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CASE REPORT

Extremely young case of small bowel intussusception due to Peutz–Jeghers syndrome with nonsense mutation of *STK11*

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Abstract

Intussusception is a frequent and severe complication of Peutz–Jeghers syndrome (PJS). We herein present the case of a 3-year-old girl who experienced jejuno-jejunal intussusception due to PJS polyps. Despite no apparent family history of PJS, she had exhibited mucocutaneous pigmentation since infancy and recurrent abdominal pain and vomiting from 2 years of age. Segmental resection of the jejunum during emergency laparotomy for the intussusception revealed multiple hamartomatous polyps. Genetic analysis uncovered a germline nonsense mutation of c.247A>T in exon 1 of *serine/threonine kinase 11* (*STK11*). Biannual follow-up surveillance for polyps by esophagogastroduodenoscopy, colonoscopy, and small bowel capsule endoscopy is ongoing. Reports describing the clinical and genetic features of extremely young PJS with intussusceptions are rare, although a literature review of *STK11* germline mutations revealed several other pediatric cases of complicating intussusception at ≤ 8 years old. Considering the recent advances in surveillance and treatment options for the small bowel, earlier management of symptomatic children with PJS may be warranted to avoid surgical emergency.

Keywords Peutz–Jeghers syndrome · Intussusception · *STK11* · Child

Abbreviations

ACG	American College of Gastroenterology
BAE	Balloon-assisted enteroscopy
CS	Colonoscopy
EGD	Esophagogastroduodenoscopy
DBE	Double-balloon enteroscopy
GI	Gastrointestinal
PJS	Peutz–Jeghers syndrome
SBCE	Small bowel capsule endoscopy
SD	Standard deviation
STK11	*Serine/threonine kinase 11*
US	Ultrasonography

Introduction

Peutz–Jeghers syndrome (PJS) is a rare autosomal dominant disorder affecting 1 in 50,000 to 1 in 200,000 births [1]. The syndrome was first identified in 1921 by Peutz [2] and later described by Jeghers in 1949 [3]. PJS is characterized by mucocutaneous or skin pigmentations, hamartomatous gastrointestinal polyposis, and an increased risk of various malignancies [4]. Early symptom onset is often indicated by the presence of mucocutaneous pigmentation. Polyps are found predominantly in the small bowel, but also appear in the stomach and colorectum. The most common polyp-related symptoms in children are anemia, gastrointestinal (GI) bleeding, abdominal pain, GI obstruction, and intussusception [1]. Intussusception is a serious complication of PJS with a high risk of mortality if left untreated.

The affected gene in PJS is *serine/threonine kinase 11* (*STK11*), a tumor suppressor gene on chromosome 19p13.3 that encodes a serine/threonine kinase [1]. Pathological

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variants of *STK11* can be found in 26.8–100% of clinically affected cases [5, 6]. We recently encountered an extremely young case with intussusception of the small bowel due to PJS polyps along with a *STK11* mutation that required emergency laparotomy.

Case report

A 3-year-old girl presented to the emergency department after a sudden onset of abdominal pain and vomiting that had persisted for 5 h. Her parents reported abdominal pain and vomiting once in 3 months since 2 years of age. She had no remarkable perinatal medical history or history of hematemesis or melena, allergic diseases, intussusception, hospitalization, or previous surgery. Her parents did not have mucocutaneous pigmentation nor significant past history of suspected PJS. The patient's maternal grandfather had undergone gastrectomy for stomach cancer, and he also had a solitary colon polyp in the absence of mucocutaneous pigmentation.

On physical examination, the patient was pale and in severe distress. Body weight was 10.1 kg [− 2.0 standard deviation (SD)], body height was 94.2 cm (− 1.5 SD), blood pressure was 106/68 mmHg, heart rate was 106/min, and body temperature was 37.3 °C. She had brown spotty pigmented macules on her lips, fingers, and toenails since infancy (Fig. 1). Her abdomen was soft and not distended, but with a palpable mass in the left lower abdomen. Blood in the stool was noted during an enema. A blood test disclosed anemia (hemoglobin, 5.7 g/dl; hematocrit, 21.1%; serum Fe, 103 μg/dl; ferritin, 5.8 ng/ml). Abdominal ultrasonography (US) demonstrated a characteristic "target sign" in cross-sectional images (Fig. 2) and "pseudo-kidney sign" in longitudinal images of the left lower quadrant of the abdomen. Intussusception was diagnosed based on these findings.

The patient was transferred to a tertiary emergency hospital. Non-invasive reduction by high-pressure enema could not achieve intestinal tract reduction, resulting in emergency laparotomy. A transverse incision of 5 cm in length was made on one horizontal finger above the umbilicus. Pediatric surgeons chose this type of incision instead of an umbilical incision because it can approach any part of small bowel and it is easy to deal with large mass. Intraoperatively, a part of the proximal jejunum 14 cm distal to the Treitz ligament had become invaginated into the anal jejunum. The length of the intussusception was 50 cm. Open reduction with Hutchinson procedure was performed. There were large polyps in the advanced part of the intussusception. Although no signs of bowel ischemia were evident, segmental resection of 15 cm of the jejunum containing multiple polyps and primary anastomosis were performed.

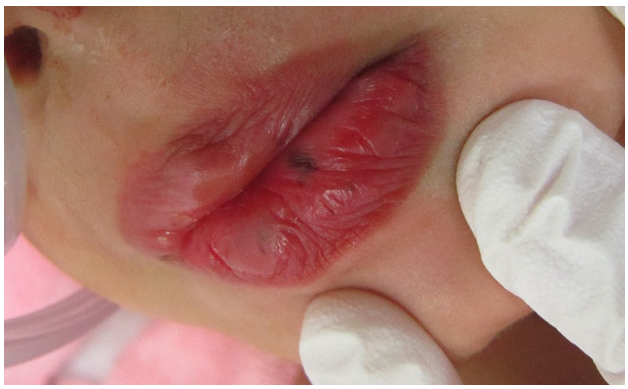

Fig. 1 Brown spotty pigmented macules on her lips

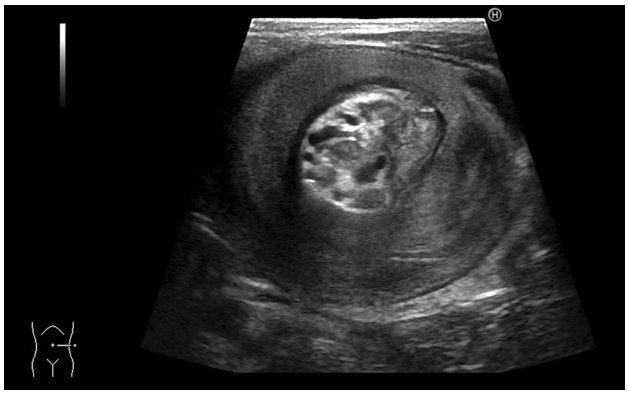

Fig. 2 Abdominal ultrasonography image demonstrating a characteristic "target sign"

A polyp of 3 cm in diameter was observed at the lead point of the intussusception (Fig. 3). Palpation by the surgeon detected no other polyps in the ileum or jejunum. Histological examination of the resected tissue revealed characteristic features of PJS-related hamartomas: a frond-like elongated epithelial component and cystic gland dilatation extending into the submucosa or muscularis propria, and arborizing smooth muscle extending into polyp fronds. The patient was diagnosed as a sporadic case of PJS based on mucocutaneous pigmentation and gastrointestinal hamartomatous polyposis. No further events were recorded after surgery.

The patient was referred to Shinshu University Hospital for endoscopic polyp surveillance and genetic testing. Esophagogastroduodenoscopy (EGD) revealed a polyp of 18 mm in diameter in the second part of the duodenum, which was endoscopically removed. Colonoscopy (CS) disclosed several small polyps in the rectum. Two years later, EGD, CS, and small bowel capsule endoscopy (SBCE) showed small polyps (< 5 mm) in the rectum and ileum. As long as these endoscopic examinations, there was no adverse effect related to post-surgical adhesions. Endoscopic examinations will be repeated every 2 years. Germline

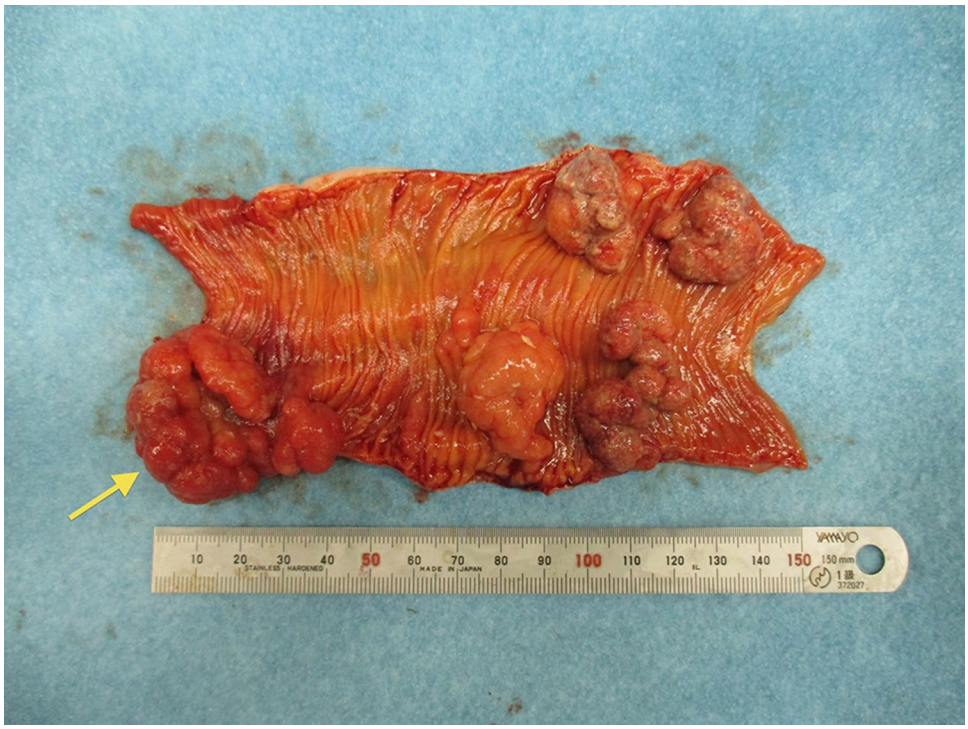

Fig. 3 Multiple polyps were found in the resected jejunum. A polyp of 3 cm in diameter (arrow) was located in the leading point

mutation screening of the *STK11* gene was performed using Sanger sequencing to reveal a heterozygous substitution of c.247A>T in exon 1 of *STK11*(NM_000455.4:c.247A>T NP_000446.1:p.Lys83Stop NC_000019.9:g.1207159A>T). This nonsense mutation resulted in the amino acid substitution of p.Lys83Stop (p.K83X). This is a novel germline mutation that has not been reported before. Genetic test had not been carried out on the patient's parents up to now because they had no specific signs of suspected PJS.

Discussion

Peutz–Jeghers syndrome is a rare disease that can cause severe complications, such as intussusception and GI obstruction, especially in children. Until recently, the youngest cases of PJS complicated with small bowel intussusception were 3 years old in China and in the Netherlands [7, 8]. However, *STK11* genotype was not addressed. The present case represents the youngest case of PJS complicated with intussusception of the jejunum with an identified mutation of *STK11*.

Most polyps from PJS occur numerously in the small bowel to increase a risk of intussusception. Hinds et al. reported that 30% of patients with PJS required laparotomy for intestinal obstruction by the age of 10 years, which increased to 68% by age 18 years [9]. Another study showed the cumulative risk of intussusception in PJS to be 15% by age 10 years and 50% by age 20 years, with the strongest risk factors being polyp location and size of > 15 mm [8].

There is a general consensus that surveillance is needed for PJS patients. Beggs et al. and the American College of Gastroenterology (ACG) guidelines recommend baseline EGD and CS at 8 years of age, with subsequent examinations every 3 years if polyps are found [10, 11]. Similarly, a cohort study in the Netherlands suggested commencing small intestinal surveillance from 8 to 10 years of age at 2- to 3-year intervals for intussusception prevention [8]. A French group also recommended biannual enteroscopy after 8 years of age by SBCE as first-line surveillance [12]. In contrast, Goldstein SA et al. recommended much earlier screening of the digestive tract for such complications as intussusception and rectal bleeding, advocating EGD, CS, and SBCE for initial polyp screening from 4 to 5 years of age. If polyps are found, examinations should be repeated every 1–2 years [13]. The above differences in screening age and procedure likely stem from the perceived degree of invasiveness and necessity of endoscopy depending on the age and clinical condition of each patient. In the present case, the girl had mucocutaneous pigmentation suggestive of PJS and recurrent abdominal symptoms during the year prior to intussusception. When patients exhibit hallmark abdominal symptoms of GI polyps, clinicians should consider GI tract screening, especially of the small bowel, even at an early age to prevent intussusception.

There is debate on how to screen and treat small bowel polyps in younger children with PJS. Gastineau et al.

Table 1 Reported cases of early onset intussusception (≤ 8 years old) due to PJS-related polyps with detected germline mutations

Reference no.	Country of presentation	Sex	Age at intussusception (years)	Location of leading polyp	Location of mutation in *STK11*	Sporadic/familial
26	China	F	5	Jejunum	c.A527G (exon 4)	Familial
7	China	F	3	SB	c.943_944het_delCCinsG (exon 8)	Sporadic
7	China	M	7	SB	c.1062C>C/G (exon 8)	Sporadic
7	China	M	8	SB	c.348_349het_delGT (exon 2)	Sporadic
Present case	Japan	F	3	Jejunum	c.247A>T (exon 1)	Sporadic

PJS Peutz–Jeghers syndrome, *SB* small bowel

described that SBCE was easily feasible in 27 children with PJS (age range 5.4–20.9 years), which revealed jejunal polyps in 72% and ileal polyps in 55% of patients [14]. European guidelines recommend SBCE and magnetic resonance enterography for small-bowel surveillance in patients with PJS [15]. Currently, the use of SBCE is approved under special precautions in Japan, having been performed safely in patients as young as 10 months of age [16]. Capsule retention is a serious adverse event of SBCE, and it is related to an intestinal stricture from inflammation, prior surgery (ie, adhesions or anastomosis), or small intestinal tumors [17]. As far as we have examined, there is no report in children with PJS that the previous abdominal surgery increases the risk of capsule retention. In the present case, we performed SBCE without confirmation of the capsule passing using patency capsule based on careful clinical evaluation of intestinal obstruction. Hence, we propose SBCE for the surveillance of small bowel polyps in children with PJS under particular attention for capsule retention in patients with post-abdominal surgeries. Based on early screening results of the total GI tract, endoscopic resection using balloon-assisted enteroscopy (BAE) may be beneficial to avoid surgical emergencies. Sakamoto et al. reported that resection of polyps in patients with PJS by BAE was carried out with 6.8% complication rate, and there were no severe events in adults [18]. To date, the youngest patient with PJS receiving successful polypectomy by BAE was 5 years old, in whom 2 polyps (maximum size 6 cm) were resected in the jejunum through oral insertion of single balloon enteroscopy without any severe adverse effects [19]. Yokoyama et al. performed double-balloon enteroscopy (DBE) on 117 pediatric patients (median age 12.5 years) [20]. Antegrade (oral-route) and retrograde (anal-route) DBE was achieved in youths of 3 and 2 years of age, respectively, and endoscopic polypectomy by DBE was performed in children of ≥ 6 years of age with hereditary polyposis syndrome. On the other hand, Spahn et al. described a case of perforation during endoscopic polypectomy in the proximal jejunum in a 3-year-old patient with PJS [21]. Based on the current literature, endoscopic polypectomy for children of < 5 years remains challenging. Tsuji et al. reported on novel hybrid treatments using DBE combined with transumbilical minimal incision surgery [22]. They also remarked that endoscopic procedures using DBE in children were more difficult than in adults due to a thin intestinal wall and narrow lumen. In the present case, earlier total GI tract screening and prophylactic polyp resection using the latest minimally invasive methods may have prevented the intussusception. It has been suggested that the presence of adhesions from previous laparotomies might limit the success rate of total enteroscopy by using DBE and increase procedure time in PJS patients [18]. If the clearance of significant polyps by DBE is not achieved in cases of post-abdominal surgeries, laparoscopically assisted DBE can be considered [23].

The search for genotype–phenotype correlations in PJS is ongoing. Salloch et al. reported that truncating mutations in PJS were associated with larger numbers of polyps, surgical interventions, and cancers [24]. However, their observations were based on a relatively small patient series; more data are needed for confirmation. In the present case, a c.247A>T p.K83X nonsense mutation in exon 1 of *STK11* was identified by Sanger testing. Hemminki et al. reported that the stop codon either in codon 70 or 84 in *STK11* were pathogenic in patients with PJS [25]. Therefore, the germline truncating mutation p.K83X which locates between codons 70 and 84 may also be pathogenic. We reviewed the literature to identify if specific mutations of *STK11* were associated with the early onset of intussusception in children (Table 1). Germline mutations of *STK11* were reported in five patients with PJS who experienced intussusception at ≤ 8 years old [7, 26], although a definitive *STK11* mutation type and site remain unknown.

In summary, this case report presented clinical information and identified a germline mutation of *STK11* in an extremely young sporadic case of PJS complicated with jejunal intussusception. In children with suspected PJS based on mucocutaneous pigmentation or a family history who exhibit symptoms related to GI polyps, clinicians should consider total GI tract screening and polyp resection to prevent intussusception and possible surgical emergency.

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Compliance with ethical standards

Conflict of interest Tomomitsu Sado, Yoshiko Nakayama, Sawako Kato, Hitoshi Homma, Mai Kusakari, Nao Hidaka, Suguru Gomi, Shigeru Takamizawa, Tomoki Kosho, Shinya Saito and Kokichi Sugano declare that they have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

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