CLINICAL CASE

Gastric involvement in juvenile polyposis associated with germline \textit{SMAD4} mutations: An entity characterized by a mixed hypertrophic and polypoid gastropathy

Atteinte gastrique de la polyposse juvénile associée à une mutation du gène \textit{SMAD4} : une entité caractérisée par un aspect de gastropathie mixte, hypertrophique et polypoïde

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Summary  Exclusively gastric form of juvenile polyposis associated with germline \textit{SMAD4} mutation is a rare clinical entity and is usually difficult to diagnose in the absence of colorectal lesions. We describe the phenotype of two unrelated cases of exclusive or predominant gastric expression of juvenile polyposis. Endoscopically, we found an unusual hypertrophic and polypoid gastropathy with abundant mucus adhering to the mucosal surface. Initially diagnosed as hyperplastic polyps, examination of gastric macrobiopsy specimens and identification of \textit{SMAD4} gene mutation in both cases confirmed the diagnosis. Close upper GI surveillance was proposed.

Abbreviations:  JP, juvenile polyposis; GJGP, generalized juvenile gastrointestinal polyposis; GJP, gastric juvenile polyposis.

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in case 1 and prophylactic total gastrectomy in the second one. Juvenile polyposis limited to
the stomach is a rare condition that is linked to \textit{SMAD4} mutations. Such a diagnosis should be
considered whenever a mixed, hypertrophic and polypoid gastropathy is encountered.
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Résumé  Les atteintes gastriques exclusives sont rares au cours de la polyposie juvénile. Elles sont de diagnostic difficile du fait de l’absence de lésions colorectales, mais sont volontiers associées à une mutation du gène \textit{SMAD4}. Nous rapportons deux cas non apparentés de forme gastrique exclusive ou quasi-exclusive de polyposie juvénile. À l’endoscopie, l’atteinte gastrique se présentait sous forme de gastropathie mixte, hypertrophique et polypoïde, avec présence de mucus abondant en surface. Le diagnostic initial de polypes hyperplasiques fut redressé par un nouvel examen histologique des macrobiopsies après l’identification de mutations du gène \textit{SMAD4}. Une surveillance endoscopique a été proposée dans un cas et une gastrectomie prophy-lactique dans l’autre. Les formes gastriques exclusives de polyposie juvénile sont volontiers associées à une mutation du gène \textit{SMAD4}. Il faut savoir effectuer cette recherche devant un cas de gastropathie mixte, hypertrophique et polypoïde.
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Introduction

Juvenile polyposis (JP) is a rare disorder with a prevalence of approximately one per 100,000 people [1]. An autosomal dominant trait is recognized in 20–50% of patients [2]. Clinically, it is characterized by multiple hamartomatous and non-neoplastic polyps in the gastrointestinal (GI) tract, usually between 50 and 200 [2—4]. The most common location of polyps is the colorectum (98%), followed by the stomach (14%), small intestine (7%) and duodenum (2%) [5]. Extraintestinal manifestations of JP occur in 11–20% of cases [2] and commonly include pulmonary arteriovenous malformations, cardiac anomalies and macrocephaly [6].

JP is traditionally classified into three subtypes: JP of infancy, JP coli and generalized juvenile gastrointestinal polyposis (GJGP) [7]. JP limited to the stomach without intestinal polyps at initial presentation is exceptional and is termed gastric juvenile polyposis (GJP). Though rarely described, this clinical entity seems to be associated with an increased risk of GI cancer. Since 1979, when Watanabe et al. [8] first described a family with members affected by GJP, similar hereditary and nonhereditary cases have been reported in the literature, sometimes associated with Rendu-Osler disease [9].

Recent investigations have identified two genes involved in JP: \textit{SMAD4} [10] and \textit{BMPR1A} [11], both of which encode proteins that play different roles in TGF-beta signal transduction pathways. In the largest series of JP patients reported to date, the prevalence of germline \textit{SMAD4} and \textit{BMPR1A} mutations is approximately 20% for each gene [12], leaving 60% of cases with no definitive genetic background. The higher prevalence of massive gastric polyposis has recently been reported among \textit{SMAD4} mutation carriers [12—14]. This observation of genotype—phenotype correlation is underlined in the following two unrelated cases presenting with similar endoscopic gastric features and \textit{SMAD4} mutations.

Case reports

Patient 1

A 51-year-old woman was referred to our hospital with an unusual polyposis of the stomach in 2005. She had a 15-year history of dyspepsia, which was treated intermittently with proton-pump inhibitors. Her medical background was marked by the diagnosis of gastric polyps in 1985, and hysterectomy for uterine fibroma in 1999. The patient’s family history revealed a first-degree colorectal cancer and a second-degree gastric cancer.

Three years earlier upper endoscopy showed a mixed pattern of hypertrophic and polypoid gastropathy. Biopsies taken from both the gastric body and the antral areas were interpreted as foveolar hyperplasia and excluded \textit{H. pylori} infection and lymphocytic gastritis. On the basis of those findings, the patient was discharged without specific recommendations.

At admission, physical examination was normal. She was free of alopecia, onycolysis, cutaneous telangiectasia or hyperpigmentation and cardiovascular manifestations. She reported no weight loss, hematemesis, or chronic diarrhea. Standard laboratory data showed mild anemia (hemoglobin: 100 g/l), but no hypoproteinemia. Serum level of gastrin was within normal limits, as was gastric acid secretion. Serology for \textit{H. pylori} was negative.

Upper endoscopy confirmed a mixed pattern of hypertrophic and polypoid gastropathy occupying the entire body (except the greater curvature), part of the antrum and sparing the fundus. Enlarged and congestive gastric rugae, reminiscent of cerebral convolutions, arose right under the subcardial region. Areas of normal mucosa were discernible between gastric folds. Multiple different sized sessile and pedunculated polypoid projections were clustered over the thickened rugae, mostly in the gastric body (Fig. 1). Some pedunculated giant polyps in the subcardial region were covered with translucent mucus; the largest was approximately 4 cm across. Examination of the polyps at a magnification of about 50 (Fujinon EG-4902W5) revealed a mosaic-like...
mucosal surface, with continuous depressed areas characteristic of the so-called "mesh pattern" (Fig. 2). No other lesions were detected in the duodenum. Two 2 × 1.5 cm macrobiopsy specimens were taken, one from the anterior wall of the body and one from the largest subcardial polyp. No other colorectal polyp was detected at colonoscopy. Endoscopic ultrasound (Pentax© FG38UX) demonstrated non-specific thickening of the gastric body wall that involved the mucosa and submucosa but spared the third layer. Wall stratification was preserved. The thickened layers appeared homogeneous and rather hyperechoic, without anechoic areas.

**Patient 2**

A 38-year-old woman was admitted to our hospital in 2005 with severe iron deficiency anemia. Her history included immature right ovarian teratoma at the age of 16, uterine fibroma, infraclinical autoimmune hyperthyroidism and left infiltrating lobular breast carcinoma at 37. At 32, the patient had undergone right hemicolectomy for a villous tumor of the caecum. No family history of polyps was discovered. Her mother had been diagnosed with breast cancer at the age of 42, and one aunt died of a brain tumor.

Follow-up colonoscopy three years after intestinal surgery revealed three small (about 3–4 mm) sessile hyperplastic polyps in the left colon. Concomitant upper GI examination for dyspepsia revealed gastric polyposis of hyperplastic type. Regular endoscopic GI tract surveillance and genetic testing were initiated.

After three years free of symptoms, the patient underwent upper and lower endoscopy because of severe microcytic anemia. As in the first case, a mixed pattern of hypertrophic and polypoid gastropathy was observed, affecting mainly the antrum and, to a lesser extent, the gastric body. However, compared with first patient, more importance was attached to mucosal hyperemia and red point hemorrhagic lesions on the surface of the polyps (Fig. 3). The greater curvature and the fundus were spared, as was the prepyloric antrum. Mucus covering the polypoid lesions had a gelatinous, translucent "bunch of grapes" appearance, particularly in the angular region, where the largest polypoid pro-
Figure 4  Case 2: upper endoscopic view showing the same hypertrophic and polypoid gastropathy of the gastric body, with a large, "bunch of grapes" type polypoid projection in the angular region. Note the translucent mucus at the top of the polyp’s head (double arrow) and the mosaic-like pattern of the mucosal surface (arrow).

Injection was observed (Fig. 4). Endoscopic ultrasound findings were consistent with the diagnosis of Menetrier’s disease. Inspection of the colon revealed no polyps.

Histopathology

Histopathological examination of gastric macrobiopsy specimens (corpus and antrum) produced similar findings in both cases. The characteristic features were elongated and tortuous foveolae with focal cystic dilatations (Fig. 5), lined with a hypersecreting normal epithelium in the first case, and low-grade dysplastic changes in the second. The stroma exhibited marked edema with inflammatory infiltrates (neutrophils or eosinophils) and focal ulcerations of surface epithelium. No other heterologous stromal components, such as smooth muscle fibers or abnormal neural tissue, were identified. The biopsies excluded H. pylori infection and lymphocytic gastritis. Reexamination of the colectomy specimen, and of samples of the gastric and colic polyps taken three years earlier, revealed a similar histological pattern. Contrary to the original histopathological description, the final diagnosis was hamartomatous juvenile type polyposis, with no evidence of malignancy in the first case, and low-grade dysplasia in the second.

Genetic testing

Having obtained informed consent, DNA was extracted from both patients’ whole-blood samples for genomic DNA sequencing and identification of mutations in SMAD4, BMPR1A and PTEN, the genes responsible for hamartomatous polyposis. Neither patient carried PTEN or BMPR1A mutations, but germline mutations of the SMAD4 gene were detected in both cases. The first patient exhibited a nonsense mutation (c.1527 G > A) which resulted in a stop codon (Trp509X) in exon 11. In the second case a four base-pair deletion in exon 9 (codon 415) was detected (1245_1248delCAGA).

Based on clinical histologic and genetic findings, the final diagnosis was diffuse GJP in both cases. In the absence of severe symptoms or polyp’s dysplasia in the first patient, endoscopic upper GI surveillance at two years was decided. In the second case a prophylactic gastrectomy was proposed, which was delayed to allow the patient to recover from a...
recent breast cancer operation.

Discussion

The above cases are of particular interest because of the exclusively, or predominantly, gastric localization of SMAD4-JP (a rare clinical entity), the unusual endoscopic appearance, and the questions that arise concerning optimal management.

In 1998, Jass et al. proposed the following diagnostic criteria for JP:

- more than five colonic juvenile polyps;
- juvenile polyps throughout the GI tract;
- any number of juvenile polyps in an individual with a family history of JP [4].

The present cases did not fulfill any of the criteria. They exhibited profuse gastric polyposis with histopathological features of a juvenile pattern, without colonic involvement in the first case and with fewer than five juvenile polyps in the second.

At present, it is unclear whether the few reported cases of GJP represent a distinct clinical entity or a subtype of GJGP. In Hizawa’s literature review, 12 of 41 patients with JP had only gastric involvement at the time of diagnosis, but no difference in clinical and pathological features between GJP and GJGP involving the stomach was reported, other than a female preponderance among people with GJP.

To our knowledge, only 43 cases of JP affecting the stomach have been reported in the literature [14–16]. The most common location of polyps is the gastric antrum, where they are larger, more numerous and more pedunculated than those in the corpus [15,17]. The polyps usually range from 0.5 to 5 cm in size, are pedunculated or sessile, have a smooth, spherical or lobulated red head, often with superficial ulcerations. Some may be hemorrhagic [18], as in case 2 above, in which cherry red spots on the surface of the polyps may explain the severe anemia.

Of particular interest in our patients is the mixed hypertrophic and polypoid gastropathy, clustered mainly in the gastric body in the first case and in the corpus-antral junction in the second, with the greater curvature as well as the fundus spared in both. To our knowledge, the literature contains two cases of diffuse gastric polyposis in the context of giant gastric folds, one of a juvenile type and the other of a hyperplastic and fundic gland type [19,20]. The consistent finding of abundant mucus adhering to the surface of the large polyps has not previously been reported; as well as, the mosaic-like pattern observed over the thickened folds of gastric mucosa under magnifying endoscopy (ME), corresponding to the "mesh-pattern" in Sakaki’s classification of fine gastric mucosal patterns [21]. These aspects may be suggestive of juvenile polyps.

Gastric juvenile polyps are also difficult to diagnose histologically because there are unusual patterns of polyps, which could mimic hyperplastic polyps. This is why our two cases presented a diagnostic challenge. Typical juvenile polyps are characterized by abundant stromal polymorphic infiltration by a variable number of lymphocytes, plasma cells, neutrophils and eosinophils, associated with dilated and cystic mucinous glands lined by a normal overlying epithelium. In both our cases, the elongated foveolae and hypersecreting surface epithelium initially suggested a hyperplastic pattern, but closer examination revealed cystic dilatation of the glands and more inflamed and infiltrated stroma with less foveolar hyperplasia than hyperplastic polyyps.

Two genes predisposing to JP have been identified: SMAD4 [10] on chromosome 18q21 [10,22] and BMPR1A [11] on chromosome 10q22–23. In the largest group of JP patients reported to date, the prevalence of germline mutations was approximately 20% for each gene [12,10,19,22–25], leaving 60% of cases. A wide range of SMAD4 mutations (n = 26) have been identified until now [3]. The most frequent – a 4 bp deletion (1244_1247delAGAC mutation) in exon 9 – has been reported to be a mutational hotspot in six unrelated pedigrees [5,11,22], and is known to result in a more virulent form of JP, with a high incidence of gastric and colonic polyposis, as well as of upper and lower GI malignancy [26]. None of the known mutations have been found in our cases. In case 1, we detected a new nonsense mutation (c.1527 G > A) in exon 11 of SMAD4, which resulted in a stop codon (Trp509X). In case 2, the 4bp deletion found in exon 9 (1245_1248delAGCA) is very close to the previously reported hotspot mutation [27], perhaps explaining the severity of the phenotype.

Genotype–phenotype correlation in JP patients is not well-defined. However, Friedli et al. [19] were first to report a remarkably high prevalence of profuse GJP in patients with SMAD4 mutations, like in our cases. There is no doubt that JP is a premalignant condition, particularly among mutation positive subjects, who are at increased risk of cancer compared with mutation negative subjects in Sayed’s study [23]. However, the risk of gastric cancer in GJP related to SMAD4 mutation has not been fully elucidated. Dysplastic or adenocarcinoma foci are present in approximately 30% of gastric juvenile polyps [15,28]. In the largest JP kindred survey, consisting of 117 members [29], the prevalence of colorectal cancer in affected patients was 38%; the figures for gastric cancer and upper GI cancer were 11 and 21%, respectively.

The optimal management of patients affected by profuse GJP related to SMAD4 gene mutation remains a matter of debate: prophylactic partial gastrectomy versus endoscopic surveillance with iterative polypectomies at intervals of one to three years. Surgery should be reserved for massive gastric involvement with severe anemia or uncontrolled hypoproteinemia and/or dysplastic changes [15,19,29], but the ability of endoscopic surveillance to confirm all polyps’ benignity is questionable. Nevertheless, most GJP cases reported in the literature required total or partial gastrectomy. Genetic testing should also be recommended to high-risk family members of mutation positive or affected probands.

In conclusion, the two cases presented here demonstrate the existence of exclusively, or predominantly, gastric forms of JP associated with germline SMAD4 mutations: the most aggressive GI phenotype. This rare clinical entity appears to be difficult to diagnose because of its unusual endoscopic appearance and the potential for histopathological evidence to be misinterpreted as hyperplastic polyyps. GJP should be diagnosed whenever a mixed hypertrophic and polypoid gastropathy, with abundant mucus adhering to the mucosal
surface is encountered (even in the absence of colorectal lesions) and genetic testing should be proposed. Because of the increased risk of cancer, a balance must be struck between endoscopic surveillance and prophylactic total gastrectomy in these cases.

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**References**


