BACKGROUND
Hereditary hemorrhagic telangiectasia, otherwise known as Rendu-Osler-Weber syndrome, is a rare autosomal dominant genetic disorder characterized by multisystem features of dysregulatedangiogenesis. This case report describes the diagnosis and treatment of a 52-year-old male patient that presented recently in our clinic with recurrent epistaxis, fatigue, dyspnea, and facial telangiectasias. MRI revealed a large pulmonary arteriovenous malformation. Endoscopic evaluation showed extensive telangiectasias in the jejunum. Genetic testing identified a mutation in the ENG gene. Substantial improvement in his clinical status followed ecoiling of the pulmonary arteriovenous malformation, iron infusions, and subacute bacterial endocarditis prophylaxis.

CASE PRESENTATION
A 52 year-old-man was seen in our clinic because of fatigue that had become progressively worse in the weeks before his first visit. At the age of 40, he developed his first seizure and was diagnosed with a stroke. At 46 years old, he was diagnosed with anemia but did not receive treatment. The patient did not report presence of hematemesis, coffee ground vomiting, melena or hematochezia. He has recurrent epistaxis, which started to occur at the age of 10 but had become worse at age 45. Approximately 6 years ago, he received a blood transfusion for the first time and has been receiving one almost every year. However, his transfusion requirement increased to twice a month following his first visit at our clinic. Workup for his anemia included an esophagogastroduodenoscopy and a colonoscopy that were not diagnostic. However a capsule endoscopy disclosed the presence of multiple arteriovenous malformations along the jejunum.

This now 53 year-old man presented with unresolved recurring epistaxis, fatigue and anemia. The patient had been receiving iron infusions and transfusions for the past two years for iron deficiency anemia. Despite treatment, he reported that he couldn’t walk from the parking lot to the clinic without feeling completely exhausted and his daily activities had been severely affected. Workup for his dyspnea on exertion included a normal echocardiogram and a CT scan of the chest that revealed a large pulmonary arteriovenous malformation in the right lung [Figure 1]. His history of seizures prompted a brain MRI that did not show an AV malformation.

On physical examination he appeared pale, anicteric sclera, neurologically intact, poor dentition, no jugular venous distention, his heart exam revealed an S1 and S2 with an outflow murmur, lungs were clear, liver and spleen were not palpable. Clubbing of the fingers was not present. Skin and mucosal evaluation revealed multiple telangiectasias in the malar area, bridge of the nose, and tip of the fingers, as well as the oral and nasal mucosa as shown [Figure 2].

Laboratory evaluation revealed hypochromic microcytic anemia, low ferritin, reticulocytopenia, and normal LDH. His stool Hemocult™ was positive. Genetic testing revealed the presence of an ENG mutation (c.816:+2T>A) [Table 1].

Family history: 3 sons, the eldest is 30 years old and started having epistaxis at 15 years of age. The second does not report any epistaxis or anemia. However, his 11 year-old son was recently noted to have telangiectasia on his face. Patient’s brother started having epistaxis at 51 and has history of gastric ulcers. Patient has 4 other brothers and 2 sisters with no reported bleeding episodes. Father died at 74 and mother at 84, and there were no reports of bleeding. His paternal uncle had bouts of epistaxis that began at age 20. Patient is of Mexican ancestry on both mother’s and father’s side. Consanguinity denied.

DISCUSSION
Hereditary hemorrhagic telangiectasia was first described in a series of clinical papers that came together at the turn of the 20th century. Initial case reports focused on the hemorrhagic complications such as recurrent epistaxis and anemia. More recently, specific mutations have been identified as the molecular etiology, some correspond with phenotypic variants of the disease [Table Continued on page 8
55 Year Old Man With Epistaxis and Dyspnea
(Continued)

Figure 2

Black arrows pointing to facial telangiectasias

1. Mutations in the ENG and ACVR1 genes account for the vast majority of cases.1,4

The constellation of epistaxis, dyspnea, history of seizure disorder, anemia and diffuse facial telangiectasias was highly suggestive of hereditary hemorrhagic telangiectasia. Genetic work-up confirmed a mutation of the ENG gene; which in part has been associated with a high incidence of pulmonary arteriovenous malformation, as was present in this case, and explained the patient’s dyspnea related to venous shunting.

Genetic tests are not required for diagnosis. A definitive diagnosis can be established if three of four Caracão criteria are met: recurrent spontaneous epistaxis, multiple telangiectasias in typical locations, proven visceral arteriovenous malformation(s), 1st-degree relative with hereditary hemorrhagic telangiectasia.5

Subsequent coiling of the pulmonary malformation promptly resolved the shunting and dyspnea [Figure 2]. Anemia was due to chronic GI bleeding from multiple telangiectasias identified on capsule endoscopy along the jejunal. He was treated with IV iron infusions. The patient is on subacute bacterial endocarditis prophylaxis mainly to prevent brain or liver abscesses, for which patients with ENG mutations are at considerable risk, putatively because of the susceptibility of multiple AV malformations to seeding during episodes of bacteremia. Mutation in the ENG gene leads to reduction of functional endoglin to disruption of a complex signaling pathway (TGFβ), resulting in microvascular fragility underlying the abnormal bleeding seen in this disease.5

Several recent and ongoing clinical trials are aiming to advance the understanding and treatment of hereditary hemorrhagic telangiectasia (https://ClinicalTrials.gov search under "hereditary hemorrhagic telangiectasia"). Results of preliminary trials of vascular endothelial growth factor inhibitors, bevacizumab, ranibizumab and aflibercept, appear promising and rational as risk-reducing strategies for bleeding complications and anemia arising from this genetic disorder characterized by multisystem features of dysregulated angiogenesis.5

REFERENCES


Table 1

<table>
<thead>
<tr>
<th>TYPE</th>
<th>MUTATION</th>
<th>PHENOTYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHT1</td>
<td>ENG</td>
<td>High incidence of pulmonary AVMs</td>
</tr>
<tr>
<td>HHT2</td>
<td>ACVR1</td>
<td>Primary pulmonary hypertension</td>
</tr>
<tr>
<td>JPH5</td>
<td>MADH4</td>
<td>Polyposis</td>
</tr>
<tr>
<td>HHT3</td>
<td>UNKNOWN</td>
<td>UNKNOWN</td>
</tr>
<tr>
<td>HHT4</td>
<td>UNKNOWN</td>
<td>UNKNOWN</td>
</tr>
</tbody>
</table>

ENG encodes for endoglin, ACVR1 encodes for ALK-1 (TGFβ1 receptor), MADH4 encodes for SMAD4, (3)(4)(5)(6)(7)

Raul M. Portillo, MD, Texas Oncology, PA, El Paso, Texas.

Fernanda Mejia, BA, Toxicology MSc Program, Colorado State University, Fort Collins, Colorado.