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Hereditary hemorrhagic telangiectasia diagnosis: A case report

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ABSTRACT

This case report presents a 13-year-old patient with a lung nodule identified on a chest radiograph in the emergency department during an evaluation of knee and side pain after a fall. The patient had nosebleeds, family history of hereditary hemorrhagic telangiectasia (HHT) and after chest computed tomography with angiography, the nodule was defined as a single pulmonary arteriovenous malformation (PAVM). Neither parent nor patient had been evaluated for HHT, an autosomal dominant disease, despite the family history. This patient satisfied the clinical criteria for the diagnosis and had a confirmatory genetic test, which led to diagnosis in mother also. The patient's PAVMs were treated, decreasing the risk of life threatening complications. Diagnosing HHT in children is often delayed or missed, even in families with HHT, as in this case report. Without any physical signs or clinical symptoms, families and healthcare providers often dismiss the possibility of the diagnosis. Children with HHT are at the same risk for complications of stroke, anemia, hypoxemia, heart failure and increased morbidity as adults. It is essential to recognize the importance of family history when evaluating children in primary care and urgent settings, as this patient's diagnosis was delayed 13 years. Awareness of HHT signs and symptoms are essential to early referral to an HHT specialist, for diagnosis and management.

Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu, is an autosomal dominant blood vessel disease. Patients with HHT have abnormal development of some blood vessels resulting in a direct connection between an artery and a vein or a fistula (Shovlin et al., 2000). These abnormal blood vessels, or arteriovenous malformations (AVMs), have potential to rupture and bleed (Zhang et al., 2022). Flow through an AVM causes a shunt which can lead to hemoptysis, anemia, hypoxemia, stroke, brain abscess, heart failure and early death. AVMs may be present in solid organs that include the spine, brain, liver, and lungs. Smaller AVMs, referred to as telangiectases, are characteristically found on fingertips, nailbeds, face, nose, and the gastrointestinal tract. In the United States, the incidence of HHT is approximately 1: 5000 (Kjeldsen et al., 1999). Brain AVMs are present in 10% to 15% of patients (Brinjikji et al., 2017) while the incidence of lung AVMs is 50% (Dupuis-Girod et al., 2017). Any child born to a parent with HHT has a 50% chance of having HHT and may be asymptomatic for several years, putting them at risk for developing complications associated with delayed diagnosis (Pierucci et al., 2012). There is variable expressivity of HHT signs and symptoms within the same family with the identical gene mutation. By the fourth decade of life, approximately 90% of patients will have frequent epistaxis, the most common symptom of HHT. Early diagnosis of HHT allows for planned, preventative care and treatment throughout the lifespan. Definitive diagnosis is made using either the Curaçao criteria or genetic testing (Shovlin et al., 2000). The Curaçao criteria were developed in 2000 prior to commercial genetic testing availability for HHT (Shovlin et al., 2000). A patient has definite HHT if they have three or four of these criteria, possible HHT if they have two, and HHT is unlikely if they only have one criterion (Table 1). The Second International Guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia recommend genetic testing for the most affected individual in a family to increase positive yield (Faughnan et al., 2020). Genetic test panels for HHT include endoglin (ENG), activin receptor like kinase 1 (ACVRL1), SMAD related protein 4 (SMAD4), RASA1, growth differentiation factor 2 (GDF2) and capillary-malformation-AVM syndrome (EPHB4) (Hammill et al., 2021). According to Faughnan et al. (2020), if a gene mutation is identified in a family member of the proband, all family members should be tested for that targeted gene. HHT is most prevalent in Dutch

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Table 1
Curaçao criteria.

1. Spontaneous, recurrent nosebleeds/epistaxis
2. Mucocutaneous telangiectases in typical locations of fingertips, nailbeds, lips and tongue
3. Solid organ AVM in lung, brain, spine or liver
4. First degree family member with HHT

populations (Westermann et al., 2003). Symptoms of HHT generally include shortness of breath, migraine headache and nosebleeds, but here we report an asymptomatic patient who was diagnosed after presenting to an emergency department with a fall injury.

Patient presentation

A 13-year-old patient presented to the emergency department (ED) with reports of back and thigh pain after falling down a hill while running. The patient fell forward to the ground after tripping, had left side and knee pain at home and was transported for evaluation. On arrival, pain was rated seven on a pain scaled of one to ten. The patient also reported mild tenderness in the right distal knee, no deformity and the knee joint was stable. There was no loss of consciousness, abdominal or chest pain, fever, nausea and vomiting.

Past medical history included urinary tract infection and vesicoureteral reflux with no surgeries. Medications included lisdexamfetamine 40 mg daily for attention deficit hyperactivity disorder (ADHD) and vitamin D 2000 units daily. The patient reported not smoking, vaping, drinking or using other drugs. Family history included ADHD in parents, diabetes, and hypertension in patient's father. Maternal grandmother was deceased from heart disease. Vital signs included B/P 107/69, heart rate 112 bpm, respiratory rate of 18, temporal temperature of 97.2, SpO2 98%, height of 165.1 cm (85%), and weight of 52.1 kg (73%). A review of systems was negative except for mild right subscapular tenderness without crepitus, deformity, or bruising.

There was no finding on a chest x-ray that correlated with the patient's right sided chest pain. However, a 2.2 × 1.4 cm well-defined nodule in the right lung base with a cylindrical structure that appeared to be a vessel was identified (Fig. 1). The left lung was clear and there was no pneumothorax or pleural effusion. The cardiac and mediastinal silhouettes appeared normal. The radiologist's differential diagnosis included a pulmonary arteriovenous malformation (PAVM) with recommendation for a chest computed tomography (CTA) for further evaluation. The solitary lung nodule finding was shared with patient and father as well as recommendation and referral to a pulmonologist for further evaluation. The concluding diagnosis in the ED included encounter for a fall, sprain of the right knee, thoracic myofascial strain, and a pulmonary nodule. The patient was discharged to home in stable condition. The discharge provider prescribed an over-the-counter pain medication as needed and recommended an appointment with a primary care physician (PCP), and a pulmonologist.

Primary care appointment

The patient had an appointment with their PCP the next day. During the visit, there were no new concerns except for left sided soreness. The vital signs were within normal range, physical exam had no additional findings. A referral was placed for a pulmonary specialist and the patient was advised to follow up with the PCP in one month, after seeing the pulmonologist.

Pulmonary appointment

During the visit, the patient reported frequent nosebleeds, occasional blood-streaked sputum after a nosebleed and passing out when feeling too hot. The patient's mother offered additional family history of maternal grandmother having HHT. The pulmonologist's differential diagnosis included a PAVM and a bronchial cast, or foreign body. To further evaluate the lung lesion, a chest CTA was recommended. The patient had a chest CTA two weeks later and an AVM was identified in the right lower lobe measuring 1.6 × 2.4 cm (Fig. 2). The radiologist reported multiple bilateral PAVMs. In addition to the AVMs, there were several areas of ground glass opacities throughout both lungs, and some had small adjacent tortuous vessels that were consistent with smaller PAVMs. There was an area of 1.7 × 0.9 cm of ground glass opacities in the left apex. The pulmonologist referred the patient to a pediatric HHT physician.

The HHT appointment

The HHT consultation occurred three months after initial evaluation in the ED for trauma. At the appointment, the patient's mother

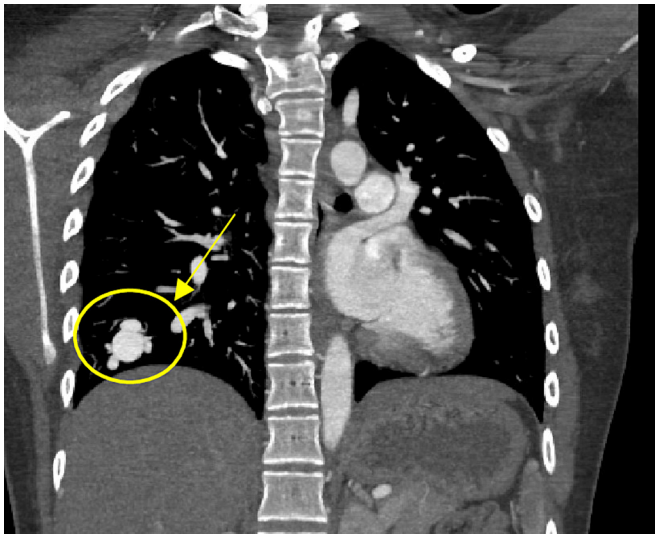

Fig. 1. Chest x-ray right lung nodule.

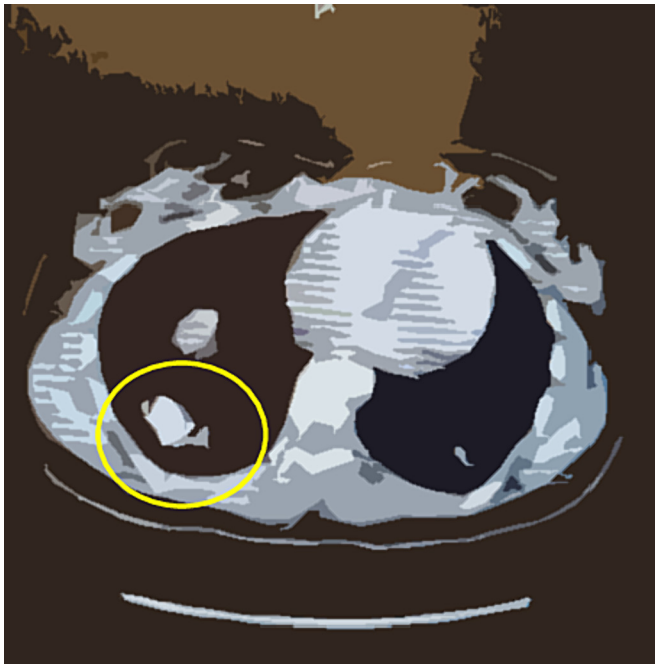

Fig. 2. Chest CTA Right lower lobe AVM.

confirmed that her mother had HHT. In addition, the maternal grandmother was reported to have had numerous gastrointestinal telangiectases diagnosed on endoscopies with over 100 cauterized, and severe anemia treated with multiple blood transfusions. The patient's family were of Irish, Spanish, and Dutch ancestry. Neither the mother, nor her siblings (one brother and a sister) had been evaluated clinically or genetically for HHT (Fig. 3).

At the appointment, frequent nosebleeds and a single telangiectasia on the tongue were identified. There was no exercise intolerance or shortness of breath, hemoptysis, cyanosis, or blood in stool. The patient was diagnosed with definite HHT, satisfying three of the four Curaçao criteria. These criteria included a PAVM, nosebleeds and a tongue telangiectasia. The HHT physician recommended a pulmonary angiogram with embolization, brain MRI, genetic testing for HHT, prophylactic antibiotic dosing prior to dental cleaning, supportive care for nosebleeds and guidance to report any symptoms.

In the case report patient, the genetic test identified a mutation in endoglin (ENG) gene c.-127C > T or HHT1, as well as a variant of unknown significance in RASA1 c.346 > G. Mutations in ENG and ACVRL1 account for 95% of the pathogenic variations, followed by SMAD4 accounting for 2 % (McDonald et al., 2020). Few patients have been found to have mutations in RASA1, EPHB4 and GDF2 (Hammill et al., 2021). MRI of the brain was negative for BAVMs.

The patient returned to the HHT physician five months after the initial appointment for interim history, physical exam, review of test results and discussion of treatment of PAVMs. Since the previous office visit, the patient's mother had genetic testing which confirmed HHT in the familial ENG mutation. The patient had no further episodes of fainting, shortness of breath, hemoptysis, blood in stool, cyanosis, or other concerns. The patient had rare nosebleeds, some headaches and fatigue. Treating the pulmonary AVM was recommended during the visit.

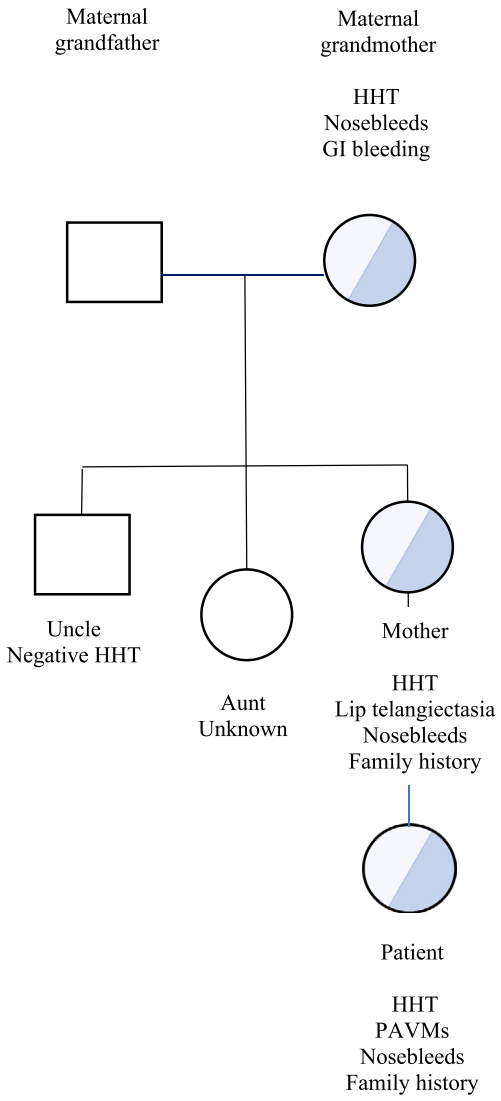

Fig. 3. Family Genogram.

Treatment phase

The patient returned four moths later for pulmonary embolization. On the day of procedure, a repeat chest CTA revealed the PAVMs noted previously in the left upper lobe and right lower lobe, with some diffuse smaller PAVMs. There was a slight increase in size of right lower lobe PAVM, measuring 2.3 × 1.5 × 1.8 cm and left upper lobe PAVM, measuring 1.0 × 0.7 × 1 cm. Each of the AVMs were treated with a microvascular plug 5Q device with no residual flow. After four hours in recovery, the patient was discharged home with a follow up HHT appointment.

Screening for HHT in children

Clinical screening is recommended for children with definite HHT from a positive genetic test or satisfying the Curaçao criteria, beginning in the first year of life or age at diagnosis (Faughnan et al., 2020). Delaying the screening process in children may increase morbidity, as they may have asymptomatic AVMs in their lungs (Gefen & White, 2017) or brain without any outward physical signs (Danesino et al., 2023). The Curaçao criteria are less reliable in children under 11 years of age (Pahl et al., 2018). In a report by Pahl et al. (2018) there was low sensitivity and high specificity in using Curaçao criteria in 0–21 year olds who meet three of four criteria. As many as 50% of children can have nosebleeds and many children may have red spots or telangiectasias without a diagnosis of HHT. It is common for families to dismiss concern for HHT if their children do not have nosebleeds or skin telangiectasias (A. J. White, personal communication, November 28, 2023). In children with a solid organ AVM, the Curaçao criteria supports the HHT diagnosis (Pollak et al., 2023). In addition, Pollak et al. (2023) caution that relying solely on clinical criteria may lead to underdiagnosing HHT in children. A confirmatory genetic test is ideal in diagnosing children with HHT (Danesino et al., 2023). Routine HHT care and assessment is imperative to identify changes or development of symptoms to prevent complications (Faughnan et al., 2020).

Initial clinical evaluation for children with a diagnosis of HHT includes comprehensive history and physical with vital signs and pulse oximetry including a bubble echocardiogram and brain MRI with and without contrast. Important screening questions include the occurrence of nosebleeds, the presence of skin telangiectases, hemoptysis, shortness of breath, clubbing, cyanosis, and migraine headaches. The contrast echo is the preferred test to assess for evidence of intrapulmonary shunting that could be a result of a PAVM (Faughnan et al., 2011). If shunting is present, a chest CT can be obtained to guide size and location of PAVMs. The Second International Guidelines for the Diagnosis and Management of Hereditary Haemorrhagic Telangiectasia recommend screening children with echocardiogram or CT and brain MRI (Faughnan et al., 2011). A brain MRI is necessary in screening for presence of BAVMs at diagnosis and at recommended intervals based on results (Faughnan et al., 2011). It is prudent to consider diagnostic challenges since patients six years and under often require sedation to obtain MRI and CT images. These challenges require detailed planning and coordination between many departments and the patient.

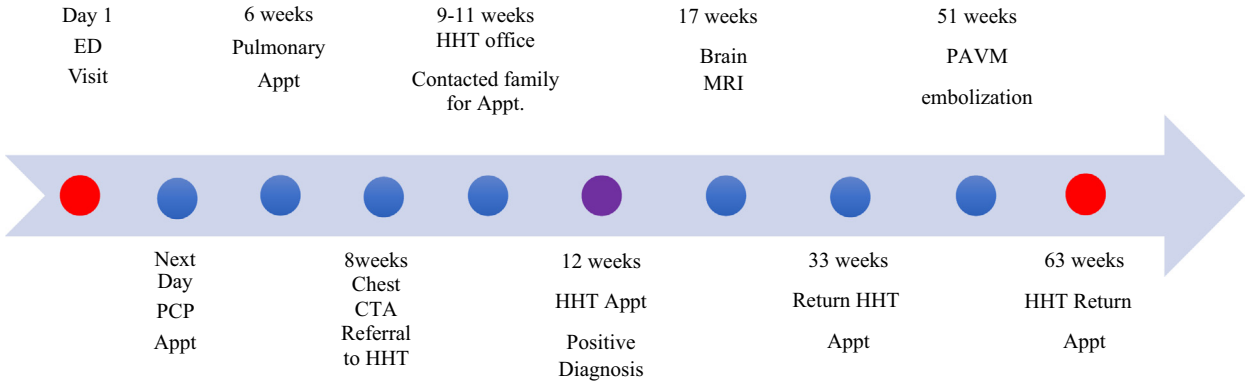

Fig. 4. Timeline from presentation to treatment.

HHT patient follow up appointment

A telemedicine visit three months after embolization of the PAVMs occurred in which the patient was engaged and had no symptoms (Fig. 4). There were no concerns reported by parent and a subsequent HHT appointment was planned for one year. Recommendations included antibiotic prophylaxis prior to dental cleanings to decrease risk for brain abscess, and good nasal hygiene with educational resources. The HHT center contact information with guidance to call with concerns for prolonged nosebleed or bleeding, cyanosis, shortness of breath, headaches or hemoptysis was provided to the patient and family.

Discussion

This case report is a serendipitous presentation from an activity of daily living that led to a genetic diagnosis of HHT. The patient's diagnosis had been missed for years, despite possible fatal consequences. Some children with HHT have sustained life altering complications from an initial presentation of undiagnosed AVM. Such cases may present as a ruptured AVM in the lung or brain, prolonged seizure, brain abscess, or stroke. In some cases of life-threatening symptoms, resuscitation efforts fail, ending with the loss of a child with HHT that was never diagnosed. Recognizing that family history is crucial when caring for children, especially when a family member has a genetic disorder, bleeding with anemia, and nosebleeds, should lead the provider to further investigate family history. This is rarely pursued in emergency departments. Many families do not think there are treatments available for HHT and reluctantly do not share their diagnosis with the rest of their family. Some families pass it off as a bleeding disease and there is nothing to be done. According to Palmer, 2017, concerns are heightened about other family members when HHT is diagnosed and it is hard to engage family members in a frank discussion of HHT and its potential consequences for the whole family. Pierucci et al. (2012) reported an average delay in diagnosis of 27 years, from first symptom to diagnosis of HHT. During that delay, 20% of the patients were reported to have suffered from severe complications. There are clear benefits to early diagnosis and management of HHT (Poisson et al., 2009). Clinicians need to be aware of subtle presentations and consult specialists that can provide guidance on diagnosis and management.

The patient was diagnosed with HHT after presenting to an ED for trauma. The incidental finding of a potential life threatening PAVM is a warning to all clinicians to entertain a high index of suspicion for screening underlying medical conditions, despite lack of symptomatology. The patient and family are now aware of their diagnosis, have established care with an HHT physician and have a follow up appointment in the future.

CRediT authorship contribution statement

Lynne Sekarski: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Conceptualization. **Andrew J. White:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources. **Katheryne Tifuh Amba:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Conceptualization.

Declaration of competing interest

We have no financial interest or relationship in this work. We have nothing to disclose and no conflicts of interest.

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