

Juvenile polyposis syndrome with germline SMAD4 mutation: case series in tertiary care and critical review of literature

F. Vulsteke¹, V. D'Cruz¹, L. Krott², S. Moura Ribeiro¹, E. Van Daele³, B. Poppe⁴, B. Menten⁴, R. De Putter⁴, P. Hindryckx¹, A. Hoorens⁵, E. Callebaut¹, V. Casneuf^{1,6}, K. Geboes¹

(1) Department of Gastroenterology, University Hospital Ghent, Ghent, Belgium; (2) Department of Gastroenterology, AZ Sint Blasius, Dendermonde, Belgium; (3) Department of Gastrointestinal Surgery, University Hospital Ghent, Ghent, Belgium; (4) Centre for Medical Genetics, University Hospital Ghent, Ghent, Belgium; (5) Department of Pathology, University Hospital Ghent, Ghent, Belgium; (6) Department of Gastroenterology, AZorg, Aalst, Belgium.

Abstract

Background: Juvenile polyposis syndrome (JPS) is a rare autosomal dominant disorder characterized by the presence of multiple hamartomatous polyps in the gastro-intestinal (GI) tract with an increased risk for developing GI cancer. Two causative genes have been identified, of which SMAD4 germline mutations show more upper GI tract involvement and appears to be a more aggressive form. In addition, SMAD4 JPS is linked with hereditary haemorrhagic telangiectasia (HHT).

Case history: We present 4 patients in our tertiary care hospital with a challenging treatment of extensive gastric polyposis who all had a late diagnosis, some of them despite the early discovery of polyposis or colon tumors.

Conclusion: Diagnosing SMAD4 JPS can be challenging but is important for the management of patients. The malignant potential in the upper GI tract is underestimated in clinical practice. Germline genetic analysis should be awaited before performing surgical interventions. (*Acta gastroenterol belg.*, 2025, 88, 277-280).

Keywords: Juvenile polyposis syndrome, SMAD4 germline mutation, massive gastric polyposis, JPS-HHT overlap syndrome.

List of abbreviations

ACG: American College of Gastroenterology
aFAP: attenuated FAP
CRC: colorectal cancer
EGD: esophagogastroduodenoscopy
ESGE: European Society of Gastrointestinal Endoscopy
FAP: familial adenomatous polyposis
HHT: hereditary haemorrhagic telangiectasia
IDA: iron deficiency anemia (IDA)
JPS: juvenile polyposis syndrome
MAP: MUTYH-associated polyposis
MMRp: mismatch repair proficient

Introduction

Juvenile polyposis syndrome (JPS) is a rare, autosomal dominant, gastrointestinal (GI) cancer predisposition syndrome affecting 1:100.000 to 1:160.000 individuals, characterized by the development of numerous hamartomatous polyps located in the colorectum (98%), stomach (14%), jejunum and ileum (7%), and duodenum (7%) (1–3). The syndrome is predominantly resulting from mutations in the SMAD4 or BMPR1A genes. SMAD4 JPS shows more upper GI tract involvement and appears to be a more aggressive form (1,4). Hamartomatous polyps are prone to bleeding, resulting in anemia and/or rectal bleeding as most common presentation (2,5). Because of the low prevalence, clinical and endoscopic data remain sparse, and guidelines are formed on expert opinion. We present

four interesting cases of patients with SMAD4 JPS, leading to a critical reflection of current knowledge.

Case histories

Case 1

The first patient underwent an esophagogastroduodenoscopy (EGD) at the age of 32 due to recurrence of iron deficiency anemia (IDA). Large gastric folds were seen (Figure 1A), as well as a large antral polyp (10 cm) and multiple duodenal polyps (Figure 2A). The patient had undergone surgery at the age of 10, because of an invagination caused by a small bowel polyp, considered as a Peutz-Jeghers polyp. At the age of 26 he underwent right hemicolectomy because of polyposis causing IDA. Histological examination showed 11 polyps, some smaller polyps classified as inflammatory, and larger as adenomatous polyps. His mother had colon cancer at the age of 31. Germline genetic analysis for adenomatous polyposis syndromes and Peutz-Jeghers syndrome failed to identify a pathogenic defect. After multidisciplinary discussion, endoscopic resection of the duodenal polyps was performed, followed by a surgical myotomy and antral polypectomy in order to keep endoscopic surveillance of the duodenal region feasible.

Histological examination of the duodenal polyps showed features consistent with hamartomatous polyps, some classical juvenile polyps, as well as more atypical juvenile polyps (Figure 2B, C and D). The antral polyp showed microscopic features of a hyperplastic (regenerative) gastric polyp but was much larger than usual, suggestive for a hamartomatous polyp, lacking the pronounced muscularis mucosae hyperplasia of a Peutz-Jeghers polyp (Figure 1B and C). Germline analysis for JPS showed a heterozygous germline SMAD4 c.613_616dup, p.(ser206fs) mutation causing

Correspondence to: K. Geboes, Department of Gastroenterology, University Hospital Ghent, Corneel Heymanslaan 10, B-9000 Belgium. Tel. + 32 9 332 23 71.

Email: Karen.Geboes@uzgent.be
Submission date: 26/03/2025
Acceptance date: 15/06/2025

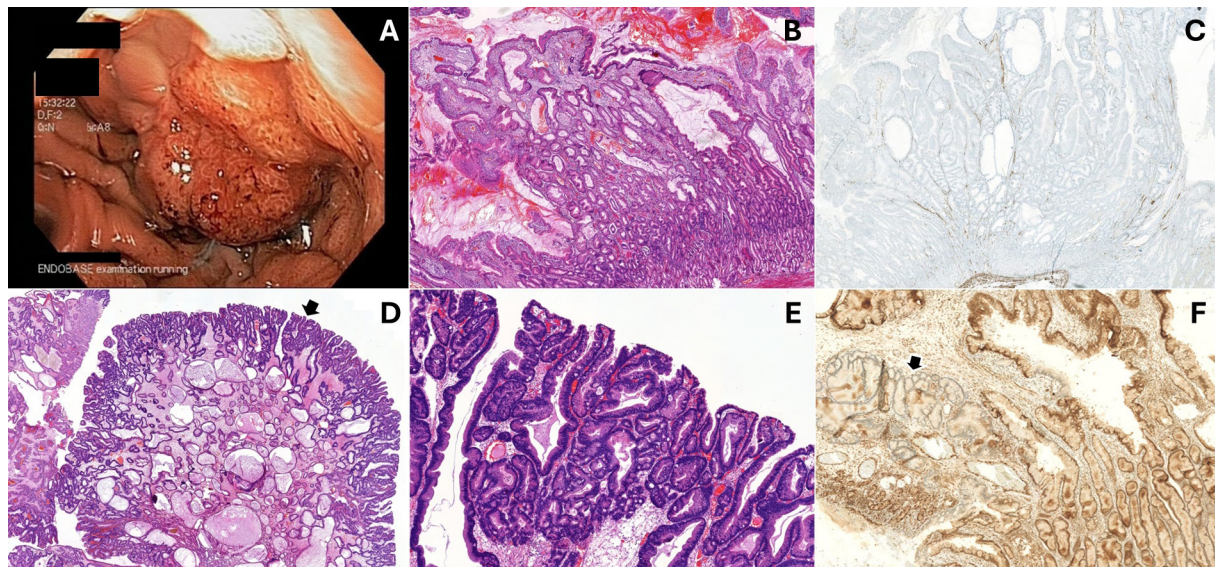


Figure 1. — Large gastric folds and large antral polyp.

A: SMAD4 juvenile polyposis syndrome (JPS) patient with typically large gastric folds of the corpus and an antral gastric polyp. B: Gastric antral polyp resembling a hyperplastic (regenerative) gastric polyp with irregularly dilated hyperplastic glands and villiform structures lined by foveolar epithelium with background mucosa showing mild inflammation, but much larger than usual (diameter of 10 cm), suggesting a hamartomatous polyp (magnification X25). C: Desmin immunohistochemistry shows less pronounced muscularis mucosae hyperplasia than is usually observed in Peutz-Jeghers polyps, suggestive of a juvenile polyp, however, significant overlap exists (magnification X15). D: Gastric polyp showing irregular and cystic dilated hyperplastic glands lined by foveolar epithelium. The lamina propria is expanded by oedema. Focally high grade dysplasia can be observed (arrow) (magnification X8). E: Higher magnification of the area with high grade dysplasia indicated in the lower left figure (magnification X50). F: SMAD4 immunohistochemistry shows focal loss of SMAD4 expression in a gastric juvenile polyp (arrow).

a premature stop codon, a mutation that has not been described before. During follow-up a gastric juvenile polyp with focal high grade dysplasia was resected (Figure 2D and E). The patient is now 43 years old and requires intravenous iron biannually.

Case 2

The second patient had been diagnosed with diffuse hemorrhagic gastritis, with a suggestion of Menetrier disease, and colon cancer during work-up of anemia at the age of 48. A right hemicolectomy was performed for a pT4aN2bM0 tumor. One year later he was admitted with melena due to bleeding of a big antral polyp (6 cm). A surgical myotomy was performed, histological analysis showing a hamartomatous polyp with focal loss of SMAD4 expression (Figure 1F). Due to symptomatic scarring postoperatively, a pyloroplasty was needed. EGD showed early relapse of many hamartomatous polyps leading to a total gastrectomy at the age of 50. Germline analysis showed a mutation in SMAD4.

Case 3

The third patient was a 55-year-old man referred because of severe anemia (Hb 4,3 g/dl) and weight loss of 10 kg with a thickened gastric wall on CT scan. He had undergone a right hemicolectomy for colon cancer (pT3N0) and was diagnosed with atrophic gastritis and pseudopolypoidosis 10 years earlier. EGD on admission showed endoscopically unresectable hamartomatous polyps requiring a total gastrectomy. Germline analysis

revealed a SMAD4 mutation. Since gastrectomy, he had no relapse of IDA.

Case 4

The fourth patient was a 44-year-old woman, suffering from IDA (hemoglobin 9 g/dl). At the age of 34 she had undergone a EGD because of anemia. Because of nausea and dyspepsia, a new EGD was performed at the age of 42 with diagnosis of Menetrier disease. EGD on admission showed a significant villous hypertrophy, mainly in the distal corpus and angulus. Endoscopically no areas of overt dysplasia were found. Mapping biopsies showed hamartomatous polypoid transformation of the gastric mucosa, without dysplasia. A pathogenic SMAD4 mutation was detected in a DNA NGS solid tumor gene panel and confirmed by germline analysis. At 45, the patient underwent prophylactic total gastrectomy.

In conclusion, we presented 4 cases of young patients with severe IDA due to gastric polyposis, all diagnosed as having SMAD4 related JPS. There was a median diagnostic delay of 8.5 years (range 2-10) because either a polyposis syndrome was not considered, or another diagnosis was put forward on phenotypic presentation solely (e.g. Menetrier disease or another polyposis syndrome).

Discussion

JPS is a hamartomatous polyposis syndrome, like Peutz-Jeghers, PTEN hamartoma tumor (including

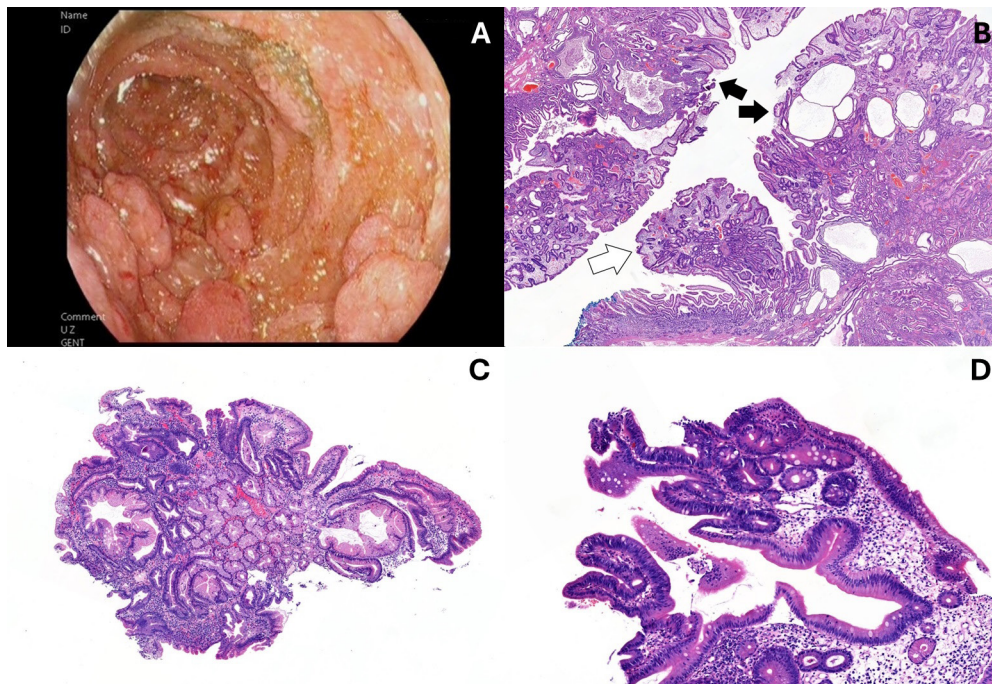


Figure 2. — Duodenal polyps.

A: Duodenal polyps of a SMAD4 juvenile polyposis syndrome (JPS) patient on endoscopic examination. B: Biopsy from duodenal polyps showing rounded lobes and cystic dilated crypts with focal expansion of the lamina propria consistent with juvenile polyps (filled arrows). A smaller polyp has more finger-like lobes without cystic change (magnification X10). C: Biopsy from a duodenal polyp consistent with an atypical juvenile polyp showing finger-like lobules, more branching and less cystic glands, than a typical juvenile polyp (magnification X60). D: Biopsy from a duodenal polyp consistent with an atypical juvenile polyp showing finger-like lobules, a reactive increase in the amount of epithelium versus stroma, and glands showing more budding and branching and less cystic change, than a classical juvenile polyp. Regenerative changes of the epithelium, as in this case, may mimic an adenomatous polyp (magnification X100).

Cowden), and hereditary mixed polyposis syndrome. JPS should be distinguished from adenomatous polyposis syndromes, such as familial adenomatous polyposis (FAP), attenuated FAP (aFAP) or MUTYH-associated polyposis (MAP) (2). The diagnosis of JPS is based on clinical presentation, histological findings and genetic analysis (Table 1). Correct diagnosis is important as management differs for each syndrome, due to different extra-intestinal symptoms and cancer risks.

The most typical symptom is IDA (as in our patients), followed by abdominal pain, diarrhea, protein-losing enteropathy, intussusception and polyp prolapse. However, patients can also be asymptomatic (2,5). Patients with SMAD4 JPS are more prone to profuse gastric polyposis and at risk to develop Hereditary Hemorrhagic Telangiectasia (HHT), formerly Osler-Weber-Rendu disease, when combined: HHT-JPS Overlap Syndrome (6). It is recommended to routinely screen individuals with SMAD4 JPS for HHT.

The polyps in JPS vary in size and histological features (Table 1). They may resemble sporadic polyps and can be difficult to distinguish from inflammatory or mucosal-prolapse type polyps. Pedunculated polyps may show fibromuscular proliferation, resembling Peutz-Jeghers polyps, while regenerative changes may mimic serrated

and adenomatous polyps. Distinguishing them without clinical context can be challenging or even impossible (2,7). SMAD4 immunohistochemistry can be helpful, but epithelial SMAD4 inactivation is not required for polyp formation or neoplastic progression in JPS. Gastric hamartomas can mimic Menetrier disease in adulthood (as in 2 of our patients).

The SMAD4 and BMPR1A genes are both tumour suppressor genes. The cancer risk in JPS is believed to arise from adenomatous tissue within the juvenile polyp, as up to 50% of juvenile polyps in JPS contain areas of adenomatous change. A cumulative risk of colorectal cancer (CRC) of 39–68% has been estimated, with mean age of 34 years (2,8). Individuals with SMAD4 gene mutations have significantly higher risk of gastric cancer (30%, median age 58 years) and gastric polyposis (83% versus 8%) compared to those with BMPR1A mutations (2,3).

European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend starting surveillance colonoscopy at the age of 12–15 years with an interval of 1–3 years. EGD should start at age 18 in asymptomatic individuals with a SMAD4 mutation (at 25 in BMPR1A mutation) with an interval of 1–3 years (9). Gastric management should be discussed in expert

Table 1. — **Diagnostic criteria and key features of juvenile polyposis syndrome (JPS).**

Criteria for JPS diagnosis (4)	Any of the following: - ≥ 5 juvenile polyps in the colon or rectum - juvenile polyps throughout the digestive tract (≥ 1 in the upper and ≥ 1 in the lower tract) - any number of juvenile polyps and a positive family history of JPS
Clinical findings	- multiple juvenile polyps (1 to >100) - small sessile nodules to pedunculated lesions ≥ 3 cm
Mean age at diagnosis (2)	18.5 years
Histological characteristics	- eroded surface - edematous lamina propria with inflammatory cells - cystically dilated glands with reactive epithelium
Atypical JPS polyps	- multilobulated or atypical shape (rounded or finger-like lobes) - increased epithelium-to-stroma ratio - gland budding and branching with less cystic change
Germline genetic analysis (4,12)	- In 60% SMAD4 or BMPR1A pathogenic variants are identified - SMAD4 accounts for 20 - 30% of cases
Inheritance (2)	- 75% familial - 25% sporadic (de novo mutations)

multidisciplinary teams and no clear algorithm can be proposed based on the available data. Small bowel polyps are less often seen. However, screening is important, and polyps are frequently found in the ileal pouch of patients who have undergone proctocolectomy (10). ESGE does not recommend small-bowel surveillance in asymptomatic individuals, but the American College of Gastroenterology (ACG) guidelines do, if duodenal polyposis is present or if there is unexplained anemia, protein-losing enteropathy, or other small bowel symptoms (9). Sporadically, pancreatic cancer is seen in JPS patients, but screening is not recommended (2).

Patients with a limited number of polyps in any area of the GI tract can usually be managed with endoscopic polypectomy. However, colectomy with ileorectal anastomosis, proctocolectomy with ileal pouch-anal anastomosis and partial or total gastrectomy may be necessary for patients with advanced dysplasia, cancer, or massive polyposis that cannot be effectively controlled endoscopically. Total gastrectomy is often preferred over partial gastrectomy since recurrence of gastric cancer in the remnant stomach has been reported (11). On the other hand, total gastrectomy leads to higher surgical and functional morbidity and Roux-and-Y anastomosis will render surveillance of the remaining small bowel difficult. Therefore, the decision should be made in multidisciplinary meetings (9,11).

In conclusion, we present four cases of SMAD4 JPS, with diverse phenotypic presentations and significant diagnostic delays, highlighting the limited awareness of JPS in clinical practice. Involvement of the upper digestive tract in SMAD4 JPS is often underestimated and sharing correct clinical information with the pathologist is crucial as histological findings are not pathognomonic. In patients presenting with nodular gastric mucosa and multiple polyps, clinicians should consider an underlying

polyposis syndrome, even without family history. Genetic testing is crucial to confirm the diagnosis.

Declarations

Conflicts of interest statement: The authors declare that they have no competing interest.

References

1. Heald B, Hampel H, Church B, Hampel H, Church J, Dudley B, *et al.* Collaborative Group of the Americas on Inherited Gastrointestinal Cancer Position statement on multigene panel testing for patients with colorectal cancer and/or polyposis. *Fam Cancer*, 2020, 19(3): 223-39.
2. Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol*, 2015, 110(2): 223-62.
3. Cubuk E, Portillo TP, Barakat O, Al Doheyan TA, Jain S. Economical diagnostics for gastric polyposis in juvenile polyposis syndrome: Unveiling insights with SMAD4 immunostaining. *Arch Pathol Lab Med*, 2024, 148(9): e288.
4. Cao K, Plazzer JP, Macrae F. SMAD4 variants and its genotype-phenotype correlations to juvenile polyposis syndrome. *Hereditary Cancer in Clinical Practice*, 2023, 21(27).
5. Singh AD, Gupta A, Mehta N, Heald B, Macaron C, Liska D, *et al.* Occurrence of gastric cancer in patients with juvenile polyposis syndrome: a systematic review and meta-analysis. *Gastrointest Endosc*, 2023, 97: 407-14.
6. Gonzalez ML, Vazquez C, Argüero MJ, Santino JP, Braslavsky A, Serra MM. Overlap syndrome of hereditary hemorrhagic telangiectasia and juvenile polyposis syndrome: ten years follow-up-case series and review of literature. *Fam Cancer*, 2025, 24(1).
7. Gonzalez RS, Adsay V, Graham RP, Shroff SG, Feely MM, Drage MG, *et al.* Massive gastric juvenile-type polyposis: a clinicopathological analysis of 22 cases. *Histopathology*, 2017, 70(6): 918-28.
8. Dal Buono A, Gaiani F, Poliani L, Laghi L. Juvenile polyposis syndrome: an overview. *Best Pract Res Clin Gastroenterol*, 2022, 58-59: 101799.
9. van Leerdam ME, Roos VH, van Hooft JE, Dekker E, Jover R, Kaminski MF, *et al.* Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*, 2019, 51(9): 877-95.
10. Brosens LAA, Langeveld D, van Hattem WA, Giardiello FM, Offerhaus GJA. Juvenile polyposis syndrome. *World J Gastroenterol*, 2011, 17(44): 4839-44.
11. Jaoude JB, Hallit R, Rassy EE, Abboud B. The role of prophylactic gastrectomy in patients with juvenile polyposis syndrome. *Clin Res Hepatol Gastroenterol*, 2019, 43(3): e42-3.
12. Muller M, Baldysiak E, Benech N, Pioche M, Hervieu V, Calavas L, *et al.* Deciphering the clinical spectrum of gastric disease in patients with juvenile polyposis syndrome. *Gastrointest Endosc*, 2024, 100(5): 867-77.