
Case Report

Breast metastasis as initial manifestation of occult colon cancer: Report of an autopsy case

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Abstract: We report a case of breast tumor which was revealed to be metastasis from occult colon carcinoma at autopsy. A 75-year-old woman consulted a breast surgery clinic with a three-week history of a painless, firm lump in the left breast. A core-needle biopsy specimen of the breast lesion was diagnosed as invasive ductal carcinoma. Despite anti-cancer chemotherapy for 5 months, during which time the patient presented hematemesis originating from the second portion of the duodenum and subsequent obstructive jaundice, she died. Post-mortem examination revealed an exophytic, centrally ulcerated tumor in the sigmoid colon, which was histopathologically identified as papillary and mucinous carcinomas with an invasive micropapillary component. The lesions in the breast and duodenum were both comprised of the micropapillary carcinoma, which was morphologically similar to that identified in the colon. Immunohistochemical examination revealed that the breast lesion was metastasis from the colon because cancer cells were stained with cytokeratin 20, and not with cytokeratin 7 or progesterone/estrogen receptors. This valuable case provides us an important message: a possibility of metastasis should be considered in the diagnosis of breast tumor even when the initially identified lesion appears to be primary. The importance of immunohistochemistry in conjunction with routine morphological examinations is also suggested.

Key Words: Breast, Autopsy, Colon, Metastasis, Immunohistochemistry.

Introduction

While primary breast cancer is the most common malignant neoplasm in women¹, metastasis to the breast from extramammary malignant neoplasm is uncommon. The incidence of breast metastasis in extra-mammary malignancy is reportedly ~2% of all breast malignancies in clinical practice² and ~7% at autopsy^{3,4}. Except in the case of contra-lateral breast carcinoma, the most common source of primary tumors is hematological neoplasms, especially lymphomas and leukemias, followed by melanoma and cancers of the lung, ovary, and stomach⁵⁻⁷. On the other hand, colorectal cancers are an extremely rare primary source for breast metastasis^{8,9}. Within our knowledge, as few as 8 cases have been reported in English literature for breast metastasis of colorectal malignancy¹⁰⁻¹⁶. We herein report a case of breast carcinoma noted at the time of initial clinical diagnosis, which was revealed to be metastasis from a sigmoid-colon carcinoma at autopsy. The unexpected origin for this breast lesion was eventually confirmed by immunohistochemical examination. Histopathological features of the tumor that may be related to the uncommon clinical manifestation are discussed.

Case presentation

A 75-year-old woman was referred to a breast surgery clinic with a three-week history of a painless lump in the left breast. Otherwise, the patient was in good health, without any symptoms of widespread disease. There was no family history of malignancy except breast cancer in her sister. Physical examination revealed a 4.5 cm×4.5 cm firm lump with rubor in the center of the left breast. The core-needle biopsy specimen of the breast was diagnosed as invasive ductal carcinoma. The patient received chemotherapy with paclitaxel, which slightly reduced the lump size, followed by development of urticarial rash and nausea. Due to the adverse symptoms with the agent, she was subsequently treated with falmorubicin and cyclophosphamide, which were also discontinued because of the persistent nausea. After two months of chemotherapy, hematemesis developed. The upper gastrointestinal endoscopy revealed a stenotic region showing ulceration and active bleeding in the second duodenal portion, where no biopsy was performed. The patient subsequently presented obstructive jaundice and died five months after the initial diagnosis.

Autopsy findings

Post mortem examination revealed a large tumor in the sigmoid colon, showing exophytic configuration measuring 6 cm×6 cm with central ulceration (Fig. 1a). Microscopically, the colon tumor was papillary and mucinous carcinomas with a micropapillary component in mucus lakes (Fig. 1b-d). The breast also showed invasion of micropapillary-shaped cancer cells similar to that identified in the colon (Fig. 2a). Predominant lymphatic invasion was evident in the breast tissue as confirmed by immunohistochemistry for a lymphoendothelial marker, D2-40 (Fig. 2b). Cancer cells in the breast were both stained positively with cytokeratin 20 (CK20) and negatively with cytokeratin 7 (CK7) (Fig. 2c). Estrogen- and progesterone-receptor stainings were histochemically negative in both neoplastic lesions (not shown). These findings indicated that the colon carcinoma was the primary lesion, whereas the breast lesion is considered to have been metastasis of the primary colon cancer. Dissemination of cancer cells in lymphatics showed a characteristic 'micropapillary' configuration with immunohistochemically positive for MUC1 glycoprotein on the outer surface of the cluster (Fig. 2d). The

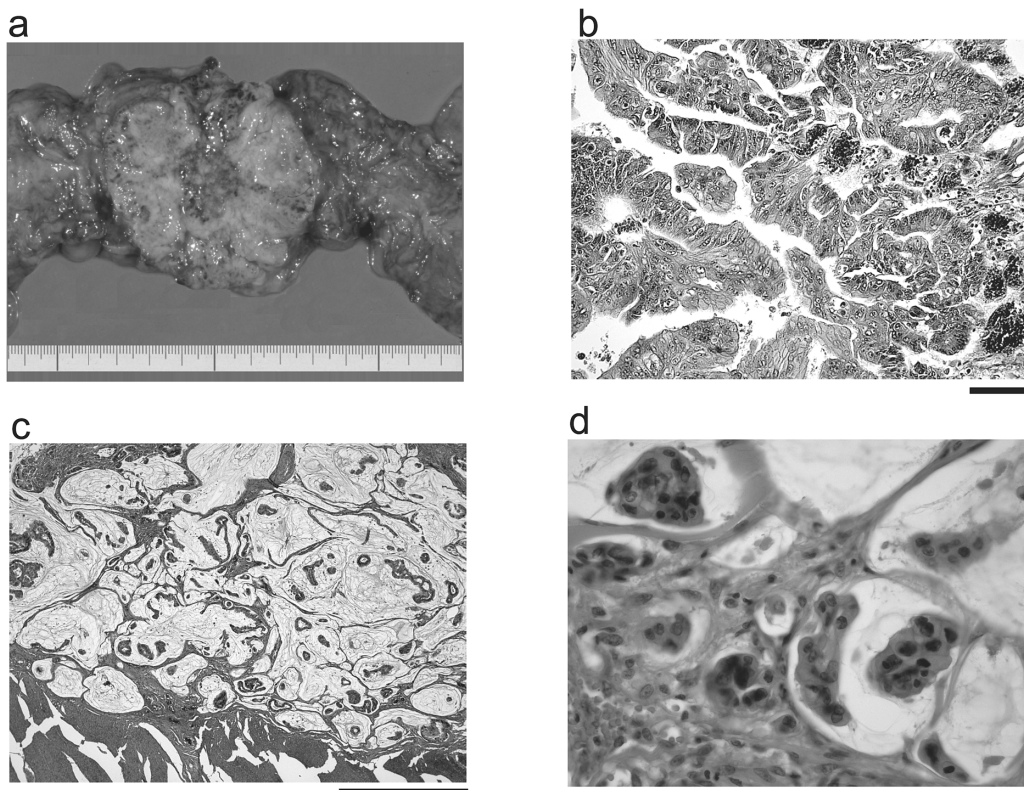


Fig. 1. (a) Photomicrograph showing tumor in the sigmoid colon. (b) - (d) Histological appearance of the carcinoma in the sigmoid colon. Carcinoma showing papillary growth (b) and mucinous carcinoma (c) at lower magnification. Micropapillary structure of cancer-cell cluster is identified in mucous lakes (d) at higher magnification. Scale bars in b, c, and d denote 100 μ m, 1 mm, and 50 μ m, respectively. H & E staining.

duodenal lesion also exhibited lymphatic invasion of the cancer cells that were analogous to those found in the breast, with no obvious mucosal lesion (not shown). Extension of the cancer cells was identified microscopically in the right breast, para-aortic tissue, mesentery, right adrenal gland, head of the pancreas, and small sub-pleural regions of bilateral lungs. In spite of the disseminated invasion, no metastasis was detected in the liver.

Discussion

Colorectal cancer is an extremely rare source for breast metastasis. In the English literature, only 8 cases have hitherto been published¹⁰⁻¹⁶. In most of these, primary colorectal lesions had already been diagnosed or surgically resected six months to four years before detection of the breast metastasis, where widespread extension to other organs, such as the liver and lungs, was concomitantly observed. Analogous to these reports, the present case also exhibited widespread metastasis of the cancer cells, although 1) the breast lesion was initially detected both physically and histopathologically with no prior indication of colonic lesion and 2) there was no evidence of metastasis to the liver.

In the present case immunohistochemical analyses played a key definitive role in diagnosis of the

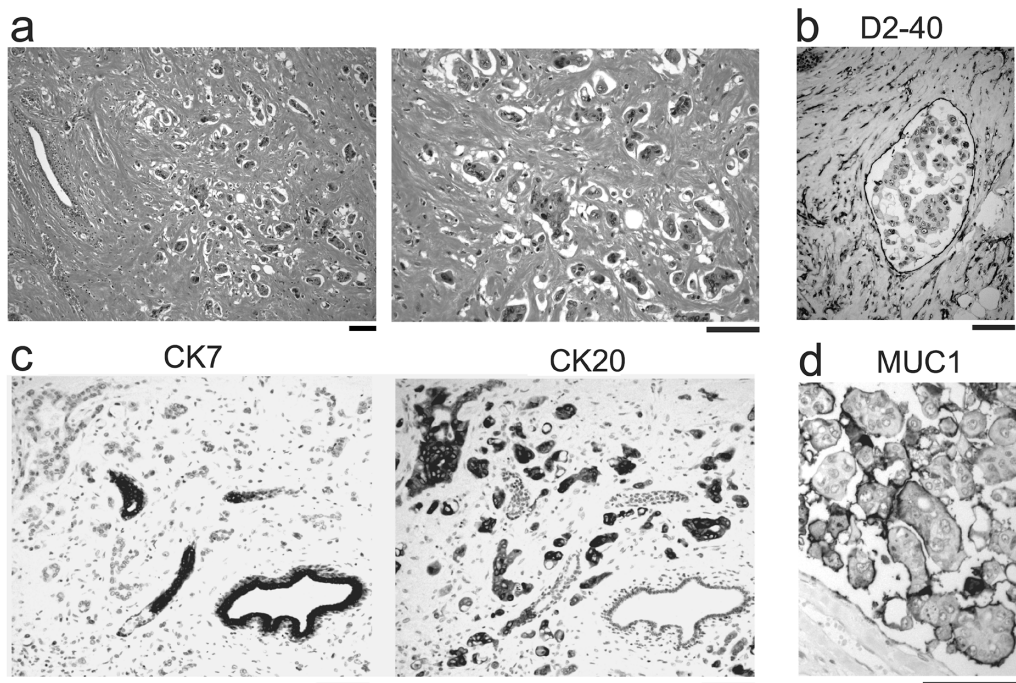


Fig. 2. Histological appearance of carcinoma in the left breast. (a) Atypical cells distributed in fibrous stroma. A normal duct is seen on the left. High-power image of the carcinoma on the right. (b) Cancer cells identified in lymphatic space. The lympho-endothelial layer is stained with D2-40. (c) Immunohistochemical images for CK-7 (left) and CK20 (right). (d) Immunohistochemical staining for MUC1 of micropapillary carcinoma showing 'inside-out' pattern. Scale bars in a - d denote 100 μ m.

primary lesion. In general, the combination of CK20 and CK7 is useful for categorizing carcinomas, especially metastatic lesions from an unknown primary site^{17/18}. Breast carcinomas (both the ductal and lobular carcinomas) are typically positive for CK7 and negative for CK20, while opposite pattern is observed for colorectal carcinomas. In addition, both estrogen- and progesterone-receptors are expressed in mammary carcinoma, but not in colorectal carcinoma¹⁸. The present case clearly exhibited the typical immunohistochemical profiles that indicate colorectal carcinoma as the primary lesion; cancer cells in both the colon and breast were stained with CK20, but with neither CK7 nor estrogen/progesterone receptors. We confirmed that the core-needle biopsy specimen, which was diagnosed based solely on hematoxylin/eosin staining, also exhibited the same immunoreactivity patterns for these antibodies as in the autopsy tissue (not shown). Retrospective review of the biopsy specimen indicated no definite possibility of extramammary metastasis, although apparent lympho-vascular invasion was suggested in the small sample (not shown). Thus, immunohistochemistry would have been indispensable for correct diagnosis in this case.

It is noteworthy that the present case exhibited no definite liver metastasis. In practice, no discernible venous invasion was detected in the primary colonic lesion, and instead, predominant lymphatic invasion was noted in other metastasized lesions. In this respect, morphological feature of the cancer cells would be a key representation of the distinctive biological behavior. The metastasized lesions were composed of micropapillary carcinoma, which exhibits small clusters of cells within a

lacunar space, facing their apical surface outward^{19,22}. This pattern of carcinoma is considered as aggressive variant that exhibits predominant lymphovascular invasion and poor clinical outcome²⁰. The reverse cell polarity pattern can be confirmed by immunohistochemistry for MUC1 glycoprotein¹⁹. This protein is normally located on the apical surface of normal glandular epithelium to inhibit interaction between epithelial cells and stroma¹⁹. In micropapillary carcinoma, MUC1 is expressed on the outer surface of the cell cluster showing 'inside-out' pattern²⁰, which is considered to be related to lymphatic invasion and aggressive behavior^{21,22}. We confirmed that the micropapillary cell clusters in this case also exhibited MUC1 protein on the outer surface (Fig. 2d). According to Kim et al.²¹, micropapillary component was found in 19% of the colorectal carcinomas in their institutional analysis. They demonstrated that distribution of the single component of micropapillary carcinoma was extremely rare and was usually associated with conventional carcinoma. In our case both the papillary and mucinous components were histologically identified in the primary lesion. Because of the aggressive biological behaviors²¹ recognition of the micropapillary component is important for assessment of the colorectal carcinoma, and presence of this component may indicate a poor prognosis²⁰. In the previous reports on breast metastases of colorectal carcinomas the micropapillary carcinoma was apparently not identified¹⁰⁻¹⁶: significant numbers of cases reported mucinous or poorly differentiated carcinoma.

In summary, we present a case of colonic carcinoma with widespread metastases that initially manifested as a breast lump. We should constantly be aware of the possibility of metastasis in diagnosing malignant neoplasm. Immunohistochemistry may well be helpful to identify metastatic origin and specify cancer cells. However, the most essential points for diagnosis of metastasis to the breast should be the accurate clinical evaluation and morphological assessment by hematoxylin and eosin staining.

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〈和文抄録〉

剖検により明らかになった結腸潜伏癌乳房転移

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大腸潜伏癌の乳房転移と考えられた剖検例を報告する。75歳の女性。左乳房の腫瘤を自覚し、浸潤性乳管癌と診断され、化学療法で一時腫瘤の縮小を認めたが、5ヶ月後に死亡した。剖検により、S状結腸に6×6cmの全周性の2型腫瘍が検出された。腫瘍は、組織学的に微小乳頭癌を伴う粘液癌であり、同様の微小乳頭癌細胞は、両側乳腺においても浸潤性に増殖していた。免疫組織化学では、癌細胞は、サイトケラチン20に陽性、サイトケラチン7陰性、エストロゲン・プロゲステロン受容体に陰性であり、S状結腸癌の乳房への転移が示唆された。乳腺外悪性腫瘍の乳房への転移は稀であるが、臨床的、組織病理学的に原発病変との鑑別は重要である。