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Peutz-Jeghers Syndrome With Diffuse Gastrointestinal Polyposis: Three Cases in a Family With Different Manifestations and No Evidence of Malignancy During 14 Years Follow Up

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Introduction: Peutz-Jeghers syndrome (PJS) is a rare disorder characterized by mucocutaneous perioral pigmentation, gastrointestinal hamartomatous polyposis, and an increased risk of malignancy. Families with PJS may show a variable spectrum of manifestations in spite of their consecutive generations. A probable explanation is novel mutations in contributing genes.
Case Presentation: This report describes 3 cases of a family. Two daughters presented the classic PJS, while their father only manifested mucocutaneous perioral pigmentation. The junior daughter was underwent 3 and the eldest daughter 2 laparotomies for intussusception. The patients were visited annually and their medical findings were recorded during a follow-up period of 14 years. They were periodically examined in our hospital and despite conveying diffuse polyposis from the esophagus throughout the rectum in these three cases, even a simple hyperplasia was not found in obtained specimens.
Conclusions: The patients with diffuse PJS may be asymptomatic and without gastrointestinal or extragastrointestinal malignancies.

Keywords: Peutz-Jeghers Syndrome, Cancer; Intestinal Polyposis, Intussusception, Pigmentation

1. Introduction

Peutz-Jeghers syndrome (PJS) is a rare disease with autosomal dominant inheritance. Patients display a typical mucocutaneous pigmentation and hamartomatous polyps in the gastrointestinal tract (1). The polyps take on a risk of potential complications, including bleeding, intestinal obstruction, intussusception, and malignant transformation (2). Furthermore, cancers may involve other organs aside from the gastrointestinal system (3). Therefore, a watchful care should be provided for the patients.

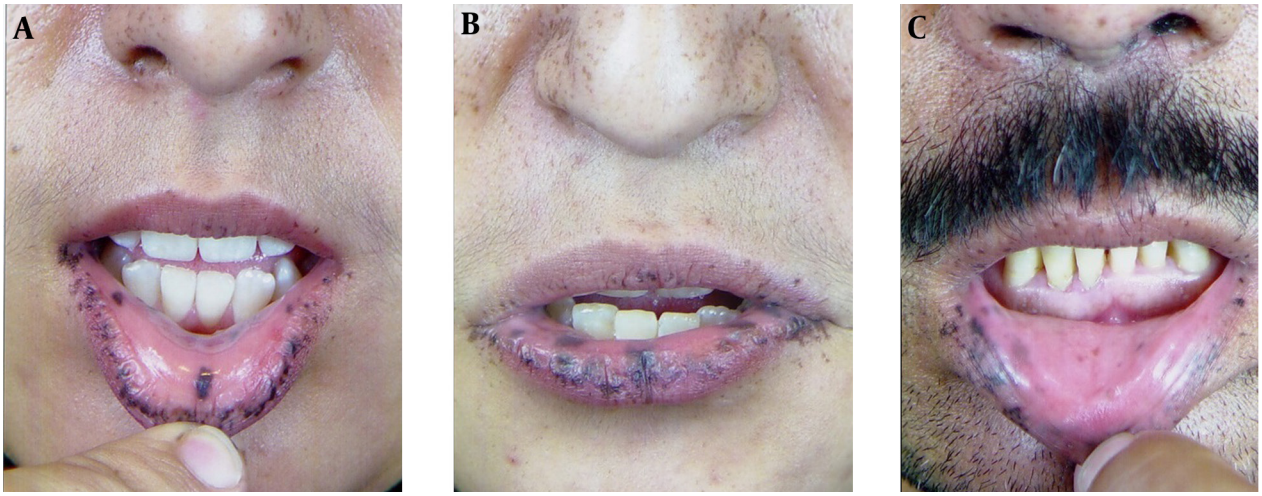
The clinical course of PJS is unpredictable, even in the members of a family (4). Accordingly, development of lifetime malignancies should be monitored with periodic examinations (5). This screening method would help the physicians in the premier detection of cancer (6). The present report describes 3 cases of PJS in two consecutive generations of the same family, a father and his daughters. The family was followed-up during a period of 14 years (from November 1999 to November 2013). Distinct clinical manifestations in two generations and all screening tests for malignancies were negative.

2. Case Presentation

A 6-year-old girl with typical mucocutaneous hyperpigmentation (Figure 1) of PJS was visited in our hospital (Amir-al-Momenin hospital, Tehran, Iran) enduring fever, loss of appetite, and abdominal pain. Her symptoms had begun one day before showing up at the clinic asking for treatment from a physician. The physical examination showed generalized abdominal tenderness without rigidity. The oral temperature was 38.2°C. There were no additional findings on physical examination and past medical history of the patient. The patient was evaluated with ultrasonography and a sausage-shape mass was found in the imaging. Accordingly, she underwent emergency laparotomy and the segment was resected. The etiologic cause of intussusception was determined to be a solitary polyp with the size of 2 × 1 cm which showed a hamartomatous feature in histopathological evaluation (Figure 2). Regarding the typical facial pigmentation of the patient and coexistence of intussusception due to a hamartomatous polyp, we definitely diagnosed her as a PJS case. Consequently, we found out that her only sister (an 8-year-old girl) and her father (a 35-year-old man)

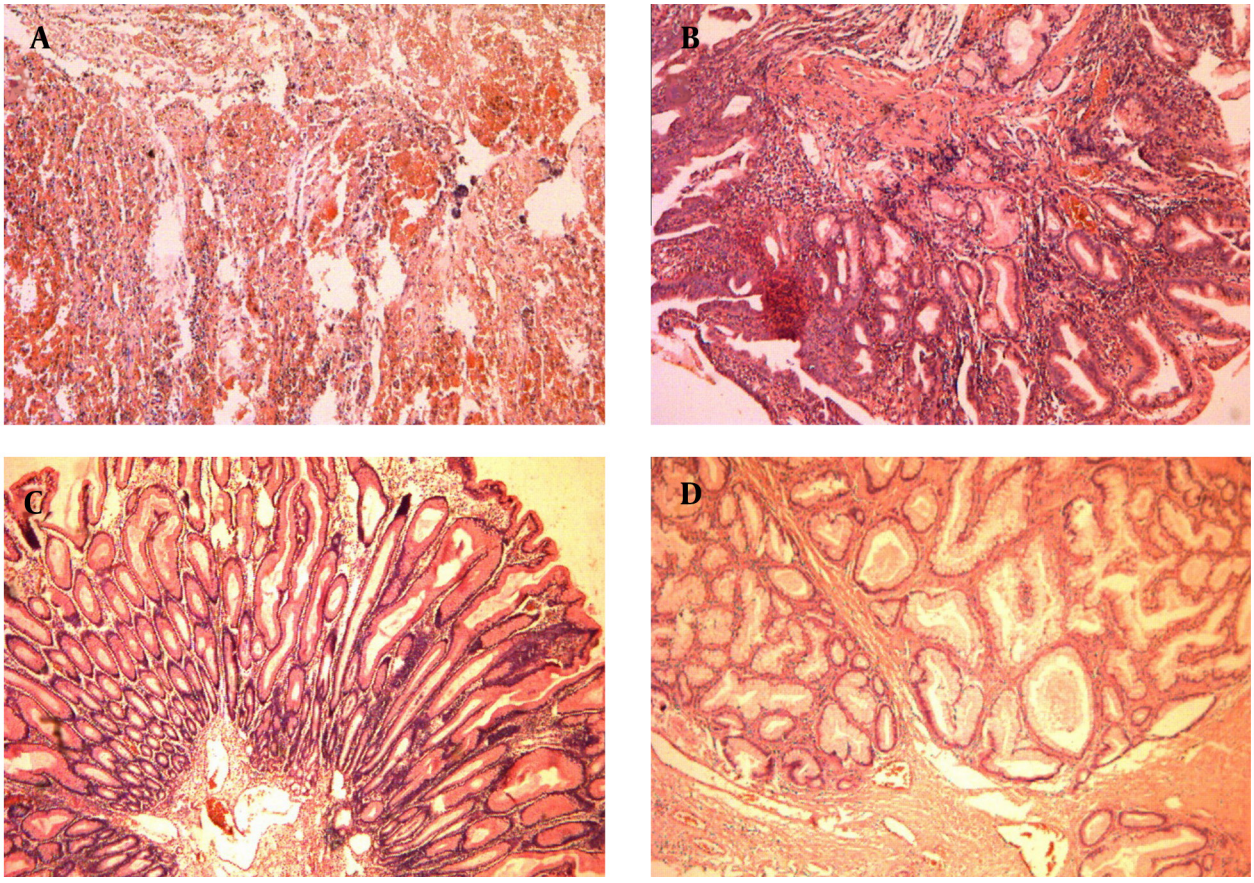
also had typical perioral pigmentation (Figure 1) without any other symptoms. The father told us about the presence of similar mucocutaneous pigmentation in his father, grandfather, and two uncles. But they had no other presentations and his grandfather and one uncle died a natural death.

Figure 1. Typical Mucocutaneous Pigmentation in PJS



A: Perioral hyperpigmented lesions in the junior daughter when she was 15, B: The elder daughter when she was 17, C: The father when he was 44.

Figure 2. The Microscopic Images of Hamartomatous Polyps Without any Evidence of Malignancy in The Gastrointestinal Tract of Patients (H&E × 100)



A: The small bowel polyp in the junior daughter when she was 6, B and D: The esophageal and rectal polyp in the father when he was 35, C: The gastric polyp in the elder daughter when she was 8.

We decided to trace these 3 patients for probable malignancies, especially in the gastrointestinal tract. However, both the elder daughter and her father borne diffuse gastrointestinal hamartomatous polyps (from the esophagus throughout the rectum) but there was no evidence of malignancy in endoscopical and histopathological evaluations (Figure 2).

All patients underwent annual upper and lower gastrointestinal endoscopy, thyroid and abdominal ultrasonography (US) and abdominal computed tomography (CT). Breast US for female and testicular US for male patients were done too. Tumor markers, including CEA, a-FP, CA 19 - 9, CA 15 - 3, and CA 125 were detected. Besides, complete blood cell count (CBC) and ESR were performed every 6 months. There were no complications and evidence of malignancies during a period of 8 years. However, 9 years later, when the junior daughter was 15, she was readmitted for intussusception. One year later the elder daughter, who was 18 by then and had no symptom up to that time, was admitted for intussusception. Thereafter, the junior daughter was observed for the third time with intussusception. All those admissions were lead to emergency laparotomies, but the excised small bowel segments and coexistent hamartomatous polyps were negative for malignancies (Table 1).

So far, the father and both daughters were visited in our hospital annually for probable complications and malignancies. Despite the existence of several polyps in gastrointestinal tract of these patients, the findings of US, CT studies, and laboratory tests for neoplasm of gallbladder, biliary tract, pancreas, breast and male sex cords were negative during these 14 years.

Table 1. Some Characteristics and Symptoms of the Affected Patients [a]

Variables	Father	Elder Daughter	Younger Daughter
Clinical Manifestations			
Mucocutaneous pigmentation	Pos	Pos	Pos
Gastrointestinal polyposis	Pos	Pos	Pos
Clinical Symptoms			
Abdominal pain	Neg	Neg	Pos (n = 3)
Anemia	Neg	Neg	Neg
Acute rectal blood loss	Neg	Neg	Neg
Chronic rectal blood loss	Neg	Neg	Neg
Intussusception	Neg	Pos (n = 1)	Pos (n = 3)
Abdominal surgery	Neg	Pos (n = 1)	Pos (n = 3)
Cancer			
Gastrointestinal	Neg	Neg	Neg
Extragastrointestinal	Neg	Neg	Neg

[a] Abbreviations: Pos, positive; Neg, negative.

3. Discussion

Despite their consecutive generations, families with PJS may have a variable spectrum of manifestations. The probable explanation is novel mutations in contributing genes (7). The presented family in this report was of particular interest since there are few reported cases of PJS with long-term follow up. We were able to visit the patients annually and record their medical findings. There was not even a simple hyperplasia in obtained specimens during the annual evaluations.

Another important issue in our report was different course of the disease. Although, we had little information about previous generations, but the available undocumented data showed a clear history in them. This matter demonstrates that there was at least one patient in each generation of the family to transmit the disease and he only showed perioral hyperpigmented lesions of disease without further symptoms. This issue seemed correct just before the last generation, including these two sisters. When the PJS affected these two patients, the clinical manifestations developed from lone dermatology's signs to gastrointestinal presentations. In previous reports, consecutive generations would show a different clinical course throughout their families and there were no completely symptom-free generations (8). Nevertheless, we noticed two completely asymptomatic generations (the father, grandfather, and uncles) who had only perioral hyperpigmentation.

The last but not the least important issue in this report was the complete involvement of the gastrointestinal tract. All these 3 patients had hamartomatous polyps from the esophagus throughout the rectum. To the best of our knowledge, there was no previously reported case of PJS affecting all gastrointestinal tract. There was only one similar report in the literature in PubMed, but without

esophageal involvement (9) and also with diffuse bleeding from polyps leading to iron-deficiency anemia. In spite of diffuse polyposis, the 3 reported cases in our study developed no hemorrhage and their polyps were marked with no blood clot or hemorrhage during follow-up.

The increased risk and young age of onset of cancer in patients with PJS have already been described. However, the onset of these malignancies are thought to be occurred approximately 30 year after the diagnosis (10), and our patients had no evidence of cancer, particularly in the gastrointestinal tract after a period of 14 years. As noted previously, some studies indicated that PJS gene encodes the serine threonine kinase LKB1 or STK11 (7). As a limitation in this report, there was not mutation analysis to find out whether a defect in the LKB1 gene is responsible for the PJS phenotype in the original PJS kindred. In conclusion, the account of the presented patients who were the first family with PJS reported from Iran showed that clinical manifestations of disease may be varied in different generations and the clinical course of PJS is not predictable. Even the patients with diffuse gastrointestinal polyposis may be asymptomatic and without gastrointestinal or extragastrointestinal malignancies.

Footnote

Authors' Contributions: Writing the manuscript: Ehsan Jangholi and Ali Farshad. Critical revision of the article for important intellectual content: Reza Najibpour, Ehsan Jangholi, and Esfandiar Matini. Performing procedures and following up of the patients: Esfandiar Matini, Hooman Houshangi, Pantea Farjad Azad, and Reza Najibpour.

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