CASE REPORTS

RARE CASE OF INTRAINTESTINAL STROMAL TUMORS IN THE PATIENT WITH FAMILIAL ADENOMATOUS POLYPOSIS

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Aim: To describe the case of metachronous gastrointestinal stromal tumors in a proband with familial adenomatous polyposis (FAP), carrier of APC gene mutation in codon 1309. Material and Methods: The physical examination, genealogical analysis and molecular genetic analysis of peripheral blood in 15-years-old girl with FAP and her sister, were carried out. Macroscopic, standard histological and immunohistochemical study of surgical specimens — intraintestinal tumors of the small intestine in proband was performed. Results: Extraintestinal manifestations, including congenital abnormalities of facial skeleton, typical for Gardner’s syndrome, were observed in the sisters with FAP as the addition symptoms of the disease. Frameshift mutation in codon 1309 in the APC gene was detected in these patients. A rare neoplasia — metachronous gastrointestinal stromal tumor was found in proband 15 months after total colectomy for FAP. This is the third case described in the accessible medical literature. Conclusion: The possible role of APC gene mutation in the development of mesenchymal neoplasms is discussed. The study of stromal tumors is important for understanding of their pathogenesis that will enable to develop effective targeted therapy.

Key Words: familial adenomatous polypsis, extraintestinal manifestations, APC gene mutations, gastrointestinal stromal tumors.

In 1951 Gardner described a rare clinical case of familial adenomatous polyposis (FAP) with autosomal dominant pattern of inheritance with almost complete penetrance associated with extracolonical manifestations (ECM), FAP represents less than 1% of all colorectal cancer cases, and is the most common gastrointestinal polyposis syndrome with an incidence of 1:10000–15000 subjects [1, 2]. APC mutations were found in 80% (95% CI 71–87%) of individuals with more than 1000 adenomas, 56% (95% CI 54–59%) in those with 100–999 adenomas, 10% (95% CI 9–11%) in those with 20–99 adenomas, and 5% (95% CI 4–7%) in those with 10–19 adenomas [3]. The human APC gene (OMIM 611731) is located on the long (q) arm of chromosome 5 in band q22.2. Since the identification of the APC gene, more than 1100 unique likely pathogenic germline mutations have been reported (http://www.lovd.nl/apc). The APC gene encodes a protein of 2,843 aminoacids (310 kDa) that plays an outright role in the Wnt signaling pathway [4]. The APC protein functions as a tumor suppressor by negatively regulating the β-catenin oncoprotein. The APC protein leads to ubiquitination and degradation of β-catenin; so in the absence of it, β-catenin accumulates in the nucleus and interacts with factors that up-regulate the transcription of genes involved in cell cycle entry, proliferation, differentiation, migration, apoptosis, and progression [5]. Approximately 15–20% are considered as “de novo” cases without any family history of the disease [6]. In patients with FAP first symptoms are often manifested in puberty. These include dyspepsia with frequent liquid defecation, abdominal pain, anaemia, metabolic disorders leading to a delay in physical development. More than 80% of patients had low level of total protein, albumin, cholesterol, decreased immunity when the disease to progresses [7]. These symptoms increase with the advance of the disease, leading to infantilism, exhaustion that caused to the development of cachexia. The earlier FAP is manifested, the severer is its course, and the sooner decomposition state follows. The average age of the disease manifestation is about 26–33 years [8–10]. FAP often combined with different malignant tumors such as: colon cancer, duodenal and periampullary cancer [11], hepatoblastoma, gastric cancer, thyroid cancer [12], pancreatic and breast cancer [13] that is in 10 or 100 times greater than general population level.

Gardner’s syndrome is characterized by the following ECM used for screening of the disease: congenital malformations of the facial skeleton [8, 14], tumors of soft tissues (desmoid tumors, fibromas, lipomas, epidermal cysts, nasopharyngial angiofibromas), congenital hypertrophy of the retinal pigment epithelium [1, 15]. Desmoid intra-abdominal tumors are detected in 80% of patients with FAP [16]. In more than half of the patients epidermal cysts that can occur on the extremities, face, and head, much earlier than polyps, causing a cosmetic defect, are diagnosed. Multiple osteomas of the mandible, extremities and bone tumors are also frequent. All of these processes affirm the changes of mesenchymal tissue [15].

Gastrointestinal stromal tumors (GIST) are the most common primary mesenchymal neoplasms of the gastrointestinal system. GIST can occur anywhere along the gastrointestinal tract, but most often are found in the stomach (66%) and only 25% of cases — in the small intestine [17]. They may
Primers were used including individual exonic splicing chemical studies of tumors of mesenchymal genesis by standard hematoxylin and eosin. Immunohistochemical study of surgical specimens — in intestinal tumors of the small intestine in proband according to the manufacturer’s specifications [28].

500 sequencer (General Electric Health Care, USA) patterns in the SSCP analysis were further analysed DNA fragments detected in the HD analysis or various national polymorphism (SSCP) [27]. The heteroduplex analysis (HD) and detection of single-stranded conformational polymorphism (SSCP) 

RESULTS AND DISCUSSION
We report a case of a 15-year-old girl with FAP. Colonoscopy revealed multiple adenomas (> 100) in all parts of the colon in this patient. Her sister had polyps in colon and her father had polyps in colon and in stomach. Gardner’s syndrome was diagnosed in proband at the age of 15 years. The diagnosis was confirmed using molecular genetic studies of blood samples. Screening of the APC gene in this case revealed frame shift mutation in codon 1309 (c.3927_3931delAAAGA p.Q1309fs). The mutation leads to premature termination of the APC gene protein product [5, 7]. This deletion is the most frequent mutation in the Polish FAP patients [28]. In Europe its frequency is 8–20%, in Singapore it is 36% of all of APC gene mutations, but it has not been detected in Spain and Portugal [7, 15]. The obtained data show irregular distribution of this mutation in different populations. Although some authors found intra- and inter-family variation of phenotypes in patients with the same APC gene mutation, but in most cases mutation in codon 1309 leads to early onset of the disease accompanied by hundreds of polyps at a young age, early occurrence of colorectal cancer and ECM [15]. 

In proband FAP was combined with congenital anomalies of growth and development of teeth with high arch palate as the typical features of Gardner’s syndrome. Proband’s father, who died at the age of 43 years, was previously diagnosed with polyposis of the stomach and colon, had congenital malformations of the facial skeleton also. Proband’s sister at the age of 13 years was referred to DNA analysis because of the presence of ECM: abnormalities in growth and development of teeth, high arch palate, arachnodactyly, presence of sandal-type gap with fault detection of finger line, joint hypermobility, scoliosis of spine of I–II levels. The marker mutation of the APC gene was confirmed in the sister of proband before the manifestations of intestinal symptoms. Congenital hypertrophy of the retinal pigment epithelium, the frequent phenotypic marker of Gardner’s syndrome, was not found in the proband and her sister. According to the literature data the ECM among relatives of patients with FAP would enable clinicians to predict affected members and provide a useful lead for genetic testing [7, 8].

The pedigree of proband’s family with Gardner’s syndrome is shown in Fig. 1. At the age of 22 years proband underwent total colectomy, supraanal resection of the rectum with ileoanal pouch with the formation of S-shaped anastomosis for FAP. Fifteen months after total colectomy in the proband it was diagnosed an intestinal obstruction caused by tumors with multiple localization in the small intestine, ulceration and secondary inflammatory...
changes. The patient was re-operated on intestinal obstruction caused by the overgrowth of tumors. Operation was completed with the formation single lumen jejunal tube. Microscopic examination of the tumor revealed that it was made up of bundles of elongated fusiform, oval and epithelioid cells interspersed with fibrous layers and located in hyalinized stroma. Some clusters formed palisade-shaped structures. Tumor cells had eosinophilic cytoplasm and centrally located fusiform nuclei contained fine-grained chromatin. Some of them were hyperchromic nuclei. Low mitotic activity was revealed. Necrosis was not observed. The obtained results confirmed the detection of GIST in the small intestine (Fig. 2). Immunohistochemical studies revealed that tumor cells express vimentin (Fig. 3) and CD117 (Fig. 4).

Fig. 1. The pedigree of proband’s family with Gardner’s syndrome

Fig. 2. GIST sample from the small intestine. Hematoxylin and eosin (H & E), × 40

Fig. 3. GIST sample from the small intestine. Cytoplasmic expression of vimentin by tumour cells, × 400

Fig. 4. GIST sample from the small intestine. Marked cytoplasmic expression of CD117 by tumour cells, × 400

Immunohistochemical study also determined that tumor cells do not express desmin and CD34. The negative reaction with antibody to desmin allowed us to exclude the presence of tumor that has arisen in muscle tissue.

In this report we describe a case of GIST in 24-year-old woman in 15 months after total colectomy due to the FAP. Two similar cases of GIST in the small intestine in FAP are described in the literature: a 30-year-old man who presented with severe debilitation, anemia and diarrhea over two months [24] and the 29-year-old woman with metachronous GIST 15 months after proctocolectomy indicating the possible occurrence of these neoplasms after surgery [25]. About 80–90% GIST are known to be caused by KIT proto-oncogene mutations or mutations in proto-oncogene of platelet-derived growth factor receptor alpha polypeptide (PDGFRA), receptor tyrosine kinase (RTK). More than 100 different mutations have been described, each being associated with specific clinical and/or histological property of tumors. Prognosis depends on the spectrum of mutations. In particular, patients with a mutation in the 11th exon of KIT gene respond to treatment better and have a favourable prognosis [29, 30]. Although the role of KIT or PDGFRA mutations in the pathogenesis of GIST is certain, their value in the origin of GIST, which developed in FAP is not very clear, due to low incidence of disease. We have described the case of GIST in the woman with Gardner’s syndrome, the mutation of APC gene carrier. It indicates possible importance of such mutation in the occurrence of this neoplasm. We suggest that is necessary the dynamic monitoring of the proband’s sister, the carrier of marker APC gene mutation, for identify the prognostic dangerous type of neoplasia, including GIST. The study of stromal tumors is given much emphasis in current literature, as understanding of their pathogenesis will enable us to develop effective targeted therapy.

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