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# Long-term Outcome in a Patient With Pulmonary Hypertension and Hereditary Hemorrhagic Telangiectasia*

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**Hereditary hemorrhagic telangiectasia (HHT) may be associated with pulmonary hypertension (PH). In the context that little attention has been given to long-term follow-up of such individuals, we report a patient with PH associated with HHT with special attention to clinical features and long-term response to therapy. To our knowledge, this case represents only the second with a 10-year follow-up reported and demonstrates that aggressive therapy can lead to long-term improvement in clinical parameters and survival.** ***(CHEST 2007; 131:984–987)***

**Key words:** genetic; hereditary hemorrhagic telangiectasia; pulmonary hypertension; pulmonary vascular disease; shunt

**Abbreviations:** AVM = arteriovenous malformation; HHT = hereditary hemorrhagic telangiectasia; PH = pulmonary hypertension; TGF = transforming growth factor

Since the association between pulmonary hypertension (PH) and hereditary hemorrhagic telangiectasia (HHT) was first recognized by Trembath et al[1] and Harrison et al,[2] much attention has focused on germ line mutations of activin receptor-like kinase type 1 (*ALK1/ACVRL1*), which encodes a member of the transforming growth factor (TGF)-β receptor family, as a causal link. Less attention has been given to the natural history of patients with both PH and HHT, particularly those managed with vasoactive medications. The current report extends the sparse available long-term experience by presenting the case of a 24-year-old woman with PH and a clinical diagnosis of HHT we followed up over 10 years on a variety of vasoactive medications.

## Case History

At presentation in 1995, our patient was a previously healthy 24-year-old woman with dyspnea that began during the seventh month of her first pregnancy and worsened significantly thereafter, causing her to seek attention 7 months postpartum. She had been adopted at age 8 years, and had no knowledge of her birth parents. She had previously enjoyed good health save for an initial episode of minor epistaxis at age 20 years, which recurred yearly thereafter, but no hemoptysis, GI bleeding, or neurologic symptoms.

Her initial physical examination in May 1995 showed clear lung fields, a loud P2, grade 2/6 systolic ejection murmur, a parasternal heave, and congestive hepatomegaly. Laboratory assessment included a chest radiograph showing cardiomegaly (Fig 1), a ventilation-perfusion scan that showed multiple subsegmental mismatched perfusion defects, and a transthoracic echocardiogram showing a dilated right ventricle, moderate tricuspid regurgitation, an estimated right ventricular systolic pressure of 106 mm Hg, and no right-to-left shunt. Pulmonary function testing showed normal $FEV_1$, FVC, $FEV_1$/FVC, and normal lung volume

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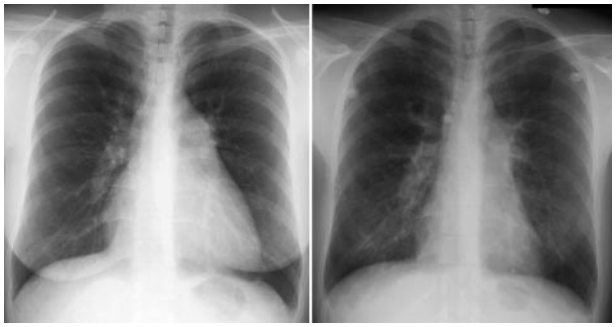

FIGURE 1. Chest radiographs of the patient at the initiation of prostanoid therapy (*left*) and 6 years later (*right*), showing a decrease in size of the cardiac chambers.

measurements but a decreased diffusion capacity of the lung for carbon monoxide (59% of predicted). A pulmonary angiogram showed no evidence of acute or chronic pulmonary emboli and no evidence of arteriovenous malformations (AVMs) at that time.

As shown in Table 1, a baseline right-heart catheterization showed marked PH (pulmonary artery pressure, 126/80 mm Hg, mean 110 mm Hg) and a preserved cardiac index (2.4 L/min). As she declined consideration of IV prostacyclin therapy or lung transplantation, initial therapy (from May 1995 through April 1997) included warfarin and nifedipine, 70 mg tid. In response to initial treatment, she had a short-lived improvement, with decreased shortness of breath and increased walk distance. However, because of worsening lightheadedness and declining functional capacity over the next 23 months (through April 1997), she agreed to repeat right-heart catheterization (Table 1) and initiate IV epoprostenol (in April 1997). A shunt study breathing 100% oxygen showed a 9.7% shunt fraction.

As shown in Tables 1 and 2, 9-year follow-up on IV prostacyclin therapy (epoprostenol from April 1997 to February 2006 followed by IV treprostinil initiated at her request to lessen the frequency of cartridge changes in February 2006) has shown progressively declining mean pulmonary artery pressure measurements (from 110 mm Hg at baseline to 65 mm Hg on the most recent measurement [in April 2006]), accompanied by increasing 6-min walk distance (from 305 m in May 1997 to 445 m in May 2006 [Table 2]).

While she has had no further epistaxis since beginning vasodilator therapy, the onset of nonmassive hemoptysis in April 2006 prompted a CT scan of the chest that showed multiple tiny AVMs scattered in the periphery of both lungs (Fig 2), the largest of which measured 8 mm in diameter. This was confirmed by pulmonary angiography in April 2006 (Fig 3), and the patient underwent coil embolization of the large left upper lobe AVM with cessation of the hemoptysis.

In the context of her epistaxis and the emerging appreciation of an association between PH and HHT, the finding of the pulmonary AVMs following recurrent epistaxis from nasal telangiectasia established a clinical diagnosis of HHT.[3] Clinical genetic mutation analysis for the two known susceptibility genes, *ALK1/ACVRL1* and *ENG*, was performed by polymerase chain reaction-based nucleotide sequencing of all exons and flanking intronic regions. Despite the patient's meeting criteria for a clinical diagnosis of HHT, no mutations were detected in either of these genes.

## DISCUSSION

The current case extends available experience with PH and HHT in several ways. First, in contrast to the now well-recognized association of HHT and PH mediated by mutations of *ALK1/ACVRL1*,[2] our patient has a clinical diagnosis of HHT (including epistaxis, mucocutaneous telangiectasia, and pulmonary AVMs) without a detectable *ALK1/ACVRL1* or *ENG* abnormality. Experience with this patient demonstrates that not all patients with HHT have an identifiable mutation in the *ENG* or *ALK1/ACVRL1* genes. In considering reasons that a known mutation was not detected, it is important to point out that the relative prevalence of *ENG* and *ALK1/ACVRL1* mutations in HHT appears to be region specific.[4] Polymerase chain reaction-based direct sequencing of these genes detects approximately 60 to 80% of mutations in individuals with HHT[4–6] but will not detect certain mutations, including large deletions and rearrangements. The latter of these should not

**Table 1—*Results of Right-Heart Catheterization Over Time**

| Medications | Systolic/Diastolic Pulmonary Artery Pressures (Mean), mm Hg | Mean Right Atrial Pressure, mm Hg | Cardiac Index by Thermodilution Method, L/min/m$^2$ | Mixed Venous Oxygen Saturation, % | Pulmonary Vascular Resistance, dyne·s·m$^{-5}$ | Mean Pulmonary Artery Occlusion Pressure, mm Hg |
|---|---|---|---|---|---|---|
| Baseline (May 1995) | | | | | | |
| None | 136/80 (110) | 22 | 2.4 | 66 | NA | NA |
| Nifedipine challenge | 95/46 (58) | | | | | |
| Two years (April 1997) | | | | | | |
| Nifedipine, 70 mg tid | 146/74 (99) | 13 | 2.5 | NA | 19 | 18 |
| Seven years (April 2002) | | | | | | |
| Epoprostenol, 68 ng/kg/min | 84/38 (58) | 2 | 2.95 | 78.4 | NA | NA |
| Eight years (April 2003) | | | | | | |
| Epoprostenol, 79 ng/kg/min | 130/50 (76) | 12 | 2.08 | 60 | 15 | 12 |
| Eleven years (April 2006) | | | | | | |
| IV treprostinil, 70 ng/kg/min† | 97/44 (65) | NA | NA | NA | NA | NA |

*NA = not available.

†Measured during pulmonary angiography.

**Table 2—*Follow-up Assessments**

| Variables | Baseline (May 1995) | After 1 Month on PGI2 (May 1997) | After 6 Months on PGI2 (November 1997) | After 16 Months on PGI2 (August 1998) | After 5 Years on PGI2 (October 2002) | Most Recent (11 Years on Vasoactive Therapy and 9 Years on PGI2) [May 2006] |
|---|---|---|---|---|---|---|
| Medication | None | Epo | Epo | Epo | Epo | Trep |
| New York Heart Association class | III | III | III | II | II | II |
| Six-minute walk distance, m | ND | 305 | 347 | 434 | 428 | 445 |
| Brain natriuretic peptide, pg/mL | ND | ND | ND | ND | 21 | 11 |
| Estimated right ventricular systolic pressure (by surface echocardiography), mm Hg | 106 | 120 | 80 | 69 | 67 | 54 |
| Supplemental oxygen need with 6-min walk, L | RA | 2 | RA | RA | RA | RA |

*PGI2 = prostacyclin; Epo = epoprostenol; Trep = treprostinil; ND = not done; RA = room air.

account for > 10 to 15% of those with a clinical diagnosis of HHT. The remainder of mutations are probably caused by other genes.[7] *ALK1/ACVRL1* and *ENG*, which are associated with HHT, are members of the TGF-β pathway. *ALK1/ACVRL1* encodes the membrane-bound receptor, and *ENG* encodes endoglin, which is a transmembrane glycoprotein.[8] As evidence of the wide impact of the TGF-β pathway, mutations have been implicated in cancer predisposition syndromes, bone disorders, vascular diseases, and others.[4,8] Indeed, many members of the TGF-β pathway have dual roles in effecting cell proliferation and suppression.[9] Overlapping clinical features have been observed in conditions caused by different genes in the TGF-β pathway.

As a second extension of available knowledge, our patient has been followed up for 10 years on various vasoactive medications, including nifedipine, epoprostenol and, most recently, IV treprostinil, and has remained clinically stable with good functional status (New York Heart Association class II), stable exercise capacity, and freedom from the need for supplemental oxygen. Indeed, to our knowledge, she represents only the second such patient followed up for an extended interval. Schlag et al[10] described the 10-year follow-up of a 49-year old woman with HHT and PH (pulmonary artery pressures at right-heart catheterization, 74/33 mm Hg; mean, 51 mm Hg; Fick cardiac output, 6.4 L/min) who was treated initially with calcium-channel blockers and then inhaled iloprost, beraprost, and finally bosentan.

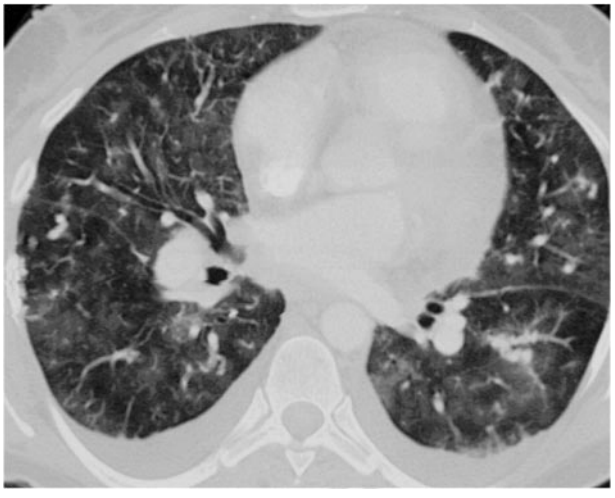

FIGURE 2. CT scan of the lungs performed as a result of hemoptysis showing multiple tiny AVMs scattered in the periphery of both lungs. The largest AVM was in the left upper lobe, measuring 8 mm.

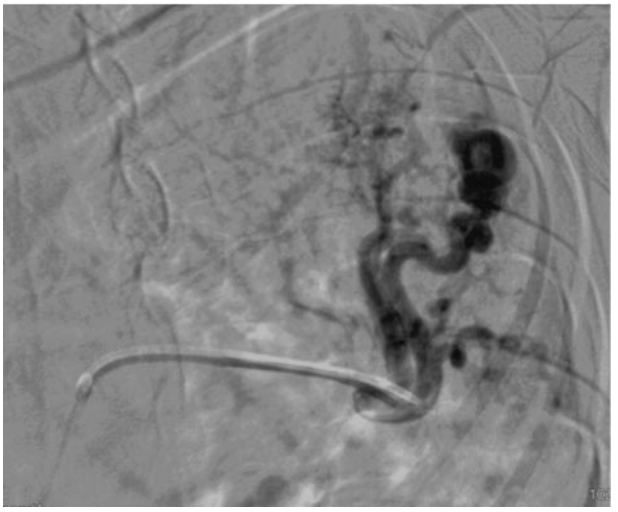

FIGURE 3. The AVM in the left upper lobe was confirmed by pulmonary angiography, and coil embolization resulted in resolution of hemoptysis.

Over the course of her follow-up, her mean pulmonary artery pressure remained stable at approximately 50 mm Hg. To our knowledge, our patient represents only the second patient with HHT and PH to be described with long-term follow-up after treatment with a variety of vasoactive medications. Taken together, these two reports demonstrate the possibility of decade-long survival, clinical stability and, in our patient, even functional and physiologic improvement over the course of treatment. Clearly, longer follow-up of larger cohorts is required before definitive conclusions are possible, but this early experience provides strong rationale for aggressive therapy, most certainly in this special subset of patients with both HHT and PH.

In summary, the current patient extends the sparse clinical experience with patients with PH and HHT by prompting consideration of mediators of vascular abnormality other than the recognized *ALK1/ACVRL1* mutations and offers only the second reported instance of 10-year follow-up. Her overall encouraging course should prompt clinicians to remain optimistic about the value of current and emerging therapies for this complex condition, while serving as a reminder of the need for more extensive, long-term study of this patient group. With further molecular understanding of the basis for PH in HHT, specific molecular-targeted therapies can be fashioned. However, such molecular-based therapies need to be mindful of the balance of the TGF-β and bone morphogenetic protein pathways as they relate to both vascular disease and malignancy.

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