Peutz-Jeghers Syndrome and Management Recommendations

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Peutz-Jeghers syndrome (PJS) is an autosomal dominant disease caused by germline mutation of the serine threonine kinase 11 and characterized by hamartomatous polyps in the gastrointestinal tract and mucocutaneous melanin pigmentation. Patients with PJS are at increased risk for common and unusual types of gastrointestinal and nongastrointestinal tumors. This review analyzes currently available literature and describes the clinical characteristics of PJS, assesses the risk of malignancy in this disorder, and delineates management and surveillance recommendations for affected individuals.

Clinical Manifestations

History

Peutz-Jeghers syndrome (PJS) first appeared in the literature in the case report of Connor[1] published in 1895. Dr Connor, a British physician, described identical twin sisters with oral and labial pigmentation. Interestingly, one of the sisters died of intestinal obstruction at age 20 years and the other of breast cancer at age 59 years.[2,3] However, the presence of intestinal polyposis in these patients was not described. These twins were then illustrated by British surgeon J. Hutchinson[4] in 1896 and were subsequently known as the "Hutchinson twins." In 1921 Dr Johannes Peutz,[5] chairman of medicine at Johannes de Deo Hospital (Westeinde Hospital) The Hague, reported a Dutch family with gastrointestinal polyposis and distinctive pigmentation of the skin and mucous membranes and highlighted the inherited nature of the syndrome. In 1949 the combination of intestinal polyposis and pigmentation of the skin and mucous membranes was established as a distinct entity in a publication by Jeghers et al.[3] In 1954 A. Bruwer[6] coined the eponym "Peutz-Jeghers syndrome" in the title of his article on this disorder.[7]

Clinical Features

PJS is an autosomal dominant disease characterized by mucocutaneous pigmentation and hamartomatous polyps in the gastrointestinal tract.

This diagnosis can be made in patients with hamartomatous polyp(s) with at least 2 of the following clinical criteria also present: labial melanin deposits, a family history of the syndrome, and small bowel polyposis.[8] The syndrome appears equally in males and females and is found in all racial groups. Estimates regarding the incidence of PJS range from 1/50,000[9] to 1/200,000 live births.[10]

Pigmentation

PJS is characterized on physical examination by mucocutaneous pigmentation, usually occurring in infancy and fading in late adolescence[11] (Figure 1). The melanotic pigmented macules are dark brown or blue-brown, 1–5 mm in size, and located on the vermilion border of the lips (94% of patients), the buccal mucosa (66%), hands (74%), and feet (62%).[12] Periorbital, perianal, and genital pigmentation has also been noted. Present in more than 95% of affected patients, the pigmented spots are caused by pigment-laden macrophages in the dermis.[9] In contrast to PJS pigmentation, freckles are never located on the buccal mucosa or profusely around the nostrils and mouth.

Although similar type and location of pigmentation can be seen in the benign condition Laugier-Hunziker syndrome, several distinctions exist. First, Laugier-Hunziker syndrome lesions are progressively acquired in young or middle-age adults, profusion of periorificial pigmentation is usually not seen, conjunctival pigmentation can be seen, and these patients can have longitudinal melanonychia of the digits.[13,14]

Another syndrome, isolated melanotic mucocutaneous pigmentation, involves circumscribed macular pigmentation of the lips histologically similar to PJS. These patients have no small bowel polyps or mutation of the serine threonine kinase (STK)11/LKB1 gene, as seen in PJS, but female patients appear to have an increased risk of breast and gynecologic cancers.[15]

Abbreviations used in this paper: CLs, confidence limits; CT, computed tomography; MRI, magnetic resonance imaging; PJS, Peutz-Jeghers syndrome; STK, serine threonine kinase.

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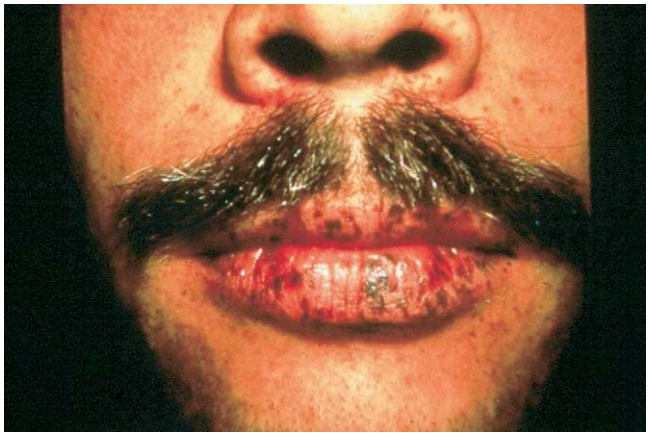

Figure 1. The classic labial melanin pigmented macules noted in PJS.

Hamartomatous Polyps

The Peutz-Jeghers polyp is a true hamartoma with unique histopathologic characteristics. These include the characteristic frond-like structure, appropriate epithelium for each area of the gastrointestinal tract, and associated smooth muscle proliferation (Figure 2). Histologically, Peutz-Jeghers polyps consist of a branching framework of connective tissue and smooth muscle lined by normal intestinal epithelium, rich in goblet cells. The polyps have elongated and convoluted glands and an arborizing pattern of growth.

In one study, polyps were detected in 88% of patients affected with PJS.[9] Peutz-Jeghers polyps occur most numerously in the small intestine but frequently in the colon and stomach.[16] The polyps usually number between 1–20 per segment of the intestinal tract and vary in size from 0.1–5 cm in diameter.[16] In affected individuals, polyps are seen at the following locations and frequency: small intestine (64%), colon (64%), stomach (49%), and rectum (32%).[9] They can also occur elsewhere with appropriate epithelium for that area,[17] and in case reports, they have been found in the renal pelvis, urinary bladder, lungs, and nares.[18,19]

Clinical Presentation

Peutz-Jeghers polyps grow during the first decade of life, and most patients become symptomatic between the ages of 10–30 years.[9] The average age of diagnosis of PJS is 23 years in men and 26 years in women. The presenting complaints of PJS are intestinal obstruction (43%), abdominal pain (23%), blood in the stool (14%), and anal extrusion of polyp (7%). The remaining 13% of cases are diagnosed because of melanin pigmentation. The most frequent complication in young age is intussusception, occurring in 47% of patients, primarily in the small intestine (in 95% of cases).

Genetic Defect

PJS is an autosomal dominant disorder with incomplete penetrance and variable expression that was initially linked to chromosome 19p13.3 in 1997.[20,21] In 1998, two separate laboratories described the cause of PJS as mutation in the STK11 gene, also known as the LKB1 gene.[22,23] STK11/LKB1 gene mutation is found in approximately 30%–70% of sporadic cases of PJS and 70% of affected individuals with a family history of the condition. The rate of spontaneous mutation in this disorder is unknown. The lack of identification of a STK11 gene mutation in all affected patients suggests the limitation of current molecular techniques, genetic mosaicism, or additional PJS loci.[24–27] With regard to the latter, some studies suggest linkage to loci on chromosome 19q and 16q.[28,29]

The STK11/LKB1 gene extends over 23 kb, is composed of 9 exons, and encodes a 433 amino acid STK protein.[22,23] Most mutations in PJS patients, including nonsense deletions, insertions, and rearrangements, lead to null alleles.[26] Of known STK11 mutations detected, about 65% affect the protein structure. However, missense mutations noted in the others are often of unclear clinical significance, leading to an inconclusive genetic testing result. Some evidence suggests that the STK11 gene is a tumor suppressor gene.[30] The serine/threonine kinase acts as a regulator of cell-cycle metabolism and cell polarity.[31] A genotype-phenotype correlation study

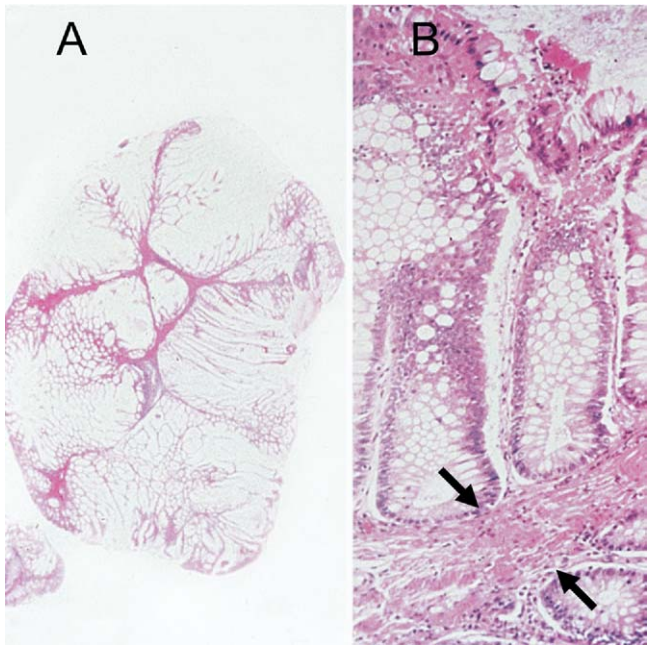

Figure 2. (*A*) Peutz-Jeghers polyp with branching framework of connective tissue on low power. (*B*) Smooth muscle (*between arrows*) lined by normal intestinal epithelium on high power.