SMAD4 mutation and the combined syndrome of juvenile polyposis syndrome and hereditary haemorrhagic telangiectasia

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ABSTRACT
Juvenile polyposis syndrome (JPS) and hereditary haemorrhagic telangiectasia (HHT) are autosomal dominant disorders with characteristic clinical phenotypes. Recently, reports of the combined syndrome of JPS and HHT have been described in individuals with mutations in the SMAD4 gene, whose product—SMAD4—is a critical intracellular effector in the signalling pathway of transforming growth factor β (TGFβ). This report describes a 24-year-old man who presented to the Respiratory Institute after colectomy for JPS with a SMAD4 mutation and who was subsequently diagnosed to have HHT with asymptomatic cerebral and pulmonary arteriovenous malformations (AVMs). Patients with JPS due to a SMAD4 mutation should be screened for the vascular lesions associated with HHT, especially occult AVMs in visceral organs, which may potentially present catastrophically with serious medical consequences.

Due to the diagnosis of JPS, molecular genetic tests were conducted to identify mutations in the BMPR1A and SMAD4 genes. Mutation analysis with PCR identified a deletion mutation, 1228-1229delCA, located within the MH2 domain of the SMAD4 gene. His parents and five other siblings underwent screening genetic testing and the same mutation was identified in his mother, two brothers and one sister. He was subsequently referred to the Respiratory Institute for further evaluations. On taking his history, besides the single episode of haematochezia, he reported recurrent spontaneous episodes of epistaxis since childhood, but denied haemoptysis, melaena or haematemesis. He denied history of iron deficiency anaemia, or symptoms suggestive of stroke or seizures. Physical examination was remarkable for the presence of telangiectasias on the lips and nasal cavity. He had normal heart and lung sounds on auscultation, there was no evidence of cyanosis or digital clubbing, and a detailed neurological examination was normal.

Contrast-enhanced helical CT of the chest with maximum intensity projection reconstructions identified an arteriovenous malformation (AVM) in the right middle lobe with a 3.6 mm feeding vessel (figure 1) and a smaller AVM in the right lower lobe with a 1.3 mm feeding vessel. MRI of the brain showed a supratentorial dural arteriovenous fistula that was confirmed by cerebral angiography (figure 2). Doppler ultrasonography of the liver did not identify any telangiectasias or vascular masses. With this constellation of findings he met the Curacao criteria for a diagnosis of definite haemorrhagic telangiectasia (HHT).1 Given the history of JPS and the presence of a SMAD4 mutation, diagnosis of the combined syndrome of JPS—HHT was established. Due to the risks of serious neurological events with pulmonary AVMs supplied by a feeding artery at least 5 mm in diameter or larger, he underwent prophylactic coil embolotherapy of the right middle lobe AVM.

On follow-up in 6 months, he felt well and denied any respiratory or gastrointestinal symptoms. He continued, however, to have mild infrequent episodes of epistaxis with normal haemoglobin levels and no requirements for blood transfusions.

DISCUSSION
The combined syndrome of JPS—HHT is a rare disorder caused by SMAD4 mutations that tend to cluster in the MH2 domain of the protein.23 Since 1980 case reports of patients with phenotypic features of both JPS and HHT began to be published and this prompted questions about a single genetic mutation...
involved most commonly manifests as pulmonary AVMs, although hepatic and cerebral AVMs have also been infrequently noted.5 The mean age of AVM detection is 26 years (range: 4 months to 60 years).11 Thus far, there has been no identification of patients with SMAD4-positive JPS—HHT with pulmonary arterial hypertension.

SMAD4 is a critical intracellular effector in transforming growth factor β (TGFβ) signalling which controls a plethora of cellular responses.12 Despite the pleiotropy of TGFβ, its downstream messenger elements remain relatively constant, including cell membrane-based type II, type I and accessory receptors, and intracellular receptor-regulated SMADs (R-SMADs) and the co-SMAD, SMAD4.12 TGFβ is essential for vascular integrity, as ENG (accessory receptor) and ALK1 (type II receptor) mutations lead to the failure to form cord-like vascular structures which leads to the fragility of small vessels with bleeding characteristic of HHT, or to disrupted and abnormal angiogenesis after injuries, and may explain the clinical symptoms associated with this disease.13 In the gastrointestinal system, TGFβ signalling is thought to exert a landscaping effect from within the micro-environment as SMAD4 and BMPR1A (type I receptor) mutations lead to mucosal hyperplasia and polyp formation.14

Greater awareness of this rare syndrome and its implications is needed among respiratory physicians caring for these patients. Patients with JPS and SMAD4 mutations should be screened for the vascular lesions associated with HHT, especially occult AVMs in visceral organs that may otherwise present suddenly with serious medical consequences. Similarly, in patients with HHT with neither ENG nor ALK1 mutations, molecular testing for SMAD4 mutations should be included as their presence suggests an elevated risk of gastrointestinal polypsis, and screening for colonic and gastric polyps associated with JPS needs to be conducted.

Competing interests None.

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