diagnosis. Moreover, granulomas may occur in both diseases but corticosteroid treatment is known to adversely affect this disease.[10]

In cases of suspected Whipple disease with or without pulmonary involvement, duodenal biopsy with PAS staining is indicated, even in the absence of intestinal clinical symptoms. It is also essential to perform PCR for *T whipplei* PCR on stool samples, saliva, and frozen biopsy specimens from the bronchi and duodenum. This is more sensitive than PAS staining. In our case, the bronchial location of the bacterium was confirmed retrospectively by immunohistochemical analysis with anti-*T whipplei* antibodies. This technique, or PCR analysis, may make it possible to obtain a diagnosis retrospectively, even from fixed bronchial biopsy specimens.

In conclusion, even in the absence of GI symptoms, a diagnosis of Whipple disease should be considered in middle-aged men presenting with ILD or lung nodules if they have a history of unexplained arthralgia and/or fever. This is further supported by the presence of mediastinal adenopathies or pleural effusion, or evidence of granuloma. Whipple disease may be fatal in the absence of treatment but is responsive to antibiotic treatment.

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The Intersection of Genes and Environment

Development of Pulmonary Arterial Hypertension in a Patient With Hereditary Hemorrhagic Telangiectasia and Stimulant Exposure

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Pulmonary arterial hypertension (PAH) is a rare complication of hereditary hemorrhagic telangiectasia (HHT). The triggers that promote the development of PAH in HHT remain poorly understood. We present the case of a 45-year-old woman with decompensated right-sided heart failure secondary to newly diagnosed PAH. The clinical diagnosis of HHT was confirmed on the basis of recurrent spontaneous epistaxis, multiple typical mucocutaneous telangiectasia, and the presence of pulmonary arteriovenous malformation. There was also a suggestive family history. The patient was discovered to have active and extensive stimulant abuse in addition to HHT. We concluded that there may be a temporal relationship between exposure to stimulants and development of PAH in a host with underlying gene mutation. This case highlights the paradigm of PAH development after environmental exposure in a genetically susceptible host.

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Abbreviations: ACVRL1 = activin receptor-like kinase-1; AVM = arteriovenous malformation; HHT = hereditary hemorrhagic telangiectasia; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension

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Hereditary hemorrhagic telangiectasia (HHT) is an inherited autosomal-dominant vascular disorder with an estimated minimum prevalence of 1:10,000.[1] Among the complications of HHT, pulmonary hypertension (PH) occurs in <1% of patients[2] but can significantly impact patient survival and quality of life. As with familial pulmonary arterial hypertension (PAH), genetic mutations in members of the transforming growth factor-β superfamily have been documented, namely in endoglin, activin receptor-like kinase-1 (ACVRL1), and SMAD4.[2,3] However, given the limited penetrance of these mutations, it is likely that mutations alone do not lead to PH. Environmental factors may have the potential to modify and increase the risk of PAH in patients with HHT.

We report the case of a patient with HHT and an endoglin gene mutation who developed PAH in the setting of chronic stimulant use. To the best of our knowledge, this is the first case to suggest a possible interaction between genetic and environmental factors in the development of PAH in the setting of HHT.

Case Report

A 45-year-old white woman presented with a 1-year history of progressive dyspnea and reduced exercise tolerance. She reported worsening lower-extremity swelling, abdominal distention, and a 20-pound weight gain, which improved after aggressive diuresis. She was referred to the Stanford PH clinic for further evaluation.

Her medical history was significant for three episodes of cryptic GI bleeding requiring blood transfusion and for spontaneous nose bleeds. Family history was noncontributory, except for a father with spontaneous nose bleeds and pulmonary hemorrhage. We were unable to obtain a detailed family pedigree because the father was adopted. The patient admitted to monthly cocaine and marijuana use for 4 years while in college but denied any active illicit drug abuse. Her medications included furosemide, coumadin, calcium carbonate, and iron sulfate. On physical examination, BP was 127/52 mm Hg, pulse was 82 beats/min, respiratory rate was 16 breaths/min, pulse oximetry was 100% on room air, and she was afebrile. Cardiopulmonary examination revealed clear breath sounds, a 2/6 holosystolic murmur best heard at the left upper sternal border, and a prominent P2. Mucosal and skin examination demonstrated extensive telangiectases on skin, buccal mucosa, and tongue.

Laboratory testing was negative for HIV, autoimmune diseases, hepatitis, and hypercoagulability. Pulmonary function was normal, and 6-min walk distance was 664 m. Transthoracic echocardiogram demonstrated normal left ventricle size and function, a mildly dilated right ventricle with preserved systolic function (right ventricular fractional area change of 39%, tricuspid annular plane systolic excursion of 2.0 cm), severe tricuspid regurgitation, estimated right ventricular systolic pressure of 83 mm Hg, right atrial pressure of 15 mm Hg, and positive bubble study for late targets suggesting an extracardiac shunt. Chest CT scan showed two small pulmonary arteriovenous malformations (AVMs) (Fig 1), and an MRI of the liver demonstrated multiple small AVMs. Right-sided heart catheterization showed a mean right atrial pressure of 9 mm Hg, mean pulmonary arterial pressure of 35 mm Hg, pulmonary capillary wedge pressure of 12 mm Hg, cardiac output of 3.5 L/min, pulmonary vascular resistance of 5.8 Wood units, and lack of vasoreactivity. Wedge angiography demonstrated rapidly tapering vessels and an absence of capillary blush without visible AVMs in the injected pulmonary arteries (Fig 2).

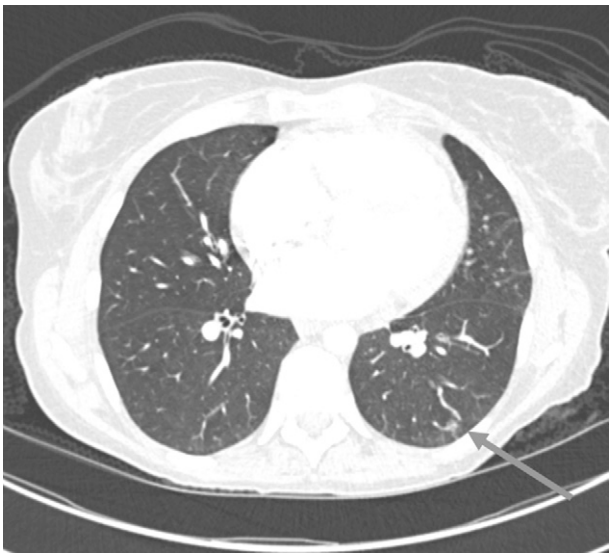

Figure 1. CT scan showing a small arteriovenous malformation.

Given her clinical history and physical examination findings, genetic testing for known HHT and familial PAH mutations was done. Testing revealed the heterozygous presence of a gross deletion of exons 1 to 4 in the endoglin gene, a gene that is located on chromosome 9.[3] The result was consistent with a diagnosis of HHT. Additionally, the patient's routine toxicology screen was positive for amphetamine/methamphetamine metabolites. The patient then admitted to active methamphetamine use for several years but did not provide any objective measure of frequency and amount of use. She relocated shortly after she was started on sildenafil. She was strongly advised to continue medical care at a local PAH center and to seek drug and genetic counseling.

Discussion

HHT is a clinical diagnosis consisting of epistaxis, mucocutaneous telangiectases, visceral AVMs, and a family history of HHT.[2] Genetic mutations may impact PAH progression and prognosis. In HHT associated with PAH, carriers of ACVRL1 mutations present at a younger age and have worse outcome than patients with bone morphogenetic protein receptor type 2 (BMPR2) mutations.[3] Also, compared with ACVRL1, endoglin mutations are less frequent and may confer a lower risk of PAH development.[3]

We believe that our case highlights the following temporal relationship: The vascular effect of an already present endoglin mutation was further compounded by exposure to cocaine and methamphetamine later in life, leading to PAH. Interestingly, both cocaine and methamphetamine are risk factors associated with PAH.[4] It may be

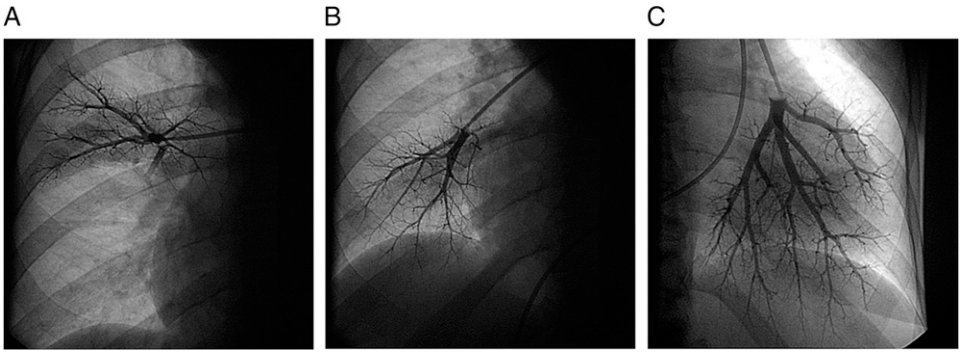

FIGURE 2. Pulmonary angiogram showing the absence of capillary blush. A, right upper lobe. B, right lower lobe. C, left lower lobe.

possible that HHT served as a risk factor and a second hit for development of PAH. Although the patient had hepatic AVMs, which are also known to cause PH in HHT, her cardiac output was low and there was no evidence of portal hypertension.

In conclusion, we hypothesize that our case demonstrates the need for heightened awareness of potential environment-gene interactions in the diagnosis of PAH. Future epigenetic studies should focus on the potential temporal association between toxin exposures and PAH development in susceptible hosts. If these studies are positive, they may guide clinicians in advocating avoidance of stimulants in genetically vulnerable populations.

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