Angular cheilitis and oral pigmentation as early detection of Peutz-Jeghers syndrome

Maharani Laillyza Apriasari¹ and Amy Nindia Carabelly²
¹ Departement of Oral Medicine
² Departement of Oral Pathology
Faculty of Dentistry, Universitas Lambung Mangkurat
Banjarmasin - Indonesia

ABSTRACT

Background: Peutz-Jeghers syndrome (PJS) is an inherited autosomal dominant disease determined by a mutation localized at 19p13.3 characterized by the occurrence of gastrointestinal hamartomatous polyps in association with mucocutaneous hyperpigmentation. The manifestation of PJS may first be encountered by a dentist during routine examination due to the presence of pigmented spots in the oral cavity. Purpose: To prevent a high risk of PJS, the dentist must establish its oral manifestation through early detection. Case: A 14-year-old male patient attended complaining of a week-long pain at the corners of the lips. An extra-oral exam revealed fissure lesions, redness, white crust and pain. The patient had experienced bleeding in his bowel movements, abdominal pain, nausea and vomiting since childhood. A number of black, painless, macular lesions, some 1-3 mm in diameter, were present on the upper lips, lower lips, fingers and palms. Case management: The patient was referred for a complete blood count check. The results obtained confirmed him to be suffering from severe anemia and he was, therefore, referred to an internist for treatment for PJS. Conclusion: It can be concluded that the early detection of PJS is crucial in order that the patient receives prompt treatment.

Keywords: anemia; gastrointestinal polyps; hyperpigmentation; malabsorption; Peutz-Jeghers syndrome

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is an inherited autosomal dominant disease determined by a mutation localized at 19p13.3. PJS results in polyps and mucocutaneous pigmentation evident since childhood or early adulthood.¹² In the United States, PJS is a rare disease with an incidence rate of between one case per 60,000 people and one case per 300,000 people. PJS has a prevalence of 1 in 120,000 live births, irrespective of race or gender. The mutant gene STK11 (also known as LKB1) is located at 19p13.3. STK11 is a tumor-suppressing, germline mutation gene which is documented in up to 70–80% of patients with PJS and as many as 15% of cases show complete or partial eradication of STK11.³⁵ Diagnosis of PJS is based on clinical findings and the histopathological patterns of polyps. Histologically, these lesions show increased basiler melanin without a rise in the number of melanocytes.³ The manifestation of PJS may first be encountered by a dentist during routine examination in the form of pigmented spots in the oral cavity. Round, oval or irregular, 1-5 mm diameter patches of brown or almost black pigmentation, irregularly distributed throughout the oral mucosa, gums, hard palate and lips are observed. The pigmented facial maculae, particularly encountered around the nose and mouth, are smaller.¹⁶ Melanotic macules may be present in other body parts including the extremities, rectum, intranasal mucosa and conjunctiva.⁶ The intensity of macular pigment is unaffected by exposure to sunlight. Fading or disappearance of the spots is usually observed in older age.⁵⁷
PJS is characterized by the occurrence of gastrointestinal hamartomatous polyps in association with mucocutaneous hyperpigmentation. This condition is usually accompanied by bowel obstruction and severe abdominal pain. Acute upper gastrointestinal bleeding and chronic fecal blood loss may be present during the course of the disease.

PJS is associated with significant morbidity, variable clinical causes and considerable predisposition to gastrointestinal and non-gastrointestinal malignancies. There is also an increased risk of malignant transformation of internal organs such as the gastrointestinal tract, pancreas, breast and thyroid. The purpose of this article is to prevent the high risk condition of PJS whose oral manifestation dentists must recognize through early detection.

**CASE**

A 14-year-old male patient sought medical treatment having experienced week-long pain at the corners of the lips. An extra-oral examination revealed fissure lesions, redness, a white crust and pain. The patient had suffered a history of frequent abdominal pain, nausea and vomiting since childhood, while bleeding had accompanied his bowel movements for a week. The lesions at both corners of the lips were diagnosed as angular cheilitis. There were a number of black, painless, macular lesions, 1-3 mm in diameter on the upper and lower lips, as well as on the fingers and palms and the buccal and labial mucosa. These lesions had first appeared in infancy and had subsequently increased considerably in size. In terms of anamnesis, the patient complained of often having experienced dizziness and light-headedness. According to the patient’s account, during his infancy, his father had passed away due to unknown causes. An extra oral examination showed paleness on the face, palms and conjunctiva.

**CASE MANAGEMENT**

The definitive diagnosis of lesions at both corners of the lips was angular cheilitis which constituted the main reason for the patient having consulted a dentist. The patient was prescribed miconazole gel to be applied topically four times a day for two weeks. It was suspected that the patient was suffering from angular cheilitis due to anemia, a diagnosis confirmed by a history of frequent, week-long bouts of abdominal and bowel pain accompanied by bleeding. The results of an examination of alleged extra-oral melanotic lesions on the surface of the lips, hands, and labial and buccal mucosa represented the clinical manifestations of PJS. The patient was referred for a complete blood count, the results of which revealed the patient as suffering from severe anemia. Therefore, the patient was referred to an internist for treatment for PJS.

**DISCUSSION**

The diagnosis of pigmented oral lesions and perioral tissues is challenging. Even though epidemiology can assist in orientating the clinician and certain lesions may be diagnosed on the basis of clinical manifestation, but the definitive diagnosis is usually based on histopathologic evaluation.

PJS lesions within the oral mucosa and perioral are accompanied by several symptoms of gastrointestinal diseases. Oral lesions may occasionally occur before the onset of GI disease, be present during the development of...
the disease or persist in a worsening form after the disease has been cured.\textsuperscript{9}

Patients with PJS often have a history of intermittent abdominal pain due to small bowel intussusceptions caused by polyps usually found in the gastrointestinal tract. On occasion, the oral lesions are similar to gastrointestinal lesions while, at other times, oral changes are caused by gastrointestinal disease which results in malabsorption disorders.\textsuperscript{9} Lesions can also occur in other extraintestinal tissue such that in the kidneys, ureter, gall bladder, bronchial tree and nasal passages.\textsuperscript{1}

The cause of PJS is related to the mutation of the STK11/ LKB1 (serine/threonine kinase 11) tumor suppressor gene located in chromosome 19p13. STK11 is a tumor suppressing gene. Over-expression induces the arrest of cell growth at the G1 phase of the cell cycle and somatic inactivation of the allele of STK11. It is often observed in polyps or cancers in PJS patients.\textsuperscript{3}

The STK11/LKB1 encodes a 433 amino acid, ubiquitously expressed protein with a central catalytic domain, and regulatory N- and C-terminal domains. The function of LKB1 is to regulate downstream kinases. It includes adenosine monophosphate–activated protein kinase (AMPK), together with the related kinases MARK1 through MARK4 and brain-specific kinases of the amphib-defective kinase SAD. These are involved in cellular metabolic regulation-stress response and cellular polarity through tubulin stabilization, tight junction formation and E-cadherin localization. This occurs between the LKB1 pathway along with other tumor suppressor p53 and tensin homologue PTEN. The abnormalities in LKB1 function causes polyposis together with a loss of heterozygosity that influences tumorigenesis. The gene mutation is variable, resulting in a spectrum of phenotypic manifestations among patients with Peutz-Jeghers syndrome (localization of polyps or cancers in PJS patients).\textsuperscript{3}

A diagnosis of anemia was supported by the patient’s clinical symptoms such as fatigue and dizziness, as well as angular cheilitis and tongue depapilation. Anemia causes disruption to the circulation of oxygen around the body whose tissues receive it from red blood cells. If the number of such cells decreases, this will cause reduced hemoglobin resulting in a lack of oxygen. Chronic anemia produces clinical manifestations in patients, including: fatigue, weakness and palpitations.\textsuperscript{5,12}

Anemia pathophysiology which leads to angular cheilitis is a form of anemia that causes enzyme activity in the mitochondria in the cell to decrease by disrupting the transport of oxygen and nutrients. This impairs cellular immunity, reduces the activity of bactericidal polymorphonuclear leukocytes, resulting in an inadequate antibody response and abnormalities in the epithelial tissues. Anemia causes the activity of enzymes in cell mitochondria to decrease by disrupting the transport of oxygen and nutrients, thus inhibiting the differentiation and growth of epithelial cells. As a result, the process of terminal differentiation of epithelial cells toward the stratum corneum will be impeded, and subsequent oral mucosa will be thinner because of the absence of normal keratinization, atrophy and greater susceptibility to ulceration. This causes depapilation of the tongue in patients, a condition often occurring in individuals suffering from a deficiency of vitamin B12, folate, and iron.\textsuperscript{12-14}

The therapy used to treat angular cheilitis consists of the topical application of Miconazole gel four times a day for two weeks. Supplements are administered orally as a maintenance dose once a day for a month. The supplements contain 250 mg of Fe gluconate, 0.2 mg of manganese sulfate, 0.2 mg of copper sulfate, 50 mg of vitamin C, 1 mg of folic acid and vitamin B12 is prescribed for nutritional deficiency-related anemia. These supplements contain ferrous gluconate which is iron essential for energy metabolism. Manganese sulfate and copper sulfate are both substances that support the absorption of iron by the intestines and subsequent introduction into the bloodstream through blood serum. Vitamin C supports the liquidiising of iron facilitating its easy absorption by the intestines.
Vitamin B12 and folic acid are important cofactors for blood cell DNA synthesis. The patient was referred to an internist for treatment of digestive disorders.1,13,14

Patients with PJS are at greater risk of developing gastrointestinal and non-gastrointestinal malignancies. Other non-gastrointestinal sites of malignancy include: the pancreas, lung, breast, uterus, cervix, ovary, testis and thyroid.1 A common recommendation for PJS patients is that they undergo not only gastrointestinal multiple polyp examination, but also regular lifelong cancer screening.

Early detection and proper observation are vital in order to minimize the risk of carcinoma.1 The management of PJS has to be undertaken by an interdisciplinary team and aids in the early detection and monitoring of this disease.2 In the final stage of the management of PJS, after oral lesion treatment, the patient was referred to an internist for treatment of this systemic condition. It can be concluded that the early detection of PJS is important to enable dentists to provide patients with appropriate therapy.

REFERENCES