesting that in the present study the older girl (case 2) became symptomatic at a time when her sister (case 1) was suffering from a severe, fatal relapse. In addition, the girls’ mother also experienced cough and fever at this time, but her chest roentgenogram was normal, and she has remained asymptomatic for the past four years.

A primary disorder of alveolar epithelial cells and a structural defect of pulmonary capillaries are two currently favored theories. Arguing against the former is the lack of specificity of the changes in the structure of epithelial cells, and arguing against the latter is the disparity of the electron-microscopic findings. Furthermore, the finding of free red blood cells in the interstitium, which led some workers to suggest a widespread vascular abnormality, has not been confirmed by others who report only nonspecific fibrosis in this region of the lung. The results of studies of the clotting system in patients with idiopathic pulmonary hemosiderosis have been essentially normal.

Although environmental factors cannot be entirely excluded, it is now possible to suggest that an inherited variant of idiopathic pulmonary hemosiderosis exists and that a careful review of the history of the family is an important part of the study of patients suspected of having this condition. This report of two cases of idiopathic pulmonary hemosiderosis is the first documentation of the occurrence of the condition in siblings who were not twins. The possibility that the disease was also present in their paternal grandmother (as outlined in Fig 2) is intriguing. A familial tendency for idiopathic pulmonary hemosiderosis was first reported in probable monozygotic twins, in a boy born of a consanguineous marriage, and in 13 of 26 cases from a central area in Greece where intermarriage is common. More recently, idiopathic pulmonary hemosiderosis was described in a mother and her son. Of note is the fact that both of these individuals contracted the disease as adults; the mother was 62 years old, and her son was 26 years old. It is also interesting to observe that the mother was not symptomatic until approximately one year after her son had died, while the two sisters in our study were symptomatic concurrently; however, the overwhelming majority of cases of idiopathic pulmonary hemosiderosis have occurred in the absence of a familial background, and the role of inheritance has not been featured heavily in the most recent discussions of the etiology of this disease.

ACKNOWLEDGMENTS: Alexander T. Parkinson, M.D., made the diagnosis at autopsy in case 1. Mr. Robert Tunnicliffe, FIMLS, provided technical and photographic assistance, and Thomas Hayden, M.D., supplied clinical and historical data.

REFERENCES
9 Livingstone CS, Boczarow B: Idiopathic pulmonary haze-
Prolonged Survival Following the Superior Vena Cava Syndrome*

Bernard Percario, M.D.** and Stephen Gray, M.D.†

Bronchogenic carcinoma complicated by the syndrome of superior vena caval obstruction has been considered uniformly fatal. A patient with this syndrome due to small cell undifferentiated carcinoma of the lung has survived for 13 years following radiation therapy without evidence of recurrence. It is recommended that radical irradiation should remain as part of the management of patients with this disease confined to the chest until better chemotherapeutic regimens are developed.

The obstruction of the superior vena cava by compression or infiltration of a malignancy is one of the few emergencies encountered in clinical oncology.1 Although surgical or chemotherapeutic decompression has been proposed for some clinical situations, mediastinal irradiation is more commonly employed as primary therapy for this life-threatening syndrome.2 Patients with the superior vena cava syndrome secondary to Hodgkin disease or malignant lymphoma may be cured by radical irradiation, but few, if any, patients with the syndrome due to bronchogenic carcinoma have had prolonged survival following treatment.3 Because of the commonly held opinion that the syndrome is uniformly fatal for the patient with lung cancer, we report a case of 13 years' disease-free survival following treatment for the superior vena cava syndrome.

*From the Departments of Radiation Therapy and Pathology, Walter Reed Army Medical Center, Washington, DC.**Chief, Radiation Therapy Service.†Staff Pathologist.

Reprint requests: Dr. Percario, Department of Therapeutic Radiology, Yale-New Haven Hospital, New Haven 06510

CASE REPORT

A 47-year-old woman presented to Walter Reed Army Medical Center in May 1964 with a three-month history of cough, dysphagia for solid foods, “fullness” in the chest and neck, and a 4-kg (9-pound) weight loss. Physical examination on admission revealed multiple 1-cm lymph nodes in the right cervical and supraclavicular regions, facial plethora and edema, neck vein distension, and prominence of the venous pattern on the chest and upper extremities. The clinical diagnosis of superior vena caval obstruction was confirmed by an elevated upper extremity venous pressure of 324 mm of saline compared to a lower extremity pressure of 117 mm of saline solution. A large superior mediastinal mass was present on chest x-ray film which was noted to compress the esophagus on a barium swallow. Biopsy of a right scalene lymph node was interpreted as “undifferentiated carcinoma consistent with bronchogenic origin.” The patient was treated with 6,000 rads of mediastinal and neck irradiation over a seven-week period. The superior vena caval syndrome resolved with irradiation, and the mediastinal mass decreased in size. In December 1964, a 3-cm mass was noted in the lateral aspect of the right supraclavicular fossa just outside of the original radiotherapy portal. This also resolved following an additional 6,000 rads. The patient has been symptomatic since that time, and when last seen in December 1977, had no abnormalities noted by physical examination, complete blood count, or chemistry profile. A chest x-ray film taken 13 years following treatment revealed paratracheal fibrosis secondary to irradiation but no evidence of tumor (Fig 1).

PATHOLOGY

Hematoxylin and eosin, periodic acid-Schiff, mucicarmine, and reticulin stained sections, prepared from the original paraffin-embedded lymph node removed in 1964, were examined microscopically. Cohesive sheets of tumor cells filled the peripheral sinuses of the node and extended through the paracortical region into the medullary cords. The malignant cells varied in size but were approximately three times larger than the adjacent, displaced lymphocytes on the average (Fig 2). Mitoses were numerous and frequently atypical. The nuclei were

---

*From the Departments of Radiation Therapy and Pathology, Walter Reed Army Medical Center, Washington, DC.**Chief, Radiation Therapy Service.†Staff Pathologist.

Reprint requests: Dr. Percario, Department of Therapeutic Radiology, Yale-New Haven Hospital, New Haven 06510

Figure 1. Posteroanterior view 13 years following treatment showing paratracheal fibrosis but no evidence of tumor.