UDC 616-006.5-031.81-056.7-053.2
DOI: 10.14739/2310-1210.2024.6.306583

What is known about Peutz–Jeghers syndrome (a literature review)

M. H. Melnychenko*[A,D], E. S. Buriachkivskyi[C,F], L. B. Eliy[B,E]

Odesa National Medical University, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Peutz–Jeghers syndrome (PJS) is an autosomal dominant disease, which in most cases is caused by mutation of the tumor suppressor gene *STK11* and is characterized by the development of hamartomatous polyps in the digestive tract and the presence of hyperpigmented spots on the skin and mucous membranes. Late diagnosis of PJS leads to acute intestinal obstruction or bleeding.

The aim of the study is to summarize the data and current views on the early diagnosis and treatment of PJS in children and processing information on monitoring of PJS complications.

To achieve this goal, we have analyzed the sources of professional literature indexed in scientometric databases for the period 2014–2024. The analysis of the professional literature has shown that the triad is characteristic for PJS diagnosis: pigmented spots on the skin and oral mucosa, digestive tract polyposis, and heredity. The timing of symptom onset is an important aspect that requires further study of the clinical course and prognosis of the disease.

Conclusions. Phenotypic suspicion involves the formation of risk groups using extraintestinal signs – pigmentation of the mucous membranes and lips – an early visual symptom that makes it possible to recognize PJS, prescribing timely examination and treatment long before the onset of complications. Dynamic observation and prevention of complications in risk groups – both in the presence of a family history and in newly diagnosed children with polyps and specific pigmentation should be provided. The main method of PJS diagnosis is endoscopic, and the main treatment is surgical.

Keywords: Peutz–Jeghers syndrome, polyposis, children, diagnosis.

Zaporozhye Medical Journal. 2024;26(6):501-505

***E-mail:** marina_gm@i.ua

Що відомо про синдром Пейтца–Єгерса (огляд літератури)

М. Г. Мельниченко, Е. С. Бурячківський, Л. Б. Елій

Синдром Пейтца–Єгерса – аутосомно-домінанте захворювання, що спричинене здебільшого мутацією гена-супресора пухлин *STK11* і характеризується розвитком гамартомних поліпів у травному тракті, а також наявністю пігментованих ділянок на шкірі та слизових оболонках. Пізня діагностика синдрому Пейтца–Єгерса призводить до виникнення гострої кишкової непрохідності або кровотечі.

Мета роботи – узагальнення відомостей і сучасних поглядів на ранню діагностику та лікування синдрому Пейтца–Єгерса у дітей, а також опрацювання інформації щодо можливих ускладнень цього синдрому.

Проаналізували джерела фахової літератури, що індексуються у наукометричних базах, за період 2014–2024 рр. Аналіз відомостей наукової літератури показав, що для діагностики синдрому Пейтца–Єгерса характерна тріада: пігментні плями на шкірі та слизових оболонках дигестивних отворів, поліпоз травного тракту та спадковість. Строки виникнення симптоматики – важливий аспект, що потребує продовження вивчення клінічного перебігу і прогнозу захворювання.

Висновки. Фенотипова настороженість передбачає формування груп ризику, з огляду на такі позакишкові ознаки, як пігментація слизових оболонок і губ. Це ранній візуальний симптом, що дає змогу діагностувати синдром Пейтца–Єгерса, своєчасно призначити обстеження та лікування задовго до появи ускладнень. Динамічне спостереження та запобігання розвитку ускладнень у групах ризику доцільні і в разі наявності сімейного анамнезу, й у дітей, у яких вперше виявлено поліпи та специфічну пігментацію. Основний метод діагностики синдрому Пейтца–Єгерса – ендоскопічний, основне лікування – хірургічне.

Ключові слова: синдром Пейтца–Єгерса, поліпоз, діти, діагностика.

Запорізький медичний журнал. 2024. Т. 26, № 6(147). С. 501-505

Peutz–Jeghers syndrome (PJS) is a rare and very threatening hamartomatous gastrointestinal polyposis of genetic origin. The polyps can be located in the stomach, small and large intestine and bladder with a high risk of malignization. In addition, this syndrome is characterized by melanin pigmented spots on the skin and mucous membranes, that is the hallmark of this disease [1,2,3,4,5]. PJS was first described in 1921 by the Dutch physician John Peutz, who noted the association between intestinal polyps and mucosal macules among members of a Dutch family [6]. In 1949, the American physician Harold Jeghers proposed the concept of this disease [7].

PJS is an autosomal dominant inherited disease, the only known cause of which is a germline pathogenic variant of the *STK11* gene. About 17–50 % of cases are isolated with no family history of the disease. The syndrome incidence ranges from 1:25 thousand to 1:280 thousand of newborns [3,8,9,10].

In PJS, hamartomatous polyps are located throughout the gastrointestinal tract and can be complicated by bleeding and small bowel intussusception, which can potentially lead to emergency surgery [2,9,11].

Late diagnosis of PJS leads to acute intestinal obstruction or gastrointestinal bleeding.

PJS is phenotypically characterized by melanotic pigmentation of the mucous membranes. These hyperpigmented macules can be distinguished from ordinary freckles, as the latter never appear in the oral cavity, locate near the lips rarely and are absent at birth. The diagnosis is determined by the presence of histopathologically confirmed hamartomatous polyps and at least two of the following clinical criteria: family history, hyperpigmentation and polyps in the small intestine [8,12,13,14,15,16].

Hamartomatous polyposis syndromes are characterized by excessive growth of cells or tissues peculiar to the area in which they usually occur without any predictable neoplastic potential. Hamartomatous polyps consist of normal cellular elements of the gastrointestinal tract, but have a markedly distorted architecture [1,17,18,19]. PJS is associated with specific genetic mutations and an increased risk of developing both intestinal and extraintestinal malignant tumors during life. Large hamartomas often contain foci of adenomatous tissue [14,17,20].

However, owing to the diversity of clinical manifestations and low incidence, there are no recommendations for the diagnosis, treatment and follow-up of PJS.

Aim

The aim of the study is to summarize the data and current views on the early diagnosis and treatment of Peutz–Jeghers syndrome in children and processing information on monitoring of Peutz–Jeghers syndrome complications.

Inheritance and etiology. PJS is inherited in an autosomal dominant manner from a parent who carries the *STK11* mutation. Each first-degree relative of a person with PJS has a 50 % chance of inheriting the same mutation that causes the disease. First-degree relatives include parents, children, and siblings [8,17].

Mutations in the *STK11* gene are found in 70–80 % of patients with PJS. The *STK11* gene is a suppressor gene (encoding a serine/threonine kinase), mapped to the short arm of chromosome 19. The *STK11* gene is known to regulate cell proliferation by arresting the *G1* cell cycle and also plays an important role in apoptosis. Mutations of this gene lead to structural disorders and loss of kinase activity [14,21].

There is evidence about genetic heterogeneity and still undiscovered gene(s) that may be responsible for this disease. Since most mutations in PJS are null alleles dispersed throughout the *STK11 / LKB1* gene, the mutation screening strategies combining both DNA and RNA approaches are preferred. Based on the identification of new mutational mechanisms, the impact of RNA screening on germline *STK11* / *LKB1* mutations in PJS syndrome is discussed [8,13,22].

Loss of *STK11* function leads to cell polarity disruption, activates the epithelial-mesenchymal transition, disrupts apoptosis, angiogenesis and normal cell cycle progression, which ultimately leads to the accumulation of secondary changes in the intestinal epithelium and hamartomatous polyp formation [22]. Due to these different intracellular functions, *STK11* is considered a tumor suppressor gene, and its variants have been identified in various carcinomas and not just in PJS.

New methods of mutation analysis, such as multiplex ligation-dependent probe amplification, are also used to efficiently detect the type of mutation, increasing identification rate up to 94 %. The possibility of other gene mutations causing PJS is also considered. Timely detection of mutation types enables more effective chemotherapy, for example, the identification of a mutation in the *mTOR* pathway that causes PJS has led to the use of *mTOR* inhibitors for chemoprevention of PJS [22,23,24].

According to statistics, in 10–20 % of patients, PJS occurs as a result of a *de novo* mutation without a family history; in 30–70 % of patients, PJS occurs as a result of the *STK11* mutation [5,17,25].

To reduce morbidity and mortality, a lifelong follow-up from early childhood is recommended. It has been shown that the risk of cancer development depends on age with a high cumulative risk of 75–89 % at the age of 70 years [4,5,11,26].

Clinical picture. The diagnosis of PJS is based on clinical criteria that include the presence of two or more characteristic histopathological features: polyps (Peutz–Jeghers hamartomatous polyps) and/or pigmentation of the skin and mucous membranes [2,13,15,16]. Pigmentation is mainly localized on the mucous membrane of the lips and/or fingers, hands, and feet.

Small-bowel polyps can manifest as pseudo-invasion when they penetrate the muscle layer without cellular atypia and can be mistaken for malignant tumors. They are localized mostly in the small and large bowel, but can also be found in the stomach and rectum. Polyp enlargement causes gastrointestinal bleeding and anemia. Polyps over 15 mm can cause intussusception, which requires surgical treatment. The number of patients with PJS who do not require surgical intervention is approximately 30 % at the age of 18–20 years [1,12,27,28].

In children, intestinal polyposis can manifest itself with such nonspecific symptoms as anemia, blood in feces, and signs of malabsorption. One should keep in mind that small bowel intussusception and bowel obstruction caused by polyposis are one of the most frequent and serious complications of PJS in children. In many cases, surgical treatment was performed after the initial diagnosis of PJS in childhood [1,13,27,29,30]. Pigmentation is often found on the lips or around, but can also be found on the mucous membrane of the cheeks, palms and fingertips, phalanges and heels, and the anus. The rash is represented by small hyperpigmented black-brown or brown spots, 1–5 mm in diameter, usually round or longitudinal in shape, prone to fusion. Hyperpigmented spots are the most frequent symptoms and are present in 95 % of patients with PJS. Melanin pigment and melanocytes increase in the basal layer of the epidermis, which can be related to inflammation that inhibits melanin migration from melanocytes to keratinocytes. Pigmentations occur at birth, in early childhood and intensify before puberty. With age, they can become invisible, but often remain on the cheek mucosa. There are no cases of malignant transformation of pigmented spots, which eliminates the need in biopsy, and laser treatment is sometimes used for cosmetic reasons [14,16,26].

Other symptoms are associated with polyps in the gastrointestinal tract (especially in the intestine or sto-

mach) or polyp-related complications. These symptoms usually appear between the age of 10 and 30 years. Signs and symptoms of polyps include abdominal pain, nausea and vomiting, gastrointestinal bleeding, bloody stool, and anemia.

When the gastrointestinal tract is affected, polyps with a diameter of several millimeters to 5 cm or more are formed. Large polyps can cause intussusception and obstruction. Polyps of the small bowel develop over time in 90 % of patients. In the small bowel, a very common location for polyps is the jejunum, followed by the ileum and duodenum, and the gallbladder. Colon, stomach and rectum involvement is observed with disease progression [12,31,32].

Gastrointestinal bleeding is a characteristic manifestation of Peutz–Jeghers syndrome. Occult bleeding often leads to anemia, and children have weakness and physical developmental delay. The mean age of clinical manifestation of bleeding ranges from 10 to 12.5 years, however, in some cases, symptoms develop during the first years of life [2].

Polyps can become malignant during life. Patients with the diagnosed PJS are recommended a regular follow-up using endoscopic gastrointestinal imaging methods.

Diagnosis of PJS. The World Health Organization, Mayo Clinic, Tomlinson and Houston independently proposed recommendations for PJS diagnosis [2,4,26,33]. Among them, the World Health Organization criteria are usually used, namely:

– in patients without a family history, the diagnosis of PJS is made based on three or more histologically confirmed polyps or any number of PJS polyps and characteristic skin and mucosal pigmentation;

– in patients with a family history, the diagnosis can be made based on any number of polyps or characteristic severe mucocutaneous PJS lesions.

The diagnosis is considered final if at least one of the following features is present: distinct pigmentation of the mucous membranes or hyperpigmented macules (periorbital area, lips, nose, fingers and toes, anus); any number of PJS polyps detected in a person with a family history within at least one close relative; two or more hamartomatous PJS polyps of the gastrointestinal tract; family history of intestinal intussusception.

Intraoperative enteroscopy remains a unique method of examining the small bowel and management of pathological findings simultaneously. The examination is invasive, and therefore accurate indications are obligatory [26,34,35].

Today, double balloon enteroscopy in combination with the capsule enteroscopy is the “gold standard” for the diagnosis and treatment of small bowel diseases. Reports on the double balloon enteroscopy suggest that this new method can replace at least intraoperative enteroscopy in many cases [2,33,36].

The following methods are used for polyp detection [34,35,36,37]:

– endoscopic methods (colonoscopy, upper gastrointestinal endoscopy, video capsule endoscopy of the gastrointestinal tract);

– magnetic resonance enterography or contrast CT-enterography;

– examination of blood samples to check for signs of iron deficiency anemia, and genetic blood tests for the presence of the *STK11* gene mutation.

Despite the autosomal dominant type of PJS inheritance and a high risk of malignant tumors, the molecular genetic testing of probands with PJS and at-risk people is not carried out in Ukraine.

Complications of PJS [12,25,27,28,29,30,31,38]: small bowel intussusception, including double intussusception; small bowel obstruction caused by polyps occupying the whole lumen; gastrointestinal bleeding when polyps press on the gastrointestinal tissues and cause bleeding, or in case of malignancy; iron deficiency anemia: blood loss can deplete iron stores and, as a result, lead to anemia.

However, the more intestinal wall incisions performed, the higher the risk of postoperative complications (suture failure, peritonitis, ileal obstruction, intestinal stenosis). Bowel resections of a great extent create a risk of short bowel syndrome and disability of patients [5,12].

Further treatment is based on the preventive removal of polyps over 1 centimeter using endoscopy and imaging techniques to avoid symptoms associated with their growth. Surgical resection is necessary in the case of polyps that cannot be treated endoscopically. Balloon enteroscopy can also be used to remove distal polyps of the small bowel. Surgery is the most common method of treatment for intestinal intussusception due to large polyps [2,4,8,10,12,39].

This strategy has two aims: to reduce the consequences of large polyps, such as bleeding, anemia, and intestinal obstruction; to reduce the risk of developing cancer due to malignant transformation of PJS polyps.

Follow-up. The main sticking point in the follow-up and timely treatment of these patients is the lack of knowledge on PJS among patients and the medical community resulting in delayed diagnosis and early reference. Progress is hampered by the lack of national and international databases for collecting and summarizing data on rare disorders, including PJS. Strict adherence to follow-up protocols will extend the life expectancy of these patients. Genetic counseling should be obligatory for all patients. Gene editing, which is still in the embryonic stages of development, may provide a future for the treatment of these rare inherited diseases [2,8,12,13,14].

Due to the high incidence of small and large bowel cancer in PJS syndrome, it is necessary to perform esophago-gastro-duodenoscopy at 3-year intervals starting at the age of 25, capsule endoscopy starting at the age of 20, and annual ultrasound of internal organs [2,4,5,11].

It is also necessary to create a database and a bank of DNA samples from peripheral blood of patients with PJS in Ukraine and to conduct molecular genetic testing of probands and risk groups. Molecular genetic diagnostics allows to conduct genetic counselling in time, to detect the disease in the risk group for PJS, predict its course and perform surgical intervention due to early polyps malignancy [10,11,32,38].

According to international requirements, in case of family history or detection of PJS, monitoring of the condition in children and adolescents is carried out as follows: colonoscopy and upper endoscopy at the age of 8 years; examination of the small bowel with MRI or endoscopy every 1–3 years starting from the age of 8 years. In case of a negative result, examinations need to be repeated at the age of 18 years. If polyps are detected, endoscopic monitoring is repeated every 1–3 years, depending on the polyp size, number and histopathology. Examination for

signs of premature puberty in girls – every year, starting from the age of 8 years. Testicular examination and checkup for feminizing changes in men annually, starting from the age of 10 years. In addition, depending on the part of the digestive tract and the possibility of malignancy, the following monitoring is generally accepted [2,4,5,9]:

– the rectum: the first colonoscopy is offered at an early age and then repeated every 1–3 years if the result is negative; polyps will be removed by elective polypectomy;

– the stomach: the first esophago-gastro-duodenoscopy is offered at a young age and then repeated every 1–3 years if t he result is negative; polyps will be removed by elective polypectomy;

– the small bowel: enteroscopy with video capsule is offered from the age of 8 years and repeated every 1–3 years; polyps will be removed by elective polypectomy;

– the pancreas: as the risk of developing pancreatic cancer is 30–60 % at the age of 70 years, pancreatic monitoring is recommended as a part of examination protocols, regardless of whether family members have pancreatic cancer or not;

– the mammary glands and ovaries: MRI of the mammary glands, gynecological ultrasound.

So, the main criteria for diagnosis of PJS are the presence of the clinical triad of signs:

– distinct pigmentation of the skin and mucous membranes (phenotype);

– two or more histologically confirmed polyps (histology);

– hereditary disease (medical history).

In the future, the primary and further differential diagnosis of PJS is carried out, which includes the following hereditary congenital syndromes: juvenile polyposis, Birt–Hogg–Dubé syndrome, neurofibromatosis, Gorlin–Goltz syndrome, associated Proteus syndrome caused by the presence of mutated genes.

Conclusions

1. Phenotypic suspicion involves the formation of risk groups using extraintestinal signs – pigmentation of the mucous membranes and lips – an early visual symptom that makes it possible to recognize PJS, prescribing timely examination and treatment long before the onset of complications.

2. Dynamic observation and prevention of complications in risk groups, both in the presence of a family history and in newly diagnosed children with polyps and specific pigmentation, should be provided.

3. The main method of PJS diagnosis is endoscopy, the main treatment is surgical.

4. In case of diagnosis of iron deficiency anemia in children resistant to treatment with iron preparations, the possibility of PJS should be considered.

Conflict of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Надійшла до редакції / Received: 19.06.2024
Після доопрацювання / Revised: 18.08.2024
Схвалено до друку / Accepted: 28.08.2024

Information about the authors:
Melnychenko M. H., MD, PhD, DSc, Professor of the Department of General, Pediatric and Military Surgery with a course in Urology, Odesa National Medical University, Ukraine.
ORCID ID: 0000-0001-9066-4801
Buriachkivskyi E. S., MD, PhD, Associate Professor of the Department of Histology, Cytology, Embryology and Pathological Morphology with a Course of Forensic Medicine, Vice-Rector for Scientific and Pedagogical Work, Odesa National Medical University, Ukraine.
ORCID ID: 0000-0001-7637-674X
Eliy L. B., MD, PhD, Associate Professor of the Department of General, Pediatric and Military Surgery with a course in Urology, Odesa National Medical University, Ukraine.
ORCID ID: 0009-0005-8219-4770

Відомості про авторів:
Мельниченко М. Г., д-р мед. наук, професор каф. загальної, дитячої та військової хірургії з курсом урології, Одеський національний медичний університет, Україна.
Бурячківський Е. С., канд. мед. наук, доцент каф. гістології, цитології, ембріології та патологічної морфології з курсом судової медицини, проректор з науково-педагогічної роботи, Одеський національний медичний університет, Україна.
Елій Л. Б., канд. мед. наук, доцент каф. загальної, дитячої та військової хірургії з курсом урології, Одеський національний медичний університет, Україна.

References

1. Ben Hammouda S, Njima M, Ben Abdeljelil N, Bellalah A, Njim L, Zakhama A. An unusual presentation revealing Peutz-Jeghers syndrome in adult. Ann Med Surg (Lond). 2020;58:87-90. doi: 10.1016/j.amsu.2020.08.034
2. Latchford A, Cohen S, Auth M, Scaillon M, Viala J, Daniels R, et al. Management of Peutz–Jeghers syndrome in children and adolescents: a position paper from the ESPGHAN Polyposis Working Group. J Pediatr Gastroenterol Nutr. 2019;68:442-52. doi: 10.1097/MPG.0000000000002248
3. Xu ZX, Jiang LX, Chen YR, Zhang YH, Zhang Z, Yu PF, et al. Clinical features, diagnosis, and treatment of Peutz-Jeghers syndrome: Experience with 566 Chinese cases. World J Gastroenterol. 2023;29(10):1627-37. doi: 10.3748/wjg.v29.i10.1627
4. Yamamoto H, Abe T, Ishiguro S, Uchida K, Kawasaki Y, Kumagai H, et al. Japanese clinical guidelines 2020 for diagnosis and treatment of Peutz–Jeghers syndrome in children and adults. J Hereditary Tumors. 2020;20(2):59-78. doi: 10.18976/jsht.20.2_59
5. Yamamoto H, Sakamoto H, Kumagai H, Abe T, Ishiguro S, Uchida K, et al. Clinical Guidelines for Diagnosis and Management of Peutz-Jeghers Syndrome in Children and Adults. Digestion. 2023;104(5):335-47. doi: 10.1159/000529799
6. Peutz JLA. A Very Peculiar Familial Polyposis of the Mucous Membrane of the Digestive Tract and the Nasopharynx Together with Peculiar Pigmentation of the Skin and Mucous Membrane. Nederl Maandschr v Geneesk. 1921;10:134-46.
7. Jeghers H, McKusick VA, Katz KH. Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits; a syndrome of diagnostic significance. N Engl J Med. 1949;241(25):993, illust; passim. doi: 10.1056/NEJM194912222412501
8. Amru RL, Dhok A. Peutz–Jeghers Syndrome: A Comprehensive Review of Genetics, Clinical Features, and Management Approaches. Cureus. 2024;16(4):e58887. doi: 10.7759/cureus.58887
9. Shukla RM, Tiwari P, Dariya S, Jain S, Sharma SS, Laddha A, et al. Peutz-Jeghers Syndrome: Lessons to be Learned in the Clinical Diagnosis. J Indian Assoc Pediatr Surg. 2023;28(3):218-22. doi: 10.4103/jiaps.jiaps_197_21
10. Zvizdic Z, Milisic E, Ibisevic N, Pasic IS, Vranic S. Appendiceal carcinoid in a pediatric patient with Peutz-Jeghers syndrome: A case report and comprehensive literature review. Medicine (Baltimore). 2021;100(39):e27389. doi: 10.1097/MD.0000000000027389
11. Wagner A, Aretz S, Auranen A, Bruno MJ, Cavestro GM, Crosbie EJ, et al. The management of Peutz–Jeghers syndrome: European hereditary tumor group (EHTG) guideline. J Clin Med. 2021;10(3):473. doi: 10.3390/jcm10030473
12. Matiyash OY, Didukh IM. [Peutz–Jeghers syndrome with clinical manifestations of mixed intestinal obstruction in a child]. Klinichna khirurhiia. 2019;86(4):74-5. Ukrainian. doi: 10.26779/2522-1396.2019.04.74
13. Daniell J, Plazzer JP, Perera A, Macrae F. An exploration of genotype-phenotype link between Peutz–Jeghers syndrome and STK11: a review. Fam Cancer. 2018;17:421-7. doi: 10.1007/s10689-017-0037-3

14. Fostira F, Mollaki V, Lypas G, Alexandrakis G, Christianakis E, Tzouvala M, et al. Genetic analysis and clinical description of Greek patients with Peutz–Jeghers syndrome: creation of a National Registry. Cancer Genet. 2018;220:19-23. doi: 10.1016/j.cancergen.2017.11.004
15. Rosty C. The role of the surgical pathologist in the diagnosis of gastrointestinal polyposis syndromes. Adv Anat Pathol. 2018;25:1-13. doi: 10.1097/PAP.0000000000000173
16. Shin H, Hur K, Lee JS, Seong MW, Mun JH. Acral Pigmentation in Peutz-Jeghers Syndrome: Dermoscopic Findings and Treatment with the Q-Switched Nd:YAG Laser. Ann Dermatol. 2023;35(Suppl 2): S201-S204. doi: 10.5021/ad.21.215
17. Butel-Simoes GI, Spigelman AD, Scott RJ, Vilain RE. Low-level parental mosaicism in an apparent de novo case of Peutz–Jeghers syndrome. Fam Cancer. 2019;18:109-12. doi: 10.1007/s10689-018-0093-3
18. Jedrzkiewicz J, Quencer K, Matynia AP, Morrow E, Pletneva M, Barraza G. Peutz-Jeghers Type Polyp of the Appendix with Review of Literature. Case Rep Pathol. 2019;2019:7584070. doi: 10.1155/2019/7584070
19. Oluyemi AO, Odeghe EA, Awolola NA. Solitary peutz-jeghers type hamartoma in a Nigerian: A case report of a rare finding and review of literature. Ann Afr Med. 2021;20(4):307-9. doi: 10.4103/aam.aam_37_20
20. Liu BL, Zhou H, Risech M, Ky A, Houldsworth J, Ward SC. Solitary Peutz-Jeghers Type Polyp of Jejunum with Gastric Fundic and Antral Gland Lining Mucosa: A Case Report and Review of Literature. Int J Surg Pathol. 2022;30(5):539-42. doi: 10.1177/10668969211067760
21. Byrjalsen A, Roos L, Diemer T, Karstensen JG, Løssl K, Jelsig AM. Preimplantation genetic testing in two Danish couples affected by Peutz–Jeghers syndrome. Scand J Gastroenterol. 2023;58(3):314-8. doi: 10.1080/00365521.2022.2129031
22. Jelsig AM, Bertelsen B, Forss I, Karstensen JG. Two cases of somatic STK11 mosaicism in Danish patients with Peutz–Jeghers syndrome. Familial Cancer. 2021;20:55-9. doi: 10.1007/s10689-020-00191-4
23. De Brabander J, Eskens FA, Korsse SE, Dekker E, Dewint P, van Leerdam ME, et al. Chemoprevention in Patients with Peutz–Jeghers Syndrome: Lessons Learned. Oncologist. 2018;23(4):399. doi: 10.1634/theoncologist.2017-0682
24. Khanabadi B, Najafgholizadeh SD, Rejali L, Taleghani MY, Tavallaei M, Shahrokh S, et al. A novel stop codon mutation in STK11 gene is associated with Peutz-Jeghers Syndrome and elevated cancer risk: a case study. Gastroenterol Hepatol Bed Bench. 2023;16(3):341-6. doi: 10.22037/ghfbb.v16i2.2751
25. Sado T, Nakayama Y, Kato S, Homma H, Kusakari M, Hidaka N, et al. Extremely young case of small bowel intussusception due to Peutz–Jeghers syndrome with nonsense mutation of STK11. Clin J Gastroenterol. 2019;12(5):429-33. doi: 10.1007/s12328-019-00964-0
26. Haneda R, Sato S, Ohno K, Yoshikawa T, Takagi M. Usefulness of virtual enteroscopy for the detection of small polypoid lesion in the small bowel, a case report. Int J Surg Case Rep. 2020;67:5-8. doi: 10.1016/j.ijscr.2020.01.009
27. Aytin YE, Türkyılmaz Z. A rare cause of mechanical intestinal obstruction due to small bowel intussusception: 'A solitary Peutz-Jeghers type hamartomatous polyp'. Ulus Travma Acil Cerrahi Derg. 2022;28(6):879-83. doi: 10.14744/tjtes.2021.34560
28. Hudson VE, Rooney S, Pursglove S, Bhojwani D, Gourgiotis S. Small bowel intussusception and concurrent jejunal polyp with neoplastic transformation: a new diagnosis of Peutz-Jeghers syndrome. Ann R Coll Surg Engl. 2022;104(3):e84-e86. doi: 10.1308/rcsann.2021.0142
29. Barhmji H, Alsalehi A, Kammasha A, Alkheder A. Uncommon manifestation of Peutz-Jeghers syndrome: a case of jejuno-jejunal intussusception and volvulus leading to small bowel obstruction. J Surg Case Rep. 2024;2024(5):rjae335. doi: 10.1093/jscr/rjae335
30. Kamath B, Doddamallappa S, Roy A, Dhobale S. Small Bowel Intussusception due to Solitary Peutz-Jeghers Jejunal Polyp: A Rare Entity. J Indian Assoc Pediatr Surg. 2023;28(3):250-2. doi: 10.4103/jiaps.jiaps_160_22
31. Verma A, Kanneganti P, Kumar B, Upadhyaya VD, Mandelia A, Naik PB, et al. Peutz-Jeghers syndrome: management for recurrent intussusceptions. Pediatr Surg Int. 2024;40(1):148. doi: 10.1007/s00383-024-05723-y
32. Yoshikawa T, Abe T, Amano H, Hanada K, Minami T, Kobayashi, T. et al. Metachronous triple cancer associated with Peutz–Jeghers syndrome treated with curative surgery: A case report. Surg. Case Rep. 2018;4(1):84. doi: 10.1186/s40792-018-0492-6
33. Iwama I, Shimizu H, Nambu R, Okuhira T, Kakuta F, Tachibana N, et al. Efficacy and safety of a capsule endoscope delivery device in children. Eur J Gastroenterol Hepatol. 2019;31(12):1502-7. doi: 10.1097/MEG.0000000000001513
34. Pennazio M, Rondonotti E, Despott EJ, Dray X, Keuchel M, Moreels T, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Guide- line: update 2022. Endoscopy. 2023;55(1):58-95. doi: 10.1055/a-1973-3796
35. Stasinos I, Kamperidis N, Murino A, Jenkins JT, Warusavitarne J, Fraser C, et al. Single incision laparoscopic assisted double balloon enteroscopy: a novel technique to manage small bowel pathology. Surgical Endoscopy. 2020;18:1-7. doi: 10.1007/s00464-020-07446-2
36. van Leerdam ME, Roos VH, van Hooft JE, Dekker E, Jover R, Kaminski MF, et al. Endoscopic management of polyposis syndromes: European society of gastrointestinal endoscopy (ESGE) guideline. Endoscopy. 2019;51(9):877-95. doi: 10.1055/a-0965-0605
37. Mongardini FM, Nazzaro L, Fuschillo G, D'Alelio A, Gambardella C, Docimo L, et al. Gentle Giant? Giant Gastric Solitary Peutz-Jeghers Polyp. Dig Dis Sci. 2024;69(2):349-54. doi: 10.1007/s10620-023-08240-5
38. Kurihara K, Suganuma T. Appendiceal cancer leading to intussusception detected incidentally during follow-up for Peutz-Jeghers syndrome. Clin J Gastroenterol. 2020;13(6):1136-43. doi: 10.1007/s12328-020-01200-w
39. Tan JR, Co JT. Ischemic Polypectomy Through Detachable Snare and Rubber Band Ligation in Peutz-Jeghers Syndrome. ACG Case Rep J. 2024;11(2):e01272. doi: 10.14309/crj.0000000000001272