Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(4): 85
https://doi.org/10.31083/j.ceog4904085

Case Report

Peutz-Jeghers syndrome a review of gynecological implications and the management of these patients through the presentation of a case report

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Academic Editor: Michael H. Dahan
Submitted: 1 September 2021 Revised: 21 October 2021 Accepted: 29 October 2021 Published: 8 April 2022

Abstract

Background: Peutz-Jeghers Syndrome (PJS) is a rare autosomal dominant genetic condition caused by mutations in STK11 (Serine/threonine kinase 11) gene (OMIM 602216 Serine/Threonine Protein Kinase 11) located in the short arm of chromosome 19 (19p.13.3). **Case**: We report the case of a 4 and ½ year-old female child with a rare Peutz-Jeghers Syndrome. She was admitted to the Clinic of Gynaecology, the Faculty of Perinatology and Gynaecology, Chair of Adolescence Gynaecology and Sexology at Poznan University of Medical Sciences, in order to undergo preventive medical examinations. The patient was accompanied by her mother. Age and sex-appropriate development. Age-appropriate dental condition. Gynaecological examination was conducted. No changes were identified through palpation. Normal ultrasound picture. No symptoms of genital mucosa estrogenization, which is typical of the patient's age. A small amount of vaginal discharge was found. Pap smear was conducted to assess vaginal biocenosis. Lacidobacilli deficiency was found and feminine hygiene products, such as Iladian, were recommended. Melanotic macules around the mouth, typical of Peutz-Jeghers Syndrome were identified. **Conclusions**: Due to the increased cancer risk in patients with Peutz-Jeghers Syndrome, more frequent medical and gynaecological examinations are recommended for the girl. It should be noted that the girl's mother decision to have her daughter examined at such a young age was appropriate.

Keywords: Children; Polyposis; Peutz-Jeghers syndrome

1. Introduction

Peutz-Jeghers Syndrome (PJS) is a rare autosomal dominant genetic condition caused by mutations in STK11 gene (OMIM 602216 Serine/Threonine Protein Kinase 11) located in the short arm of chromosome 19 (19p.13.3).

Peutz-Jeghers Syndrome was first described in 1921 by J.L.A. Peutz, and eight years later, H. Jeghers defined the clinical features of the syndrome. As mentioned earlier, PJS is an autosomal dominant disease, and the first symptoms such as hamartomatous polyps and pigmented skin lesions appear as early as around the age of 12.

Peutz-Jeghers Syndrome is a medical condition with an estimated prevalence ranging from 1:25,000 to 1:280,000 [1]. Polyps along the gastrointestinal tract are found during the second and third decades of life in 80–100% of patients. It should be emphasized that the frequency of their occurrence varies and depends on the section of the digestive system. They most commonly appear in the small intestine (93%) [2,3] colon and stomach. In histopathological examination, they resemble branch-like smooth muscle bundles with the core of polyps composed of stromal tissue and smooth muscles. Colon polyps can resemble adenomatous polyps, increasing the potential for neoplastic transformation. The entire lesion is covered with a properly looking epithelium. Moreover, benign polyps can also be found outside the gastrointestinal tract: in the nose, bronchi, gall bladder and urinary bladder [4].

Peutz-Jeghers Syndrome is a serious cancer-predisposing syndrome. Affected individuals have a 39% risk of developing colon cancer (27–77 years of age), 13% risk of small intestine cancer (21–84 years of age), 36% risk of pancreatic cancer (16–60 years of age), 15% risk of lung cancer, 9% risk of testicular cancer (3–20 years of age), 54% risk of breast cancer (19–48 years of age), 9%

of endometrial cancer, 21% of ovarian cancer (4–57 years of age), 10% risk of cervical cancer (23–54 years of age).

The risk of developing cancer before the age of 20 is 2%, before the age of 30 5%, before the age of 40 17%, before the age of 50 31%, before the age of 60 60%, before the age of 70 85%.

2. Case study

A female patient aged 4 ½ years, with a rare Peutz-Jeghers Syndrome, was presented to the Clinic of Gynaecology, the Faculty of Perinatology and Gynaecology, Chair of Adolescence Gynaecology and Sexology at Poznan University of Medical Sciences, in order to undergo preventive medical examinations.

Age and sex-appropriate development according to the Tanner Scale A1Th1P1. Age-appropriate dental condition. Gynaecological examination was conducted. Virgo, hymen anularis. No changes identified through palpation. Normal ultrasound image. Uterus infantilis. Linear endometrium. Ovaries of age-appropriate size and structure (ovarian follicles of maximum 3 mm).

No symptoms of genital mucosa estrogenization were found, which is typical of the patient's age. A small amount of vaginal discharge was found, and pap smear was conducted to assess vaginal biocenosis. Lacidobacilli deficiency was found. Feminine hygiene products, such as Iladian, were recommended. Labial melanin pigmented macules typical of Peutz-Jeghers syndrome were confirmed during physical examination. The patient's family history: father with Peutz-Jeghers Syndrome (negative molecular genetic test result but in compliance with the clinical diagnostic criteria), the father's brother with testicular cancer, the patient's first cousin diagnosed with leukaemia at the age of 20 years, the father's maternal grandfather with gastrointestinal cancer (no further data available), the father's maternal grandfather's sister with gastrointestinal cancer.

The patient's father did not have the STK11 gene mutation. HRM screening method and DNA sequencing were used in GENSCREEN laboratory. However, Peutz-Jeghers Syndrome cannot be excluded on the basis of the negative genetic test result. Gene mutations can be found in approximately 64% of the PJS patients. The examination does not exclude changes such as large deletions or duplications in the gene (30% of changes in the gene), changes in the gene regulatory sequences and in other genes, not yet known, which may cause Peutz-Jeghers Syndrome. Moreover, skin lesions were found in a first-degree relative of a person with Peutz-Jeghers Syndrome. Therefore, the 4 ½-year-old patient can be diagnosed with Peutz-Jeghers Syndrome without molecular testing.

The patient should undergo rigorous preventive medical examinations, similar to those recommended for the patients with STK11 gene mutations:

(1) Annual complete blood count and liver function tests.

(2) Gastroscopy and colonoscopy at the age of 8. If polyps are found, gastroscopy and colonoscopy should be conducted in another 3 years' time. If not, colonoscopy and gastroscopy should be repeated at the age of 18 and then every 3 years. After the age of 50, every 1–2 years.

(3) Video capsule endoscopy at the age of 8, repeated every 3 years if polyps are present. The procedure can be conducted earlier, if no polyps are found but the patient reports gastrointestinal symptoms.

(4) Clinical breast examination at the age of 18. Breast self-examination performed monthly. From the age of 24 onwards, monthly ultrasound imaging. If abnormalities are detected, MRI or mammography should be included.

(5) Ultrasound examination of the ovaries is recommended once a year, from birth to 12 years of age and then from age 21 onwards.

(6) Screening for ovarian cancer is recommended, with the combined use of transvaginal ultrasound and blood tests for the serum marker CA-125 from age 25 [5–7].

3. Discussion

A characteristic symptom of the hamartomatous polyposis syndrome is mucocutaneous pigmentation observed in infancy and early childhood in the form of dark brown, black or blue spots, 1 to 5 millimetres in size, occurring in over 90% of patients. The spots are observed around the mouth, nostrils, eyes, cheeks, tongue and palate, but also less frequently on the hands, feet, around the navel and perianal area. Skin pigmentation changes may fade after puberty and in adulthood.

In the case of people with a family history of the disease, the diagnosis of Peutz-Jeghers polyposis is made by identifying clinical characteristics based on the adopted diagnostic criteria for the disease:

(1) three or more histologically confirmed Peutz-Jeghers polyps,

(2) any number of polyps, characteristic of PJS in patients with family history of PJS,

(3) characteristic mucocutaneous pigmentation in patients with a family history of PJS.

Women with Peutz-Jeghers Syndrome are at an increased risk of developing malignant neoplasms not only in the gastrointestinal tract, but also in the reproductive organs and the mammary glands [8]. The most prevalent ovarian neoplasms are SCTAT (sex cord tumours with annular tubules) tumours having morphologic features intermediate between granulosa cell tumours and Sertoli cell tumours, which can produce both estrogen and progesterone [3]. Irregular menstruation, postmenopausal bleeding and isosexual precocious puberty can be related to hypoestrogenism. If this is manifested, the tumours are usually benign, multifocal, calcified, small and bilateral.

Sharply circumscribed rounded epithelial nests composed of ring-shaped tubules encircling hyalinized basement membrane-like material are found during a microscopic examination.

The nests can have a simple pattern, with single tubules encircling the rounded hyaline mass, or a complex pattern characterized by communicating tubules encircling multiple hyaline masses. Microscopically, the appearance of the tumours is similar to that encountered in patients with Peutz-Jeghers Syndrome but in minor portions of the tumours some variations from the typical patterns are observed.

Apart from ovarian cancer, patients with Peutz-Jeghers Syndrome can develop endocervical mucinous adenocarcinoma gastric type [9]. It should be highlighted that the diagnosis of the endocervical adenocarcinoma is difficult. It is detected incidentally, usually during hysterectomy for other gynaecologic indications. The prognosis for the patients is generally poor.

It is also worth mentioning that in the girl patient under study, the Peutz-Jeghers Syndrome symptoms are not strongly manifested.

Peutz-Jeghers Syndrome is a rare autosomal dominant genetic condition caused by mutations in STK11 gene (OMIM 602216 Serine/Threonine Protein Kinase 11) located in the short arm of chromosome 19 (19p.13.3) [10–13]. STK11 is believed to be involved in cellular energy metabolism, cell proliferation, cell polarity, p53-dependent apoptosis, the regulation of vascular endothelial growth factor (VEGF) and Wnt signal transduction. Loss of heterozygosity (LOH) due to a mutation, including a deletion in the normal allele, in addition to a germline STK11 mutation, may cause the clinical features of PJS, including gastrointestinal polyposis and cancerization of other organs [14].

The clinical picture shows mucocutaneous melanin spots, hamartomatous polyps and tumours located in various organs. Unfortunately, they also appear as genital neoplasms. The incidence of genital tract, breast and gastrointestinal neoplasms is estimated at 20%–50% [15,16]. The well-known gynaecologic neoplasms associated with Peutz-Jeghers Syndrome include epithelial ovarian and ovarian stromal tumour, endocervical mucinous adenocarcinoma gastric type. The most common ovarian tumours are SCTAT and Sertoli cell tumours [17,18]. It is estimated that approximately 10% of women with PJS will develop SCTAT that require surgery and approximately 1/3 of the patients with SCTAT have PJS [19], with low malignancy potential and good prognosis. Mucinous epithelial ovarian tumours, serous tumours or mature teratomas are rare. The girl should be closely monitored due to the elevated cancer risk, including genital tract cancer risk related to PJS. It is therefore recommended to increase the frequency of medical check-ups and gynaecological examinations. The girl's mother decision to bring her daughter for a gynaecological examination at an early age was appropriate.

4. Conclusions

Adult and adolescent female patients should be particularly closely followed up. They have an estimated 10-fold to 18-fold increased risk of developing cancers of the colon, breast and genital tract.

Full analysis of the genes requires research on a large number of patients in highly specialized centres. The study of the underlying genetic mechanisms of SCTAT and endocervical mucinous adenocarcinoma gastric type related to Peutz-Jeghers Syndrome should be a consequence of a better understanding of the progression mechanisms and the numerous gynaecologic tumours that complicate PJS [20]. Further research in this area should be developed.

Author contributions

KP-R, GJ-B, EJ and MW analyzed the data; WK, MM, W-SK, PM and SG performed the review and editing. KP-R, GJ-B, WK, KW-S, PM, EJ, MM, SG and MW wrote the paper. All authors read and approved the manuscript.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study.

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest. KP-R is serving as one of the Guest editors of this journal. We declare that KP-R had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MHD.

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