

MEDICAL SCIENCE

To Cite:

Taori K, Kirnake V, Mukewar S, Acharya S, Kumar S, Giri A, Nimkar S. Peutz-Jeghers Syndrome, A Rare Polyposis Syndrome: A Case Report. *Medical Science* 2023; 27: e328ms2745. doi: <https://doi.org/10.54905/disssi/v27i138/e328ms2745>

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Peer-Review History

Received: 04 January 2023

Reviewed & Revised: 07/January/2023 to 27/July/2023

Accepted: 31 July 2023

Published: 06 August 2023

Peer-review Method

External peer-review was done through double-blind method.

Medical Science

pISSN 2321-7359; eISSN 2321-7367

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Peutz-Jeghers Syndrome, A Rare Polyposis Syndrome: A Case Report

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ABSTRACT

Peutz-Jeghers Syndrome (PJS) is an uncommon familial disorder that leads to the development of gastrointestinal and extragastrointestinal hamartomatous polyps, mucocutaneous pigmentation with an increased risk of malignancy. This polyposis syndrome is associated with variable clinical course with significant mortality & morbidity and is known to cause complications like intussusception, obstruction, anemia, and bleeding. Here, we report a case of a 21 years old young female suffering from PJS to increase awareness amongst clinicians regarding this rare syndrome. She presented to us with complaints of pain in the epigastrium and left hypochondrium, constipation and malena. She had hyperpigmented mucocutaneous macules of brownish-black colour on the buccal mucosa and lips and also had numerous sessile-pedunculated polyps in stomach, duodenum, jejunum and colon. She was decided to undergo double-balloon enteroscopy and polypectomy (more than 35 polyps were removed). After an interval of 4 weeks, colonoscopic polypectomy was also done. There was a history of jejuno-jejunal intussusception for which resection and anastomosis of proximal jejunal was done in past. Hence, it is advisable for young cases having a presentation of intestinal obstruction, intussusception or malena, in presence of mucosal pigmentation and other pathognomonic signs of PJS, to screen for PJS. In case of PJS, a surgical emergency like intussusception may be present which if missed may turn into bowel ischemia which may have a grave sequel. In PJS, early intervention (polypectomy) preferably by double-balloon enteroscopy method is important to prevent morbidity and mortality caused by PJS. Follow-up of gastrointestinal polyps and regular lifelong screening for malignancy is recommended in PJS.

Keywords: Hamartomatous polyps, Pigmentation, Double-balloon enteroscopy, Polypectomy

1. INTRODUCTION

Peutz-Jeghers syndrome (PJS) is an uncommon polyposis syndrome having autosomal dominant pattern of inheritance with variable to high penetration.

It is characterized by gastrointestinal hamartomatous polyps and pigmented mucocutaneous lesions. The estimated prevalence of PJS is from 1 in 8300 to 1 in 280000 individuals (Kopacova et al., 2009). PJS is probably caused by a germline mutation in STK11 (LKB1) gene (Latchford et al., 2019). The first case of PJS was reported by Peutz in the year 1921 (Tweedie and Mc-Cann, 1984; Chowdhry et al., 2015), and later, the detailed cases of PJS were described by Jeghers, Mc-Kusick, and Katz in the year 1949 (Foley et al., 1988).

This rare disorder is diagnosed based on the WHO's clinicopathological criteria (Schreibman et al., 2005):

1. Three or more polyps with histological characteristics consistent with PJS.
2. Any number of PJS-related polyps with a family history of suggestive of PJS.
3. Typical mucocutaneous pigmentation with a family history suggestive of PJS.
4. Any number of PJS-related polyps with characteristic mucocutaneous pigmentation.

PJS has a variable clinical course characterized by asymptomatic intervals interspersed with symptoms like abdominal pain which may progress to grave complications like intussusception, bleeding, intestinal obstruction, and anemia leading to significant mortality and morbidity (Butt et al., 2012; Rebsdorf-Pedersen et al., 1994; Loureiro et al., 2015). PJS is characterized by hyperpigmented mucocutaneous macules present on the perioral region, lips, buccal mucosa, periorbital region, and eyelids. This syndrome also has characterized by hamartomatous gastrointestinal polyps occurring most commonly in small intestine followed by stomach and colon; extra gastrointestinal polyps can also occur.

Previously, PJS was considered as a benign condition, however recently reports are published showing its association with various malignancies, including those of the gastrointestinal tract, lung, pancreas, testes, breast, uterus, and ovary. PJS patients commonly experience bleeding, obstruction, and intussusception. Thus, nowadays more aggressive approach for management of PJS has been adopted. Double balloon enteroscopy (DBE) allows evaluation as well as treatment (polypectomy) of the small bowel. The need for repeated urgent operation and bowel resection leading to short bowel syndrome can be obviated by the use of DBE (Polypectomy). Timely clearance of all polyps as well as careful screening is considered the gold standard for PJS.

Even though the prevalence of PJS is low, for clinicians it is important to diagnose these disorders to prevent the grave outcome of these disorders, and also to screen the first-degree relatives for PJS during their pre symptomatic period. A very few cases of PJS are reported, especially in Indian contest, hence, we report 21 years old female case with Peutz-Jeghers syndrome to increase awareness amongst clinicians regarding this rare syndrome.

2. CASE PRESENTATION

A 21 years old female came to gastroenterology OPD with complaints of epigastric and left hypochondriac region abdominal pain, it was intermittent, dull-aching for about 30-60min, non-radiating for 8 days. She had a history of passing black-tarry stools as well. She also had constipation and a loss of appetite. The patient was found to be tachycardic and hypotensive from the vital signs. She also had pallor. Local examination revealed hyperpigmented mucocutaneous macules of brownish-black colour on the buccal mucosa and lips; these pigments were present since the age of 6month (Figure 1) and a post-operative linear scar on the right breast at 9'O clock position. She had no significant family history.

On abdominal examination, she had tenderness over the epigastrium and left hypochondrium; the rest was normal. Laboratory tests revealed microcytic, hypochromic anemia with a hemoglobin of 8.2 gm%, total leucocyte count was 12,200/mm³. Other routine blood investigations were normal. On endoscopy, the stomach (Figure 2) and duodenum (Figure 3) revealed numerous sessile - pedunculated polyps, biopsy of which revealed hamartomatous polyp of stomach and duodenum (Figure 4 & 5). On colonoscopy, multiple small colonic polyps in descending and transverse colon; also, a large transverse colon polyp was noted (Figure 6), biopsy of which revealed hamartomatous polyp of the colon (Figure 7).

Contrast-enhanced CT was done which revealed multiple mildly enhancing polypoidal lesions noted attached to pyloric part of stomach, first, second, third part of duodenum, and proximal jejunal loops. Similar polypoidal lesions are noted in ascending colon, and transverse colon (Figure 8).

She was decided to undergo double balloon enteroscopy (DBE) and polypectomy. More than 35polyps were removed (Figure 9). Post-procedure intravenous broad-spectrum antibiotics and analgesics drugs were administered. She had a satisfactory course post-procedure, tolerated oral feeding, and was discharged. After an interval of 4 weeks, colonoscopic polypectomy was also done (Figure 10).



Figure 1 Hyperpigmented mucocutaneous macules of brownish-black colour on the buccal mucosa and lips

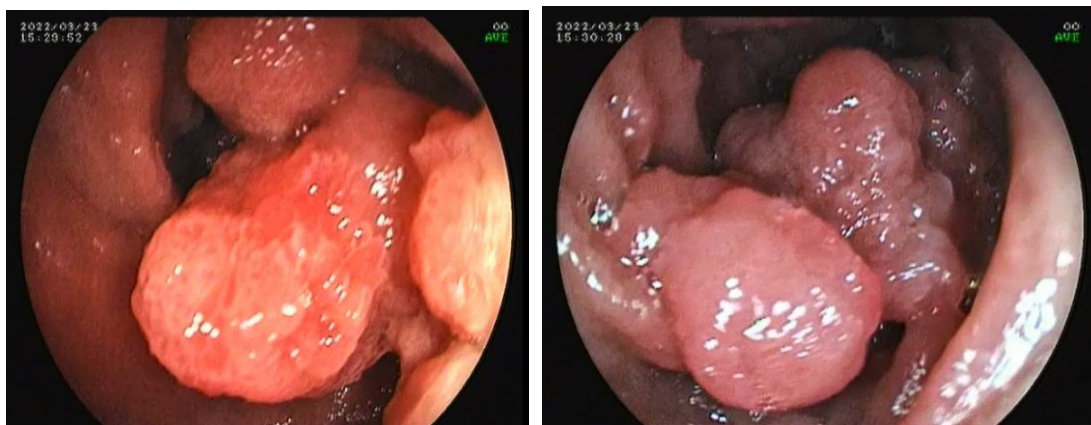


Figure 2 & 3 Endoscopic images showing numerous sessile-pedunculated polyps in stomach and duodenum

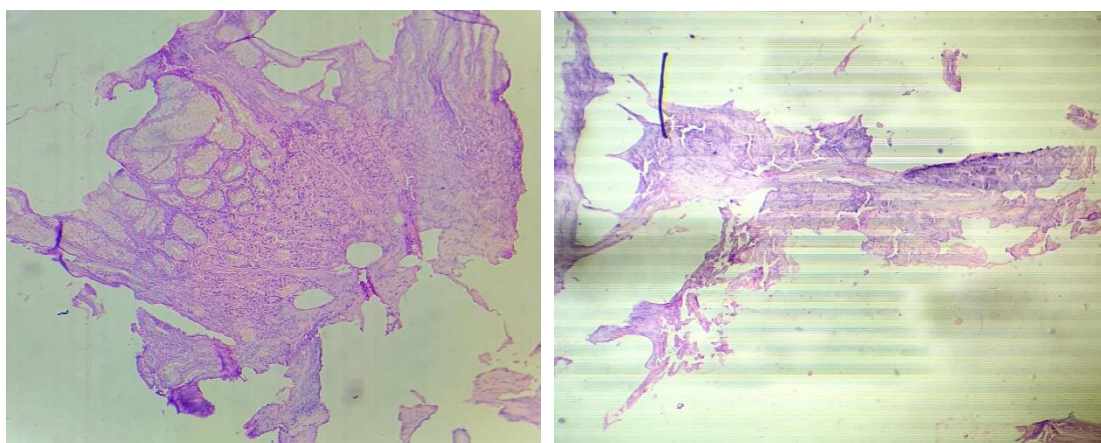


Figure 4 & 5 H & E staining of stomach and duodenal biopsy showing hamartomatous polyp of stomach and duodenum respectively

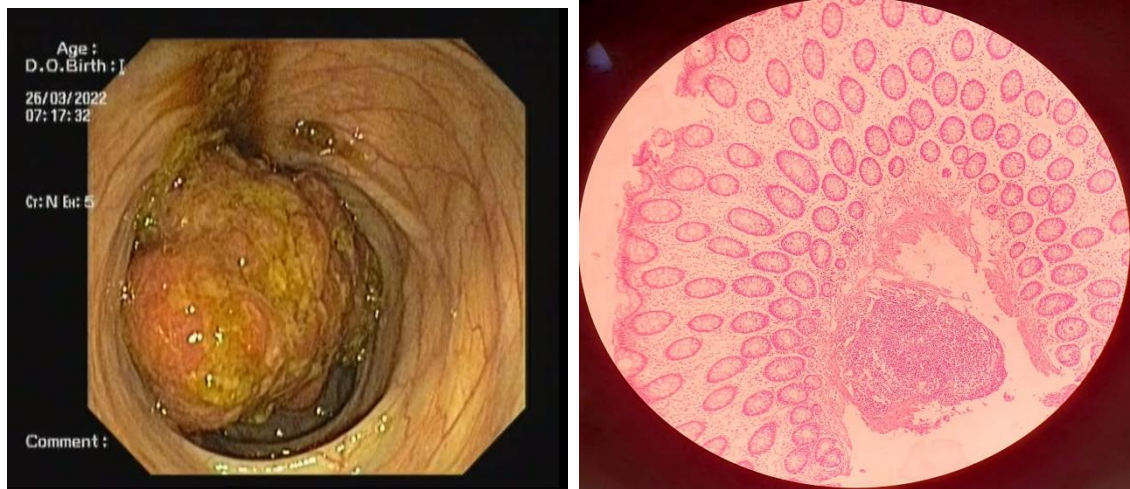


Figure 6 & 7 Colonoscopic image of large transverse colon polyp and its H & E staining showing Hamartomatous polyp of colon

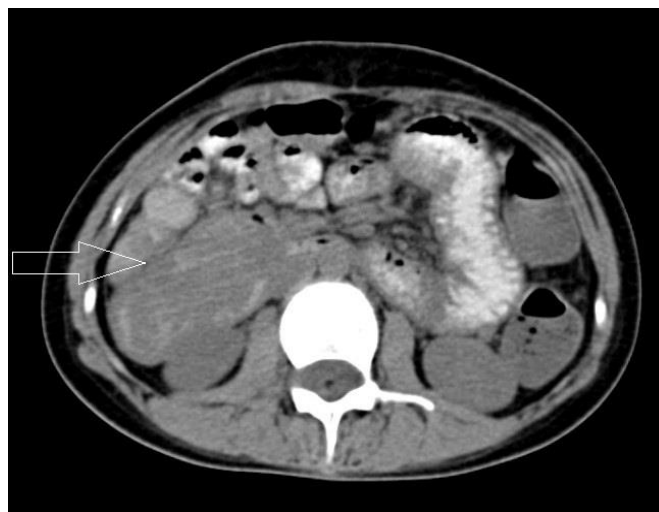


Figure 8 CECT abdomen Showing multiple mildly enhancing polypoidal lesions ascending colon, and a large polyp in transverse colon

The patient had a similar history of abdominal pain, loss of appetite, and constipation on and off since the age of 5 years, for which she used to take symptomatic treatment. However, she never had any investigation till she became 14 years of her age, by this time symptoms were increased, and for which she was admitted to our institute (7 years back). During this episode, patient had a presentation of acute pain in abdomen in epigastrium and tenderness over the same region. Lab parameters were normal. On CECT features of colo-colic intussusception were noted. Endoscopy revealed multiple polyps in the stomach and duodenum.

Colonoscopy revealed splenic flexure sessile polypoidal lesion. She underwent open laparotomy, and intra-operative jejuno-jejunal intussusception was found. Resection and anastomosis of proximal jejunal for jejunal intussusception was done. Histopathological examination of resected jejunal loop revealed hamartomatous polyp. The post-operative course was satisfactory and she was discharged. But after that patient had lost follow-up. After the surgery patient enjoyed a symptom-free period, until December 2021. She had again similar symptoms of pain in the abdomen in epigastrium and right hypochondrium for which she was treated symptomatically and got relief.

In January 2022, on self-breast examination, she incidentally found a lump in her right breast. Sonomammography was done which revealed right breast well-circumscribed encapsulated hypoechoic mass lesion in outer quadrant at 9 O' clock position suggestive of fibroadenoma BI-RADS category 3 FNAC of lump on histopathological examination suggested features of intracanalicular type of fibroadenoma of the breast. Excision of lump done on 26 Feb 2022.



Figure 9 More than 35 polyps removed by double balloon enteroscopic polypectomy



Figure 10 Large transverse colon polyp removed by colonoscopic polypectomy

3. DISCUSSION

PJS comprises the association of mucocutaneous pigmentation, gastrointestinal polyps, and a familial incidence (Giardiello and Trimpath, 2006). PJS is an uncommon familial disorder, having a prevalence of ranging from 1 in 8300 to 1 in 280 000 populations (Kopacova et al., 2009). Around 1 in 100000 people is estimated as a probable prevalence. Peutz-Jeghers syndrome (PJS) follows an autosomal dominant pattern of inheritance with incomplete penetrance (Cunningham et al., 1998). A germline mutation (missense, frameshift, or nonsense) in *STK11* (*LKB1*) gene (chromosome 19p13.3) leads to the inactivation of this gene and this has been proposed as the underlying cause for this abnormality (Sokmen et al., 2003).

Males and females are equally affected in this syndrome (Giardiello and Trimpath, 2006). The clinical course of this syndrome is characterized by asymptomatic intervals interspersed with symptoms like abdominal pain, and bleeding leading to complications like intussusception, intestinal obstruction, and anemia (Butt et al., 2012; Rebsdorf-Pedersen et al., 1994; Loureiro et al., 2015).

Characteristic pigmentations are noted in 95% of PJS patients which are probably due to pigment-laden macrophages in the layer of dermis. These are hyperpigmented mucocutaneous macules (blue-gray to brown spots) present in the perioral region, lips, buccal mucosa, around eyes, and nostrils; they also can be present rarely around intestinal and anal mucosa, soles and palms.

In extremely rare cases this lesion can undergo malignant degeneration. These hyperpigmented spots can commonly be confused with freckles. Oral cavity freckles are never observed, and they are sparsely found near the nostrils and lips and are never present at birth. During adolescence hyperpigmentation even can fade or disappear. The average time of initial presentation of polyp in this syndrome is about 11-13 years, and around 50% of cases experience symptoms by age of 20 years (Gammon et al., 2009; Schreibman et al., 2005). The diameter of polyp can range from 5 to 50 mm (median size- 35 mm).

In PJS, polyps occur more common in the small intestine, greatest in jejunum, and then in a decreasing order in ileum and duodenum (Gammon et al., 2009; Soares et al., 2004; Mehta et al., 2006). Stomach (49%), colon (53%) and rectum (32%) involvement are also seen (Chang et al., 2009; Nath et al., 2002; O'Loughlin et al., 2002; Zbuk and Eng, 2007). Performing a timely polypectomy can eliminate the necessity for repetitive emergency laparotomy and bowel resection which may lead to short bowel syndrome (Kopacova et al., 2007; Lin et al., 2000). Extraintestinal polyps like nasal polyps (De-Leng et al., 2007) and gallbladder polyps (Vogel et al., 2000) are also reported.

PJS-related polyps are histopathologically hamartomatous which are characteristically overgrowth of native cells to area where they occur normally. They have a marked distorted cellular architecture but are composed of normally occurring cellular elements of the GI tract (Chen and Fang, 2009; Zbuk and Eng, 2007). Adenomatous foci are often seen in larger polyp; a malignant development in these polyps has been described (Bouraoui et al., 2008; Defago et al., 1996; Bujanda et al., 1996). A previous study reported an elevated risk of gastrointestinal (GI) and extra-GI malignancies in patients with PJS compared to the general population (Butt et al., 2012).

A meta-analysis of 210 patients involving six studies suggested a cumulative risk of 93% for the age group of 15 to 64 years for all types of malignancies. Thus, the patient with PJS will have a relative risk of up to 15 times higher (compared with the general population) to present for malignancy in any region (Loureiro et al., 2015; Giardiello and Trimbath, 2006). Commonly occurring malignancies in PJS in decreasing order are colonic (57%), breast (45%), followed by pancreas (36%) stomach (29%) then ovary (21%), small intestine (13%), and uterus (10%) tumors (Loureiro et al., 2015).

Increased risk for the small intestine, colon, pancreas, and stomach malignancy has been reported among GI cancers. Also, males with PJS are more prone to testicular and prostate cancer and female with PJS are more prone to breast, ovary, cervical and uterine cancer. Meanwhile, an increase in the risk of renal cancer, pulmonary cancer, leukemia, and bone cancer has also been reported (Chen et al., 2017). It was thought that PJS was benign until recently, and was treated conservatively (Rebsdorf-Pedersen et al., 1994).

A more aggressive approach to manage PJS has been adopted in recent years. Once the diagnosis of PJS is confirmed most publications suggest removing all polyps as far as possible, they recommend that those polyps > 5mm should be at least removed; aiming to prevent intussusception, bowel obstruction leading to bowel ischemia, and gangrene which ultimately requires bowel resection, which may lead to short bowel syndrome (Rebsdorf-Pedersen et al., 1994). For management of hamartomas present in small bowel there are two modalities: Double-balloon enteroscopy (DBE) and intra-operative enteroscopy (IOE). IOE comprises a combination of laparotomy and endoscopy which allows manipulation to visualize the entire small bowel and remove polyps (Fraser et al., 2009).

Prior to the DBE era, IOEs were considered as ultimate diagnostic and therapeutic procedure for the evaluation of small bowel of PJS patients. Double-balloon enteroscopy in combination with capsule enteroscopy is the preferred method for diagnosing and managing small bowel lesions in patients with Peutz-Jeghers syndrome (PJS) (Li et al., 2007). Single-balloon enteroscopy (IOE) is now reserved for cases with adhesions (post-surgery), DBE failure, carcinoid, blue rubber bleb nevus syndrome, and multiple small transmural lesions not treatable by endoscopy.

Studies conducted by Udd et al., (2004) and De-Leng et al., (2003) suggest that COX-2 inhibitor chemoprevention is beneficial in treating Peutz-Jeghers syndrome (PJS) due to the presence of COX-2 expression in PJS carcinomas and dysplastic hamartomas, which supports its rationale for use. Rapamycin/sirolimus is an immunosuppressant with antiangiogenic properties that may have a role in polyp size reduction is under clinical trials that could be used for treatment of PJS patients in future (Wei et al., 2009; Wei et al., 2008; Robinson et al., 2009).

Lifestyle risk factors, such as alcohol consumption, smoking, and excess weight, are linked to a raise in risk of malignancy in individuals with PJS. It is recommended that PJS patients should adopt a healthy lifestyle, even though no study has shown that modifying these risk factors could reduce cancer risk. Regular lifelong screening for cancer is recommended in PJS patients

(Colonoscopy, upper GI endoscopy, chest X-ray, ultrasound, CT scan, MRI scan, testicular examination in men and mammography, breast examination, and pelvic examination by USG in females).

4. CONCLUSION

PJS was thought benign until recently, however recent reports showed premalignant potential of PJS, moreover these patients commonly encounter complications like intussusception, obstruction and bleeding. Thus, nowadays a more aggressive approach to manage PJS is advised. Screening for PJS should be done in young patients presented with intussusception, malena or obstruction in presence of mucocutaneous pigmentation or a positive family history. Timely clearance of all polyps (at least all polyps more than 5mm) preferably by DBE and careful screening is considered gold standard. Although the prevalence of this syndrome is not high, it is essential for physician to recognize this disorder in order to prevent the morbidity and mortality caused by this disorder, and also to screen the first-degree relatives during their pre symptomatic period for PJS.

Acknowledgement

We thank the patient in this case report for consenting to publish the findings. We thank Dr Vijendra Kirnake, Dr Saurabh Mukewar and Dr Sourya Acharya and Dr Sunil Kumar for their continual support and guidance.

Author's Contribution

All authors have contributed substantially for the concept, assessment and evaluation, data acquisition and development of this work. All authors read and approved the final version of the manuscript.

Informed Consent

Written & oral informed consent was obtained from the patient in this case report.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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