DOI: https://doi.org/10.2298/SARH221212042Z
UDC: 616.345-006-071: 616-005.1-083.98

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Large bowel's tumor of unclear histogenetic origin from the group of neuroendocrine tumors with life-threatening hemorrhage and hemorrhagic shock

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SUMMARY
Introduction Neuroendocrine neoplasms (NENs) of the gastrointestinal tract (GIT) are slow-growing and rare tumors with different clinical, histological, and biological characteristics with an increased incidence in recent years. Most of them are indolent and colonic NENs are rare among all GIT-NENs. Compared to colorectal adenocarcinoma neuroendocrine tumors of the colon and sigmoid colon are uncommon.
Case outline We present a 25-year-old female patient, who was admitted to our department in hemorrhagic shock due to life-threatening bleeding from a tumor on the sigmoid colon, and after unsuccessful endoscopic hemostasis during colonoscopy. The complaints started the day before admission to the ward with hematochezia. The patient had no complaints before that. Emergency operation and colon resection with terminal colostomy were performed. Pathohistological and immunohistochemical analysis of the tumor showed unclear histogenetic origin from the group of neuroendocrine tumors.
Conclusion Regardless of the asymptomatic period of the disease, these tumors can cause severe bleeding as the first symptom, which can be life-threatening.
Keywords: neuroendocrine neoplasms; hemorrhagic shock; colon tumors; surgery

INTRODUCTION

Colorectal tumors are one of the most common malignant tumors with around 1.9 million new cases diagnosed in 2020, and the second most common cause of cancer death with the highest incidence in developed countries representing significant medical problems [1]. Although there is a decrease in the frequency of colon neoplasms in the elderly in recent time, in younger adults the frequency is increasing. About 10% of newly diagnosed cases are identified in people younger than 50 years old [2]. Men are at higher risk of developing these neoplasms, in comparison to women with worse prognosis and higher mortality [1].

Neuroendocrine neoplasms (NENs) are rare and among them, large bowel neuroendocrine carcinoma (NEC) appears in less than 1% of all cases. NENs can be benign or cancerous; if they are malignant, these tumors have the property of metastasizing, even though the tumor itself grows very slowly [3].

We are presenting a rare emergency case report of a previously healthy young woman with a life-threatening hematochezia and hemorrhagic shock as a first manifestation of a previously asymptomatic sigmoid tumor from the group of neuroendocrine tumors (NET).

CASE REPORT

A 25-year-old female patient was transferred from the Department of Gastroenterology to the Department of Surgery at the Novi Pazar General Hospital, as an emergency, after a colonoscopy, due to bleeding from the colon. The complaints started the day before admission with bloody stools, followed by weakness, dizziness, and malaise. The patient states that before the onset of bleeding from the colon, she had no complaints. She had a vaginal delivery four months ago; pregnancy course and labor were normal. Abdominal ultrasound and lung X-ray were normal. The patient had no significant comorbidities. In the family medical history, she mentioned the death of the mother and aunt at a young age due to an obscure tumor in the abdomen. During the colonoscopy, a tumor formation in the sigmoid colon with bleeding from an arterial blood vessel at the base of the tumor is observed. Endoscopic hemostasis was attempted, but without success, and as an emergency case, surgery was performed. On admission, the patient was pale, hypotensive, and malaise with red blood cell count 2.14×10^{12}/L, hemoglobin count 68 g/L, platelet count 132×10^{9}/L. The indication for urgent laparotomy was established. The abdomen was opened by medial laparotomy. The abdomen was without the presence of free fluid. A tumor formation was present on the sigmoid colon (Figure 1 A and B), which is why a 130-mm-long resection of the rectosigmoid part of the colon was performed, with a terminal colostomy (Hartman operation). The patient's postoperative course was normal. Treated with conservative therapy with blood transfusion and other supportive therapy. She

Received • Примљено: December 12, 2022
Revised • Ревизија: April 10, 2023
Accepted • Прихваћено: April 11, 2023
Online first: May 10, 2023

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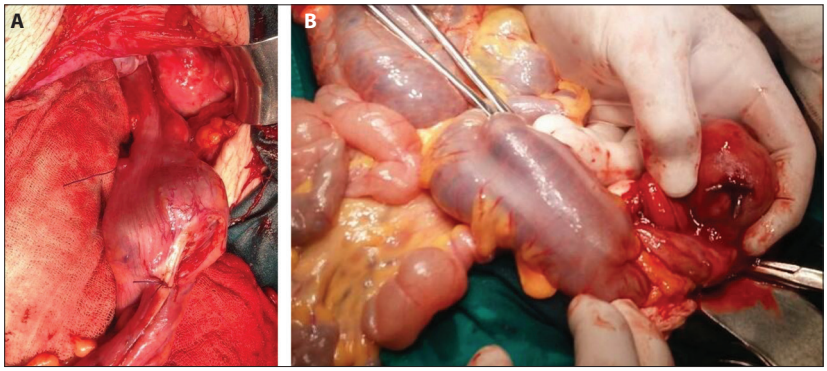

Figure 1. A – sigmoid colon before opening the intestine; B – sigmoid colon after opening and surgical hemostasis – clips from endoscopic hemostasis are observed

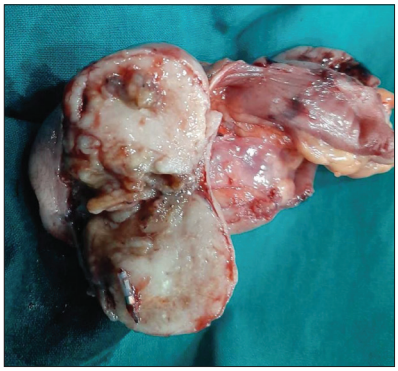

Figure 2. Macroscopic view of the tumor

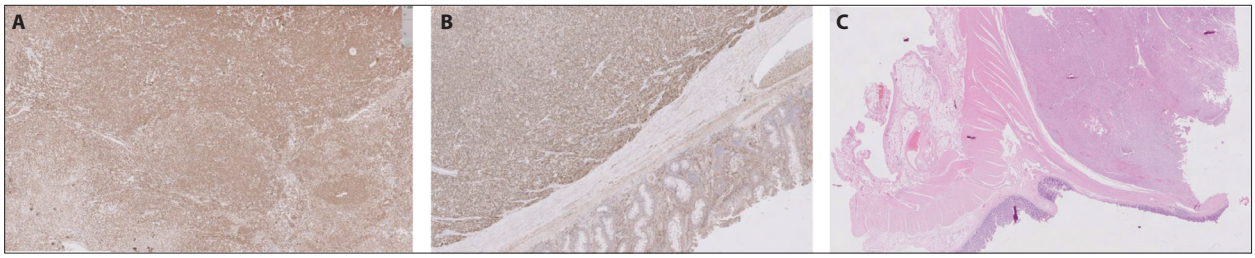

Figure 3. A – NB84 (magnification × 10); B – CD-56 (magnification × 5); C – H&E staining (magnification × 1.25)

was discharged seven days after the operation. After two months, the reconstruction of the colon with colorectal terminal-lateral anastomosis was performed and the continuity of the digestive tract was established. Control computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen and pelvis, six and 12 months after the operation, were normal.

The pathohistological findings of the tumor indicate that it is an intramural, predominantly submucosal tumor of size 40 × 35 × 35 mm, with a clear limitation towards the muscular layer of the intestinal wall and minor ulcerative changes in the mucosa (Figure 2). Found and analyzed lymph nodes were tumor-free (0/6). There were no tumor cells at the line of bowel resection – R0 resection. Tumor tissue preparation stained with a hematoxylin-eosin method and immunohistochemical staining NB84. The largest number of tumor cells shows strong immunoreactivity to NB84 and synaptophysin, and focally observed immunoreactivity to myogen and actin (SMA-alpha). No immunoreactivity for desmin, Myo-D1, CD117, DOG-1, PDGFRA, CD34, ALK, S-100 protein, GFAP, SOX-10, AE1-AE3, EMA. Positivity on NB84 points to a ganglioneuroblastoma, but the presence of a ganglioneuroma component rich in Schwannoma stroma is not observed in the sample, which is also confirmed by S-100 negative staining. Considering the obtained focal positivity for muscle markers, additional immunohistochemical staining were performed to rule out the presence of a rhabdoid tumor (INI-1+), a tumor from the Ewing/PNET group (CD99-). Only the focally obtained positivity for Melan A. Additional immunohistochemical staining revealed clear membrane positivity for CD56 (Figure 3), and in part of the sample cytoplasmic positivity for chromogranin A. The mitotic index is < 2, and Ki 67 < 3%.

We obtained verbal and written consent from the patient to publish the case report. This article was planned in compliance with the Patient Rights Directive and ethical rules by considering the ethical principles of the Declaration of Helsinki.

DISCUSSION

NENs represent an expansive group of neoplasms that differ from each other by a clinical spectrum of manifestations, localization, applied treatment response, geographical distribution, morphology and survival rate. They are primary epithelial neoplasms, with signs of neuroendocrine differentiation diffusely distributed across the mucosa of the gastrointestinal and respiratory tract, but they are also described in the other organs [4]. According to WHO 2019 scheme, NENs are classified into NEC, NET, and mixed neuroendocrine-non NEN (MiNEN) [5]. While NETs can behave indolently (appendix) or more aggressively (in the colon), NEC and MiNEN are aggressive neoplasms that are usually diagnosed at an advanced stage [5]. Based on the degree of differentiation and proliferation activity based on mitotic rate and/or Ki-67 proliferation index. gastrointestinal NETs are categorized into: grade 1 (low grade), grade 2 (intermediate), and grade 3 (high grade). NECs are always high-grade neoplasms, and they are not assigned any grade [6, 7].

About two-thirds of NEN locations are located in the digestive tube and pancreas with the biggest incidence in the

small bowel and rectum [4, 5]. NENs of the colon represent up to 7% of all well-differentiated gastroenteropancreatic NETs and 25% of all gastroenteropancreatic NEC [5]. The frequency of NEN has increased in recent years, probably due to earlier diagnoses, new genetic-molecular and immunohistochemical methods development as well as more available sophisticated diagnostic procedures such as endoscopy and radiology imaging (CT, MRI, and ultrasound), but they are still rare. The incidence of rectal and colonic NENs is 0.2 and 1.2 new cases per 100,000 persons/year [6], and colon NEC accounts for 1% of all colorectal cancers [3].

Genetic studies of NET and NEC are still ongoing. It has been found that in gastrointestinal NEC there are mutations in the TP53 and RB1 genes similar to those in pancreatic lesions. On the other hand, NETs often do not have recurrent mutations, so genetic analysis for diagnostic purposes in NETs has not proven to be relevant [6]. Riechelmann et al. [8] indicate that in NENs carcinogenesis in young adults there is a significant role of inherited genetic alterations, particularly in DNA repair genes, which can lead to the possibility of a higher frequency of cancer and NEN in the family. In our case, a positive family history of the death of the mother and aunt at a younger age from an obscure tumor in the abdomen may raise the suspicion that it is a hereditary disorder, but the cause of the death of the mother and aunt was not identified through the medical documentation.

These tumors most often appear in the seventh decade of life. The most common site of occurrence of colon NENs is the right colon and cecum [3]. In our case, the patient was a young 25-year-old woman and a tumor was located on the sigmoid colon.

A large percentage of these tumors are asymptomatic and are discovered as an incidental finding during the surgery or colonoscopy, but there are patients who also have symptoms. Clinical symptoms also depend on whether they occur in the right or left colon and may manifest as anemia, weight loss, abdominal discomfort, dyspeptic symptoms, bleeding, obstructive symptoms and constipation. The diagnosis is usually made after a biopsy during a colonoscopy or after surgery. About 10% of patients with NETs will experience carcinoid syndrome, caused by the overproduction of serotonin or other hormones secreted by some NETs [9]. Our patient was asymptomatic until the lower gastrointestinal bleeding occurred.

Acute lower gastrointestinal bleeding accounts for up to 20% of all cases of gastrointestinal bleeding and is defined as bleeding distal to the Treitz ligament. It can manifest as melena or hematochezia. Endoscopic diagnostic methods (colonoscopy and gastroscopy) with endoscopic hemostasis are indicated in patients with these symptoms [10, 11, 12]. Sometimes these bleedings can lead to massive blood loss and emergency conditions in some patients. In our case, due to failed endoscopic hemostasis during colonoscopy, and due to the poor general condition caused by sudden bleeding and huge blood loss, an urgent surgical intervention was performed. We did not wait for the findings of the tumor biopsy to operate, because it was an emergency case, and therefore the operation was not performed according to all oncological principles.

Diagnosis of NEN, apart from clinical examination and history, involves determining the level of tumor markers (5- HIAA and chromogranin A (CgA), radiological methods (CT, MRI), positron emission tomography (PET); PET combined with CT, has become imaging gold standard and simultaneous high-contrast PET-MRI can be important clinical tool for the whole-body imaging in one place [13]), upper and lower endoscopy, pathohistological verification and immunohistochemical methods. Pathohistological verification represents the gold standard for the diagnosis of NENs (recommended by the European Neuroendocrine Tumor Society) [14] and includes standard hematoxylin-eosin staining and supplementary immunohistochemical tests [including cytosolic markers (neuron-specific enolase), synaptophysin, cell membrane-specific markers (CD 56) and CgA] [4]. Histologic features of colorectal NETs and NECs are similar to those in other organs. Ki-67 index and mitotic index correlate with cellular proliferation. Ki-67 proliferation index alone cannot be used to distinguish NETs from NEC [6].

From the above, it can be said that in our case report it is a tumor of unclear histogenetic origin and that the immunohistochemical activity of tumor cells with neuroendocrine markers is most indicative of belonging to the group of NETs.

In conclusion, due to all the characteristics of NEN, it is difficult to manage; and that is why early diagnosis, knowledge of this disease, and adequate treatment are very important. Also, regardless of the asymptomatic period of the disease, these tumors can cause severe bleeding as the first symptom, which can be life-threatening.

Conflict of interests: None declared.

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Тумор дебелог црева нејасног хистогенетског порекла из групе неуроендокриних тумора са крварењем опасним по живот и хеморагичним шоком

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Општа болница Нови Пазар, Нови Пазар, Србија

САЖЕТАК

Увод Неуроендокрине неоплазме гастроинтестиналног тракта су споро растући и ретки тумори различитих клиничких, хистолошких и биолошких карактеристика са повећаном инциденцом последњих година. Већина њих је индолентна и неуроендокрине неоплазме дебелог црева су ретке међу свим неуроендокриним неоплазмама гастроинтестиналног тракта. У поређењу са колоректалним аденокарциномом, неуроендокрини тумори дебелог и сигмоидног колона су ретки.

Приказ болесника Представљамо болесницу стару 25 година, која је примљена на наше одељење у хеморагичном шоку због животно опасног крварења из тумора на сигмоидном колону, а после неуспешне ендоскопске хемостазе током колоноскопије. Тегобе су почеле са хематохезијом дан пре пријема на одељење. Болесница је навела да пре тога није имала никаквих тегоба. Урађена је хитна операција и ресекција дебелог црева са терминалном колостомом. Патохистолошка и имунохистохемијска анализа тумора показале су нејасно хистогенетско порекло из групе неуроендокриних тумора.

Закључак Без обзира на асимптоматски период болести, ови тумори као први симптом могу изазвати јака крварења, која могу бити опасна по живот.

Кључне речи: неуроендокрине неоплазме; хеморагични шок; тумори дебелог црева; хирургија