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ORIGINAL ARTICLE

Observational Study

Clinical features, endoscopic polypectomy and *STK11* gene mutation in a nine-month-old Peutz-Jeghers syndrome Chinese infant

Zhi-Heng Huang, Zai Song, Ping Zhang, Jie Wu, Ying Huang

Zhi-Heng Huang, Jie Wu, Ying Huang, Department of Gastroenterology, Children's Hospital of Fudan University, Shanghai 201102, China

Zai Song, Department of Pediatric Surgery, Children's Hospital of Fudan University, Shanghai 201102, China

Ping Zhang, The Molecular Genetic Diagnosis Center, Shanghai Key Lab of Birth Defects, Translational Medicine Research Center of Children's Development and Disease, Pediatrics Research Institute, Children's Hospital of Fudan University, Shanghai 201102, China

Ying Huang, Department of Gastroenterology, Children's Hospital of Xiamen, Xiamen 361006, Fujian Province, China

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Correspondence to: Ying Huang, MD, PhD, Professor, Department of Gastroenterology, Children's Hospital of Fudan University, No. 399 WanYuan Road, Shanghai 201102, China. yhuang815@163.com
Telephone: +86-21-64931727
Fax: +86-21-64931901

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Abstract

AIM: To investigate multiple polyps in a Chinese Peutz-Jeghers syndrome (PJS) infant.

METHODS: A nine-month-old PJS infant was admitted to our hospital for recurrent prolapsed rectal polyps for one month. The clinical characteristics, a colonoscopic image, the pathological characteristics of the polyps and X-ray images of the intestinal perforation were obtained. Serine threonine-protein kinase 11 (*STK11*) gene analysis was also performed using a DNA sample from this infant.

RESULTS: Here we describe the youngest known Chinese infant with PJS. Five polyps, including a giant polyp of approximately 4 cm × 2 cm in size, were removed from the infant's intestine. Laparotomy was performed to repair a perforation caused by pneumoperitoneum. The pathological results showed

that this child had PJS. Molecular analysis of the *STK11* gene further revealed a novel frameshift mutation (c.64_65het_delAT) in exon 1 in this PJS infant.

CONCLUSION: The appropriate treatment method for multiple polyps in an infant must be carefully considered. Our results also show that the *STK11* gene mutation is the primary cause of PJS.

Key words: Peutz-Jeghers syndrome; Perforation; *STK11* gene; Chinese infant; Polyps

Core tip: This is the first report detailing a nine-month-old Chinese Peutz-Jeghers syndrome (PJS) infant with multiple polyps. A perforation and pneumoperitoneum developed after polypectomy and were followed by sepsis. *STK11* gene sequencing and pathology results confirmed that this infant had PJS with a novel, *de novo* mutation. This article also gives some thoughts to PJS management in children, especially in infants.

Huang ZH, Song Z, Zhang P, Wu J, Huang Y. Clinical features, endoscopic polypectomy and *STK11* gene mutation in a nine-month-old Peutz-Jeghers syndrome Chinese infant. *World J Gastroenterol* 2016; 22(11): 3261-3267 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i11/3261.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i11.3261

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder characterized by hamartomatous polyps in the gastrointestinal tract, mucocutaneous pigmentation and an increased risk of cancer[1]. A mutation in the tumor suppressor gene serine threonine-protein kinase 11 (*STK11*) located on 19p13.3 has been found to be primarily responsible for this disease[2]. Presentation of PJS in infancy is rare. This is the first detailed report of a nine-month-old Chinese PJS infant with multiple polyps. A perforation and pneumoperitoneum developed after polypectomy in this patient, followed by sepsis. The *STK11* gene sequencing and pathology results confirmed that this infant had PJS.

MATERIALS AND METHODS

Patient

A nine-month-old infant was admitted to our department with recurrent prolapsed rectal polyps (PRPs) for one month. This infant was female, and she had no family history of PJS.

Polypectomy via colonoscopy

The infant underwent polyp screening, and the polyps were removed during colonoscopy, which was performed using gastrointestinal endoscopy (GIF-XQ260, Olympus, Japan) and an argon plasma coagulation device (VIO200D + APC2, German) with detachable snares (MAJ339, Olympus, Japan). The polyps that were removed were subject to pathological analysis. In our study, polyps > 1 cm were classified as "large", and those > 2 cm were classified as "giant".

Sample collection and variant detection

A blood sample was collected, and genomic DNA was extracted according to the *STK11* gene testing protocol. All of the *STK11* coding exons and its boundary regions were amplified by PCR and analyzed by direct sequencing[3].

Functional significance prediction and analysis

Three online software packages, including mutation taster (http://mutationtaster.org/) and PolyPhen 2 (http://genetics.bwh.harvard.edu/pph2/), were used to predict the functional significance of the variants.

RESULTS

Clinical characterization and laboratory results

The body weight of this infant was 9.5 kg. She was delivered by cesarean section due to social factors after 40 wk of gestation and had a birth weight of 3500 g. Her chief complaint was recurrent PRPs for one month. The size of the first PRP was similar to that of a pigeon egg. However, the PRP size increased to as large as a chicken egg after one month. Mucocutaneous pigmentation was not detectable in any part of her body. Her complete blood count (CBC) and fecal occult blood test were normal. Her mother was 28 years of age (1 gravida, 1 para), and her father was 31 years of age. She had no brothers or sisters. Both parents were healthy, and neither had a family history of PJS.

Polypectomy

Under general anesthesia, colonoscopic examination revealed five polyps (Figure 1). The first large polyp was located at the outlet of the anus and was approximately 1.5 cm × 1.5 cm in size. The second polyp was small and was located in the sigmoid, with a size of approximately 0.6 cm × 0.8 cm. The third polyp was also small and was located in the sigmoid, with a size of approximately 0.4 cm × 0.5 cm. The fourth polyp was a cucurbit-shaped giant polyp that was located in the descending colon, with a size of 4 cm × 2 cm. The fifth polyp was also a giant polyp with three lobulations and was located in the transverse colon, with a size of approximately 2.5 cm × 2 cm. All of the polyps were removed smoothly during colonoscopy. The polyps were confirmed as hamartomatous polyps and were pathologically diagnosed as PJS (Figure 2).

Laparotomy

The infant was transferred to the general ward for routine hemostasis with dicynone, p-aminomethyl

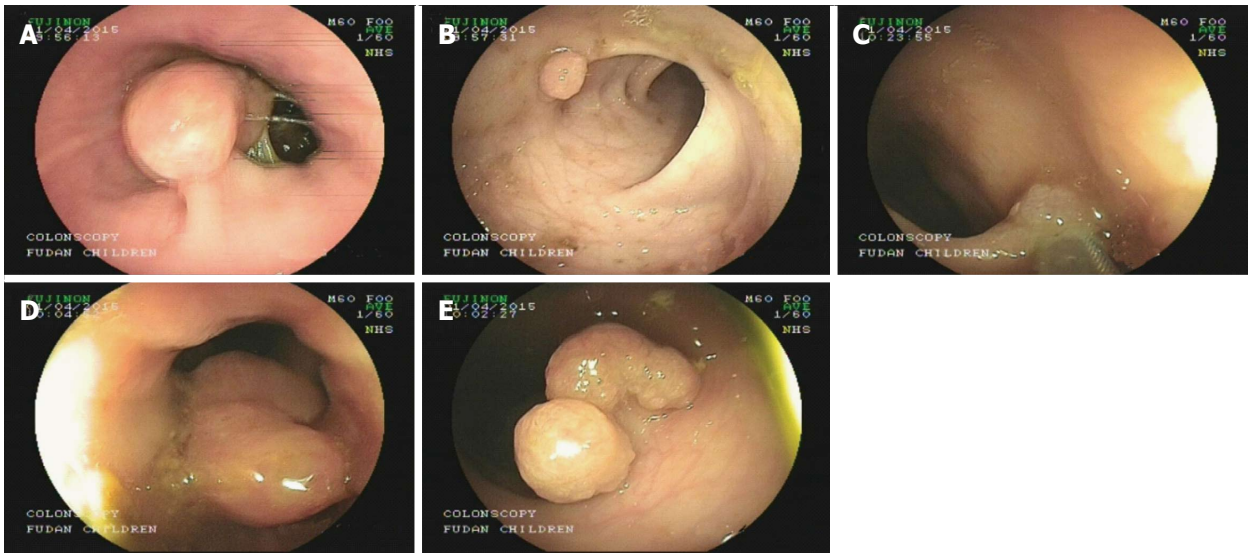

Figure 1 Endoscopic images of the five polyps located in different parts of the intestine (A-E).

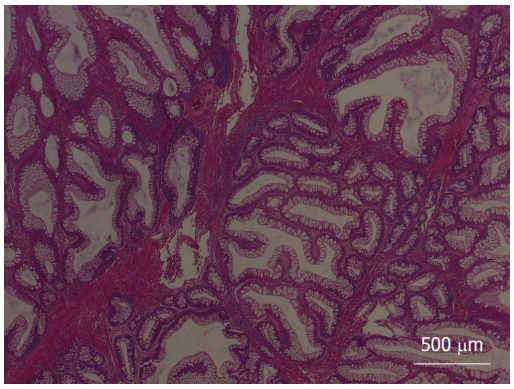

Figure 2 Hematoxylin-eosin stained image showing the pathological characteristics of the hamartomatous polyps in the infant with Peutz-Jeghers syndrome.

benzoic acid and supplemental fluid due to fasting. Her blood pressure was normal. The infant had a low fever for approximately 2 h after polypectomy, and her abdomen was soft. We believed that she had an absorption fever due to the extent of polypectomy. Therefore, no further action was taken. The infant still had a low fever and was slightly agitated after 3 h. Physical examination showed that her abdomen was slightly inflated. Still, no further action was taken. Her temperature increased after 4 h, and physical cooling was performed. The infant became more agitated, and after 6 h, her abdomen became more inflated. A CBC test was performed, which revealed that the white blood cell (WBC) count was 3.1 × 10^9/L and the C-reactive protein (CRP) level was 12 mg/L.

Symptoms of shock were observed in the infant, as evidenced by low spirit and poor peripheral limb circulation after 8 h. A CBC test was performed, and the results showed that the WBC was 3.5 × 10^9/L and the CRP was 68 mg/L. A crystalloid solution was administered quickly to improve the shock symptoms. After approximately 10 h, the infant underwent abdominal X-ray examination. The X-ray image showed pneumoperitoneum (Figure 3A and B).

The infant immediately underwent emergency surgery. During surgery, a perforation of 0.5 cm^2 in size was found in the descending colon where the fourth giant polyp was removed. This part of the intestine was resected by anastomosis.

Postoperative course

The infant was transferred to the pediatric intensive care unit for further postoperative support. A CBC test showed that the WBC was 3.0 × 10^9/L and the CRP was 84 mg/L. The infant was intubated and placed on ventilator support for 4 d. The blood culture was positive for *Escherichia coli*. Antibiotics, including ceftriaxone, metronidazole, meropenem, and vancomycin, were used for the treatment of sepsis and acute peritonitis. Albumin was used to treat hypoproteinemia caused by inflammatory exudation. Abdominal X-ray showed that the pneumoperitoneum had disappeared five days after surgery (Figure 3C and D).

The infant was discharged from our hospital when her CBC was nearly normal and her blood culture was negative. The changes in the WBC and CRP that occurred during this period are described in Figure 4.

Mutation analysis

Molecular analysis of the *STK11* gene revealed a novel and *de novo* frameshift mutation (c.64_65het_delAT, p.M22Gfs*140) in exon 1 in this PJS infant (Figure 5). This mutation leads to the partial loss of the kinase domain and the complete loss of the C-terminus, and it has not been previously reported. We also found an SNP (c.920+7G>G/C) in intron 7.

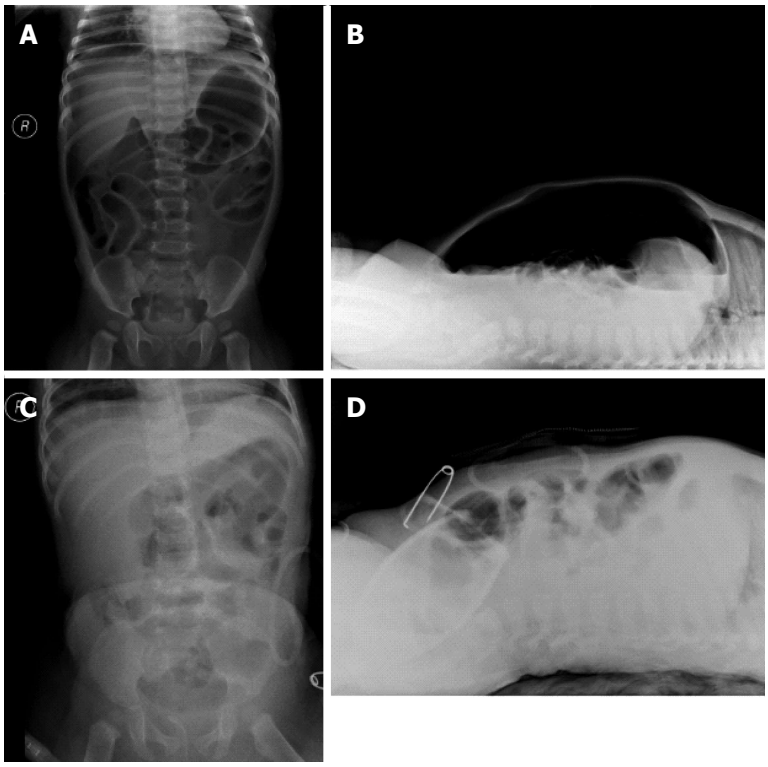

Figure 3 X-ray images of the abdomen. A, B: Images showing the pneumoperitoneum; C, D: Images showing recovery of pneumoperitoneum after intestinal repair.

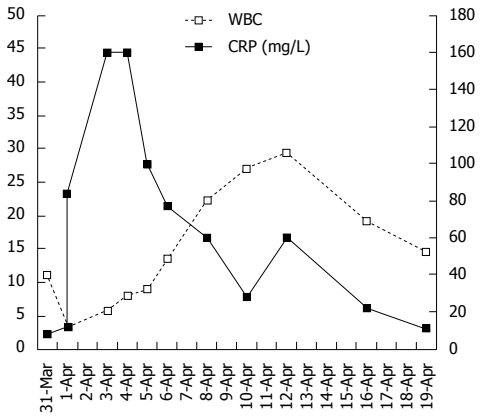

Figure 4 Changes in the white blood cell and C-reactive protein preoperatively and postoperatively.

Systematic literature concerning pediatric PJS

A total of 679 papers were identified (PubMed = 183, Embase = 112, Scopus = 297, Cochrane = 0, Web of Science = 87), and 27 papers were considered potentially relevant. All articles discussing PJS in children were retrieved. The criterion for inclusion in the study was patient age of 0-18 years. Only English-language articles published from 1995, when the first case of neonatal PJS was reported, up to July 31, 2015 were retrieved, and all articles were reviewed independently for suitability (Table 1). The clinical manifestations in PJS vary among patients. In the above-mentioned literature, some children exhibited mucocutaneous pigmentation, abdominal pain, anemia

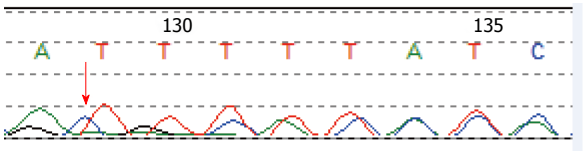

Figure 5 Infant had a frameshift mutation in codon 64 (64_65het_delAT) in exon 1. The arrow indicates the mutation site.

and bloody stool, intussusception or prolapsed rectal polyps. Fernandez Seara *et al*[4] first reported PJS in a neonate with abdominal distention and bloody stool initially due to multiple polyposis. This patient died at 12 mo of age with multiple complications. Al Faour and Burgmeier respectively reported another neonate with PJS due to an oblong abdominal mass[5,6]. Those neonates with PJS were diagnosed by pathology but *STK11* gene information was not collected for these cases. Some of the retrieved studies focused on the clinical information whereas some focused on genetic information related to *STK11* and other genes[7,8]. Few studies focused on both clinical features and gene information, and all children in the previous PJS reports were 1 year of age or older[9-11]. Morrison reported a nine-month-old PJS infant with umbilical pigmentation[12]. This infant had a family history of PJS and had a novel mutation (c.88dupG) in exon 1 of the *STK11* gene. And in our study, we report the youngest PJS infant in China with recurrent prolapsed rectal polyps, and her clinical information, laboratory data, image data, pathological images and *STK11* gene data are also described in detail.

Table 1 Systematic literature reports of pediatric Peutz-Jeghers syndrome

Ref.	Year	Study type	Country	Age range	Manifestation	Treatment	Gene information
Fernandez Seara *et al*[4]	1995	Case report	Spain	15 d	PRPs	ED and Died	NA
Corley *et al*[21]	1997	Case report	United States	15 yr	Gastric outlet obstruction, abdominal pain	ED and OP	NA
Al Faour *et al*[5]	2002	Case report	France	4 d	Abdominal mass	OP	NA
Boseto *et al*[22]	2002	Case report	Australia	14 mo	Gastric outlet obstruction	OP	NA
Homan *et al*[23]	2005	Case report	Slovenia	10 yr	Abdominal pain, vomiting, intussusception	OP	NA
Hearle *et al*[7]	2006	Letter	United Kingdom	1-38 yr	NA	NA	Yes
Zuo *et al*[8]	2007	Article	China	5-10 yr	MP	NA	Yes
Adolph *et al*[24]	2008	Review	United States	Children	MP, intussusception, abdominal pain, *etc.*	ED and OP	NA
Vidal *et al*[25]	2009	Article	France	4.8-15.1 yr	MP, PRPs, intussusception, *etc.*	ED and OP	NA
Ausavarat *et al*[26]	2009	Case report	Thailand	14 yr	MP, abdominal pain, intestinal obstruction, *etc.*	ED or OP	Yes
Resta *et al*[9]	2010	Article	Italy	1-17 yr	NA	NA	Yes
Yang *et al*[27]	2010	Article	Korea	6 mo-13.8 yr	MP, hematochezia, intussusception, anemia,*etc.*	ED or OP	Yes
Liu *et al*[11]	2011	Article	China	6 yt	MP, abdominal pain, hematochezia	ED and OP	Yes
Burgmeier *et al*[6]	2012	Case report	Germany	2 d	Vomiting, abdominal mass	OP	NA
Chen *et al*[28]	2012	Article	China	14 yr	MP	ED	Yes
Thakkar *et al*[29]	2012	Review	United States	children	MP, PRPs, intussusception, *etc.*	ED and OP	Yes
Liu *et al*[30]	2012	Article	China	12 and 16 yr	MP, abdominal pain, hematochezia, *etc.*	ED	Yes
Goldstein *et al*[31]	2013	Article	United States	1-14 yr	MP, PRPs, intussusception, *etc.*	ED and OP	NA
Zheng *et al*[32]	2013	Article	China	1-5 yr	MP, abdominal pain	NA	Yes
Vageli *et al*[33]	2013	Case report	Greece	12 yy	MP	NA	NA
Chae *et al*[34]	2014	Case report	Korea	12 yr	MP, abdominal pain, anemia	OP	Yes
Morrison *et al*[12]	2014	Case report	United Kingdom	9 mo	Umbilical pigmentation	NA	Yes
Wang *et al*[35]	2014	Article	China	1-43 yr	MP, histopathologic examination, *etc.*	ED and OP	Yes
Cohen *et al*[36]	2014	Article	Israel	4-16 yr	MP, abdominal pain, hematochezia	ED or OP	Yes
Kimura *et al*[37]	2015	Case report	Japan	13 yr	MP, abdominal pain	OP	NA
Kuroda *et al*[10]	2015	Article	Japan	12 yr	MP, intellectual disability	ED	Yes
Armijo *et al*[38]	2015	Case report	United States	4 yr	gynecomastia, MP, testicular lesions	Orchiectomy	Yes
Our group	2015	Article	China	9 mo	PRPs	ED and OP	Yes

ED: Endoscopy; MP: Mucocutaneous pigmentation; NA: Not available; OP: Operation; PRPs: Prolapsed rectal poly.

DISCUSSION

In 1995, Fernandez Seara *et al*[4] first reported on the occurrence of PJS in a neonate. The *STK11* gene responsible for PJS was discovered in 1998. However, there are still few reports of PJS presenting in infants, and there are no relevant reports of this syndrome affecting infants in China. This study presents a nine-month-old Chinese PJS infant with multiple intestinal polyps. To our knowledge, this is the first report to describe the clinical characteristics, colonoscopic findings, pathological results, and surgical treatment of the youngest Chinese infant with PJS and the *STK11* gene mutation.

PJS may have varying clinical manifestations, and most clinical complications occur in adults who are 20 to 30 years of age; however, 1/3 of patients are younger than 10[13]. Symptoms of PJS include abdominal pain, rectal bleeding, intussusception, and mucocutaneous pigmentation. The nine-month-old infant in this study suffered recurrent PRPs for one month. No mucocutaneous pigmentation was detectable in any part of the patient's body, and she only had growing PRPs. Colonoscopy revealed five intestinal polyps, two of which were giant polyps.

For large polyp (≥ 2 cm) removal, endoscopic polypectomy is commonly considered safe, efficacious and cost-effective in the management of complex colon polyps compared with surgical removal. However, this procedure is not free from complications[14]. For polyps in children, surgical removal may influence physical and psychological development and endoscopic follow-up. Endoscopic resection of large polyps, which is minimally invasive, is associated with lower morbidity and mortality rates compared with surgery, and it is not only indicated, it is also considered the most appropriate approach. In children, and especially in infants, the lumen size is small and the intestinal wall is thin. Thus, endoscopic polypectomy has a greater risk of perforation in young patients than in adults. For adults, there is still debate as to whether large polyps should be removed under laparoscopy or under colonoscopy[15]. For children, no guidelines are available for removal of a large polyp *via* laparoscopy, colonoscopy or surgery. We considered that the polyp size, its pedunculated or sessile nature, its location, the age of the child, and the experience of the endoscopist are important factors when selecting between endoscopic or surgical removal of a large polyp[16]. Wiseman *et al*[17] presented two patients with very large polyps in the proximal colon that were not amenable to colonoscopic removal. These large

polyps were removed using minimal-access surgical techniques under laparoscopy. For our patient, surgery may have been the best choice to avoid perforation and sepsis.

Bleeding and perforation are common adverse events in polyposis patients after endoscopy. Bleeding from the large feeding vessels could induce unexpected hypovolemic shock, especially in young toddlers. Perforation can occur during or after resection. Immediate perforation occurs due to deep resection, whereas delayed perforation occurs from a rupture of the wall caused by coagulation necrosis[18]. In our study, the PJS infant had intestinal perforation, serious pneumoperitoneum and sepsis. The large intestine is full of detrimental bacteria, especially *Escherichia coli*. Migration of *Escherichia coli* into the blood stream from a perforation site can lead to sepsis. For large polyp removal, careful examination is very important. Performing timely postoperative abdominal examination, abdominal X-ray and ultrasound aids in the early detection of complications. There are fewer risks of sepsis and other complications if bleeding and perforation are found earlier.

For children with PJS, especially infants, mucocutaneous pigmentation may develop after birth or later. It is difficult to distinguish PJS from other polyp syndromes if mucocutaneous pigmentation presents late. Pathological examination and *STK11* gene testing are the gold standards for PJS diagnosis[19]. The patient in this study was initially diagnosed with juvenile polyposis syndrome; however, pathological examination of the polyps led to a diagnosis of PJS. *STK11* gene testing further confirmed this diagnosis. This PJS patient had a *de novo,* novel frameshift *STK11* gene mutation. This type of truncating mutation in PJS is associated with the presence of more polyps, as well as increased risks of surgical intervention and cancer[20]. Therefore, additional follow-up of this child and similar patients is needed in the future

In conclusion, we have detailed the first case of PJS occurring in a Chinese infant without mucocutaneous pigmentation. For infants with PJS, the treatment strategy should be individualized, and careful postoperative examination should be conducted. Pathological and genetic testing is also indispensable.

COMMENTS

Background

Peutz-Jeghers syndrome (PJS) is an uncommon autosomal dominant inherited disease characterized by the occurrence of hamartomatous polyps in the gastrointestinal tract, and mucocutaneous pigmentation. Germline mutations of *STK11* gene are responsible for most PJS cases. However, the report of Chinese infant with PJS is rare.

Research frontiers

PJS is associated with mutations of the *STK11* gene located on chromosome 19p13.3. Germline point mutations are responsible for most patients with PJS and large genomic deletions have also been identified in few patients with PJS. Currently, there is no guideline available on polypectomy by endoscopy or surgical intervention for the children with PJS.

Innovations and breakthroughs

This is the first study to report the youngest PJS infant in China without mucocutaneous pigmentation, and her clinical information, laboratory data, image data, pathological images are also described in detail. *STK11* gene sequencing results confirmed that this infant had PJS with a novel, *de novo* mutation. Further, systematic literature concerning pediatric PJS is analyzed and explained.

Applications

The present study suggested that for patients with multiple polyps, histopathological examination and gene testing are essential. This article also gives some thoughts on management of the children, especially infants with PJS cost-effectively.

Terminology

PJS refers to a rare autosomal dominant inherited disorder characterized by gastrointestinal hamartomatous polyposis, mucocutaneous pigmentations, and high risk of cancer. Germline mutations of *STK11* gene are the main cause of PJS.

Peer-review

The authors described a PJS infant with an *STK11* gene mutation who developed intestinal perforation following endoscopic polypectomy.

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