Fatal Hemoptysis in Ehlers-Danlos Syndrome : Old Malady With a New Curse

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Fatal Hemoptysis in Ehlers-Danlos Syndrome*

Old Malady With a New Curse

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We describe the case of a 27-year-old man with Ehlers-Danlos syndrome, type IV. The patient had recurrent and eventually fatal pulmonary hemorrhage. Type IV Ehlers-Danlos syndrome is a rare disorder of type III collagen synthesis. It is characterized by an unusual facies, thin, translucent skin with venous vascular pattern, and hypermobility of the small joints. The cause of death is usually due to rupture of a viscus or a major arterial hemorrhage and, in women, rupture of the gravid uterus. Fatal lung hemorrhage in Ehlers-Danlos syndrome, to our knowledge, has not been previously described.

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Key words: diffuse alveolar hemorrhage; Ehlers-Danlos syndrome; lung hemorrhage; pulmonary capillaritis

The Ehlers-Danlos syndrome is a group of inherited disorders of collagen synthesis. With genetic and biochemical studies, at least nine, possibly more, types are now recognized.[1,2] Historically, the first case of this disorder was described in 1682 by Job Van Meekeren[3] in a 23-year-old patient with "extraordinary dilatibility of the skin." In 1901, Ehlers[3] of Denmark pointed out the association of loose joints and subcutaneous hemorrhages. In 1908, Danlos[3] contributed to the clinical description of tumors that may occur at subcutaneous sites.

The Ehlers-Danlos syndrome has three major clinical manifestations: hyperextensibility of the skin, hypermobility of the joints, and bleeding tendency. The mode of inheritance can be autosomal dominant, recessive, or X-linked recessive. Clinically, the most aggressive type is type IV Ehlers-Danlos syndrome. Its inheritance is autosomal dominant. The disorder is caused by mutation within the Col 3A1 gene resulting in a disorder of type III collagen.[1,4-7] The syndrome is characterized by abnormal fragility of blood vessels and hollow viscus that often leads to premature death by spontaneous rupture of a major blood vessel or viscera. We describe the case of a 27-year-old man with Ehlers-Danlos type IV who died of recurrent pulmonary hemorrhage, a complication to our knowledge not previously described.

Case Report

The patient was a 27-year-old man whose symptoms progressed over 6 years. He presented with the spontaneous onset of hemiparesis. Despite an extensive workup that included a computed tomographic scan of the head, cerebral angiography, and Holter monitoring, the cause remained unclear. Twelve and 16 months later he experienced two episodes of temporary paralysis with concurrent pulmonary hemorrhage. After the second bleeding episode, the patient underwent a thoracotomy with left lower lobectomy for massive focal hemoptysis. During the surgical procedure, the lung parenchyma was noted to be remarkably friable. The patient's postoperative course was uneventful. Subsequently, the patient underwent genetic consultation and biochemical study of a skin biopsy specimen that was consistent with a heterozygous-type mutation in the Col 3A1 gene that encodes the chains of type III procollagen (see Results). Hematologic studies initiated during the hospitalization for the lobectomy showed a bleeding time twice normal (12½ min with reference range 1 to 6½ min), the remainder of the coagulation studies (prothrombin time, partial thromboplastin time, fibrinogen, procoagulant factor VIII activity, immunoreactive factor VIII antigen, Ristocetin Von Willebrand cofactor, factor IX assay, factor X assay, factor XII assay, and platelet count) were normal to increased. The increased studies were the procoagulant factor VIII activity, immunoreactive factor VIII antigen, and platelet count considered to be acute-phase reactants. Results of platelet aggregation studies were within normal limits.

After a 6-year clinical course with multiple episodes of concurrent hemoptysis and paralysis, the patient was found unresponsive at home and could not be resuscitated.

Results

Genetic Studies

Dermal fibroblasts were cultured from a skin punch biopsy specimen that had been performed with informed consent. The synthesis and structure of type I and type III procollagens were studied as previously described.[9] Briefly, cells were plated at high density (250,000 per 35-mm culture dish) and allowed to attach and spread overnight. They were preincubated with ascorbic acid for 2 h (50 μg/mL) and then incubated for 16 h with [^{3}H]-proline in the presence of ascorbic acid but without serum. The cell layer and secreted medium proteins were harvested separately and examined by sodium dodecyl sulfate polyacrylamide gel electrophoresis. In addition, the proteins in both samples were cleaved with pepsin to remove the nontriple helical domains from both ends of the central triple helix and the protease-resistant collagen molecules were examined by gel electrophoresis followed by autoradiography.

The cells from the patient secreted less type III procollagen than control cells and the proα1(III) chains migrated as a diffuse blur, rather than a distinct band. The cells contained a band that migrated above the proα1(I) chain of type I procollagen and more slowly than the normal proα1(III) chain. Following digestion with protease, the amount of type III collagen retained within the cells was slightly higher than that in the control cells.

These findings are consistent with a heterozygous-type mutation in the Col 3A1 gene that encodes the chains of type III procollagen. The mutation has not yet been sequenced.

Autopsy

At autopsy, the patient was a thin, tall, white man with narrow facies and long digits. Excessive friability of the fibroconnective tissue and of the aorta was noted. There was massive hemorrhage of the right lung and left upper

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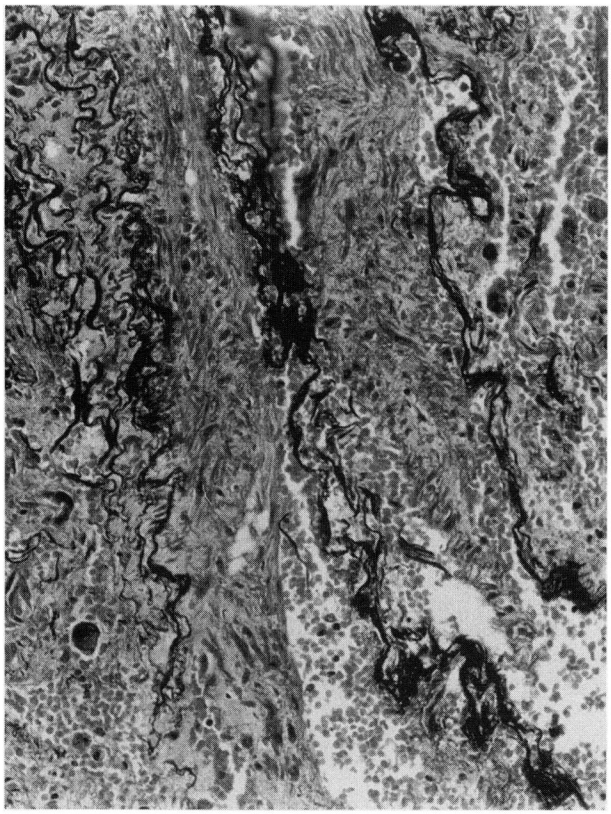

FIGURE 1. Vascular wall disruption in an area of lung hemorrhage (elastic stain, original magnification×200).

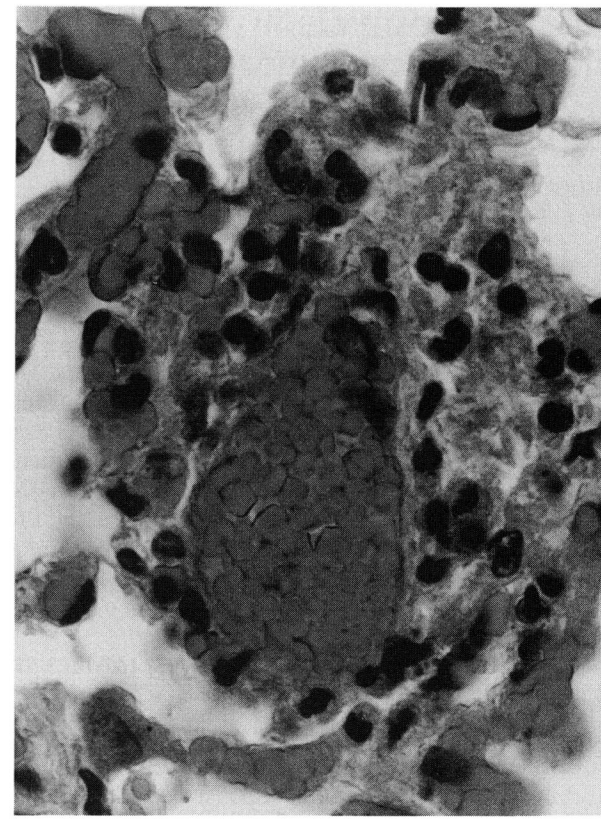

FIGURE 2. Pulmonary capillaritis in an area of lung hemorrhage (hematoxylin-eosin, original magnification×600).

lobe with tracheal aspiration. Pertinent microscopic findings were limited to the lung that showed marked acute diffuse alveolar hemorrhage (Fig 1), pulmonary capillaritis (Fig 2), hemosiderosis, and focal osseous metaplasia. Additional findings included a limited dissection of the thoracic aorta that was probably clinically insignificant. No arterial aneurysms were found. No systemic vasculitis was seen. The central nervous system was unremarkable.

DISCUSSION

Type IV Ehlers-Danlos syndrome, known as the vascular or ecchymotic type, was first recognized as a distinct entity by Barabas in 1967.[3,7] This rare form of Ehlers-Danlos syndrome has a prevalence rate ranging from 1 in 100,000 to 1 in 1,000,000.[7] It is transmitted as an autosomal dominant hereditary disorder.[1,8] Affected individuals have thin, translucent skin in which the venous vascular pattern is visible.[1,3,7] They have marked bruising and mild joint hypermobility that may be limited to the small joints of the hands and feet.[1,3,7] There is an "Ehlers-Danlos syndrome type IV facies" that is characterized by a "stare, very thin nose, and tight-skinned appearance."[1,7]

The major clinical complications of Ehlers-Danlos syndrome type IV include visceral and arterial rupture as well as rupture of the gravid uterus.[1,7] The location of arterial hemorrhage determines the presenting symptoms: stroke, intra-abdominal or intrathoracic bleeding, or compartmental syndrome.[7] Life expectancy is shortened, with few afflicted individuals living past the third or fourth decade.[1,2,7]

The biochemical basis of type IV Ehlers-Danlos was first recognized in 1975. Although no treatment is currently available to correct the defective synthesis of normal type III collagen, the condition, when suspected, should be confirmed by biochemical means. The key reasons for diagnosis are genetic counseling and the institution of prompt surgical intervention when the clinical complications occur. Ehlers-Danlos syndrome type IV results from abnormalities in the structure, synthesis, or secretion of type III procollagen. The disease is linked to the Col 3A1 gene encoding this protein. Within the gene, point mutations, small deletions or insertions that interrupt the triple helix, could all result in the same biochemical phenotype.[7] The diagnosis can be confirmed by measuring the amount of type III collagen in skin or by examining the biosynthesis of type III procollagen by cultured dermal fibroblasts followed by gel electrophoresis.[9]

Our case is distinctive because of the unusual presentation with repeated pulmonary hemorrhage. The differential diagnosis of pulmonary hemorrhage can include infection, neoplasm, cardiovascular disorders, trauma, autoimmune disorders, hematologic, and collagen vascular diseases.[10] Clinical, histologic, and laboratory studies excluded many of these disorders. The pivotal finding of connective tissue fragility was discovered by the surgeon during the patient's lobectomy.

In summary, this case emphasizes the importance of

considering both common and rare developmental vascular abnormalities in young adults who present with unusual spontaneous and recurrent lung hemorrhage.

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High-Output Congestive Heart Failure Following Transjugular Intrahepatic Portal-Systemic Shunting*

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A hyperdynamic circulatory state with elevated cardiac output, decreased peripheral vascular resistance, and sodium retention occurs in patients with portal cirrhosis. Surgical portal-systemic shunts and transjugular intrahepatic portal-systemic shunts (TIPS) have been shown to worsen the high-output state in these patients. However, clinical evidence of high-output congestive heart failure has been reported only rarely to complicate cirrhosis. We describe a patient who developed high-output congestive heart failure with markedly elevated filling pressures after TIPS and had complete resolution of heart failure after liver transplantation.

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TIPS=transjugular intrahepatic portal-systemic shunting

Key words: high-output state; hyperdynamic circulation; liver transplantation; portal hypertension; transjugular intrahepatic portal-systemic shunts

A hyperdynamic circulatory state with elevated cardiac output and decreased peripheral vascular resistance has been described in patients with portal cirrhosis.[1-3] Sodium and water retention may accompany and contribute to the high-output state.[4,5] Surgical portal-systemic anastomoses created to treat complications of portal hypertension may worsen the hyperdynamic circulation in cirrhosis.[6-8] Despite this hyperkinetic state, high-output congestive heart failure is rarely reported to complicate cirrhosis.[2]

Transjugular intrahepatic portal-systemic shunts (TIPS), by creating an artificial fistula between branches of the hepatic vein and intrahepatic portal veins, has been developed as a less invasive method of portal-systemic shunting.[9-11] Patients previously considered at highest risk for surgical shunts may now be considered candidates for TIPS in treating complications of esophageal varices and ascites.[9] Complications from TIPS include worsening of encephalopathy, shunt closure, precipitation of liver failure, infection, and bleeding.

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