CASE REPORT

Peutz–Jeghers syndrome: case report and literature review

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Abstract

Periorificial lentiginosis, also knew as Peutz–Jeghers Syndrome (PJS), is an autosomally dominant inherited condition determined by a mutation localized at 19p13.3 responsible for mucocutaneous pigmentation and gastrointestinal polyps. Skin- and mucosal pigmentation may be present at birth but usually occur in early childhood, and occasionally may develop later. Round, oval or irregular patches of brown or almost black pigmentation 1 to 5 mm diameter, irregularly distributed over the oral mucosa, gums, hard palate and lips (especially the lower) are observed. The pigmented maculae on the face, encountered especially around the nose and mouth are smaller. Polyps may appear in the stomach, small bowel or colon, with hamartomatous aspects on histology. Acute upper gastrointestinal bleeding and chronic fecal blood loss may appear during the course of disease. There is a higher risk of intestinal and extraintestinal cancers in those patients. We present the case of an 18-year-old young girl accusing since the age of 3 slight intermittent episodes of bloating and abdominal pain without a particular localization, as well as mild iron-deficiency anemia. Physical examination revealed pigmented lesions suggesting PSJ on the palatine and jugal mucosa while endoscopy found a lot of polyps in stomach and a few, isolated in the colon, all having the same hamartomatous pattern. The presence in early infancy of small, well-demarcated and dark-brown to blue-black lentigines on the lips, buccal mucosa and perioral skin, should alert the clinician to PJS.

***Keywords*:** hamartoma, gastrointestinal polyps, Peutz–Jeghers syndrome, mucosal lentigines.

Introduction

Y. Peutz, a Dutch pediatrician, described in 1921 a family with skin pigmentation and polyps of the small bowel. Similar cases were reported in US by H. Jeghers and colleagues in 1949 [1] and consequently the name of Peutz–Jeghers syndrome (PJS) was adopted for this disorder. PJS is an inherited, autosomal dominant disorder characterized by mucocutaneous pigmentation and gastrointestinal polyps. Melanic spots are the earliest manifestation of PJS, typically appearing in the first year of life. Although most of the polyps reside in the jejunum, it may also occur in ileum, stomach, duodenum and/or colon. Those polyps are present from childhood and may sometimes lead to intussusception or gastrointestinal bleeding.

Case report

An 18-year-old young girl has been referred in our Service for a long history of abdominal pain and bloating, having a mild iron-deficiency anemia. The pain was somewhat diffuse and capricious, very poorly characterized, without a precise localization and any specific causative factor.

There was no history of diarrhea, constipation, vomiting and/or gastrointestinal bleeding and family history was negative for colonic polyps and colon cancer.

Physical examination was normal except for the presence of dark-brown pigmented maculae on perioral, perinasal and periocular skin, as well as on the lower lip (Figure 1).

Well-demarcated, dark brown to blue-black pigmented maculae has been noticed on the palatine and jugal mucosa (Figure 2, A and B).

According to her mother, these pigmented lesions of the skin have been present at birth but they faded at puberty and since the age of three, the girl systematically accused slight intermittent abdominal pain, without any particular localization and no diarrhea, constipation, vomiting, weight loss or rectal bleeding.

No abdominal tenderness, masses, infiltration or organomegaly were observed at physical examination. Abdominal ultrasound and CT-scan were normal. Laboratory check-up was also within the normal range except a mild anemia, with microcytosis and iron depletion, but stool was positive for occult blood.

We then decided further endoscopic investigation. Upper digestive endoscopy discovered more than 30 polyps in the stomach, 5- to 15 mm in diameter, located especially in the fornix and antrum (Figure 3, A and B).

Multiple biopsies have been performed from those polyps. Colonoscopy showed subsequently two 1 to 1.8 cm pedunculated polyps in the sigmoid colon and one 1.2 cm polyp on the hepatic flexure (Figure 3C), all resected endoscopically.

Histologic examination of bioptic fragments from the stomach, as well as of the polyps removed from colon showed proliferation and ramification of myocytes from muscularis mucosae, surrounding the glandular epithelium and spreading in submucosa and muscularis propria (Figure 4, A–C).

No sign of malignancy has been observed.

No conventional cytogenetic analysis was possible to be executed.

Discussions

PJS is an autosomal dominant inherited syndrome consisting of gastrointestinal hamartoma and mucocutaneous hyperpigmentation, having an estimated prevalence of 1 in 120000 live births [2] without racial or sexual predilection [3]. The mutant gene is STK11 (also know as LKB1) and is located at 19p13.3 [4]. Germline mutation of STK11 are documented in up to 70–80% of patients with PJS and up to 15% of cases have deletions of all or part of STK11 [5].

The STK11 gene is a tumor suppressor gene that encodes a serine-threonine kinase that modulates cellular proliferation, controls cell polarity, and seems to have an important role in responding to low cellular energy levels [6].

To exert this last role, the STK11 protein is involved in the inhibition of AMP-activated protein kinase (AMPK), and signals downstream to inhibit the mTOR (mammalian target of rapamycin; also known as FRAP; FKBP12 – rapamycin complex-associated protein) pathway [7]. The mTOR pathway seems dis-regulated in patients with PJS [8].

Genotype–phenotype correlation suggests that patients with PJS who have mutations in SKT 11 that result in truncation of the encoded STK11 protein have a significantly earlier age of onset than those who have missense mutation of detectable mutation of STK11 [9].

The characteristic pigmentation is present in more than 90% of patients with PJS [10]. The pigmented maculae may be present at birth but usually develop in early childhood, and even may develop later in life occasionally. Round, oval or irregular patches of brown or almost black pigmentation 1–5 mm in diameter are most commonly find around the mouth, nose, lower lip, buccal mucosa, hands and feet.

Perianal and genital regions may also be involved. Oral pigmentation is usually permanent, but the maculae on the lips and skin may fade after puberty. Rarely, the nails may be pigmented, diffusely or in longitudinal bands.

The pigmented maculae arise from increased number of melanocytes at the dermoepidermal junction, with increased melanin in basal cells. It should distinguish these melanin deposits from ordinary freckles. Freckles are absent at birth (but may occur in infancy) are sparse near the nostrils and mouth, and never appear on the oral mucosa.

Gastrointestinal polyps in PJS are hamartoma. Hamartomatous polyps are composed of the normal cellular elements of the gastrointestinal tract, but have a markedly distorted architecture.

The hamartomatous polyposis syndromes are a heterogeneous group of disorders inherited in an autosomal-dominant manner. Apart PJS, these syndromes include juvenile polyposis syndromes and PTEN hamartoma tumor syndrome (PHTS). PHTS include Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome (BRRS), and all syndromes in which there are germline PTEN mutations.

The Peutz–Jeghers polyp is a unique hamartomatous lesion characterized by glandular epithelium that covers an arborizing framework of well-developed smooth muscle that is continuous with the muscularis mucosae. The smooth muscle band fan out into the head of the polyp and become progressively thinner as they project toward the surface of the polyp. Unlike the case of the juvenile polyp, the lamina propria is normal, and the characteristic architecture of the lesion appears to derive chiefly from the abnormal smooth muscle tissue. These polyps are usually multiple and their distinctive appearance, in association with extra-intestinal manifestations, makes Peutz–Jeghers syndrome easily identifiable.

The most common location for polyps is the small bowel (64%), although involvement of the colon (53%) stomach (49%) and rectum (32%) is also described [11]. Usually there are fewer than 20 polyps present in each case, varying in size from several millimeters to more than 5 cm diameter [12].

Patients are diagnosed usually in the second or third decade of life and common presentations include abdominal pain, rectal bleeding, anemia, small intestinal intussusception, bowel obstruction, and rectal prolaps of polyps [13]. Abdominal symptoms tend to occur early in life, with more than 50% symptomatic patients before the age of 20 [14].

Macroscopically, in PJS the polyps have no specific feature, although sometimes they can develop long stalks that predispose to intussusception [13]. Microscopically, extensive smooth-muscle proliferation, with an elongated, arborized pattern of polyp's formation, can be seen [15].

The diagnostic criteria for PJS include the presence of characteristic muco-cutaneous pigmentation, small-bowel hamartomatomatous polyps and family history of PJS. Patients need to fulfill two of these three criteria for the diagnosis [16].

The differential diagnosis of pigmented lesions include LEOPARD syndrome, Langier–Hunziker syndrome, Carney complex, Cowden syndrome and a normal variant, particularly in African Americans [10, 11].

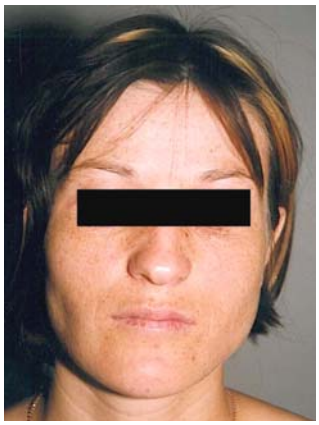

Figure 1 – ***Dark-brown pigmented maculae on perioral, perinasal and periocular skin, as well as on the lower lip***

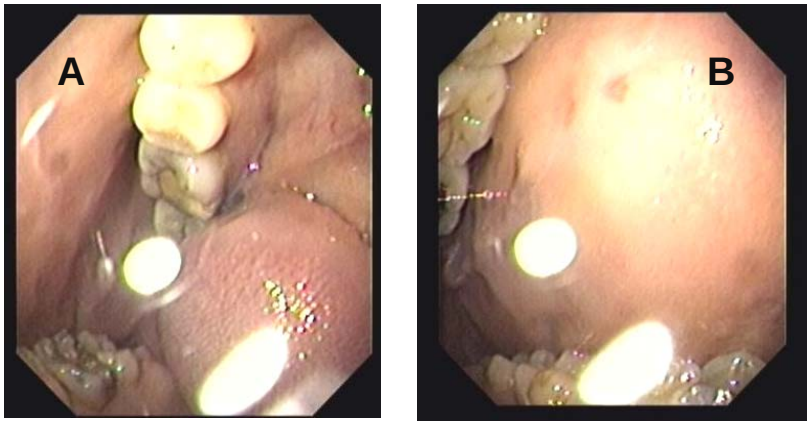

Figure 2 – ***Dark brown to blue-black pigmented maculae on the jugal (A) and palatine (B) mucosa of the mouth***

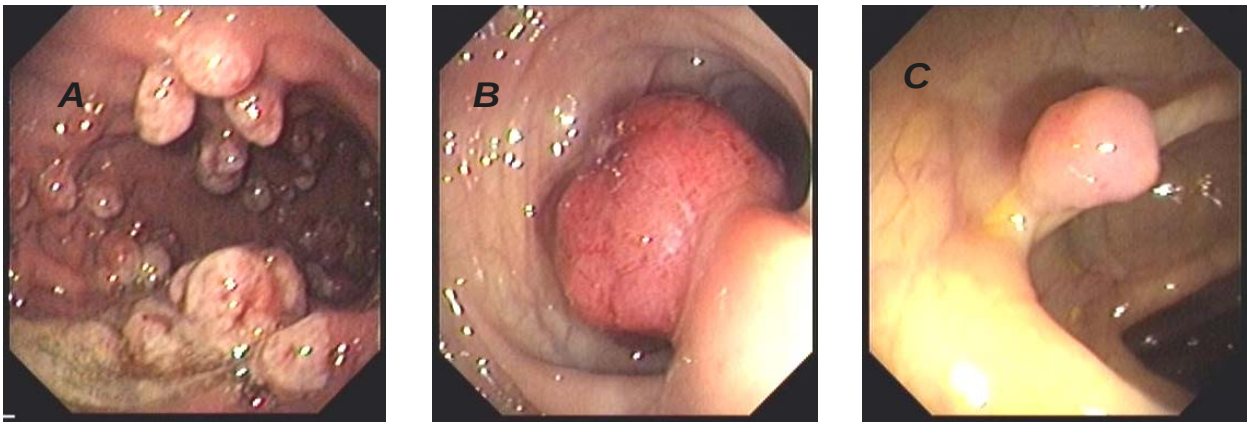

Figure 3 – ***Upper digestive endoscopy with more than 30 gastric polyps especially in the fornix and antrum (A). Colonoscopy with two 1 to 1.8 cm pedunculated polyps in the sigmoid colon (B) and one 1.2 cm polyp on the hepatic flexure (C)***

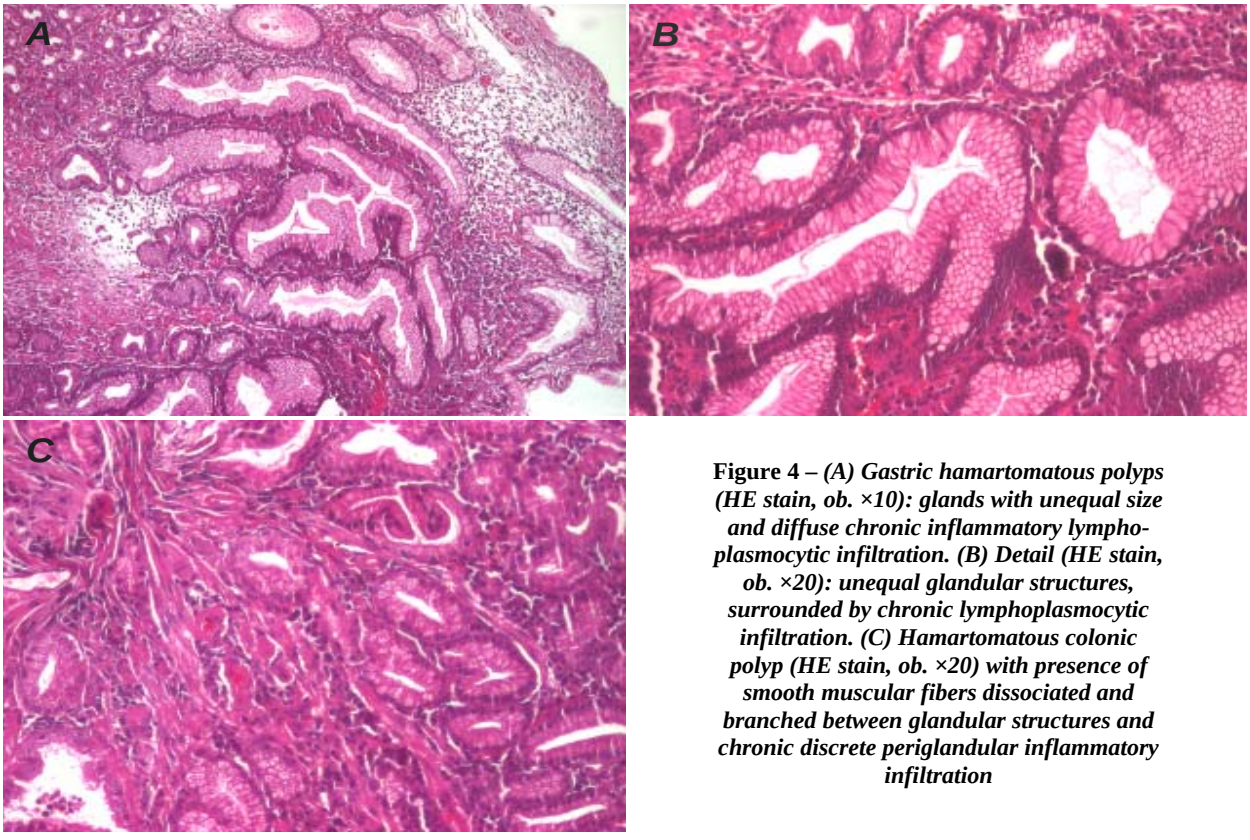

Figure 4 – ***(A) Gastric hamartomatous polyps (HE stain, ob. ×10): glands with unequal size and diffuse chronic inflammatory lympho-plasmocytic infiltration. (B) Detail (HE stain, ob. ×20): unequal glandular structures, surrounded by chronic lymphoplasmocytic infiltration. (C) Hamartomatous colonic polyp (HE stain, ob. ×20) with presence of smooth muscular fibers dissociated and branched between glandular structures and chronic discrete periglandular inflammatory infiltration***

In addition, acquired lesions may be due to minocycline-induced hiperpigmentation of lips [16].

When confronted with the combination of abnormal pigmentation and gastrointestinal polyps, one must also consider Ruvalcaba syndrome. However, this condition is readily differentiated from PJS by the location of the lentigines (penis) macrocephaly, and mental retardation [3].

PJS is associated with a markedly increased risk for development of cancer of the gastrointestinal tract. It may be also associated with the development of extracolonic manifestations, both malignant and nonmalignant.

It is now clear that the gene for PJS confers an increased risk for both gastrointestinal and non-intestinal cancer. A higher risk was observed for cancer of the small intestine, stomach, pancreas, colon, esophagus, and a lesser one for breast, lung and ovarian cancer [17].

Other tumors that may occur in this syndrome include polyps or cancers of the biliary tree and gallbladder [18].

Guidelines for screening are difficult to make but should be directed toward organs at risk for which early detection and treatment are reasonable, such as the entire gastrointestinal tracts, gonads and breasts (in women) [18].

A follow-up study restricted to patient with PJS who had a germline mutation in the tumor suppressor gene STK11 confirmed that these patients have a very high risk of developing cancer. The cumulative risk of developing any type o cancer was 81% while the cumulative risk of developing any gastrointestinal cancer was 66% by the time they were 70 years of age. Female patients had a cumulative risk of developing breast cancer of 32% by the time they were 60 years of age [19].

Treatment depends upon the severity. In case of intussusception or bowel obstruction, surgical intervention is most often required. In patients with abdominal pain or gastrointestinal bleeding, radiographic imaging, endoscopy, or even virtual colonography may allow discovery of polyps that can be resected either endoscopically or by enterotomy, depending on their size [6].

Advances in capsule and double-balloon endoscopy have markedly improved surveillance and management of polyposis of the small intestine.

Although the precise role of these techniques in the management of patients with PJS has not yet been fully established, they will be undoubtedly proven as useful tools in the non-surgical treatment of patients with polyps of the small intestine [20], and might replace surveillance performed by small-bowel barium follow-through [8].

Conclusions

The presence early in infancy of lentigines on the lips, buccal mucosa and perioral, which are small, well-demarcated and dark brown to blue-black in color, should alert the clinician to Peutz–Jeghers syndrome.

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Received: January 4th, 2008

Accepted: March 25th, 2008