

Case study

Recurrent intestinal obstruction in a teenager with small-bowel adenocarcinoma in a classic case of Peutz-Jeghers syndrome

Abstract

Introduction: Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited disorder with incomplete penetrance characterised by gastrointestinal (GI) hamartomatous polyps and mucocutaneous pigmentation, including the lips and gums. The gastrointestinal hamartomatous polyps in PJS are associated with a significantly increased risk of malignant transformation. Intestinal lesions may be evident from bleeding but more commonly arise from painful intestinal cramps related to obstruction due to recurrent intussusception. Small-bowel surveillance in the Paediatric population with PJS is not designed to identify small-bowel malignancy, which is thought to arise in adulthood.

Case Presentation: We reported the case of a 13-year-old African descent boy who presented with colicky abdominal pain and passage of mucoid non-bloody stool. Pigmentation of the buccal mucosa was noted, and examination revealed a painful distressed child with distended abdomen, and generalised tenderness. An urgent abdominal ultrasound scan (USS) showed dilated bowel loops with increased peristalsis suggestive of intestinal obstruction. Laparotomy was undertaken, and adhesiolysis and polypectomy were done. Histology of the polyp revealed a malignant epithelial tumour consistent with carcinomatous transformation of hamartomatous polyp.

Conclusion: This report is an earliest onset of small-bowel adenocarcinoma in PJS-like case, an observation relevant to surveillance guidelines.

Keywords: Adenocarcinoma, Mucocutaneous, Peutz-Jeghers, Recurrent, Teenager.

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare, autosomal dominant inherited gastrointestinal (GI) hamartomatous polyposis syndrome with incomplete penetrance.¹ The syndrome is characterised by mucocutaneous pigmentation that includes the lips and gums and hamartomas of the GI tract, with an incidence of 1 in 30,000 to 120,000 live births.² Deeply pigmented discrete freckles are occasionally seen at birth or during infancy on the lips, buccal mucosa, and even around the mouth. Intestinal lesions may be evident from bleeding but

more commonly arise from painful intestinal cramps associated with obstruction due to recurrent intussusception. Peutz-Jeghers syndrome is also associated with gastrointestinal and extra gastrointestinal hamartomatous polyps with a significantly increased risk of malignant transformation.³ The relative mortality risk from a gastrointestinal malignancy is 13 times higher. The risk of any other cancer, especially in the testes and ovary, pancreas, breast, and lungs, is nine times higher than in the general population.^{4,5} Most patients have a characteristic clinical course of recurrent episodes of polyp-induced bowel obstruction and bleeding from intussusception. Therefore, the syndrome has no gender preference and affects males and females equally.

The molecular and genetic basis of PJS has been a subject of in-depth study. Over time, it has primarily been established by Jeghers proposal as a "single pleiotropic gene"⁶ Germline mutations in the tumour suppressor gene STK11 are identified in most cases of PJS.^{7,8} While some authors have proposed the existence of other loci, STK11 has been the only gene known to be associated with PJS. Both heterozygous point mutations and gene deletions of STK11 are responsible for the PJS phenotype.⁹ As molecular technology has advanced, cases previously classified as "STK11 negative" were noted to be due to STK11 deletions that were not detected by sequencing methods.⁹ Recent studies combining diagnostic procedures sensitive to deletions and point mutations have suggested that all cases may be due to some STK11 mutation.^{10,11} The genotype-phenotype correlation in PJS is complex, but higher cancer risk may be associated with mutations in exon 3 or premature truncation alleles.¹² While STK11 is the only known gene; there are also no reported cases in which an individual with an STK11 mutation does not show clinical manifestations leading some authors to suggest that these mutations are fully penetrant.¹⁰ STK11 is involved in epithelial polarity and the regulation of proliferative signals of the mTOR pathway through phosphorylation of AMP kinase.

Giardiello *et al.* proposed criteria for diagnosing this rare syndrome, requiring histological confirmation of hamartomatous gastrointestinal (GI) polyps and two of the following features: small bowel polyposis, positive family history of PJS and distinctive features of characteristics pigmented skin or mucosal brown macules.⁴

CASE PRESENTATION

A 13-year-old boy of African descent was apparently well until three months prior to presentation when he started passing loose stool 5-6 episodes per day, small volume, mucoid,

non-bloody. It was associated with vomiting at the same time of about 1-2 attacks per day, large volume bilious, non-projectile, not blood-stained, containing recently ingested feed.

There was associated colicky abdominal pain (mostly periumbilical) lasting for about 10-30 minutes, non-radiating, with no known relieving or aggravating factors. The pain was severe enough to make the patient cry, with no associated abdominal distention or yellowish discolouration of the eyes. The patient had had a similar episode three years ago and was managed as an intestinal obstruction secondary to intussusception. The patient is not known to have sickle cell anaemia or diabetes. There was no family history of similar presentation or malignancy. At the onset of his illness, he was taken to a Non-Governmental Organisation (NGO) facility. He was admitted for nine days and treated with IV medications that the mother was unsure of. He was then discharged a week before presentation following improvement in abdominal pain. Abdominal pain reoccurred four days before his presentation, prompting his presentation to our Emergency Paediatric Unit (EPU).

On examination, the child was in painful distress; oral cavity examination showed oral mucosal macular hyperpigmentation (Figure 1). The abdomen was slightly distended and moved with respiration, and there was a supra-umbilical surgical scar with a generalised tenderness preventing further examination. However, bowel sound was hypoactive. Digital rectal examination revealed good perianal hygiene, normal sphincteric tone, the rectum was filled with faeces and examining gloved finger was stained with well-formed stool. There was no mass felt in the rectum.

The patient was initially evaluated and managed as a case of acute abdomen secondary to intestinal obstruction secondary to adhesion. He had surgery done four years ago for intestinal obstruction secondary to intussusception.

Abdomino-pelvic ultrasound scan showed dilated bowel loops with increased peristalsis, given impression and featured suggestive of intestinal obstruction. No feature suggestive of intussusception was seen.

A plain abdominal X-ray showed dilated bowel loops with bowel gas. No multiple air-fluid levels were seen.

The patient was placed on nil per Os (NPO), IV ceftriaxone at 100mg/kg/day, IV Metronidazole at 7.5mg/kg/dose 8-hourly, and a nasogastric tube passed for gastric decompression.

The patient was then reviewed by the Paediatric Surgery team on admission and assessed to have sub-acute intestinal obstruction secondary to intestinal adhesion. An initial line of management was maintained with the observation of the patient.

The patient was managed conservatively for six days and was noted to have not passed stool for the period of admission with progressive abdominal distension.

On the 7th day of admission, the patient had an exploratory laparotomy. Adhesiolysis and polypectomy were done. Intraoperative findings were dilated duodenum of about 20cm from the ligament of Treitz, intramural duodenal polyp with a long peduncle, and adhesion of omentum to the anterior abdominal wall. The polypoid sample was sent for histology, and the report revealed polypoid tissue measuring 5x3x2.5 cm surface appearing grey.

Microscopy revealed intestinal tissue with a malignant epithelial neoplasm composed of irregular glands invading the muscle coat and lined by columnar cells that are pleomorphic and have hyper-chromatic to vesicular nuclei with prominent nucleoli and moderate cytoplasm. They are nuclear stratified in most areas and have few mitotic figures, consistent with adenocarcinoma with a tumour margin of 4mm (Figure 2).

Diagnosis of Adenocarcinoma was made.

The family was counselled for further risk of extra-intestinal malignancies and the need for continuous surveillance.

The patient was discharged one week after surgery as the pain subsided and he opened the bowel. He was discharged on oral Cefuroxime 250mg twice daily for five days, per oral Metronidazole 200mg thrice daily for five days, tabs ascorbic acid 200mg thrice daily for one week, and per oral dihydrocodeine 30mg thrice daily for five days.

The patient was commenced on adjuvant chemotherapy and completed six cycles consisting of:

IV Vincristine 1.5mg day 1, 8 and 15. IV Actinomycin D 1.5mg day 1. IV

Cyclophosphamide 500mg day 1. Per oral Allopurinol 100mg thrice daily to prevent tumour lysis syndrome. Per oral Proguanil 100mg daily prophylaxis against malaria, and oral Cotrimoxazole 24mg/kg body weight alternate days for prophylaxis against Pneumocystis carinii pneumonia.

Our patient is currently doing well with no relapse, at one year of completion of chemotherapy and back to school.

DISCUSSION

The first published report of Peutz-Jeghers with gastrointestinal familial polyposis and pigmentation was by Peutz in 1921, and later in 1949, documented increased risk and association of these with malignancy.^{13,14} Peutz-Jeghers syndrome is a rare familial disorder with an incidence of 1 in 30-120,000 live birth.² It is inherited in an autosomal dominant fashion with incomplete penetrance.¹ There is also about 25% of cases with the sporadic transmission. Two independent research groups identified the mutated gene responsible for developing PJS.^{7,8} The gene was localised to chromosome 19p34-p36, also known as STK11, a serine-threonine kinase that regulates growth control. Even though not all patients with PJS have a mutation in this gene, mutations of chromosomes 6q and 19p have also been implicated as an underlying abnormality in the aetiology of PJS in a few families.¹⁵ In this index case, the diagnosis was made due to the hamartomatous small bowel polyps that were identified as the lead point of intussusception and subsequent recurrent intestinal obstructions, as well as the mucocutaneous hyperpigmentation similar to the case reported by Santosh *et al.*³ Our patient also has a similar presentation to the 13-year-old otherwise healthy Hispanic boy who developed sudden onset periumbilical abdominal pain which worsened over 24 hours reported by Wangler *et al.*¹⁶ We did not find a family history of PJS in the present case suggesting the possibility of a sporadic new mutation.

A close differential diagnosis of PJS that worth considering is the rare sporadic disorder, Laugier-Hunziker syndrome (LHS) which shares some dermatological features with PJS. However, whereas PJS is associated with hamartomatous gastrointestinal polyposis and carries a high risk of malignancy, justifying intensive screening protocols, LHS is known to be an entirely benign condition with no systemic manifestations, which requires patient reassurance as the only intervention. Laugier-Hunziker syndrome is characterised essentially by acquired and benign melanotic pigmentation of the oral cavity and lips which is often associated with spotted macular pigmentation of the fingertips and longitudinal melanonychia.¹⁷ Since its first description by Laugier and Hunziker in 1970,¹⁸ more than 100 cases have been described worldwide. The basic skin lesions manifest as irregular lenticular hyperpigmented macules of 2–5 mm diameter which can be slate to dark brown in colour

with well-defined or indistinct margins. These occur singly or as multiple groups and are sometimes confluent.¹⁹

Complications that hamartomatous small intestinal polyps may induce include colicky abdominal pain and bowel obstruction due to intussusception, which is found recurrently in this case. Intestinal bleeding may also be seen; however, our patient did not have bleeding, which is at variance with the report of Bhattacharya report.¹⁹ This patient is prone to many other extra-intestinal tumours like pancreatic adenocarcinoma, adenoma malignum, papilloma in bladder and pelvis, testicular Sertoli cell tumours, cholangioma, and papilloma with squamous metaplasia.²⁰

In symptomatic polyps or a significant size larger than 1.5cm in diameter, a laparotomy with enteroscopy is recommended.³ It has been widely argued whether the reduction of intussusception should precede bowel resection. Reduction of large bowel intussusception runs the risk of bowel perforation and peritoneal cavity contamination with faeces or more devastating tumour cells, mainly when the lead point is a tumour that is more commonly found in large bowel than small bowel intussusception. For this reason, en bloc resection is advocated with large bowel intussusception, whereas a reduction in small bowel intussusception should precede resection.^{21,22} Our patient had intussusception that was entirely small bowel and was successfully managed through surgical laparotomy, the first with bowel resection four years earlier. However, he has not developed short bowel syndrome. Santosh *et al.* recommended intra-operative endoscopy and endoscopic polypectomy rather than segmental resection of the bowel to avoid consequent development of short bowel syndrome. Periodic endoscopic screening is also advocated every two years.²³ The mouth to anus (M2A) capsule endoscopy has become the most useful screening tool.

CONCLUSIONS

We conclude that intestinal obstruction in a case of PJS indicates a surgical emergency like intussusception. If not promptly diagnosed and appropriately managed, it can result in devastating bowel ischaemia with consequent long segment bowel gangrene and short bowel syndrome in the long run even if it is successfully managed.

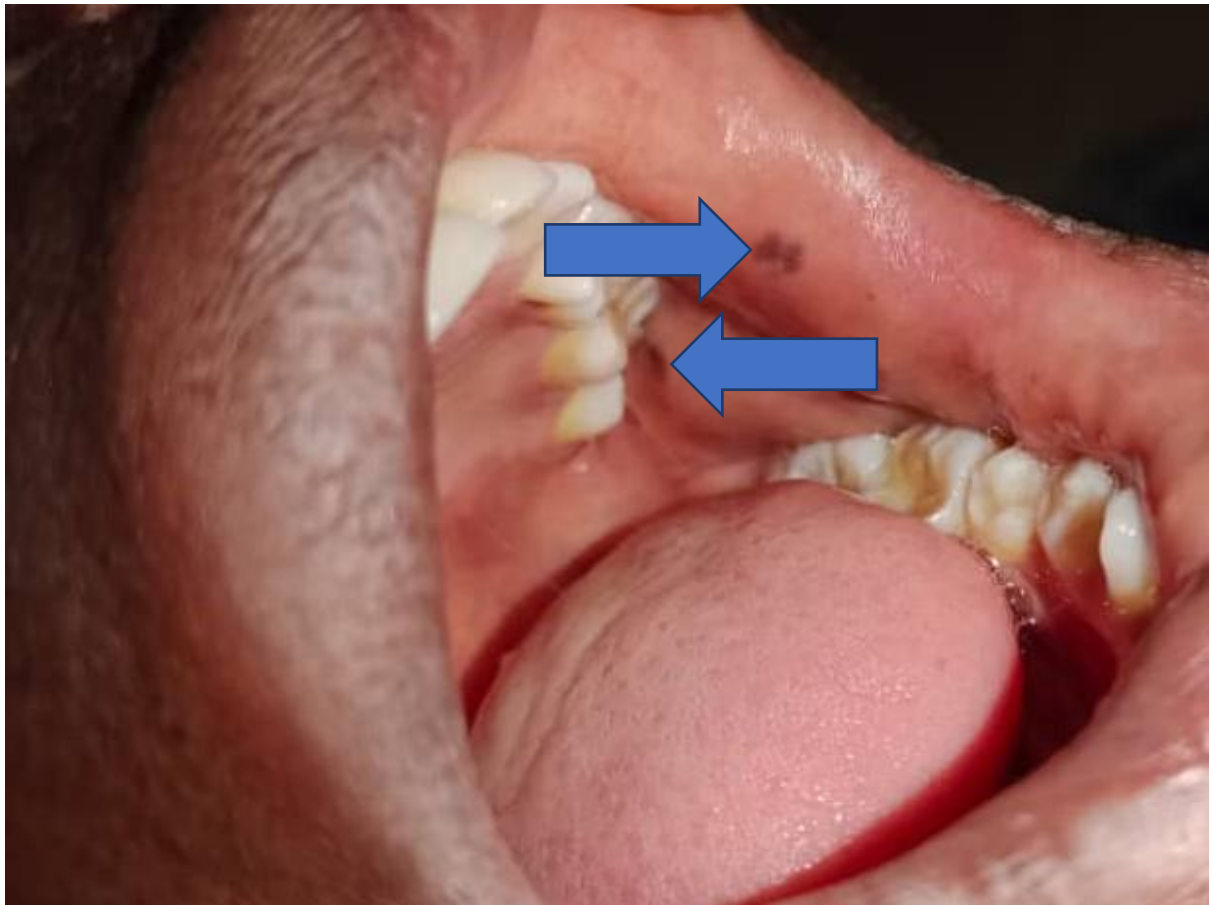


Figure 1: Oral cavity with hyperpigmented spots (blue arrows) at the left inner part of the cheek

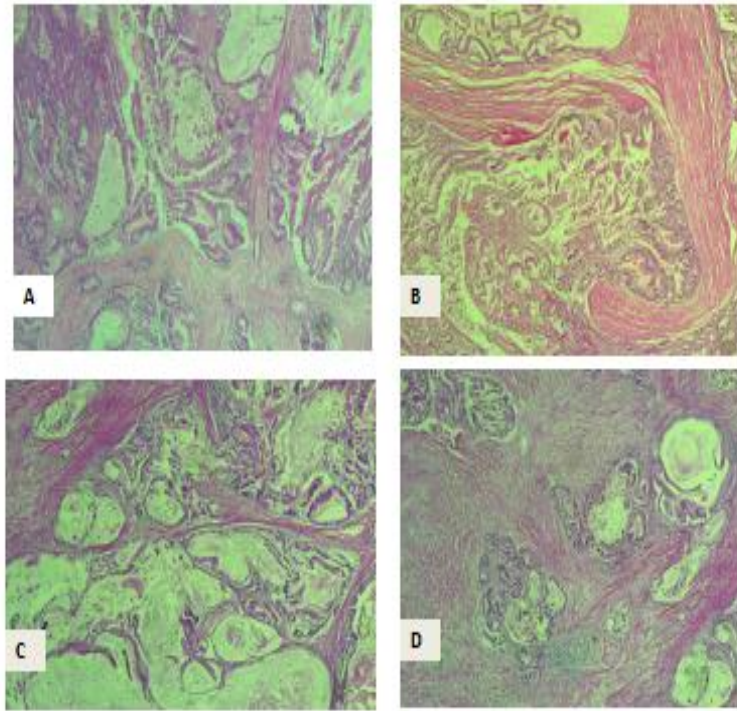


Figure 2: Photomicrographs:

A and B - Hamatomatous polyps with arborising smooth muscle in the lamina propria.

C - Dilated glands exhibiting enteritis cystica profunda,

D - Dysplastic glands invade the muscle coat. (H and E X 100).

Consent

Written informed consent was obtained from the patient's caregiver (Biological father) and assent from the patient to publish this report and any accompanying images. A copy of the written consent is available for review by the journal's Editor-in-Chief.

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