CASE REPORT

A 21-year-old female patient with Peutz-Jeghers syndrome

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KEY WORDS

colonic polyposis, endoscopic investigations, Peutz-Jeghers syndrome

ABSTRACT

The paper describes a case of a 21-year-old woman admitted to the Department of Internal Medicine with signs and symptoms of microcytic anemia. The presence of characteristic skin lesions, results of laboratory tests and positive family history led to the diagnosis of a rare colonic polyposis, Peutz-Jeghers syndrome. The article presents also history, symptomatology, recommended tests and treatment of Peutz-Jeghers syndrome. Particular attention has been paid to necessity of periodic endoscopic investigations of the gastrointestinal tract with concurrent polyp resection.

INTRODUCTION Peutz-Jeghers syndrome (PJS) is a rare genetic disorder. Patients affected by the syndrome have numerous dark melanocytic lesions dotting certain areas of the body and numerous polyps within the gastrointestinal tract.

According to Herrer et al. the first report on patients with symptoms characteristic of PJS were noted in the history of medicine already in 1895. In 1921 a Dutch pediatrician – Dr Johannes Peutz described pigmentation changes accompanied by numerous intestinal polyps in 3 generations of a Dutch family.

In 1939 Dr Harold Joseph Jeghers observed similar symptoms and signs in a 14-year-old girl admitted to the Boston Hospital. The family described by Jeghers, in literature referred to as the "Harrisburg family", in which 12 cases of the disease were diagnosed, is the largest family with PJS described up-to-date. Much later in December 1949, Jeghers and his co-workers, McKusick and Katz, used the name of "Peutz-Jeghers syndrome" for the first time. The name was officially accepted in 1954.[1]

A prevalence of PJS is estimated at 1/25,000 to 1/280,000 births. The syndrome is equally common in females and males, appears in every race and all ethnic groups.

PJS is an autosomal dominant hereditary disorder. The associated risk is equal in each pregnancy.

Family disorders constitute 70% of PJS cases. Other 30% of cases occur without any previous family history as a result of spontaneous genetic mutations (*de novo* mutations).[2] A real number of *de novo* mutations is not known because of subtle clinical symptoms that do not allow to diagnose the disease in patient's relatives. A mutation of *STK11* gene (suppressor gene) on the chromosome 19p13.3 is found in approximately half of all the cases. Other name of the gene responsible for the disease is *LKB1*. The gene codes serine/threonine protein kinase. Mutations of *STK11* combined with acquired genetic disorders in the second allele in somatic cells cause formation of phenotypic traits of PJS. The *STK11* gene is located in a telemetric end of the 19th chromosome. Therefore, complete loss of mild type allele because of the telomere shortening or loss of the whole chromosome is possible. The most recent studies suggest existence of a complex of *LKB1* with MO25α protein and STRADα pseudokinase. Presence of STRAD and MO25 subunits is of crucial importance for activity of the *LKB1* gene.[3] Associations of PJS with gene mutation in the chromosome 19p13.4 and *MYH11* gene mutation in the chromosome 16 were confirmed.[4] A gene responsible for susceptibility to psoriasis has been recently discovered in the 19th chromosome. That explains cases of the syndrome associated with psoriasis. The risk of passing the disease by a person with diagnosed PJS and a positive result of the genetic test is 50%. In the case of individuals with a positive result of the genetic test and without a positive family history is also 50%.

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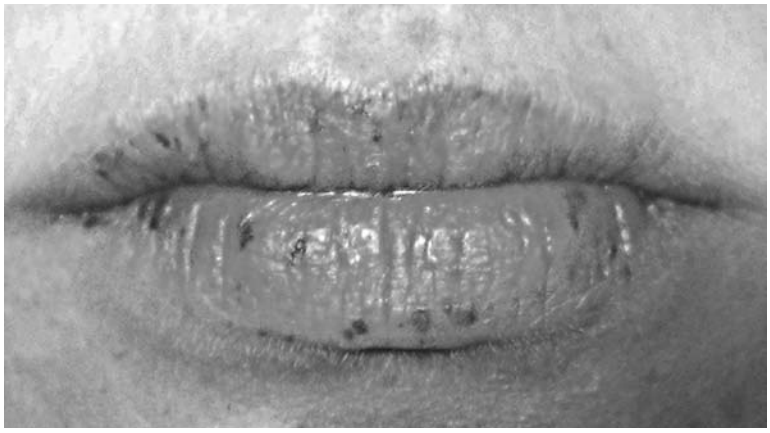

FIGURE Pigmented lesions on the lips of a patient with Peutz-Jeghers syndrome

CASE RESPORT A 21-year-old female patient was admitted to the Department of Internal Medicine in February 2006 with symptoms including weakness, periodical extensive abdominal pain and diarrhea. At the age of 12 the patient was treated in a surgical department because of the symptoms of acute intestine obstruction in the course of intussusception, with partial resection of the ileum (20 cm) with a polyp. Histopathological examination described the polyp as a hamartoma.

Laboratory tests performed in outpatient setting two weeks before hospitalization showed a distinct microcytic anemia: hemoglobin (Hb) – 5.5 g/dl, hematocrit (Htc) – 19.0%, mean corpuscular volume (MCV) – 62.6 fl, mean corpuscular hemoglobin (MCH) – 16.8 pg.

On admission patient was in good general condition. On lips and buccal vestibule mucosa numerous pigmented lesions in form of flat melanin changes of dark-brown and violet color with size ranging from several to over 10 mm were observed (FIGURE). Those lesions appeared when the patient was 2 years old. The patient's mother has had similar pigmented lesions on lips since she was 2 years old. In the age of 23 the mother was operated on because of intussusception of the small intestine (partial resection of the intestine with polyps). Histopathological examination was not performed. No clinical signs characteristic for PJS were noted in the patient's sibling (sister). The patient's father history could not be taken due to the lack of contact. The patient's mother stated that there were no pathological symptoms in other members of the family. Moreover, examination of the patient showed arterial pressure 110/60 mmHg, regular heart rhythm of approx. 88 bpm, body temperature 37.8°C. Normal vesicular lung sounds were audible over lung fields. On examination soft abdomen, a little tender to palpation, negative peritoneal signs, preserved peristalsis were observed. The liver and the spleen were not enlarged, the pancreas was normal. An irregular, mobile and painless mass was palpable within the lower abdomen. *Per rectum* examination showed no pathological mass and trace of feces on the glove. Laboratory tests performed in the Department showed: Hb – 5.3 g/dL, Htc – 19.8%, red blood cells (RBC) – 3.17 M/µl, MCV – 62.6 fl, MCH – 16.8 pg, Fe level –20 µg/dl (norm: >60 µg/dl), reticulocytes 20‰, C-reactive protein – 4.4 mg/l, prothrombin index – 96%, international normalized ratio – 1.05, activated partial thromboplastin time – 30.4 s, total protein – 6.9 g/dl, erythrocyte sedimentation rate – 11 mm/h. The ECG examination showed: heart axis normal, regular sinus rhythm of 75 bpm, no signs of myocardial injury or ischemia. The chest X-ray was normal. The ultrasound examination of the abdominal cavity showed presence of a small volume of free fluid in the peritoneum, mainly in the lower abdomen. At the site of palpable mass in the lower abdomen a conglomerate of the small intestinal loop, with thickened wall, increased peristalsis and inconclusive appearance was visualized, what was an indication for further diagnostic work-up. A loss of contrast saturation in the pyloric region of the stomach was observed on computed tomography (CT). It might have corresponded to a hyperplastic lesion. In the lower abdomen there was an abnormality with signs of left-sided intestinal intussusception. Occult blood test was negative. In the performed intestinal passage, an irregular loss of contrast agent in the pylorus, sized 7 × 5 cm, with cyclic outline and low mobility compared to the gastric wall was observed. Gastroscopy showed non-obstructed esophagus; in the stomach, a tumor in the half-length of the posterior wall, with uneven surface, with diameter of approx. 5–7 cm was found. On the anterior wall and in the antepyloric area there were numerous tubercles, with diameter of 0.5–1 cm. Samples have been obyained for histopathological examination which showed polypus hyperplasticus. In stromal tissues there was local abundant inflammatory infiltration composed of lymphocytes and cells of the macrophage series. Suspicion of malignant hyperplasia was not justified on the basis of the obtained presentation.

The diagnosis of PJS was made on the basis of the obtained history, subjective examination and results of the laboratory tests.

During the hospitalization the patient received a transfusion of 3 units of RBC concentrate which resulted in improved general condition and Hb to 11.0 g/dL, Htc – 36.8%, MCV – 73.3 fl, MCH – 30.3 pg. The patient was referred for further therapy and observation in the Department of Gastroenterology and Hepatology in Warsaw (Maria Skłodowska-Curie Oncology Center).

DISCUSSION The case of a 21-year-old female patient with severe anemia, uncommon skin lesions and a tumor-like lesion detected on gastroscopy has been presented here. Further diagnostic evaluation to establish causes of the observed pathologies led to diagnosis of PJS.

The syndrome is characterized by presence of both polyps in the gastrointestinal tract and numerous pigmented lesions of *lentigo*-like in the

mucosa. Hamartoma polyps, characteristic for PJS, occur most commonly in the jejunum, ileum and duodenum, but may be also present in the stomach and large intestine of affected patients. Prevalence of polyps (according to a study on 182 patients) is 96% – small intestine, 27% – colon, 24% – rectum, 24% – stomach (reported in 1962).[5] Polyps were also found in the respiratory tract, ureters, bile ducts and genitals. A size of polyps may be variable, ranging from 0.1 to 10 mm, but much larger polyps are sometimes observed, and their growth is usually very slow. They are commonly located on a long pedicle and have a tendency for self-amputation causing gastrointestinal bleeding. Hamartoma polyps originate from smooth muscle cells of the lamina muscularis of the mucosa. Adenoma-type polyps may rarely be observed besides hamartoma. A phenomenon of polyp infiltration resembling invasive cancer is characteristic of PJS.

The number of polyps may reach a thousand, although usually it does not exceed one hundred. Polyps may favor chronic bleeding and cause secondary anemia; they may attribute to diarrhea, constipation, periodical abdominal pain, and even to intestinal obstruction leading to necessary urgent surgical treatment and partial resection of the intestine. The average age of patients with diagnosed polyps and first gastrointestinal symptoms is 12.5 years.

Melanoderma appears in early childhood (usually before the 5th year of life, rarely at birth). Those are dark-brown spots around lips, eyes, nostrils, in the private parts area and buccal mucosa. Pigmentation of the palm and feet skin is also common. The lesions, size ranging from several to over 10 millimeters, may blanch with age. They do not have a tendency toward neoplastic transformation. They are caused by hyperpigmentation of the epidermal basal layer. From the histological point of view those are spotty lesions of *lentigo*-like with tree-like structural disorder lamina muscularis of the mucosa.

Girls may suffer from menstruation disorders and less common symptoms of precocious puberty resulting from hyperestrogenism caused by the hormone secretion from benign ovarian cancers. In males testicle tumors and gynecomastia may occur.

Individuals with PJS are at higher risk of cancer – both in the gastrointestinal tract and other organs. It must be noted, however, that the risk is much lower compared to other genetically determined diseases. According to some authors, malignant transformation of polyps occurs in as much as 20% of cases; other authors report the rate of 5–15% of cases. Total age-related risk of cancer is 1%, 9%, 15% and 33% for the age 30, 40, 50 and 60 years, respectively. The risk of breast cancer in 40-year-old women is 8%, and 31% at the age of 60. The most common cancers in PJS patients are observed in the gastrointestinal tract: colon (39%), stomach (29%), small intestine (13%), and pancreas (36%), lung (15%), ovary (21%), urinary bladder (9%), testicles (9%).[6]

Diagnose of PJS is based on the following:

1) histopathologically determined type of polyp – hamartoma
2) at least 2 of the following clinical symptoms:
   a) positive family history (PJS is inherited as a autosomal dominant trait)
   b) hyperpigmentation of mucosa, in the genital area or on the finger skin
   c) presence of polyps in the small intestine.

According to some physicians, diagnosis should be based only on the presence of 2 of the clinical symptoms, without a necessary histopathological confirmation. Usually PJS is diagnosed only after surgery for the so-called "acute abdomen", when a section of intestine with a polyp, obtained during the surgery, is examined.

Prenatal diagnostic evaluation in pregnancies in high-risk of PJS is feasible based on DNA testing of cells obtained during amniocentesis at 12th–16th week of pregnancy or of cells from trophoblast biopsy obtained at 6th–10th week of pregnancy. It is recommended that tests associated with mutation of the gene responsible for PJS should be performed prior to a planned pregnancy.

Patients with PJS should be covered by special medical examination programs and remain under close medical supervision, mainly because of the increased risk of cancer localized in the gastrointestinal tract and elsewhere.

A recently suggested program of prophylactic examinations for patients with diagnosed PJS includes:

1) for both sexes:
   a) colonoscopy once every 2–3 years, starting from the age of 18
   b) endoscopy of the upper section of alimentary tract once every 2–3 years, starting from the age of 8
   c) endoscopic ultrasonography and possibly a CT or CA 19-9 determination once every 1–2 years, from the age of 25
2) for women:
   a) monthly self-examination of breasts starting from the age of 18
   b) annual mammography or ultrasonography of breasts and medical breast examination once every 6 months
   c) annual intravaginal ultrasonography and CA 125 determination, from the age of 25
   d) annual medical history taking and subjective examination for benign ovarian tumors, from birth to the age of 12
   e) gynecological examination and cytology, from the age of 21
3) for men:
   a) annual medical history taking and subjective examination for testicle Sertoli cell tumours, from birth to the age of 12
   b) ultrasonography of testicles to be considered, once every 2 years during the a/m period.

No separate recommendations of periodical examination for children from families affected by PJS but showing no clinical symptoms of the disease were defined.

Endoscopic examinations and polypectomy remain the basic method of PJS diagnostics and therapy. Surgical endoscopy is used for removal of polyps from the small intestine, but double-balloon endoscopy is a method of choice.[7] It is a modern technique used in examination of the small intestine that allows low-invasive examination of the whole length of the intestine, collecting specimen and performing endoscopic surgical procedures. Endoscopic ultrasonography is also a satisfactory diagnostic method, especially in case of rare diseases, such as PJS. A study by Fukomoto et al. presents experiences gained during echoendoscopy performed for the examination of the small intestine and confirms effectiveness of the method.[8] An endoscopic capsule is a promising diagnostic technique, more effective than X-ray and CT of the abdomen, and especially useful in detection of minor lesions in the small intestine. Despite the fact that biopsy cannot be performed during the examination due to its low invasiveness, it is an excellent diagnostic procedure.[9] Dynamic development of gastrointestinal tract imaging techniques allows also increasingly precise analysis using the most modern techniques, including computed tomographic virtual colonoscopy, magnetic resonance (MR)/CT enteroclysis, or less invasive MR/CT enterography.

Good outcomes in removal of persistent mucosal lesions are achieved using a ruby or argon gas laser.

Intensive studies on application of non-steroidal anti-inflammatory drugs (NSAID) in therapy of people with PJS have been continued for over a decade. It is suggested that the drugs are able to delay polyp development. Studies confirmed that polyps occurring in the syndrome have increased cyclooxygenase-2 (COX-2) enzyme level. It should be noted, however, that NSAID-induced inhibition of COX-1 and COX-2 is associated with numerous side effects. There are no clinical tests confirming effectiveness of selective NSAID inhibiting only COX-2.[10]

Isolated in 1975, rapamycin is a promising drug in PJS therapy. Potential therapeutic route of the drug is a result of inhibition of kinase coded by the *STK11* gene. Effectiveness of rapamycin is supported by studies on mice carried out in 2007, confirming inhibitory effect of the drug on the growth of hamartomatous polyps.[11]

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