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Metastatic Colorectal Cancer in two Young Patients with Inflammatory Bowel Disease – Relevance of Tight Endoscopic Surveillance Especially in Early-Onset IBD and Review of the Literature

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1. Abstract

1.1. Background: The Risk of Colorectal Cancer (CRC) in Inflammatory Bowel Diseases patients (IBD) is still higher than in the general population. In this report, we present two cases of early-onset and longstanding, highly active IBD (one patient with Crohn`s Disease (CD), one patient with Ulcerative Colitis (UC)), who developed metastatic CRC at a young age due to lack of surveillance endoscopies and suboptimal medical treatment and correlate our findings with available literature.

1.2. Case Report: In Case 1 a 35-year-old male patient with a 20-year history of CD presented with progressive abdominal pain, nausea, and diarrhoea. In Case 2 a 31-year-old man with a 11-year history UC presented with abdominal pain, an increased frequency of bloody diarrhoea, weight loss and night sweats. Both suffered from a CRC and died within a short time despite therapy.

1.3. Conclusion: In both cases, the primary risk factor that led to CRC was severe, uncontrolled inflammation. Adequate treatment and surveillance endoscopies may have prevented the development of colorectal disease. Patients and their family care physicians should be made more aware of possible disease complications, and patients should be referred to IBD specialized centers where optimised and personalised treatment and surveillance strategies can be initiated accordingly.

2. Introduction

Crohn`s Disease (CD) and Ulcerative Colitis (UC) are chronic Inflammatory Bowel Diseases (IBD) with increasing incidences in the last years [1-4]. Disease manifestation is usually between 20 and 30; however, disease onset can occur much earlier. Incidences range between 0.4 – 22.9 per 100.000 patient-years and 2.3 – 44 per 100 000 patient-years for CD and UC, respectively. Clinical symptoms can vary from asymptomatic to severe and recurrent disease flares with bloody diarrhoea, weight loss, and abdominal pain. While UC is predominantly found in the colon with proctitis, left-sided colitis, or pancolitis, CD can manifest in the entire gastrointestinal tract, with so-called „skip lesions". In addition, extraintestinal manifestations, such as arthralgia, skin disorders, ocular manifestations, and Primary Biliary Cirrhosis (PSC), can occur.

Due to a better understanding of the underlying molecular pathomechanism of IBD, various targeted therapies, including anti-TNF drugs (infliximab, adalimumab, golimumab), anti-integrine (vedolizumab), IL-12/IL-23 antibodies (ustekinumab), and JAK-inhibitors (tofacitinib) have been developed for the treatment of patients with CD and UC. This has led to effective control of inflammation, clinical remission, and long-term beneficial outcomes with reduced surgery and fewer long-term complications [5-12].

According to the STRIDE criteria, the primary aim for patients

with IBD and acute inflammation is to achieve clinical response and remission, followed by endoscopic improvement and remission („mucosal healing") [13]. These aims and goals are associated with the best long-term course and outcome. Especially for patients with UC, histologic remission might be superior to clinical and endoscopic remission alone [14]. Despite optimised medical therapies and treatment strategies, these treatment goals cannot be achieved in all patients. Persisting inflammation and the extent of colitis are confirmed risk factors for consecutive development of complications such as stenosis, fistula, and Colorectal Cancer (CRC).

The prognosis of CRC depends on the early detection of premalignant lesions, but the risk of CRC in IBD patients is still higher than in the general population [15]. Besides optimal medical treatment strategies, endoscopic surveillance of patients with IBD is necessary and is highly effective in reducing CRC incidence.

Although surveillance strategies to detect dysplastic lesions at an early stage have been established, the risk for CRC may still be underestimated in patients with early-onset IBD, whose initial disease manifestation occurred at a young age. Furthermore, surveillance endoscopies may not be offered to all patients at risk as recommended in daily routine.

In this report, we present two cases of early-onset and longstanding, highly active IBD (one patient with CD, one patient with UC), who developed metastatic CRC at a young age due to lack of surveillance endoscopies and suboptimal medical treatment and correlate our findings with available literature.

3. Case 1

A 35-year-old male patient with a 20-year history of CD (first diagnosed at the age of 15) with a predominant manifestation at the terminal ileum presented to our hospital with a 6-week history of progressive abdominal pain, nausea, and diarrhoea. The last colonoscopy, which was performed about six years before presentation, had revealed a highly active CD at the terminal ileum, with the indication for biologics, e.g., anti-TNF therapy. However, due to the subjective absence of symptoms, no intensive form of therapy was initiated. Further surveillance endoscopies were not performed; instead, his general practitioner repeatedly treated the patient with steroids. On presentation in our emergency department at the end of 2020, physical examination showed periumbilical pain, and laboratory examination revealed signs of mild systemic inflammation (white blood cell count: 15.8/nl, CRP 1,25 mg/dl) and microcytic hypochromic anaemia (Hb 91 g/l). The tumour cell marker CEA was 68 ng/ml, and CA 19/9 was elevated at 9500 U/ml.

MRI enterography and Computed Tomography (CT) were performed; both were highly suspicious of malignancy with intestinal wall thickening of the ascending colon and cecum. Hepatic and pulmonary metastases, as well as multiple suspicious lymph nodes, were seen. Furthermore, severe rectosigmoid inflammation

with a blind-ending fistula and signs of a ileus in the terminal ileum were seen. Subsequent colonoscopy initially showed massive inflammation of the ascending colon, cecum, sigmoid, and rectum. However, histology showed only severe inflammation without malignancy. Histopathological examination of the liver biopsies revealed an adenocarcinoma, G2, Microsatellite Stability (MSS) of the intestinal tract.

Two weeks later, the patient presented for systemic chemotherapy but was in severely reduced general condition. He complained of further weight loss and diffuse upper abdominal discomfort; food intake was no longer possible. Chemotherapy was postponed because laboratory tests showed inflammation. Intravenous fluids and antibiotics were administered. Due to clinical signs of ileus, a CT scan of the abdomen was repeated. Mechanical small bowel ileus in the area of the known coecal tumour was seen. The patient subsequently underwent a palliative ileostomy. The postoperative course was complicated by a high-output stoma and poor wound healing. Chemotherapy was initiated according to the FOLFOX IV regimen 2 weeks later.

The patient received palliative chemotherapy for two months but developed an allergic reaction to oxaliplatin and new onset of hypercalcemia. An inpatient appointment for a second CT scan and change of chemotherapy regimen was arranged for two days later.

CT showed massive progression of the primary tumour with the development of multiple new metastases, including thoracic and abdominal lymph node metastases as well as liver, adrenal, spleen, umbilical, osseous, and pulmonary metastases. In addition, subsegmental pulmonary artery embolism in the right lower lobe was described. The patient's general condition deteriorated rapidly. He was transferred to the palliative care department, where he died of tumour-associated multiple organ failure a few days later.

4. Case 2

A 31-year-old man with a past medical history of UC (pancolitis), initially diagnosed in 2009, presented to the emergency department for further evaluation of abdominal pain and an increased frequency of bloody diarrhoea with a feeling of incomplete stool emptying. The patient also complained of weight loss and night sweats during the last weeks. His treatment regime from disease onset included mesalazine, budesonide, and azathioprine. Two years after the initial diagnosis, colonoscopy revealed persistent, highly active pancolitis; however, the medication regime was not optimised. Also, the patient had refused further regular colonoscopies due to uncomfortable experiences in the past.

When examined in our emergency department, he was found to have local pain and a palpable resistance at the left lower abdomen. The white blood cell count was 14.54/nl, CRP was 13.87 mg/dl, CEA 39 ng/ml, and CA 19/9 was elevated with 1900 U/ml.

The patient underwent colonoscopy, which revealed severe proctitis with suspicious areas of malignancy (Figure 1). Additionally,

there was stenosis at 20 cm, and endoscopic passage was not possible. Biopsies taken from these areas revealed adenocarcinoma of the rectum and the sigmoid colon. Tumourdifferentiation was poor (G3), with Microsatellite Stability (MSS), and BRAF wild type. An abdominal CT scan confirmed a concealed perforated sigmoid tumour and the presence of hepatic metastases. Emergency laparotomy was not indicated due to the absence of an ileus at this time. An ileostomy was intended after staging and preparation for palliative chemotherapy had been completed. However, the patient developed an acute abdomen, and tumour perforation was suspected. Laparotomy and Hartmann´s discontinuity resection with a terminal stoma were performed. The patient developed postoperative sepsis and was transferred to the Intermediate Care Unit (ICU) where he received high-dose catecholamines, antibiotics, and volume substitution.

Further postoperative complications included poor wound healing, constipation, and intraperitoneal fluid collection, which needed external drainage. Histology showed adenocarcinoma with lymph nodal metastasis and peritoneal carcinosis, pT3, p2Nb (8/15), pM1, L1, V0, Pn1, local R1, G3, UICC IV. The first course of palliative chemotherapy with 5-fluorouracil and irinotecan was given without further complications. However, the patient was admitted with malaise, weight-loss, and poor general condition three months later. A CT scan revealed massive progression of the liver metastases with signs of liver failure and hyperbilirubinemia. No further chemotherapy could be applied, and the patient was referred to the palliative care department, where he passed away four months after the initial diagnosis of metastatic CRC.

Figure 1A

Figure 1B

Figure 1: Endoscopy in a patient with UC after hospitalization. Stenosis in the sigma due to massive tumour infiltration (figure 1 A), suspicious rectal involvement macroscopically (figure 1B).

5. Discussion

In these two cases of early-onset IBD, high inflammation burden and uncontrolled continuous inflammation over many years led to the development of colorectal cancer with a lethal outcome in both patients.

An association between CRC and IBD was first described in 1925. 10-15% of all-cause mortality in IBD is due to colon cancer [16]. The risk of developing colon cancer is comparable for UC and CD [17]. Overall, the incidences reported in the literature vary widely. The decreasing incidence in recent years can be attributed to better control of inflammation with optimal medical treatment strategies and tight endoscopic surveillance protocols. Despite more intensive preventive measures, there still is an increased risk for IBD patients to develop CRC. Compared to sporadic CRC, IBD patients develop CRC 7.7 years earlier and have worse survival rates. The colitis to CRC interval in the literature is given at 16 -21 years [18-21].

Known risk factors for the development of IBD-associated CRC are long duration of disease, geographic characteristics for example a north-south gradient, presence of strictures, PSC, and positive family history. Younger age at diagnosis is another independent risk factor for CRC: 0–19-year old patients had a relative risk of 43.8 %, while 20–39-year old patients had a relative risk of 2.65 %. Early-onset IBD leads to a potentially more prolonged duration of disease [22-24]. Thus, the only modifiable risk factor is adequate IBD therapy to achieve mucosal healing [25].

In case 1, IBD was diagnosed at 15 years of age and the time interval between IBD diagnosis and CRC diagnosis was 20 years. In case 2, on the other hand, a more aggressive course of disease than described in the literature was observed. Although the initial diagnosis of UC was at 20 years of age, the colitis to CRC time interval was only 11 years. In both cases, the primary risk factor that led to CRC was severe, uncontrolled inflammation without adequate medical therapy and endoscopic surveillance.

IBD-associated colonic carcinoma does not follow the usual adenoma-carcinoma sequence as in sporadic carcinomas. From a pathophysiological point of view, chronic inflammation plays a central role in triggering dysplasia, and an inflammation-dysplasia-carcinoma sequence is thought to lead to more aggressive growth and early development of metastatic disease [25, 26].

According to the current German guidelines, surveillance should begin about 6-8 years after disease-onset to detect CRC early. However, guidelines differ regarding screening intervals and recommended techniques. While the American societies endorse screening every 1-3 years, the European and Australian guidelines recommend risk stratification for every patient after an index endoscopy [18, 27].

In addition to primary and secondary prevention, therapy adherence and patient empowerment are essential aspects of disease

control. Patients must be educated about the link between IBD and CRC, which is essential to guarantee adherence to treatment and surveillance protocols. In a study of 156 patients with colitis, only 50% were aware of the correlation between their disease and CRC [28, 29]. Unfortunately, surveillance endoscopies are still not offered to all high-risk patients as recommended by the guidelines.

In both presented cases, it must be concluded that endoscopic surveillance, medical therapy, and treatment adherence failed. Suboptimal therapy led to uncontrolled and severe inflammation over many years. Screening colonoscopies were either not offered due to lack of symptoms and underestimation of the disease or were not accepted by the patient. In both cases, adequate treatment and surveillance endoscopies may have prevented the development of colorectal disease.

Finally, education of family care physicians and general practitioners caring for IBD patients is necessary to improve adherence to treatment and surveillance protocols. Patients and their family care physicians should be made more aware of possible disease complications, and patients should be referred to IBD specialized centers where optimised and personalised treatment and surveillance strategies can be initiated accordingly.

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