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Case report

A Thirty-Seven-Year Follow-Up of Peutz–Jeghers Syndrome across Three Generations

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SUMMARY

Peutz-Jeghers syndrome (PJS) is a rare genetic disorder with autosomal-dominant pleiotropic inheritance, variable penetrance and characteristic signs of the disease that predisposes persons to increased risk of developing cancer, particularly in the gastrointestinal tract and the breast. Due to genetic nature of disease, in the familial Peutz–Jeghers syndrome, a multiplication of symptoms in the three-generation family members was established.

This paper represents an insight into the anamnesis of PJS in one family over thirty-seven years of follow-up, and is part of the broader study of this disorder. Article presents family history, clinical and histological findings and multiplication of symptoms of PJS across three generations.

Over thirty-seven years, PJS has been present in this family in the form of only mucocutaneous pigmentation but without clinically manifested signs (father), or with both melanine hyperpigmentation and gastrointestinal hamartomatous polyposis (his daughter and her son).

The symptoms rose suspicion of the existence of PJS complication, i.e. carcinoid-like syndrome with watery diarrheas accompanied by constipations in the affected mother and son who were surgically treated. Diagnosis of PJS was histopathologically confirmed in both cases: the presence of the polyps with hamartomatous pattern and conspicuous hyperplasia of chromogranin-positive (EC and L cells) and serotonin-positive (EC) cells. Malignant transformation of PJ- removed polyps was not found. Besides hamartoma, polyps as well as a tubular adenoma were found, with a low degree dysplasia without malignant transformation (son).

The authors discuss the findings in relation to the important role of the gastrointestinal endocrine cell hyperplasia, not only for better understanding of the growth and clinical symptoms of the PJ polyposis, but also for new approach and the possible application of anti-hormonal therapy in the treatment of these patients in the future, that is not currently in use.

Key words: **Peutz- Jeghers polyposis, gastrointestinal endocrine cell hyperplasia, immunohistochemistry**

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INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare (1) autosomal-dominant disorder characterized by the occurrence of hamartomatous polyps in any part of the alimentary tract and mucocutaneous dark blue or dark brown pigmentation on the lips, perioral and buccal regions, as well as on the hands and feet (1-6). The incidence of PJS ranges from 1/50 000 to 1/200 000 live births (6-7). Molecular pathogenesis of gastrointestinal polyposis in PJS has been linked to the mutation of a tumor suppressor gene known as STK11/Lkb1 on chromosome 19p13.3 that encodes the serine/threonine kinase STK11 (also named LKB1) (7-8). This gene has variable penetrances that cause differentiated phenotypic manifestations in people with PJS. This means that the signs of the disease are similar in nature but vary between different cases of the disease.

There are usually fewer than 20 polyps present in each case, and they vary in size from several millimeters to more than 5 cm in diameter (5-7). Hamartomatous growth of normal-appearing tissue transforms polyp into a benign neoplasm over time. However, some authors have reported not only solitary PJ polyps, but also their odd origin in mucosa of the upper and lower respiratory tract and gall bladder and malignant alteration in younger patients. The appearance of PJS symptoms that include abdominal pain, rectal bleeding, anemia, small intestinal intussusceptions, bowel obstruction, and rectal prolapse of polyps typically occur in the second or the third decade of patient's life (1-7).

CASE HISTORY

We report the members of the three-generation PJS family, followed up over 37 years: father, his two daughters and older daughter's son. The father had only characteristic mucocutaneous melanin pigmentation, however, without gastrointestinal polyposis. He had neither endoscopical nor surgical polypectomy of the gastrointestinal tube, but he died at 52 years of age from primary liver cancer. His younger daughter had neither gastrointestinal polyposis nor mucocutaneous pigmentation, but died from breast cancer. Her two daughters are alive and in good health. Older daughter was 14 old (37 years ago) when she was urgently hospitalized for a one-week history of bloody diarrhea, increasing painful abdominal cramps, nausea and vomiting, which caused the suspicion of ileus. Abdominal ultrasonography (US) confirmed the diagnosis displaying the presence of large (24x16mm) solitary polyp in the form of obstructing, circumscribed, pedunculated mass originating from the jejunum. Minimal jejunal resection and polypectomy were performed urgently. Macroscopically, solitary, large dark hyperaemic polypoid mass was found at the lead point of the intussusception. Histologically, the polyp consisted of branching bundles of muscle fibers derived from the muscularis mucosa and covered by hyperplastic small intestinal mucosa, without dysplasia, corresponding to Peutz-Jeghers type hamartomatous polyp. Hyperpigmentation was present on the lips and around the mouth and on the buccal mucosa. She died from large cell lung cancer at the age of 38.

The only alive member of this PJS family is the son of the older daughter, who is twenty-five years old now. So far, he has been operated four times with a diagnosis of ileus: at 8, 10, 20 and 21 year of age. Nine giant polyps were removed from the small intestine and one from the rectum.

Figure 1. Large cauliflower-like, pedunculated and lobulated PJ polyp pattern

The first laparotomy and surgical resection of jejunal large polyp (22 mm in the greatest diameter) were done when he was 8 years old, the second intervention was the resection of ileal large polyp (33 mm) exhibiting haemorrhagic infarction due to itussusception at the age of ten (Fig.1); the third bisegmental jejunal and one-segmental ileal resection were performed at the age of 21. The last three surgical specimens contained four large PJ polyps, three in the jejunum (22 to 33 mm) and the largest (55 mm in diameter) in the ileum; in the surrounding of

these two polyps that also exhibited haemorrhagic superficial infarction due to intussusceptions, the bulk of polyps one millimeter in size was found. The fourth surgical resection of the largest sigmo-rectal hamartomatous polyp (70 mm in diameter) was done after one year, when he was a 22 years old. Abdominal ultrasonography discovered small polyps in the stomach and one in the gallbladder that have not induced symptoms so far, and are controlled every sixth months.

MATERIALS AND METHODS

Tissue specimens obtained from the resected polyps were fixed in 10% buffered formaldehyde, routinely processed and embedded in paraffin. Sections were stained with: HE, Grimelius', Masson's argentaffine reaction and formaldehyde-induced fluorescence methods. For immunohistochemical study (LSAB2 method), we used the antibodies for the following antigens: Chromogranine A, NSE, Synaptophisin, Serotonin, Desmin and Ki-67, according to the manufacturer's protocol (Dako, Glostrup, Denmark).

PATHOLOGY

Macroscopically, all polyps exhibited a cauliflower-like, pedunculated and lobulated pattern, except for the small-sized ones that were of sessile type. Histologically, branching bundles of smooth muscle cells, confirmed with anti-desmin antibody (Fig. 2), separated intestinal glands into lobules, were covered by hyperplastic small intestinal type of epithelium, intermingled with scattered areas of low grade intraepithelial dysplasia, mostly in the superficial villous areas that surrounded haemorrhagic infarction due to intussusception. One seemingly small-sized polyp was in fact tubular adenoma with low grade dysplasia. Immunohistochemical analysis with MIB-1 showed higher proliferative activity only inside the fields covered by dysplastic cells. In addition, the hamartomatous polyps of the jejuno-ileal localization contained the striking chromogranine positive neuroendocrine cell hyperplasia of EC (enterochromaffine) and L (large) type (Fig. 3).

Hyperplasia and hypergranulatia of EC cells with strong serotonin immunoreactivity were confirmed immunohistochemically (Fig. 4).

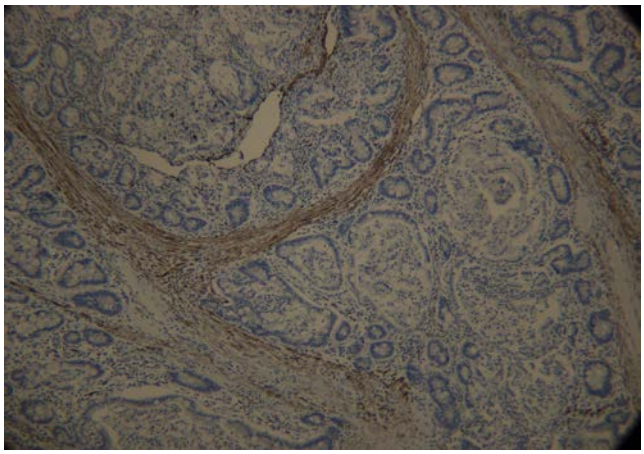

Figure 2. Brunching bundles of smooth muscle cells separating intestinal glands. Anti-desmin anti-body BCL2 x 200

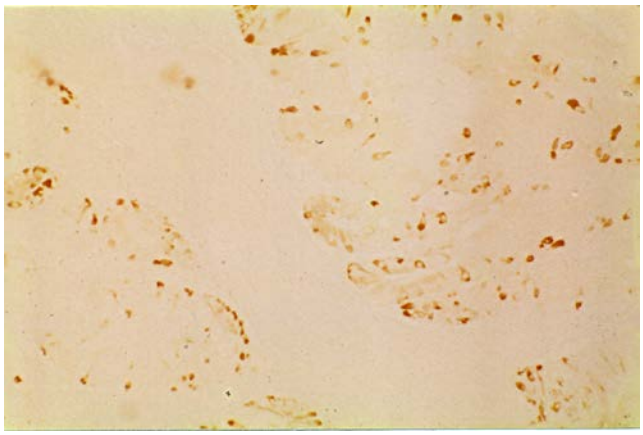

Figure 3. Immunohistochemical high chromogranin A reactivity in EC cell and L cell hyperplasia. ABC x 200

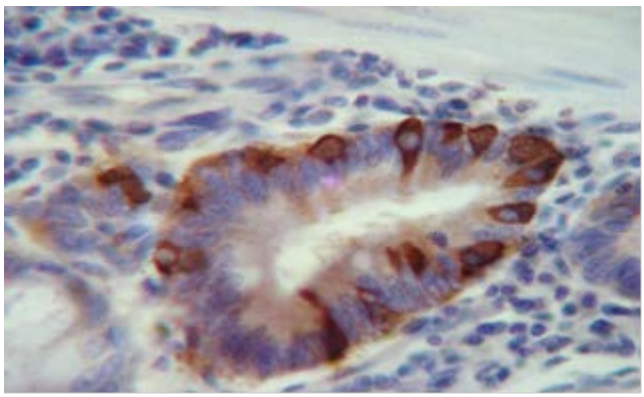

Figure 4. Strong serotonin immunoreactivity of hyperplastic EC cells. LSAB2 x 300

DISCUSSION

The primary description of PJS was published by Peutz in 1921 in one Dutch (Harrisburg) family as gastrointestinal familial polyposis with pigmentations. Jeghers, in his work in 1949, specified the description of disease in 10 cases from different families, and defined the relationship between pigmented lesions, gastrointestinal polyposis and increased risk of carcinoma (6). Approximately, half of his patients suffered from gastrointestinal malignancy (6). The penetrance of disease within the same family is variable i.e. some members will only manifest hyperpigmentation, while others may manifest pigmentations and hamartomatous polyps, which was also confirmed by our results.

Solitary PJ polyps are extremely rare, with an estimated incidence of 1:120 000 (3). In this PJS family, solitary and benign PJ polyps appeared in the small intestine in the second generation (daughter of the first PJS affected member). There were no other surgical polipectomies. Amplification of the disease was obvious in her son, the third generation in inheritance, who is the most affected PJS family member: earlier onset, higher frequency and multiplication, and complication of intestinal polyposis (intussusceptions or ileus) with four polipectomies so far (at 8, 10, 21 and 22 year of age). The reason is, in our opinion, much higher level of inductor hormonal signaling, which was derived from intestinal enteroendocrine cell hyperplasia.

Multifocal epithelial dysplasia, confirmed by high nuclear expression of Ki-67, was found within the superficial third of the largest, ileal, PJ polyp. This finding corresponds to the fact that, although these hamartomatous polyps themselves do not have malignant potential, patients with the syndrome must have an increased risk of developing adenocarcinoma (7-10). When gastrointestinal adenocarcinoma occurs, it probably arises from coincidental adenomatous lesions that we have observed inside the polypous bulk surrounding the largest ileal polyp. Undoubtedly, disturbance of hormonal regulation must increase the risk of developing primarily gastrointestinal carcinoma following PJ polyposis as well as cancers of other locations described in the literature (pancreas, breast, lung, ovary, uterus and Sertoli cell tumours of the testis). The cumulative risk of developing cancer by the age of 70 years has been calculated as high as 85% (4-7).

Gastrointestinal tract is the largest endocrine organ in the body being a source of several endocrine secreting cell types and activities which regulate gastrointestinal functions by paracrine and endocrine ways of signaling. Intestinal hormones such as duocrinin, cholecystokinin, pancreozymin, enterocrinin, enteroglucagon, gastrin, somatostatin, motilin and secretin as well as the amines of histamine and serotonin allow not only the motility of villi and glands secretion i.e. enable the processes of digestion and apsorption, but also protect small intestine from acidic chime, stimulate pancreas to secrete enzymes and help in the growth of the intestinal mucosa (9-10).

Having in mind that the human digestive system behaves like a "high developed centre of hormonal control ", the strong neuroendocrine cell hyperplasia is an expected characteristic of hamartomatous PJP and was confirmed in our previously report (11). Hypersecretion of small intestinal hormones is probably an explanation why those PJ polyps located in the small and large intestine reach the largest size and why these patients have carcinoid-like syndrome with mucionous diarrhoea. The clinical follow-up of the diseased persons such as the last alive member of this family is therefore necessary, as well as further research on the new anti-hormonal therapy, which can save life not only of our patient, but also of many young people in the world suffering from PJ polyposis.

CONCLUSION

It would be very useful to establish therapeutic effect of somatostatin analogues (octatetroide) on both clinical symptoms and growth of Peuts-Jeghers polyps in the treatment of these patients in the future, which requires further research.

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Tridesetsedmogodišnje praćenje Pojc-Jegersovog sindroma kroz tri generacije

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SAŽETAK

Pojc-Jegersov (Peutz-Jeghers) sindrom (PJS) je redak genetski poremećaj sa autozomno-dominantnim plejotropnim nasleđivanjem, promenljivom penetrantnošću i karakterističnim znacima bolesti, koji predisponira obolele na povećani rizik od dobijanja karcinoma, naročito organa gastrointestinalnog trakta i dojke. Kod postojanja familijarnog PJS-a je zbog genetske prirode bolesti utvrđena multiplikacija simptoma kod članova porodice iz različitih generacija.

U radu je prezentovana porodična istorija, umnožavanje simptoma PJS-a, kliničke manifestacije i patohistološki nalaz bolesti kod obolelih članova porodice iz tri generacije.

Tokom 37 godina praćenja nađeni su različiti simptomi prisustva PJS-a, od samo mukokutanih pigmentacija, ali bez kliničkih manifestacija bolesti (otac), i sa melaninskom hiperpigmentacijom i hamartomatoznom gastrointestinalnom polipozom (njegova ćerka i njen sin).

Klinički znaci suspektni na postojanje komplikacija PJS-a, tj karcinoidni sindrom sa vodenim dijarejama, praćenim opstipacijama kod obolelih, majke i sina, hirurški su i patohistološki potvrđeni. Nađeno je prisustvo polipa sa hamartomskom strukturom i utvrđena hiperplazija hromogranin-pozitivnih (EC i L) i serotonin pozitivnih (EC) ćelija. Osim hamartomskih polipa nađen je i jedan tubularni adenom sa niskim stepenom displazije bez maligne transformacije

Autori naglasavaju važnu ulogu hiperplazije endokrinih ćelija gastrointestinalnog trakta, ne samo sa aspekta boljeg razumevanje pojave kliničkih simptoma i rasta PJ polipa, nego i zbog moguće primene anti - hormonske terapije ovih pacijenata u budućnosti.

Ključne reči: **Pojc-Jegersova polipoza, hiperplazija endokrinih ćelija gastrointestinalnog trakta, imunohistohemija**