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Peutz–Jeghers syndrome in a 14-year-old boy: case report and review of the literature

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Summary. Peutz–Jeghers syndrome (PSJ) is a relatively rare but well-recognized condition, with a prevalence of approximately one in 120 000 births in the USA. It is generally inherited as an autosomal dominant trait, although 35% of cases are new mutations. This disorder is characterized by melanocytic macules on the hands, feet, peri–oral skin and oral mucosa, and multiple gastrointestinal hamartomatous polyps. People with PSJ have an increased risk for developing a variety of malignant tumours. The aim of the present study was to report one case of PSJ in a 14-year-old boy with mucocutaneous pigmentation associated with duodenal hamartomatous polyps.

Introduction

Peutz–Jeghers syndrome (PJS) is a rare inherited disease characterized by gastrointestinal hamartomatous polyposis associated with mucocutaneous melanin pigmentation [1–5]. Peutz first described the entity in 1921, associating the mucocutaneous pigmentations with the intestinal polyps [3]. However, a definitive characterization of the syndrome was only accepted after a detailed description was reported by Jeghers *et al*. in 1949 [4]. Bruwer *et al*. finally defined the disease as PJS in 1954 [5].

The disease occurs among males and females, with no ethnic or racial predisposition [2]. Although multiple polyps in the gastrointestinal tract are the main feature of this syndrome [1,2,6–8], patients typically have mucocutaneous pigmentation, which is often noticed before the polyps are diagnosed [7]. The melanin-containing skin lesions are brown to black [8,9], and most commonly found around the mouth, lips, nose, hands, feet and genital region [2,7,9].

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Several reports have described the association of PJS with malignancy in different locations, such as the gastrointestinal tract, pancreas, breast, ovary, testis, uterine cervix and gallbladder. An increased prevalence of malignant tumours, approximately 18 times higher than that seen in nonaffected people, has been reported in previous studies [7,9–11]. However, no malignant transformation has been described in the pigmented areas of PJS [2].

Case report

A 14-year-old boy was referred to the Oral Diagnosis Clinic (OROCENTRO) at the School of Dentistry, State University of Campinas, Piracicaba, Brazil, for evaluation of oral spots. His mother reported that the mucocutaneous pigmentation had appeared when he was 3 years old. His past medical history revealed that he had developed abdominal pain at the age of 6 years. Endoscopy had been performed when he was 12 years old, and eight polyps were found on the lumen of duodenum; these were surgically removed. His family history revealed that his grandmother had also undergone surgery for resection of intestinal polyps. In addition, one cousin had died because of intestinal cancer.

On physical examination, the patient showed multiple pigmented macules measuring approximately

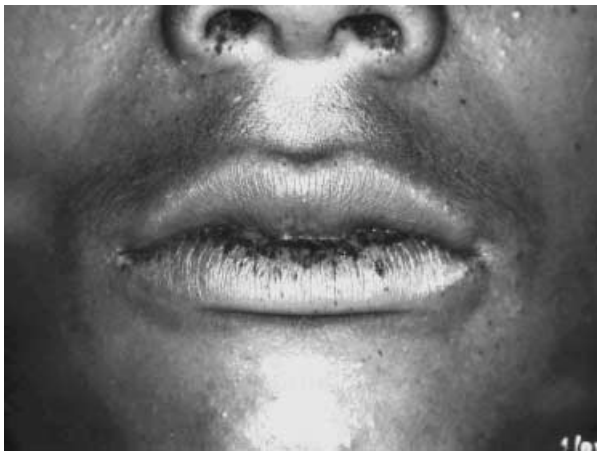

Fig. 1. Melanotic macules on the lips, nose and skin of the face.

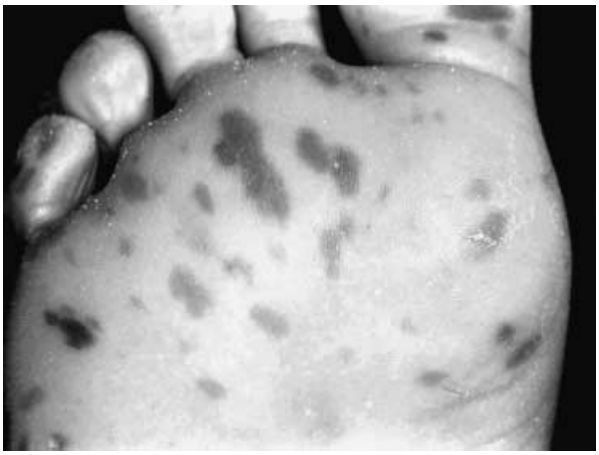

Fig. 3. Pigmented spots on the right planta pedis.

Fig. 2. Pigmented spots on the palm of the right hand.

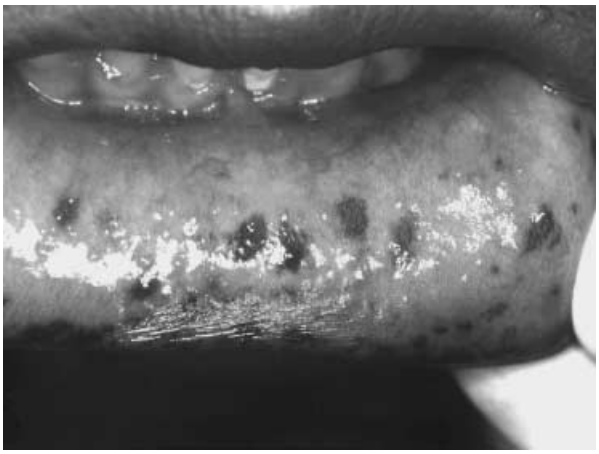

Fig. 4. Intraoral manifestation with multiple melanotic macules on the lower lip.

0·1–0·3 cm, involving the perioral area (Fig. 1), hands (Fig. 2) and feet (Fig. 3). Oral manifestations were also noted, particularly on the buccal mucosa, hard and soft palate, and lips (Figs 4 & 5). Biopsy of one macule from the mucosa of the subject's lower lip showed hyperpigmentation of the basal layer.

Histological examination of the material obtained from the oesophagogastro-duodenoscopic procedure 2 years earlier had shown a glandular epithelium supported by a branching framework of well-developed smooth muscle, which was contiguous with the muscular mucosa [Fig. 6]. The clinical and pathological features allowed the diagnosis of PJS. The patient is currently being reviewed for further evaluation of the mucocutaneous macules and intestinal polyps.

Discussion

Peutz–Jeghers syndrome is genetically transmitted, with a family history being present in the majority of cases. However, isolated cases may also occur [2,7,8]. The present subject had two cases in his family history suggestive of PJS. His maternal grandmother had a history of intestinal polyps and one cousin had intestinal cancer. Both were related through the patient's mother and both were also reported to have spots on the skin.

Gastrointestinal polyps and mucocutaneous pigmentation are the main features of the syndrome, occurring in more than 95% of patients [7,8]. About one-third of patients with PJS show their first clinical signs during their first decade and more than 60% before the age of 20 years [2,9]. The case

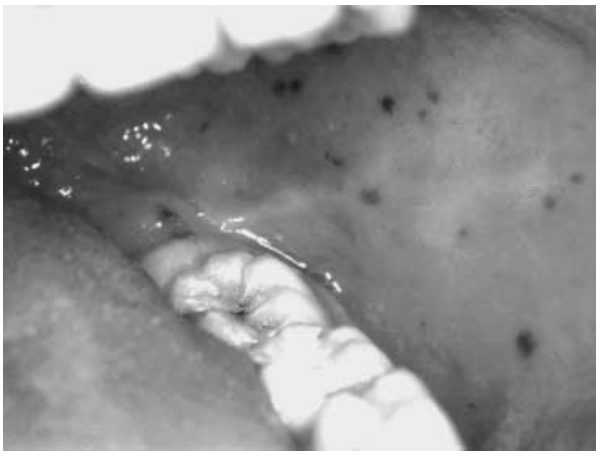

Fig. 5. Buccal mucosa showing multiple pigmented macules.

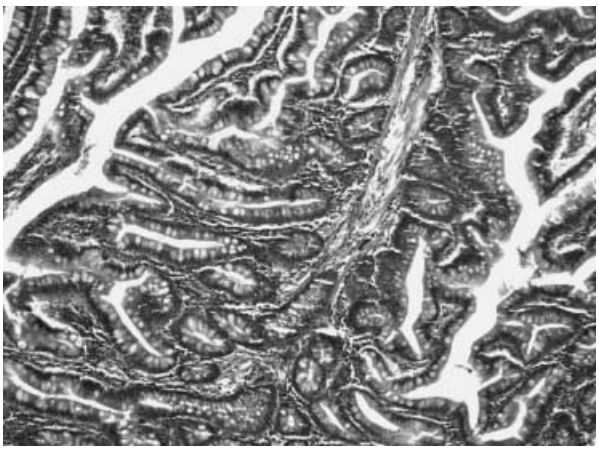

Fig. 6. Microscopic examination of the intestinal polyps showing benign overgrowth of glandular epithelium (hematoxylin-eosin, ×100).

reported in this paper followed the same pattern since both symptoms appeared during childhood. The melanocytic macules had appeared at the age of 3 years, whereas the intestinal polyps were diagnosed at the age of 12 years.

The polyps occur essentially in the gastrointestinal tract, with 70–90% of patients having them in the small bowel. Polyps can also occur outside the gastrointestinal tract; for example, in the nose, uterus, respiratory tract and gallbladder [7,12]. Symptoms attributed to the polyps are nonspecific, with abdominal pain and mild distension being the most common [7,11]. The majority of cases with polyps require surgical treatment because of the risk of haemorrhage, anaemia and abdominal pain [9,11]. In the present case, the only symptom related to intestinal polyps was abdominal pain.

Melanocytic macules on the skin affect the extremities in about 50% of patients. The lesions resemble freckles, but they do not wax and wane according to sun exposure, as true freckles do [12]. These spots generally develop during the first decade of life [6,8] and usually fade from the third decade onwards [7]. However, intraoral macules tend to persist [2]. In the present case, the patient had macules on his hands and feet, and perioral skin; intraorally, they affected the buccal mucosa, hard and soft palate, and lips.

The intraoral macules represent an extension of the perioral lesions [9]. The small, brown-to-black macules primarily affect the vermilion border of the lips, the labial and buccal mucosa, and the tongue [2,7–9]. Although this alteration can be seen in more than 90% of cases, the number and extension of the lesions may vary from patient to patient [7,9].

Microscopically, the pigmented macules are characterized by slight acanthosis of the epithelium with elongation of the rete ridges [9]. The melanocytes may have elongated dendritic processes, although no apparent increase in melanocyte number is detected [2,9]. In addition, no malignant transformation has been described in hyperpigmented areas associated with PJS [2]. The melanotic macule removed from the present patient displayed similar features to those reported previously.

Although the polyps do not appear to be premalignant, gastrointestinal adenocarcinomas develops in 2–3% of affected patients [13,14]. Unusual histological features of the polyps may be mistaken for tumour infiltration or distant metastasis, and some reports of small bowel cancers in patients with PJS may be attributable to overdiagnosis of malignancy in polyps [7,13,15–17]. The intestinal polyps in the case reported in this study showed many histopathological similarities to cases which have been previously reported [9,12,13], including a benign overgrowth of the intestinal glandular epithelium supported by a core of smooth muscle. The mucosal component consisted of the normal cell population, but crypts, glands and villi were organized in abnormal patterns, producing pseudo-invasive features.

Recently, the genetic locus of this condition was identified on chromosome 19p [18]. More recently, two independent groups of investigators have defined the mutated gene responsible for PJS [19,20]. This gene, *LKB1(STK11)*, has a strong homology with a cytoplasmatic *Xenopus*, serine/threonine protein kinase *XEEK1* [18], and a weaker similarity with

many other protein kinases. This is the first gene that predisposes to cancer as a result of disabling to encoded kinase activity, and consequently, PJS is the first cancer-susceptibility syndrome to be identified [19].

In summary, the present paper emphasizes the importance of the participation of dentists in the diagnosis of systemic alterations, particularly in subjects in whom the oral manifestations are the first signs. In the present case, although the oral spots appeared when the boy was 3 years old and abdominal pain was present 3 years later, the diagnosis of intestinal polyps was performed only at the age of 12 years, with the final diagnosis of PJS being established 2 years later. In addition, considering the higher risk for malignancy, patients with PJS need to be regularly screened for early diagnosis of this or other gastrointestinal complications. With the discovery of the genetic alteration in PJS, clinicians may be better able to manage and follow-up patients affected by this syndrome in the future.

Résumé. Le syndrome de Peutz-Jeghers (PSJ) est une maladie relativement rare mais bien reconnue, avec une prévalence de environ 1 sur 120 000 naissances aux Etats-Unis. Le mode de transmission est généralement autosomique dominant, bien que 35% des cas soient des nouvelles mutations. Ce désordre est caractérisé par des macules mélanocytiques sur les mains, les pieds, la peau péri-orificielle, la muqueuse buccale et des polypes hamartomateux gastro-intestinaux multiples. Les patients présentent un risque accru de développer différentes tumeurs malignes. L'objectif de cette étude a été de décrire un cas de PSJ chez un garçon de 14 ans avec pigmentation cutanéo-muqueuse associée à des polypes hamartomateux duodénaux.

Zusammensassung. Peutz-Jeghers Syndrom (PJS) ist eine seltene aber gut abgegrenzte Erkrankung mit einer Inzidenz von etwa 1 bei 120 000 Geburten in den U.S.A. Der Erbgang ist autosomal dominant, allerdings sind 35% der Fälle Neumutationen. Die Erkrankung ist gekennzeichnet durch pigmentierte Flecken an Händen, Füßen, perioraler Haut, oraler Mukosa und zahlreiche hamartomatöse Polypen des Gatrointestinaltraktes. Die Patienten weisen ein erhöhtes Risiko der Entstehung maligner Tumoren auf. In der vorliegenden Arbeit wird ein Fall eines 14jährigen Jungen mit PJS mit mukokutanen Pigmentierungen und Duodenalpolypose vorgestellt.

Resumen. El síndrome de Peutz-Jeghers (SPJ) es una patología relativamente rara pero bien conocida con una prevalencia de aproximadamente 1 de cada 120 000 nacimientos en los Estados Unidos. Generalmente se hereda como un rasgo autosómico dominante, aunque el 35% de los casos son nuevas mutaciones. Esta alteración se caracteriza por máculas melanóticas en las manos, pies, piel periorificial, mucosa bucal y múltiples pólipos hamartomatosos. Los pacientes tienen un mayor riesgo de desarrollar una variedad de tumores malignos. El objetivo de este estudio fue informar de un caso de SPJ en un varón de 14 años con pigmentación mucocutánea asociada a pólipos hamartomatosos en duodeno.

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