



Intestinal intussusception in a child with Peutz–Jeghers syndrome: case report

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Introduction and importance: Peutz–Jeghers syndrome (PJS), an uncommon inherited autosomal dominant disorder, is distinguished by mucocutaneous pigmentations, many gastrointestinal hamartomatous polyps, and a higher incidence of gastrointestinal tract, genitourinary, and extracolonic malignancies. Recurrent acute intestinal obstruction, in particular intussusception in the young, is a serious sequelae of PJS.

Case presentation: A clinical observation of a 5-year-old patient with a complicated course of PJS is presented. Emphasis on recurring episodes of acute abdomen, clinical diagnosis including polyp histopathology, and surgical management is emphasised.

Clinical findings and investigations: While an inpatient, bloodwork demonstrated severe iron deficiency anaemia (haemoglobin 72 g/l, red blood cell $3.1 \times 10^{12}/l$) and multiple melanin pigmentations measuring 2–4 mm in size on the lip mucosa during a physical examination. Erosive duodenopathy and polyposis of the stomach were discovered via fibroesophagogastroduodenoscopy (multiple gastric polyps 5–10 mm in size). Acute intussusception of the intestine was discovered by ultrasonography.

Interventions and outcome: A mid-median laparotomy was performed alongside manual disinvagination with gut viability intact. Histopathology of excised polyps revealed smooth muscle hyperplasia and Ki67 protein (MIB-1) positivity with small intestinal hamartomatous polyps seen macroscopically. Conservative management was initiated for standard postoperative care and intestinal motility. Patient was discharged 9 days postoperatively.

Relevance and impact: Based on literature data, modern ideas concerning aetiology, diagnosis, and management of patients with PJS are considered. Attention is focused on the high risk of developing cancer of various localisation in PJS, recommendations are given for cancer screening and clinical observation of patients with hereditary gastrointestinal syndromes in childhood.

Keywords: children, intestinal intussusception, intestinal polyposis, peutz–jeghers syndrome

Introduction

PJS is an orphan autosomal dominant genetically inherited disease characterised by punctate melanin pigmentation of the mucous membrane of the lips, mouth, palms, soles, perianal region, and vagina with the formation of multiple hamartoma polyps of the GIT. PJS manifests itself in childhood, causing an intestinal obstruction, chronic intestinal bleeding, and iron deficiency anaemia (IDA)^[1,2]. According to the International Classification of Diseases (ICD)-10, PJS refers to phakomatoses

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HIGHLIGHTS

- Peutz–Jeghers syndrome (PJS) is a very rare genetic condition distinguished by many gastrointestinal hamartomatous polyps in various parts of the human body, but predominantly in the gastrointestinal tract (GIT).
- The birth rate of children with PJS ranged from 1:25 000 to 1:280 000 cases per year, with no significant racial or sex differences in incidence.
- The relative risk (RR) of developing malignancies in various organs in PJS is 15 times higher than in the general population.
- The patient had multiple melanin pigmentations on the lip and gastric polyps, which were characteristic features of PJS.
- The histopathological examination of the polyps showed smooth muscle hyperplasia, elongated branching pattern, focal up to 60% Ki67 Protein (MIB-1), and small intestine hamartomatous polyps, which supported the diagnosis of PJS.

[class XVII “Congenital anomalies (malformations), deformities and chromosomal disorders”; block Q80-Q89 “Other congenital anomalies”; heading Q85.8 “Other phakomatoses, not elsewhere classified headings”]. PJS is classified as a hereditary hamartoma

polyposis of the GIT. Hamartoma polyposis is a heterogeneous group of diseases, which also includes juvenile polyposis syndrome, Bannayan–Riley–Ruvalcaba syndrome, and Cowden syndrome^[3]. These groups of nosologies are characterised by two features: multiple polyps in any part of the GIT and the risk of developing malignant tumours of various organs^[4]. The birth rate of children with PJS was from 1:25 000 to 1:280 000 cases per year; no racial or sex differences in incidence were found^[4].

For the first time, the relationship between polyps of the GIT and spots on the skin and mucous membranes was described in 1921 by the Dutch doctor Jan Peutz (1886–1957). In 1949, Harold Joseph Jaegers (1904–1990) with his colleagues McKusick and Katz collected more detailed information about PJS in the United States. The eponym PJS was first introduced by radiologist Andre Brewer in 1954 in the United States^[5]. Polyps of the GIT in PJS develop in 90% of patients and 1/3 are detected in the first decade of life^[4].

Typical for PJS is punctate melanin pigmentation—maculae (spots from 1 to 5 mm in diameter) at the border of the skin and mucous membranes, most often around the mouth, on the lips (94%), nostrils, in the perianal region, on the skin of the fingers, hands and stop (62–74%). These small, flat, brown or dark blue patches are present in more than 90% of PJS cases and may disappear after puberty, but the buccal mucosal lesions tend to persist. Isolated melanin mucocutaneous pigmentation in the absence of polyposis is also possible as a genetic variant of the syndrome^[6].

The number of polyps is from 1 to 100, the sizes are from 0.1 to 3 cm in diameter. The frequency of polyps along the GIT is maximum in the jejunum, gradually decreasing towards the ileum and duodenum. The macroscopic structure of polyps in PJS is very variable: from small on a wide base (type 0-Is) to large on a stalk (type 0-Ip), capable of completely blocking the lumen of hollow organs or provoking invagination, shifting under the influence of peristalsis^[7]. In this regard, a wide range of clinical manifestations is formed—from an asymptomatic course in the presence of a small number of “miniature” polyps to acute intestinal obstruction (AIO), due to obturation or intussusception with a massive growth of large hamartomas^[7]. Gastrointestinal bleeding of varying intensity is also common, arising from traumatism or self-amputation of polyps.

Therefore, we present a case of a 5-year-old female presenting with recurrent intussusception associated with PJS and severe IDA.

Case report

An Ukrainian 5-year-old female with a BMI of 14 presented with a complex paediatric history. The patient’s parents became concerned regarding the child’s increasing pallor during the preceding month and referred this complaint to their family physician. On examination, the family physician revealed in the patient the pallor and changes of automated complete blood cell count (CBC)—red blood cell 3.4×10^6 / μ l, haemoglobin 71 g/l, mean corpuscular volume 71,2 fl, serum ferritin 18 μ g/l. The child was subsequently diagnosed with IDA of unknown aetiology. As a result, IDA therapy of oral ferrous sulfate was initiated (6 mg/kg/day). The patient was also referred by the family physician to the Sумы Regional Children’s Hospital for further examination.

Upon initial hospital examination, pallor and asthenia were of major patient findings. The medical history was obtained from

the patient’s grandmother, who is considered to be a reliable historian. Since the age of 3, the patient has lived in the family of his maternal grandparents, where the biological parents do not reside with the child, but provide financial support. According to the anamnesis, the child had asthenic syndrome and recurrent abdominal pain (i.e. short attacks 2–3 times per month) for two years prior, and chronic constipation (deliberated as infrequent, difficult passage of stool) since the age of one year. On physical examination, skin pallor and multiple melanin pigmentations on the lip (ranging in size from 2–4 mm) were exhibited (Fig. 1).

No other obvious peripheral signs of gastrointestinal stigmata were observed during the first hospital physical examination, with no obvious pathologies found during examination of the breast. To our knowledge, the patient’s vaccinations were administered according to the national immunisation schedule. The patient had no prior surgical history, no known drug allergies, and an unremarkable family history comprising gastrointestinal disease, congenital anomalies, chromosomal mutations, growth and development issues, consanguinity, or ethnic background contributors. On admission, bloods were taken which revealed a CBC—red blood cell of $3,1 \times 10^6$ / μ l, haemoglobin 72 g/l, mean corpuscular volume 75,1 fl, and serum ferritin 18 μ g/l. The faecal occult blood test was performed which returned positive.

To aid our differential diagnoses of chronic abdominal pain according to the patient’s history, an oesophagogastroduodenoscopy was performed. The results of the respective oesophagogastroduodenoscopy demonstrated erosive duodenopathy and numerous gastric polyps ranging in size from 5 to 10 mm. We suspected PJS since the patient also had stomach polyps in addition to the typical pigmented lip lesions. We lacked the syndrome’s histological features that were specific to polyps, though. Additionally, due to financial constraints, the patient’s

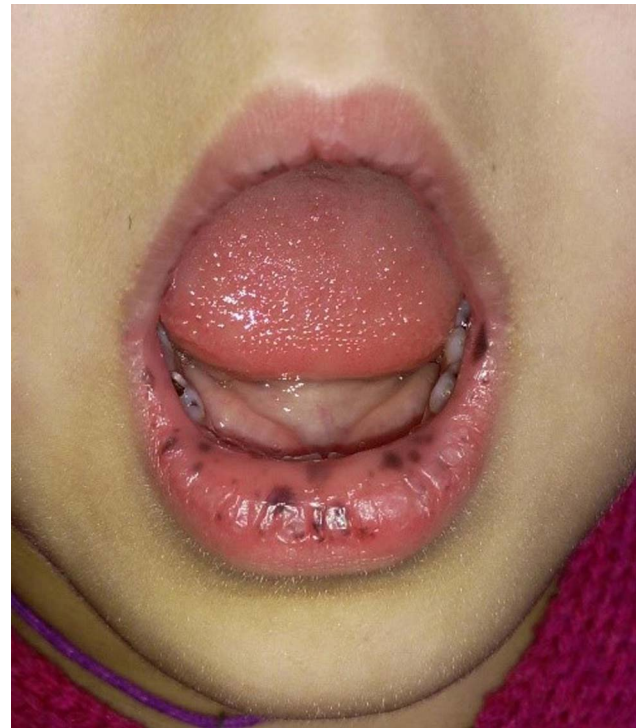


Figure 1. Melanin pigmentation of the lips.

grandparents declined to undergo molecular genetic testing for the analysis of the *STK11/LKB1* locus.

As the patient was clinically stable, hospital discharge was warranted. However, 5 days following the first consultation, the patient suddenly developed acute abdominal pain described as intermittent colicky pain occurring every 10–15 min emesis comprising yellow vomitus. Subsequently, the patient was referred for urgent consultation with a general surgeon.

On observations, the patient's body temperature was 37.4°C with a slight tachycardia alongside normal blood pressure and oxygen saturation. Palpation of the abdomen in the mesogastrium was exquisitely painful and did not reveal any obvious signs of an intra-abdominal mass. The spleen and liver were nonpalpable and normal bowel sounds were present. Percussion of the abdomen produced an audible differentiated tympanic resonance. However, no abdominal distention was observed. The patient had not passed flatus or stool in the last 24 h. No other pathological changes were found during the physical examination.

An emergency ultrasound revealed standard findings suggestive of small-bowel intussusceptions, with clinical suspicion of two concurrent intestinal intussusceptions. Abdominal X-ray was not performed at the time of diagnosis as the pathologies were confirmed via abdominal ultrasonography. Given the high suspicion of PJS in which intussusception is caused by polyps (a point of case interest), we decided not to perform conservative management with air insufflation via fluoroscopic imaging guidance, but rather conduct major abdominal surgery.

A mid-median laparotomy was performed. Multiple small intestine intussusceptions (precisely three lesions) were detected intraoperatively, and manual reduction was performed. The intestine's viability was intact and no obvious bowel necrosis was evident. During the revision of the small intestine at 5, 12, 20, and 45 cm from the Ligament of Treitz, rounded formations of 1.5–2.5 cm in diameter were palpated in the intestinal lumen, each 12 cm apart. All polyps were captured in turn by the instrument, removed from the bowel wound, and resected (Fig. 2)^[8]. The lesions were sent for pathohistological examination. The intestinal lumen was then sutured transversely.

Standard postoperative management of this patient included prophylactic antibiotic chemotherapy, where ceftriaxone, amikacin, and metronidazole were administered, correction of water and electrolyte imbalances, and stimulation of intestinal motility. The diagnosis was made based on the anamnesis, clinical, and ultrasound data, as well as the intraoperative picture: PJS, acute small-bowel intussusceptions, and IDA.

On histopathology, smooth muscle hyperplasia with an elongated branching pattern directed towards the epithelial layer, Ki67 protein (MIB-1)—focal up to 60%, and small intestine hamartomatous polyps were all observed. Histopathological examination of polyps yielded the following results: PJS is not ruled out based on the clinical data, the patient's age, and the morphological structure of the polyps (Fig. 3).

The postoperative period passed without complications. On the ninth day, the patient was discharged in satisfactory condition under the supervision of the family physician. One year post-operatively, the patient still complained of rare intermittent abdominal pain (i.e., 1–2 times a month) and intermittent constipation. A follow-up ultrasound revealed no evidence of any pathology. The CBC and faecal occult blood test returned as normal. This clinical case is useful for better understanding of the PJS and drawing attention to the aetiology of intussusception.



Figure 2. Hamartomatous polyps.

This case report has been reported in line with the SCARE Criteria^[9].

Discussion

Generally, polyp histology is characterised by the elongation of the plate of the epithelial component of the intestinal mucosa into the stroma of the polyp and the branching of smooth muscle fibres, which creates a picture of epithelial invasion into the thickness of the intestinal wall^[2,4]. Rarely, polyps outside the GIT are observed in PJS: in the nasal cavity, upper respiratory tract, gallbladder, or bladder. The cause of PJS in most cases (> 90%) seems to be a mutation in the *STK11* or *LKB1* gene (serine/threonine kinase) located on chromosome 19p13^[1,2,5]. *STK11/LKB1* encodes a 433 amino acid protein containing a central catalytic domain and regulatory N-terminal and C-terminal domains. *STK11* is a tumour suppressor gene because its over-expression can induce cell growth arrest at the G1 phase of the cell cycle. The biological function of *LKB1* includes the regulation of kinases in signalling pathways, including adenosine monophosphate-activated protein kinase and MARK1-MARK4, Brsk/SAD kinases, which stimulate the cellular metabolic stress-regulating response, cell polarity, tight junction formation, and E-cadherin distribution^[1,10]. The abolition of *LKB1* function leads to polyposis along with the loss of heterozygosity, as well as, probably, a separate process leading to the formation of tumours^[1,10].

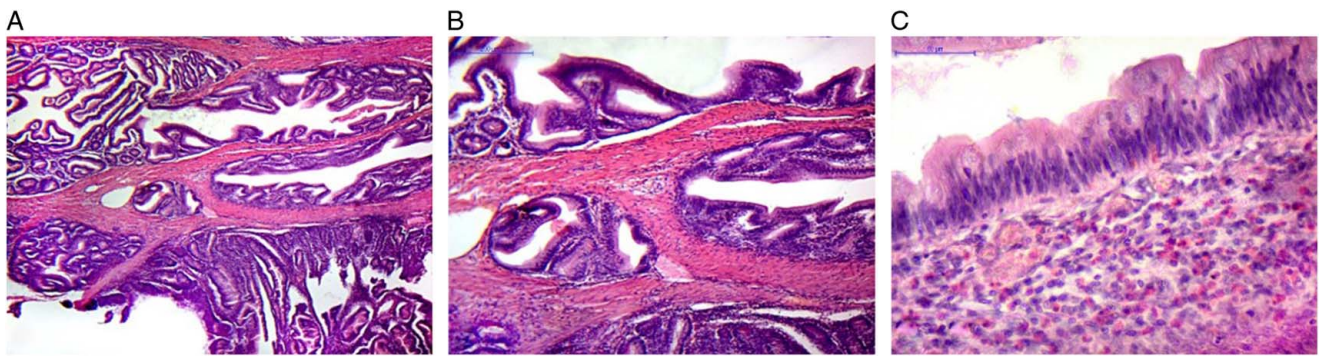


Figure 3. (A, B) Growth of muscle fibres between the glands of the large intestine. (C) Eosinophils as part of an inflammatory infiltrate in the stroma of polyps. Stained with haematoxylin and eosin. Magnification 200 μm ($\times 40$), 100 μm ($\times 100$), 50 μm ($\times 400$).

Data on the influence of the type and localisation of the LKB1 mutation on the manifestations of the disease are contradictory. It is believed that mutations in *STK11* predispose to a more severe phenotype, and the severity of the phenotype is due to the earlier manifestation of the pathology arising from the nature of the polyps^[1]. The penetration of the mutation into the gene is variable, which leads to the appearance of a wide range of phenotypic manifestations of PJS (various numbers and localisation of polyps, variations of maculae on the skin and mucous membranes) and the development of various types of cancer^[11]. Mutations in other genes may also play a role in the development of this syndrome, such as those encoding the MARK protein, and homologues of the polarity Par1 protein associated with LKB1. However, the *STK11/LKB1* mutation remains the main mechanism triggering the development of PJS. For patients with the PJS phenotype, but without identified mutations in the *STK11* gene, heterogeneity, and the possibility of the existence of a second gene responsible for the syndrome at the 19q13.4 locus are discussed^[4].

There are works in the literature that study the correlation between genotype and phenotype in PJS, but they are contradictory and require further confirmation. Currently, the genotype is not considered for the formation of prognosis and management of the disease. Toby *et al.*^[12] showed that in polyps with PJS, the precancerous marker Adnab-9 is often detected (89% in SPE, 88% in juvenile polyposis, 11% in hyperplastic polyps), the detection of which can be used for differential diagnosis and identification of polyps with a higher risk of malignant degeneration. WHO suggests that the following criteria (any of the following) be used to make a diagnosis of PJS: three or more histologically confirmed polyps characteristic of PJS; any number of polyps and a burdened family history; characteristic pigmentation on the mucous membranes and skin and burdened family history; any number of polyps and characteristic pigmentation on the mucous membranes and skin^[13]. The RR of developing malignancies in various organs in PJS is 15 times higher than in the general population^[14,15]. With age, the risk of developing cancer increases: by the age of 20 it is 1–2%, by 50 years—more than 30%, by 70 years—more than 80%. At the age of 15–64 years, the total risk for cancer in all locations is 93% [Giardiello]. The risk of developing cancer in individuals with PJS and the average age of onset of malignancy^[14,15].

The overall RR of cancer in women is higher than in men; gastrointestinal, pancreatic, and gynaecological (cervical) forms of cancer are more common^[15]. Breast cancer in PJS may occur at a

young age and be bilateral. According to the protocol of the American Association for Cancer Research (AACR), for cancer screening and clinical observation of patients with hereditary gastrointestinal syndromes in childhood, it is recommended to perform FOEGDS and capsule endoscopy from 8 years of age or earlier, with symptomatic PJS (at the age of 4–5 years). If polyps are found, examinations should be repeated every 3 years; in the absence of polyps, the next FOEGDS and capsule endoscopy should be performed at 18 years of age^[2]. Also, from the moment of diagnosis of PJS, an annual physical examination is recommended: the search for gynecomastia and testicular masses in boys and the detection of precocious puberty in girls. Recommendations for adult patients include screening for breast cancer and onco-gynaecological pathology from the age of 25, as well as screening for pancreatic cancer from the age of 30^[2]. It should be noted that recently in modern clinics MR-enterography is often used as a method potentially superior to capsule endoscopy in the diagnosis and assessment of polyp size in adult patients with PJS.

Genetic studies are desirable to understand the full picture of the pathology, however, not all patients with PJS find changes in the *STK11/LKB1* locus. Thus, a negative genetic test result does not exclude the diagnosis. In addition, at present, it is not possible to reliably predict the course of the disease by the genotype. Individuals with PJS usually undergo many surgeries during their lifetime. These interventions include laparotomy and laparoscopy of all gastrointestinal and extraintestinal complications. Surgical treatment of extraintestinal cancer detected during patient follow-up is often necessary. Important in the treatment of PJS is the periodic observation of patients and the removal of large polyps to reduce the risk of complications of the disease. Therefore, at present, the strategy for the treatment of patients with PJS includes the use of modern methods of enteroscopy (intraoperative, single-balloon, or double-balloon), which allows avoiding emergency open abdominal operations or laparoscopies in time, reduces the risk of AIO, bowel resection and the development of short bowel syndrome^[4,7,16].

Conclusion

PJS is a rare autosomal dominant condition characterised by multiple gastrointestinal hamartomatous polyps, mucocutaneous pigmentations, and an increased risk of bowel and associated GIT, genitourinary, and lung malignancies. In our clinical case, timely attention to the pigmentation of the lips and the presence

of polyps in the stomach made it possible to suspect the syndrome and, in the future, with the development of intussusception, to choose a surgical treatment strategy. The diagnosis is also greatly influenced by genetic testing alongside thorough clinical, paediatric, and family histories. Genetic testing ought to be performed on the family members of confirmed PJS cases. Recurrent AIO and intussusception should be important differential diagnoses to consider when managing such patients.

Ethical approval

None.

Patient consent

Written consent has been sought from the patient's family to use this case report for research and educational purposes.

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Author contribution

D.O.: conceptualisation. W.A.A., J.W., F.T.A., R.M., S.D., T.A.R., Y.O.: writing, editing. All authors approved the final draft of the manuscript.

Conflicts of interest disclosure

No conflicts of interest reported.

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