

Life-Threatening Pulmonary Hemorrhage With Pulmonary Arteriovenous Malformations and Hereditary Hemorrhagic Telangiectasia*

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The occurrence of significant pulmonary hemorrhage associated with pulmonary arteriovenous malformations (PAVMs) and hereditary hemorrhagic telangiectasia (HHT) and the incidence of PAVMs in family members of patients with PAVMs and HHT are poorly defined. We reviewed our experience in 143 patients with PAVMs and HHT. Eleven (8 percent) of the 143 patients with HHT and PAVMs had a history of either massive hemoptysis or of hemothorax which required hospitalization. One patient died directly related to the pulmonary hemorrhage. There were four men and seven women. Three of the seven women experienced pulmonary hemorrhage during pregnancy. Seven of the 11 families participated in screening for PAVMs. Thirty-six (80 percent) of the 45 screened family members were found to have HHT. Thirteen (36 percent) of the 36 family members with HHT were proven to have PAVMs

by pulmonary angiography. Pulmonary hemorrhage due to spontaneous rupture of the PAVM is a potentially life-threatening complication that should be treated aggressively with transcatheter embolotherapy. It occurs more frequently than previously recognized in patients with PAVMs and HHT. In addition, because of the increased incidence of PAVMs in family members of patients with HHT and PAVM, screening of family members with HHT is recommended especially in women of childbearing age. (Chest 1994; 106:1387-90)

HHT=hereditary hemorrhagic telangiectasia; PAVM=pulmonary arteriovenous malformation

Key words: embolotherapy; hemoptysis; hemothorax; pulmonary angiography; pulmonary arteriovenous malformations

Hereditary hemorrhagic telangiectasia (HHT) is an uncommon autosomal dominant disorder associated with progressive development of vascular malformations.¹ The most common manifestations of this disorder are cutaneous telangiectasias and recurrent epistaxis. Other manifestations of HHT include arteriovenous malformations of the lungs, brain, and gastrointestinal tract.¹⁻³

Pulmonary arteriovenous malformations (PAVM) are associated with significant morbidity and mortality.²⁻⁴ Anatomically, PAVMs consist of a direct communication between a pulmonary artery and vein resulting in a low resistance right-to-left shunt. Patients with multiple PAVMs experience fatigue and dyspnea and are often severely hypoxic. Paradoxical emboli may occur leading to transient ischemic attacks and strokes in 30 to 40 percent of patients.^{2,4} An additional 5 to 9 percent of patients are at risk for cerebral abscess.

Less frequently, the dilated thin walls of the aneurysmal center of a PAVM may spontaneously rupture, leading to life-threatening pulmonary hemorrhage.^{5,7} Depending on the site of rupture, massive hemoptysis or hemothorax results. The purpose of this report is to review the incidence of significant pulmonary hemorrhage among 143 patients with HHT and PAVM referred to us for embolotherapy. Because of the concern about pulmonary hemorrhage in other family members and because the familial incidence of PAVMs in family members of patients with PAVMs and HHT is poorly defined, we performed screening of family members for PAVM.

METHODS

From a database of 143 patients with HHT referred for transcatheter embolotherapy of PAVM between May 1978 and December 1992, 11 patients with massive hemoptysis or with hemothorax were identified. A subset of the first 76 patients has been previously reported.⁴ Detailed review of the patients' prior admissions to the Johns Hopkins or Yale-New Haven Hospitals was undertaken. In all instances, their admissions were for transcatheter therapy of multiple PAVM. Family history and hospital records were reviewed on all 11 patients. Nine of 11 patients were directly examined and interviewed. In the remaining two patients, post mortem reports were available for review.

Only instances of massive hemoptysis or hemothorax requiring hospitalization were included. Any instances of "pseudohemoptysis" defined as expectoration of blood associated with epistaxis

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were excluded. Hemothorax was proven by thoracentesis in all instances. Using the criteria of Plauchu et al¹ HHT was confirmed if two of the three following conditions were met: monthly epistaxis, eight or more; a primary relative with HHT; and a multiple dermal telangiectasias.

Families of the 11 patients and the physicians caring for them were advised to screen other family members for the presence of PAVM using arterial blood gases and chest radiography.⁸ If either the chest radiographs or the arterial blood gases were abnormal, patients were referred to us and underwent diagnostic pulmonary angiography.

RESULTS

In a review of our experience of 159 patients referred for transcatheter embolotherapy of PAVMs in the past 15 years, 16 (10 percent) had isolated PAVM and 143 (90 percent) had PAVM associated with HHT. Only the results of the 143 patients with PAVM and HHT are reported. Of the 143 patients, 50 (35 percent) were men and 93 (65 percent) were women. Their ages range from 5 to 76 years (mean: 40 years).

Eleven patients (8 percent) with HHT and PAVM, four men and seven women, experienced massive pulmonary hemorrhage. In 9 of the 11 patients, pulmonary hemorrhage was the first symptom of their PAVM. Five patients, three men and two women, ranging in age from 15 to 59, had massive hemoptysis resulting in death in one, lobectomy in two, and emergency cesarean section in a fourth patient. A fifth patient initially stabilized without specific therapy for hemoptysis but died several months later because of complications of an unrelated illness. Five patients, one man and four women, ranging in age from 19 to 62, experienced spontaneous hemothorax leading to tube thoracostomy or multiple thoracenteses for drainage (Fig 1). The 11th patient, a woman, experienced both massive hemoptysis and hemothorax at age 24 and 33 years, respectively. Four hemothoraces occurred on the right side and two occurred on the left. Three (27 percent) of our 11 patients experienced a second episode of massive pulmonary hemorrhage resulting in either death or rehospitalization. These hemorrhages occurred 7 days, 2 years, and 9 years after the initial episode. The patient who had recurrent massive hemoptysis 7 days after the first episode died at home from cardiopulmonary arrest. The second patient with recurrent hemothorax at 2 years was managed by chest tube, and the third patient's recurrent hemoptysis, 9 years after the first, stopped spontaneously in the hospital.

Three of the seven women patients (43 percent) experienced hemoptysis (one) or hemothorax (two) during pregnancy. The mean length of the time of hemorrhage was 32.3 weeks (range 19 to 39 weeks). Massive hemoptysis in one patients necessitated emergency cesarean section and subsequent embolotherapy. A second patient experienced spontaneous

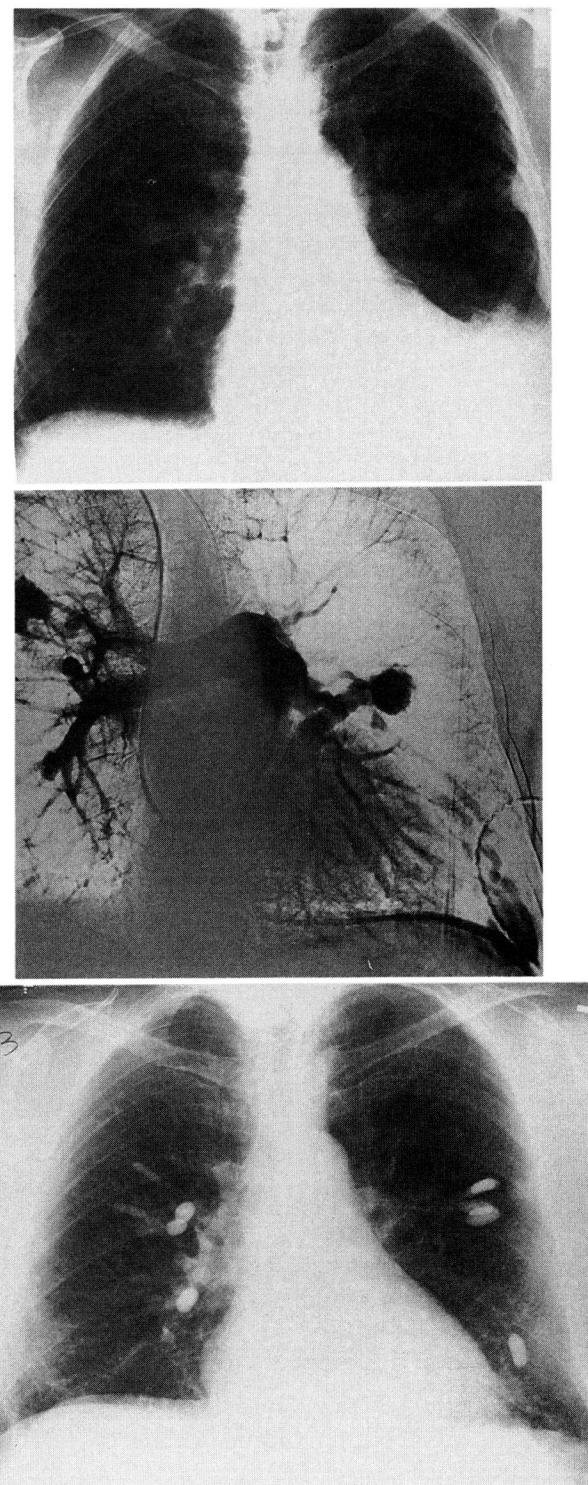


FIGURE 1. The chest radiograph shows a left hemothorax (*upper*) in a 62-year-old man who developed symptoms and required hospitalization and chest tube drainage. Central pulmonary angiogram (*center*) obtained 2 months later in our hospital shows large PAVMs in the right and left lung. After two short admissions for embolotherapy in 1983, the final discharge radiograph was obtained (*lower*). Multiple detachable balloons are shown occluding large and small PAVMs in both lungs. This patient has been followed up for 10 years, continues to do well, and follow-up pulmonary angiography in 1993 showed continued occlusion of all PAVMs.

hemothorax at 19 weeks' gestation and was treated with bed rest and tube thoracostomy without further complication. A third patient experienced a massive hemothorax requiring multiple thoracenteses at the time of spontaneous delivery. All pregnancies were delivered successfully. Two of the three patients had prior pregnancies without complication; none became pregnant subsequently.

The interval between the initial treatment of the 11 patients with pulmonary hemorrhage and subsequent referral for embolotherapy varied between 2 months and 33 years (mean: 10.2 years). All patients had a PAVM on the side of hemorrhage. In most cases, it was not possible to determine which PAVM was responsible for the hemorrhage. No evidence of a neoplastic or infectious cause for pulmonary hemorrhage was discovered either immediately or in follow-up.

Family Demographics

After identification of the 11 patients who experienced massive pulmonary hemorrhage, family screening was advised. Seven of 11 families participated. Full compliance was not achieved and a definite selection bias toward family members with epistaxis was present. A total of 45 family members were screened with arterial blood gases, chest radiographs, and histories. Thirty-six of the 45 family members screened (80 percent) were found to have HHT. Thirteen of the 36 patients with HHT (36 percent) had PAVM proven by pulmonary angiography.

DISCUSSION

Although sporadic case reports of massive hemoptysis and hemothorax as a complication of HHT and PAVM exist, this report is the first description of the occurrence of massive pulmonary hemorrhage in a large series of patients with PAVM and HHT.^{5,6} We have identified 11 patients who experienced either massive hemoptysis or hemothorax due to spontaneous rupture of a PAVM. Nine of these patients were ultimately treated by transcatheter embolization of multiple PAVM, whereas two patients died before referral for embolotherapy. In an earlier article, we described 13 and 9 percent of patients with PAVM developing hemoptysis and hemothorax, respectively.⁴ In our current study, we used hospitalization for the hemorrhage as the criterion for inclusion. Thus, stricter criteria were used in this investigation since some of the patients in the earlier report were not hospitalized nor were they examined by a physician at the time of the original hemorrhage. The 11 patients reported here represent 8 percent of a highly select group of 143 patients with PAVMs and HHT all of whom were hospitalized for pulmonary hemorrhage. Our experience suggests that patients with

HHT and PAVMs are at a significantly higher risk for massive pulmonary hemorrhage due to spontaneous rupture of a PAVM than previously recognized.

Physicians caring for patients with HHT and PAVM who develop massive pulmonary hemorrhage must realize that this is a potentially life-threatening complication that requires prompt intervention. Our series included a 15-year-old boy who died suddenly after experiencing a recurrent episode of massive hemoptysis. Seven days after being hospitalized for massive hemoptysis and while awaiting elective embolotherapy, he was discharged home where he experienced a fatal recurrence. A large, ruptured PAVM was discovered at autopsy. In addition to our experience, several cases of massive hemoptysis and hemothorax leading to death in patients with PAVM have been reported.^{2,3,5-7} Therefore, this complication should be considered a life-threatening emergency. Prompt intervention is necessary to minimize morbidity and prevent potentially fatal recurrence. Embolotherapy using detachable balloons or stainless-steel coils appears to be an effective therapy for treatment of PAVM.^{4,9,10} From our previous work, we have determined that occluding all arteries, supplying a PAVM, which are 3 mm or larger in diameter, appear to be associated with the best results.⁴ This approach preserves lung function and minimizes morbidity associated with thoracotomy and resection. Once the diagnosis of massive pulmonary hemorrhage because of spontaneous rupture of a PAVM is established, patients should probably undergo pulmonary angiography and transcatheter occlusion of the PAVM. Furthermore, based on our experience with a patient who experienced both massive hemoptysis and hemothorax on separate occasions and because insufficient data exist to allow prediction of which PAVM is most likely to rupture based on size or location, we believe that occlusion of other existing PAVM should be considered. This approach may have the additional benefit of reducing the risk of paradoxical emboli and other complications associated with unoccluded PAVM.

Massive pulmonary hemorrhage is one of several complications of unoccluded PAVM. Early detection and treatment of asymptomatic PAVM can probably prevent many of these complications.^{4,10} The need for screening patients with HHT for PAVM is emphasized by the observation that life-threatening pulmonary hemorrhage was the first and presenting symptom of PAVM in 9 of our 11 patients. Our screening program detected PAVM in 36 percent of patients with HHT from seven families. Despite a strong selection bias for patients with epistaxis, these data suggest that family members of patients with PAVM and HHT may be at a significantly higher risk for PAVM than previously reported. Although con-

tinued investigation of the expressivity of PAVM in HHT families is desirable, we believe our results justify screening of families of affected individuals with PAVM.

There appears to be a relationship between pregnancy and spontaneous rupture of PAVM. Three of our seven female patients (43 percent) experienced life-threatening pulmonary hemorrhage during pregnancy, including two cases of hemothorax and one case of massive hemoptysis. Including our cases, 8 of the 28 cases (29 percent) of hemothorax associated with PAVM reported in the literature have occurred during pregnancy.⁷ To our knowledge, massive hemoptysis complicating a pregnancy has not been previously reported. In all cases, pulmonary hemorrhage occurred beyond 19 weeks' gestation, suggesting that the risk of spontaneous rupture increases as blood volume and cardiac output increase. We believe that all women with HHT should be screened for PAVM before becoming pregnant.

Because of the retrospective nature of this study and the multi-institutional referral basis, outcome analysis and determination of risk factors for which PAVM is likely to hemorrhage are not possible. Despite this, several conclusions and recommendations can be made. Rupture of a PAVM is a potentially life-threatening complication, which occurs more frequently than previously recognized in patients with PAVM and HHT. From our experience and review of the literature, it appears that patients with PAVM are particularly predisposed to pulmonary hemorrhage during the latter half of pregnancy. When hemorrhage occurs, it should be treated aggressively by transcatheter embolotherapy. Since the

incidence of PAVM appears increased in the family members with HHT of the patient who hemorrhaged, we recommend family screening especially in women of childbearing age.

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