CASE REPORT

Standard anticoagulation for mesenteric vein thrombosis, revealing a 'zebra' diagnosis: hereditary haemorrhagic telangiectasia—the dripping truth!

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SUMMARY

A 60-year-old man was treated in the hospital for mesenteric vein thrombosis and discharged home on anticoagulation. On warfarin the patient started to bleed profusely from the nose and tongue. He was evaluated by ENT (ears, nose and throat); a nasal endoscopy revealed several vascular ectasias. Subsequent detailed history and general physical examination established the diagnosis of hereditary haemorrhagic telangiectasia also known as Osler-Weber-Rendu syndrome. On further evaluation, pulmonary arteriovenous malformations were diagnosed on imaging and treated by intervention radiology. In hindsight, the diagnosis could have been made in the general practitioner's office with just a routine thorough history and a physical examination at a new patient visit. We report this case to stress upon the importance of vigilant clinical, medical and family history and a thorough examination to establish an early diagnosis of this not-so-rare entity.

BACKGROUND

Hereditary haemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu syndrome is an autosomal dominant disorder of the fibrovascular tissue. Even though reported as a rare disorder, affecting one in 5000–8000 population,¹ it is still under-reported due to poor recognition of the cases even though signs and symptoms are not very unusual (eg, nose bleed and the red spots). It is imperative that health professionals should be familiar with HHT to entertain this diagnosis as a possible cause. Classically there is triad of mucocutaneous telangiectasias, recurrent haemorrhages and familial occurrence of bleeding. Awareness of consequences of diagnosis for the patient and the family is extremely important. Also they should be aware of possible complications, avoidance of those potential life threatening complications and further management.

Although stigmata of the disease were present at the outset in the index case but diagnosis of HHT was not kept initially in mind due to the presence of superior mesenteric vein thrombus and it was unmasked after use of oral anticoagulation.

We reported this case to illustrate that a knowledgeable physician can pick up so-called 'zebra diagnoses' just based on a detailed history and physical examination and thinking outside the box. Our case report aims to make healthcare professionals especially internists and family medicine practitioners aware of a relatively rare disease as HHT so that when they see a patient reporting of

epistaxis or mucocutaneous telangiectasias on physical examination, a red flag goes up in their mind and they at least consider HHT as a differential diagnosis even if the eventual diagnosis is totally benign. HHT should be considered if there is a history of recurrent epistaxis, telangiectasias on physical examination and positive family history—all of which do not require any expensive testing, but just a high degree of suspicion.

CASE PRESENTATION

A 60-year-old Caucasian man presented to the emergency room with the sudden onset of nausea, vomiting, severe cramping abdominal pain and constipation. His vital signs were stable and other systemic examination was normal except for extreme tenderness in the left side of the abdomen. A CT scan of the abdomen revealed a superior mesenteric vein thrombus and conservative management was carried out. Hypercoagulable work-up (genetic testing for factor V Leiden mutation and prothrombin gene mutation and protein assays for protein C, S and antithrombin III) was normal. He was started on anticoagulation with warfarin with bridging with heparin drip. After starting warfarin, the patient started to have significant episodes of epistaxis up to 7–10 episodes a week, and had several episodes of bleeding from the tongue as well. At this time, ENT (ear, nose and throat) referral was made and detailed history revealed life-long self-limiting nasal bleeds for which patient never bothered to report. Additionally, he gave the history of having a brain tumour removed as a child but was not aware if it was a vascular lesion and medical records regarding this could not be obtained. It also came forward that multiple members in his family including three of his other brothers and his father were also suffering from nasal bleed that had been plaguing them all their life and one of them had undergone nasal cautery procedure also to control the bleed. His father had been told to be haemophilic and had apparently died of some bleeding complication. The patient himself had been tested and deemed negative for haemophilia. Also the patient had been diagnosed with iron deficiency anaemia, was on iron supplementation after a normal gastrointestinal (GI) endoscopy and colonoscopy. Careful physical examination revealed several mucocutaneous telangiectasias (figure 1) on the lips and tongue and several arteriovenous malformations (AVMs) on the ear lobes (figures 2 and 3). Several vascular ectasias in his nasal cavity

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Figure 1 Mucocutaneous telangiectasias.

and telangiectasias along the tongue were found on nasal endoscopy. A repeat CT scan of the abdomen showed that the superior mesenteric vein thrombus had resolved, but there were small nodules at the base of the lung for which a CT of chest was performed which showed AVMs. CT angiography of head was negative for cerebral AVMs. Given all of the above history and clinical symptoms a diagnosis of HHT was made and warfarin was stopped.

Since epistaxis ceased following stoppage of warfarin, no surgical intervention was performed. He was advised regarding nasal hygiene, use of nasal saline gel, increase of topical and systemic hydration and avoidance of nasal drying. Patient was referred to interventional radiology for coil embolisation of pulmonary AVMs to prevent pulmonary haemorrhage, paradoxical emboli, strokes and cerebral abscesses. He had pulmonary embolisation for the pulmonary AVMs uneventfully in two sessions. Genetic testing for mutations of the endoglin, SMAD-4 and ALK gene was advised. His brothers with similar symptoms were advised screening for pulmonary AVMs.

INVESTIGATIONS

The diagnosis is usually made based on medical history, family history and clinical finding of mucocutaneous telangiectasias. Investigations in a case of HHT include workup for anaemia, urine analysis for haematuria and stool examination for the presence of occult blood. Coagulation studies may be performed to exclude any other cause of coagulopathy. Once diagnosis of HHT is made, pulse oximetry and arterial blood gas

Figure 2 Arteriovenous malformations.

Figure 3 Ear lobe arteriovenous malformations.

examination may be used for screening of pulmonary AVMs. For evaluation of pulmonary and cerebral AVMs, imaging studies include chest radiography, CT scans or MRI scans of the chest and head. Angiography may be required in case surgery is planned. Upper and lower GI endoscopy is carried out for accurate diagnosis and treatment of GI AVMs. Skin biopsy may be needed in some cases for confirmation of the diagnosis. Genetic testing for the mutations of the endoglin, SMAD-4 and ALK gene may help in 75% of cases.

DIFFERENTIAL DIAGNOSIS

The possibility of HHT should be considered in a patient presenting with nosebleed, red spots on skin and symptoms suggestive of solid organ AVMs. Mucocutaneous telangiectasias need to be differentiated from other dermatological conditions. The vigilant medical history and a strong family history are helpful and presence of three or more Curacao criteria is needed for the definite diagnosis. In our patient, the diagnosis of HHT was not specifically considered at the time of first admission due to acute presentation with abdominal pain and finding of superior mesenteric vein thrombus and the condition was unmasked after start of anticoagulation. A good history and thorough systemic examination would have led to the diagnosis initially thus avoiding the complications of anticoagulation.

TREATMENT

A multidisciplinary team including various specialists is needed in the management of these patients as the lesions involve multiple systems. The principles of treatment in HHT include symptomatic treatment of bleeding, according to the severity and site and surveillance of visceral lesions to avoid potential major complications associated with cerebral, pulmonary and GI AVMs.

Supportive treatment includes iron supplementation, blood transfusions, nasal hygiene and lifestyle modifications and avoidance of drugs like aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants etc. Severe cases of HHT may be given oestrogen therapy to control the bleeding.

The AVMs warrant surgical treatment. Endoscopic treatment or surgical resection may be needed for GI lesions. Embolisation or surgical resection is indicated for pulmonary AVMs ≥ 3 mm to prevent pulmonary haemorrhage, paradoxical emboli, strokes and cerebral abscesses. Antibiotic prophylaxis may be considered at the time of surgical treatment of pulmonary lesions. Our patient had coil embolisation of the pulmonary AVM by the intervention radiologist under vancomycin prophylaxis.

Other family members need to be evaluated for presence of HHT.

OUTCOME AND FOLLOW-UP

Our patient has been doing well after the pulmonary AVMs have been embolised. Since the warfarin has stopped, his epistaxis has reduced considerably and he continues to be followed up in the outpatient clinic every 3 months.

DISCUSSION

HHT or Osler-Weber-Rendu syndrome, first recognised in the 19th century is an autosomal dominant vascular disorder with abnormal vascular structures, mucocutaneous telangiectases, causing bleeding from the nose and GI tract. Epidemiological studies suggest prevalence rates between 1:5000 and 1:8000 with much higher rates in certain geographical populations like Afro-Caribbean residents of Curacao and Bonaire.^{1 2}

Diagnosis is mainly clinical. Epistaxis is commonest³ (90%) and usually the earliest sign of disease followed by skin lesions and AVMs generally become apparent after puberty as abnormal blood vessels usually do not develop before this time, even though a few case reports do report life-threatening symptoms in young children.⁴ By the age of 16 years approximately 70% individuals will have developed some clinical sign of HHT, approaching 90% by the age of 40 years. Usually history of recurrent bleeding in the family members is present. Family history is the most crucial in making a diagnosis.

International consensus diagnostic criteria (Curacao criteria) include (1) spontaneous and recurrent epistaxis, (2) multiple mucocutaneous telangiectasias, (3) visceral involvement (GI, pulmonary, hepatic or cerebral AVMs), and (4) strong family history of first-degree relative with HHT. These criteria define 'definite', 'suspected' and unlikely HHT when three or four, two or zero to one of these criteria are present, respectively.⁵ Our patient had all the four criteria positive.

Majority of the patients have a normal life expectancy. Prognosis is poor in patients presenting at an earlier age due to visceral involvement especially pulmonary, hepatic and central nervous system involvement. Up to 10% of patients die from complications of the disease.

Screening family members for signs of HHT is reasonable and should include a complete history, physical examination, chest radiography and arterial blood gas testing.⁶⁻⁹ Genetic testing may not prove 100% accurate due to presence of large number of mutations.¹⁰⁻¹² However, it can be helpful in diagnosing a child of known family mutation.

Management of HHT involves management of the GI bleed or epistaxis etc, similar to management as in a patient without HHT. Education should be provided regarding nasal hygiene, supportive treatment and avoidance of drugs that can lead to bleeding such as aspirin, NSAIDs, etc.

Guidelines also recommend treating pulmonary and cerebral AVMs to prevent stroke, medical management or liver transplantation for hepatic AVMs. As these lesions grow with time, lifelong periodic monitoring might be needed. However,

currently there are no guidelines available to guide the frequency and modality of imaging for surveillance.^{13 14}

Acute venous thrombosis can be inherited (mentioned in the case presentation section) or acquired. Acquired causes include malignancy, the presence of a central venous catheter, prolonged immobilisation, surgery, trauma, pregnancy, oral contraceptives, hormone replacement therapy, antiphospholipid antibody syndrome, nephrotic syndrome, etc. However, our patient did not have any of the acquired or inherited risk factors for venous thrombosis hence we were unable to determine the aetiology of the venous thrombosis.

Learning points

- Comprehensive history including medical and family history and physical examination by the general practitioner is extremely important to pick up 'zebra' diagnoses.
- Whenever a patient presents with nosebleed, red skin spots or symptoms suggestive of various arteriovenous malformations (AVMs), possibility of hereditary haemorrhagic telangiectasia (HHT) should be entertained.
- Diagnostic criteria include spontaneous and recurrent epistaxis, mucocutaneous telangiectasias, visceral AVMs (gastrointestinal (GI), pulmonary, hepatic or cerebral) and strong family history of first-degree relative with HHT.
- Management includes symptomatic management of GI bleed/epistaxis, but prophylactic treatment of pulmonary, cerebral and hepatic AVMs.
- Venous thrombosis can be inherited (factor V Leiden or prothrombin gene mutation, protein C, S and antithrombin III deficiency) or acquired (malignancy, surgery, oral contraceptives, etc).

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Competing interests None.

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