Review paper

Cutaneous metastasis of rectal adenocarcinoma: a case report and literature review

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All authors have equal implication in this study.

According to the latest data provided by Globocan 2020, the incidence of colorectal cancer ranks third, after lung cancer and breast cancer, becoming a more and more important global health issue. Of the cases diagnosed with colorectal cancer, more than 25% are diagnosed in the metastatic stage, with the presence of secondary tumors more frequently in the liver, lung and bone. Skin metastases from colorectal cancer are still rare today (< 4%).
We want to present a rare, unique case in our department of a 74-year-old patient diagnosed 9 years ago with a malignant rectal tumor who, after a disease-free period of approximately 8 years and a half, developed multiple skin metastases of rectal adenocarcinoma.

Key words: colorectal cancer, cutaneous metastasis, immunohistochemistry.

Introduction

Colorectal cancer is a worrying medical problem in terms of its incidence-according to the latest data provided by Globocan 2020 (third place after breast and lung cancer). As a 5-year prevalence, it will reach 2nd place (by 2025) in both females and males (after breast and prostate cancer, respectively). The GLOBOCAN 2020 data also showed an increase in colorectal cancer mortality, reaching 9.4% (the 2018 mortality rate was 9.2%). Out of a total of 1 931 590 new cases of colorectal cancer in 2020, the number of deaths in both sexes was 935 173 (48.41%), which reflects that approximately half of the newly diagnosed cases are followed by death.

About one-third (25-30%) of patients diagnosed with colorectal cancer are diagnosed with metastatic cancer, with the remaining patients at increased risk of later developing secondary tumors [1]. Colorectal cancer frequently spreads to the lymph nodes, lung, liver, and peritoneum, but only rarely to the skin [2]. Only 0.001% of all skin biopsies result in metastatic skin cancer, which is considered to be very uncommon [3]. The development of cutaneous metastasis from colon cancer is a very rare occurrence that usually occurs in patients with widely disseminated illness and a poor prognosis [4]. Cutaneous metastases of adenocarcinoma of the rectum are considerably rarer, occurring in only 4% of patients [5]. Up until 2018, only 43 cases of cutaneous metastasis secondary to rectal cancer were reported [3, 6].

Case report

A 74-year-old male patient presents to the emergency department complaining of eruptions in

the form of indurated, dark red-purple papules with a diameter of 0.7-1.5 cm, disseminated on the lower and upper limbs, with agglomeration on the forearms and legs (Fig. 1). From the patient's history we found out that 9 years ago he was diagnosed with adenocarcinoma of the prostate and a few months later, the same year, was diagnosed with a rectal tumor having the histological characteristics of a moderately differentiated adenocarcinoma of the rectum. The histopathological report of the primary rectal tumor describes in macroscopic examination a vegetative cauliflower-like, stenotic tumor formation located at 2 cm from the distal resection margin, with areas of ulceration, of increased consistency, of 4.6/3.2 cm, which completely obstructs the intestinal lumen. In the sections examined microscopically from the ulcerated rectal tumor formation, a tumor proliferation was observed, having the histological characteristics of a moderately differentiated rectal adenocarcinoma infiltrating the perirectal tissues, deep through the muscularis propria into the subserosa, the glandular component occupying 80% of the tumor bed. Areas with dystrophic calcification were detected focally. Perineural and vascular tumor invasion was present. The adjacent sigmoid mucosa showed aspects of non-specific chronic sigmoiditis. 26 perirectal lymph nodes with sizes between 1 and 19 mm were isolated, 10 of which showed tumoral infiltration. The resection margins were free of malignancy (T3N2Mx) (Figs. 2, 3). Following this diagnosis, he underwent oncological treatment (26 courses of radiotherapy and chemotherapy with oxaliplatin).

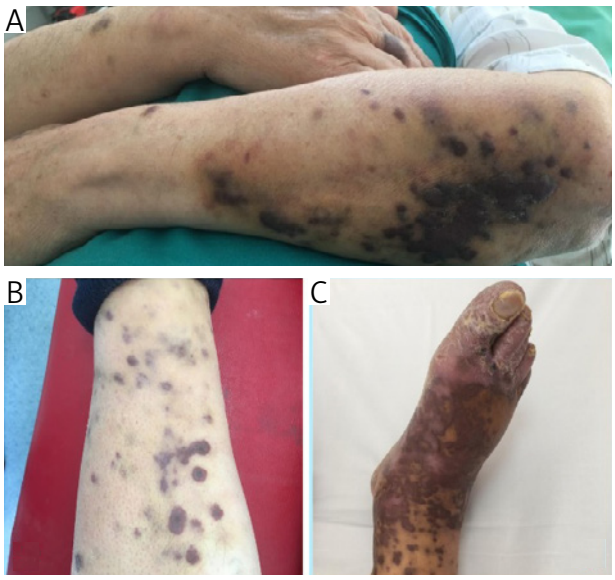

Fig. 1. Multiple metastatic cutaneous papules on the lower and upper limbs in a patient with rectal adenocarcinoma

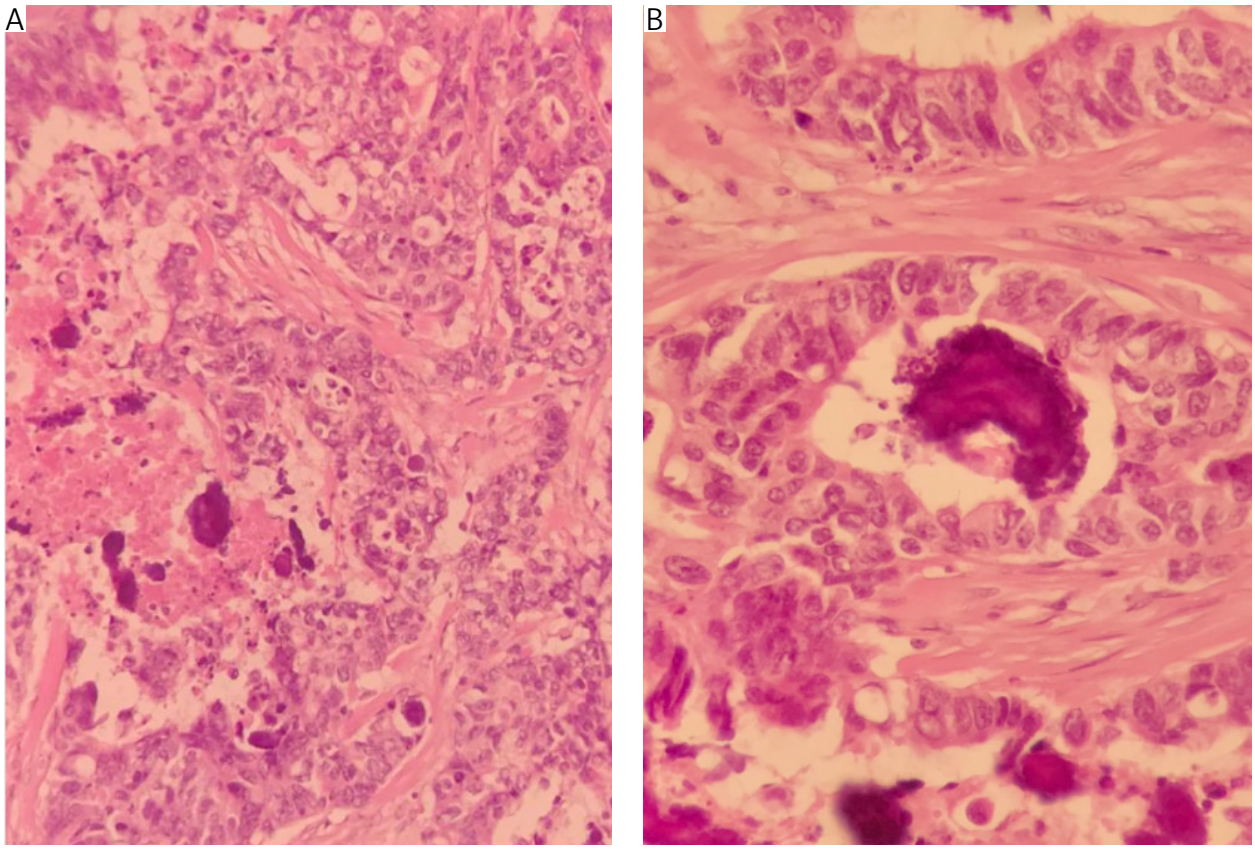

Fig. 2. Light microscopy of the rectal tumor. **A**) HE ×10; **B**) HE ×40

The biopsies taken from the skin lesions revealed dermal tumor proliferation composed of glands of different sizes and shapes, lined by columnar cells arranged in several layers, with eosinophilic cytoplasm, moderately pleomorphic vesicular hyperchromatic nuclei with visible nucleolus and frequent atypical mitoses present. Dirty necrosis was observed in the lumen of the atypical glands (Fig. 4).

The tumor stroma with moderate diffuse inflammatory infiltrate composed out of lymphocytes and plasmocytes, and scattered extravasated erythrocytes. Complementary IHC tests reveal the following: CK 7 negative, CK 20 positive, CDx2 positive, TTF1 negative, PSA negative, S100 negative, thus confirming the colorectal origin. Molecular tests for *KRAS* and *BRAF* mutations were also documented, both of them being wild-type. The evolution of the patient worsened and due to the extent of the metastasis he was under palliative chemotherapy regimen for a short period of time. Unfortunately he died 4 months after the diagnosis of skin metastasis.

Discussion

Rarely occurring, skin metastases from solid tumors typically occur late in the course of an advanced visceral malignancy. Following the removal of the primary colorectal tumor, the surgical scar located in the abdomen is the most common site for skin metastasis, followed by the extremities, perineum, head, neck, and penis [7]. Although clinical presentations might vary significantly, lesions often manifest as single nodules. Nevertheless, clustered nodules, red-purple or skin-colored, hard or soft, erythematous plaques, non-healing ulcers, and infiltrating scars are further possibilities [8]. Rarely, it may mimic an infection, in which case it is known as inflammatory metastatic car-

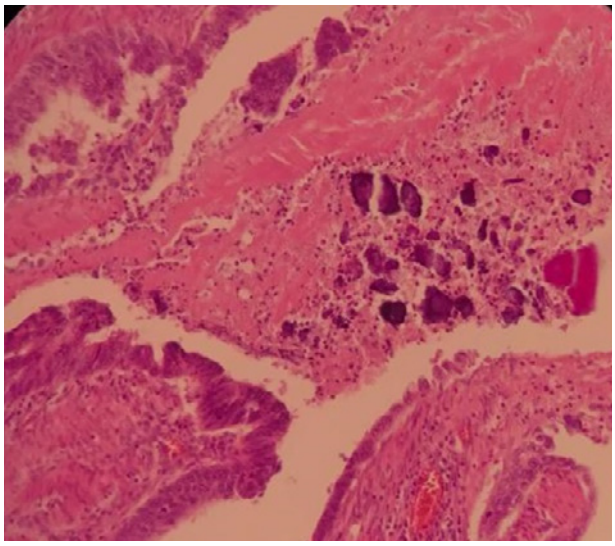

Fig. 3. Light microscopy of the primary rectal tumor with areas of dystrophic calcifications. HE ×4

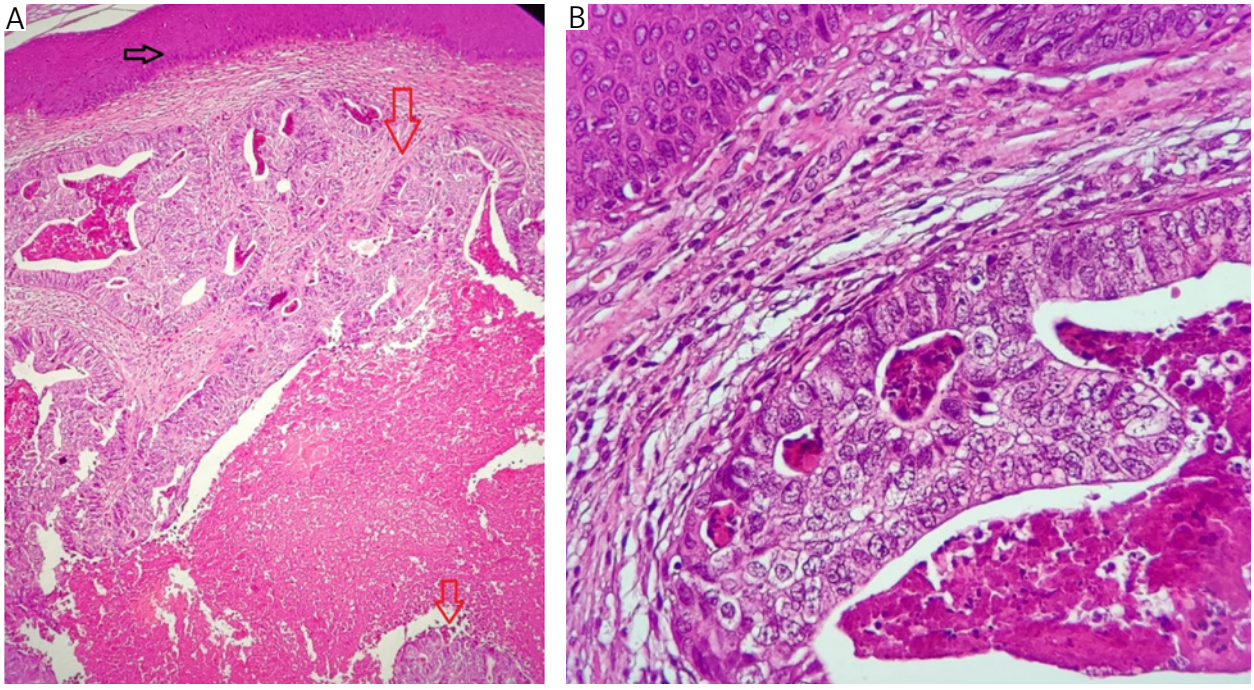

Fig. 4. Histopathological examination of the cutaneous lesions – black arrow – intact epidermis; dermal tumor proliferation composed of glands of different sizes and shapes (red arrows), lined by columnar cells arranged in multiple layers, with eosinophilic cytoplasm, moderately pleomorphic vesicular hyperchromatic nuclei with visible nucleolus and frequent atypical mitoses present. Dirty necrosis phenomena present. Tumor stroma with moderate diffuse inflammatory infiltrate composed out of lymphocytes and plasmocytes, and scattered extravasated erythrocytes. **A**) HE ×10; **B**) HE ×40

cinoma or erysipeloid carcinoma [9]. Along with these forms, various other clinical presentations recorded in the literature also include ulcers, blisters, alopecia plaques, lesions similar to herpes zoster, epidermal cysts, neurofibromas, lymphomas, annular erythema, condylomas, and elephantiasis verrucosa [10, 11]. In our case, most of the lesions were hard, indurated nodules, violaceous and at the level of the foot, non-healing ulcers were observed.

An uncommon occurrence, cutaneous metastases from colorectal cancer typically portends a dismal prognosis and there is a 1 to 34 month range in survival following diagnosis [12, 13], but according to a more recent study performed by Schoenlaub *et al*., the median survival period for people with cutaneous metastases from colorectal original tumors is 4.4 months [14]. The status of our patient started to deteriorate after the diagnosis of cutaneous metastases despite being under chemotherapy, and died after 4 months after diagnosis.

The morphologic characteristics, histo-morphology, and immunohistochemistry of the cutaneous lesion are used to make the diagnosis in the majority of metastases [15]. An essential auxiliary tool for histopathological examinations is the immunohistochemistry study. More than 70% of lesions in cutaneous metastases arising from colorectal cancer have the CK7-negative/CK20-positive pattern [10]. From the proximal duodenum to the distal rectum, intestinal epithelial cells contain the transcription factor caudal-type homeobox 2 (CDX2), which controls gut epithelial development and maturation [16, 17]. Approximately 90-95% of colorectal adenocarcinomas have elevated CDX2 expression, which is thought to be a highly sensitive and specific diagnostic marker for adenocarcinomas of intestinal origin [18, 19].

Routine *KRAS* and *BRAF* mutation testing has completely changed how metastatic colorectal carcinoma is molecularly characterized over the past two decades. *BRAF* and *KRAS* mutations are reportedly associated with very poor prognoses. Patients with these mutations respond poorly to anti-EGFR therapy in terms of treatment. Compared to patients with wild type *KRAS* and wild type *BRAF*, patients with these mutations exhibited poorer progression-free survival and overall survival rates. Because of this, finding BRAF or KRAS mutations can help treat metastatic colorectal carcinoma more effectively and increase patient survival [20, 21]. In our case, both *KRAS* and *BRAF* were wild type.

Management of these secondary tumors located in the skin depends on their location and extent. Surgical removal of a single cutaneous metastases is required. Since they are associated with much greater odds of distant metastases, uncontrolled local illness, and worse survival rates, large cutaneous metastases only get palliative care [22].

Acknowledgments

Cutaneous metastasis due to colorectal cancer, although very rare, indicate a severe and accelerated progression of the disease, conferring a poor prognosis for the patient.

The latest data from the literature show an incidence of less than 4%, much more frequent in this anatomical site are metastasis with the origin of the primary tumor in the lungs and breasts. The diagnosis of skin metastasis is quite complicated in the absence of a history that would indicate evidence of a primary tumor.

The concrete and correct diagnosis is based on the histopathological examination, together with the complementary immunohistochemical examinations, which are otherwise very useful. The identification of BRAF and KRAS mutations can be of great help in the subsequent establishment of a targeted treatment in the case of these patients.

The authors declare no conflict of interest.

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