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CASE REPORT

Multifocal colorectal cancer in ulcerative colitis patient with sclerosing cholangitis – case report

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Introduction: U lcerative colitis (CU) is an inflammatory disease predisposing to colorectal cancer. Colorectal cancer in ulcerative colitis is more often metachronous or synchronous.

Case report: In this case report we present a patient with multifocal colorectal cancer in the course of CU and operative treatment that was implemented. Additionallyprimary sclerosing cholangitis was diagnosed in this patient post-operatively.

KEYWORDS: adenocarcinoma, multifocal colorectal cancer, primary sclerosing cholangitis, ulcerative colitis

ABBREVIATIONS

CCA – cholangiocarcinoma
CU – ulcerative colitis
IBD – Inflammatory Bowel Diseases
MRCP – magnetic resonance imaging cholangiography
PSC – primary sclerosing cholangitis

CASE REPORT

A forty-year-old female patient with many years of ulcerative colitis (CU) was admitted in February of 2015 with a diagnosis of cecal cancer for surgical treatment. Colonoscopy performed prior to hospitalization showed a change in the caecum. The remaining sections of the large intestine showed fragile, contact bleeding mucosa devoid of vascular pattern, and furthermore anal stenosis. Beside typical CU symptoms, the patient complained of rectal bleeding persisting for one year with a bowel movement, and reported sporadic abdominal pain in the left iliac region.

The woman was treated with sulfasalazine, azathioprine and folic acid. In addition, her clinical history included: iron-deficiency anemia treated with iron intramuscularly for a year, status post appendectomy due to acute appendicitis 10 years ago, status post hysterectomy with removal of the right appendix due to fibrosis 3 years ago. Negative family history.

On the basis of interview and physical examination as well as additional tests, the patient was qualified for surgery. After presenting all aspects of the disease and discussing them with the patient, it was proposed to perform restorative proctocolectomy. Due to the advanced pathological process and a suspicion of multifocal cancer, the surgery was divided into stages. On February 27, 2015, a colectomy was done with preservation of the rectum and construction of an end ileostomy. Cecal cancer was confirmed, but a second, hard lesion could be felt in the mid-way along the length of the transverse colon. There was a noticeable narrowing in the rectum. The large bowel was removed by Hartmann's procedure, leaving a 12 cm rectum. An end ileostomy was exteriorized. No metastatic lesions were found in the liver or in the small intestine. Histopathological examination of resected intestinal fragments showed as many as four adenocarcinoma lesions. Two were palpable and macroscopically visible during surgery for changes in the cecum and transverse colon. However, the other two were not visible during the procedure: 1 cm lesion-, the nearest 2 cm from the incision line. Joint histopathological diagnosis: adenocarcinoma mutifocale invasivum coli G2, pT4a, pN2a, Dukes C, Astler-Coller C2.

This was followed by qualification of the patient for chemotherapy according to the FOLFOX 4 regimen. However, she only underwent 9 out of 12 treatment cycles. Subsequent cycles were abandoned due to agranulocytosis.

Over a year of colectomy, the patient was hospitalized for jaundice with signs of cholangitis. Laboratory tests showed bilirubin 7.6 mg/dl, CRP 198.5 mg/l, ALT 268 U/l, AST 172 U/l. Abdominal ultrasonography revealed slightly expanded intrahepatic bile ducts peripherally up to 3 mm, with a predominance of the left lobe. ERCP showed critical narrowing with complete separation from the lobar ducts, expanded lobar ducts with a jagged image of the ducts of right lobe at the height of the division of the common hepatic duct. Papillotomy and bile duct dilatation were performed and discharge of purulent biliary content was obtained. A bile duct prosthesis was inserted. The status of the patient improved.

MR examination of the liver performed for the purpose of further diagnosis revealed an abnormal picture of extrahepatic and intrahepatic bile ducts with numerous multilevel stenoses. This aroused the suspicion of primary sclerosing cholangitis (PSC). Since then, the patient was hospitalized three times for cholangitis with replacement of prostheses. Imaging examinations reveal progressive narrowing of intrahepatic bile ducts. The patient remains under the care of a transplant clinic and liver transplantation is under consideration.

DISCUSSION

Ulcerative colitis (CU) is an inflammatory disease predisposing for colorectal cancer [1]. Research shows that the risk of its occurrence

Tab. I. Histopathological examination of the surgical specimen – February 2015.

FIRST TUMOR:	*Adenocarcinoma tubulopapillare partim mucinosum invasivum coli* G3, pT3. The tumor infiltrates the entire wall thickness, grows into adipose tissue, does not overgrow the peritoneum.
SECOND TUMOR:	*Adenocarcinoma tubulopapillare invasivum coli* G2, pT4a. The tumor infiltrates the entire wall thickness, overgrows the visceral peritoneum. Vascular invasion.
THIRD TUMOR:	*Adenocarcinoma tubulopapillare invasivum coli* G2, pT1. The tumor infiltrates the mucosa and submucosa.
FOURTH TUMOR:	*Adenocarinoma tubulare* G1 *in situ*, pTis.
TUMOR METASTASES TO LYMPH NODES 6/24. ENDS OF THE INTESTINE FREE FROM NEOPLASTIC LESIONS.	
JOINT DIAGNOSIS:	*Adenocarcinoma multifocale invasivum coli* G3, pT4a, pN2a, Dukes C, Astler-Coller C2.

increases significantly 8–10 years after the onset of CU symptoms [2]. Colorectal cancer an inflammatory bowel disease (IBD) is associated with chronic inflammation that has a destructive effect on the epithelium of the large intestine, leading to its excessive proliferation and, consequently, to the formation of foci of dysplasia, which over time transform into a malignant tumor. Therefore, the development of colorectal cancer associated with CU differs from the sporadic form, the development of which is dominated by the sequence: adenoma – adenocarcinoma. The role of chronic inflammation is confirmed by the fact that effective anti-inflammatory treatment in CU, e.g. with mesalazine (5-ASA) or thiopurines, can reduce the risk of colorectal cancer [1]. In addition, chronic inflammation causes genetic and epigenetic changes that can initiate the development of colorectal cancer. We should also not overlook the role of proinflammatory cytokines such as TNF-alpha, IL-1, IL-6 in the neoplastic process, as well as intestinal biofilm transformations, resulting in the promotion of chronic inflammation, mucosal damage and, as a consequence, the development of dysplasia [3]. The development of colorectal cancer in patients with CU is also associated with free oxygen radicals, which are formed in excessive amounts in the inflamed mucosa; this, in turn, leads to cellular damage and cancer. However, this mechanism has not yet been fully clarified, as demonstrated by the fact that CU-associated colorectal cancer does not always occur in sites of production of the largest amount of free oxygen radicals, i.e. in the rectum. On the contrary, studies show that the focus is more often found in the left colon [1]. It has also been reported that CU-related colon cancers are more often multifocal and with a higher degree of histological differentiation than sporadic forms [4].

Therefore, CU-related colorectal cancer is characterized by several features that differentiate it from the sporadic form: it appears in younger patients, it is more often synchronous, histologically it contains signet-ring and mucous cells more frequently, and, as already mentioned, it has a different mechanism of formation. It is reported to arise from flat foci of dysplasia, which may be accompanied by: inflammatory lesions, scarred lesions, and pseudopolyps. Dysplasia often has no clear macroscopic boundaries, which makes endoscopic diagnostics and possible resection more challenging [4]. Hence, endoscopic surveillance of patients with CU lasting over 8 years is associated with the use of chromoendoscopy, as research shows its higher effectiveness in detecting dysplasia from white light endoscopy [5].

The formation of CU-related colorectal cancer differs from the sporadic form at the molecular level. Mutation in the TP53 gene and chromosomal instabilities appear earlier than in sporadic form; they have even been identified in non-cancerous colon mucosa. Chronic inflammation therefore seems to accelerate the development of mutations that lead to cancer [4].

The treatment of CU-related colorectal cancer is in most cases the same – it involves proctocolectomy with the formation of an intestinal reservoir with ileoanal anastomosis [6]. Such radical management results from the increased risk of synchronous and metachronous cancers in patients with CU [7]. This treatment can consist in one stage or be divided into two or three stages [8]. The described patient underwent a complete resection of the large intestine using Hartmann's procedure with the exteriorization of an end ileostomy and the use of adjuvant chemotherapy. Due to the multifocality of colorectal cancer, a severe postoperative course and the need for further oncological treatment, with the patient's approval, it was decided to abandon further stages of surgical treatment. The woman lives to this day with an exteriorized ileostomy.

Just under a year after surgery, the woman was diagnosed with primary sclerosing cholangitis (PSC). PSC is an autoimmune disease that accompanies IBD in 2/3 patients in Northern Europe and the United States. However, only 5% of IBD patients will develop PSC [9]. Diagnosis of PSC may precede the diagnosis of IBD, but we could also encounter a reverse situation in which PSC is diagnosed after colectomy due to CU – just like in the described patient. There is an increased risk of colorectal cancer and bile duct cancer– cholangiocarcinoma (CCA) in people with PSC. PSC is diagnosed by excluding other diseases that could cause sclerosing cholangitis, such as: CCA, Vater's papillary stenosis, carcinoma of the papilla of Vater, chronic pancreatitis, pancreatic cancer, hilar lymphadenopathy, recurrent purulent cholangitis, congenital biliary atresia, parasitic diseases and others. The diagnosis is made on the basis of a radiological image – the most effective according to modern research is magnetic resonance cholangiography [10], which shows characteristic stenoses with subsequent expansion of bile ducts – both in the intra- and extrahepatic segments [11]. This is usually accompanied by biochemical exponents of cholestasis. PSC is a degenerative disease; over the years, bile duct fibrosis increases leading to cirrhosis, and eventually most patients develop extreme liver failure or CCA. The most common symptoms of PSC include: weakness, fatigue, itching, abdominal pain, and recurrent cholangitis. The latter, if it occurs often and reduces the patient's quality of life, can be an indication for liver transplantation. After diagnosing PSC, the patient requires constant supervision in the form of: clinical examination, measurement of liver enzymes and cholestasis markers, AFP level, CA19.9 marker measurement, abdominal ultrasound, possibly magnetic resonance cholangiography (MRCP) every 6–12 months. Furthermore, due to the heightened risk of colorectal cancer, it is recommended to perform colonoscopy once a year in IBD-related PSC; chromoendoscopy is also advised [10].

In patients with IBD, cholangitis may be initially asymptomatic, therefore it is recommended to perform annual PSC screening in the form of liver enzymes and serum cholestasis markers. In patients after colectomy due to IBD, it is also recommended to perform the abovementioned tests at the same time intervals due to the still heightened risk of PSC compared to the general population. Cholangiography is performed with elevated liver markers – the abovementioned MRCP is the gold standard. Regarding the

coexistence of IBD and PSC, the results of the tests are not homogeneous: most often IBD is preceded by the occurrence of PSC by a minimum of 10 years, but we also observe PSC following colectomy due to IBD, the occurrence of IBD many years after diagnosis of PSC, and even after liver transplantation.

There is no treatment to stop the progression of the disease. PSC relapses occur even in a transplanted liver. Currently, pharmacotherapy involves the use of ursodeoxycholic acid at a dose of 13–15 mg/kg/d (it is believed to reduce the risk of dysplasia and colorectal cancer), in addition to symptomatic treatment of pruritus, and prophylaxis and treatment of osteoporosis [10]. Research into immunological treatment is underway. According to one of the theories of the emergence of PSC, in the IBD picture, after being activated lymphocytes from the intestinal mucosa pass into the liver due to enterohepatic circulation. This theory is supported by data showing that the network of adhesive molecules and chemokine receptors normally found in the gut is also expressed in the liver. Hence the possibility of treatment with vedolizumab antibodies (an antibody directed against the alpha4beta7 adhesive molecule) that could have anti-inflammatory effects in the liver [9].

The patient has been in a good general condition since the surgery in 2015, and she has remained under the control of a transplant clinic. Due to frequent episodes of cholangitis, she could be qualified for liver transplantation. Other indications for liver transplantation in patients with PSC include: end-stage liver disease, cirrhosis and biliary tract cancer. Due to the degenerative course of the illness, approximately 40% of patients will receive a transplant. Unfortunately, on average a quarter of patients after liver transplantation will experience recurrence of PSC within 10 years of surgery [12].

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