An unusual case of Peutz–Jeghers syndrome with polyposis-associated adenomatous change

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ABSTRACT

Introduction: Peutz–Jeghers syndrome (PJS) is a rare autosomal dominant syndrome associated with mucocutaneous pigmentation and hamartomatous gastrointestinal polyps. It is associated with increased risk of intestinal and extraintestinal malignancies. Case Report: This is a rare case of PJS with multiple polyps with features of villous adenoma and high grade dysplasia. A 48-year-old female presented with the complaints of bleeding per rectum since five months. Hyperpigmented spots were present on the buccal mucosa. On endoscopy, multiple polyps in distal colon, stomach, duodenum, and periampullary region were noted. Polypectomy was done and sent for histopathological evaluation. Grossly, the largest polyp was in sigmoid colon measuring 2.6 × 1.5 × 1 cm and smallest polyp was in stomach measuring 3 × 2 × 1 mm. On microscopy, polyps from transverse colon showed polypoidal tissue traversed by branching muscularis mucosae forming arborizing pattern. Polyps from sigmoid colon showed similar features with a focus of dysplasia and villous adenoma. Conclusion: Further the patient was advised to undergo mandatory periodic evaluation on follow-up.

Keywords: Gastrointestinal polyp, Hamartomatous, Peutz–Jeghers syndrome, Polypectomy

INTRODUCTION

Peutz–Jeghers syndrome (PJS) is an autosomal dominant inherited disorder, caused by germline mutations in PJ gene STK11 (LKB1). It is characterized by hamartomatous polyposis of gastrointestinal tract in association with hyperpigmented mucocutaneous lesions [1]. The incidence of PJS is reported to be 1 in 150,000–200,000 individuals [2]. The case is reported in line with the SCARE criteria [3].

CASE REPORT

A 48-year-old woman presented with bleeding per rectum since five months. On examination, hyperpigmented lesions were seen on the buccal mucosa and pallor was present. Per abdominal examination was within normal limits. Per rectal examination was normal. Rest of the systemic examinations had insignificant findings. Peripheral smear examination revealed normocytic normochromic anemia. Further investigations like computed tomography (CT) enterography of abdomen (Figures 1 and 2), colonoscopy (Figure 3), and upper gastrointestinal (GI) endoscopy (Figure 4) were done which gave following results.

Procedure

Preoperatively, the patient was kept on liquid diet 24 hours prior to colonoscopy. Bowel wash in the form of...
enema was performed followed by overnight fasting until the procedure. With aseptic precautions, colonoscopy and endoscopic polypectomy were done under general anesthesia. Side-viewing endoscopy and polypectomy were also done. Breast and gynecological malignancy were screened. Postoperatively, the patient was monitored for bleeding, pain abdomen, or fever. The patient was stable following the procedure.

**Histopathological examination**

Macroscopically, multiple polyps from stomach, periampullary region, and colon noted. The largest polyp was from sigmoid colon measuring $2.6 \times 1.5 \times 1$ cm and the smallest polyp was from stomach measuring $3 \times 2 \times 1$ mm. On microscopy, polyps from transverse colon showed polypoidal tissue traversed by branching muscularis mucosae forming arborizing pattern and divides the polyp into lobules (Figure 5). Polyps from sigmoid colon showed similar features with a focus of high grade dysplasia and villous adenoma (Figures 6 and 7). Gastric and periampullary polyps showed hyperplastic polyps.

On follow-up, none of the family members had similar complaints. Genetic study was done where no genetic mutations were detected. The patient is counseled for regular follow-up and screening for possible malignancies. Now, the patient is stable and doing her regular routine activities.

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**Figure 1:** Multiple polyps in colon ranging in size 4–12 mm in diameter. Post-contrast study shows mild enhancement.

**Figure 2:** Polyp in rectum measuring 12 mm in diameter. Post-contrast study shows mild enhancement.

**Figure 3:** Multiple polyps in distal colon.

**Figure 4:** Polyps in stomach, duodenum, and periampullary region.

**Figure 5:** Arborizing muscularis mucosa (H&E, 10×).

**Figure 6:** Villous pattern (H&E, 10×).
DISCUSSION

Peutz–Jeghers syndrome is characterized by hamartomatous polyps in gastrointestinal tract. Hyperpigmentation is usually seen as mucocutaneous macules on the buccal mucosa, lips, nostrils, and around the mouth. The age of presentation is common in young individuals, but our patient was middle-aged. There were multiple polyps in gastrointestinal tract showing high grade dysplasia and villous adenoma associated with hyperpigmented spots on the buccal mucosa.

Diagnostic criteria for PJS are given below [1].

1. Three or more histologically confirmed Peutz–Jeghers polyps.
2. Any number of Peutz–Jeghers polyps with family history of PJS.
3. Characteristic prominent mucocutaneous pigmentation with family history of PJS.
4. Any number of Peutz–Jeghers polyps and characteristic prominent mucocutaneous pigmentation which disappears with time.

Several school of thoughts explain the pathogenesis of hamartoma-adenoma-carcinoma sequence in PJS. In PJS polyps, the second hit in \( \text{LKB1} \) causing loss of heterozygosity (LOH) in adenomatous and carcinomatous lesions was explained by several studies [4–6]. Also, LOH of \( p53 \), \( K-Ras \), and \( \beta\)-catenin mutations was present in the adenomatous change found in hamartomatous polyps. This indicates that the molecular alterations in these genes are responsible carcinogenesis in PJS as well [4, 7].

One theory suggests mucosal prolapse as a pathogenic mechanism underlying the development of typical hamartomatous polyps in PJS. In this hypothesis, PJS hamartomatous polyps represent an epiphenomenon to the cancer-prone condition and the hamartoma-adenoma-carcinoma sequence as such does not exist [4, 8]. \( \text{STK11/LKB1} \) is a tumor-suppressor gene which is involved in cellular polarity and intracellular signal transduction [4, 9]. The important role of \( \text{LKB1} \) in cellular polarity and the loss of polarity function may also affect asymmetric stem cell division in PJS and lead to expansion of the stem cell pool [4, 10]. It could lead to polyp formation and also explain the increased cancer risk. A recent study found that \( \text{STK11} \)-deficient mesenchymal cells produced less TGF-\( \beta \) and defective TGF-\( \beta \) signaling to epithelial cells which were coincided with epithelial proliferation. This explains that stromal-derived mechanism of tumor suppression is also relevant to PJS [4, 11].

Over the years, the standard therapy for PJS has been laparotomy and bowel resection to remove symptomatic gastrointestinal polyps that cause persistent or recurrent intussusceptions [12]. Few patients may require multiple surgical resections which can lead to short gut syndrome. Therefore, it has been recommended that endoscopic procedures to be performed to remove all polyps. Surgical resection is done for the patients with giant polyps or the ones presenting with complications, such as obstruction, intussusceptions, or gastrointestinal bleeding [13]. In our case, since the size of the polyps were small, endoscopic polypectomy was performed. Nowadays, Double Balloon Enteroscopy (DBE) in combination with capsule enteroscopy is the gold standard for the diagnosis and treatment of hamartomatous polyps [2, 14]. Laparoscopic-assisted enteroscopy offers less invasive option for both polyp removal and bowel resection.

Endoscopic polypectomy for PJS requires expertise and should only be performed by the expert in polypectomy. It has been studied that muscularis mucosa commonly invaginates into the large pedunculated stalk which increases the risk of perforation at electrocautery. The risk of perforation from polypectomy in PJS may be higher than other GI polyps. Techniques like mucosal lifting, postpolypectomy clips, and electrosurgical knife can be employed to decrease the risk of perforation and bleeding need to be employed at polypectomy [15].

Histopathologically, the most characteristic feature of PJS polyp is a central core of smooth muscle extending into the polyp in an arborizing fashion (Christmas tree like appearance) and covered by normal or hyperplastic mucosa. Adenomatous and carcinomatous changes can be seen [16]. The cumulative cancer risk at 40 years is 20% and increases to 76% at 70 years [17]. Germline mutations in \( \text{STK11/LKB1} \) gene are found in 30–70% of PJS cases [18].

CONCLUSION

Although the incidence of PJS is low, it is important to recognize the disease to the earliest in order to prevent
the complications. These patients require regular lifelong mandatory periodic evaluation on follow-up by endoscopy. Early detection and proper surveillance are essential to minimize the risk of gastrointestinal carcinoma.

REFERENCES


Author Contributions
Karthis Hariprasad Shetty – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Disha Shetty – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

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All relevant data are within the paper and its Supporting Information files.

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