ADENOCARCINOMA OF THE JEJUNUM: A CASE REPORT AND LITERATURE REVIEW

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ADENOKARCINOM TANKOG CREVA: PRIKAZ SLUČAJA I PREGLED LITERATURE

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ABSTRACT

Small intestine cancers account for 1-3% of all gastrointestinal tumors, with only 11-25% of these tumors located in the jejunum. We report the case of a woman who has been experiencing abdominal pain for the last six months, accompanied by nausea, vomiting and appearance of dark-colored stools, who has lost 20 kg in weight during the last few months. Laboratory findings indicated anemia and no significant changes were identified in the abdominal ultrasound. By endoscopic examination of the stomach and duodenum and by colonoscopy, no infiltrations were found. Serum markers were elevated and CT scan of the abdomen showed thickening of a part of the jejunum wall with swollen lymph nodes in the mesentery, along the inferior vena cava and abdominal aorta, in the retroperitoneal space. By opening the abdominal cavity, we observed an infiltration in the initial part of the jejunum with an infiltration of the entire wall. Resection of the jejunum with related mesentery, vessels and lymph nodes therein was performed. Histopathology revealed an invasive adenocarcinoma of the small intestine, with an invasion of all layers of the wall and mesentery. Adjuvant FOLFOX chemotherapy was introduced, 6 cycles in total, and following each cycle, tumor markers have been constantly decreasing. No relapse has been identified after nine months. Due to often deep position in the small intestine, atypical symptomatology and lack of screening, an early diagnosis is difficult. Surgical resection of the affected small intestine followed by an additional chemotherapy is the optimal treatment strategy.

Keywords: Adenocarcinoma, jejunum, therapy, prognosis.

SAŽETAK

Karcinomi tankog crijeva čine 1-3% svih gastrointestinalnih tumora, a svega 11-25% ovih tumora se nalazi u jejunumu. Pri- kazujemo slučaj žene koja posljednjih šest mjeseci osjeća bolove u epigastrijumu, praćene mučninom, povraćanjem i pojavom tamno prebojenih stolica. Posljednjih mjeseci izgubila je na težini preko 20kg. U laboratorijskim nalazima su prisutni znaci ane- mije, na ultrazvuku abdomena nisu evidentirane signifikantne promjene. Emdoskopskim pregledom želuca i duodenuma i kolon- oskopskim nisu nađene infiltrativne promjene. Serumski markeri povišeni, a na MSCT-u abdomena je vidljivo zadebljanje dela zida jejunuma sa uvećanim limfnim nodusima u mezenterijumu, uz donju šuplju venu i trbušnu aortu, retroperitonealno. Otvaranjem trbušne duplje smo verificovali infiltrativnu promenu u početnom delu jejunuma sa infiltracijom svih slojeva zida. Urađena jeresekcija jejunuma sa pripadajućim mezenterijumom i limfono- dusima u njemu. Histopatološki je dijagnostikovao invazivni ade- nokarcinom tankog crijeva, sa invazijom svih slojeva zida i me- zenterijuma. Započeta je adjuvantna FOLFOX hemoterapija, ukupno 6 ciklusa, a nakon svakog ciklusa tumor markeri kon- stantno padaju. Poslije devet mjeseci nisu verificovani recidivi bolesti. Zbog često dubokog položaja u tankom crijevu, atipične simptomatologije i nedostatka skrininga rana dijagnoza je ote- žana. Hirurška resekcija zahvaćenog dijela tankog crijeva praćena dodatnom hemoterapijom je optimalna strategija li- ječenja.

Ključne reči: Adenokarcinom, jejunum, terapija, prognoza.

INTRODUCTION

The small intestine occupies 70-80% of the length and about 90% of mucosa of the digestive tract, but small intestine cancers are rare and they are 1-3% of all gastrointestinal tumors, and only 11-25% of these are in jejunum (1,2).

In the US, malignant tumors of the small intestine account for only 0.6% of all cancers (1,2,3). Despite its low incidence, small bowel cancer has been on the rise with an estimated incidence growth of over 100% in the last half a century. It has been noted that the incidence of all small intestine cancers in the United States has increased from 11.8 cases / million in 1973 to 22.7 / million in 2004 (4).

Malignant tumors of the small intestine occur more frequently in the male population. In the United Kingdom, the diagnosis of small bowel cancer occurs with a frequency of 3.1 / 100,000 in men and 2.2 / 100,000 in women (5). The incidence of those tumors in Serbia, according to the Batut Institute of Public Health, is 1.2 / 100,000 for men and 1 / 100,000 for women (6). The average age of a patient at the time of diagnosis in the US is 66 years, in the UK it is 80-84 years (5), and in Serbia the highest number of cases is recorded around the age of 60 (6).

The risk factors for small bowel cancer are divided into non-modifiable and modifiable. Non-modifiable risk factors are gender, race and ethnicity, age, inherited mutations and inflammatory bowel disease (5,7,8,9). Known modifiable risk factors are diet, excessive alcohol use, cigarette smoking, obesity, occupations associated with exposure to radiation, organic solvents and dyes (10,11,12,13,14).

In relation to histogenesis, malignant tumors of the small intestine may be epithelial (carcinomas and neuroendocrine cancers), mesenchymal (sarcomas), lymphomas and secondary tumors (15).

Atypical clinical presentation, lack of screening due to low incidence and inappropriate treatment experience due to lack of prospective randomized trials, make early diagnosis of malignant tumors of the small intestine very difficult.

CASE REPORT

Patient BR, 62 years old female, with a positive family history (her sister was treated for colon cancer) felt abdominal pain, in the middle upper quadrant, followed by nausea and vomiting over the period of last six months. She was treated with oral proton pump inhibitors and iron preparations drugs due to gastritis and chronic anemia, but the symptoms became more frequent. The weight loss was over 20kg in the last two months, with the appearance of increasingly frequent dark-colored stools. The patient was admitted to the Center for Abdominal Surgery, Clinical Center of Montenegro.

Physical examination revealed a soft abdomen, with the tenderness in the epigastric region, without muscular defense of the anterior abdominal wall and peritoneal irritation, without palpable neoproliferations in the abdominal cavity. Laboratory findings showed that signs of anemia were present (Red blood cells $3.67 \cdot 10^{12}/L$, hemoglobin 103 g/L, hematocrit 0.325 L/L). Abdominal ultrasound showed no significant changes. Upper gastrointestinal endoscopy was normal, except for antral hyperemia. Colonoscopy was with no pathological findings.

Serum markers increased (CEA = 22.1; Ca 19-9 = 731.5). CT scan showed a thickening of a part of the jejunum wall and many swollen lymph nodes in the mesentery, adjacent to the abdominal aorta and inferior vena cava in the retroperitoneal space. After adequate preparation for surgical treatment, the patient underwent a surgery. By upper and partly lower midline laparotomy we opened the abdominal cavity and observed an infiltration of the initial part of the jejunum with infiltration of the entire wall, at a distance of about 10cm from the ligament of Treitz. The resection of the jejunum with the clear margins was performed with the related mesentery, vessels and lymph nodes there. Subsequently, the jejunum was reconstructed with termino-lateral anastomosis using an intraluminal stapler of 33mm on the very ligament of Treitz (Figure 1). We sent the resected jejunum with the mesentery, vessels and lymph nodes (Figure 2), the proximal and distal resection margin of the jejunum for histopathological analysis.

The patient began with liquid diet "per os" on the second postoperative day and soft diet on the third postoperative day. The patient was discharged from the Center for Abdominal Surgery of Clinical Center of Montenegro on the sixth postoperative day with normal digestive functions in good general condition.

Histopathological examination (Figure 3.) revealed the invasive adenocarcinoma of the small intestine of histologic and nuclear grade 2, with invasion of all layers of the wall and mesentery up to 3 mm. The tumor had infiltrative growth with lymphovascular invasion and absence of perineural invasion. Free surgical margins were achieved. Secondary deposits were histopathologically identified in all the three examined lymph nodes. Adjuvant FOLFOX chemotherapy was initiated for the patient, 6 cycles were administered in total and it was well tolerated by the patient.

The control CT scan showed a significant reduction of the preoperatively swollen lymph nodes along the aorta and inferior abdominal vena cava. The tumor marker CEA and Ca 19-9 have been constantly decreasing after each cycle of chemotherapy.

After nine months of postoperative follow-up, no disease relapse could be identified in the patient.

Figure 1. Stapler T-L anastomosis of the jejunum on the ligament of Treitz

Figure 2. Resected the involved jejunum, mesentery and vessels.

Figure 3. Microscopic images of the tumour from the pathologic specimen; haematoxylin and eosin staining (HE x 40)

DISCUSSION

The small intestine is located between the stomach and the large intestine and is the main site of ultimate absorption of nutrients from ingested foods. It consists of the duodenum, jejunum and ileum. The duodenum is 20-25cm in length and food, stomach acid, bile and pancreatic juices with enzymes come together there. In the jejunum and ileum, digested food is absorbed and the absorbed substances are transported from the small intestine via the portal vein to the liver.

Malignant tumors of the small intestine are localized in the duodenum in 55-83% of cases, about 11-25% are localized in the jejunum, and 7-17% in the ileum (16,17,18). In

our patient, the tumor was localized in the initial part of the jejunum at a distance of about 10cm from the ligament of Treitz.

Adenocarcinoma is the most common malignant tumor of the small intestine, it accounts for 40% of cases and it is most commonly localized in the duodenum, it metastasizes early to regional lymph nodes and is already in advanced stages at the time of diagnosis. Neuroendocrine tumors are second in frequency, followed by gastrointestinal stromal tumors, sarcomas and lymphomas, which together account for about 20-25% of small intestine tumors (16,17,18). It has been

observed that neuroendocrine cancers are most commonly localized in the terminal ileum (19).

The incidence of various histological types of small intestine cancer has changed over the last decades. Thus, in the United States, between 1985 and 2005, the proportion of adenocarcinomas decreased from 42 to 33%, and the proportion of neuroendocrine cancers increased from 28 to 44%. In the same period, the proportions of sarcoma and lymphoma did not change. The rise in neuroendocrine cancers is thought to be due to the use of more sensitive diagnostic methods for the recognition of neuroendocrine tumors (20,21).

Adenocarcinoma occurs by malignant proliferation of small intestinal mucosal epithelial cells, and it is thought that, like those in the colon, small intestine polyps or adenomas can be transformed into adenocarcinomas after a latent period of 10-20 years. Only about 10% of adenomas are known to progress to cancer through the adenoma-carcinoma sequence, which is characterized by numerous chromosomal instabilities associated with mutation accumulation (22). On the other hand, there are suggestions that the pathogenesis of adenocarcinoma in the small intestine differs from that in the colon, since there is a shorter transit time through the small intestine, by which exposure of its mucous membrane to carcinogens from food is limited (23). The low incidence of small intestine adenocarcinoma and lack of screening comparable to endoscopy are also thought to make it difficult to study the pathogenesis of these tumors, but that large differences in the incidence of colon and small intestine adenocarcinoma indicate to different pathogenesis (2).

Small intestinal adenocarcinomas can occur sporadically (without associated intestinal disorders) or associated with various precursor conditions such as familial polyposis, Peutz-Jeghers and Lynch's syndrome or with immunological intestinal disorders (Crohn's disease, celiac disease, etc.) (24,25, 26, 27).

Numerous studies reports indicate that primary adenocarcinomas most commonly appear as solitary lesions (28,29,30), whereas metastatic tumors of the small intestine generally occur as multiple lesions (31,32). Metastasis of breast, lungs, stomach, and melanoma cancers to the small intestine have been described in the literature so far (33,34,35,36). Primary adenocarcinoma was presented as a solitary lesion in our patient. With regard to the mode of growth, adenocarcinomas are divided into vegetative, ulcerative, and infiltrative ulcerative types (31, 32).

The clinical picture of adenocarcinoma of the small intestine is nonspecific. Often there is pain in the upper and middle abdomen, changes in bowel movements, blood in the stool (melena) and weight loss with lack of appetite. Unfortunately, all these symptoms have been treated as functional disorders for a long period of time. As it is often located deep in the small intestine, due to low incidence and atypical symptomatology, early diagnosis is difficult, so these tumors are usually diagnosed at a relatively late stage (37). There is

a report in the literature that nearly 60% of patients could not be diagnosed until obstruction or intestinal perforation had occurred (38).

Despite the report that only 50% of patients with small intestine adenocarcinoma have elevated levels of CEA and CA19-9 (37), numerous studies have highlighted their significant role in monitoring the effects of antitumor therapy (38, 40). As regards our patient, tumor markers CEA and Ca 19-9 were constantly decreasing after each cycle of chemotherapy.

Numerous predisposing mutations (such as APC and KRAS), mutations of suppressor genes and oncogenes have been involved in the development of adenocarcinoma of the small intestine, and modern molecular therapies, which include these targets, give hope for future patients. Mutations of the p53 gene were described in about 50% of small intestine adenocarcinomas, the APC gene was mutated in about 10% of cases, and mutations of the β catenin gene were observed in 10-40% of cases. KRAS, an oncogene that normally functions in cell signaling and proliferation, is present in about 50% of adenocarcinoma cases (39). SMAD4 mutations and activation of the RAS-RAF-MAPK signaling pathway have also been described in this tumor (15).

Contemporary literature points out that surgical resection of the affected part of the small intestine, followed by additional chemotherapy, is the optimal treatment strategy, especially in cases with bleeding or perforation (37,38). Our patient's jejunum was resected with the clear margins and with the related mesentery, vessels and lymph nodes therein, and then adjuvant FOLFOX chemotherapy was introduced, which was well tolerated by the patient.

The length of survival of patients is greatly influenced by the stage of the disease at the time of diagnosis and the choice of anticancer therapy. The noted five-year survival of operated patients is 40-65% as opposed to 15-30% of cases in the non-operated group of patients (38). Median survival time for patients receiving chemotherapy is 32 months (ranging from 20 to 72 months), while for patients not receiving anticancer therapy it is 18 months (ranging from 6 to 60 months). Other factors associated with poor prognosis are tumor size, age, intestinal obstruction or perforation, peritoneal metastases, etc. (18,37). It is noted that median survival time was 28 months (range from 4 to 72 months) in a patient with a tumor smaller than 5cm, while in those with a tumor larger than 5cm median survival time was 14 months (range from 4 to 41 months) (38).

The study of risk factors, pathogenesis and treatment modalities for small intestine cancer is limited as it is a very rare neoplasm.

CONCLUSION

Due to the often deep position in the small intestine, atypical symptomatology and lack of screening, early diagnosis is difficult. Surgical resection of the affected small intestine followed by additional chemotherapy is an optimal treatment strategy.

The study of risk factors, pathogenesis and treatment modalities for small bowel cancer is limited as it is a very rare neoplasm.

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