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Early Perianastomotic Tumor Recurrence in a Patient with Sigmoid Colon Adenocarcinoma with Perineural and Lymphovascular Invasion

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Abbreviations:
PNI: perineural invasion;
LVI: lymphovascular invasion.

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Rezumat

Recidivă tumorală perianastomotică precoce la pacient cu adenocarcinom sigmoidian cu invazie limfovasculară și perineurală

Introducere: La nivel național, cancerul colo-rectal reprezintă prima cea mai frecventă neoplazie, urmată de cancerul de sân, cu o incidență în uşoară creştere în ultimii ani. Această creştere a incidenței a condus la necesitatea dezvoltării unor programe de screening mai eficiente, care prezintă avantajele de a fi reproductibile şi uşor accesibile, destinate populației aflate la risc, cu scopul de a stabili cât mai curând posibil un diagnostic pozitiv, care să permită un tratament adecvat. Invazia tumorală a ganglionilor limfatici peritumorali constituie unul dintre cei mai importanți factori de prognostic negativ, alături de invazia perineurală. Cea de-a 8a ediție a clasificării TNM impune examinarea histopatologică a minimum 12 limfoganglioni pe piesa de exereză pentru a permite o stadializare corectă şi evitarea unei subclasificări într-un stadiu mai puțin avansat. Invazia perineurală în procesele neoplazice colo-rectale asociază un prognostic nefavorabil independent de celelalte căi de diseminare, fiind implicate numeroase mecanisme moleculare. Bellis D. Et all au raportat o rată crescută a recidivei locoregionale, asociată cu un prognostic negativ la 5 ani, în prezența invaziei perineurale, documentată de acesta la 33% dintre cazurile studiate.
Prezentare caz: Expunem cazul unui pacient în vârstă de 68 de ani cu adenocarcinom sigmoidian moderat diferențiat stadiul III B, operat în Clinica de Chirurgie Generală a Spitalului Clinic Colțea cu rezultat histopatologic T3N1M0 cu invazie limfovasculară şi perineurală prezentă pe piesa operatorie, la care s-a practicat o rezectie R0 cu anastomoza colo-rectală termino-terminală, cu recidivă loco-regională la 1 an de la intervenție.
Concluzii: Recidiva precoce postoperator a fost favorizată de invazia perineuțiile

unor rezecții R0 cu margini de siguranță oncologică, la un pacient cu chimioterapie adjuvantă postoperator în concordanță cu ghidurile actuale. Diagnosticul histopatologic pozitiv pentru recidiva loco-regională a fost dificil de stabilit datorită multiplelor biopsii prelevate cu rezultat negativ.

Cuvinte cheie: adenocarcinom sigmoidian, invazie limfo-vasculară, invazie perineurală (PNI), recidivă tumorală

Abstract

Introduction: Nationally, colon cancer is the most common malignancy, followed by breast cancer with an incidence in a slight increase in recent years. This increase in incidence has led to the necessity of development of more effective screening programs, which possess the advantages of being reproducible and easily accessible, destined for the population at risk, with the purpose of establishing, as soon as possible, a positive diagnosis, allowing adequate treatment. Tumoral invasion of the peritumoral ganglia represents one of the most important negative prognostic factors, alongside perineural invasion. The 8th edition of the TNM classification imposes the histopathological examination of at least 12 lymph nodes from the resected piece to facilitate precise staging and avoid downgrading. Perineural invasion in colorectal malignancies is associated with an unfavorable evolution unlinked to the other ways of dissemination, due to the multiple molecular mechanisms. Bellis D. et al. reported an increased rate of locoregional recurrence associated with a negative 5 years prognosis, in the presence of perineural invasion, documented in 33% of the studied cases.
Case report: We present the case of a 68-year-old patient with moderately differentiated stage III B sigmoid adenocarcinoma, operated on in the General Surgery Clinic of Colțea Clinical Hospital with histopathological staging T3N1M0 with lymphovascular and perineural invasion present on the surgical specimen, who underwent an R0 resection with end-to-end colorectal anastomosis, with loco-regional recurrence at 1 year after the intervention.
Conclusions: Early postoperative malignant recurrence was favored by the perineural and lymphovascular invasion, although a resection with oncologic safety margins was practiced, in the presence of adjuvant chemotherapy, in concordance with actual guidelines.

Key words: sigmoid adenocarcinoma, perineural invasion, lymphovascular invasion, tumoral recurrence

Introduction

Nationally, colorectal cancer is the most common cancer, followed by breast cancer and lung cancer, with a slightly stationary incidence (1). Of all the cancers detected in our country, the incidence of colorectal neoplasm associates a reported percentage of 12.9% in 2022, compared to 13.3% in 2018 (1). The diagnosis is established in late stages of the disease, and that is associated with high mortality. Numerous risk factors are described, the genetic ones accounting for only 30% of the cases (2). At the time of diagnosis, the median age is 70 years for males and 72 years for females (3).

The invasion of the lymph nodes represents an important parameter and negative prognosis factor, included in the latest TNM classification, thus, the presence of the malignant cells at this level signifies a stage IIIA. In order to facilitate an accurate grading, the 8th edition of the TNM classification requires at least 12 lymph nodes to be examined by a trained pathologist, avoiding in this manner the understaging of the case as less severe (4,5). The important statistical difference in the rate of survival in patients staged as minimum stage III, led to the necessity of renewing TNM classification so that N1 and N2 to be differentiated by the number of invaded nodes (4). Until recently, the perineural metastatic path showed little interest, its importance being acknowledged in the colorectal malignancies as well, as an independent negative prognosis factor, unlinked to the other ways of dissemination (6).

The first definition of perineural invasion was established by Batsakis as an invasion of the connective tissue surrounding the nerve, this structure being considered to have minimal resistance, or through endolymphatic dissemination (7).

Currently, the diagnosis criteria for perineural invasion imply the presence of malignant cells in any of the 3 layers which form the nerve sheet (8). In this manner, the certainty of the perineural invasion is sustained by the malignant extension to at least 33% of the circumference of the nerve, any

value below the mentioned one signifying focal tumoral invasion (6). Bellis et al. have reported an increased rate of local recurrence, associated with a negative 5-year prognosis, in patients with colorectal cancer and perineural invasion (9). There are multiple ways of dissemination described for colorectal cancer, and vascular invasion must be mentioned alongside, being a venous invasion in over 99% of the cases and associated with a severe impact on evolution and 5-year survival (10).

The purpose of this paper is to present the case of a patient with operated sigmoid cancer, with multiple early recurrences. The interest for this subject is given by the presence of lymphovascular and perineural invasion on the histopathological examination of the resected specimen.

Case Report

A 68-year-old patient, without any significant associated pathology, is admitted to the Surgery Clinic of Coltea Clinical Hospital on 27.08.2018 for persistent lower digestive tract bleeding and slowing abdominal bowel movement with the tendency towards constipation, symptoms started 3 months previously, with progressive worsening. The initial physical examination revealed a patient in a good general state, afebrile, with a distended abdomen, without any signs of peritoneal guarding rebound rigidity, without spontaneous pain or on palpation, with normal gastrointestinal transit time. Biologically, the investigations revealed increased mean platelet volume, decreased platelet distribution width, and increased carcinoembryonic antigen.

On 29.08.2018 an incomplete colonoscopy was performed, due to major tumoral obstruction, which revealed a mass located 25 cm from the pectinate line, with 75% stenosis and active bleeding. Multiple biopsies were taken. The histopathological examination detected G2 invasive moderately differentiated adenocarcinoma. In order to facilitate a complete staging of the case, a contrast enhanced toraco-abdomino-pelvic computed tomography was performed, which established the case as being a stage III B (cT3N1M0), which was subsequently discussed within the tumor board of the hospital. Due to the subocclusive phenomena and the subsequent potential for clinical-biological degradation, it was decided to postpone neoadjuvant treatment in favor of surgery as the first therapeutic approach. The surgery was scheduled for 05.09.2018 and a rectosigmoid resection was performed with partial excision of the mesorectum, and low ligation of the inferior mesenteric artery (11), operation completed by termino-terminal colorectal manual anastomosis located at the level of the middle rectum. The resected specimen was analyzed histopathologically and moderate differentiated adenocarcinoma was observed, with metastatic disease involving 3 out of 13 lymph nodes with positive lymphovascular and perineural invasion. Postoperative evolution is favorable, and the patient is discharged 9 days later with oncologic dispensary and recommendation for endoscopic examination after 3 months.

On 31.10.2018, the patient was readmitted to the Surgical Clinic, reporting repetitive subocclusive phenomena and an endoscopic examination was performed, which revealed, 18 cm from the anal orifice, an anastomotic line with multiple granulomas, and 22 cm from the anal orifice, a stenotic area. This result implied an anastomotic fistula or a local malignant recurrence, both suspicions ruled out by the contrast enhanced computed tomography that was performed and biopsies obtained (*Fig. 1*).

Conservative treatment was selected, and close monitoring. Eight months later, colonoscopy examination identified a 90% stenotic area with inflammatory markers, located 18-20 cm from the anal orifice. Multiple biopsies were taken, malignant recurrence was invalidated, and 2 sessions of endoscopic dilations were recommended, with satisfactory evolution. Thirty days after the last endoscopic dilation session, the patient returns in the Clinic for symptomats suggesting lower intestinal bowel obstruction, and thus, in emergency, was the resection of the anastomotic

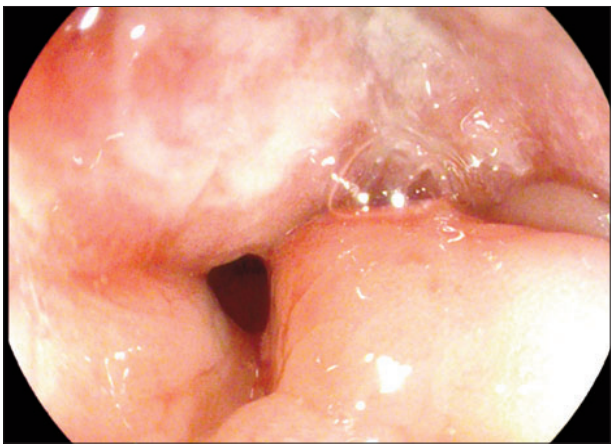

Figure 1. Anastomotic stenosis, endoscopic view (Coltea Surgery Clinic Archive)

area was performed with a mechanical latero-terminal reanastomosis. The pathology report of the resected specimen revealed relapsed moderately differentiated colorectal adenocarcinoma, with the involvement of the visceral peritoneum, lympho-vascular and perineural invasion, with clean resection margins, stage rpT4aNxM0. Follow-up inferior digestive endoscopy at 3 months post-operatively described a mechanical anastomosis area of normal appearance, without any alterations suggesting local malignant recurrence.

On 27.07.2020, the patient was re-evaluated colonoscopically and an area of friable mucosa was identified, located circumferentially at the level of the anastomosis and with alterations consistent with local malignant recurrence, confirmed histo-pathologically as recurred moderately differentiated adenocarcinoma.

The patient was subsequently operated on for palliative purposes and a terminal colostomy was performed. After the surgery, the case was lost from our records (*Fig. 2*).

It has to be mentioned that, throughout the entire period, starting from the first surgical intervention, the patient benefited from an adjuvant polychemotherapy regimen, in accordance with international guidelines (12) with oxaplatin in combination with 5-fluorouracil.

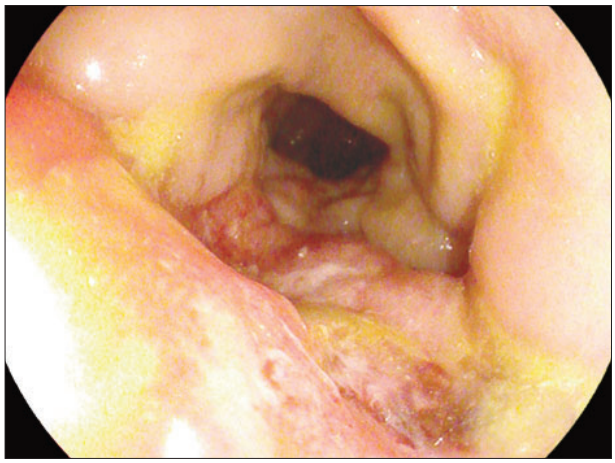

Figure 2. Tumoral recurrence, endoscopic view (Coltea Surgery Clinic Archive)

Discussion

Early cancer recurrence involving the patient with colorectal malignancy is extensively studied, many specialists joining their abilities in order to precisely establish the involving risk factors. Shah Zeb Khan et al. identified as risk factors age above 60 years and resection of less 12 lymph nodes (13). Fernandez-Vergara et al. mention as a risk factor resection of less than 10 lymph nodes and note that these patients have an increased risk of local recurrence and metastatic disease, considering the perineural invasion as an independent prognostic factor, which influences the disease-free survival (14). The patient in the present paper is aged above 60 years, but the initial surgery involved the resection of over 12 lymph nodes.

It is important to be mentioned that, in our opinion, perineural invasion favors local recurrence. The involving mechanism implies alterations at the level of enteric nervous system, with atrophy of the submucous and mienteric nervous plexus through the growing number of the galanin-immunoreactive neurons and the galanin content in the colonic regions adjacent to the tumor, and also, by the increasing density of the intrinsic neuronal network facilitated by the increased release of neurotrophic growth factors (15,16).

Biopsies performed with false negative histopathological results for malignancy and loco-regional recurrence, indicate, in the present case, the possible extrinsic origin of the tumor with a possible starting point at the lymph node or perineural level.

Renato Costi et al. present the genetic analysis of two cases with early loco-regional recurrence at the anastomotic level after colorectal neoplasm surgery (17). In the study carried out, they state that approximately 16% of patients undergoing an intervention for colorectal neoplasm will develop a recurrence over time, and 2% will present a peri-anastomotic recurrence (17).

Satkin et al. noted that another two hematological markers can be used as prognostic factors: mean platelet volume and platelet distribution width (18). They considered that increased mean platelet volume and decreased platelet distribution width seem to be negative prognostic factors in patients with colorectal malignancy stage III. The patient in the current paper had biological alteration that support the remarks mentioned by our colleagues, alteration present on admission, and consistent during all the surgical history of the patient in our clinic.

Conclusions

We can strongly state that, in the case of our patient, early postoperative malignant recurrence was favored by the perineural and lymphovascular invasion, in the situation of a resection with onco-

logic safety margins, in the presence of adjuvant chemotherapy in concordance with current guidelines.

A positive histopathological diagnosis of locoregional recurrence was difficult to establish due to multiple negative biopsies.

Approximately 16% of patients undergoing radical oncological surgery for colorectal cancer experience local recurrence and approximately 2% experience early perianastomotic recurrence (17).

Likewise, since admission, mean platelet volume was increased, and platelet distribution width was decreased, meeting another negative prognosis factor.

Conflicts of Interests

Nothing to declare.

Ethical Statement

The approvel of the Ethics Committee of Coltea Clinical Hospital was obtained prior to study initiation.

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