Uncomissioned Review

Peutz-Jeghers Syndrome: Current State-of-the-Art

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ABSTRACT

Abstract: Peutz-Jeghers Syndrome (PJS) is rare hereditary disease. Mucocutaneous pigmentations and gastrointestinal polyps are the most prominent features. To date, the only approved treatment for this syndrome is to eliminate the polyps found during the extensive inspection of the patient's body by snare endoscopy and/or invasive abdominal laparotomy surgery. Patients with PJS have a high lifetime risk of various cancers and warrants regular surveillance to screen for possible early signs of malignancies. These requirements may render the patients susceptible to acquire depression and desperation due to the chronic, burdensome nature this disease entails. Due to this vulnerability, these patients need to be well-informed and guided by the treating physicians to help in coping with their PJS status. More research is needed to help alleviating or even curing the PJS disease to ease the patient's burden.

Keywords: Peutz-Jeghers; PJS; pigmentation; polyp; endoscopy

INTRODUCTION

Peutz-Jeghers Syndrome (PJS) is an autosomal dominant hereditary polyposis syndrome. The main characteristics are hamartomatous polyps, mucocutaneous pigmentations, and increased vulnerability to malignancies.[1] The frequency of PJS is estimated to be 1 in 25.000-300.000 individuals, which makes such syndrome is rare in the general population.[2]

GENETICS ABNORMALITIES

In more than 90% of PJS cases, the genetic defect involves the Serine/threonine kinase (STK11) (previously known as Liver kinase B1/LKB1) gene locus,[3] which is mapped to chromosome 19p13.3.[4,5] STK11 is a tumor suppressor gene that plays a role in the induction of the cell cycle's growth arrest at G1 phase.[6] This enables rapid regeneration of the cells without significant risk to develop a malignancy.[1] Therefore a defect in the STK11 gene often promotes the development of polyps and cancers in people with PJS.[6] Moreover, the mutation is also linked to hypoactivity of p53 tumor suppressor pathways.[7] The type of mutation the STK11 gene may give different severity of clinical manifestations. Truncating (nonsense) variants are associated with earlier onset of symptoms and cancers, compared to non-truncating (missense) and deletion variants.[1,8,9]

Although PJS is fundamentally of hereditary origin, de novo mutations without family history of PJS can occur in about 25% cases.[4,10] Two case reports of two patients with PJS by Zhao et al uncover a new truncating mutation in the STK11 gene locus, resulting in a premature codon termination not previously reported in their respective family.[11,12] Similar to the two Zhao et al reports, a case report by Gao et al also described a new missense mutation in a Chinese patient with PJS, of which was not found in the patient's family members.[13]

A recent retrospective study involving 15 patients with PJS in Taiwan has identified a normal STK11 gene in 4 patients; another 1 patient had a mutation in mTOR gene locus.[14] It is not known whether the mTOR defect was an up- or downregulation-yielding in the study. It is described that a mutation in STK11 apparently disables mTOR gene locus inhibition, resulting in its activation and causes an increase in a cell's size and mass, a phenotype that frequently occurs in a polyp pathogenesis.[15,16] Hence it is suspected that the mTOR defect in the study's patient was an upregulation type.

CLINICAL MANIFESTATIONS AND HISTOLOGY

Mucocutaneous pigmentations are the main sign of PJS in 95% of cases.[2] The lesions are generally black- or brownish macules, round or oval in shape (about 1-5 mm in diameter), and mostly found on the buccal mucosa and lips (Figure 1).[17] Other locations of the pigmented lesions can be observed around the mouth, eyes, nostrils, and perianal area, as well as fingers and toes (Figure 2).[2,18] These spots usually appear during infancy or early childhood, with inclination to increase in size during adolescence.[17] The spots may fade away as the child grows however, but the spots in the buccal mucosa tend to persist.[18]

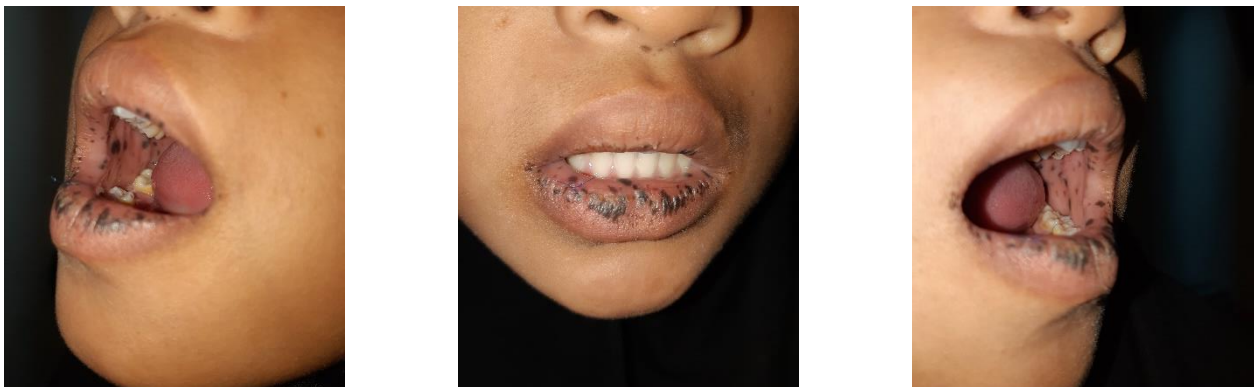

Figure 1. Macules on buccal mucosa and lips of a child with Peutz-Jeghers Syndrome.

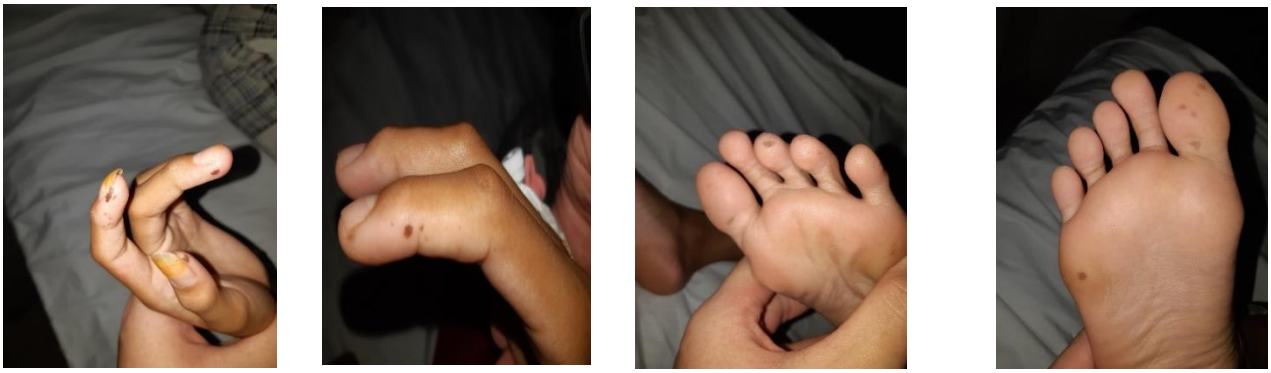

Figure 2. Black-brownish spots on the fingers and toes.

The main clinical manifestations of Peutz-Jeghers Syndrome are the hamartomatous polyps. The majority of cases have polyps in the gastrointestinal tract, especially in the jejunum of the small intestine (Figure 3, box A), but polyps can be found in the large intestine and in the stomach. In rare cases, the polyps can be identified outside the gastrointestinal tract (extraintestinal) such as in the gallbladder and its tracts, bronchi, urinary bladder, and ureter.[19]

Histologically, the polyps in the small intestine are typically sessile, pedunculated or lobulated, with arborizing pattern, composed of nondysplastic epithelial cells and bundles of smooth muscle tissues originating from the muscularis mucosa layer (Figure 3, box B).[20] In some PJS cases, dilated mucinous cysts[21] and dysplastic epithelial cells[22] can be recognized in the polyps on examination. The lamina propria layer is usually normal without signs of inflammation.[22] However, it can be identified otherwise.[21] People with PJS have an increased risk of adenomas in their digestive tract.[22]

In a minority of PJS polyps (around 10% of cases), a pseudoinvasion phenomenon, which exclusively develops in the small bowel, may be seen on histology examination (Figure 3, box C).[20] This must be thoroughly inspected due to a resemblance with a more invasive adenocarcinoma. A polyp with a pseudoinvasion trait has the following microscopic features: lack of atypical glands, normal composition of the epithelial cell types, hemosiderin deposition, and presence of mucinous cysts.[20]

When presented in the large bowel, hamartomatous polyp may appear similar to a polyp from a mucosal prolapse (Figure 3, box F).[22] On the other hand, the PJS polyp in the stomach is often indistinguishable from the juvenile polyps or other types of hamartomatous hyperplastic polyps (Figure 3, box D and E).[22] In this case, the

other characteristics are important to differentiate between the two, i.e. patient's age, number of polyps and their locations. The clinical contexts also play a role in the discrimination, in that the other traits associated with the PJS (mucocutaneous pigmentations, history of surgery due to polyp complications, personal and/or family history of PJS and PJS-related malignancies) should assist in the diagnosis of PJS. The lobular organization of the colonic crypts and desmin-positive smooth muscle fibers around the lobules aid in PJS diagnosis when the polyps are found in the large intestine.[22] Table 1 compares histological traits between PJS and juvenile polyps identified in the small intestine, colon, and stomach.

DIAGNOSTIC CRITERIA

The diagnosis of PJS can be established when at least one of the following four criteria is satisfied in the patient:[1,3,6]

1. Discovery of three or more polyps confirmed histologically to be a PJS-type.
2. Any number of PJS-type polyp found, with a positive history of PJS in patient's family.
3. Characteristic, prominent mucocutaneous pigmentations with a positive family history of PJS.

Characteristic, prominent mucocutaneous pigmentations with any number of PJS-type polyps.

Table 1. Polyp comparisons between Peutz-Jeghers Syndrome and Juvenile Polyposis Syndrome.[22]

Location	Peutz-Jeghers Syndrome	Juvenile Polyposis Syndrome
Predominance	Small intestine > colon > stomach	Colon > stomach > small intestine
Small intestine	Lobulated, smooth muscle fibers with arborizing pattern	Rare
Colon	Smooth surface, noneroded	Eroded, reddish appearance
	Lamina propria usually normal	Lamina propria usually inflamed and extended
	Smooth muscle proliferation	Scarce smooth muscle fibers
	Lobulated, distorted crypts	Mucinous and neutrophilic cystic glands
Stomach	Hyperplastic/inflammatory	Hyperplastic/inflammatory

The histological confirmation of the polyps is essential to ensure that the polyps identified are actually PJS polyps, since there are not any specific macroscopic features of a PJS polyp when visualized endoscopically.[23] Furthermore, patients with PJS may present with both mucocutaneous pigmentations and polyps but can also present with either the polyps or the pigmentations alone.[22] Thus the presence of just one out of the four criteria above is sufficient enough to establish a PJS diagnosis.

In addition to the conditions above, some of the following signs and symptoms may present in patients with PJS to support the diagnosis:[6]

- Recurrent abdominal pain
- Hematochezia and/or melena
- Feeling of weakness (due to anemia)
- Rectal prolapse
- Precocious puberty
- Irregular menstruation (in females) or gynecomastia (in males)

The menstruation irregularities are induced by the hyperestrogenism status which is generated from the sex cord tumors with annular tubules.[6] In chronic cases, long-term high estrogen exposure could affect the cervix and lead to malignant cervical adenoma.[18] Meanwhile, the male's gynecomastia may be due to estrogen production by the Sertoli cell testicular tumors as the result of higher aromatase expression and thus higher rate of testosterone conversion to estradiol.[6,23] The most recent 2019 European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guideline emphasizes to undertake testicular ultrasound to check the presence of Christmas tree-like pattern appearance in the testes, which is a pathognomonic for this kind of tumor.[23]

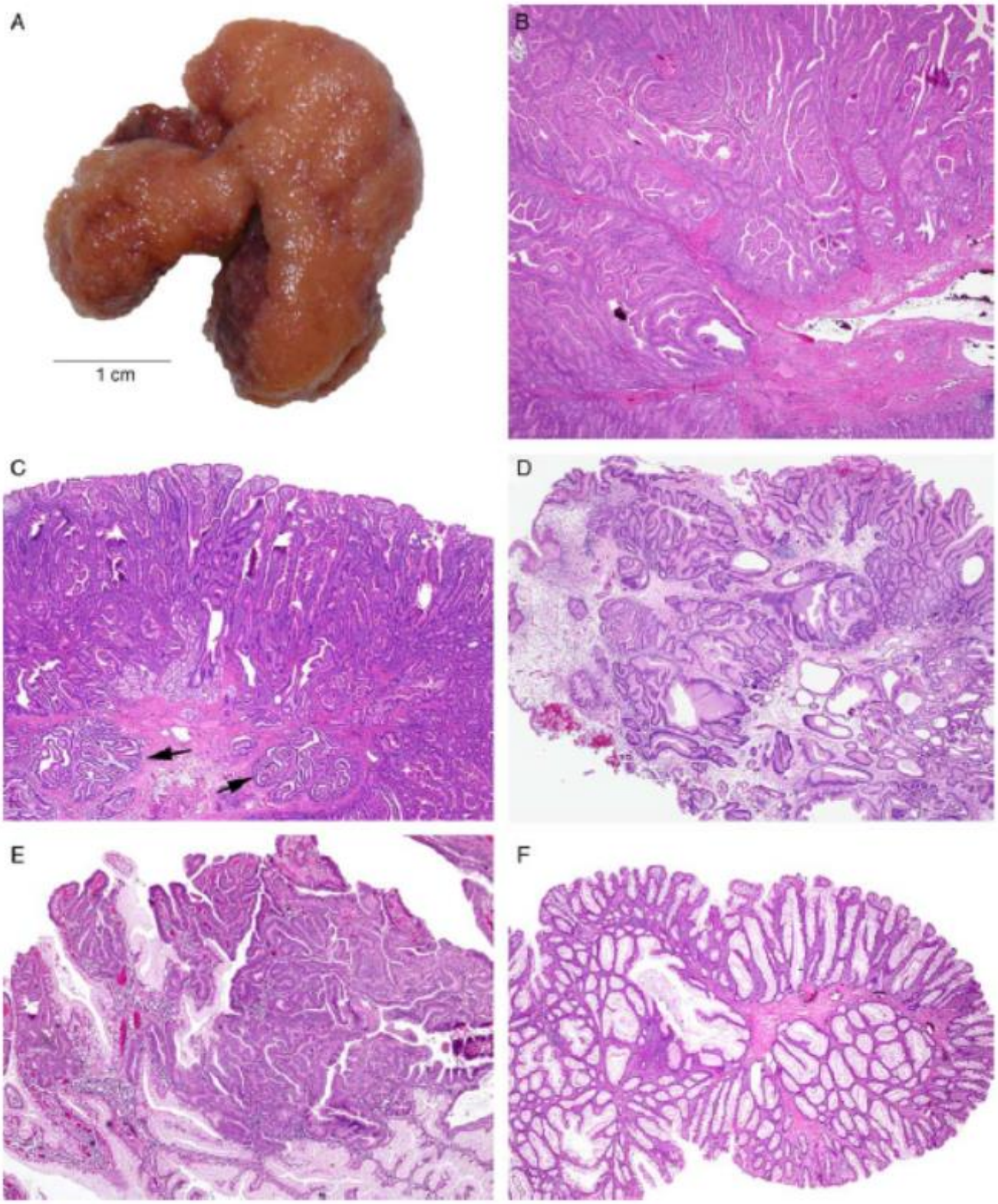

Figure 3. Macroscopic jejunal polyp from a patient with PJS, appearing lobulated (A). Arborizing pattern growth of the smooth muscle bundles (B). Pseudoinvasion phenomenon (misplaced benign glands) can be identified in submucosa layer (C, arrows). In stomach, PJS polyps are often difficult to differentiate from other hyperplastic or hamartomatous-related gastric polyps (D). Dysplastic epithelial cells can be found in PJS gastric polyps although rare (E). PJS polyps in the colon are often appear to be lobulated with distorted, nondysplastic crypts and may correspond to polyps from a mucosal prolapse (F).[22]

The majority of PJS polyps start to develop in the first ten years of life, but the complications are usually emanating in the next one or two decades after, i.e. anemia, rectal bleeding, abdominal pain, obstruction, and/or intussusception.[10,24] These manifestations are especially prominent with large-sized polyps, in which the occurrence of infarction and ulceration are frequent.[10] Risk of intussusception predominates in the first three

decades of life,[41] in which approximately 15% of PJS patients have experienced the risk before reaching the age of 10 and the percentage increases to 50% before the age of 20.[3] The chronic nature of this disease may result in protein-losing enteropathy, complicating the syndrome even further.[6]

Genetic testing for an STK11 mutation, although not required for an established PJS diagnosis, should be done for additional supporting evidence. In pediatric patient populations, the ESPGHAN guideline recommends performing genetic testing from the age 3 years old if asymptomatic and should be earlier if the patient shows symptoms.[23] However as discussed before, it is possible for some positive PJS cases to lack the mutation in the indicated gene locus. Consequently, the negative finding in such testing does not rule out the PJS diagnosis.

Imaging modalities can aid the visualization of existing polyps in patients with PJS. Some modalities are small bowel follow-through (SBFT), enteroclysis/enterography (magnetic resonance enteroclysis/MRE), computed tomography scan (CT scan), and magnetic resonance imaging (MRI).[25] Compared to other modalities, the combined use of MRI and enteroclysis is deemed sensitive enough as a diagnostic method for polyp detection, particularly the large-sized (>15 mm) ones.[25] Together with the MRE, the use of video capsule endoscopy (VCE) is also recommended by the 2019 European Society of Gastrointestinal Endoscopy (ESGE) to detect polyps in the small bowel.[26] However, in contrast to the ESGE recommendation, Korsse et al suggests to avoid VCE as standard surveillance tool because it has some drawbacks. Although theoretically VCE is able to detect small polyps (<5 mm), it cannot determine the location and precise size of the polyps well due to rapid capsule transit.[25] Consequently, false-negative results are often obtained from VCE examination and sometimes even large-sized polyps may be undetected by VCE.[25] Nevertheless, VCE is considered to be safe and sensitive method for small bowel polyp surveillance in children.[25] It is also the simplest diagnostic tool to use. Even so, these imaging techniques are starting to be abandoned after the inception of endoscopy. This device can be used as a therapeutic instrument (i.e. polypectomy) to manage the polyps in addition to diagnostic tool.

The closest differential diagnosis for PJS is Laugier-Hunziker Syndrome. It is a rare acquired macular hyperpigmentation of the oral mucosa and lips which is frequently associated with longitudinal pigmentation of the nails.[28] The pathogenesis of this syndrome is unknown and unlike PJS, no systemic involvement and malignancy vulnerabilities have been found.[28] Some other differential diagnoses of PJS include juvenile polyposis syndrome, hereditary mixed polyposis syndrome, PTEN hamartomatous tumour syndrome, and Carney Syndrome.[3]

MANAGEMENT

The principal therapy for patients with PJS is to eliminate the presenting polyps, which are the core origin of PJS-related complications. The majority of polyps develop inside the gastrointestinal tract, making endoscopy the first choice for visualization. Endoscopic polypectomy may be executed for small (<1 cm) polyps, while laparoscopy or laparotomy is preferred for the larger (>1 cm) polyps.[20] Polypectomy is recommended for all polyps identified to reduce the risk of polyp-related complications and evolution to malignancies.[18] The nature of polyp development – particularly large polyps - in patients with PJS frequently causes repeated bouts of obstruction and intussusception, creating repetitive laparotomy and resection procedures of the gastrointestinal tract.[27] These surgeries may lead to bowel adhesions and short bowel syndrome morbidities, adding even more burden to the patients. According to ESGE and ESPGHAN, it is recommended that elective polypectomy should be done for polyps >2 cm to prevent incidence of intussusception.[23,26] However for those who are symptomatic, all obstructing polyps should be eliminated regardless of size.[26]

Kopacova et al described two endoscopic methods which are often used to diagnose and manage the polyps, i.e. intraoperative enteroscopy (IOE) and double-balloon enteroscopy (DBE).[24] The DBE technique is the preferred choice because it essentially does not demand for laparotomy to access the small intestine, avoiding the need of surgery.[27,29] In children, Belsha et al have reported the use of DBE to be effective with minimal risk.[30] Nonetheless, the DBE modality should be considered for PJS patients with a history of abdominal surgery, especially if repeated, regarding the risk of altered anatomy and existence of adhesions.[25] For these patients, a repeat laparotomy is the only way to clear up the polyps. Subsequently, the IOE method can be chosen to further thoroughly examine the gastrointestinal tract and remove all detected polyps – small and large ones – from the lumen.[27] The endoscopic polypectomy procedure (snare endoscopy) must be commenced carefully

since there is always a risk of bleeding and perforation, particularly for patients with thin intestinal walls, short pedunculated polyps, and sessile-type polyps.[25]

In a circumstance where there is no DBE device available, a single-balloon endoscopy (SBE) technique is an alternative consideration. Korsse et al have mentioned a similar performance and diagnostic value between SBE and DBE for small intestine evaluation.[25] An enteroscopy study by Bizzarri et al using SBE to treat children with PJS in a hospital in Italy concluded the therapeutic use of such a method is effective.[31] Another study in Taiwan by Chen et al have also reported similar positive outcomes for both SBE and DBE techniques.[32] Meanwhile, Goverde et al has described that MRE can be used as an alternative for DBE to visualize and detect the lumen, since that both methods have similar diagnostic yield for polyps ≥15 mm.[33] However, unlike MRE, DBE has an advantage because the DBE allows for direct intervention right after the detection of polyps.

A number of potential medications to manage PJS has been described to inhibit the cells' proliferation. Sirolimus (rapamycin) and everolimus have been reported to be quite efficacious in some preclinical studies.[34] Both drugs are classified as mTOR pathway inhibitor. A human study by Klümpen et al has achieved successful partial remission in a PJS patient suffering from an advanced pancreatic cancer.[35] They reported a partial response of the carcinoma's acinar cells and clearance of colon polyps concomitantly. Moreover, there was not any significant adverse reaction other than mild myalgia/athralgia. Meanwhile, a mouse study by Wei et al using rapamycin as the trial drug has shown to reduce the polyp burden, indicated by decreased microvessel density seen in polyps from the rapamycin-treated mice.[36] The authors suggested that rapamycin may have an antiangiogenic property. However, given the current dearth of drug research in PJS, these drugs are still unused as a standard for treatment of PJS patients to date.[23]

In addition to sirolimus and everolimus, cyclooxygenase inhibitor (COX inhibitor) drugs have also been reported to be potentially used as medication for the patients with PJS. A study by Rossi et al in mice with induced PJS (STK11/LKB1 mutant) has exhibited a metabolic increase in the COX-2 pathway among the mice, signifying that the use of such medicine may give benefit to reduce the polyps' tumorigenesis.[37] This was confirmed in the in-vivo, human study by Udd et al, observing an 86% decrease in polyp burden with the consumption of celecoxib, a COX-2 inhibitor drug.[38] Similar to the mTOR pathway inhibitor nevertheless, the use of COX inhibitor as standard therapy has not been established.

The PJS-related mucocutaneous pigmentations will fade away with time in most cases. Even so, it may issue a cosmetical problem, creating a psychological stressor for the patients. Laser therapies (intense-pulsed light, Q-switched ruby laser, CO2-based laser) can be offered to improve the lesions.[18]

COMPLICATIONS

Adhesions, intestinal obstructions, and short-bowel syndrome due to recurrent abdominal surgeries are the most common complications occurring in PJS patients. The utilization of an endoscopy method for polyp resection can avoid the necessity for surgery to reduce the risk of complications.

A report by Utsunomiya et al studying 222 patients with PJS has described the four most common complications detected in the included patients, i.e. obstruction (42.8%), abdominal pain due to infarction (23%), ulcerative rectal bleeding (13.5%), and polyp extrusion (7%).[6] A study by Hearle et al recruiting 225 PJS patients detected a mutated STK11 gene among 60% of the studied patients and 48% had experienced an intussusception during their life.[39] There was no significant difference in the number of patients suffering PJS-related complications between those who had a mutation in STK11 gene and those who do not have such a defect. A case report by Burgmeier et al has described a gastric outlet obstruction as a complication in a neonate.[40]

MALIGNANCY SCREENING AND EDUCATION OF THE PATIENTS

Patients with PJS have a significant risk of developing malignancies even from a relatively young age.[41] An article by Soiman and Holloman states that 48% of patients with PJS developed cancer, of which 73% emerged outside the gastrointestinal tract, i.e. breasts, pancreas, thyroid, multiple myeloma, and skin.[20] A review by van Lier et al reveals the relative malignancy risk in PJS patients to be 4.8-18 times, compared to the general population, with lifetime cumulative cancer risk up to 93%.[41] The mean relative cancer risk appears to be higher in females than males, and the organs in the digestive and reproductive systems have highest risk of acquire malignancies.[6] Table

2 displays the percentage of relative cancer risks for individual body organs and the mean age range for the first appearance of respective organ-related malignancies.

Table 2. Relative cancer risk and mean age range in patients with Peutz-Jeghers Syndrome.[10]

Body organ	Relative cancer risk (%)	Mean age range for first appearance (years)
Stomach	29	30-40
Small bowel	13	37-42
Pancreas	11-36	41-52
Breast	32-54	37-59
Ovarium	21	28
Uterus	9	43
Cervix	10	34-40
Testicle	9	6-9
Lungs	7-17	47

Given the high number of such relative cancer risk percentages, a regular cancer surveillance for patients with PJS is of paramount importance. Generally, the ESGE recommends to start surveillance using VCE tool when the patients' age turn 8 years old, with an interval of 1-3 years.[26] This is also in line with ESPGHAN guideline which recommends to start surveillance no later than 8 years old. If no polyp is found, the next examination should take place at age 18 years, with the same interval.[10] More detailed, a 2018 clinical guideline issued by the National Comprehensive Cancer Network (NCCN) gives recommendations pertaining to optimal age to start regular screening in PJS patients to minimize the cancer risk:[42]

- Breast cancer : around age 25 years old
- Colon or stomach cancer : about late teenage
- Small bowel cancer : around age 8-10 years old
- Pancreatic cancer : around age 30-35 years old
  (or 10 years younger than the earliest age of familial onset)
- Ovarian/cervical/uterine cancer : around age 18-20 years old
- Testicular cancer : around age 10 years old

A variance in time interval recommendations for surveillance in patients with PJS exists; Tan et al, van Lier et al, and the ACG have proposed recommended time intervals for the screening in their respective articles (Table 3). These recommendations were developed based on their respective literature reviews,[27,41] local clinician's experience and expert opinions.[41]

Table 3. Starting age to begin cancer risk screening in body organs and their respective time interval for patients with Peutz-Jeghers Syndrome.

Body organ	Tan et al (2010)[27]		van Lier et al (2010)[41]		ACG (2015)[10]	
	Starting age (year)	Time interval (year)	Starting age (year)	Time interval (year)	Starting age (year)	Time interval (year)
Stomach	10	2	20	2-5	8, 18	3
Small bowel	10	2	20	2-5	8, 18	3
Large bowel	20	2-3	25-30	2-5	8, 18	3
Pancreas	30	1-2	30	1	30	1-2
Breast	25	1-3	30	1	25	1
Ovarium	20	1	25-30	1	25	1
Uterus	20	1	25-30	1	-	-
Cervix	-	-	25-30	1	25	1
Endometrium	-	-	25-30	1	25	1
Testis	10	1	10	1	Birth to teenage	1

Due to paucity of available clinical trials to assess surveillance effectiveness, different authors may give different timing recommendations.[18,41] In addition, they also suggested the optimal ages to begin the surveillance, which differ from the 2018 NCCN guideline. Annual hemoglobin level checking is also critical for the patient, regarding the possibility of recurrent anemia that commonly occurs in PJS.[6] Furthermore, ESGE has suggested that the surveillance should be done even earlier than the recommended starting age if the patient starts to show symptoms.[26]

Breast cancer screening can be performed using methods such as x-ray mammography, ultrasound, MRI, and also self-examination.[18] MRI offers greater sensitivity over mammography and ultrasound, although expensive and may not be widely available or tolerated by some patients.[18] Meanwhile, there is insufficient evidence to support regular screening for genital tract malignancies in patients with PJS. Nevertheless, Beggs et al advocates 2-3 yearly cervical smears using liquid-based cytology from age 25 years and testicular ultrasound if an abnormality is found during the clinical examination.[18] Again, due to the dearth of clinical trials, there is still no evidence to support other body organs' screening surveillance, e.g. pancreas and thyroid.

Although the ESPGHAN states that cancer incidence in children with PJS is very rare,[23] patients with PJS should still be informed about the cancer risk and potential complications that may result in later adulthood. The overall risk of cancer development increases dramatically, starting from the fourth decade of life (Table 4). The malignancy risk screening should be routinely performed to monitor for emergence of cancer tissues in the patient. In male children with suspected PJS, the presence of gynecomastia and signs of accelerated growth should raise suspicion for the treating clinician as this may indicate the occurrence of Sertoli cell tumor.[23] Similar to their male counterparts, the female children with PJS should also be routinely screened for sex cord tumor because of the increased risk for such tumor in these children.[23] PJS as a hereditary illness implies that such syndrome has a probability to be inherited to patient's offspring. Hence, genetic counseling is necessary for patients with PJS to inform about the transmission risk, in case the patient wants to have children later on.

Table 4. Overall risk of cancer development in patients with Peutz-Jeghers Syndrome.[10]

Age	Overall risk (%)
20	1
30	3
40	19
50	32
60	63
70	81

The chronicity of PJS disease and its relatively high susceptibility for cancer development may lead some vulnerable PJS patients to perceive their health status negatively. Subsequently, these patients might be prone to depression. This problem creates a new burden, which will further decrease his/her quality of life. In such a case, a referral to psychologist or psychiatrist should be done to help the patient cope with the disease.[43,44] A personal history of cancer, female sex, having first-degree relatives with cancer, and a negative coping style are risk factors for a poor psychological outcome in patients with PJS disease.[45]

CONCLUSION

Peutz-Jeghers Syndrome (PJS) is a rare hereditary disease, with gastrointestinal polyps as its most prominent feature. So far, the only approved definitive treatment for the syndrome is to eliminate the polyps found during the extensive inspection of the patient by snare endoscopy or invasive abdominal laparotomy surgery. Patients with PJS have a lifetime risk of various malignancies, rendering them susceptible to acquire depression. Therefore, these patients need to be well-informed and guided by the treating physicians to help in coping with their PJS status. Hopefully the research in PJS continues and results in a better management with new modalities, especially for drug or gene therapies that may aid in alleviating the patient's burden or even curing the PJS disease.

COMPLIANCE WITH ETHICAL STANDARDS

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