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Hepatoblastoma of early childhood as an indicator of Gardner's syndrome

Złośliwy guz wątroby wieku dziecięcego jako wyznacznik syndromu Gardnera

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ABSTRACT

Familial adenomatous polyposis (FAP) is a genetically determined disease characterized by the presence of multiple colorectal adenomatous polyps (usually more than 100). FAP and its variants are caused by mutations in the tumor suppressor gene (adenomatous polyposis coli - APC), located on chromosome 5q21-q22 and also MUTYH gene mutation. This syndrome accounts for about 1 percent of all colorectal cancers. FAP connected with APC follows an autosomal dominant pattern, MUTYH gene mutation is recessively inherited, but up to 25 percent cases are due to new or de novo gene mutations. Clinical manifestations of FAP are not only a presence of multiple colorectal polyps, but also a number of extracolonic manifestation associations with this disease. We present a case of Gardner's syndrome being a rare variant of FAP diagnosed in 21-year-old male patient who has been treated due to hepatoblastoma in early childhood.
Key words: Familial adenomatous polyposis, tumor suppressor gene APC, Gardner's syndrome.

STRESZCZENIE

Rodzinna polipowatość gruczolakowata (FAP) jest uwarunkowanym genetycznie schorzeniem charakteryzujące się obecnością mnogich polipów gruczolakowatych jelita grubego (zazwyczaj>100). Istotę FAP stanowią mutacje (zarodkowe i somatyczne) antyonkogenu w genie supresorowym APC (*adenomatous polyposis coli*) zlokalizowanym na chromosomie 5q21-q22, a także mutacja dotycząca dwóch alleli w genie MUTYH. Zespół ten odpowiada za około 1% wszystkich zachorowań na raka jelita grubego. Dziedziczy się w sposób autosomalny dominujący (mutacja APC), lub autosomalnie recesywnie (MUTYH), lecz 25% przypadków jest związanych z mutacjami powstającymi de novo. Poza obecnością licznych polipów w obrębie jelita grubego, FAP charakteryzuje się występowaniem szeregu objawów pozajelitowych. Przedstawiamy przypadek zespołu Gardnera będącego rzadkim wariantem FAP rozpoznanego u 21-letniego pacjenta, który był leczony we wczesnym dzieciństwie z powodu wątrobiaka zarodkowego.
Słowa kluczowe: Rodzinna polipowatość gruczolakowata, antyonkogen APC, zespół Gardnera.

Udział współautorów / Participation of co-authors: A – przygotowanie projektu badawczego/ preparation of a research project; B – zbieranie danych / collection of data; C – analiza statystyczna / statistical analysis; D – interpretacja danych / interpretation of data; E – przygotowanie manuskryptu / preparation of a manuscript; F – opracowanie piśmiennictwa / working out the literature; G – pozyskanie funduszy / obtaining funds

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Introduction

Familial adenomatous polyposis (FAP), associated with an anti-oncogene /APC suppressor gene/ is a precancerous condition. Colorectal cancer develops in almost every patient, usually before 45 years of age. Such an early development of cancer in FAP patients is associated with the occurrence of a plural number of colorectal polyps (>100) usually between the second and third decade of life. Most of the patients do not present any symptoms, nor any abnormalities in laboratory studies. This condition should be suspected in every patient with more than 10 polyps found during a colonoscopy. The requirement obliges to consider performing a genetic test for mutations of the ACP gene. In case of confirmation of the mutation, family members of the first and second stage should be tested too [1,2,3].

We present a case of Gardner's syndrome being a rare variant of FAP diagnosed in 21-year-old male patient who has been treated for hepatoblastoma in early childhood.

Case report

21-year-old male patient was admitted to the Department of Gastroenterology and Hepatology of Specialist District Hospital in Rzeszow to be tested for familiar adenomatous polyposis given the fact that the condition had been diagnosed in patient's mother. Based on the data from medical history, it was found that at the age of 2 patient had undergone resection of the tumor situated in the left lobe of the liver. It was histologically defined as a fetal hepatoblastoma. Due to the presence of the tumor infiltration of the veins and lymphatic vessels of the resected part, after surgery the patient underwent chemo- and radiotherapy.

When he was 15, he had surgery in Clinical Department of Maxillofacial Surgery of Specialist District Hospital in Rzeszow. The reason was an odontogenic tumor located on alveolar process of maxilla around 21-22nd tooth and related dentocclusal abnormalities (persistent deciduous tooth 61 and impacted tooth 21). The tumor was detected by accident in X-ray of jaw during preparation for an orthodontic treatment. The surgery had revealed a tumor with a diameter of about 15 cm, which was removed. It revealed the 21st tooth crown, which was covered before. Corticotomy was performed. The crown of the tooth was evacuated to impose a catch for ligature of braces. The treatment and postoperative period was held without any complications. Histopathology results of the removed tumor corresponded to odontoma calcificans.

During admission to the Department of Gastroenterology and Hepatology, the patient's condition was good. He denied alcohol abuse or smoking. Physical examination showed psoriasis on trunk skin and on the boarder of the hairy parts of the scalp, as well as hollowed chest. Laboratory examinations during hospitalization did not expose any abnormalities. Markers of the neoplastic process stayed in the reference range. Ultrasonography of abdomen did not reveal any irregularities except resected left lobe of the liver. CT of the abdomen was performed, too. In addition to the removed left lobe, a 5 mm hepatic cyst appeared. The thyroid ultrasound examination was normal. The patient had an ophthalmologist examination, during which retinal pigment rearrangement at the periphery of the retina was found (Fig. 1). Gastroscopy revealed at the bottom and in the core of stomach presence of multiple adenomatous polyps of various sizes from which material for histopathologic examination was taken (Fig. 2). Colonoscopy showed hundreds of sessile and halfpedunculated polyps of different sizes (1-10mm) on the entire length of the colon (Fig. 3). Also, from them, samples were taken. Moreover, small polyps (diameter of 1 to 3mm) were seen in terminal parts of the ileum (Fig. 4). Currently, histopathological examination of all collected samples are not classified as a malignant.

Results of histopathological examination of samples taken during gastro- and colonoscopy:

1. Pars cardiaca ventriculi – Hyperplasia foveolaris
2. The core of stomach, anterior wall – Polypus hyperplastycus
3. The core of stomach – Polypi Elsteri
4. Ileum – Hyperplasia nodularis
5. Ascending colon – Adenoma tubulare (low grade glandular dysplasia)
6. Transfere colon – Polypus hyperplasticus
7. Rectum – Adenoma tubularia (low grade glandular dysplasia).

Based on the data from the medical history, the results of endoscopic examinations and genetic testing (DNA isolated from cells of peripheral blood) performed in Department of Molecular Genetics of Maria Skłodowska-Curie Institute of Oncology in Warsaw, Gardner's syndrome was diagnosed.

Discussion

Gardner's syndrome is inherited in autosomal dominant, associated with mutations in the APC gene form of FAP with a number of extracolonic symptoms related to mesenchymal tissue growth abnormalities. The severity of changes depends on mutations in gene fragment between codons 1403 and 1587 [4, 5]. The incidence in the general population ranges from 2.29 to 3.2 cases per 100,000 people/year. In 20 to 30 percent of newly diagnosed cases, Gardner's syndrome is not present in any of the family members, which shows the creation of de novo mutations [3, 4, 6]. In this syndrome, except multiple polyps, in the entire length of the gastrointestinal tract are nodular skin lesions and soft tissue changes, such as epidermoid cysts, desmoids tumors, cutaneous and subcutaneous fibromas, sebaceous cysts, neurofibromas, lipomas, pigmentary lesions and osteomas of the facial skeleton, and changes in the stomatognathic system [4, 7, 8]. These relate to the

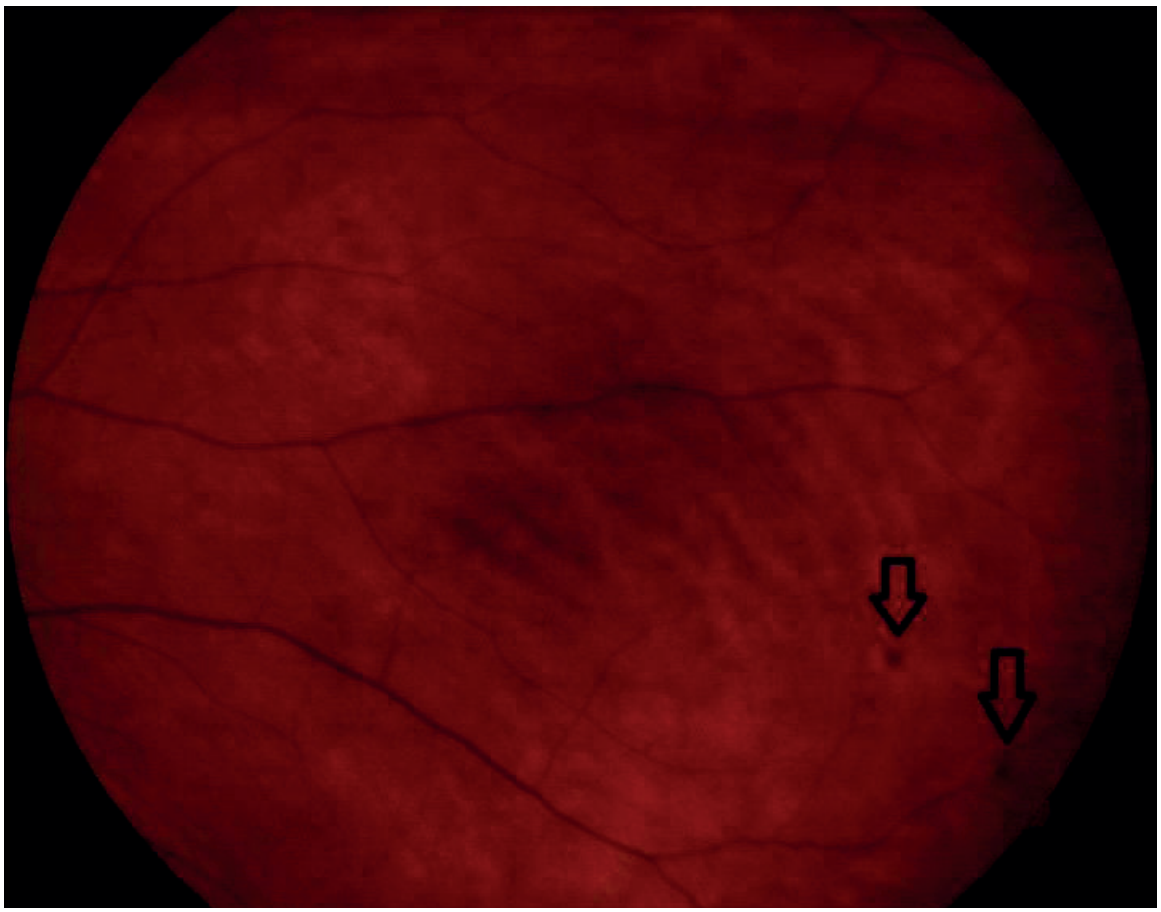

Figure 1. Retinal pigment rearrangement at the periphery of the retina – arrows

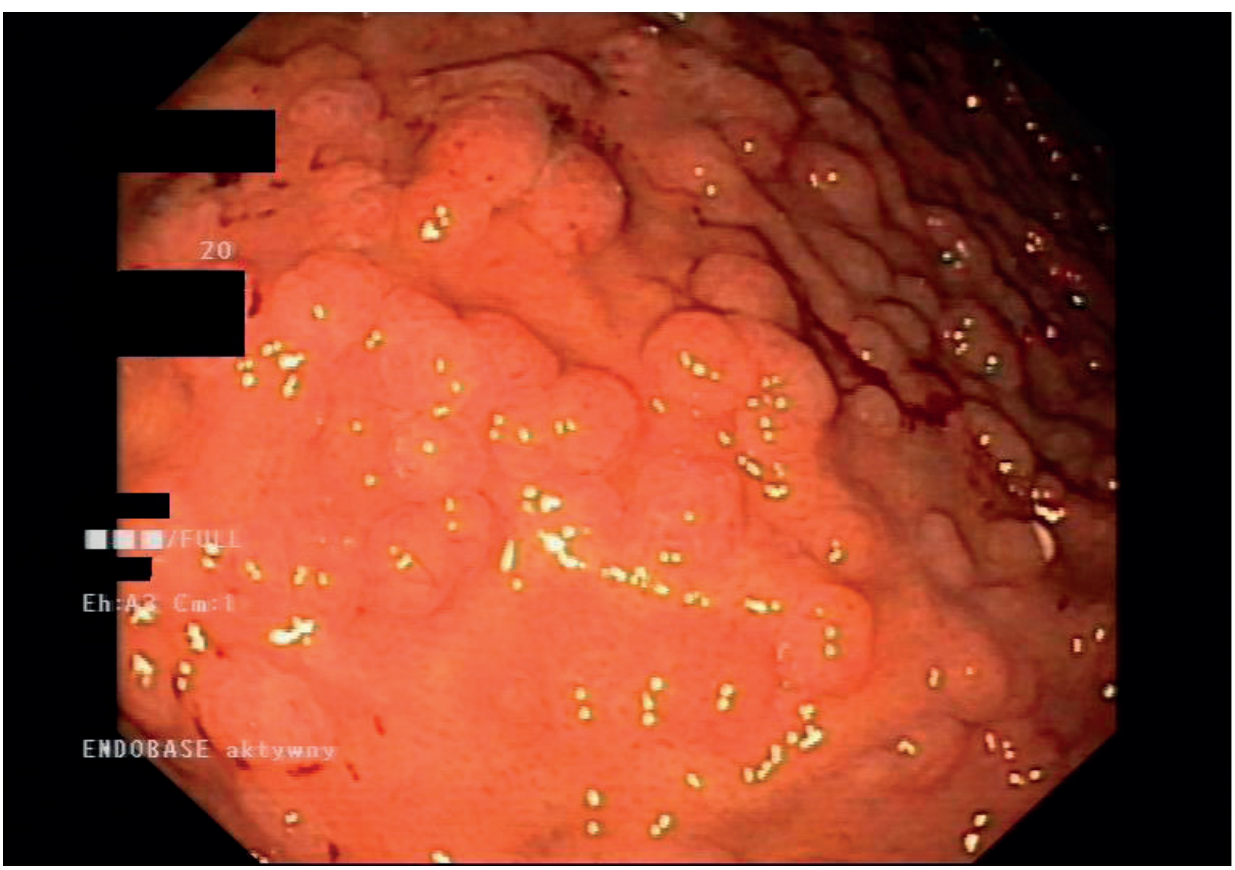

Figure 2. Multiple polyps in the stomach

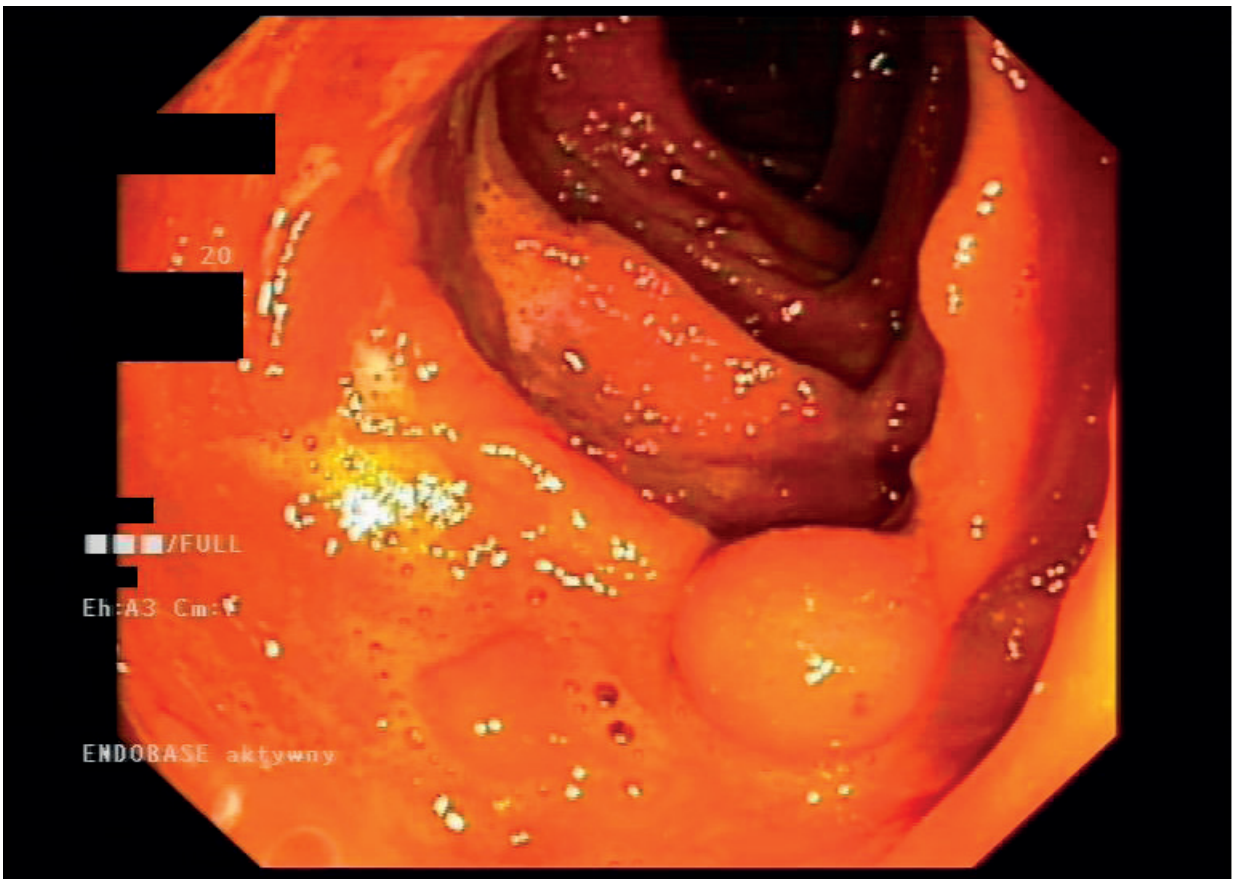

Figure 3. Multiple polyps in the colon

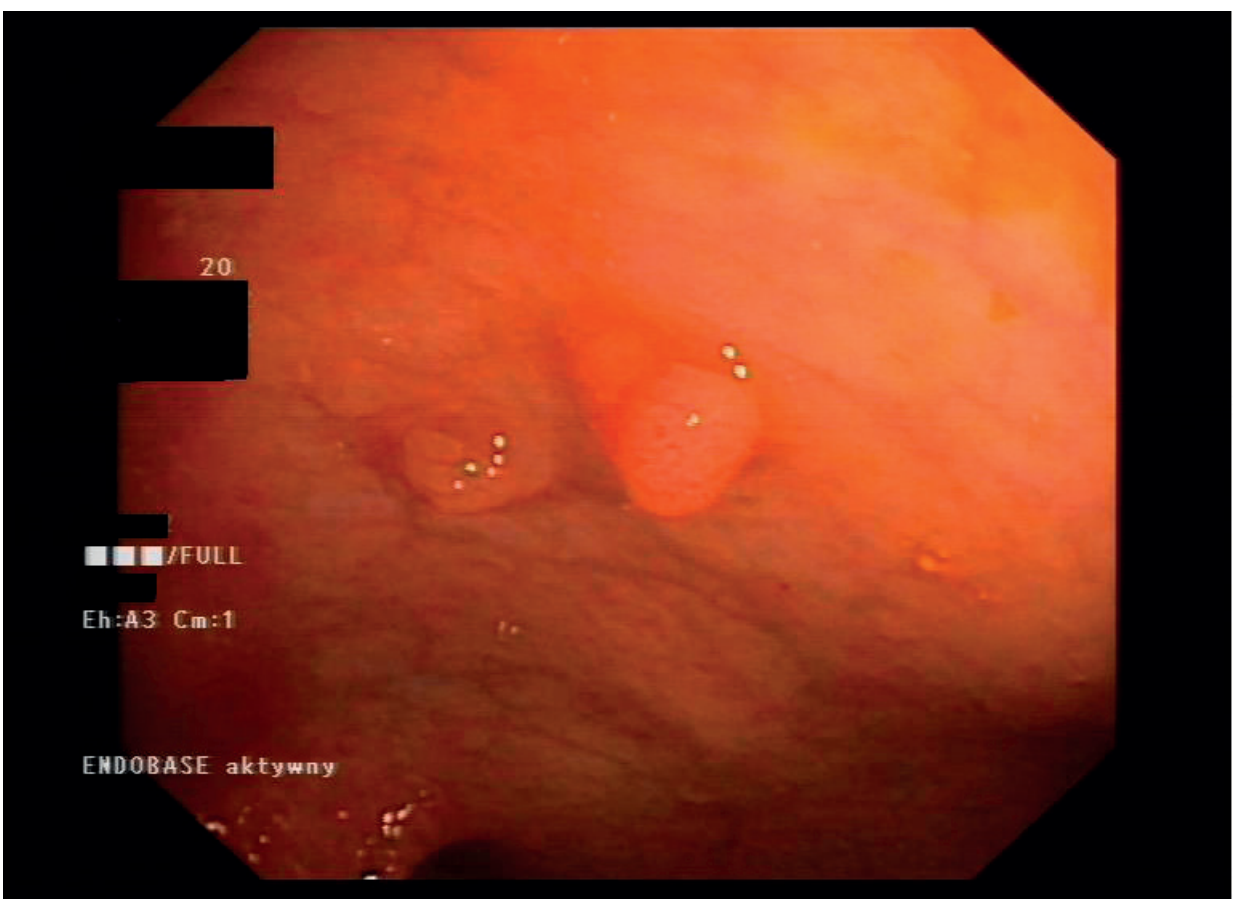

Figure 4. Single polyp in the ileum

Table 1: Spiegelman staging system for the severity of duodenal adenomatosis

Factor	1 point	2 points	3 points
No. of polyps	1-4	5-20	>20
Polyp size, mm	1-4 mm	5-10 mm	>10 mm
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Interpretation: stage 0: no polyps , stage I: 1-4 points, stage II: 5-6 points, stage III: 7-8 points, stage IV: 9-12 points

Table 2. Duodenal endoscopic surveillance interval depending on the patient's Spiegelman classification

Spiegelman Stage	Surveillance interval
0/I	5 years
II	3 years
III	1-2 years
IV	Surgery consideration

morphological abnormalities and the number of teeth (hypodontia, supernumerary teeth, enormous teeth, dentinomas, delayed eruption of permanent teeth). The roots of teeth in patients with Gardner's syndrome are long and pointed [8, 9].

Gardner's syndrome predisposes to the development of tumors both malignant and benign. The spectrum of changes includes cancers of the duodenum and around ampulla of Vater (12%), gallbladder and biliary tract cancer, hepatoblastoma (1,6%), medulloblastoma (<1%), craniopharyngioma, cancer of the thyroid (about 2%), pancreatic cancer (2%), adrenaladenomas (7–13%), osteosarcoma, chondrosarcoma and liposarcoma [2, 4, 6]. The diagnostic symptom suggestive of Gardner's syndrome is congenital hypertrophy of the retinal pigmented epithelium – CHRPE, which is observed in 60-90 percent of patients [3, 5, 10]. This defect can be found in ophthalmic examination by using a slit lamp, as discrete, small, oval or round, dark pigment changes that occur individually or multifocally. The changes do not impair vision [4, 7].

Patients with Gardner's syndrome should be periodically tested for signs of all clinical manifestations of the disease. Endoscopic examination of the lower gastrointestinal tract for the colorectal cancer should begin at 10–12 years of age and be repeated every two years. In the presence of adenomas the test should be repeated every year until the planned colectomy [2, 4, 11, 12]. Close supervision of the duodenum should be initiated in patients around 25-30 years of age. Endoscopic examination of the upper gastrointestinal tract must be repeated with a frequency dependent on the severity of duodenal polyposis according to the Spiegelman's classification (Tab. 1 and Tab. 2) [2, 4, 12].

Palpation and ultrasound of the thyroid should be performed annually starting at 10–12 years of age. BACC should be considered in patients with nodular changes [2, 4]. Palpation and ultrasonography of the liver, as well as marking the level of α-fetoprotein – especially in patients with a positive family history of hepatoblastoma – should be performed every six months until the age of 6 [4, 13].

The risk of desmoid tumors is increased if they were found in the patient's family, when the patient had osteotomas, or had any abdominal surgery. There are no clear guidelines for screening for the presence of desmoids. Sulindac and/or tamoxifen is recommended as a first-line treatment in patients with intra-abdominal desmoid tumors. Chemotherapy and radiotherapy may be helpful in treating desmoids growing aggressively. Surgery is not recommended for intra-abdominal desmoids, but it is the treatment of choice for those located in the coatings [4, 7, 14]. FAP and Gardner's syndrome patients should undergo regular neurological monitoring. MRI of the brain should be considered too, especially when family members were diagnosed with changes in central nervous system [2, 4].

As an adjuvant therapy – to reduce the risk of cancer in patients with FAP – the use of drugs from the group of non-steroidal, analgesic or anti-inflammatory may be considered. Based on the results from clinical studies, demonstrating the efficacy in reducing the size of duodenal polyps in patients with FAP, the Food and Drug Administration (FDA) approved the use of cyclooxygenase-2 inhibitor, celecoxib, as an supportive treatment in this group of patients [2, 4].

Conclusions:

1. Gardner's syndrome should be suspected in patients who have had multiple polyps in gastrointestinal tract and the presence of various symptoms, which are not associated with intestines, especially soft tissue tumors and osteomas.
2. Hepatoblastoma in childhood may be an early indicator of Gardner's syndrome.
3. The closest family members of Gardner's syndrome patients should be included in screening.

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