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HEREDITARY MIXED POLYPOSIS SYNDROME – OWN EXPERIENCE

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Hereditary mixed polyposis syndrome (HMPS) is a rare condition of unknown genetic origin. The paper presents 25-year clinical follow up in a female patient with multiple gastrointestinal tract polyps of varied histology. They most likely served as sites of multiple colorectal cancers development. The clinical course is interesting in terms of diagnostics and therapy. The patient required extended genetic testing, intensive conservative treatment and numerous surgical procedures. This is the first case of HMPS presented in Polish publications.
Key words: hereditary mixed polyposis syndrome, HMPS, colorectal cancer, surgical treatment

Hereditary mixed polyposis syndrome is a rare condition of dominant autosomal heredity. It is characterised by coexistence in the gastrointestinal tract of polyps with varied histology, which may undergo malignant transformation. The term HMPS was first introduced in 1997, based on the many-year follow up in a multigenerational family with predisposition to mixed large bowel polyposis and colon cancer (1). In the course of the 40-year study on 42 relatives, there were diagnosed colorectal polyps and/or cancer. It was a picture of coexisting polyps with varied histology. By microscopy, there were diagnosed polyps of tubular and villous adenoma nature, hyperplastic polyps and atypical juvenile polyps with a glandular and/or hyperplastic component. The mean age of studied patients, referred to as the "SM96 family" in publications, was 40. Their main complaints included lower gastrointestinal tract bleeding, abdominal pain, irregular bowel evacuation, anaemia and mechanical constipation. The performed genetic testing allowed to rule out, as the genetic background, the presence of mutations within genes important for colorectal carcinogenesis, such as: *APC*, *hMSH2*, *hMLH1*, *DCC*, *TP53* (2). There were also considered mutations in genes responsible for juvenile polyposis syndrome. The studies on HMPS families, conducted among others in China and Israel, have not provided unambiguous results on the genetic background of this rare syndrome (3, 4, 5).

In the typical picture of the disease, the localisation of polyps is limited to the colon and rectum only. However, there have been reported cases of polyposis affecting the entire gastrointestinal tract (6).

The paper presents 25-year follow up in a female patient with colorectal cancer most likely of HMPS origin.

CASE REPORT

A female patient, aged 42, post bowel obstruction surgery underwent in 1984, was diagnosed at the Gastroenterology Department due to periodic abdominal pain. Endoscopy revealed gastric, duodenal, ascending, transverse and sigmoid colon polyps of 2-40 mm in diameter. By histopathology, there were found hyperplastic gastric polyps. In the course of performed diagnostics and treatment, symptoms of severe gastrointestinal obstruction developed. The patient underwent surgery as

an emergency case at the Department of General and Gastroenterological Surgery due to intussusception. The intussusceptum was a polyp localised in the second jejunal loop. The performed intussusception reduction was followed by intestinal segment resection.

In 1996, the patient again underwent surgery as an emergency case due to intussusception. At that time, the intussusceptum was also a large jejunal polyp. The polyp was resected and treatment with celecoxib was initiated. This selective COX2 inhibitor is characterised by highly effective inhibition of polyp development in familiar adenomatous polyposis (FAP). The patient wilfully terminated the treatment after two years. She became pregnant and delivered another child.

Bowel obstruction symptoms developed again in 2006. Perioperatively, it was found that the cause of obstruction was ascending colon cancer (fig. 1). There also coexisted: polyp of 5 cm, three smaller sigmoid colon polyps and numerous small intestine polyps. Right hemicolectomy with regional lymphadenectomy was performed, the duodenal polyp was resected as well as all small intestine, descending and sigmoid colon polyps (fig. 2 and 3). Table 1 presents the histopathological diagnosis on resected lesions.

Following the surgical treatment, postoperative chemotherapy was applied with the use of leucovorin and 5-fluorouracil. The patient received six courses.

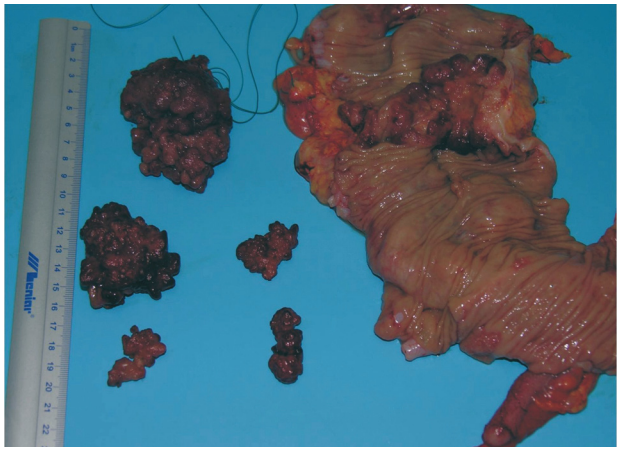

Fig. 1. Picture of the right half of the colon with ascending colon cancer and resected small and large bowel polyps

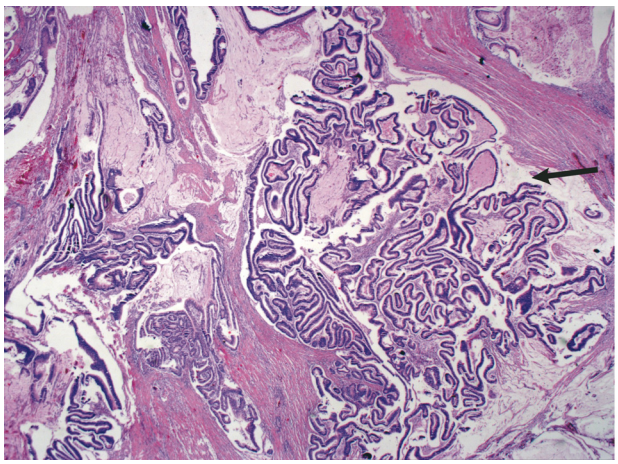

Fig. 2. Adenocarcinoma G2 localised in the descending colon polyp. The arrow indicates neoplastic infiltration of the muscular coat, with mucus production to the tube lumen

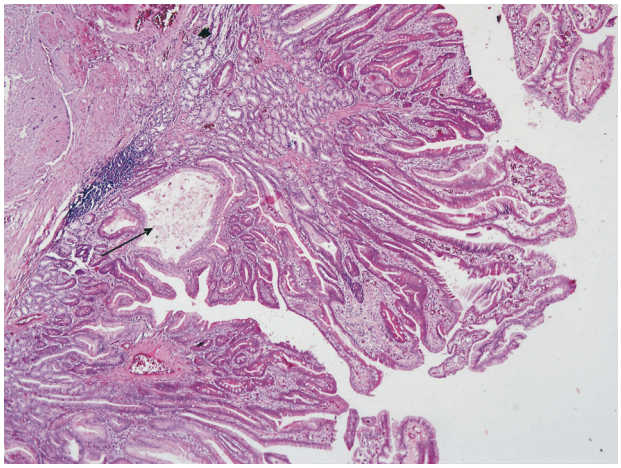

Fig. 3. Hamartomatous polyp. The arrow indicates tubular dilated glands layered with normal epithelium, organised around the ramifications of the muscular layer of the mucosa

Table 1. Histopathological diagnosis on resected lesions

Lesion localization	Histopathological diagnosis
Ascending colon	mucinous adenocarcinoma G2 pT3
Descending colon	mucinous adenocarcinoma G2 pT2 in the polyp
Small intestine	hamartomatous polyps
Sigmoid colon	hamartomatous polyps

In 2007, genetic testing was performed, revealing *NOD2* gene mutation. The pedigree diagnosis suggested suspected hereditary non-polyposis colorectal cancer (HNPCC). Following the performed genetic testing, the patient refused check-up examinations.

In autumn 2010, the patient delivered another child (the patient has given birth 4 times). Over the four months following the delivery, the patient experienced abdominal pain, irregular bowel evacuation, general weakness and marked body weight loss. The patient was hospitalised at the district hospital, where she was diagnosed with a ploriferative lesion at the level of splenic flexure, with high CEA (20.5 ng/ml). The patient was transferred again to the Department. On admission, grave general condition was observed with symptoms of bowel obstruction and general kwashiorkor malnutrition. The patient was staying in a lying position, with severe dyspnoea on exertion. The body mass index (BMI) stood at 17, and the patient lost 15 kg in weight in the previous three months, i.e. 23% of the baseline body weight.

The blood serum albumin level was 1.2 g/dl. There were observed marked intercellular electrolyte disturbances: phosphates – 1.53 mg/dl, magnesium – 0.75 mmol/l, potassium – 3.7 mmol/l. There also coexisted anaemia due to iron deficiency: HGB – 8.6 g/dl, iron < 6 µg/dl, TIBC – 84 µg/dl. The patient was started on total parenteral nutrition. The existing water and electrolyte disturbances were compensated, with a slight improvement in the general condition achieved.

On day 14 of treatment, massive haemorrhage from the lower gastrointestinal tract occurred, requiring emergency laparotomy. Perioperatively, there was found a bleeding neoplastic tumour at the splenic flexure, of approx. 10 cm in diameter, with tissue lysis signs. The neoplastic infiltration involved the body and tail of pancreas, first jejunal loop and the left renal capsule. At a single block, the splenic flexure tumour with transverse, descending and sigmoid colon, jejunum segment, spleen, the body and tail of pancreas were resected (fig. 4). The infiltrated left renal capsule and regional lymph nodes were excised. The small intestine was exteriorised in the left mesogastrium in the form of artificial anus. Microscopic examination of collected lymph nodes (24 nodes) revealed reactive lesions only. Apart from cancer (fig. 5), numerous descending colon and jejunum polyps were found (fig. 6 and 7). Table 2 presents the histopathological diagnosis on resected lesions.

The postoperative course was uncomplicated. The patient remains in outpatient follow up. She has gained 17 kg in weight and does not report subjective complaints. The imaging examinations do not indicate recurrence and the CEA level remains within the normal range.

DISCUSSION

Diagnosis of colorectal cancer at a young age always suggests a hereditary background

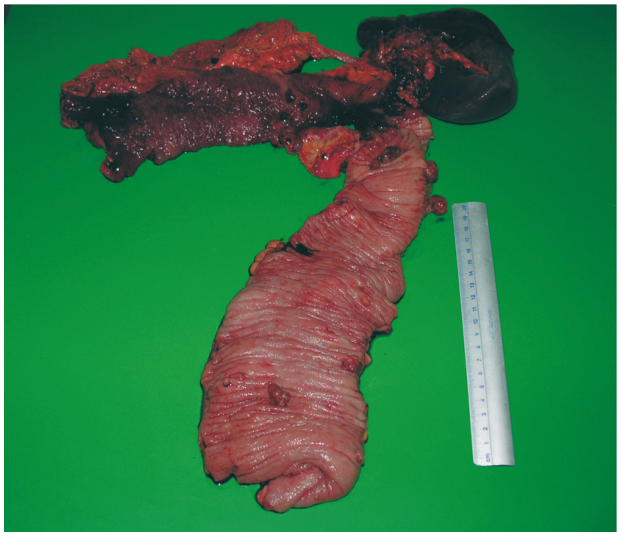

Fig. 4. Organs resected during last surgery. Visible lytic splenic flexure cancer with infiltration to the body and tail of pancreas. Coexisting ascending colon polyps

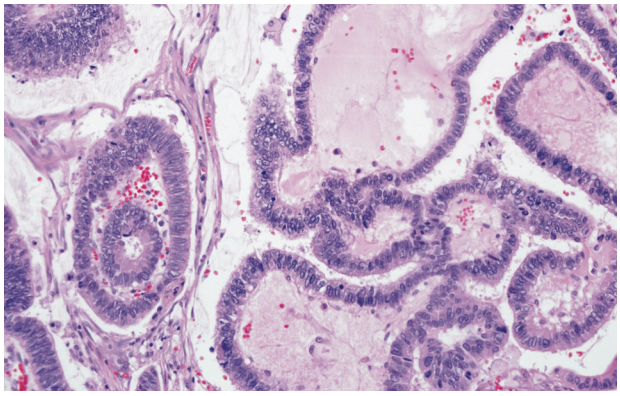

Fig. 5. Mucinous adenocarcinoma of the splenic flexure. Visible signs of cellular malignancy: atypical nuclei, hyperchromasia, presence of nucleoli, loss of basal arrangement of nuclei in glandular tubes, appearance of cell nuclei stacking

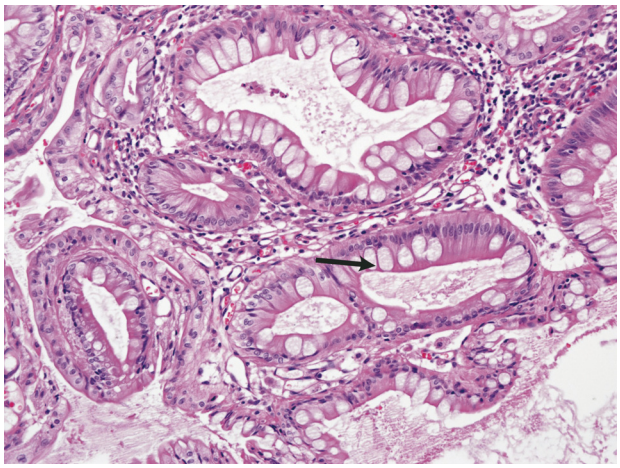

Fig. 6. Tubular adenoma of the ascending colon. Visible neoplastic glandular tubes with goblet cells producing mucus

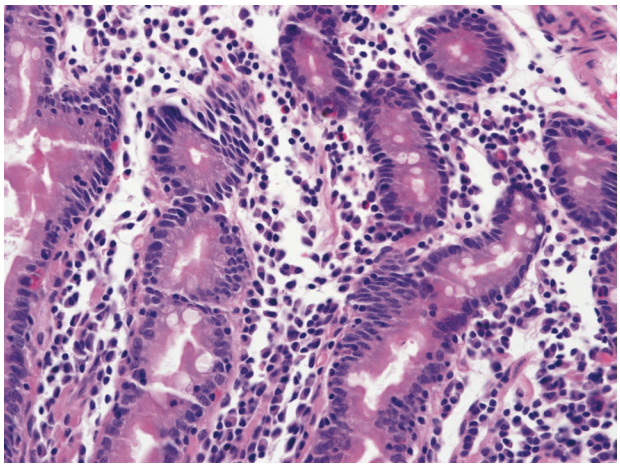

Fig. 7. Reactive polyp of the jejunum. Visible infiltration by lymphocytic cells

Table 2. Histopathological diagnosis on resected lesions

Lesion localization	Histopathological diagnosis
Splenic flexure	mucinous adenocarcinoma G2 pT4
Pancreas	adenocarcinoma infiltration of the head of pancreas – no cancerous lesions found
Descending colon	tubular adenomas
Spleen	hyperaemia
Omentum	focal inflammation
Jejunum	reactive polyp

of the disease. In addition, the large number of intestinal tract polyps might suggest the presence of one of the hereditary polyposis syndromes. However, the genetic testing did not confirm the *APC* suppressor gene mutation typical of FAP (7). There were not found coexisting extraintestinal tumours characteristic for the Gardner's syndrome or Turcot syndrome in the patient either, or cutaneous and mucosal melanosis present in the Peutz-Jeghers syndrome (8). On the other hand, the varied histology of collected polyps is characteristic. In the gastrointestinal tract of the patient, there was found coexistence of hyperplastic, hamartomatous, glandular and reactive polyps. The entire clinical picture suggested potential HMPS in the patient.

The uncomplicated period between hospitalisations in 1996 and 2006 might indicate the efficacy of applied treatment with celecoxib. There have been published reports on overexpression of COX-2 in polyps in HMPS (9). The administered therapy might have inhibited the polyp development and the disease progression.

The lack of identified gene and mutations in it, responsible for HMPS development, hinder the diagnosis based on molecular testing. On the other hand, there was found in the patient a mutation in the *NOD2* gene in which aberrations have been evidenced to be associated with Crohn's disease (CD) pathogenesis (10). Due to the increased risk of neoplastic proliferation in the course of CD, an association between *NOD2* mutations and colorectal cancer has been searched for (11-14). Studies conducted in Poland, Greece, Finland and New Zealand, among others, have proven ambiguous. Currently, it cannot be stated whether such an association exists, or whether a *NOD2* mutation might predispose the patient to cancer development.

In a patient with mixed polyposis, due to the risk of colorectal cancer development, it seems pertinent to perform frequent (every 1-2 years) endoscopic examinations and preventive polypectomy (1, 4, 15). In the case of patients with colon adenoma and positive family history, it is indicated to perform total colectomy (15). During the last surgery, despite the grave general condition of the patient, it was decided

to resect not only the splenic flexure tumour, but also the remaining pathologically changed segment of large bowel.

There have been a limited number of reports published on HMPS, and there have been no publications on the problem in Poland to date. The presented case seemed interesting due to the small incidence of HMPS in Polish population, as well as the atypical clinical picture in the patient, with the presence of polyps in the entire gastrointestinal tract.

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