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PEUTZ-JEGHERS SYNDROME.

Internal Medicine

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ABSTRACT

Peutz-Jeghers syndrome is a rare, hereditary disease defined by the presence of hamartomatous polyps within the gastrointestinal tract (with the exception of the esophagus) and the development of mucocutaneous pigmented lesions, which are most commonly observed in the mouth, buccal mucosa, genitals, periorbital region, and the palm and fingers of the hand. The disorder is transmitted in an autosomal dominant manner. A mutation of the serine/threonine kinase 11 gene (STK11) is identified in the majority of cases, occurring in 50-90% of instances. The manifestations may arise during adolescence or childhood, with no sex predilection. The most prevalent complications associated with Peutz-Jeghers syndrome arise from the presence of intestinal polyps, including gastrointestinal hemorrhage, iron deficiency anemia resulting from blood loss, small intestinal intussusception, and short bowel syndrome due to repeated small intestine resection as part of the therapeutic intervention. To prevent intussusception, elective polypectomy must be performed via an endoscopic, surgical, or combined approach. In the event of symptomatic intussusception, the patient must be promptly referred for reduction. Laser treatments may be employed to address pigmented lesions for cosmetic purposes. Those affected by this condition are at an increased risk of developing cancer, both gastrointestinal and extragastrointestinal. The lifetime risk of malignancy is 37-93%, resulting in a mortality rate of 66%. A variety of international organizations have published recommendations regarding the surveillance of malignant conditions in patients with this condition.

KEYWORDS

Peutz-Jeghers Syndrome; Intestinal Polyposis; Hyperpigmentation.

INTRODUCTION.

Peutz-Jeghers syndrome is a rare, hereditary disease defined by the presence of hamartomatous polyps in the gastrointestinal tract and pigmented mucocutaneous lesions. Additionally, individuals with this syndrome have an increased risk of developing neoplasms in various organs. The syndrome was first described in 1921 by Peutz, who reported it in a family with gastrointestinal polyps and pigmented lesions. Subsequently, in 1949, Jeghers proposed that it should be regarded as a distinct syndrome rather than an isolated clinical entity (1).

A mutation of the serine/threonine kinase 11 gene (STK11) is present in the majority of cases, occurring in 50-90% of instances. Given the low prevalence of this condition, there is a significant need for further research into the underlying molecular mechanisms involved in carcinogenesis and the development of more effective pharmacological therapies (1).

Epidemiology.

This condition has an autosomal dominant inheritance pattern, with an estimated prevalence of 1 in 50,000 to 200,000 individuals. In most cases, the condition manifests during adolescence or childhood, with no significant difference between the sexes. Patients with this condition are at an increased risk of developing malignant neoplasms during their lifetime, with a mortality rate of up to 66% (2).

Genetics.

The SKT11 gene is found within the 19p13.3 locus. It encodes the serine/threonine kinase, which participates in multiple signaling pathways, including the regulation of cellular growth, apoptosis, and cellular division. This contributes to the formation of polyps and an elevated risk of developing cancer. The majority of identified mutations are truncations or "senseless," despite the presence of up to 30% large deletions, which are not consistently observed in molecular sequences. Approximately 25% of cases are of patients who meet the diagnostic criteria but lack a family history and do not have STK11 mutations. This suggests the presence of other, as yet unidentified, gene mutations (2).

Clinical Manifestations and Diagnosis.

Pigmented lesions manifest as mucocutaneous spots, exhibiting a brown or black coloration. Their diameter is approximately 1-5 mm, and they assume a longitudinal shape. These lesions are most frequently observed on the lips, buccal mucosa, and perioral region. However, they may also manifest on other areas, including the conjunctiva, perianal region, hand palms, foot soles, and vagina. The lesions are caused by an increase in melanocytes in the basal cell layer of the skin, and they often appear during childhood (1)(3).

Intestinal polyposis is distinguished by the presence of hamartomatous lesions, which are identified histologically as hyperplasia in the muscularis mucosae. It is distributed throughout the gastrointestinal tract (with the exception of the esophagus), most frequently observed in the duodenum and the jejunum, and less commonly in the rectum. Gastrointestinal symptoms typically manifest at age 14, although nearly half of patients remain asymptomatic until age 20. The most recent symptoms of Peutz-Jeghers syndrome are presented in Table 1 (3).

Table 1. Peutz-Jeghers Syndrome Diagnosis Criteria.

A. Symptoms	Mucocutaneous pigmentations measuring between 1 and 5 mm in diameter are observed in the lips, mouth, and fingertips.
B. Examination results	1. Endoscopic findings included the presence of hamartomatous polyps in any portion of the gastrointestinal tract, with the exception of the esophagus.
	2. The pathological findings included the presence of polyps exhibiting hamartomatous hyperplasia of the epithelial mucosa and dendritic growth of the smooth muscle fiber bundles within the muscularis mucosae.
C. Differential diagnosis.	This condition differs from the following: familial adenomatous polyposis, juvenile polyposis syndrome, Cowden syndrome/PTEN hamartoma tumor syndrome, tuberous sclerosis, inflammatory polyposis, Cronkhite-Canada syndrome, and Laugier-Hunziker-Baran syndrome.
D. Genetic testing.	Pathogenic variants in the germ line of the STK11 gene.
Diagnostic categories: 1. Criteria A, B and C are met. 2. Criteria A is met in a case with close family history with Peutz-Jeghers syndrome, and criteria C is met. 3. Criteria B is met in a case with close family history with Peutz-Jeghers syndrome, and criteria C is met. 4. Criteria B-1 is met, B-2 is met in multiple lesions, and criteria C is met. 5. Criteria D is met.	

In patients who meet some but not all of the diagnostic criteria, the

Peutz-Jeghers syndrome can be identified through the identification of pathogenic variants in the STK11 germline, based on the symptoms and findings observed in clinical studies.

Disease Prevention.

Patients with Peutz-Jeghers syndrome who have an identified pathogenic STK11 variant may be candidates for prenatal and preimplantation genetic diagnosis (4). In children with parents affected by this entity, predictive genetic testing is recommended at age 3 in the absence of symptoms and before that if symptoms are present (5).

Complication Prevention.

The most prevalent complications associated with Peutz-Jeghers syndrome are attributed to the presence of intestinal polyps, including gastrointestinal hemorrhage, iron deficiency anemia resulting from blood loss, small intestinal intussusception, and short bowel syndrome due to repeated small intestine resection as part of the treatment (6). In patients with a confirmed diagnosis, the potential for preventing polyps and reducing the risk of malignancy has been demonstrated with the use of polyamine inhibitors, including papamycin, sirolimus, and everolimus, as well as COX-2 inhibitors. Nevertheless, the current state of clinical studies does not yield definitive results, thus precluding the formulation of recommendations (5)(6).

In the presence of polyps measuring between 1.5 and 2 cm in size, or smaller if symptomatic, an elective polypectomy must be performed to prevent intussusception. This may be carried out via an endoscopic, surgical, or combined approach, depending on the location, size, and level of endoscopic experience (5). Device-assisted enteroscopy (including double balloon enteroscopy, spiral enteroscopy, and single balloon enteroscopy) has become the gold standard for the reduction of intestinal polyps in this condition (6).

Treatment

It is imperative that patients diagnosed with Peutz-Jeghers syndrome presenting symptoms of intussusception be promptly referred for urgent reduction. It is not advised to pursue radiological reduction in these cases. The main technique previously employed was laparotomy with intraoperative enteroscopy to remove other polyps from the small intestine (4)(5)(6). Nevertheless, its utility has diminished considerably in the management of small hamartomas in Peutz-Jeghers syndrome, with minimally invasive treatments of intussusception via modern enteroscopy techniques gaining prominence (6).

At present, intraoperative enteroscopy is primarily indicated in cases of unsuccessful device-assisted enteroscopy (in patients with multiple abdominal surgeries and intestinal adhesions) or for large polyps with a high risk of complications. It has been demonstrated that a combination of device-assisted enteroscopy and intraoperative enteroscopy significantly reduces the number of residual polyps. Additionally, a recently described technique is the ischemic polypectomy endoscopy (6). Pigmented lesions may be treated with various laser applications for cosmetic purposes (3).

Malignity Risk and Monitoring.

Patients with this condition are at an elevated risk of developing cancer, both gastrointestinal and extragastrointestinal. The lifetime risk is estimated to be between 37 and 93 percent (6). The accumulated malignancy risk is 2% at 20 years of age, 16.3% at 30 years of age, 35.2% at 40 years of age, 64.1% at 50 years of age, 76.5% at 60 years of age, and 83% at 70 years of age (3). The primary affected organs are the colon and rectum (12-39%), the breast (24-54%), the stomach (24-29%), the small intestine (10-14%), the pancreas (11-55%), the gallbladder and bile duct, the esophagus, and the lungs (7-17%), the thyroid, the ovaries (10-21%), the cervix (10-23%), the uterus (9-47%), and the testicles (9%) (3)(4)(6).

The malignancy potential of hamartomatous polyps is uncertain, though it is likely secondary to the development of dysplasias in the sequence of hamartoma-carcinoma, altered rates of stem cell turnover, and the co-occurrence of adenomas within polyps. Table 2 presents a summary of the recommendations regarding the monitoring of malignancy in these patients, as outlined by the current international guidelines (American College of Gastroenterology [ACG], National Comprehensive Cancer Network [NCCN], and European groups of experts, including the European Society for Pediatric Gastroenterology, Hepatology and Nutrition [ESPGHAN], the European Society of Gastrointestinal Endoscopy [ESGE], and the European Hereditary Tumour Group [EHTG]) (3)(4)(5)(6).

Table 2. Monitoring Of Malignancy In Patients With Peutz-Jeghers Syndrome.

Organ.	Age of onset of monitoring	Monitoring interval	Monitoring method.
Stomach	8 years old (if there are no polyps, restart monitoring at 18 years old)	1-3 years old	Upper gastrointestinal endoscopy
Colon and rectum	8 years old (if there are no polyps, restart monitoring at 18 years old)	1-3 years old	Colonoscopy
Small intestine	8 years old (if there are no polyps, restart monitoring at 18 years old)	1-3 years old	Capsule endoscopy Magnetic resonance enterography
Breast	18 years old	6-12 months	Self-exploration
	25 years old	1 year old	Ultrasonography / Breast magnetic resonance imaging
	After 50 years old	1 year old	Mammography
Ovary	18-25 years old	1 year old	Internal test / transvaginal (or transabdominal) ultrasonography
Cervix	18-25 years old	1-3 years old	Pap smear
Cervix	18-25 years old	1 year old	Internal test / transvaginal (or transabdominal) ultrasonography
Testicle	From birth to adulthood	1 year old	Palpation / Ultrasonography (if palpation is abnormal or gynecomastia is observed)
Lung	None		Smoking cessation is recommended
Pancreas	30-35 years old	1-2 years old	Magnetic resonance cholangiopancreato-graphy / Endoscopic ultrasonography

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