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INTESTINAL HAMARTOMATOUS POLYPS IN ASSOCIATION WITH MUCOCUTANEOUS MELANOTIC MACULES: PEUTZ-JEGHERS SYNDROME

Oral Pathology

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ABSTRACT

Peutz-Jeghers syndrome (PJS) is a genetic, autosomal dominant disorder recognized by hamartomatous polyps in the gastrointestinal tract (especially stomach and intestine) and pigmented mucocutaneous lesions. It predisposes agonizes to diverse malignancies (gastrointestinal, pancreatic, breast, uterine, lung, ovarian and testicular tumors). History of intussusceptions, bleeding and obstruction are general complications in patients with PJS. Double balloon enteroscopy (DBE) permits inspections and treatment of the small bowel. Polypectomy applying DBE may obviate the requirement for repeated urgent operations and small bowel resection that guides to short bowel syndrome. Polypectomy and prophylaxis of the complete small bowel is the gold standard in affected patients.

KEYWORDS

Peutz-jeghers Syndrome; Hamartomas; Gastrointestinal Endoscopy

INTRODUCTION

Peutz-Jeghers syndrome is a comparatively rare but well-recognized situation such as lesions of the perioral skin, hands, and oral mucosa in association with intestinal polyposis and susceptibility for affected patients to develop cancer. It is generally inherited as an autosomal dominant trait. It is characterized by the development of hamartomatous polyps in the gastrointestinal tract (especially the intestines and stomach) and a significantly increased risk of developing specific kinds of cancer.[1]

EPIDEMIOLOGY

The prevalence of this condition is uncertain; estimates range from 1 in 25,000 to 300,000 individuals.[2]

ETIOLOGY

Mutation of a gene *STK11* (serine/threonine kinase) has been accountable for this syndrome found located on band 19p13.3. Penetrance of the gene is changeable, producing varied phenotypic manifestations between patients with this syndrome.[1]

GENETICS

Currently, the only noticeable mutations generating PJS affect the *STK11* (serine/threonine-protein kinase 11 alias *LKB1*) gene, situated on chromosome 19p13.3.This gene was recognized in 1998. It determines for a multifunctional serine-threonine kinase, crucial in second messenger signal transduction. The serine-threonine kinase regulates cellular proliferation, controls the polarity of the cell, and appears to have a principal role in responding to bottom cellular energy levels. In the presentation of this last role, the *STK11* protein is involved in the restriction of AMP-activated protein kinase (*AMPK*), and signals ulterior to restrict the mammalian target of rapamycin (*mTOR*; also called as FKBP12-rapamycin complex-related protein or *FRAP*) pathway; the *mTOR* pathway is upregulated in patients with this syndrome. Even though the proper mechanism of action of *STK11* has not been demarcated completely, the role of this protein product is likely to be crucial in inhibition of growth. Genetic changes in *STK11* may show loss of heterozygosity at a tumor suppressor gene locus. Few studies have recommended the participation of *STK11* also in more customary disorders of human involving diabetes mellitus and in a remarkable fraction of lung adenocarcinoma. These inspections have enhanced the concern towards the signaling pathways of this tumor suppressor kinase. An important proportion of sporadic and familial PJS may outcome from mutations in genes other than *STK11* or thus far unidentified means of Liver kinase B1 (*LKB1*) inactivation. In total, 91% of the studied families have shown inactivation of *LKB1*. Germline mutations in the tumor suppressor gene Phosphatase and tensin homolog (*PTEN*) (10q22-23) are accountable for a group of phenotypically various conditions, which have altogether been called the PTEN hamartoma tumor syndrome. These are infrequent autosomal dominant situations different from PJS.[3]

CLINICAL FEATURES

The skin lesions of this syndrome generally develop early in childhood and involve the periorificial areas. The disease influences males and females equally. The skin of the extremities is affected in about 50% of patients. The lesions resemble freckles, but they do not wax and wane with exposure to sun, as do true freckles.

The intestinal polyps, usually considered to be hamartomatous growths, are dispersed throughout the mucus-producing areas of the gastrointestinal tract. The jejunum and ileum are most commonly affected. The sizes of the Polyp vary from a few mm to 6 or 7 cm. Most affected patients have a distinguished clinical course of periodic episodes of polyp induced bowel obstruction and bleeding. Most episodes are self-correcting, but surgical intervention is sometimes compulsory to inhibit ischemic necrosis of the bowel, with the following peritonitis. Gastrointestinal adenocarcinoma advances in 2% to 3% of affected patients, although the polyps themselves do not noticeable to be premalignant. In supplement to polyposis, the risk of gastrointestinal and extra-gastrointestinal malignancies is remarkably increased in affected patients. The comparative risk of dying from a gastrointestinal cancer is 13 times higher. The risk of any other malignancy (especially cancer of the breast and reproductive organs, and also of the lung and pancreas) is 9 times higher than in the normal population. Other tumors influencing the male and female genital tract, breast, pancreas, and ovary may also develop, and the advanced frequency universal is estimated to be relatively 18 times greater than normal.[4,5,6]

MUCOCUTANEOUS PIGMENTATION

Melanocytic macules (MM) are not frequently present at birth; before the fifth year, they become obvious in the majority of children but then may disappear in puberty and adulthood. The dark brown to dark blue mucocutaneous macules around the mouth, eyes, and nostrils, in the perianal area, and on the buccal mucosa is usually present in children. Hyperpigmented macules on the fingers are also frequent. In one series, 94% of individuals with this syndrome had perianal MM, 73% had MM that affected the digits, 65% had MM on the buccal mucosa, and 21% had MM at other sites.[7,8]

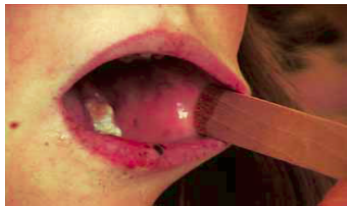

Figure 1. Showing Brown macules on the lips and on oral mucosa.

ACCUMULATIVE RISK OF CANCERS IN PEUTZ-JEGHERS SYNDROME[9] (TABLE)

Cancer Site	General Population Risk	Peutz-Jeghers Syndrome	
		Risk	Average Age at Diagnosis
Colorectal	5%	39%	42-46 years
Stomach	<1%	29%	30-40 years
Small Bowel	<1%	13%	37-42 years
Breast	12.4%	32%-54%	37-59 years
Ovarian (mostly SCTAT)	1.6%	21%	28 years
Cervix (adenoma malignum)	<1%	10%	34-40 years
Uterus	2.7%	9%	43 years
Pancreas	1.5%	11%-36%	41-52 years
Testicular (Sertoli cell tumor)	<1%	9%	6-9 years
Lung	6.9%	7%-17%	47 years

HISTOPATHOLOGIC FEATURES

Histopathological, the gastrointestinal polyps of PJS represent benign overgrowths of intestinal glandular epithelium supported by a core of smooth muscle. Epithelial atypia is not generally a prominent character, unlike the polyps of Gardner syndrome. Microscopic interpretation of the pigmented cutaneous lesions represents slight acanthosis of the epithelium with elongation of the rate ridges. No apparent increase in melanocytes number is examined by electron microscopy but the dendritic processes of the melanocytes are extended. Additionally, the melanin pigment shows to be retained in the melanocytes rather than being transferred to adjoining keratinocytes.[3,8]

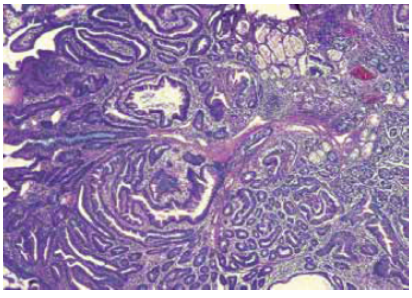

Figure 2. Histopathology: a large polyp displaying a tree-like structure of musculature covered with normal mucosa. (HE x 200)

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of Peutz-Jeghers syndrome is depending on clinical findings. It should be suspected in individuals with the following:

- Two or more PJS-type intestinal polyps
- Mucocutaneous macules
- Gynecomastia as a consequence of estrogen-producing Sertoli cell testicular tumors in males
- Documentation of intussusceptions, specifically in a child or young adult.

Recognition of a heterozygous pathogenic variant in STK11 by molecular genetic testing establishes the diagnosis and permits for family studies. Molecular testing approaches can involve single-gene testing, use of a multigene panel, and more comprehensive genomic testing: The differential diagnosis of pigmented lesions include LEOPARD syndrome, Hereditary mixed polyposis syndrome (HMPS), Juvenile polyposis syndrome (JPS) PTEN hamartomas tumor syndrome (PHTS), Langier–Hunziker syndrome, Carney complex, Cowden syndrome and a general variant, particularly in African Americans.[2,7,10]

TREATMENT

- There are two basic modalities in diagnosis and treatment of small bowel hamartomas: intra-operative enteroscopy (IOE) and double balloon enteroscopy (DBE).
- DBE is a new enteroscopy method that allows examination and treatment of the jejunum and ileum in almost all patients. The system consists of a 200-cm enteroscope and a 145-cm over-tube which have soft latex balloons at their tips. By using these balloons to grip the intestinal wall, the endoscope can be inserted further without forming redundant loops of intestine.
- IOE is a combination of laparotomy (or laparoscopy) with endoscopy. It allows manipulation to ensure the entire small bowel is visualized and nearly all polyps are removed in an endoscopic or surgical manner. IOE was accepted as the ultimate diagnostic and/or therapeutic procedure for complete investigation of the small bowel, especially before the DBE era.

Patients with Peutz-Jeghers syndrome should be monitored for development of intussusceptions or tumor formation. Genetic counseling is also appropriate. Some recent studies have demonstrated the chemo preventive efficacy of rapamycin on PJS in a mouse model. Rapamycin (sirolimus) is a macrolide compound with immunosuppr essant properties that is obtained from *Streptomyces hydroscopicus*. The antiangiogenic effect of rapamycin may play a role in polyp reduction.[3,11,12]

CONCLUSION

PJS is a rare cancer-inducing autosomal dominant genetic disease manifested by skin mucosal melanoplakia and gastrointestinal multiple polyps and is an ordinary incomplete dominant inheritance. The timely polypectomy, preferably using the DBE method, is essential for patients with PJS. Follow-up of gastrointestinal polyps is necessary. The best combination of methods is Capsule Enteroscopy and Magnetic Resonance (MR) Enteroclysis. Lifelong screening of malignancies is indispensable on a regular basis. It is necessary to investigate all first-degree relatives of the patient. Although the incidence of PJS is low, it is important for clinicians to recognize these disorders to prevent morbidity and mortality in these patients, and to perform presymptomatic testing in patients at risk.

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