CASE REPORT

Gardner syndrome with desmoid tumors – case report

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Abstract

Introduction. Gardner syndrome (GS) is characterized as a type of familial adenomatous polyposis (FAP), an autosomal dominant inherited disease which, if left untreated, with 100% risk leads to the development of colorectal cancer.

Case Report. The case is presented of a 40-year-old man who was diagnosed with Gardner syndrome at the age of 12. During his hospitalization, the patient underwent gastroscopy, colonoscopy, and computed tomography (CT) scans of head, neck and abdomen. The examination revealed the presence of extra-intestinal manifestations of GS: desmoid tumours, osteomas, and dental cavities. At present, the patient is scheduled for enteroscopy.

Conclusions. GS is a diagnosis of genetic testing, although clinicians should be aware of the fact that up to 30% of GS cases are detected as de novo mutations. The physical examination should always be performed with accuracy to avoid a too late diagnosis of FAP, including GS, which may result in death.

Key words
colorectal cancer, desmoid tumour, Gardner syndrome, familial adenomatous polyposis (FAP), adenomatous polyposis syndrome.

INTRODUCTION

The two most common inherited colorectal cancers are hereditary non-polyposis colorectal cancer (HNPPC) and familial adenomatous polyposis (FAP) [1]. Familial adenomatous polyposis is an inherited disease in an autosomal dominant manner [2]. It is essential to provide treatment as soon as possible, otherwise, according to the data, an individual with FAP will develop colorectal carcinoma (CRC) with the 100% risk around the age of 40 years [2,3]. Furthermore, prophylactic colectomy is indicated after diagnosis of FAP [2]. It is most often a familial disorder, although 20–30% of mutations arise de novo [2,3]. In the familial type, a germline mutation appears in the adenomatous polyposis coli (APC) gene located on chromosome 5q21–22 [2,4], which affects both men and women 1:1 [5]. Among FAP patients, Gardner syndrome (GS) is recognized in 10% of cases [6]. Although GS is characterized by the triad consisting of FAP, multiple osteomas, and soft tissue tumours, only 38% of individuals with GS show all components of the GS triad [6]. As polyposis remains asymptomatic, it is very difficult to set the proper diagnosis when no extraintestinal manifestation or family history are present [7]. In patients with APC mutation there is a high risk of CRC, gastric cancer, duodenal cancer, thyroid cancer, and malignant dental tumours [8]. Therefore, these patients require long-term follow-up [8].

CASE REPORT

The case is presented of a 40-year-old male with Gardner syndrome who was admitted to the Department of Gastroenterology because of epigastric pain of a stabbing nature, exacerbated on the right side. The pain was not relieved by analgesics and diastolic medications. Then days before hospitalization he had been vomiting with dark clots.

The diagnosis of Gardner syndrome had been made in the patient at the age of 12 years, based on clinical examination and genetic testing. The patient underwent multiple surgeries. At age 13, he underwent surgery of a soft tissue tumour in the thoracic region of the spine. Unfortunately, soon after the surgery, the lesion reappeared. Currently, it remains under observation and is not enlarging. At age 14, a partial bowel resection was performed, and in 2007 a definitive ileostomy was emerged carried out. Other surgeries on abdominal adhesions were performed, including a peristomal hernia operation in 2016, a partial resection of the small intestine in 2020. In 2021, he was hit in the abdomen by a cow and hospitalized. The patient has smoked a pack cigarettes a day for about 24 years.

The patient’s family history was evident. His father was diagnosed at age 30 with FAP and died at age 50 from hepatocellular carcinoma. The patient’s brother was diagnosed at age 11 and underwent a proctocolectomy; he died after surgery performed due to a bowel perforation. The patient’s other siblings, two sisters (aged 47 and 45) and one brother (aged 32), are healthy and do not have any genetic mutation. Figure 1 presents the family pedigree.

Arrow points to the proband (the patient); Squares and circles denote males and females, respectively. Roman numerals indicate generations (I and II). Black squares...
mean FAP mutation detected and the age of FAP diagnosis is written beneath the squares. White squares and circles indicate no FAP mutation.

Laboratory test results were within normal ranges: haemoglobin level – 16.2 g/dL, leukocytes – $8.96 \times 10^9$/L, thrombocytes – $3.41 \times 10^4$/µL, C-reactive protein (CRP) – 0.5 mg/L, iron – 1 170 µg/dL, lipase – 39 U/L, aspartate aminotransferase (AST) – 27 U/L, alanine aminotransferase (ALT) – 45 U/L, bilirubin – 0.71 mg/dL, alkaline phosphatase (ALP) – 91 U/L, gamma-glutamyl transferase (GGT) – 35 U/L, creatinine – 0.92 mg/dL, urea – 29 mg/dL, natrium – 142.0 mmol/L, potassium – 4.25 mmol/L, and thyroid-stimulating hormone (TSH) level – 1.326 mIU/L. Chest radiograph showed emphysema. The patient remains under pulmonology control.

Physical examination revealed features typical of extraintestinal manifestation of Gardner syndrome: presence of dental cavities, desmoid tumours, and osteomas. The patient is currently being prepared for tooth implant placements. A non-tender, hard, skin coloured, elevated and well-confined mass was also observed on the left frontal temporal area, above the left zygomatic arch, measuring 1.5 × 1 cm, which was confirmed in computed tomography (CT). Fig. 2A and 2B).

A similar mass measuring 1.6 × 1.5 cm. was observed on the right side of the paraspinal muscles. The whole length of the right sternocleidomastoid muscle is thickened to 5.5 × 3.2 cm. A CT scan showed a 4 × 3.7 cm mass surrounding the carotid arteries pressing on the right lobe of the thyroid gland, and displacing the larynx and throat to the left as shown in the photo (Figure 3).

In both the left and right ethmoidal cells, multiple small osteomas measuring 0.5–0.9 mm were detected. In the area of the left frontal-zygomatic suture there is a possible 1.8 × 1.7 cm osteoma. Interestingly, in the abdominal CT scans a heterogeneous tissue tumour $7.7 \times 5.7 \times 8.0$ cm of Th8-Th11 was revealed, described by the radiologist as suspicion of paraganglioma. In the authors’ opinion, however, it is more likely that it is a desmoid tumour in the course of GS.

Upper gastroscopy revealed multiple tubular adenomas of the duodenum with features of metaplasia in biopsy specimens.
Colonoscopy performed through an ileostomy showed 30 cm of the small intestine with the proper mucous membrane. No biopsy was taken during colonoscopy. Performing enteroscopy is proposed in the nearest possible future.

DISCUSSION

Gardner syndrome was first described in 1950s by Eldon J. Gardner et al. [9–12], the prevalence of which is 1 per one million people in the United States [10,13]. The incidence of FAP is estimated to be 1 in 8,000 patients [10]. One-fourth of GS patients have no family history [11]. Evaluation of APC and MYH mutation is recommended [5,11] as more than 200 mutations have been discovered which lead to GS [14].

The most commonly described feature in FAP syndrome is adenomatous polyposis [3]. However, there is also a spectrum of extraintestinal lesions, such as fundic gland polyps (FGPs), duodenal polyps and adenomas, fibromas, fibromatosis, nasal angiofibromas, hepatoblastomas, pancreaticobiliary tumours, brain tumours, thyroid carcinomas, and congenital hypertrophy of retinal pigment epithelium (CHRPE) [3].

In patients with Gardner syndrome, initial gastrointestinal complaints may be non-specific [10] and mostly remain asymptomatic [10]. However, patients may also report isolated pruritus, inflammation, rupture, cramping, diarrhea, rectal bleeding, constipation, and vomiting [10]. Extra-intestinal manifestation may be present before colon manifestation [11]. Aletaha et al. described the case of a 24-year-old patient with multiple osteomas in the deep supranasal quadrant of the left orbit, and at the left and right mandibular angle, which led to endoscopy being performing and GS diagnosis [11].

Extra-intestinal manifestation of GS. Benign tumours that can arise from compact or cancellous bone are called osteomas [15], the majority of which are sporadic tumours [16]. However, some of them are associated with GS [16]. Osteomas appear 4–20 times more often in GS patients than in healthy population, and are most often localized in the mandible [8,11]. Therefore, they can also occur in the paranasal sinuses, the jaw?, the skull, or even the long bones [11]. Only 0.1% – 1% appear in the temporal bone [17]. Treatment is not necessary as these lesions are usually not painful, and patients most often visit the doctor to improve aesthetics [8,17]. However, Angelo et al. described a patient with osteoma in the mandibular angle, condylar and coronoid regions bilaterally, who underwent osteoma removal surgery with bilateral customized alloplastic total temporomandibular joint replacement [18]. The surgery improved the patient’s quality of life, and improved the maximum mouth opening from 8 mm to 34 mm [18]. Heller et al., on the other hand, presented the case of a patient who had an intracranial epidermoid osteoma localized in the fourth ventricle of the brain [19]. Given the lack of clinical symptoms, conservative treatment was used [19]. Patients with FAP are at high risk of medulloblastoma as well as adrenal adenocarcinoma [20]. Osteomas require differential diagnosis as they may simulate bone islands [21].

As many as 90% of patients with Gardner syndrome will show CHRPE and lesions [3]. In the general population, these occur in only 1.2–4.4% of individuals [3], and are recognized as at least one darkly pigmented lesion with a halo in the retina [3]. Interestingly, they have no malignant potential and may be bilateral [3]. The presence of CHRPE may be one of the harbingers of FAP, which suggests that testing should be expanded to include genetic testing [3,22]. Ren et al. reported the case of a 20-year-old woman who presented with a 3-year history of propotis of her right eye [23].

Dental abnormalities seen in 30% of patients with GS include: odontomas, supernumerary teeth, impacted and ectopic teeth and hypercementosis [9,24]. The bilateral occurrence of supernumerary teeth is very rare, and if they appear they may be associated with GS or cleidocranial dysostosis [25]. Seehra et al. described the case of a 12-year-old patient with GS diagnosis made after dental manifestation of this disease, which led to the proper recognition [9]. In some cases, diagnosis of GS is made after routine orthodontic assessment [9].

Among GS patients the most common soft tissue manifestations are epidermoid or sebaceous cysts and desmoid tumours [24]. According to the recent study, six or more of pilomatrixomas is highly suggestive for various syndromes such as FAP syndrome, Turner syndrome, or Rubinstein-Taybi syndrome [26,27]. Desmoid tumours (fibromatoses) may be a manifestation of GS as in our patient. Although desmoid tumours are benign mesenchymal tumours with local aggressivity, they have no malignant potential [28]. These tumours in GS account for 15% of cases [29]. They can appear as sporadic tumours or be associated with FAP and GS [30,31]. Benign soft-tissue tumours associated with GS are Gardner-associated fibromas which may progress into desmoid fibromatosis or they co-occur with them [32,33]. Desmoid fibromas are formed by a myxoid stroma with elongated spindle cells [34]. They can develop anywhere in the human body, invade surrounding tissues, and they can grow rapidly [30,35]. They mostly occur in the abdominal wall, mesentery (about 8% of desmoid tumours), and extra-abdominal soft tissue as large tumours [36–38]. Extremely rare type of desmoid tumours are these localized in breasts and they account for less than 0.2% of all breast tumours [39]. Early diagnosis improves prognosis of GS [8]. Saito et al. described a case of Gardner syndrome with odontogenic sinusitis which is extremely rare [8]. Interestingly, Jin et al. reported a case of a 28-year-old pregnant woman whose pregnancy complicated with giant abdominal desmoid tumour in the course of FAP [40].

FAP diagnosis. The risk of polyps transformation into colon cancer in patients with FAP is 100% [11], and more than 50% of patients with FAP are found to have duodenal polyps and adenomas [3]. Duodenal polyps and malignant lesions are extremely rare, whereas benign lesions are parts of familial adenomatous polyposis, Peutz-Jeghers syndrome, and Gardner’s syndrome [41]. When duodenal involvement occurs in GS, the majority will develop duodenal carcinoma [3]. Notably, FAP patients require endoscopic surveillance to avoid duodenal carcinoma [2]. After colorectal cancer, duodenal carcinoma is the second leading cause of death among FAP patients [3]. The risk of developing duodenal carcinoma is 100 – 330-fold in FAP affected individuals [3]. Polyps of the stomach body and fundus appear in 30–88% FAP patients, and are associated with a low risk of progression to malignancy [3]. In contrast, Japanese FAP patients have 3–4 times increased gastric cancer rate [3].

Three categories of APC-associated fundic gland polyposis were distinguished:
1) classical FAP; 
2) attenuated familial adenomatous polyposis (AFAP); 
3) gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) [42].

According to American recommendations, in these patients screening for colorectal cancer should be performed by annual colonoscopy or flexible sigmoidoscopy [5]. Patients with FAP and AFAP should be evaluated by thyroid ultrasound every year [5]. Depending on the Spigelman stage of duodenal polyposis, upper endoscopy should be performed at age 25–30 years, and subsequently continued every 6 months to 4 years (Tab. 1) [5].

<table>
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<tr>
<th>Spigelman stage</th>
<th>When to perform upper endoscopy</th>
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<tr>
<td>0</td>
<td>in 4 years</td>
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<tr>
<td>I</td>
<td>in 2–3 years</td>
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<tr>
<td>II</td>
<td>in 1–3 years</td>
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<tr>
<td>III</td>
<td>in 6–12 months</td>
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<td>IV</td>
<td>surgical evaluation recommended</td>
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After colectomy FAP and AFAP, patients should be monitored with endoscopy of the rectum or ileal pouch, and an ileostomy performed every 2 years [5]. The 5-year survival rates of GS, if detected early, are 100% in patients who have had a proctocolectomy [43].

According to the Swedish data, 67% of 216 patients had CRC at diagnosis, and the mortality rate was 44% [44]. Female patients were diagnosed with CRC earlier than male patients [44]. This may indicate that the course of FAP is influenced by gender [44]. Another study performed in Finland revealed that 76 of 116 patients (65.5%) had CRC at the time of diagnosis [45], and the Danish Polyposis Register demonstrated that CRC was diagnosed in 170/252 patients (67%) [46]. Screening by colonoscopy remains crucial for patients with suspicion of AFAP, FAP and in healthy patients with no CRC family history at the age of 45 [47,48]. A study based on the Manchester Polyposis Registry revealed that survival rates increased from 57.8 years to 70.4 years by screening, and that screening reduced the incidence of CRC from 43.5%–3.8% [49]. Although it is generally believed that in FAP patients the diagnosis of CRC is mostly made at the age of 40–50, Gg et al. described the case of a 22-year-old patient diagnosed with FAP and CRC at the same time [50]. Biopsy revealed adenocarcinoma and positron emission, and tomography–computed tomography? positron emission tomography (PET-CT) revealed metastases into the liver [50]. The patient’s family history showed that 4 of the 5 brothers of her grandfather died of liver, lung, and gastric cancer [50]. According to American guidelines, depending on family history, there are groups of patients in whom the presence of colorectal adenomas and extraintestinal manifestations, who require assessment for adenomatous polyposis syndromes (Tab. 3).

<table>
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<tr>
<th>Table 3. Indications to perform assessment for the adenomatous polyposis syndromes</th>
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<td>Patients who should undergo assessment for adenomatous polyposis syndromes [5]</td>
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<tr>
<td>1. with &gt;10 cumulative colorectal adenomas,</td>
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<td>2. with a family history of one of the adenomatous polyposis syndromes,</td>
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<tr>
<td>3. with a history of adenomas and FAP-type extracolonic manifestations, such as</td>
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<td>duodenal/ampullary adenomas, desmoid tumours, papillary thyroid cancer, CHRPE,</td>
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<td>epidermal cysts, and osteomas.</td>
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</table>

CONCLUSION

The patient in the presented case is now waiting for enteroscopy. The FAP diagnosis was not the end of his management route because regular surveillance is extremely important for the further life of patients affected with polyposis syndrome. As mentioned previously, the high risk of malignancy, including 100% risk of CRC development, necessitates fast evaluation and determination of the proper diagnosis at the earliest possible time. Family history is the aspect of clinical examination which can never be omitted.

Declarations

Availability of data and materials
All data generated or analyzed during this study are available from the corresponding author on reasonable request.

Consent for publication
The patient signed an informed consent form and agreed to the presentation of his medical history.

Competing interests
The authors declare that they have no competing interests.

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REFERENCES


