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SMAD4 Germline Pathogenic Variant-Related Gastric Juvenile Polyposis with Adenocarcinoma Treated with Laparoscopic Total Gastrectomy: A Case Report

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 49-year-old
Final Diagnosis: Juvenile polyposis syndrome
Symptoms: Anemia
Medication: —
Clinical Procedure: Surgery
Specialty: Gastroenterology and Hepatology • Genetics

Objective: Rare disease

Background: Juvenile polyposis syndrome is an uncommon, autosomal-dominant hereditary disease that is distinguished by multiple polyps in the stomach or intestinal tract. It is associated with a high risk of malignancy. Pathogenic variants in *SMAD4* or *BMPR1A* account for 40% of all cases.

Case Report: A 49-year-old woman underwent esophagogastroduodenoscopy because of exacerbation of anemia. She had numerous erythematous polyps in most parts of her stomach. Based on biopsy findings, juvenile polyposis syndrome (JPS) was suspected morphologically, but there was no evidence of malignancy. Colonoscopy showed stemmed hyperplastic polyps and an adenoma; video capsule endoscopy revealed no lesions in the small intestine. After preoperative surveillance, laparoscopic total gastrectomy with D1 lymph node dissection was performed to prevent malignant transformation. The pathological diagnosis was juvenile polyp-like polyposis with adenocarcinoma. In addition, a germline pathogenic variant in the *SMAD4* gene was detected with genetic testing.

Conclusions: JPS can be diagnosed with endoscopy and genetic testing. Further, appropriate surgical management may prevent cancer-related death in patients with this condition.

Keywords: Gastrectomy • Juvenile Polyposis Syndrome • SMAD4 Protein, Human • Stomach Neoplasms

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/932241

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Background

Juvenile polyposis syndrome (JPS) is an uncommon, autosomal-dominant hereditary disease with a prevalence of approximately 1 per 100 000 to 160 000 people [1]. It is characterized by multiple polyps and most commonly affects the colon and rectum. Polyps also can develop in the stomach or intestinal tract. Thus, the entire gastrointestinal tract should be assessed. The disease often is caused by a pathogenic variant in the *SMAD4* or *BMPR1A* genes. These genetic alterations account for 40% of all cases and 67% are sporadic [2]. In most patients with JPS, it is benign, but it can become cancerous. The lifetime risk of gastrointestinal malignancy is approximately 9% to 50% and the occurrence rate for gastric malignancy is 21% among patients with JPS [3].

In the present case, JPS was suspected due to the presence of multiple gastric polyps, and laparoscopic total gastrectomy with D1 lymph node dissection was performed to prevent malignant transformation. After the surgery, some polyps were diagnosed as adenocarcinoma. Furthermore, an *SMAD4* germline pathogenic variant was detected; hence, the patient was finally diagnosed with JPS.

Case Report

A 49-year-old woman with symptoms of fatigability but an unremarkable medical history presented to the hospital for consultation. She had pale conjunctiva and examination of her blood confirmed microcytic hypopigmentation anemia (hemoglobin level, 11.3 g/dL). In addition, esophagogastroduodenoscopy revealed multiple gastric polyps. There were dense, erythematous polyps in most parts of the patient's stomach and the gross morphology was from type 0-Ip to Isp. Her mucosa was erythematous (**Figure 1**). Biopsy was performed in 4 sites. The pathological diagnosis was hyperplastic polyps and JPS was suspected morphologically. The patient's stomach had a mucus-rich crypt epithelium and the stroma was edematous. Hamartomatous polyps were suspected, but there was no evidence of malignancy. Because there was no intervening smooth muscle in the stroma, it was difficult to distinguish from JPS, Peutz-Jeghers type, and Cronkhite-Canada type. In addition, colonoscopy revealed stemmed hyperplastic polyps and an adenoma, which were resected endoscopically. Video capsule endoscopy revealed no lesions in the small intestine. Moreover, there were no significant findings on the contrast-enhanced computed tomography (CT) scan.

The patient had undergone appendectomy at the age of 7 years. Her mother, older sister, and aunt were diagnosed with breast cancer; there was no family history of gastrointestinal cancer or polyposis (**Figure 2**). Although hereditary polyposis syndrome was challenging to diagnose based on family history, JPS was suspected, based on the clinical findings.

It was extremely difficult to distinguish the patient's gastric cancer from other types of polyps. Thus, laparoscopic total gastrectomy with D1 lymph node dissection and Roux-en-Y esophagojejunostomy were performed. The resected specimen revealed multiple polyps (**Figure 3A**), which histopathologically comprised juvenile polyp-like tissues, severe edema of the interstitium, and fundic gland hyperplasia (**Figure 3B**). Nuclear enlargement of the epithelium was partially observed

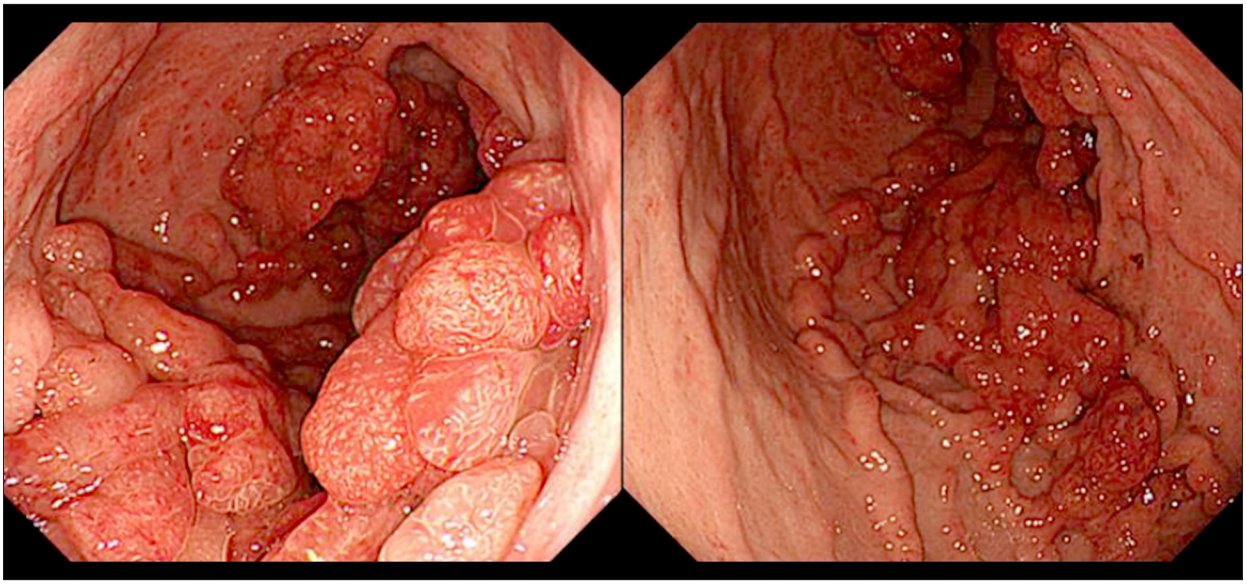

Figure 1. Multiple gastric polyps on esophagogastroduodenoscopy. There were dense, erythematous polyps in most parts of the stomach.

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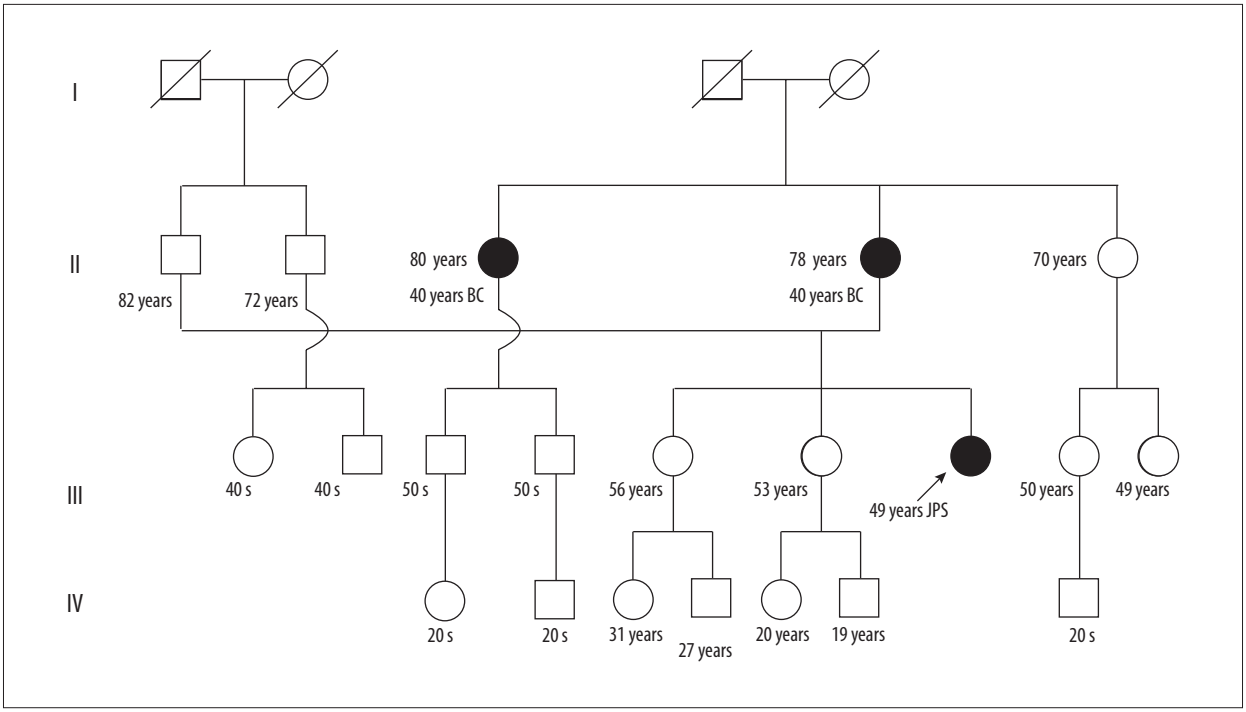

Figure 2. Family tree. The patient's mother, older sister, and aunt were diagnosed with breast cancer; however, there was no family history of gastrointestinal cancer or polyposis. BC – breast cancer; JPS – juvenile polyposis syndrome.

in the anterior wall of the upper gastric body. Atypical epithelium proliferated in a fused glandular tubular form. Therefore, a diagnosis of adenocarcinoma was made (**Figure 3C**). The final staging was T1N0M0 stage I (8th edition of the American Joint Committee on Cancer staging system for gastric cancer). Genetic testing was performed to confirm the diagnosis. Results revealed a germline pathogenic variant in exon 5 of the *SMAD4* gene. The sequence was defined as c.502 G>T, p.Gly168X.

After surgery, the patient enrolled in a surveillance program that included annual colonoscopy. Juvenile polyps were detected during the initial colonoscopy at 6 months after gastrectomy and they were completely resected. No other JPS-related lesions were observed during 1 year of surveillance. Hemorrhagic telangiectasia also did not occur.

Discussion

JPS is characterized by multiple polyps in the stomach or intestinal tract. Most juvenile polyps are benign but malignant transformation can occur. Most patients develop polyps in the colorectum (98%), followed by the stomach (14%) and small intestine (7%) [4]. JPS is generally diagnosed using 1 or more of the following clinical criteria: (1) a minimum of 5 juvenile polyps in the colon and rectum; (2) juvenile polyps in other parts of the gastrointestinal tract; and (3) juvenile polyps, regardless of number, in an individual with a family history of juvenile polyps [5].

The 2 main causative genes are *SMAD4* and *BMPR1A*, and germline mutations are observed in each gene, with a prevalence of 20%. The incidence of gastric polyposis is higher in *SMAD4* pathogenic variants than in *BMPR1A* pathogenic variants [6,7]. Both tumor suppressor genes are important for transmitting signals from transforming growth factor beta and related ligands, thereby affecting inhibition of cell growth and apoptosis [1].

The occurrence of cancers is a serious concern. For instance, the likelihood of colorectal malignancy is 34 times higher in this group of patients than in the general population. The mean age at diagnosis is 43.9 years and the lifetime risk of malignancy is 38.7% [8]. In contrast, approximately 21% of patients develop gastric cancer [9]. Gastrointestinal surveillance is recommended to monitor and assess for the risk of developing malignant tumors. The American College of Gastroenterology (ACG) guideline recommends colonoscopy and esophagogastroduodenoscopy at approximately 12 years of age if the patient is particularly symptomatic, and screening must be performed every 1 to 3 years, depending on the severity of the polyps [5]. The ACG recommends regular resection of polyps >5 mm; however, it is extremely difficult to resect multiple polyps endoscopically [5]. Despite the availability of various surgical options, including lateral pyloric gastrectomy and partial gastrectomy, recurrence of polyps and gastric cancer in the rest of the stomach has been reported [10]. Therefore, patients with abundant juvenile polyps should undergo total gastrectomy.

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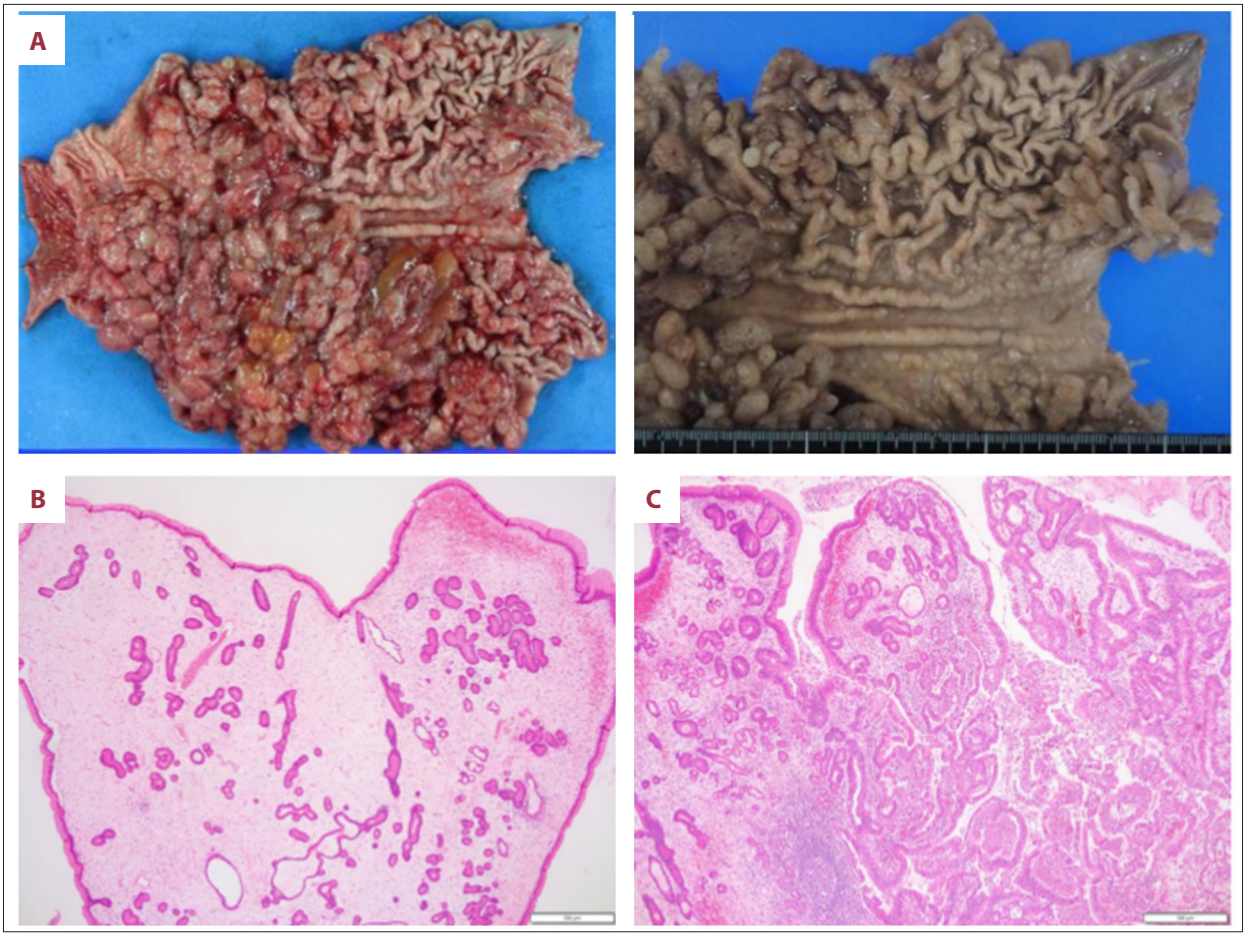

Figure 3. Pathological findings from the specimen resected from the stomach. (**A**) Polyps were found in all areas of the stomach. (**B**) Most polyps were observed on juvenile polyp-like tissue images. (**C**) Nuclear enlargement of the epithelium was observed partially in the anterior wall of the upper gastric body. Thus, a diagnosis of adenocarcinoma was made.

In the present case, multiple polyps were found in all parts of the patient's stomach and the risk of gastric malignancy was extremely difficult to rule out. When patients present with multiple juvenile polyps in the stomach and meet the clinical criteria for JPS, total gastrectomy along with lymph node dissection is the best option for managing gastric malignancy. In fact, in our case, a heterozygous c.502 G>T (p.Gly168X) pathogenic variant was detected in exon 5 of *SMAD4* (VistaSeqSM Hereditary Cancer Panel, LabCorp, Burlington, North Carolina, United States). In short, this variant is predicted to result in an absent protein. Although this variant has not been previously reported in the literature and it is likely correlated with an increased risk of JPS-associated cancers, we believe that total gastrectomy is the best method for patients with an aggressive type of gastric juvenile polyps.

Hemorrhagic telangiectasia is another concern. JPS and hereditary hemorrhagic telangiectasia (JPS/HHT) comorbidity syndrome can develop. JPS/HHT is an autosomal-dominant hereditary disease with a prevalence of approximately 1 in 10 000 people. Typically, the *ENG* and *ACVRL1* genes are initially assessed for coding sequence mutations. When no mutations are identified, the *SMAD4* gene is evaluated [11] because this syndrome is also present in approximately 20% of patients who have *SMAD4* mutations [6,12]. HHT is characterized by peripheral vasodilation of the skin and mucous membranes and arteriovenous malformation in the lungs, liver, and brain. Several clinical manifestations, such as nasal hemorrhage, cerebral hemorrhage, cerebral infarction, cerebral abscess, respiratory failure, hemoptysis, intrathoracic hemorrhage, gastrointestinal hemorrhage, and iron deficiency anemia, are observed [13]. In our case, no vasodilation was detected on chest CT scan and head magnetic resonance imaging.

Conclusions

JPS is linked with a lifetime risk of gastrointestinal cancer. Patients with an aggressive type of gastric juvenile polyps should undergo total gastrectomy along with lymph node

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dissection. Genetic testing may be important in assessing their cancer risk and in selecting the appropriate operative strategy.

Ethics statement

This study was approved by the Institutional Review Board of Okayama University (approval no. 1911-034).

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Conflict of Interest

None.

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