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

Nithya K Iyer,[1] Carol A Burke,[2] Brandie H Leach,[3] Joseph G Parambil[1]

[1]Respiratory Institute, Cleveland Clinic, Cleveland, Ohio, USA
[2]Digestive Diseases Institute, Cleveland Clinic, Cleveland, Ohio, USA
[3]Genomic Medicine Institute, Cleveland Clinic, Cleveland, Ohio, USA

Correspondence to
Joseph G Parambil, Department of Pulmonary & Critical Care Medicine, Respiratory Institute, Desk A-90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA;
parambj@ccf.org

Received 23 October 2009
Accepted 6 May 2010

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.

A 24-year-old man, who never smoked tobacco, was seen in the Respiratory Institute after identifying the presence of a deletion mutation in the *SMAD4* gene.

His history began 8 months previously, when juvenile polyposis syndrome (JPS) was diagnosed after he underwent colonoscopy for an episode of haematochezia. Colonoscopy revealed multiple polyps distributed diffusely throughout the colon; biopsy of several random polyps showed hamartomatous features without evidence of dysplasia consistent with juvenile polyposis. Due to the disease burden, total colectomy with ileo-rectal anastomosis was recommended. On the day of the operation, he was premedicated with 2 mg of midazolam in the preanaesthesia holding area, following which he developed atrial fibrillation (AF). The procedure was cancelled and bedside echocardiogram was performed along with Cardiology consultation. The echo showed no evidence of structural heart disease, with normal left and right ventricular size and function, normal atrial chambers, normal valvular apparatuses and no suggestions of pulmonary hypertension. Following the intravenous injection of agitated saline there was late appearance of bubbles in the left atrium suggestive of an intrapulmonary shunt. With the use of supplemental oxygen and 25 mg of oral metoprolol, the episode of AF spontaneously terminated within 6 h and he was sent home with an event monitor. On follow-up with Cardiology a month later, he was asymptomatic and no further episodes of AF were documented on event monitoring. He was diagnosed with lone AF that was triggered by sedation, proceeded to surgery uneventfully and was discharged home in 4 days.

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 Curaçao 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 3 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.[2 3] 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

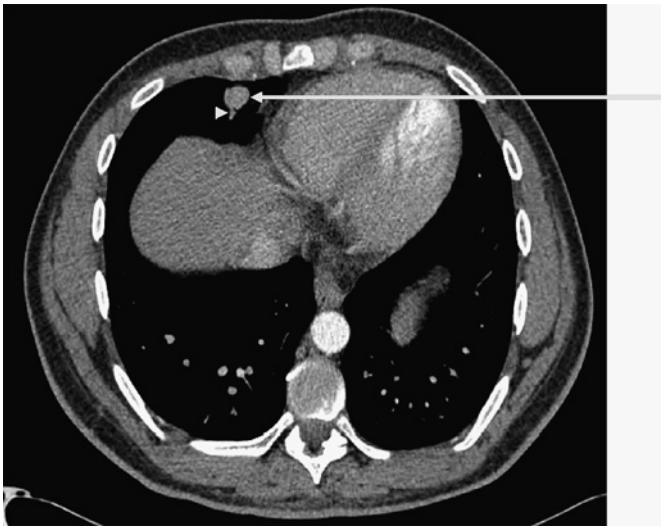

Figure 1 Contrast-enhanced CT of the chest shows a 2.1×1.3 cm well-defined nodular lesion in the right middle lobe anteriorly (arrow), with a 3.6 mm feeding artery (arrowhead), suggestive of an arteriovenous malformation.

which could account for these findings.[4–6] In 2004 Gallione *et al* identified *SMAD4* mutations in seven families with the combined syndrome of JPS–HHT, with none showing *ENG*, *ALK1* or *BMPR1A* mutations.[2] The prevalence of *SMAD4* mutations is ~20% in patients with JPS and is harboured in 10% of patients with HHT.[7 8]

SMAD4-positive patients with JPS–HHT display the spectra of symptoms of both individual diseases, and established criteria for both JPS and HHT are used for making the diagnosis, as diagnostic criteria for the combined syndrome of JPS–HHT have not yet been ascertained.[1 9] The penetrance of the JPS phenotype is complete in these patients as all exhibit gastrointestinal polyposis with a high incidence of gastric polyps.[10 11] The mean age of diagnosis of JPS is 23 years (range: 3–65 years) and, similarly to previous studies on JPS, these patients demonstrate a significant gastrointestinal malignant potential.[10] Patients with *SMAD4*-positive JPS–HHT also tend to display the full range of clinical features associated with HHT.[8 11] Visceral organ involvement most commonly manifests as pulmonary AVMs, although hepatic and cerebral AVMs have also been infrequently noted.[8] 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.

Figure 2 Cerebral angiography demonstrates a right supratentorial dural arteriovenous fistula (arrow) with arterial supply from branches of the right meningohypophyseal trunk and distal branches of the right internal maxillary artery, and draining into the sigmoid sinus.

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 microenvironment 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 polyposis, and screening for colonic and gastric polyps associated with JPS needs to be conducted.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Shovlin CL,** Guttmacher AE, Buscarini E, *et al*. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu–Osler–Weber syndrome). *Am J Med Genet* 2000;**91**:66–7.
2. **Gallione CJ,** Repetto GM, Legius E, *et al*. A combined syndrome of juvenile polyposis and hereditary hemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). *Lancet* 2004;**363**:852–9.
3. **Pyatt RE,** Pilarski R, Prior TW. Mutation screening in juvenile polyposis syndrome. *J Mol Diagn* 2006;**8**:84–8.
4. **Cox KL,** Frates RC, Wong A, *et al*. Hereditary generalized juvenile polyposis associated with pulmonary arteriovenous malformation. *Gastroenterology* 1980;**78**:1566–70.
5. **Baert AL,** Casteels-Van Daele M, Broeckx J, *et al*. Generalized juvenile polyposis with pulmonary arteriovenous malformations and hypertrophic osteoarthropathy. *Am J Roentgenol* 1983;**141**:661–2.
6. **Prieto G,** Polanco I, Sarria J, *et al*. Association of juvenile and adenomatous polyposis with pulmonary arteriovenous malformation and hypertrophic osteoarthropathy. *J Pediatr Gastroenterol Nutr* 1990;**11**:133–7.
7. **Howe JR,** Sayed MG, Ahmed AF, *et al*. The prevalence of MADH4 and BMPR1A mutations in juvenile polyposis and absence of BMPR2, BMPR1B, and ACVR1 mutations. *J Med Genet* 2004;**41**:484–91.
8. **Gallione CJ,** Richards JA, Letteboer TG, *et al*. SMAD4 mutations found in unselected HHT patients. *J Med Genet* 2006;**43**:793–7.
9. **Jass JR,** Williams CB, Bussey HJ, *et al*. Juvenile polyposis—a precancerous condition. *Histopathology* 1988;**13**:619–30.
10. **Sayed MG,** Ahmed AF, Ringold JR, *et al*. Germline SMAD4 or BMPR1A mutations and phenotype of juvenile polyposis. *Ann Surg Oncol* 2002;**9**:901–6.
11. **Gallione C,** Aylsworth AS, Beis J, *et al*. Overlapping spectra of SMAD4 mutations in juvenile polyposis (JP) and JP–HHT syndrome. *Am J Med Genet* 2010;**152A**:333–9.
12. **Heldin CH,** Miyazono K, ten Dijke P. TGF-beta signaling from cell membrane to nucleus through SMAD proteins. *Nature* 1997;**390**:465–71.
13. **van den Driesche S,** Mummery CL, Westermann CJ. Hereditary hemorrhagic telangiectasia: an update on transforming growth factor beta signaling in vasculogenesis and angiogenesis. *Cardiovasc Res* 2003;**58**:20–31.
14. **Kinzler KW,** Vogelstein B. Landscaping the cancer terrain. *Science* 1998;**280**:1036–7.