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Peutz-Jeghers Syndrome: Quantitative Study on Enterochromaffin Cells in Hamartomatous Intestine Polyps

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SUMMARY

Introduction Peutz-Jeghers (PJ) syndrome is a rare familial disorder with the autosomal transmission characterized by multiple intestinal polyps, mucocutaneous pigmentation and increased incidence of various malignancies. Some clinical manifestations of PJ syndrome may be associated with the serotonin secretion from the enterochromaffin cells (EC).

Objective Since no data have been reported so far regarding EC cells in PJ polyps, the aim of our study was to quantitatively investigate EC population in hamartomatous intestinal polyps in patients with the PJ syndrome.

Methods The samples of surgically removed PJ polyps from family members with the PJ syndrome were collected during 34-year follow-up period. Formalin-fixed paraffin-embedded specimens of twenty-one PJ polyps were stained with HE, AB-PAS, Van Gieson, Fontana-Masson, FIF and Grimelius. For immunohistochemical analysis, the following antibodies were used: chromogranin A, serotonin, Ki-67, desmin, vimentin and cytokeratin in order to eliminate differential diagnostic possibilities and to confirm diagnosis of PJ polyps.

Results Strong EC cell hyperplasia was observed within the tissue of the investigated polyps. Statistical analysis demonstrated significantly higher content of EC cells in PJ polyps than in the normal ileal mucosa.

Conclusion Marked hyperplasia of EC cells within the PJ polyps may be the most important contributor to functional disorders in patients with the PJ syndrome.

Keywords: Peutz-Jeghers syndrome; hamartomatous polyp; enterochromaffin cells; chromogranin A

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is an inherited cancer syndrome characterized by mucocutaneous melanin pigmentation and hamartomatous gastrointestinal polyposis [1-5]. These patients also have an increased risk of the extraintestinal cancer, including tumours of the uterine cervix, testis, breast and pancreas [1, 5, 6]. Polyps are the most common in the small intestine, but may occur anywhere in and outside the gastrointestinal tract. They are hamartomatous in nature, with the bundles of smooth muscle cells extending out from the center of the lesion and becoming progressively thinner as they reach the polyp surface [5, 6, 7]. Cells of the normal small bowel mucosa, including goblet, absorptive, endocrine and Paneth cells line the crypts and villi of the small intestinal PJS polyps. Columnar and goblet cells predominate in the surface portion, whereas Paneth and endocrine cells lie at the crypt bases next to the muscularis framework [5-10]. The characteristic prominent mucocutaneous pigmentation, if present, allows the diagnosis of asymptomatic patients in familial cases, although the hamartomatous PJS polyps constitute the main clinical hallmark [2, 4, 5].

Since some people with PJS are asymptomatic, genetic testing is suitable for confirmation of PJS. Nowadays, the only identifiable mutations causing PJS affect the STK11 (serine/threonine protein kinase 11 alias LKB1) gene, located on chromosome 19p13.3. Although the exact mechanism of action of STK11 gene protein products has not been elucidated completely, these proteins are suggested to play significant role in growth inhibition. Mutations in STK11 may represent loss of heterozygosity at the tumor suppressor gene locus [5, 11, 12]. Recent study has strongly suggested that STK11 genetic alterations are disease-causing events in PJP [11].

More than 30 peptide hormone genes expressing more than 100 bioactive peptides, including the hormonal messengers, e.g. monoamines and eicosanoids, have been recognized so far [9, 13, 14]. The abundance of multiple bioactive peptides secreted by the cells interspersed in the gastrointestinal system make the gut the largest endocrine organ in the body [15]. The enterochromaffin cells (EC) constitute the largest endocrine cell population in the gastrointestinal tract, and were the first gut endocrine cells to be identified [16,

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17]. They have an almost exclusive intraepithelial location, resting on the basal lamina and projecting into the gut lumen with their apical portion. The cytoplasm of the EC cells is occupied by a large number of secretory granules, which are the storage sites of the secretory products [15, 16, 17]. The main secretory product of EC cells is serotonin and the EC cells account for more than 90% of all serotonin synthesized in the body [15]. Minor amounts of peptide hormones, e.g. tachykinins, enkephalins and motilin, may also be synthesized in subsets of EC cells. Secreted serotonin influences adjacent cells by a paracrine action or reach target cells via the circulation.

Clinical manifestations of PJS include abdominal discomfort and pain, intestinal bleeding, anemia, diarrhea, intussusception, obstruction and hypotension [1-5]. Some of these symptoms may be explained by the excessive serotonin secretion.

To the best of our knowledge, no data have been published so far about the number and micromorphology of EC cells inside the polyps of PJS. In addition, dominant symptoms of patients included in this study were abdominal cramping, flushing and secretory diarrhea after food intake, which may all be potentially associated with the excessive serotonin discharge from EC cells. We have hypothesized that hamartomatous polyps found in PJS patients may contain increased number of active EC cells.

OBJECTIVE

The aim of the present study was to investigate EC population using the morphological and quantitative methodology in hamartomatous PJS associated polyps.

METHODS

Patients

This is a report of a three-generation family with the PJS, which has been followed up for 34-year period. The father presented solely with the mucocutaneous melanin pigmentation, but gastrointestinal polyposis had not been observed. He died from consequences of the liver cirrhosis at the age of 54. The older daughter had neither melanin pigmentation nor intestinal polyposis, but she died from breast cancer at 34 years of age. The diagnosis of PJS has not been established in her two children. The younger daughter and her son had typical facial pigmentations and PJS intestinal polyposis. She was 14 years old when she was operated on for removal of jejunal hamartomatous polyp that caused intussusception. She died from non small cell lung cancer at the age of 38. Her son underwent four laparotomies during 15-year period, three for removal of large polyps from the small intestine due to intussusception and one due to removal of 70 mm rectal tumor mass, discovered during the control colonoscopy. The clinical presentation of PJS in the younger daughter and her son was prominently characterized with the secretory diarrheas accompanied by the abdominal cramping, reddish spots on the face and upper extremities, as well as hypotension.

Specimen preparation, histochemical and immunohistochemical staining

Selected samples of 21 surgically removed intestinal polyps of large diameters were fixed in 10% buffered formaldehyde, routinely processed and embedded in paraffin. Ten samples of normal ileal mucosa obtained during the endoscopy served as control. Four μm thick tissue sections were stained with haematoxylin-eosin (HE) stain and Alcian blue pH 2.5 - Periodic acid Schiff (AB-PAS) methods. Following the histological confirmation of hamartomatous polyps, the sections were further stained with histochemical argentaffin Fontana-Masson and formaldehyde induced fluorescence (FIF) methods, detecting the serotonin, the main deposit within the EC cells. In addition, application of Grimelius technique localized neuroendocrine cells through the impregnation of their cytoplasmic granules with the silver salts.

Immunohistochemical analysis was performed using the monoclonal antibodies against chromogranin A (dilution 1:200), serotonin (1:50), Ki-67 (dilution 1:300), desmin (dilution 1:100), vimentin (dilution 1:100) and cytokeratin (dilution 1:50), all provided by Dako, Glostrup, Denmark) and a standard avidin–biotin immunoperoxidase complex detection system according to the manufacturer's protocol (Dako LSAB2R system-HRP). Briefly, 4 μm tissue sections were deparaffinized and rehydrated. Antigen retrieval was performed in 0.1 m citrate buffer (pH 6.0) in the microwave oven. Endogenous peroxidase activity was quenched with 0.3% hydrogen peroxide in methanol. After applying primary antibody, the slides were incubated for 60 minutes at room temperature, followed by the extensive washes with the phosphate-buffered saline. Subsequently, the sections were incubated with the secondary biotinylated antibody and with the streptavidin/avidin–biotin–peroxidase complex solution. Staining was developed using the liquid 3,3'-diaminobenzidine (DAB) substrate kit and counterstained with Mayer's haematoxylin. Negative controls were carried out by omitting the primary antibodies.

Quantitative evaluation of EC cells and statistical analysis

The number of argentaffine and serotonin positive EC cells per 10 high-power fields (HPF), with 1 HPF=0.16 mm^2, were statistically studied. Positive EC cells were counted in ten randomly selected HPFs of tumor sections by two independent pathologists (MK and VK). Control samples of ileal mucosa were also analyzed by random selection of 10 HPF, where the number of argentaffine and serotonin positive EC cells was determined.

The counts of positive EC cells in PJ polyps and normal ileal mucosa are expressed as means (average value) and standard deviations. All data analyses were processed using the Student's t-test in statistical software (SPSS, Chicago, IL) version 12.0.

RESULTS

Clinical presentation

Clinical characteristics of our patients with PJS included severe recurrent colicky abdominal pain, diarrheas, reddish spots on the face and upper extremities, hypotension episodes, rectal bleeding, anaemia and intussusception, manifested in the second decade of life. Secretory diarrhea was a leading symptom in younger daughter until the surgical removal of the jejunal hamartomatous polyp at her 14th year of age, 34 years ago. That large polyp, important pathological hallmark of PJS, had 28 mm in the greatest diameter. Her son had four surgical resections (at 8, 10, 20 and 21 years of age), induced by the acute abdomen. He had almost continually watery diarrheas, 3 times per day, always after meal, associated with flushing of the face and hypotension, but without wheezing. All clinical characteristics of the carcinoid syndrome stopped after the third operation of the small intestine when four large (25, 34, 38, and 55 mm in diameter respectively) and numerous smaller size polyps surrounding them were removed. The largest (70 mm) polyp localized rectally was discovered during the control colonoscopy and was surgically removed, one year later. This polyp was not associated with previously mentioned clinical symptoms. The characteristic prominent melanotic pigmentation looked like freckles; they were localized on the lips, buccal mucosa, eyelids, fingers and around the anus, and were observed in all members of the examined family, but were most evident in younger daughter's son.

Macroscopic characteristics

Macroscopically, PJS polyps appeared as cauliflower-like pedunculated or sessile lesions with the coarsely lobulated outer surface. They ranged in size from few millimeters to 55 mm in the ileum. Grossly, they were indistinguishable from other gastrointestinal polyps. Large polyps have exhibited the hemorrhagic infarction due to intussusception (Figure 1).

Histopathological features

Histologically, brunching bundles of the smooth muscle fibers derived from the muscularis mucosa (Figure 2) were covered by hyperplastic small intestinal mature type of epithelium. The most conspicuous was Paneth cell hyperplasia and hypertrophy at base of the crypts, near the bundles of smooth muscle (Figure 2). The accompanied strong EC cell hyperplasia was discovered by using the antibody for serotonin (Figure 3) and by argentaffin and FIF positive reactions that show large quantity of serotonin deposits (Figures 4 and 5). Additionally, Grimelius staining technique impregnated endocrine cells with silver and confirmed their hyperplasia.

Immunohistochemical staining for chromogranin A, Ki-67, desmin, vimentin and cytokeratin was used as complementary diagnostic tool for confirmation of PJ polyp diagnosis and ruling out of differential diagnostic possibilities.

Statistical results

The number of argentaffin and serotonin positive EC cells per 10 high-power fields in PJ polyps and normal ileal mucosa were 39.48±5.32 and 11.23±1.16, respectively. The number of positive EC cells in PJ polyps was increased compared to these cells in normal small intestinal mucosa, with a statistically significant difference ($p<0.001$).

DISCUSSION

The hamartomatous polyposis syndromes represent a heterogeneous group of disorders, which are inherited in autosomal dominant fashion. The PJS had been described for the first time by Peutz in 1921 and later by Jeghers in 1949 [4, 7]. The incidence of PJS is one tenth that of familial adenomatous polyposis (FAP), with an estimated prevalence of 1 per 50,000 to 1 per 200,000 births [4, 5]. The disease has a variable penetrance, even within families; some members will only manifest hyperpigmentation, while others may manifest pigmentations and hamartomatous polyps. This is in accordance with clinical PJS manifestations in patents from the family that was included in the present study.

Solitary PJ polyps are extremely rare, with an estimated incidence of 1:120,000 [7, 18]. In our 3-band family, only younger daughter presented with solitary and benign PJ polyp in the small bowel. Her son, the third generation, had solitary large hamartomatous polyps at first and second polypectomy, at his 8th and 10th year of age causing an intussusceptions and ileus. During 12-year follow-up, since the second operation, polyps of the various sizes appeared: 3 large in the jejunum and the largest (55 mm in the greatest diameter) in the ileum, 50 cm far from the ileocecal valve inducing the mechanic ileus with the acute abdomen and urgent surgical intervention. With ageing of our patient, PJ polyps increased in size and spread, covering the entire gastrointestinal tract, but without the malignant alteration. Although these hamartomatous polyps do not have malignant potential, patients with the syndrome have an increased risk of developing carcinomas of the pancreas, breast, lung, ovary, uterus and Sertoli cell tumours of the testis, as well as the gastrointestinal carcinoma [1, 5, 6]. When gastrointestinal adenocarcinoma occurs, it probably arises from the coincidental adenomatous lesions, like one

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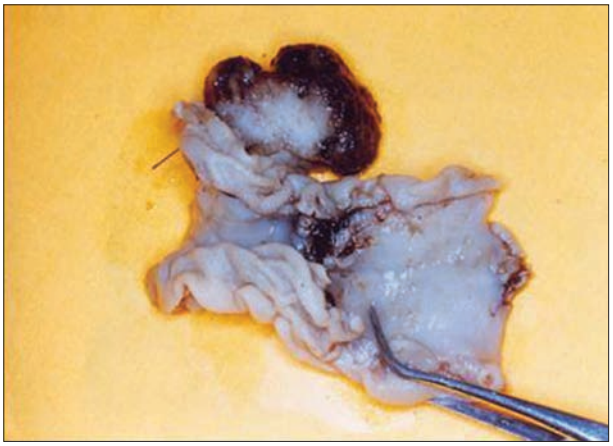

Figure 1. Macroscopic presentation of cauliflower-like pedunculated Peutz-Jeghers polyp with the hemorrhagic infarction causing the intussusception

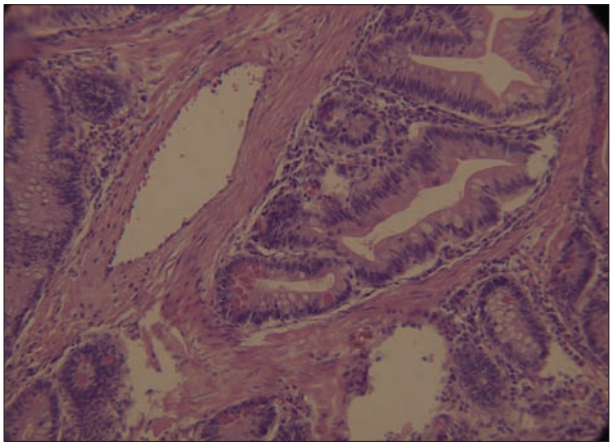

Figure 2. Arborising muscular framework in hamartomatous polyp histopathology. Note the Paneth cells that lie at the crypt bases. (HE stain, ×300 original magnification).

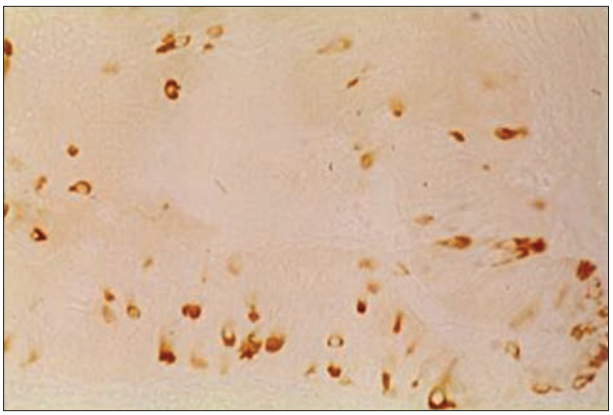

Figure 3. Marked enterochromaffin cells hyperplasia: strong immunoreactivity for serotonin (×300 original magnification)

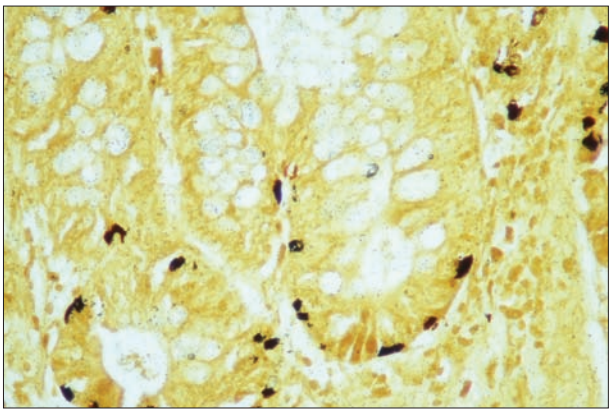

Figure 4. Black granular serotonin deposits in the EC cells (Fontana-Masson stain, ×300 original magnification)

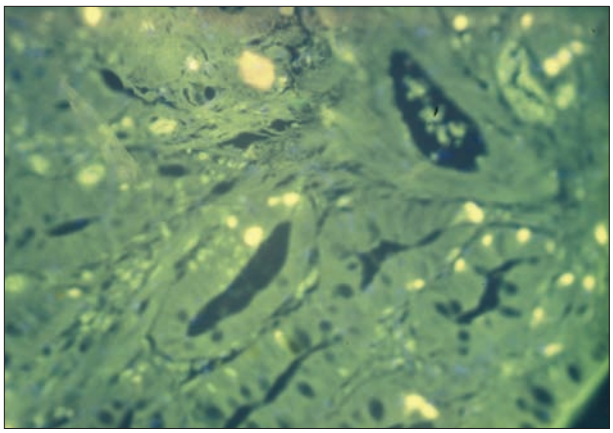

Figure 5. Strong yellow fluorescence of serotonin (FIF, ×300 original magnification)

that we have observed inside the polypous bulk surrounding the largest ileal polyp. The cumulative risk of developing cancer by the age of 70 years has been calculated as high as 85% [8]. Our patient (younger daughter) died at 38th year of age during chemotherapy for non-small cell lung carcinoma.

Considering that our digestive system is a source of various endocrine activities and behaves like a highly developed centre of hormonal control, strong neuroendocrine cell hyperplasia that we found is anticipated characteristic of hamartomatous PJP. Moreover, it is well known that gastrointestinal tract is the largest endocrine organ in the body helping the gastrointestinal function by paracrine and endocrine ways [15]. Intestinal hormones like duocrinin, cholecystokinin, enterocrinin, enteroglucagon, gastrin, somatostatin, motilin and secretin, as well as the amines of histamine and serotonin type, help to move villi and thus help in absorption of digested food components, protect small intestine from the acidic chyme, stimulate pancreas to secrete enzymes and support growth of the intestinal mucosa [19-22].

The EC cells constitute the largest endocrine cell population in the gastrointestinal tract and are derived from the same stem cells as the rest of the epithelium [15, 16, 17]. They have been shown to bind chromium salts and therefore called enterochromaffin cells; because of their capacity to bind and reduce silver ions, they have been also named argentaffin cells. EC cell function remained unknown for a long period of time. However, an endocrine function was early suggested by Feyrter, who proposed a "diffuse neuroendocrine system" in the gut [17,19]. With the introduction of the formaldehyde-induced fluorescence technique, gut endocrine cells were shown to be able to synthesize monoamines, a capacity recognized as APUD (Amine Precursor Uptake and Decarboxylation). The main secretory product of EC cells is serotonin. Secreted serotonin

may influence adjacent cells by a paracrine action or reach distant cells via the circulation. Inactivation of serotonin is accomplished by enzymatic degradation (monoamine oxidase-MAO) in the liver and lung, followed by the excretion in the urine, as the main metabolite 5-hydroxyindoleacetic acid (5-HIA) [14, 23].

Carcinoids, hyperplastic, hypoplastic and metaplastic pathology of the gastric EC cells are well known, but data about the EC cells in PJ polyps are scarce [1]. Our results demonstrating the strong EC cell hyperplasia, hypergranulation and hypersecretion of the serotonin explain functional disorders of secretory diarrhea type and other symptoms of the carcinoid syndrome observed in our patients.

Hypersecretion of the small intestine growth hormones, especially enteroglucagon, the growth hormone of the intestinal mucosa [19, 20, 21], may contribute to clarification why PJ polyps in the small intestine reach larger size compared to other localizations, and why our patients have not only secretory diarrheas, but also constipations. In order to resolve these pending questions, it is necessary to continue the follow up of the only alive member (son of the younger daughter) of this three-generation family with PJS.

CONCLUSION

Marked hyperplasia of EC cells found within PJ polyps may be the most important contributor to functional disorders like diarrhea, flushing of the face and hypotension observed in patients with the PJ syndrome. In addition, pronounced neuroendocrine EC cell hyperplasia and hyperfunction was associated with the increased number of Paneth and goblet cells.

The risk of gastrointestinal and extraintestinal cancer development requires lifelong follow up and regular endoscopic and radiologic screening and investigation of all first-degree relatives of the patient. Although PJS is very rare, early recognition of the disorder is very important for prevention of the significant morbidity and mortality in these patients.

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Појц–Јегерсов синдром: квантитативна анализа ентерохромафиних ћелија у хамартоматозним цревним полипима

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КРАТАК САДРЖАЈ

Увод Појц–Јегерсов (*Peutz–Jeghers*) синдром (ПЈ синдром) је редак наследни поремећај с аутозомном трансмисијом, који се одликује бројним цревним полипима, пигментним променама на кожи и слузницама и повећаном учесталошћу различитих малигнитета. Неке клиничке манифестације могу бити последица лучења серотонина из ентерохромафиних (ЕХ) ћелија у полипима, али засада нема објављених сазнања о ЕХ ћелијама у ПЈ полипима.

Циљ рада Циљ истраживања била је квантитативна анализа популације ЕХ ћелија у хамартоматозним цревним полипима код пацијената са ПЈ синдромом.

Методе рада Хируршки исечци цревних полипа чланова породице са ПЈ синдромом прикупљени су током 34-годишњег периода клиничког праћења. Узорци 21 полипа, фиксирани у формалину и укалупљени у парафину, обојени су *HE*, *AB-PAS*, *Van Gieson*, *Fontana-Masson*, *FIF* и *Grimelius* методом. Имунохистохемијским методама је испитивана експресија хромогранина А, серотонина, *Ki-67*, дезмина, виментина и цитокератина у диференцијалнодијагностичке сврхе и ради потврђивања дијагнозе ПЈ полипа.

Резултати У ткиву испитиваних полипа забележена је изражена хиперплазија ЕХ ћелија. Статистичка анализа показала је значајно већи број ЕХ ћелија у ПЈ полипима него у нормалној илеалној мукози.

Закључак Упадљива хиперплазија ЕХ ћелија у ПЈ полипима може бити најзначајнији фактор у развоју функционалних поремећаја код особа са ПЈ синдромом.

Кључне речи: Појц–Јегерсов (*Peutz–Jeghers*) синдром; хамартоматозни полип; енетерохромафине ћелије; хромогранин А

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