Metastases of transverse colon cancer to bilateral ovaries (Krukenberg tumor) and the left breast: A case report

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Abstract. Breast cancer has the highest rate of incidence among all types of cancer in women. Only ~0.43% of breast malignancies occur as a result of metastatic lesions from extramammary tumors. The present study reports an extremely rare case of transverse colon cancer metastasizing to the bilateral ovaries and the left breast. The patient was a 47-year old female, who had a lump in the left breast without axillary lymphadenopathy. Specimens obtained by core needle biopsy were submitted for hematoxylin and eosin examination, and results revealed that the lump was a poorly differentiated adenocarcinoma. Since the patient had elevated levels of the carcinoembryonic antigen and a medical history of a Krukenberg tumor metastasized from colon cancer, immunohistochemical examinations were applied. Results identified that caudal-related homeobox protein 2 and cytokeratin 20 were positively stained, whilst cytokeratin 7 was negatively stained. Therefore, this patient was diagnosed as having colon cancer that had metastasized to the bilateral ovaries and the left breast. As the life expectancy of patients with cancer is increasing, types of metastases that used to be seen as rare are increasingly becoming more common. For clinicians, diagnosis should be cautious, and differential diagnosis should always be kept in mind.

Introduction

Breast cancer has the highest rate of incidence among all types of cancer in women and it is also the primary cause of death due to cancer worldwide (1). Although primary breast cancer originated from breast tissue, not all malignancies in breast tissues are primary breast cancer. According to a previous study, ~0.43% of breast malignancies occur as a result of metastatic lesions from extramammary tumors, such as liver, lung and bone (2). In autopsy studies, the incidence of extramammary malignancies metastasizing to the breast was predicted to rise to ~7% (3). Therefore, differentiation between primary breast cancer and metastatic breast malignancies is important, in order to avoid misdiagnosis and subsequent inappropriate treatment. Although physical examination and radiological examination is important in the detection of breast lesions, pathological examination is the most useful way for definite diagnosis. Cases of primary colorectal cancer metastasizing to the ovaries are not rare; however, cases of primary colorectal cancer metastasizing to breast are very rare. In 1974, McIntosh *et al* (4) was the first to describe a case of colon cancer metastasizing to the breast. The present study reports an extremely rare case of transverse colon cancer metastasizing to the bilateral ovaries and the left breast, which was confirmed by a pathological examination using immunohistochemistry.

Case report

A 47-year old female patient came to the outpatient Department of The First Affiliated Hospital with Nanjing Medical University (Jiangsu, China) on 8th July 2015, due to a breast lump. Physical examination revealed a painless and mobile mass in the outer lower quadrant of the left breast, with no skin dimpling, nipple retraction, or nipple discharge. An ultrasound scan detected an irregular-shaped hypoechoic mass, which was category 4B according to the Breast Imaging Reporting and Data System (5), 2.5x1.1 cm and without axillary lymphadenopathy (Fig. 1A). A serological test reported normal levels of the carbohydrate antigen 125 and the carbohydrate antigen 15-3, but elevated levels of the carcinoembryonic antigen (CEA) of 5.36 ng/ml (reference range of The First Affiliated Hospital with Nanjing Medical University is 0-4.7 ng/ml). The breast mass specimen was then obtained using ultrasound guided core needle biopsy and submitted for pathological examination. Hematoxylin and eosin (H&E) examination demonstrated the breast mass to be an adenocarcinoma with a mucinous adenocarcinoma component (Fig. 1B). IHC examination revealed negative estrogen receptor, negative progesterone receptor and negative human epithelial growth factor 2 (data not shown).

Investigations into the patient's history revealed that the patient was admitted to Liyang City Traditional Chinese Medicine Hospital (Changzhou, China) in September 2014 for

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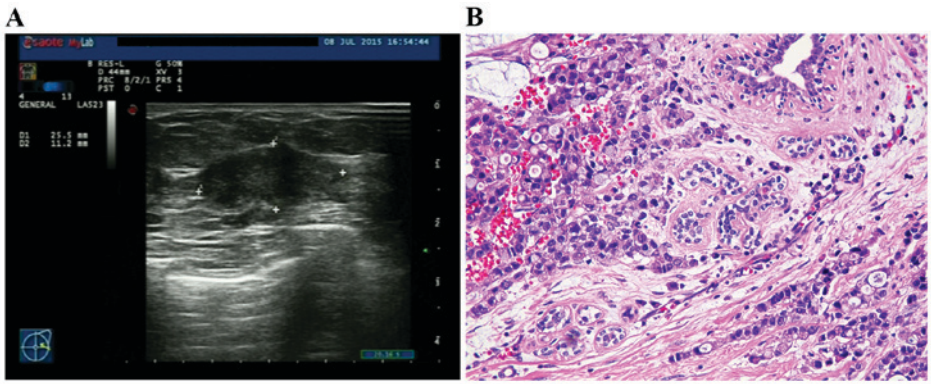

Figure 1. Ultrasound and pathological examination of breast mass. (A) Ultrasound detected an irregular-shaped hypoechoic breast mass (Breast Imaging Reporting and Data System category 4B), 2.5x1.1 cm. (B) Hematoxylin and eosin staining of a breast mass specimen obtained by ultrasound guided core needle biopsy. Magnification, x200 using Olympus BX51.

a dull persistent abdominal pain. Ultrasound identified a 5-cm mass and a 15-cm mass in the left and right pelvic cavity (data not available). The patient then received surgery on September 25th, 2014. Intraoperative palpation revealed that the two pelvic masses were on left and right ovaries, separately. The surgeon also found one mass in the greater omentum, and another mass (~3x2 cm) inside the transverse colon, which was inducing dilation in the ascending and proximal transverse colon. Since the patient did not obtain preoperative bowel preparation, the patient only received resection of bilateral ovaries and some nodules in the greater omentum.

Postoperative pathology revealed that the tumor was a metastatic adenocarcinoma (Fig. 2A). IHC examination identified that caudal-related homeobox protein 2 (CDX2) and cytokeratin 20 (CK20) were positive, while cytokeratin 7 (CK7) was negative (Fig. 2B-D). The patient was then transferred to The First Affiliated Hospital of Soochow University (Suzhou, China). Following a radical laparoscopic resection of the colon cancer, pathological examination confirmed the cancer to be a poorly to moderately differentiated adenocarcinoma. Specific areas of the adenocarcinoma were mucinous adenocarcinoma accompanied by signet ring cell (Fig. 3). Lymph nodes (7/10) were also involved. The patient then received 8 cycles of the systemic chemotherapy of the folinic acid, fluorouracil and irinotecan regimen. Subsequent to therapy, the examination revealed that levels of CEA were 2.07 ng/ml (reference range of The First Affiliated Hospital of Soochow University, 0-5 ng/ml).

Since the patient had a history of Krukenberg tumor, and exhibited elevated levels of CEA and an undetermined breast malignancy, IHC examinations on a breast biopsy specimen were then applied. Results demonstrated that the tumor cells were also positive for CDX2 and CK20, but negative for CK7 (Fig. 4). The breast tumor was then confirmed as being a metastatic lesion from the primary colon cancer. As a result, a wide excision rather than a radical mastectomy was performed. Following surgery, the patient underwent a positron emission tomography/computed tomography (PET/CT) scan with 18F-fluorodeoxyglucose. Examination of the scan identified no evidence of any other distant metastasis (including liver and lung).

All procedures reported in the present study are in accordance with the ethical guidelines of the Declaration of Helsinki and were approved by the ethics and research committee of the First Affiliated Hospital with Nanjing Medical University. Informed consent to be involved in and publish the results of present study was obtained from the patient.

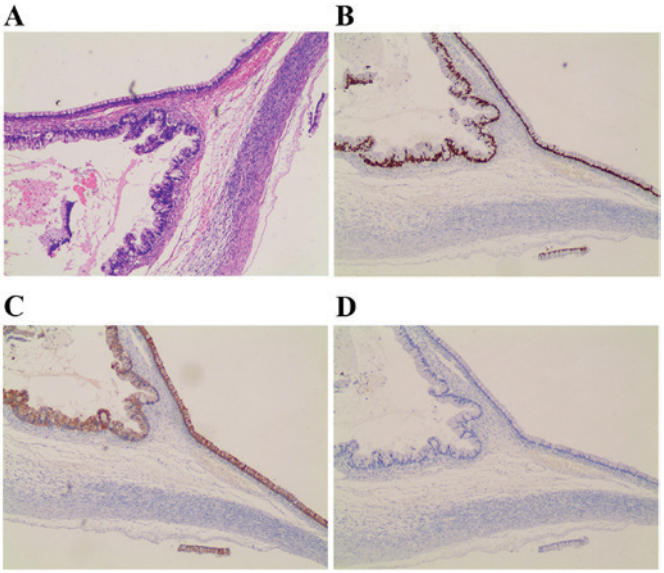

Figure 2. Pathological examinations of metastatic adenocarcinoma in the ovaries. (A) Hematoxylin and eosin examination of metastatic adenocarcinoma in the ovaries. (B) Caudal-related homeobox protein 2 was positively stained. (C) Cytokeratin 20 was positively stained. (D) Cytokeratin 7 was negatively stained. Magnification, x400 using Olympus BX51.

Discussion

In the present case, the transverse colon cancer first metastasized to the bilateral ovaries (Krukenberg tumor) and then to the left breast. In general the liver, lung and bone are the most frequent sites of metastasis from colorectal cancer (6). The Krukenberg tumor was first described by Friedrich Ernst Krukenberg in 1896 (7), and refers to a malignancy in the ovary that had metastasized from a primary site. Krukenberg tumors are known to originate from the stomach (~48.1% of cases), the intestine (42.6% of cases), and other primary sites including the breast, biliary system and the pancreas (8). Cases of primary colorectal cancer metastasizing to breast are rare (2),

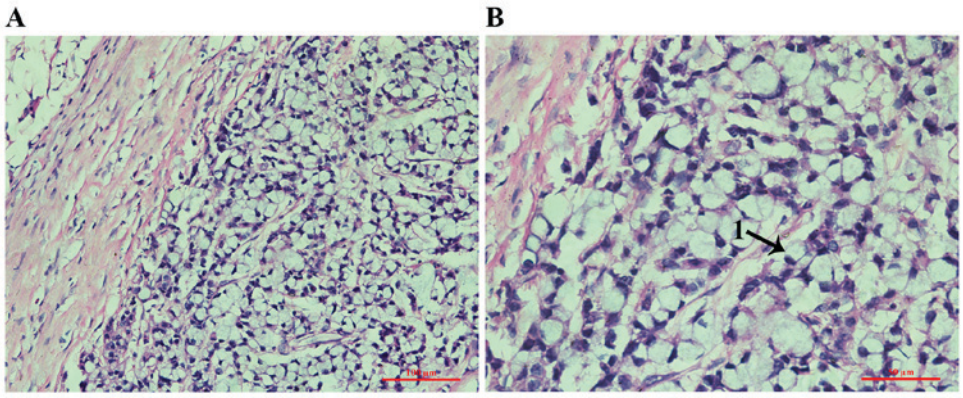

Figure 3. Hematoxylin and eosin examinations of colon cancer. (A) Moderately differentiated adenocarcinoma, with specific areas of mucinous adenocarcinoma. Magnification, x200 using Olympus BX51. (B) Signet ring cells in colon cancer. Magnification, x400 using Olympus BX51. 1 represents signet ring cells.

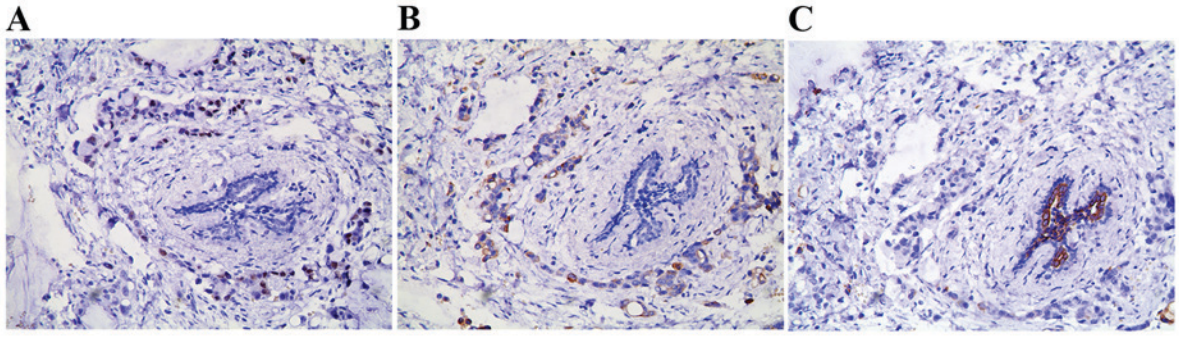

Figure 4. Immunohistochemical examinations of a breast mass specimen obtained by ultrasound guided core needle biopsy. (A) Caudal-related homeobox protein 2 was positively stained. (B) Cytokeratin 20 was positively stained. (C) Cytokeratin 7 was negatively stained. Magnification, x200 in all images using Olympus BX51.

and simultaneous metastasis to the ovaries and breast tissues occurs even more infrequently. Jiang *et al* (9) reported a young breastfeeding female (28 years old) suffering from a suspicious gastrointestinal tumor metastasizing to the bilateral ovaries and the bilateral breasts. However, the specimen of primary cancer was not obtained for pathological examination due to cachexia. Vakili *et al* (10) reported a 38-year old female patient who received ascending colon cancer surgery, and 15 months later developed metastases in the right ovary and left breast. To the best of our knowledge, the present report is the first case of transverse colon cancer metastasizing to bilateral ovaries and then to the left breast.

A malignant mass in the breast may be misdiagnosed as primary breast cancer due to its high rates of incidence (11). Therefore, differentiation between primary and metastatic breast cancer is important to avoid misdiagnosis and subsequent inappropriate treatment. Physical and radiological examination, detailed past tumor history, as well as pathological examinations are helpful.

According to the literature, metastatic malignances in breast are more common in the left breast compared with the right (12). These metastases usually grow rapidly, but do not induce skin dimpling, nipple retraction or nipple discharge (13,14). Mammographies are helpful in achieving a differential diagnosis, since a metastatic malignancy in the breast is round and well circumscribed, with no speculation, microcalcification or thickening of the skin (10). In addition, increased attention should be paid to patients who exhibit a past history of extramammary cancer. Lymphoma, melanoma, sarcoma, lung carcinoma and ovarian cancer are the most common types of primary cancer that metastasize to the breast (2,15,16). Finally, pathological examination is the most useful diagnosis technique. In H&E examination, metastatic tumor cells in the breast are shown to usually locate in the periductal or perilobular region, lacking *in situ* components and desmoplastic reaction (11,17). IHC staining may also help in differentiating the origin of the tumor. In the present case, IHC examinations of the breast and ovarian tumor consistently demonstrated that CK20 and CDX2 were positively stained, while CK7 was negatively stained. CK20 and CK7 are the widely used markers in determining primary sites of metastatic adenocarcinoma (18,19). In addition, CDX2 is also a highly specific and sensitive marker for colorectal carcinoma (20). For metastatic breast disease, diagnostic and palliative treatment for local control is recommended (12), rather than mastectomy and lymph node dissection (10). In the present case, a wide excision alone was performed, without axillary dissection.

Due to the early screening, the use of advanced equipment including PET-CT scans and the comprehensive treatment of colorectal cancer, an increasing number of patients are able to live longer. As a result, an increasing number of rare types of metastatic tissues are becoming common. For clinicians, diagnosis should be cautious, and differential diagnosis should always be kept in mind.

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