

CASE REPORT

CUTANEOUS METASTASIS OF RECTAL ADENOCARCINOMA –
A CASE REPORT AND LITERATURE REVIEW

VESA ALEXANDRA ALINA¹, OCTAVIAN MAGHIAR², LAURA MAGHIAR³, ROMINA CUC³, OVIDIU POP¹,
ANDREI PASCALAU¹, MONICA BOROS¹, ADRIAN MAGHIAR²

¹Morphological Sciences Department, Faculty of Medicine and Pharmacy Oradea, University of Oradea, Romania

²Surgical Sciences Department, Faculty of Medicine and Pharmacy Oradea, University of Oradea, Oradea, Romania

³Preclinical Sciences Department, Faculty of Medicine and Pharmacy Oradea, University of Oradea, Oradea, Romania

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 tumours more frequently in the liver, lung, and bone. Skin metastasis from colorectal cancer are still rare (< 4%).

We present a rare, unique case in our department of a 74-year-old patient diagnosed 9 years ago with a malignant rectal tumour, who, after a disease-free period of approximately 8 and a half years, 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). In terms of 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% (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 is 935,173 (48.41%), which reflects that approximately half of 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 tumours [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 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 metastasis of adenocarcinoma of the rectum is considerably rarer, occurring in only 4% of patients [5]. Up to 2018, only 43 cases of cutaneous metastasis secondary to rectal cancer were reported [3, 6].

Case report

A 74-year-old male patient presented to the emergency department complaining of eruptions in the form of indurated, dark red-purple papules with a diameter between 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



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

that 9 years ago he was diagnosed with adenocarcinoma of the prostate and a few months later, in the same year, was diagnosed with a rectal tumour with the histological characteristics of a moderately differentiated adenocarcinoma of the rectum. The histopathological report of the primary rectal tumour described at macroscopy a vegetative cauliflower-like, stenotic tumour formation located at 2 cm from the distal resection margin, with areas of ulceration, of increased consistency, size 4.6/3.2 cm, which completely obstructed the intestinal lumen. In the sections examined microscopically from the ulcerated rectal tumour formation, a tumour proliferation was observed, with 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 tumour bed. Areas with dystrophic calcification could be detected focally. Perineural and vascular tumour invasion was present. The adjacent sigmoid mucosa showed aspects of non-specific chronic sigmoiditis. Perirectally, 26 lymph nodes with sizes 1–19 mm were isolated, 10 of which showed tumoural infiltration. The resection margins were free of malignancy (T3N2Mx) (Fig. 2, 3). Following this diagnosis, he underwent oncological treatment (26 courses of radiotherapy and chemotherapy with oxaliplatin).

The biopsies taken from the skin lesions revealed a dermal tumour 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 tumour stroma had moderate diffuse inflammatory infiltrate composed of lymphocytes and plasmacytes and scattered extravasated erythrocytes. Complementary IHC tests revealed the following: CK 7 negative, CK 20 positive, CD 2 positive, TTF1 negative, PSA negative, and 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 placed on a palliative chemotherapy regimen for a short period of time. Unfortunately, he died 4 months after the diagnosis of skin metastasis.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

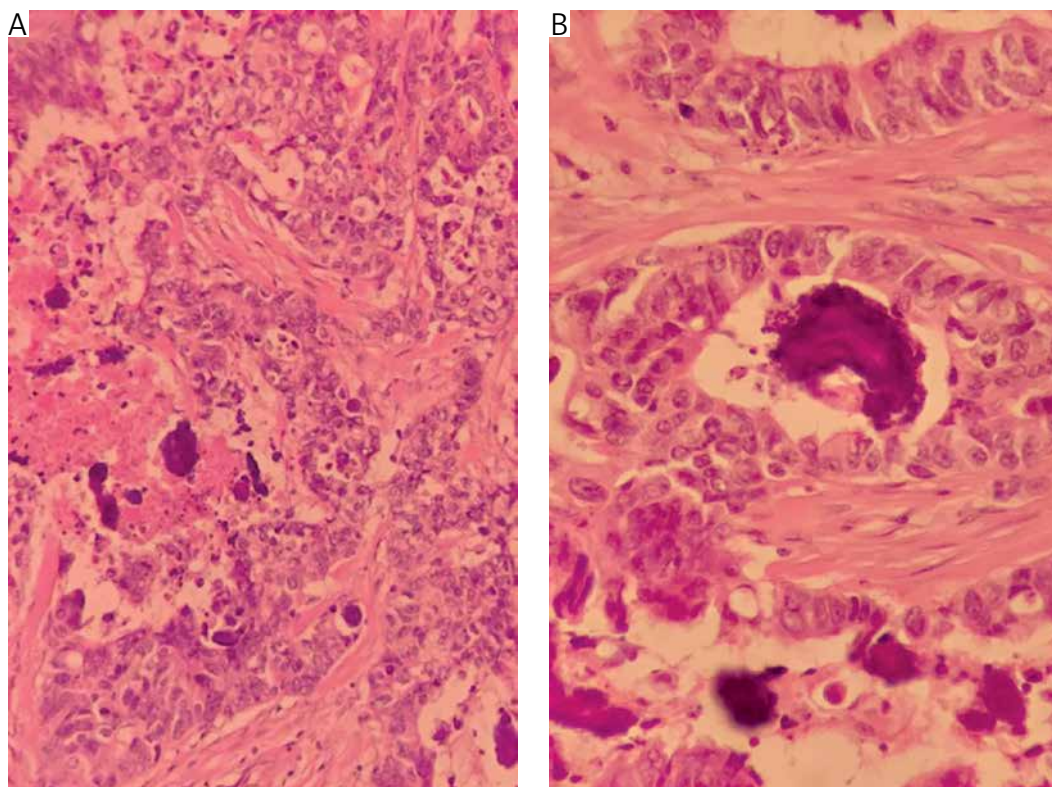


Fig. 2. Light microscopy of the rectal tumour
HE: A) 10×; B) 40×

Discussions

Rarely occurring skin metastasis from solid tumours typically occur late in the course of an advanced visceral malignancy. Following the removal of the primary colorectal tumour, 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-coloured, 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 carcinoma or erysipeloid carcinoma [9]. Along with these forms, other clinical presentations recorded in the literature 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, violaceous, indurated nodules, and at the level of the foot, non-healing ulcers were observed.

An uncommon occurrence, cutaneous metastasis from colorectal cancer, typically portends a dismal prognosis, and there is a 1–34-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 cutane-

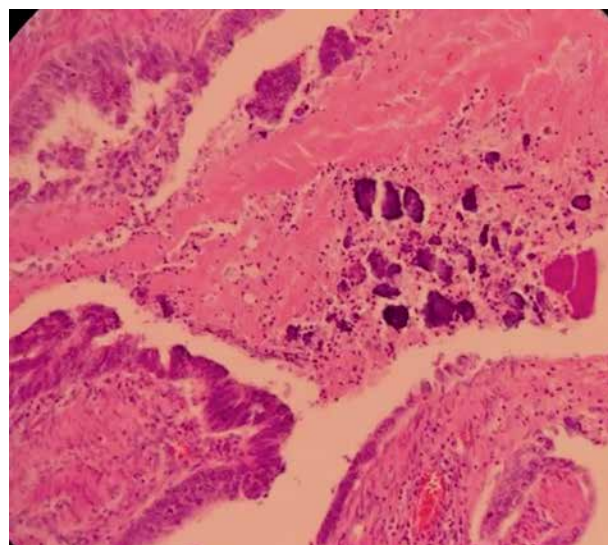


Fig. 3. Light microscopy of the primary rectal tumour with areas of dystrophic calcifications
HE: 4×

ous metastases from colorectal original tumours is 4.4 months [14]. The status of our patient started to deteriorate after the diagnosis of cutaneous metastasis despite being under chemotherapy, and he died 4 months after diagnosis.

The morphological characteristics, histomorphology, and immunohistochemistry of the cutaneous lesion are used to make the diagnosis in the majority of metastases [15]. An essential auxiliary tool for

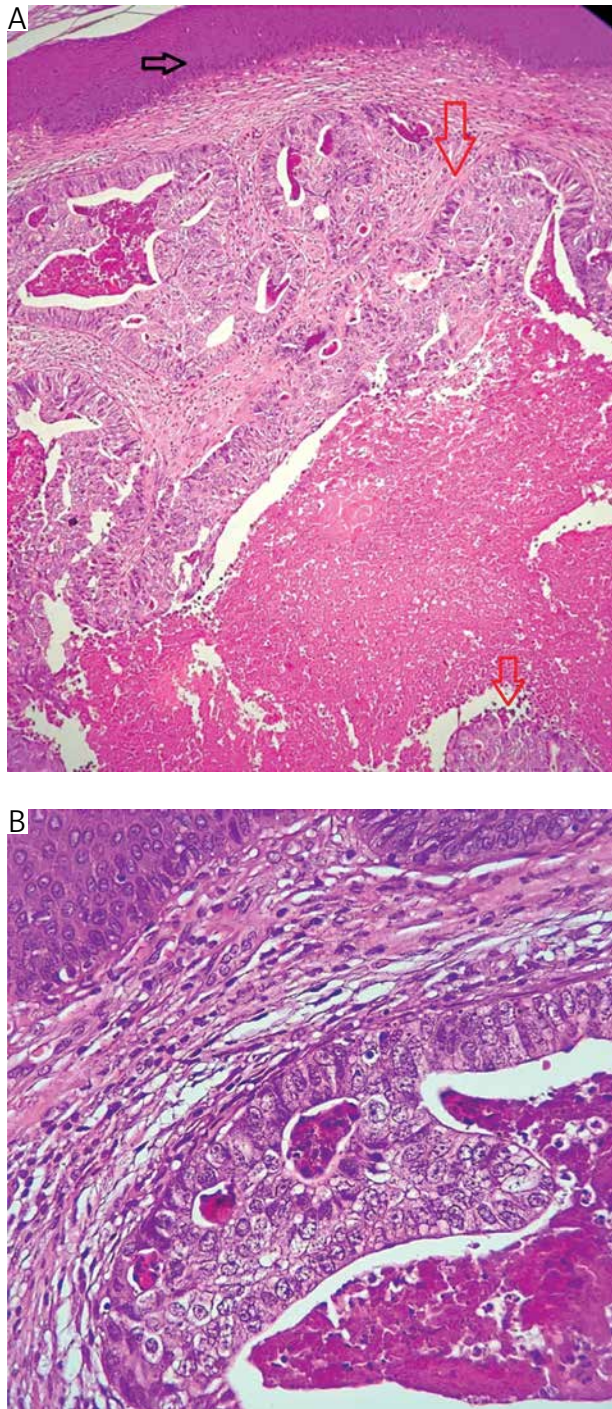


Fig. 4. Histopathological examination of the cutaneous lesions - black arrow - intact epidermis; dermal tumour proliferation composed of glands of different sizes and shapes (red arrows), lined by columnar cells arranged in multiple layers, with eosinophilic cytoplasm, moderately pleomorphic vesicular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

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].

Conclusions

Over the past 2 decades, routine KRAS and BRAF mutation testing has completely changed how metastatic colorectal carcinoma is molecularly characterized. BRAF and KRAS mutations are reportedly associated with very poor prognosis. 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 tumours located in the skin depends on their location and extent. Surgical removal of a single cutaneous metastasis is required. Because they are associated with much greater odds of distant metastasis, uncontrolled local illness, and worse survival rates, patients with extensive cutaneous metastases only receive palliative care [22].

Cutaneous metastasis due to colorectal cancer, although very rare, indicates 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%; metastases with the origin of the primary tumour in the lungs and breasts are much more frequent in this anatomical site. The diagnosis of skin metastasis is quite difficult in the absence of a history that would indicate evidence of a primary tumour.

A 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 targeted treatment in the case of these patients.

The authors declare no conflict of interest.

References

- Riihimäki M, Hemminki A, Sundquist J, et al. Patterns of metastasis in colon and rectal cancer. *Sci Rep* 2016; 6: 29765.
- Qi L, Ding Y. Analysis of metastasis associated signal regulatory network in colorectal cancer. *Biochem Biophys Res Commun* 2018; 501: 113-118.
- Hakamia R, Alali MN, Alshammari T, et al. A cutaneous metastasis of unresectable rectal adenocarcinoma: a case report and literature review. *Int J Sur Case Rep* 2020; 71: 95-101.
- Faenza M, del Torto G, di Costanzo P, et al. Large single cutaneous metastasis of colon adenocarcinoma mimicking a squamous cell carcinoma of the skin: a case report. *Int J Surg Case Rep* 2019; 56: 96-100.
- Lee TG, Lee SJ. Unusual case of solitary perineal subcutaneous metastasis from sigmoid colon cancer. *Ann Coloproctol* 2013; 29: 34-37.
- Dehal S, Patel S, Kim E, Hussain SF. Cutaneous metastasis of rectal cancer: a case report and literature review. *Perm J* 2016; 20: 74-78.
- Parente P, Ciardiello D, Bonetti LR, et al. Cutaneous metastasis from colorectal cancer: making light on an unusual and misdiagnosed event. *Life (Basel)* 2021; 11: 954.
- Beachkofsky TM, Wisco OJ, Osswald SS, Osswald MB, Hodson DS. Pulmonary cutaneous metastasis: a case report and review of common cutaneous metastases. *Cutis* 2009, 84: 315-22.
- Nesseris J, Tsamakis C, Gregoriou S, Ditsos I, Christofidou E, Rigopoulos D. Cutaneous metastasis of colon adenocarcinoma: case report and review of the literature. *An Bras Dermatol* 2013; 88: 56-58.
- Saeed S, Keehn CA, Morgan MB. Cutaneous metastasis: a clinical, pathological, and immunohistochemical appraisal. *J Cutan Pathol* 2004; 31: 419-430.
- Ocampo-Candiani J, Castrejón-Pérez AD, Ayala-Cortés AS, Martínez-Cabriales SA, Garza-Rodríguez V. Cutaneous colon metastases mimicking elephantiasis verrucosa nostra. *Am J Med Sci* 2015; 350: 517-518.
- Kemal Y, Odabaşı EA, Kemal Ö, Bakırtaş M. Cutaneous metastasis of colon adenocarcinoma. *Turk J Surg* 2018; 34: 237-239.
- Lookingbill DP, Spangler N, Sexton FM. Skin involvement as the presenting sign of internal carcinoma. A retrospective study of 7316 cancer patients. *J Am Acad Dermatol* 1990; 22: 19-26.
- Schoenlaub P, Sarraux A, Grosshans E, Heid E, Cribier B. Survival after cutaneous metastasis: a study of 200 cases. *Ann Dermatol Venereol* 2001; 128: 1310-1315.
- Wang DY, Ye F, Lin JJ, et al. Cutaneous metastasis: a rare phenomenon of colorectal cancer. *Ann Surg Treat Res* 2017; 93: 277-280.
- Grainger S, Savory JG, Lohnes D. CDX2 regulates patterning of the intestinal epithelium. *Dev Biol* 2010; 339: 155-165.
- Gao N, White P, Kaestner KH. Establishment of intestinal identity and epithelial-mesenchymal signaling by CDX2. *Dev Cell* 2009; 16: 588-599.
- Saad RS, Ghorab Z, Khalifa MA, Xu M. CDX2 as a marker for intestinal differentiation: Its utility and limitations. *World J Gastrointest Surg* 2011; 3: 159-166.
- Barbareschi M, Murer B, Colby TV, et al. CDX-2 homeobox gene expression is a reliable marker of colorectal adenocarcinoma metastases to the lungs. *Am J Surg Pathol* 2003; 27: 141-149.
- Li ZN, Zhao L, Yu LF. BRAF and KRAS mutations in metastatic colorectal cancer: future perspectives for personalized therapy. *Gastroenterol Rep (Oxf)* 2020; 8: 192-205.
- Ducieux M, Chamseddine A, Laurent-Puig P, et al. Molecular targeted therapy of BRAF-mutant colorectal cancer. *Ther Adv Med Oncol* 2019; 11: 175883591985649.
- Gu Y, Tang R, Gong DQ, Qian YL. Reconstruction of the abdominal wall by using a combination of the human acellular dermal matrix implant and an interpositional omentum flap after extensive tumor resection in patients with abdominal wall neoplasm: a preliminary result. *World J Gastroenterol* 2008; 14: 752-757.

Address for correspondence

Vesa Alexandra Alina
 Morphological Sciences Department
 Faculty of Medicine and Pharmacy Oradea
 University of Oradea
 Oradea, Romania
 e-mail: alexvesa92@yahoo.com