



Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

MEDICAL MANAGEMENT AND PHARMACOLOGY UPDATE

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Medical management update: Peutz Jeghers syndrome

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Peutz Jeghers syndrome (PJS) is an autosomal dominant disease characterized by hamartomatous polyposis and distinct mucocutaneous pigmentation. PJS is associated with an increased risk for several cancers and other complications such as small intestine intussusception, short bowel syndrome, and anemia. Medical management mainly consists of treatment of the polyps and surveillance. This medical management update will review clinical concepts, therapeutic advances, and emphasize features of PJS important to the oral health care provider. (**Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:5-11**)

Peutz Jeghers syndrome (PJS) is an autosomal dominant disease characterized by polyps and mucocutaneous pigmentation that typically manifests in childhood and early adulthood, with a common presentation of bowel obstruction and severe abdominal pain. Diagnostic criteria include hamartomatous polyps, increased melanin deposits, small bowel polyposis, and a family history of the syndrome. Treatment usually involves surgical removal of the polyps, and complications of the disease involve a higher predisposition for several types of malignancies.^{1,2} Manifestations of the disease may first be encountered by the dental professional during routine examination by the presence of melanotic pigmented spots in the oral cavity. Because oral manifestations may precede gastrointestinal onset, oral health care providers may function as part of an interdisciplinary team and aid in early detection, management, and surveillance of this syndrome.

EPIDEMIOLOGY

In 1921, Jan Peutz, a Dutch physician, published a case report on a family with gastrointestinal polyposis and distinctive pigmentation of the skin and mucous membranes.³ In 1949, an American physician named Harold Joseph Jeghers published a detailed description of patients exhibiting intestinal polyposis and abnormal pigmentation of the skin,⁴ which led to the identification of the syndrome named after both physicians.

PJS is, after juvenile polyposis, the most common hamartomatous syndrome among hereditary gastrointestinal polyposis syndromes.^{5,6} Its prevalence is approximately 1 in 200,000, with no evident gender or racial predilection.^{7,8} The average age of diagnosis of PJS was 22 years in a review of 75 PJS patients.² The median time to initial presentation with gastrointestinal polyps is approximately 11 years of age,⁹ whereas mucocutaneous manifestations usually occur in infancy and tend to disappear in late adolescence.¹⁰

ETIOLOGY

Inheritable variations in the serine/threonine kinase gene (STK11/LKB1), located in the short arm of chromosome 19p13.3, are responsible for the pathogenesis of most cases of PJS.^{11,12} STK11/LKB1 gene is known to be located both in the nucleus and cytoplasm and it has been suggested to act as a tumor suppressor gene.¹³⁻¹⁵ Deletion, insertion, or single base pair substitutions have been described, causing frame-shift and truncation of the protein and leading to a loss of its expression, and reduced kinase activity.^{12,16-19} The

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Fig. 1. Pigmentation of Peutz Jeghers syndrome (PJS) affecting the facial skin, nose, and lips. (Courtesy of Dr. Asadur J. Tchekmedyan, Department of Gastroenterology, National Medical School, Montevideo, Uruguay.)

germline mutation is identified in 30% to 80% of PJS patients. The type of mutation and where it occurs within the gene sequence correlates with onset of PJS symptoms and its association with malignancies.^{9,20} Failure to identify detectable variations in SKT11 may suggest that patients without defects in this gene might have a less severe manifestation of PJS,⁹ and indicate the existence of one or more genes that may also contribute to the pathogenesis of PJS.²¹

CLINICAL PRESENTATION

Clinical gastrointestinal manifestations of PJS include hamartomatous polyps in the small intestine, with the jejunum as the most common location, although involvement of stomach and large bowel has also been described.⁹ These polyps usually appear during the first decade of life, and patients often become symptomatic between the ages of 10 and 30 years.²² Their size can increase significantly, causing intussusceptions and bowel obstruction, manifesting as severe abdominal pain, and gastrointestinal and rectal bleeding with anemia.² In a minority of patients, PJS polyps have been reported in the renal pelvis, urinary bladder, lungs, and nares.⁸

Manifestations of PJS also include mucocutaneous hyperpigmentation presenting as dark macules on various facial, body, and oral surfaces (see Figs. 1 and 2). The characteristic pigmentation is present in more than 90% of the patients with PJS.²³ Pigmentation usually appears at an early age and fading of pigmented spots tends to occur during puberty. Macules located on the buccal mucosa may persist and potentially aid in the diagnosis of the syndrome if onset of the disease occurs later in life.^{7,10}

The differential diagnosis for conditions presenting with polyposis includes 7 other inherited polyposis



Fig. 2. PJS pigmentation affecting the facial skin, lips, and labial and buccal mucosa. (Courtesy of Dr. Asadur J. Tchekmedyan, Department of Gastroenterology, National Medical School, Montevideo, Uruguay.)

syndromes: familial juvenile polyposis, hereditary mixed polyposis, Cowden's syndrome, Cronkhite-Canada syndrome, familial adenomatous polyposis syndrome, Bannayan-Ruvalcaba-Riley syndrome, and basal cell nevus syndrome²⁴ (see Table I).

Several conditions should be considered when assessing patients with multifocal pigmented lesions. The differential diagnosis of pigmented lesions includes Leopard syndrome, Laugier-Hunziker syndrome, Carney complex, and Cowden's syndrome^{23,25} (see Table II).

DIAGNOSIS

The following are the diagnostic criteria for PJS:

1. Three or more histologically confirmed benign hamartomatous polyps.^{5,26,27} The histologic characteristic of Peutz-Jeghers polyps includes a connective tissue core infiltrated by smooth muscle, presence of goblet and paneth cells, and smooth muscle strands within the stroma. These polyps are characterized by a muscular core that extends into the superficial epithelial layer forming a tree-like framework, termed *arborization*.^{28,29} The diagnosis of the hamartomatous polyps can be accomplished by using different diagnostic tests such as upper endoscopy, colonoscopy, flexible sigmoidoscopy, and small

Table I. Differential diagnosis for polyposis

- Familial juvenile polyposis
Multiple juvenile polyps primarily in the colorectum.
No mucocutaneous pigmentation.
Malignant predisposition: adenocarcinoma (colorectal, gastric, pancreas).
- Hereditary mixed polyposis syndrome
Usually 15 or fewer polyps in colon and rectum.
No mucocutaneous pigmentation.
Malignant predisposition: adenocarcinoma (colorectal).
- Cowden's syndrome
Gastrointestinal hamartomas.
Oral papillomatous lesions, facial trichilemmomas, keratosis of palms and plantar surfaces, and mucosal lesions.
Malignant predisposition: adenocarcinoma (breast, uterus), follicular carcinoma (thyroid), carcinoma (ovary, cervix, renal pelvis).
- Cronkhite-Canada syndrome
Gastrointestinal polyposis.
Alopecia, dermal pigmentation, and atrophy of the nail beds.
Malignant predisposition: adenocarcinoma (colorectal, gastric).
- Familial adenomatous polyposis (Gardner's syndrome)
Multiple adenomatous polyposis in the large bowel.
Benign extra-intestinal lesions (lipomas, fibromas, sebaceous and epidermoid cyst, osteomas, desmoids, occult radio-opaque jaw lesions, dental abnormalities, retinal pigment hypertrophy and nasopharyngeal angiofibroma).
Malignant predisposition: adenocarcinoma (colorectal, gastric, duodenum, pancreas), papillary carcinoma (thyroid), hepatoblastoma (liver), medulloblastoma (brain).
- Bannayan-Ruvalcaba-Riley syndrome
Hamartous intestinal polyps.
Macrocephaly, developmental retardation, genital pigmentation, hemangiomas, lipomas and lipid myopathy.
Malignant predisposition: adenocarcinoma (breast, uterus), follicular carcinoma (thyroid), carcinoma (ovary, cervix, renal pelvis).
- Basal Cell Nevus syndrome (Gorlin syndrome)
Multiple gastric hamartous polyps.
Multiple basal cell carcinomas, macrocephaly, frontal bossing, hypertelorism, bifid ribs, bone cyst (especially in the mandible), meningioma (>90% are benign).
Malignant predisposition: basal cell carcinoma (skin), rhabdomyosarcoma (musculoskeletal), medulloblastoma (brain).

From Calva D, Howe JR. Hamartomatous polyposis syndromes. *Surg Clin N Am* 2008;88:779-817; Al-Sukhni W, Aronson M, Gallinger S. Hereditary colorectal cancer syndromes: familial adenomatous polyposis and Lynch syndrome. *Surg Clin N Am* 2008;88:819-44; Manfredi M, Vescovi P, Bonanini M, Porter S. Nevoid basal cell carcinoma syndrome: a review of the literature. *Int. J Oral Maxillofac Surg* 2004;33:117-24; Bhattacharjee P, Leffell D, McNiff JM. Primary cutaneous carcinosarcoma arising in a patient with nevoid basal cell carcinoma syndrome. *J Cutan Pathol* 2005;32:638-41.

bowel x-ray series. Distal small bowel polyps represent a diagnostic challenge, because they may be outside of the scope of conventional endoscopy, and barium contrast imaging may lack sensitivity to identify smaller size polyps. New technology like wireless capsule endoscopy and double-balloon

Table II. Differential diagnosis of pigmented lesions similar to Peutz Jeghers syndrome mucocutaneous lesions

- Leopard syndrome
Lentigines, brown to black, 1 to 2 mm in size.
Electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retarded growth, and deafness.
Malignant predisposition (rare): myelodysplasia, leukemia, neuroblastoma, melanoma.
- Laugier-Hunziker syndrome
Melanotic pigmentation of oral mucosa, palmoplantar area, fingers, toes, and genital region.
No presence or family history of hamartomatous polyposis.
Malignant predisposition: none reported.
- Carney complex
Pale brown to brown lentigines.
Myxomas of the skin, heart, and breast; endocrine tumors; and schwannomas.
Malignant predisposition: follicular or papillary carcinoma (thyroid).
- Cowden's syndrome
Mucocutaneous lesions, oral cobblestoning, and oral papillomatosis.
Hamartomatous intestinal polyps.
Malignant predisposition: adenocarcinoma (breast, uterus), follicular carcinoma (thyroid), carcinoma (ovary, cervix, renal pelvis).

From Calva D, Howe JR. Hamartomatous polyposis syndromes. *Surg Clin N Am* 2008;88:779-817; Sarkozy A, Digilio MC, Dallapiccola B. Leopard syndrome. *Orphanet J Rare Dis* 2008;3:13; Sabesan T, Ramchandani PL, Peters WJ. Laugier-Hunziker syndrome: a rare cause of mucocutaneous pigmentation. *Br J Oral Maxillofac Surg* 2006;44:320-1; Callender GG, Rich TA, Perrier ND. Multiple endocrine neoplasia syndromes. *Surg Clin North Am* 2008;88:863-95.

endoscopy report higher sensitivity in visualizing and identifying small polyps and polyposis syndromes.³⁰⁻³² Capsule endoscopy is a pill-sized video capsule that captures and transfers images visualized during the endoscopy.³³ Double-balloon endoscopy is a technique that includes 2 balloons attached to a tube that slides over the endoscope. The balloons, when inflated and deflated, are able to trap the small intestine allowing the scope to travel farther to better visualize the small bowel.³⁴

2. Any number of hamartomatous polyps with a family history of **PJS**.^{5,26,27}
3. Mucocutaneous pigmentation with a family history of **PJS**.^{5,26,27} The mucocutaneous pigmentation is characterized by increased number of melanocytes at the dermo-epidermal junction, with increased melanin in the basal cells.
4. Any number of hamartomatous polyps and mucocutaneous pigmentation.^{5,26,27}

Thus, the diagnosis of **PJS** and other hamartomatous polyposis syndromes remains primarily a clinical pro-

cess. The endoscopic findings, mucocutaneous features, and family history should guide the clinician toward the diagnosis, which can be confirmed by use of genetic testing. It is recommended to have screenings in at-risk individuals (first-degree relatives of PJS patients) beginning at birth, with observation of mucocutaneous pigmentation, precocious puberty, and ovarian and testicular tumors.³⁵ Asymptomatic at-risk individuals without any signs of the disease at age 8 should be offered genetic testing for the mutation of the *STK11/LKB1* gene.^{9,26,27} High morbidity in PJS patients by age 10 caused by laparotomies for small bowel obstructions explains why screening at such a young age is recommended.³⁶ Mutation is assessed by direct sequencing of the gene from peripheral blood or buccal mucosa DNA.⁸ If a mutation in *STK11/LKB1* is found, colonoscopies and upper endoscopies every 2 to 3 years are indicated.²²

MEDICAL MANAGEMENT

The medical management of PJS mainly consists of surveillance and treatment of the hamartomatous polyps.¹ Recommendations for treatment have evolved over the past decade, focusing more on conservative treatment rather than radical intestinal resections performed in the past, and emphasizing early screening and cancer detection in patients diagnosed with PJS.³⁷ Upper endoscopies are recommended every 2 years for surveillance and removal of PJS polyps.

Magnetic resonance imaging has shown success as a surveillance modality for small intestinal screening.³⁸ Testicular examinations in males, as well as mammograms, Pap smears, and transvaginal ultrasound for females are performed every 1 to 2 years for early cancer detection.³⁵ Complete blood cell counts to detect anemia caused by blood loss and pancreatic ultrasonography are also included in routine cancer screening.³⁹

Commonly, PJS patients present with intussusception and obstruction of the small bowel, which usually resolve without intervention, but if surgical treatment is required, conservative surgery should focus on removing polyps that are causative of the intussusceptions.²⁹ Treatment consists of polypectomy of lesions larger than 1 cm found during endoscopic surveillance.¹ Removal of smaller polyps can be achieved by electrocautery snare.⁶

Chemoprevention of polyps with nonsteroidal anti-inflammatory drugs (NSAIDs) has been advocated for patients with familial adenomatous polyposis (FAP) who have undergone polypectomy or were waiting for surgical treatment,⁴⁰ but has not been recommended for other polyposis syndromes, including PJS. NSAIDs that have demonstrated significant regression of existing adenomatous polyps, suppression of new polyps, and reducing the incidence of colorectal cancer in FAP

patients are celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, and sulindac.^{41,42} Celecoxib is the only NSAID that has been approved by the US Food and Drug Administration for adjuvant treatment of patients with FAP.⁴³ Significant gastrointestinal side effects such as ulceration and perforation of the gastric mucosa as well as increased risk of cardiovascular side effects are associated with COX-2 inhibitors and may be limiting factors for therapeutic use.⁴³ A small pilot study was conducted in which PJS patients were treated with celecoxib and showed reduction of the gastric polyp burden⁴⁴; however, further clinical trials are necessary to investigate the use of celecoxib as a chemoprevention agent for patients with PJS.

There is no standard treatment for mucocutaneous pigmentation that is present in most individuals with PJS. Treatment modalities for removal of these lesions, such as cryosurgery, electrodesiccation, dermabrasion, and carbon dioxide or argon laser ablation, commonly result in unsuccessful removal and scarring.⁴⁵ The use of Q-switched ruby laser (QSRL) has been proposed for the treatment of pigmented lesions by causing disruption of melanosomes.^{46,47} Promising results have been obtained by treating numerous pigmented conditions such as café au lait spots, nevus spilus, Becker's nevi, nevus of Ota, and other benign pigmented lesions with the QSRL⁴⁸⁻⁵¹; however, long-term follow up of cases and additional studies are needed to validate the effectiveness of QSRL to treat the mucocutaneous pigmentations common to PJS individuals.⁴⁶

PROGNOSIS

Increased numbers of polyps in PJS patients may result in abdominal pain, bleeding, and obstruction, which can be life-threatening.⁵² Intussusception involving the small intestine is the most frequent complication of PJS in younger patients¹; such intussusceptions often resolve spontaneously, however surgery may be required if they do not resolve. Repeated surgical removal of the intussusceptions, especially in the small intestine, could lead to an uncommon but debilitating disorder known as short bowel syndrome (SBS) that increases the risk for malabsorption, electrolyte imbalance, dehydration, and malnutrition. Patients with SBS, as well as other conditions that affect the gastrointestinal tract, are reported to have impaired health-related quality of life.⁵³

Iron-deficiency anemia in PJS patients is a result of acute upper gastrointestinal bleeding and chronic fecal blood loss related to the intussusception of large hamartomatous polyps. The anemia can be treated with supplemental iron, and no other intervention is often required.⁵⁴

Individuals affected with PJS are at increased risk for a wide variety of cancers.^{29,37,55,56} The most commonly involved organs are the gastrointestinal (GI)

tract (esophagus, stomach, small bowel, colorectum, and pancreas), lung, prostate, breast, and female reproductive organs.^{38,57} This association is based on the presence of the mutated *STK11/LKB1* gene in PJS patients as well as in patients diagnosed with different types of malignancies.^{11,58} Other studies have suggested that there is a difference in cancer risk in PJS individuals with and without undetectable mutations.⁵⁹ Some malignant tumors may also arise from the transformation of some hamartomas to dysplastic polyps.^{59,60} Outcome of PJS is related to the increased risk of malignancy development. Substantial morbidity is associated with development of malignancy and from SBS as a consequence of repeated bowel resections.

ORAL MANIFESTATIONS

Extra- and intraoral pigmentation is commonly found in PJS patients. Melanotic pigmented macules varying from 1 to 5 mm in size may be found on the vermilion border of the lips, labial mucosa, palate, and tongue.⁶¹ Presence of pigmentation may be noted at birth but usually develops early in childhood.²³ Oral lesions may be present before the onset of gastrointestinal disease. Intraoral lesions are usually flat, painless, and patients are often unaware of their existence.^{62,63} The size and color intensity of the brown to black freckle-like pigmentations found extraorally are not affected by sunlight unlike regular ephelides.⁴⁶ Skin pigmentation may fade late in puberty, but oral pigmentation is usually permanent.²³ There is no documented evidence that these mucocutaneous lesions have a higher incidence of premalignant transformation.

Infrequently, oral findings found in PJS patients are caused by systemic alterations secondary to the GI component of the disease. Decreased GI absorption owing to the presence of large hamartous polyps and intussusception as well as malabsorption caused by SBS after repeated surgical resections could induce iron-deficiency anemia.⁶⁴ With severe malabsorption, oral manifestations such as atrophic glossitis will often leave affected patients with a red, painful tongue that could interfere with taste sensation and adequate food intake.⁶⁵

DENTAL MANAGEMENT

Knowledge of the manifestations and complications of PJS is important for the oral health care provider. A detailed medical history, a thorough review of systems, and incidental findings of mucocutaneous pigmentation could aid in identifying this condition, and guide the patient toward appropriate consultation.

Modifications in the dental treatment for PJS patients compared with otherwise healthy patients are required only when they present with complications as discussed previously. Table III summarizes the recommendations,

Table III. Dental management of Peutz Jeghers syndrome patients

A. Preoperative considerations
<ul style="list-style-type: none"> ➤ Thorough review of medical history <ul style="list-style-type: none"> ● Attention to complains of abdominal pain and bleeding, in conjunction with complaint of noted changes in facial pigmentation "freckles." ● Family history of Peutz Jeghers syndrome (PJS). ➤ If known history of PJS <ul style="list-style-type: none"> ● Detailed history of the disease including date of diagnosis, course of disease, treatment to date, and medications. ➤ Thorough extraoral and intraoral examination <ul style="list-style-type: none"> ● Evaluate the presence and extension of mucocutaneous pigmentation. ● Evaluate soft tissue for presence of oral ulcers and glossitis as an indicator for anemia or severe malabsorption. ● Presence of anemia; defer elective surgical treatment if hemoglobin is less than 10 gm/dL. ➤ Consult physician to determine overall medical status of the patient <ul style="list-style-type: none"> ● Obtain complete blood count with differential and metabolic panel to evaluate hemoglobin, hematocrit, platelet count, and electrolytes. ● If unknown history of PJS but suspected, referral to primary physician or gastroenterologist is advised.
B. Postoperative considerations
<ul style="list-style-type: none"> ➤ Monitor patients for postoperative bleeding as well as appropriate wound healing. ➤ Periodic evaluation to assess changes in oral mucosa, dentition, and/or existing pigmentation is advised. ➤ Reinforce importance of proper oral hygiene and balanced diet.

based on the authors' opinions, which the oral health care provider should consider while managing PJS patients.

Patients with iron-deficiency anemia and SBS could present with extreme fatigue, pallor, weakness, and dizziness⁶⁶ and it is recommended to avoid long dental appointments and multiple procedures for these patients. In a patient with acute or chronic bleeding attributable to PJS, hemoglobin levels begin to decrease once iron is exhausted.⁵⁵ When hemoglobin and hematocrit levels reach below 10 g/dL and 30% respectively, there may be an increased risk for intraoperative bleeding and decreased wound healing.⁶⁷ If surgical procedures are anticipated, transfusion is recommended when hemoglobin levels are between 6.0 and 8.0 g/dL for patients with unknown risk factors. Blood transfusion should be also considered for patients manifesting physiologic indications for transfusion, such as hypotension and tachycardia.⁶⁸ Careful preoperative evaluation of the patient is mandatory and must account for the risks associated with transfusion, including bacterial contamination of blood products, transfusion-related acute lung injury, and transfusion reactions (hemolytic and nonhemolytic).⁶⁹ Recombinant human

erythropoietin and iron supplementation may be used to eliminate the need for blood transfusion.⁷⁰

PJS patients with SBS could have moderate to severe micronutrient deficiency, such as magnesium, zinc, electrolytes, fat-soluble vitamins, and essential fatty acids. Marked deficiency of essential fatty acids could lead to poor wound healing and alterations in platelet function.⁷¹ Patients with SBS are managed with varying doses of analgesics, opioid medications, antidiarrheals, and sleeping aids.⁵⁵ Counseling regarding drug-induced xerostomia and proper oral hygiene should be provided by the oral health care professional. The diet of patients with SBS should consist mainly of fat, protein, and decreased intake of carbohydrates.⁷² Counseling should be provided to the PJS with SBS to ensure optimal nutritional management and adequate balanced diet to maintain oral health.

CONCLUSION

PJS is an autosomal dominant disease characterized by the presence of hamartomatous gastrointestinal polyps and mucocutaneous pigmentation. Oral health care providers may play a significant role in detection and surveillance of PJS. Therefore, dental professionals should become familiar with this condition in order to provide optimal oral health care to individuals affected by this disease.

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