Turk J Gastroenterol 2004; 15 (3): 164-168

Peutz-Jeghers syndrome: Report of 6 cases in a family and management of polyps with intraoperative endoscopy

Peutz jeghers sendromu: Bir ailede 6 olgu ve intraoperatif endoskopik polipektomi

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Background/aims: *Peutz-Jeghers syndrome is an uncommon, autosomal dominantly inherited disorder characterized by mucocutaneous melanin pigmentation and gastrointestinal hamartomatous polyps. The purpose of this study was to present six cases of Peutz-Jeghers syndrome in a family.* ***Methods:*** *Enteroclysis, upper and lower gastrointestinal endoscopy, and thyroid, abdominal, and testicular or breast ultrasonography were performed in all subjects. Tumor markers including CEA, a-FP, CA 19-9, CA 15-3, and CA 125 were measured. Management of polyps and complications were evaluated.* ***Results:*** *History of the patients were as follows: patient 1 (40-year-old male) underwent surgery 20 years previously; patients 2 and 3 (19-year-old female and 17-year-old male) had undergone surgery three times between the ages of 11 and 18 years, and two times between the ages of 15 and 17 years, respectively; patient 4 (16-year-old male) had undergone surgery three times at the age of 13 years; patients 5 and 6 (14-year-old and 11-year-old males) had no history of surgery. All surgical procedures had been performed due to intestinal obstruction. Hyperpigmentation of the lips and oral mucosa were observed in all patients except patient 1, whose pigmentation disappeared 20 years previously. Patient 2 also had pigmentation of hands and feet. Enteroclysis showed small bowel polyps in all subjects except patients 1 and 6. During colonoscopy, different sizes of polyps were observed at different locations of the colon, and polyps larger than 1 cm were removed. Patients 2 and 3 underwent surgery due to complication of small bowel polyps; 69 polyps in patient 2 and 17 polyps in patient 3 were removed via intraoperative endoscopic procedure. Hamartomatous lesions were confirmed by histopathological examinations. Microscopic study of polyps of patients 2 and 3 revealed dysplastic changes. None of the patients had evidence of malignancy as of June 2003. Peutz-Jeghers syndrome demonstrated autosomal dominant inheritance in this family.* ***Conclusions:*** *The major problem during follow-up of patients with Peutz-Jeghers syndrome is the management of small bowel polyps. When encountered during surgery, intraoperative enteroscopic polypectomy should be performed.*

Keywords: Peutz-Jeghers syndrome, hamartomatous polyps, management

Amaç: Peutz-Jeghers sendromu muko-kütanöz melanin pigmentasyonu ve gastrointestinal hamartomatöz poliplerle karakterize otozomal dominant geçişli nadir görülen kalıtımsal bir hastalıktır. Bu çalışmanın amacı bir ailede görülen 6 Peutz-Jeghers sendromu olgusunu sunmaktır. ***Yöntem:*** *Tüm olgulara enteroklizis, üst ve alt gastrointestinal endoskopi, tiroid, batın ve testiküler ultrasonografi yapıldı. CEA, alfa feto protein, CA 19-9, CA 15-3 ve CA 125 tümör belirteçlerinin ölçümü yapıldı. Poliplerin ve komplikasyonlarının tedavisi değerlendirildi.* ***Bulgular:*** *Hastaların hikayesinde; 1. hasta -40 yaşında erkek-20 yıl önce ameliyat geçirmişti. 2. hasta 19 yaşında bayan olup, 11 ve 18 yaşları arasında 3 defa ameliyat geçirmişti. 3. hasta 17 yaşında erkek olup, 15-17 yaşları arasında iki defa ameliyat edilirken, 4. hasta 16 yaşında erkek ve 13 yaşına kadar 3 defa ameliyat edilmişti. 14 yaşında olan 5. hasta ve 11 yaşındaki 6. hastaya cerrahi uygulanmamıştı. Bütün ameliyatlar barsak tıkanması nedeniyle yapılmıştı. Pigmentasyonu 20 yıl önce kaybolan birinci hasta hariç tüm hastalarda dudaklarda ve ağız mukozasında hiperpigmentasyon gözlendi. İkinci hastada bunlara ek olarak ellerde ve ayaklarda pigmentasyon saptandı. Birinci ve 6. hastalar hariç tüm olgularda enteroklizisteincebarsak polipleri görüldü. Kolonoskopi sırasında değişik kolon lokalizasyonlarında değişik boyutlarda polipler gözlendi ve 1 emden büyük polipler alındı. İkinci ve 3. hastalar incebarsak poliplerine bağlı komlikasyonlar nedeniyle ameliyata alındı, intraoperatif endoskopi yardımıyla ikinci hastadan 69, üçüncü hastadan 17 polip çıkartıldı. Hamartomatöz lezyonlar histopatolojik inceleme ile verifiye edildi. İkinci ve 3. hastaların poliplerine yapılan histopatolojik incelemede displastik değişiklikler görüldü. Hiçbir hastada 2003 Haziran ayına kadar malignite-ye dönüşüm saptanmadı. Bu ailede Peutz-Jeghers sendromu otozomal dominat olarak geçişliydi.* ***Sonuç:*** *Peutz-Jeghers sendromlu hastaların takibinde rastlanan en büyük problem incebarsak poliplerinin tedavisidir. Cerrahi işlem sırasında rastlanırsa intraoperatif endoskopik polipektomi yapılmalıdır.*

Anahtar kelimeler: Peutz-Jeghers sendromu, hamartomatöz polipler, endoskopik polipektomi

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Manuscript received: 20.04.2004 **Accepted:** 13.07.2004

INTRODUCTION

Peutz-Jeghers syndrome (PJS), which was first described in 1921 by Peutz (1), followed by Jeghers et al. (2) in 1949, is an uncommon, autosomal dominantly inherited disorder characterized by mucocutaneuos melanin pigmentation, gastrointestinal (GI) hamartomatous polyps and an increased risk of GI and other organ cancers. Polyps are most commonly located in the small intestine (64-96%), but occur also in the stomach (24-49 %) and in the colon (60%) (3, 4). The size of polyps may vary from a few millimeters to several centimeters and they have a coarse and lobulated surface. Larger polyps are pedunculated, whereas smaller polyps are sessille (4). The clinical symptoms of the disease are recurrent abdominal pain, intestinal intussusception and obstruction, and rectal bleeding. Symptoms usually take place in the second or third decade of life (5, 6).

Although it is easy to remove polyps of the stomach and large bowel during esophagogastroduodenoscopy (EGD) and colonoscopy, the main problem in the management of the disease is treatment of the small bowel polyps and their complications. Thus, most patients with PJS require several small bowel resections during their lifetime, resulting in short bowel syndrome. While surgical management with multiple enterotomies and removal of all palpable polyps has been proposed in the past, a combined surgical-endoscopic approach using intraoperative enteroscopy (IOE) (7) or combined push enteroscopy (PE) and IOE has been recently advocated (8). The other difficulty in the management of the disease is to follow up the occurrence of malignant disease in these patients. Malignant change of the hamartomatous polyps and other organ cancers have been reported in patients with PJS (9).

The purpose of this study was to present our experience in the management of six cases of PJS in a family.

MATERIALS AND METHODS

Six patients with PJS in a family (a father and his five kids) who underwent surveillance were included in the present study. The history of patients was recorded. Enteroclysis, upper and lower gastrointestinal endoscopy, thyroid and abdominal ultrasonography (US), and abdominal computed tomography (CT) were performed in all subjects. Breast US for female and testicular US for male patients were employed. Tumor markers including CEA, oc-FP, CA 19-9, CA 15-3, and CA 125 were detected. Management of polyps and complications are presented.

RESULTS

Peutz-Jeghers syndrome demonstrated autosomal dominant inheritance in this family. Patient histories were as follows: patient 1 (father at the age of 40-years-old) underwent surgery 20 years previously; patients 2 and 3 (19-year-old female and 17-year-old male) had undergone surgery three times between the ages of 11 and 18 years, and two times between the ages of 15 and 17 years, respectively; patient 4 (16-year-old male) had undergone surgery three times at the age of 13 years; patients 5 and 6 (14-year-old and 11-year-old males) had no history of surgery. All surgical procedures were abdominal interventions and were performed due to intestinal obstruction and intussusception. Family history of the patients revealed no GI, gynecologic, or central nervous system malignancies.

Hyperpigmentation of the lips and oral mucosa were observed in all patients except patient 1, whose pigmentation had disappeared 20 years previously. Patient 2 also had pigmentation of the hands and feet.

EGD revealed gastric polyps at the antrum in patients 3, 4, and 6 removed by electrosurgical snare. Enteroclysis showed small bowel polyps in all subjects except patients 1 and 6. During colonoscopy, different sizes and numbers of polyps were observed in all patients at different locations of the colon, and polyps larger than 1 cm were removed.

During follow-up in our clinic, two of the six patients (patients 2 and 3) who had complication of small bowel polyps underwent surgery and IOE; Patient 2 had a palpable mass in the right quadrant and recurrent intestinal obstruction. At surgery an intussusception was observed at the terminal ileum due to a large polyp, and multiple polyps were observed in the small bowel (Figure 1). Sixty-nine polyps were removed, ranging from 1 cm to 5 cm by electrosurgical snare through IOE procedure (Figures 2 and 3). Patient 3 underwent surgery with diagnosis of intestinal obstruction due to stenosis of the jejunum at 25 cm distal to the Trietz ligament. A segment of the jejunum (40 cm) was resected, including the stenosis, and IOE

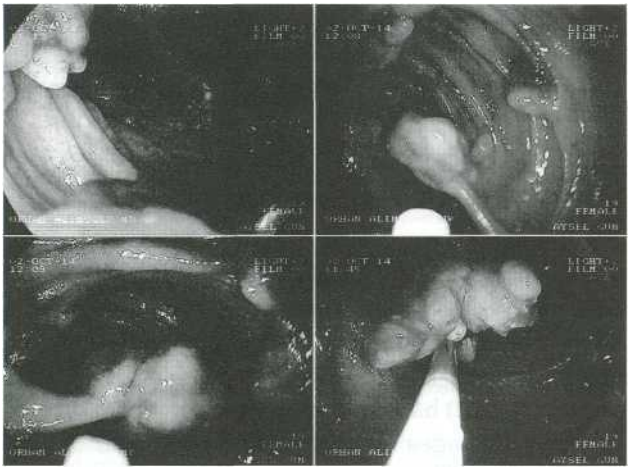

Figure I. Endoscopic appearance of small bowel polyps

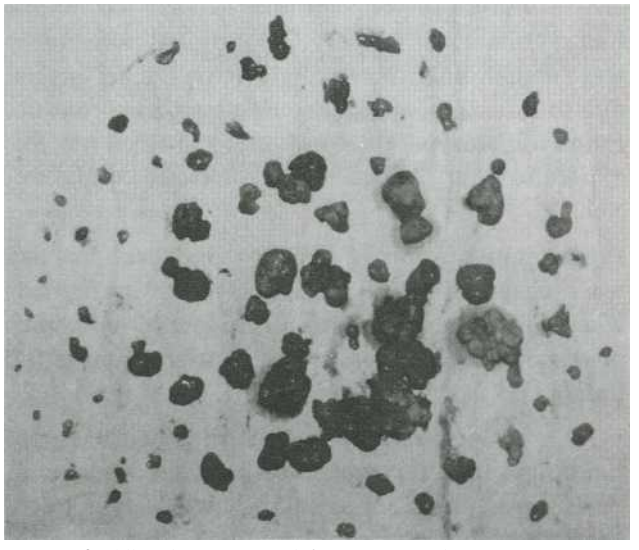

Figure 2. All polyps removed from patient 2

was performed to the duodenal, jejunal and ileal polyps.

During this procedure, 17 polyps were removed, ranging from 1 cm to 6 cm, by or in the resected jejunum. In both patients, the largest polyps were located in the duodenum and proximal jejunum, and most of the polyps were pedunculated and lobulated. No serious complications occurred in these two patients.

Overall, four of the six patients had 11 surgical operations for small bowel polyps. All hamartornatous lesions were confirmed by histopathological examinations in all patients. Microscopic study of the polyps of patients 2 and 3 revealed dysplastic changes; cancerous transformation was not observed. US and CT studies and laboratory tests were

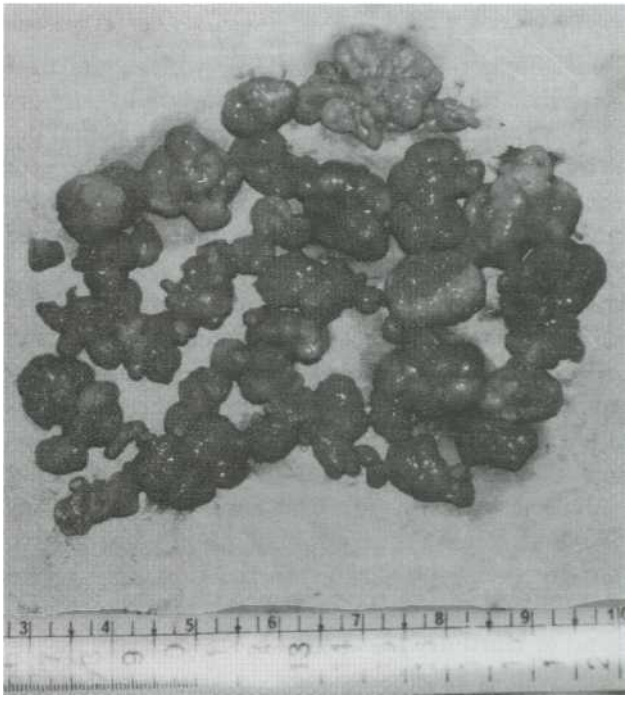

Figure 3. Appearance of large polyps from patient 2

negative for neoplasm of gallbladder, biliary tract, pancreas, breast and male sex cords.

DISCUSSION

Peutz-Jeghers syndrome is inherited in an autosomal dominant manner and the serine-threonine kinase STK 11 (or LKB1), located on 19pl3.3, is mutated in more than half of the PJS kindred (10).

The incidence of this disease is 1 in 29,000 live births (11). The clinical hallmarks of PJS are facial mucocutaneous pigmentation and diffuse gastrointestinal polyps of hamartomatous origin. The formal diagnosis of PJS requires the presence of histopathologically verified intestinal hamartomatous polyps with at least two of three additional clinical criteria of small bowel polyposis, mucocutaneous melanotic pigmentation, and a family history of PJS (12). The pigmentation is usually present on the lips, oral mucosa, vulva, or fingers and toes, although a few patients may not develop these lesions (13). The polyps may present in any GI location. All clinical manifestations of the syndrome are not always present in the affected patients: while some patients have only mucocutaneous pigmentation, others have only intestinal polyposis (14). In the present study, all patients had mucocutaneous pigmentation and GI polyps. Colonic polyps were present in all patients, small bowel

polyps in five and gastric polyps in three. All polyps from stomach and small and large bowel showed histological features of hamartomas. Dysplastic changes were observed in some of polyps of patients 2 and 3. All surgical procedures were performed during the second decade of life. However, PJS may become clinically apparent during the neonatal period (3), and mucocutaneous pigmentation may be present at birth or later in life.

The major difficulty in the management of the disease is the treatment of small bowel polyps. Furthermore, diagnosis of these polyps is difficult since they are relatively inaccessible and cause nonspecific symptoms. Large polyps tend to infarction, ulceration, and bleeding, and may cause intestinal obstruction and intussusception. During surgery, identification of intraluminal polyps by palpation may not identify all polyps, so the use of IOE may influence the number of enterotomies and guide their positioning. Polyps missed by palpation can be endoscopically identified and removed (8). The combined surgical-endoscopic procedure first performed by Mathus-Vliegen and Tytgat in 1985 is the most effective procedure for the clearance of small bowel polyps (7). Amaro et al. (15) reported more than 60 polyps, ranging from 1 to 4 cm in size, in a single surgical endoscopic session. In the present study, two patients underwent IOE surgical procedure. The clearance of small bowel polyps through IOE polypectomy may prevent the need for surgery with repeated intestinal resection and reduce the risk of short small bowel syndrome and GI cancer in patients with PJS. Another procedure for small bowel polyps is PE. PE examination of the whole small intestine is not a practical procedure for the removal of multiple polyps (16). Also, this instrument is not yet currently available in most endoscopy units. PE can be useful for periodic removal of jejunal metachronous polyps (8).

Although it is not known whether malignant tumors associated with this syndrome originate from adenomatous changes in pre-existing hamartomas or whether neoplastic (adenomas) and non-neoplastic (hamartomas) polyps coexist, an increased risk for development of GI cancer and tumors outside of the GI tract has been shown, and a hamartoma-adenoma-carcinoma sequence has been suggested (12, 17, 18). The risk of cancer of the GI tract associated with this condition is higher than in the general population, and ranges from 3% to 48% (12). Cancer related to PJS includes bilateral breast cancer (19); cervix tumor (20); ovarian tumor (21); testicular tumor (22); carcinoma of the gallbladder (23); pancreatic adenocarcinoma (24); gastric (25), duodenal (26), jejunal (27), ileal (28), and rectal (29) carcinomas; and male sex cords tumor (30).

Enteroclysis is the most useful imaging study in detecting small intestinal polyps. The major problem during follow-up of patients with Peutz-Jeghers syndrome is the management of small bowel polyps and surveillance of cancers related to the disease. When surgery is scheduled in these patients, intraoperative enteroscopic polypectomy should be considered and these patients should be followed closely for early malignant changes by periodic radiologic and endoscopic surveillance.

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