RESEARCH PAPER

Oral Manifestations as Early Indicators of Peutz–Jeghers Syndrome: Dental Perspective on STK11/LKB1 Gene Mutations

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ABSTRACT
Peutz-Jeghers syndrome is an autosomal dominant hereditary condition characterised by mucocutaneous pigmentation and hamartomatous polyps in the small intestine. Intussusception, intestinal blockage, hemorrhage, and other polyp-related problems are common surgical emergencies in Peutz-Jeghers syndrome patients. Additionally, some patients can require many surgeries, which could lead to short bowel syndrome. More recent research has indicated an elevated risk for both gastrointestinal and extra-gastrointestinal cancers in patients with this syndrome, despite early reports not showing a cancer susceptibility. Stool obstruction, bleeding, and stomach pain are among the common gastrointestinal symptoms caused by hamartomatous polyps. The skin and mucous membranes are commonly affected by the pigmentation, which typically manifests as noticeable bluish-black macules. It is possible to have both large regions with lentiginous pigmentation and few macules. Pigmentation is seen in many locations, such as the lips, fingers, buccal mucosa, and perioral region. Families with Peutz-Jeghers syndrome have recently been shown to carry the Peutz-Jeghers syndrome susceptibility gene, which codes for the serine-threonine kinase STK11 (also known as LKB1). Finding germline mutations in Peutz-Jeghers syndrome families may mark a paradigm shift in the medical management of the condition. This article aims to provide a concise overview of the current understanding of this illness, including its pathophysiology, genetics, clinical manifestations, and medical care. The article also describes the crucial part a dentist can play in identifying this hereditary condition early and lowering its morbidity.
Keywords: *peutz-jegher syndrome; genes; hamartoma; melanin; polyps*
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BACKGROUND

This rare autosomal dominant genetic condition is characterised by the development of benign hamartomatous gastrointestinal polyps and hyperpigmented macules on the oral mucosa, lips, nose, hands, feet, and anogenital region.

Jonathan Hutchinson originally reported Peutz-Jeghers syndrome (PJS) symptoms in 1986. Nonetheless, Jan Peutz (1886–1957) documented the genetic inheritance in 1921, and Harold Joseph Jeghers (1904–1990), Victor Almon McKusick (1921–2008), and Kermit Harry Katz (1914–2003) identified the dominant autosomal inheritance in 1949.

They identified small intestinal polyposis and oral and perioral melanin accumulation as the primary features of PJS and established its autosomal dominant inheritance pattern. Horrilleno et al. (1957) performed the first histological description of the hamartomatous polyps. The name PJS was first used in 1954.

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INTRODUCTION

Peutz–Jeghers syndrome (PJS) is a rare hereditary condition first described by Hutchinson and later characterised by Peutz and Jeghers in the early 20th century (Hutchinson, 1896; Peutz, 1921; Jeghers et al., 1949). It is defined by mucocutaneous pigmentation and gastrointestinal hamartomatous polyps, with a markedly increased cancer risk (Giardiello et al.,1987;Beggsetal.,2010). Given the higher risk of cancers linked to this condition, early screening and surveillance are crucial.

PJS follows an autosomal dominant inheritance pattern, with approximately 75% of cases showing a positive family history, while the remaining cases arise from de novo mutations (Beggs et al., 2010). The syndrome is caused by mutations in the serine-threonine kinase 11 (STK11/LKB1) gene located on chromosome 19p13.3 (Hemminki et al., 1998; Jenne et al., 1998).

It is inherited across the family. A family history of PJS is present in about three out of every four individuals diagnosed. 4% of people have no family history. The gene mutation in this instance might have occurred naturally. We refer to this as a spontaneous mutation. PJS can be diagnosed by genetic testing along with genetic counselling. The STK11 gene acts as a tumor suppressor regulating cell proliferation, polarity, and metabolism (Shackelford & Shaw, 2009; Alessi et al., 2006). Loss of function leads to uncontrolled cellular growth and polyp formation (Alessi et al., 2006). However, additional genetic mutations are often required for malignant transformation, supporting the “two-hit hypothesis” (Knudson, 1971).
Not all individuals with STK11 mutations develop malignancies, suggesting incomplete penetrance and the influence of modifying genetic or environmental factors (Lim et al., 2004).

This uncommon autosomal dominant phenomenon causes mucocutaneous colouration, hamartomatous polyps, intestinal haemorrhage, intussusception, and cancers. It is caused by a mutation in the serine-threonine kinase (STK11/ LKB1) gene on chromosome.

Dr. Jan Peutz presented the results of a three-generation study involving 10 cases of the syndrome: seven patients had multiple small intestinal polyps and pigmentation in the mouth region, two patients also had nasal polyps, one patient had bladder polyps, and one patient experienced jejunum intussusception. Jeghers et al. reviewed the literature and reported cases of pigmentation associated with intestinal polyposis on the lips, face, and oral cavity.

DISCUSSION

The STK11 gene is altered (mutated) in the majority of PJS cases. The STK11 gene is a tumour suppressor gene that regulates both cell division and proliferation. Before cancer can begin, mutations in multiple growth-control genes must occur. However, the initial phase of this process is the loss of STK11. The cause of the other mutations is not known.

Certain individuals with a hereditary STK11 mutation never develop cancer. This is because they never acquire the second mutation, which initiates tumour growth and disrupts control over cell proliferation. This may give the impression that cancer skips a generation in a family. However, the gene mutation persists. A person with PJS, having or not having cancer, has a one in two possibility of transferring the mutation to their offspring. It’s also critical to keep in mind that the sex chromosomes do not contain the STK11 gene. This indicates that the mutation originates on either the paternal or maternal side of the family.

Symptoms typically appear during the first decade of life (Amos et al., 2004). The characteristic features include mucocutaneous pigmentation, gastrointestinal polyps, and extraintestinal polyps (McGarrity et al., 2000; Westerman et al., 1999; Latchford et al., 2011).

The PJS symptoms arise before the age of ten and may include:

- Moles that are dark blue or brown and located in or around the lips and in the buccal mucosa, shown in Figure 1, eyes, nostrils, and anus. The hands and feet may have black moles, which typically appear in childhood and disappear as people get older.
- Hamartomatous polyps in the gastrointestinal tract lining. These begin in early life. They result in obstructions, discomfort, vomiting, bleeding, and diarrhoea.
- Polyps in other body regions, such as the bladder, lungs, and nose.

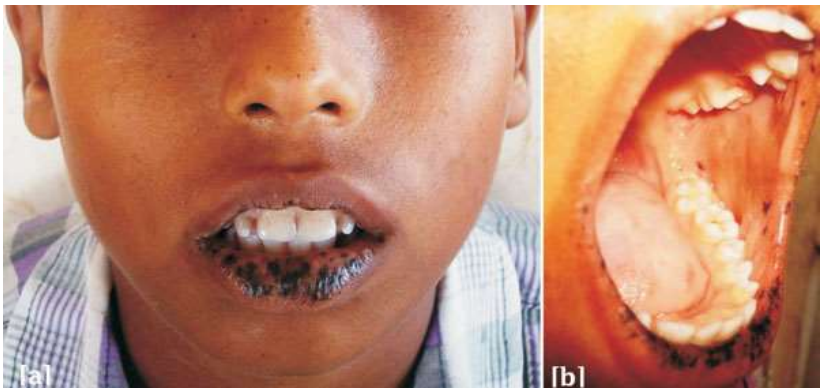

Figure 1. (a) The peri-nasal region has a few sporadic pigmented macules in addition to hyperpigmented macules on the lips, particularly on the lower lip;

(b) pigmented macules on buccal mucosa and lips.

(Image courtesy- Dutta, Abhijit & Ghosh, Sudip & Kundu, Sujit. (2015). Peutz-Jegher

Syndrome. Indian Paediatrics. 52.(176-77.)

PJS is associated with a significantly increased lifetime risk of malignancies, reaching up to 93% by age 70 (Giardiello et al., 2000; Hearle et al., 2006). Common cancers include gastrointestinal, pancreatic, breast, and gynecological malignancies (Schreibman et al., 2005; Lim et al., 2004).

Ovarian and testicular benign tumours are more common in people with PJS. They also have an extremely high chance of developing certain types of cancer. These cancers often begin in later life, such as in the 40s. Nearly all PJS patients will receive a diagnosis of one or more of the following cancers at some point in their lifetime:

- The stomach
- The small intestine
- Ovarian
- breast
- The rectum and colon
- The pancreas
- Cervix
- Lungs

PJS can be verified through genetic testing. Individuals with PJS can take measures to lower their risk of cancer. For example, they have to abstain from tobacco use and avoid tobacco smoke. Additionally, they can begin cancer screening early in life. Screening tests are employed to detect cancer even before symptoms appear. (Table 1)

Table 1: Screening tests

S.NO	SCREENING TEST	DESCRIPTION
1	**Upper endoscopy**	• In order to detect polyps, tumours, and other issues in the oesophagus, a child with PJS should have this test done regularly beginning at age 8.
2	**Colonoscopy**	• If polyps are discovered, the test should be repeated every two to three years in order to monitor any changes that may eventually develop into cancer.
3	**MRI**	• Pancreatic cancer can be monitored using these scans. This needs to begin around age 30. When a family member is diagnosed with pancreatic cancer, treatment should begin ten years earlier than the individual's actual age.
4	**Mammogram**	• Age 20 is the appropriate age to begin these examinations. Up until age 40, this ought to be performed every two to three years. A mammography should be performed annually after the age of 40.
5	**Yearly clinical breast exam**	• Annual breast exams should be performed by a medical professional. Women may also wish to discuss breast self-examinations with a healthcare professional.
6	**Yearly pelvic exam**	• Beginning at age 25, they should be performed along with a Pap test and ultrasound for women with PJS.
7	**Yearly testicular exam**	• Men with PJS should undergo these tests from an early age.

In up to 70% of cases in affected families and 30% to 67% of sporadic cases, these mutations have been identified. Nearly 90% of the pigmentations, which are small, dark brown, round, or oval macules associated with PJS, are found in the mouth, eyes, nose, and limbs. One in fifty thousand to twenty thousand individuals have PJS, which is linked to a higher risk of stomach, intestinal, pancreatic, breast, lung, uterine, ovarian, and testicular cancers. Compared to the general population, PJS has a nearly 15-fold greater risk of cancer. By the age of 70, the lifetime increased risk of cancer may reach 90%. The lifetime cancer risk of 1644 PJS patients ranged from 37% to 93%, whereas the average age of having any malignancy was 42 years. By the age of 70, the lifetime increased risk of cancer may reach 90%. Diagnostic criteria are tabulated in Table 2.

Table 2: Diagnostic criteria:

Diagnosis is based on clinical criteria and genetic testing for STK11 mutations (WHO, 2019).

I	Two or more PJ polyps
II	Any number of polyps with a family history of PJS
III	Mucocutaneous pigmentations with a family history of PJS
IV	One or more PJ polyps and mucocutaneous pigmentations

The polyps are sessile or pedunculated, with diameters ranging from microadenomas to several centimetres, and can cover large areas extensively in single or hundreds of numbers. Based on the arborising pattern seen in the hamartomatous PJ, the histopathologic diagnosis is made. The small intestine (50%) is reported to have the most PJ gastrointestinal polyps, followed by the stomach (36%) and colon (21%); and extra-intestinal locations include the bladder, nostrils, bronchi, and gallbladder. Gastrointestinal polyps can result in bleeding, intussusception, and even rectal prolapse. By age 10, the risk of intussusception is 15%, and by age 20, it can reach 50%. Of all the forms, small intestinal intussusception is the most critical and potentially fatal.

Neurofibromatosis, multiple endocrine neoplasia, Cowden and Bannayan-Riley-Ruvalcaba syndromes, and hereditary mixed polyposis are among the differential diagnoses. When someone is diagnosed with PJS, all of their at-risk relatives should also be evaluated. For suspected cases of PJS, genetic testing and informed assent are required before having children. In addition to precocious tumour resections, patients with PJS must begin screening for polyps at age 8 and undergo annual comprehensive physical examinations and blood tests.

Imaging scans of the digestive system, testes, breast, and pelvic organs are among the measures used to monitor the malignant transformation of the polyps and to prevent surgical complications. Other measures include controlling the total blood count and measuring CA-125 and CA-19-9 levels.

Since oral manifestations are the earliest signs of the condition, seeing the dentist can aid in early diagnosis. This can help identify systemic illnesses that could be fatal, such as short bowel intussusception and, if present, gastric cancer.

One distinguishing feature of PJS diagnosis is mucocutaneous pigmentation. The most prevalent locations for small, dark brown, oval, or circular macules are the hard palate, gums, lips, and oral mucosa. As demonstrated in this instance, they are most noticeable throughout infancy and may diminish following puberty. Since LEOPARD syndrome and Carney complex are among the differential diagnoses, mucosal freckling is not a pathognomonic sign of PJS. (Figure 1)

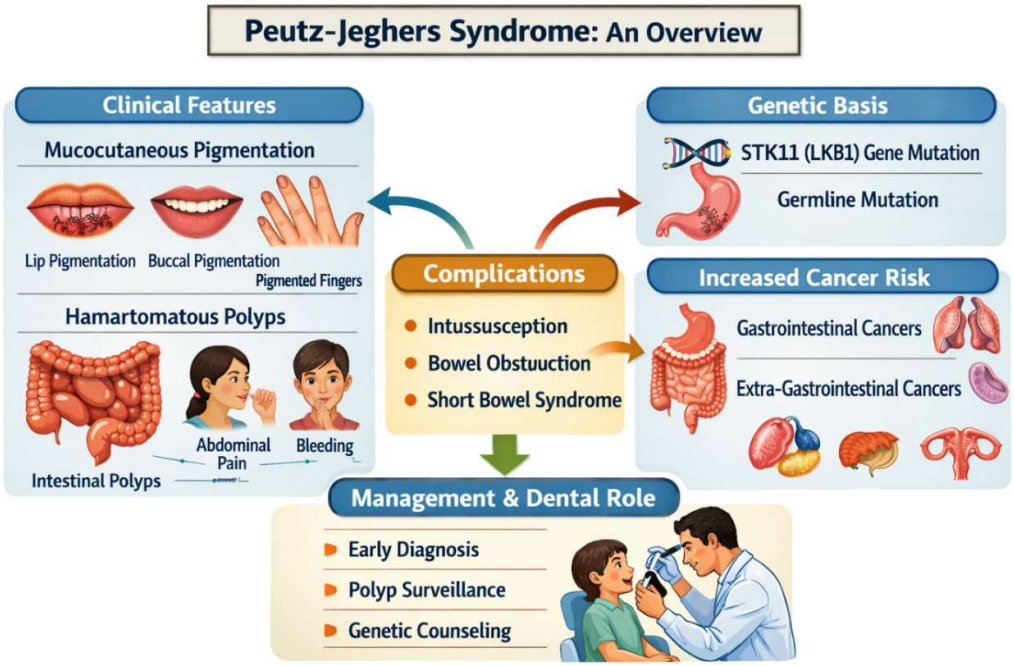

Figure 1: Overview of Peutz-Jeghers Syndrome

Although there isn't much data on tumour growth during pregnancy, it has been hypothesised that oestrogen and progesterone may affect tumour growth. When Well et al. examined how pregnancy affected the growth of neurofibromas in patients with neurofibromatosis type 1, they found no variations in plexiform growth or cutaneous neurofibromas between pregnant and non-pregnant patients.

PJS's long-term cancer risk has been extensively studied. Most of the information on cancer risk in PJS comes from small, single-cohort research. How cancer develops in PJ polyps and how PJS hamartomatous polyps contribute to cancer development are challenging concepts to explain. The polyclonal nature of PJS polyps provides evidence against their propensity for malignancy. According to Latchford et al., gastrointestinal cancer is less clinically significant than pancreatic and breast malignancies, which are the most often observed cancers in PJS.

There are no established standards for treating PJS patients more effectively. The current guidelines are still inadequate and need a collaboration of multidisciplinary experts. Management includes surveillance, endoscopic polyp removal, surgery for complications, and genetic counseling (NCCN, 2023; Beggs et al., 2010).

Gastroenterologists, geneticists, physicians, surgeons, oncologists, and nurses who can improve the disease's prognosis make up the most effective teams for management and surveillance.

CONCLUSIONS

Peutz–Jeghers syndrome is a complex hereditary disorder with significant cancer risk. Early diagnosis, genetic counselling, and lifelong surveillance are crucial for improving patient outcomes.

This article covers key aspects of PJS, including its causes and genetics, clinical presentations, diagnostic criteria, and care and surveillance strategies for individuals affected by PJS.

This review emphasises the importance of identifying PJS patients early and continuing to monitor them. By implementing appropriate care strategies, we can reduce the likelihood of cancer development and improve the patient's overall prognosis. From an oral health care professional's perspective, the clinician should be aware of both systemic problems and oral manifestations. Thus, a complete medical and dental history, as well as any unanticipated findings such as mucocutaneous pigmentation, could be useful in diagnosing this illness, and the patient can get the right advice at the right time about seeing an expert to handle the case.

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