

CASE REPORT

Juvenile polyposis syndrome and hereditary haemorrhagic telangiectasia caused by the *SMAD4* gene mutation in a paediatric patient – a case report and a review of the literature

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ABSTRACT

Germline mutations in the *SMAD4* gene cause juvenile polyposis syndrome and hereditary haemorrhagic telangiectasia. In some cases, the coexistence of these 2 syndromes can be observed among probands with the mutation in the *SMAD4* gene. A combined syndrome of juvenile polyps of the gastrointestinal tract and hereditary haemorrhagic telangiectasia caused by mutations of the *SMAD4* gene is recognized as a distinct disease entity (OMIM #175050). Herein we present a case of a teenage boy with an affected family history, who was admitted to our department in order to broaden the diagnosis of the causes of his rectal bleeding and recurrent nasal bleeding. In the course of investigation polyps in his gastrointestinal tract and arteriovenous malformations in his lungs were revealed.

KEY WORDS:

cancer, polyps, telangiectasia, organ arteriovenous malformations.

INTRODUCTION

Juvenile polyposis syndrome (JPS) and hereditary haemorrhagic telangiectasia (HHT) are 2 distinct autosomal diseases. However, in patients with mutations in the *SMAD4* gene (Mothers against decapentaplegic homologue 4 gene), they can be present as a combined syndrome. The coexistence of these diseases was first described early in the 1980s. Nevertheless, the association between this combined syndrome and mutation in the *SMAD4* gene was first reported in 2004 by Gallione *et al.* [1]. Empirical evidence indicates that patients with

JPS-HHT are at risk of an early onset of colorectal cancer (mean age 28 years) [2].

Juvenile polyposis syndrome is an autosomal dominant disorder, characterized by the predisposition to hamartomatous (juvenile) polyps in the gastrointestinal tract, especially in the stomach, small intestine, colon, and rectum. The term “juvenile” refers to the histopathology of the polyp and not to the age of the onset of polyps. The prevalence rate of the JPS ranges from 1 in 160,000 to 1 in 100,000 people [3]. Rectal bleeding is often its primary manifestation and may appear in early childhood. It is worth mentioning that this condition

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is associated with an increased risk of gastrointestinal tract cancer, with a lifetime risk of 38% to 68% [3]. The most likely cancer is that of the colon, but cancers of the stomach, upper gastrointestinal tract, and pancreas have been reported.

Hereditary haemorrhagic telangiectasia is also an autosomal dominant disorder characterized by vascular dysplasia with mucocutaneous telangiectasia and organ arteriovenous malformations (AVMs) mainly affecting the lungs, liver, and brain. It was originally known as Osler-Weber-Rendu syndrome after the 3 scientists who described it at the turn of the 20th century.

The aim of the study is to present the medical case of a teenage boy with combined juvenile polyposis syndrome and hereditary haemorrhagic telangiectasia.

CASE REPORT

An 11-year-old boy was referred to the regional Gastroenterology Department in 2014 because of rec-

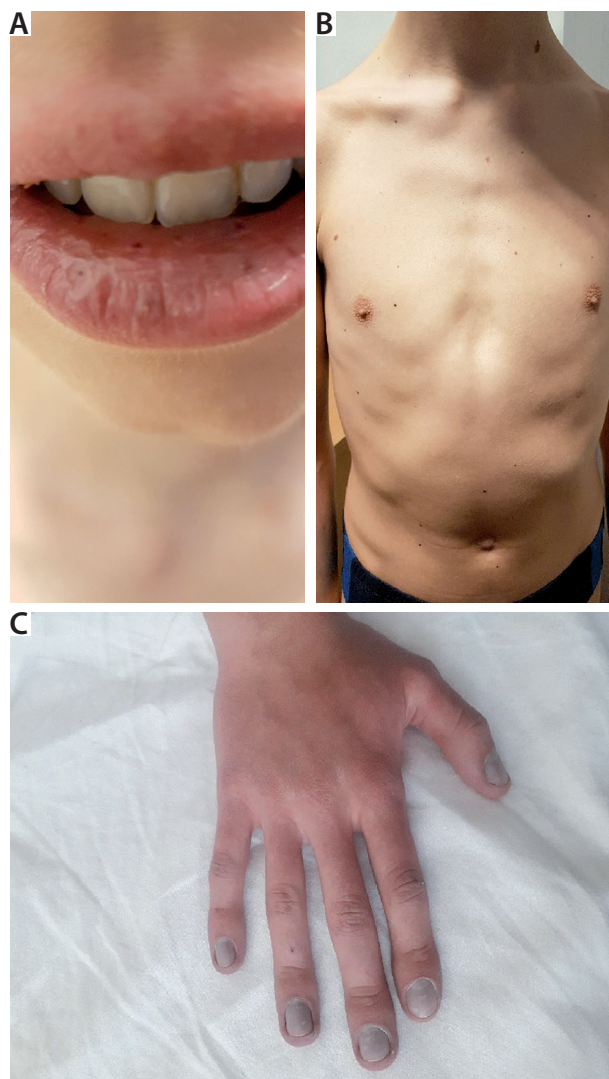


FIGURE 1. Signs revealed in the physical examination: A) telangiectasia on bottom lip; B) funnel-shaped chest; C) cyanosis of nails, clubbed fingers

tal bleeding. The rectal bleeding had been noticed for the first time 7 years earlier and was most frequent after defecation. The patient also complained of recurrent nasal bleeding. The boy's mother underwent a colectomy in adulthood because of polyposis syndrome. She suffers from arteriovenous malformations in the lungs.

During the physical examination on admission, asthenic body type, protruding shoulder blades, and skin discoloration on his left forearm were noticed. Laboratory tests revealed elevated inflammation parameters (CRP 14.2 mg/dl, normal range: 0.1–10.0 mg/l) and reduced capillary blood saturation (83.1%). The abdominal ultrasound examination was normal. During hospitalization, an endoscopy was performed and showed oesophageal erosions, a sentinel polyp in the stomach, a 1-cm polyp in the duodenum, a 1-cm polyp in the ascending colon, and six 2–4-cm polyps in the sigmoid colon and rectum. Histology revealed hyperplastic polyps. The patient was directed to our Department.

A clinical interview revealed periodical stools with a small amount of blood (3–4 times a month). In the physical examination small telangiectasias on the lower lip, a funnel-shaped chest, hypermobility of interphalangeal joints in the hands, arachnodactyly, and cyanosis of the lips and nails were noticed (Fig. 1).

Endoscopy revealed over a dozen polyps in the large intestine, the biggest aggregation in the rectum. Eight polyps were removed, the biggest being 1.5 cm in diameter. Histopathology described juvenile polyposis with a strong inflammation infiltrate.

A control colonoscopy was carried out 2 months later. During the examination 18 polyps were removed. Because of the desaturation during anaesthesia, the patient was directed to the Department of Pulmonology. CT angiography of chest was carried out and revealed arteriovenous malformations in the lungs. Home oxygen therapy was recommended and caused a rise in the oxygen saturation from 85% to 92%.

The patient was subsequently admitted to the Cardiology Department. Echocardiography showed a dilatation of the pulmonary artery to 2 cm and small tricuspid valve regurgitation. Diagnostic cardiac catheterization was carried out and showed numerous arteriovenous malformations, but their seclusion was infeasible because of the anatomy. Lung transplantation was considered. Sildenafil therapy, among other things, was introduced to the pharmacological treatment, and an improvement in effort tolerance was achieved. The patient could abstain from home oxygen therapy.

The patient underwent a gastroscopy and colonoscopy once a year (on average). Due to the diagnosis of the JPS, molecular genetic tests were conducted to exclude mutations in the *BMPRIA* (bone morphogenetic protein receptor type 1 A), *SMAD4*, and *PTEN* (phosphatase

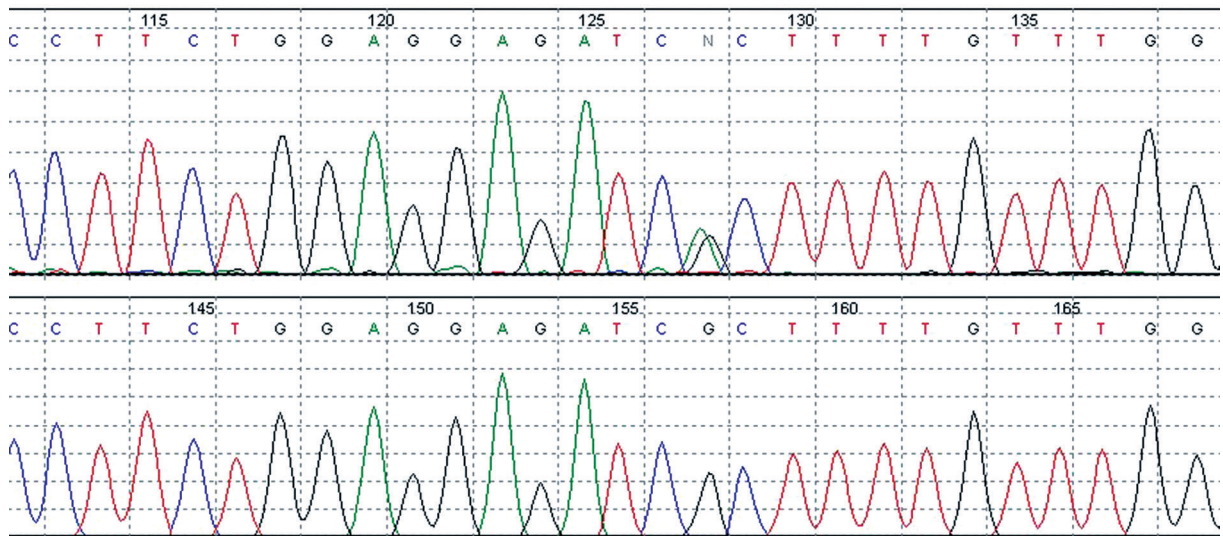


FIGURE 2. Sanger sequencing of *SMAD4* gene fragment A patient, B control, arrow indicates c.1082G>A, p.Arg361His

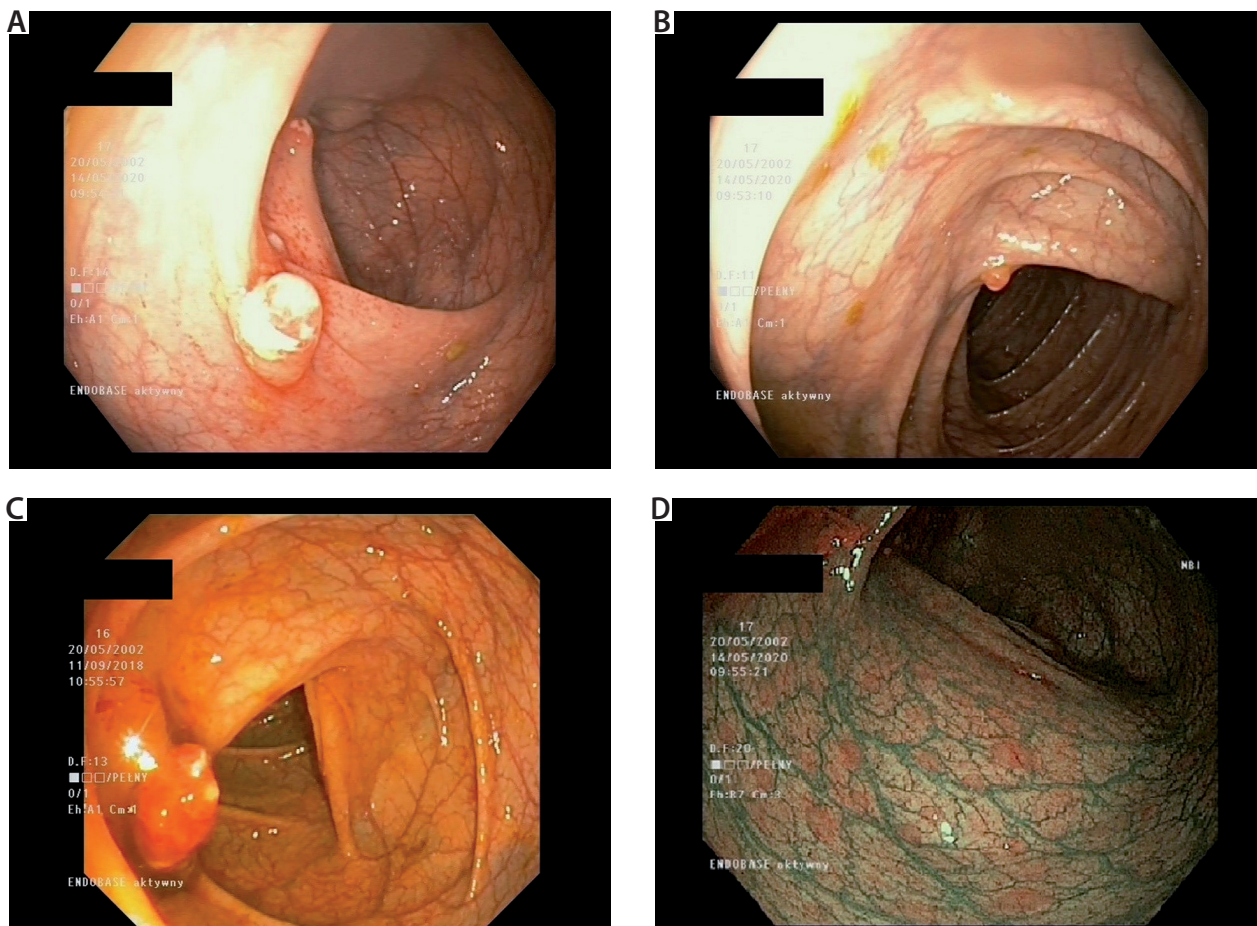


FIGURE 3. Changes revealed during colonoscopy

and tensin homologue) genes. Sanger sequencing of the *SMAD4* gene identified a pathogenic substitution c.1082G>A (p. Arg361His, Fig. 2).

The last endoscopy showed esophagitis LA B and numerous sitting and pedunculated polyps in the colon (mostly in the proximal colon, with a diameter of 4 to 10 mm, displayed in Fig. 3). The histopathology revealed juvenile polyps (presented in Fig. 4). Magnetic resonance

imaging (MRI) of the brain was carried out and did not show any malformations. An ultrasound examination also did not reveal any arteriovenous malformations in the liver.

Because of the *SMAD4* mutation and higher risk of colorectal cancer and the fact that the burden of polyps is not manageable by the polypectomy alone, a colectomy should be considered in future.

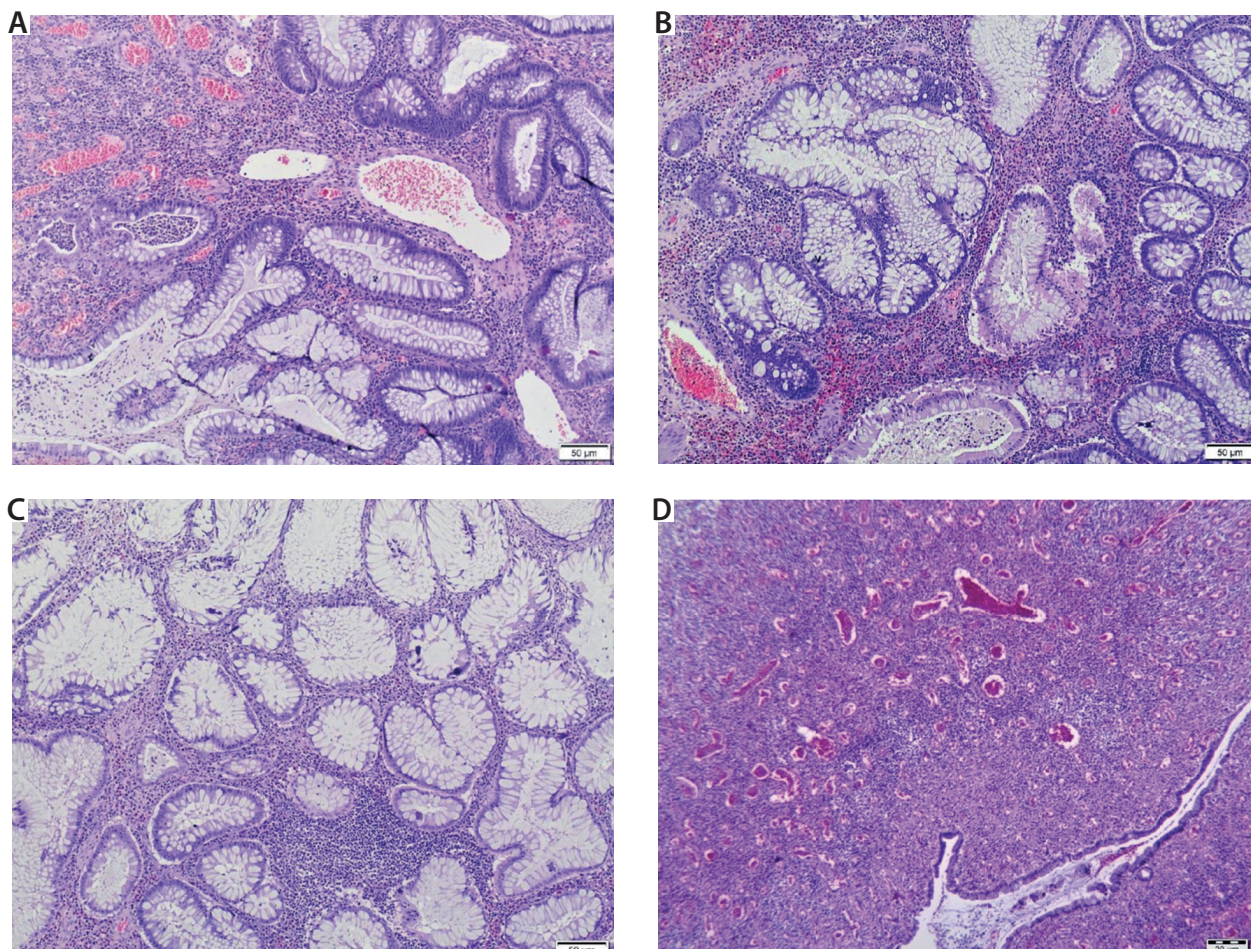


FIGURE 4. Microscopic changes in the juvenile polyp. Hematoxylin and eosin staining. A) cystically dilated glands, inflammatory infiltrates into the glands, B) and C) glandular hyperplastic changes; D) stromal vascular reaction

The patient’s younger brother also had a gastroscopy and colonoscopy. The first examination showed only a small, creating polyp in rectum. The histopathology revealed inflammation changes. An examination, which took place 3 years later, did not show any changes. Molecular genetic tests were also conducted, but they did not identify mutations in the *BMPRIA*, *SMAD4*, and *PTEN* genes; notably, the mutation c.1082G>A was not found.

DISCUSSION

The mutation in the *SMAD4* gene causes a combined syndrome of juvenile polyps of the gastrointestinal tract and HHT, also known as JP-HHT. It is a very rare condition, and it can have various clinical presentations. Juvenile polyposis (JP) can be present in infancy and in adulthood with abdominal pain, anaemia, acute or

chronic gastrointestinal bleeding, prolapsed rectal polyps, bowel obstruction, or intussusception [2]. Patients may also be asymptomatic [2]. The diagnostic criteria of JPS proposed by Jass *et al.* [4] contain 5 or more juvenile polyps of the colon or rectum, or juvenile polyps in other parts of the gastrointestinal tract, or any number of juvenile polyps and a positive family history. In 40% to 60% of patients with JPS a mutation in *SMAD4* (18q21.1) or *BMPRIA* (10q23.2) genes is reported [3]. It is worth remembering that many patients with JPS due to *SMAD4* mutation have features of HHT (epistaxis, telangiectasia, clubbing, and AVM) [5]. The most common feature of HHT is epistaxis. The arteriovenous malformations can lead to a life-threatening haemorrhage, circulatory insufficiency, brain abscesses, and stroke. Eighty per cent of families suffering from HHT have a mutation in the endoglin (*ENG*) or activin receptor-like kinase 1

TABLE 1. The Curacao criteria for HHT [7]

1.	Epistaxis – spontaneous, recurrent nose bleeds
2.	Telangiectases – multiple, at characteristic sites: lips, oral cavity, fingers, nose
3.	Visceral lesions such as gastrointestinal telangiectasia (with or without bleeding), pulmonary AVM, hepatic AVM, cerebral AVMs, spinal AVM
4.	Family history – a first-degree relative with HHT according to these criteria

(*ALK1*) genes. Twenty per cent of patients have a mutation in the *SMAD4* gene or in the new loci mapped to chromosome 5 and chromosome 7. It is known that HHT patients with *SMAD4* mutations have anaemia more frequently than do patients with alterations of the *ENG* and *ALK1* gene [2].

Clinical features of HHT in patients with *SMAD4* mutations [6] are epistaxis, mucocutaneous telangiectasias, AVM (visceral, hepatic, intracranial), aortopathy, and intrapulmonary shunting on echocardiogram.

The Curacao criteria for HHT [7] is definite if 3 criteria are present, possible or suspected if 2 criteria are present, and unlikely if fewer than 2 criteria are present (Table 1).

The first symptom, as in the case of our patient, can be hypoxia. Children with HHT are at risk of life-threatening complications. In JPS patients with mutations within the *SMAD4* gene the risk of colorectal cancer is higher (in a cohort of 14 *SMAD4* Danish patients 3 colorectal cancers occurred at a mean age of 34 years) [3]; the risk of severe gastric polyposis and gastric cancer appears to be increased [3]. Thoracic aortic disease and mitral dysfunction have also been reported [6]. That is why systematic HHT screening is recommended for JPS patients with proven *SMAD4* mutation.

A Position Paper From the ESPGHAN Polyposis Working Group recommends also that a colectomy should only be discussed in patients in whom the burden of polyps is not manageable by polypectomy alone, and/or leading to uncontrollable anaemia or hypoalbuminaemia from colonic polyposis [3]. The question is, however, whether the recommendation for polypectomy should not be expanded for patients with JPS and *SMAD4* mutations and JPS-HHT overlap syndrome in which the risk of colorectal cancer is higher.

Jelsing *et al.* [8] described the clinical characteristics of 14 Danish patients with *SMAD4* mutations. They found that probands with *SMAD4* mutation have symptoms of both HHT and JPS and that the frequency of PAVM and of gastric involvement with polyps in this group is higher than in patients with HHT or JPS not caused by mutations in the *SMAD4* gene. Furthermore, the authors detected 4 occurrences of GI – cancer at a young age. Similar results were presented in the work of Schwenter *et al.*, in which 10 patients met the clinical diagnostic criteria for both JP and HHT [2]. Three JPS-HHT patients developed early-onset colorectal cancer [2]. In a study of 80 unrelated families with juvenile polyposis syndrome, Aretz *et al.* found that 35 of the cases of JPS were caused by the *SMAD4* mutations, of which 22% exhibited features of the HHT [9]. All the described cases of gastric cancer in that publication (i.e. 7 cases) were reported in families with mutations in the *SMAD4* gene. In addition to those studies, there are also case presentations in the literature. Teekakirikul *et al.* reported 2 patients with JPS-HHT and with *SMAD4* mutations associated

TABLE 2. Summary of sample characteristics in the related literature

Author	Number of patients with <i>SMAD4</i> mutation	Number of paediatric patients	Number of patients fulfilled the diagnostic criteria for JPS	Number of patients fulfilled the Curacao criteria	Colorectal cancer	Gastric cancer	Pulmonary AVMs	Strokes/ Cerebral AVMs	Liver AVMs	Hepatic focal nodular hyperplasia	Aortopathy
Jelsing <i>et al.</i> [8]	14	0	11	7	3	1	5	1	-	-	1
Schwenter <i>et al.</i> [2]	14	Not specified	10	10	3	-	8	2	-	-	-
Aretz <i>et al.</i> [9]	23	Not specified	65	5	-	7	-	-	-	-	-
Teekakirikul <i>et al.</i> [10]	2	1	2	2	0	0	2	0	0	1	2
Iyer <i>et al.</i> [11]	1	0	1	1	-	-	1	1	0	-	-
Chung and Mortelet [12]	1	0	1	1	-	-	-	-	1	1	-

with thoracic aortic disease [10]. This report confirmed the fact that *SMAD4* mutations predispose to thoracic aortic aneurysms and aortic dissections. Their work emphasized that the thoracic aorta should be screened in patients with *SMAD4* mutations to prevent death from dissection [10]. Iyer *et al.* reported a patient with the JPS-HHT syndrome and *SMAD4* mutations [11]. The patient suffered from asymptomatic cerebral and pulmonary arteriovenous malformations. The only study that reports multiple arteriovenous malformations involving the liver was that of Chung *et al.* [12].

We found only one paper by Pantaleoni *et al.* describing a patient with severe hypoxaemia secondary to an inoperable pulmonary arteriovenous malformations treated by long-term management with sildenafil [13].

In Table 2 we summarize data from the literature concerning JPS-HHT syndrome.

We present the case because of the rarity of the JPS-HHT syndrome in the literature, particularly in paediatric patients, and the need for multidisciplinary care of these patients to avoid life-threatening complications. We highlight a positive influence of sildenafil on the respiratory function of our patient.

CONCLUSIONS

1. Patients with features of both JP and HHT should be screened for mutations in the *SMAD4* gene.

2. Paediatric patients with JPS-HHT syndrome and arteriovenous malformations of the lungs may profit from sildenafil treatment.

DISCLOSURE

The authors declare no conflict of interest.

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