Morphological features of juvenile polyposis syndrome associated with new detected BMPR1A gene mutation. Case report

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Abstract

Juvenile polyposis syndrome (JPS) is characterized by predisposition to developing multiple polyps in the gastrointestinal tract, especially in the colon and rectum. JPS is an autosomal dominant disorder associated with mutations in 2 genes: BMPR1A (bone morphogenetic protein receptor, type 1A) and SMAD4 (mothers against decapentaplegic, drosophilia, homolog of, 4). The authors present a case of JPS in a 9-year-old boy caused by new detected BMPR1A gene mutation. A total of 118 polyps were removed during 3 sessions of endoscopic polypectomy. Total proctocolectomy was performed after first colonoscopy because of unsuccessful endoscopic treatment. Examination of removed colon confirmed multiple juvenile and hyperplastic polyc without malignant transformation.

Key words: BMPR1A gene, juvenile polyposis syndrome, SMAD4 gene.

Introduction

Intestinal polyps are one of the most frequent causes of rectal bleeding in children. There are distinguished solitary and multiples polyps. The majority of children with colorectal polyps have a single lesion, located in the rectosigmoid colon. Histological examination revealed juvenile polyp in the most cases. Multiple occurrence of polyps is called polyposis syndrome. There are three most often occurred hereditary polyposis syndromes: familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome (PJS) and juvenile polyposis syndrome (JPS). Juvenile polyps are also observed in Cowden syndrome (CS), Bannayan-Ruvalcaba-Riley syndrome (BRRS), Gorlin syndrome (GS), Hereditary mixed polyposis syndrome (HMPS). Histological structure of polyps in juvenile polyposis syndrome didn’t differ from soli-
tary juvenile polyps. In children with JPS polyps may be present also in upper gastrointestinal tract (stomach, duodenum) and in the entire small bowel. Three types of JPS: juvenile polyposis syndrome, generalized polyposis and juvenile polyposis of infancy are distinguished. Juvenile polyps are benign tumours but malignant transformation is possible especially in adult patients. JPS is inherited in an autosomal dominant manner. The frequency of JPS is estimate between 1/16000 and 1/100000 persons. Mutation in two genes: bone morphogenetic protein receptor, type 1A (BMPR1A) also known as ALK3 and SMAD4 (mothers against decapentaplegic, drosophilia, homolog of, 4). SMAD4 also known as MADH4 or DPC4 may caused JPS [10, 16]. Products of both genes are involved in the transforming growth factor-b (TGF-b) signaling pathways [8, 9].

We present a case of 9-year-old boy with JPS caused by new detected BMPR1A mutation.

Case report

A 9-year-old boy was admitted to hospital because of recurrence of rectal bleeding. Laboratory data showed mild anaemia (HGB – 9.75 g/dl) with iron deficiency (Fe – 21 mg/dl). Fiberoptic colonoscopy revealed hundreds sessile and pediculated polyps throughout the entire colon. No polyps in the upper gastrointestinal tract were found. Family history of polyposis syndrome and gastrointestinal neoplasm was negative. The size of polyps were ranged from 1–2 mm to 25 mm (Fig. 1). A total of 118 polyps were removed during 3 sessions of endoscopic polypectomy. Histological examination of removed polyps showed typical juvenile polyps: prominent stroma containing numerous small blood vessels, diffuse lymphocytes, plasma cells, polymorphonuclear and eosinophilic leucocytes. Polyps were covered by single layer of cuboidal epithelial cells. Numerous ulcerations, elongated crypts with branching pattern, filled with mucus and inflammatory cells were seen. Examined polyps focally showed histological features of hyperplastic epithelium, without cellular atypia. Total proctocolectomy with ileal-anal anastomosis and isoperistaltic valve was performed 9 months after first colonoscopy because of unsuccessful endoscopic treatment (number of polyps hadn’t decreased in control examination). Histological examination of removed colon confirmed multiple juvenile (Fig. 2) and hyperplastic polyps without malignant transformation (Fig. 3). The patient is on regular follow up since surgical intervention. He is treated with colestyramine and loperamide. Now, one year after surgical intervention, patient feels well, passes about 10 stools daily.

Discussion

Genetic determination of juvenile polyps may be suspected when number of gastrointestinal polyps is above 5 or when presence of every number of polyps is associated with positive familial history of polyposis syndrome [19]. Polyps in colonoscopic examination may be small sessile or pediculated covered by normal or inflammatory changed surface with

Fig. 1. Histological view of juvenile polyp: enlargement of glandular lumen, inflammatory infiltrates and haemorrhages in the stromal space, superficial ulceration covered by granulation tissue. H&E, 200x

Fig. 2. Histological view of hyperplastic polyp: elongation of glands with intraluminal infoldings. Epithelial cells have abundant cytoplasm filled with mucus. H&E, 200x

Fig. 3. Gross appearance of resected bowel (80 cm of large intestine and last 2 cm of small intestine): multiple sessile and pedunculated polyps sized form 0.5 to 3.0 cm. Polyps are also present in the distal surgical margin.
often visible ulceration. Histologic examination showed markedly expanded lamina propria containing cystically dilated glands with ulceration covered by granulation tissue. Two genes are known to be associated with JPS: BMPR1A (bone morphogenetic protein receptor, type 1A) located on chromosome 10q22.3 and SMAD4 (mothers against decapentaplegic, drosophila, homolog of, 4) located on chromosome 18q21.1 [10].

In patients with juvenile polyps differential diagnosis should be performed for exclude others than JPS syndromes.

Juvenile polyposis of infancy is the most severe variant of JPS, which is characterized by presence of numerous polyps in the stomach, small and large bowel. Infants suffer from frequently intestinal bleeding which causes anaemia, chronic diarrhea with protein-losing enteropathy and rectal prolapse. This disease may be revealed in the first weeks of life and in the majority of cases leads to death. Juvenile polyposis of infancy is probably a contiguous gene deletion syndrome caused by the deletion of 2 tumour suppressor genes (BMPR1A and PTEN) [2]. Salvati et al reported a case of polyposis with a significantly milder phenotype (polyps observed only in the colon) caused by similar interstitial deletion of chromosome 10 [13]. Attenuated phenotype of juvenile polyposis of infancy may be caused by increased expression levels of some genes on the remaining chromosome correcting the haploinsufficiency in the 10q22.3-q23 region [14].

Two other diseases are associated with PTEN (phosphatase and tensin homolog) gene mutation: Cowden syndrome (CS) and Bannayan-Ruvalcaba-Riley syndrome (BRRS) [14,16]. The PTEN gene, located on the long (q) arm of chromosome 10 at position 23.3 is a tumour suppressor gene. In patients with CS macrocephaly, trichilemmomas, papillomatous papule and high risk of benign and malignant tumours of the thyroid, breast, uterus, endometrium and skin associated with juvenile polyps are observed [11,19]. BRRS is characterized by intestinal polyposis associated with macrocephaly, mental retardation, lipomatosis, haemangiomass and genital pigmentation [19]. Both syndromes are called as PTEN hamartoma tumour syndrome (PHSTS). Mutations of the PTEN gene are also associated with brain and prostate tumour [12].

Juvenile polyps also occur in Gorlin syndrome (GS) which is characterized by multiple naevoid basal carcinomas, skeletal abnormalities, odontogenic keratocysts, macrocephaly, intracranial calcifications, and craniofacial abnormalities. GS is caused by germline mutations in PTCH (homeologue of Drosophilia patched) gene on chromosome 9q22.1, inheritance is autosomal dominant [5,19].

In patients with Hereditary mixed polyposis syndrome atypical juvenile polyps, with mixed feature of hamartomas and adenomas are observed. This syndrome may be distinguished from JPS on histological examination [19].

Hamartomas gastrointestinal polyps are also observed in Peutz-Jeghers syndrome. This disease is easy to recognize because of presence of characteristic periorbital and perioral mucocutaneous pigmentation. In histological examination admixture of glandular epithelium with bundles of smooth muscle fibers characterized these polyps. STK11 (serine/treonine kinase) gene (also known as LKB1) is associated with PJS [6]. Inheritance of this syndrome is autosomal dominant.

Adenomotous polyps in patients with FAP are readily distinguishable from juvenile polyps in histological examination.

JPS is characterized by various clinical pictures. Some patients may have only few polyps over their lifetime, whereas others may have hundreds polyps. Patients with SMAD4 gene mutation have usually much severe phenotype than patients with BMPR1A gene mutation [3, 17]. Handra-Luca et al observed 42 patients with JPS. SMAD4 gene mutation was found in 9 cases and BMPR1A gene mutations in 5 cases. Polyps in SMAD4 gene mutation carriers were present in the upper as well as in the lower digestive, polyps in BMPR1A gene mutation carriers were seen exclusively in the colorectum. In histological examination high-grade adenomatous lesions were found in 5 from 9 patients with SMAD4 gene mutation and only in 1 from 5 patients with BMPR1A gene mutation low-grade adenomas was found [4].

Malignant transformation of juvenile polyps is estimated from 9 to 50 % [1, 7, 9]. Woodford-Richens et al observed 56 patients with JPS. Fifteen (27%) of them had developed gastrointestinal cancer by the age of 65 [19].

Molecular examination in our patient detected novel mutation of BMPR1A gene (454C>T) located in exon 5 corresponding with extracellular protein domain and caused premature protein termination. New detected BMPR1A gene mutation caused severe clinical symptoms of JPS with necessity of early surgical intervention. In our patient polyps had been observed exclusively in the colorectum as well as in group of patients reported by Handra-Luca et al.

Colonoscopy with electrocoagulation polypectomy is a routine therapeutic modality for colorectal polyps in children [18]. In children with solitary juvenile polyps repeated control colonoscopy isn’t necessary because recurrence of polyps occurs exceptionally. In cases of polyps syndrome repeated endoscopic sessions with histological examination should be performed. Prophylactic colectomy is required in cases in which endoscopic treatment is not able to control polyp development or in case of malignant transformation. In our patient we had decided a surgical treatment because after 9 months of observation and 3 sessions of multiple polypectomy patient still presented numerous polyps.


