

Cutaneous and breast metastasis from colorectal adenocarcinoma: A rare case report

XIU-YONG LIAO^{1,4}, CHAO-YUAN LIU², LI-BING LIANG³, JIANG-RONG DU¹ and TAO ZHANG⁴

Departments of ¹Oncology, ²Neurosurgery and ³Pathology, Chongqing Qiangjiang Central Hospital, Chongqing 409000;

⁴Department of Oncology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, P.R. China

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Abstract. Synchronous breast and cutaneous metastases from colorectal adenocarcinoma as the initial clinical manifestation, without visceral metastases, are extremely rare. We herein report the case of a 68-year-old female patient who presented with pruritic skin lesions and a breast lump 6 years after abdominoperineal resection of colorectal adenocarcinoma. Such cases can be easily misdiagnosed as cutaneous metastasis from breast cancer. However, the management of colorectal metastases differs from that of primary breast cancer, and mastectomy may be unnecessary. Timely and accurate diagnosis requires a high level of suspicion, thorough medical clinical history and biopsy followed by immunohistochemical examination. Specific immunohistochemical markers, such as cytokeratin (CK)7, CK20 and CDX2, may help differentiate between primary breast and metastatic colorectal adenocarcinoma.

Introduction

Colorectal adenocarcinoma synchronously metastatic to the skin and breast is extremely rare. A survey reported that secondary neoplasms of the breast account for 0.43% of all breast malignancies (1), and the colorectum as the primary site is even rarer. Cutaneous metastasis from colorectal cancer is also a rare (3%) event (2). The majority of cutaneous or breast metastases indicate widely disseminated disease and are associated with poor clinical outcome. Breast cancer frequently metastasizes to the skin in women (3), and the clinical manifestations of cutaneous metastasis vary widely. Breast metastasis may be mistakenly considered as the primary lesion, leading to misdiagnosis and inappropriate therapeutic strategy, such as unnecessary surgical intervention and chemotherapy regimen (4). We herein present the

case of an 68-year-old female patient with synchronous cutaneous and breast metastases as the initial presentation of recurrent colorectal adenocarcinoma, without visceral organ metastasis.

Case report

A 68-year-old woman visited a dermatologist in February 2017 with rapidly progressing pruritic skin lesions on her chest and neck for 1 month (Fig. 1A). The patient reported no melena, nausea, headache, cough, chest pain or weight loss. Physical examination revealed multiple painless, crimson, irregular, indurated papules and plaques distributed along the upper chest and anterolateral aspect of the left neck. On physical examination, there was diffuse redness on the left breast and thickening of the skin with nipple retraction. A palpable, painless isolated tumor measuring 4x3x3 cm with irregular borders was detected in the inner upper quadrant of the left breast, at a distance of 1.5 cm from the nipple (Fig. 1B). No masses were detected on computed tomography scans of the chest, abdomen and other organs.

The patient had a history of colorectal adenocarcinoma in September 2010, initially manifesting as hematochezia for 6 months. Colonoscopy revealed a friable, cauliflower-like mass occupying 40% of the rectal circumference. The patient was diagnosed with stage IIA (Dukes' A) rectal cancer and abdominoperineal resection was performed. Histopathological examination revealed tubular adenocarcinoma (Fig. 2). The patient had a progression-free survival of 6 years after receiving 6 cycles of oxaliplatin, 5-fluorouracil and leucovorin treatment (FOLFOX regimen).

Cutaneous lesion specimens and 4-mm punch biopsies were obtained from the left neck and breast in February 2017, respectively. The results of the immunohistochemical examination were negative for estrogen receptor (ER), progesterone receptor (PR) and cytokeratin (CK)7, and positive for CK20, CDX2, villin and carcinoembryonic antigen (CEA), with a MIB-1 labeling index of 90% (Fig. 3A-L). A diagnosis of metastatic rectal adenocarcinoma to the breast and skin was thus confirmed. The patient received four cycles of FOLFIRI chemotherapy, with marked improvement of the breast tumor and cutaneous lesions on the chest and neck. Unfortunately, the patient suffered grade IV adverse effect include nausea and diarrhea during chemotherapy with resulting poor compliance.

Correspondence to: Professor Tao Zhang, Department of Oncology, The First Affiliated Hospital of Chongqing Medical University, 1 Youyi Road, Yuanjiagang, Yuzhong, Chongqing 400016, P.R. China
E-mail: tumorzzt@163.com

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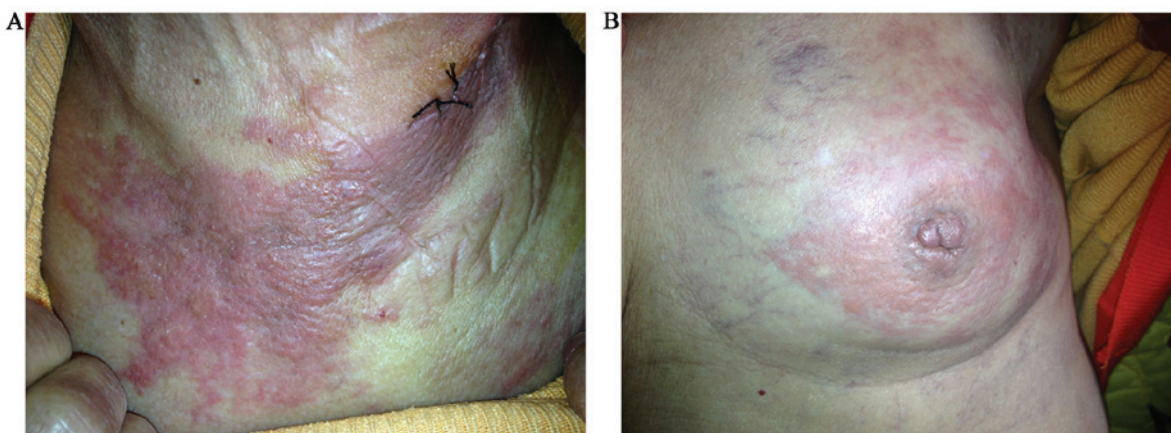


Figure 1. (A) Pruritic skin lesion of the upper chest and left neck. (B) Diffuse redness and thickening of the skin of the left breast are observed, with nipple retraction.

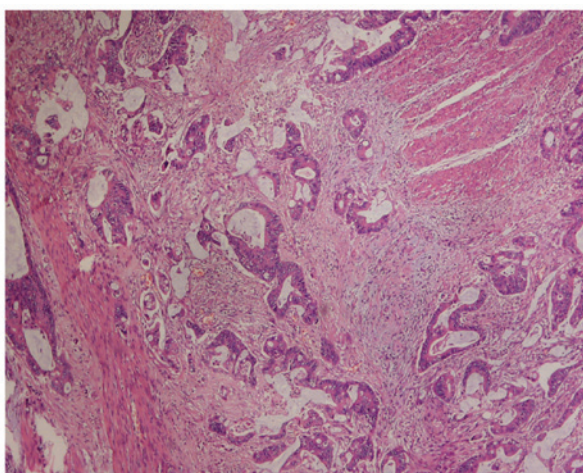


Figure 2. Histopathological examination of the primary colorectal specimen (hematoxylin and eosin staining, magnification, x100).

Alternative chemotherapy regimen such as FOLFOX was refused. The patient eventually succumbed to multiple visceral metastases after treatment discontinuation in May 2017.

Discussion

Breast metastases most frequently originate from cancers of the contralateral breast, followed by the skin, lung, ovary, melanoma and lymphoma (1). The majority of breast metastases manifest as palpable, painless tumors with rapid growth that are not accompanied by red thickened skin or nipple retraction (4). Ota *et al* (5), described a rare case of breast metastasis from lung adenocarcinoma with redness of the overlying skin. These patients commonly have a poor outcome. DeLair *et al* (6), reported a study including 85 cases of non-mammary metastases to the breast between 1990 and 2010, with a median survival of only 15 months after diagnosis. Zhou *et al* (7) reported 28 cases of non-mammary malignancies metastatic to the breast; on average, breast metastasis was reported to appear 32 months (range, 0-228 months) following primary diagnosis. Schaekelford *et al* (8) reported that, in the majority of the cases (55%), the metastases were to the

left breast, with 6 (30%) cases metastatic to the right breast; localization in the upper outer quadrant accounted for 53% of the cases. When a breast lump is detected, mammography and magnetic resonance imaging should first be performed. However, differentiating between primary and metastatic breast cancer mainly relies on immunohistochemistry. The immunohistochemical characteristics of primary breast cancer are CK20⁻, CK7⁺, and other markers (ER, PR and human epidermal growth factor receptor 2) may vary (9).

Cutaneous metastases can be the first manifestation, presenting as rapidly growing painless subcutaneous or dermal nodules, inflammatory dermatosis, macules and plaques (10). The most common skin metastatic sites are the abdomen and perineum. Cutaneous metastases differ between men and women; lung cancer and melanoma are the main primary tumors in men, while breast and colorectal cancer are the predominant types in women. Visceral cancer metastasis to the skin is often associated with a poor prognosis. Dehal *et al* (11) reported a mean recurrence time of cutaneous metastasis from rectal adenocarcinoma of 18 months and a mean survival of ~10 months after the appearance of metastases (median, 4 months; range, 1-56 months). On average, cutaneous metastasis is reportedly associated with a survival of 7.5 months following the diagnosis of cancer (12). The majority of cutaneous metastases present as painless nodules, and can be mistaken for sebaceous cysts, lipomyomas or neurofibromas. The ultimate diagnosis of cutaneous metastasis relies on pathological and morphological characteristics. The immunohistochemical properties are often consistent with the primary tumor (13).

In the present case, during follow-up chest, abdominal CT, and pelvic MRI every 3-6 months for 2 years, then every 6 months for a total of 5 years in Department of Oncology, Chongqing Qiangjiang Central Hospital, no distant metastases or local recurrence was found. The patient was lost to follow-up after the fifth year for economic reasons. The initial presentation was the skin lesions and, on subsequent physical examination, a breast mass was detected. The dermatosis raised the suspicion of breast malignancy. In all cases, diagnosis must be confirmed by pathological examination. Radiological imaging, such as mammography or magnetic resonance imaging, may be applied. Fluorodeoxyglucose-positron emission tomography

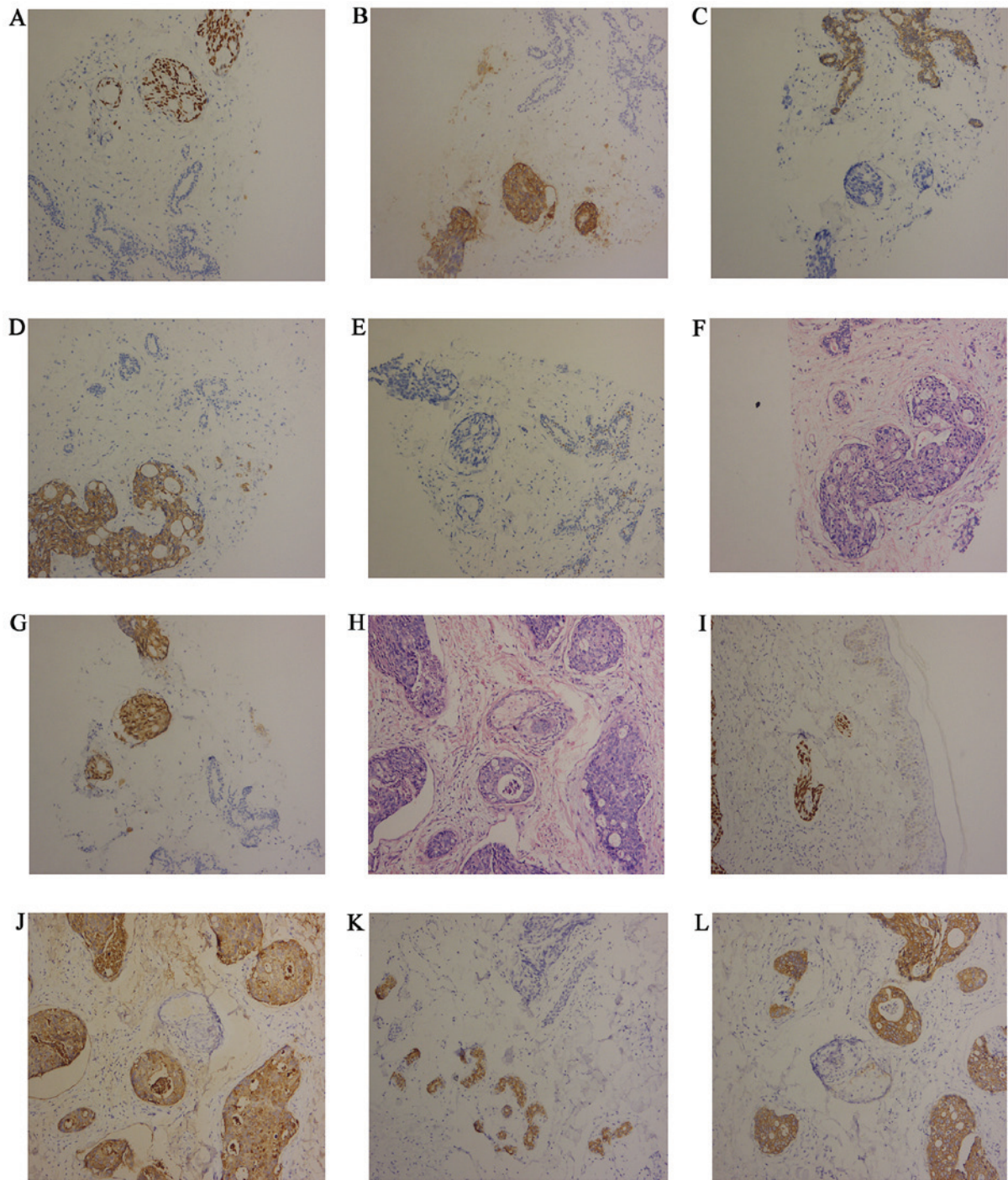


Figure 3. Immunohistochemical analysis of left breast 4-mm punch biopsies: (A) CDX2, (B) CEA, (C) CK7, (D) CK20, (E) ER, (F) H&E stain, (G) villin. Immunohistochemical analysis of left neck cutaneous lesion specimens: (H) H&E, (I) CDX2, (J) CEA, (K) CK7, (L) CK20 (magnification, x100). CEA, carcinoembryonic antigen; CK, cytokeratin; ER, estrogen receptor; H&E, hematoxylin and eosin staining.

combined with CEA measurement can be useful for determining malignant characteristics of tumor lesions (14). In the present case, a skin excisional specimen and punch biopsy were obtained from the neck and the left breast, respectively. Differentiating between breast and colorectal carcinoma as the primary malignancy may be difficult based on histomorphology alone. On immunohistochemical examination, the biopsy specimen was CK7⁺, CK20⁺, CDX2⁺, villin⁺, ER⁻ and PR⁻. Therefore, the malignancy was considered to originate from the gastrointestinal tract; combined with the patient's

medical history, the diagnosis of colorectal cancer with breast and skin metastasis was confirmed. CK7, CK20, CDX2 and villin are specific immunohistochemical markers used for the identification of breast and colorectal adenocarcinoma. The great majority of breast tumors are CK7⁺ and CK20⁻, while colorectal adenocarcinomas are usually CK7⁻ and CK20⁺. Gastric carcinoma is also usually CK7⁺. CDX2 expression is more common in gastrointestinal tumors, and 97% of all colorectal carcinomas are CDX2-positive (15), whereas thus far there has been no report of CDX2-positive breast cancer.

The first-line palliative chemotherapy for metastatic colorectal cancer includes irinotecan/5-fluorouracil (FOLFIRI), FOLFOX or XELOX combination regimens with targeted agents. Our patient received an irinotecan-based regimen, but developed severe diarrhea. Second-line treatment should include oxaliplatin (FOLFOX and CAPOX) and an anti-VEGF (bevacizumab) or anti-EGFR (cetuximab) antibody in cases in which RAS mutation has been excluded.

Cutaneous metastasis from extramammary cancer may be mistaken as primary breast tumor metastatic to the skin, leading to misdiagnosis and mistreatment. The management of colorectal metastases differ from that of primary breast cancer, and mastectomy may be unnecessary. Distinguishing between a primary and metastatic breast tumor may be difficult. The main points are listed as follows: i) A prior or current medical history of malignancy should prompt referral to an oncologist and multidisciplinary team; ii) it need to have a high suspicion of metastatic breast lump especially malignant tumor medical history, and iii) excisional or punch biopsy with histological and immunochemical evaluation are the most reliable diagnostic methods.

In conclusion, when abnormal changes are detected in the skin and breast, they should raise the suspicion of metastatic tumor, particularly in patients with a history of malignancy. Timely and accurate diagnosis can reduce misdiagnosis and mistreatment, and improve patient outcome. Biopsy followed by pathological and immunohistochemical examination is the most reliable method for distinguishing between primary and metastatic lesions. A multidisciplinary approach is crucial for avoiding unnecessary surgical procedures and ensuring optimal patient management.

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Availability of data and materials

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Authors' contributions

XYL and TZ participated in the conception and design of the case report, and wrote the manuscript. JRD evaluated the patient and participated in the therapy. LBL evaluated pathological images. CYL and TZ critically reviewed the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

A signed written consent form was obtained from the patient's family regarding the publication of the case details and associated images.

Competing interests

The authors declare that they have no competing interests.

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