Case Reports in Oncology

Case Rep Oncol 2023;16:267–272
DOI: 10.1159/000529672
Received: November 30, 2022
Accepted: February 6, 2023
Published online: April 26, 2023

Case Report

A Metastatic Breast Tumor of an Appendiceal Signet Ring Cell Carcinoma

Kenta Okumura Shoji Oura

Department of Surgery, Kishiwada Tokushukai Hospital, Kishiwada-city, Japan

Keywords
Appendiceal signet ring cell carcinoma · Lymphatic spread · Metastatic breast tumor · Pleural effusion

Abstract
A 54-year-old woman with pseudomyxoma peritonei from an appendiceal signet ring cell carcinoma was referred to our hospital. Right massive effusion with cytology-proven malignant cells was controlled with thoracentesis. Pathological study after intraperitoneal (IP) chemotherapy, hyperthermic IP chemotherapy, and cytoreductive surgery showed no malignant cells in the abdomen except for the appendix and greater omentum. Although the patient noticed a right breast mass, mammography (MMG) showed no abnormality. Ultrasonography showed right breast masses consisting of hypo- and hyper-echoic areas without clear tumor margins. Magnetic resonance imaging (MRI) with contrast medium showed multiple lesions showing persistent enhancement pattern. Pathological study of the vacuum-assisted biopsy specimen showed signet ring cells growing in diffuse, trabecular, and linear fashions, leading to the diagnosis of metastatic breast tumors from the appendiceal signet ring cell carcinoma. Positron emission tomography (PET)/computed tomography (CT) showed no fluorodeoxyglucose uptake in the breasts. The patient was treated with simple mastectomy for local control. Pathological study of the resected breast showed predominant localization of the metastatic breast tumors deep in the mammary gland and lymphovascular invasion. Metastatic breast tumors from appendiceal signet ring cell carcinomas are extremely rare and can sometimes be difficult to detect with MMG and PET/CT. General surgeon should note that appendiceal signet ring cell carcinomas can metastasize to the breast, presumably through lymphatic permeation from malignant pleural effusion, without abnormal MMG and PET/CT findings.

Correspondence to:
Shoji Oura, shouji.oura@tokushukai.jp

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Introduction

Primary appendiceal carcinoma comprises only less than 0.5% of all gastrointestinal malignant neoplasms. A signet ring cell phenotype of this disorder is less common [1] and sometimes develops into pseudomyxoma peritonei [2]. Pseudomyxoma peritonei itself is generally regarded as a disseminated disease but is sometimes treated with multidisciplinary therapy including some kind of chemotherapy and cytoreductive surgery for cure of the disorder [3, 4].

Breast cancer is one of the leading causes of malignancy in women worldwide. However, metastatic breast tumors from various solid malignancies are extremely rare except for those from contralateral breast carcinomas mainly through the mechanism of lymphatic permeation. The most common metastatic breast tumors of non-breast origin are malignant melanoma, lymphoma, rhabdomyosarcoma, lung tumors, ovarian tumors, renal cell carcinoma, leukemia, thyroid carcinoma, cervical carcinoma, gastrointestinal carcinoma, genitourinary tumors, and soft tissue sarcoma [5].

Mass formation is a typical symptom observed both in primary breast cancers and metastatic breast tumors. In addition to mass formation, typical symptoms and images of primary breast cancer are skin/nipple retraction, attenuation of posterior echoes of the tumor, nipple discharge, and linear/segmental distribution of microcalcifications on mammography (MMG), caused by the interminglement of fibrous component for the former two and a cancer spread pattern along with the duct-lobular system for the latter two, respectively. But, main symptoms and images of metastatic breast tumors are an expansive growth pattern with well-circumscribed tumor margins, no nipple discharge, and extremely rare nipple/skin retraction due to the lack of fibrous component and a cancer growth pattern unrelated to the duct-lobular system. We herein report an extremely rare case of metastatic breast tumor of an appendiceal signet ring cell carcinoma, formed presumably through the lymphatic permeation from malignant pleural effusion.

Case Report

A 54-year-old woman consulted a urologist with a chief complaint of lower abdominal pain. Computed tomography (CT) showed left hydronephrosis and an appendiceal tumor with presumed pseudomyxoma peritonei. The patient underwent diagnostic laparoscopy, showing disseminated lesions on the peritoneum and the enlarged appendix involving the omentum. Pathological study showed atypical cells with signet ring morphology forming a solid nest without tubule formation. Immunostaining showed the tumor cells to be CK7(−), CK20(+), and CDX2 (+), leading to the pathological diagnosis of pseudomyxoma peritonei from an appendiceal carcinoma. The patient was referred to our hospital for the treatment of pseudomyxoma peritonei. In our hospital, an intraperitoneal (IP) port was placed into the abdominal cavity under local anesthesia. Then the patient received four cycles of IP chemotherapy, i.e., cisplatin 40 mg and docetaxel 80 mg, with oral daily tegafur/gimeracil/oteracil 80 mg for 8 weeks. The patient further received hyperthermic IP chemotherapy, i.e., oxaliplatin 300 mg, fluorouracil 500 mg, and leucovorin 50 mg, for 60 min. Massive effusion with cytology-proven malignant cells in the right thorax was controlled by thoracentesis, concurrent with the IP chemotherapy. The patient thereafter, i.e., approximately 3 months after the initiation of chemotherapy, underwent cytoreductive surgery to the ileocecal lesion, uterus, ovaries, lesser and greater omentums, and all visible peritoneal lesions. Pathological study showed no malignant cells in the abdomen except for the appendix and greater omentum. Although the patient noticed a right breast mass just before the

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cytoreductive surgery, MMG showed no abnormalities (Fig. 1a). Due to the rapid enlargement of the right breast mass, the patient was referred to us, i.e., breast surgical oncologists. Ultrasonography showed only admixture of patchy hypo- and hyper-echoes without distinct tumor margins (Fig. 1b). Magnetic resonance imaging (MRI) with contrast medium showed multiple enhanced lesions with persistent enhancement in the right breast (Fig. 1c). Pathological study with the vacuum-assisted biopsy specimen of the largest tumor showed signet ring cells growing in diffuse, trabecular, and linear fashions, leading to the diagnosis of metastatic breast tumors from the appendiceal signet cell carcinoma. Positron emission tomography (PET)/CT showed no fluorodeoxyglucose uptake in the breasts (Fig. 2a, b). The patient underwent simple mastectomy for local control 6 weeks after cytoreductive surgery. Pathological study of the resected breast showed triple-negative atypical cells similar to the biopsy specimen, mucous lake formation, predominant localization of the metastatic breast tumors deep in the mammary gland, and lymphovascular invasion (Fig. 3a–e). The patient has further continued to receive chemotherapy for possible cure of the pseudomyxoma peritonei.

Discussion

MMG plays a central role in diagnosing breast diseases because of its diagnostic objectivity and ability to assess the entire breast. It, however, is well known that even a large breast tumor cannot be detected with MMG when the background mammary gland shows a dense breast pattern. It, therefore, is natural that MMG could not clarify the breast mass in this case because of its dense breast pattern.

Many physicians recognize that typical ultrasound images of breast cancer have an irregular shape, low internal echoes, and attenuated posterior echoes. These findings mainly depend on the cancer cell spread pattern along the duct-lobular system, high proliferating potential of cancer cells, and the interminglement of collagen fiber in the tumor. Patchy hypo-echoes observed in this case imply the formation of cancer cell clusters with similar acoustic impedances, i.e., highly proliferating characteristics. In contrast, patchy hyper-echoes were formed presumably with the admixture of various cells or components with different acoustic impedances, such as mammary gland constituting cells, signet ring cells, and mucin. Slightly elevated posterior echoes were caused both by the abundant mucin component in the signet ring cells and the surrounding mucous lake. If the tumor had been composed of phenotypic cells other than signet ring cell carcinoma, even ultrasonography could have much easily shown the metastatic breast tumor.

PET/CT is very useful to detect malignant tumor spread, especially small cancer foci in distant metastatic sites, than conventional images such as CT and MRI [6]. It, however, is well known that some non-invasive ductal carcinomas, even spreading widely in the breast, cannot be detected with PET/CT. Signet ring cell carcinoma cells formed solid masses of various sizes in the mammary gland in this case. The idea, therefore, is highly acceptable that abundant intracytoplasmic mucin in signet ring cell carcinomas and the mucous lake formation, at least seemingly, reduced the FDG uptake in the tumors. Indeed, PET/CT just before the diagnostic laparotomy also showed no apparent FDG uptake in multiple disseminated lesions, despite their sizes. Attending physicians, therefore, should note that PET/CT has limited detectability against signet ring cell carcinomas, even when forming palpable solid mass (es) [7].

Enhanced MRI clearly showed the metastatic breast tumor in this case, having led to further examination of vacuum-assisted biopsy to the largest lesion. Time-signal intensity curve of MRI generally shows so-called wash-out pattern for breast cancers of cancer cell-rich phenotype [8] and a plateau or persistent pattern for those of fibrous component- and mucinous component-rich phenotypes. In this case, a massive mucinous component both in

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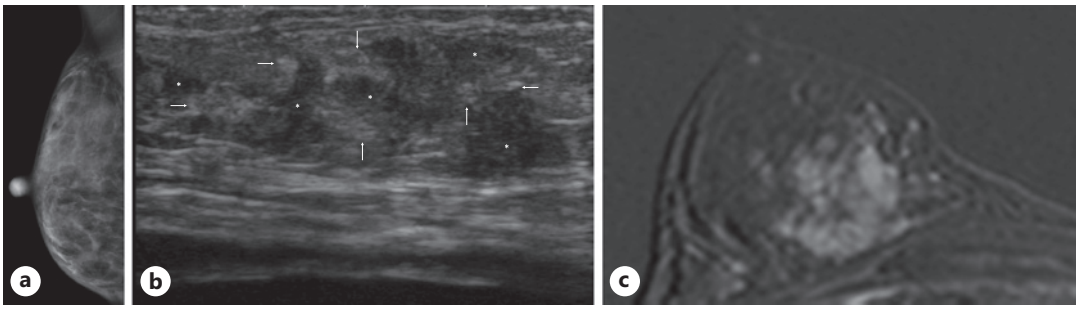

Fig. 1. MMG, ultrasonography, and magnetic resonance images of the right breast. **a** MMG with a dense breast pattern showed neither tumors nor microcalcifications. **b** Ultrasonography showed focal hyper-echoes (arrows) and hypo-echoes (asterisks) without distinct tumor formation. **c** Magnetic resonance images showed multifocal lesions with persistent enhancement.

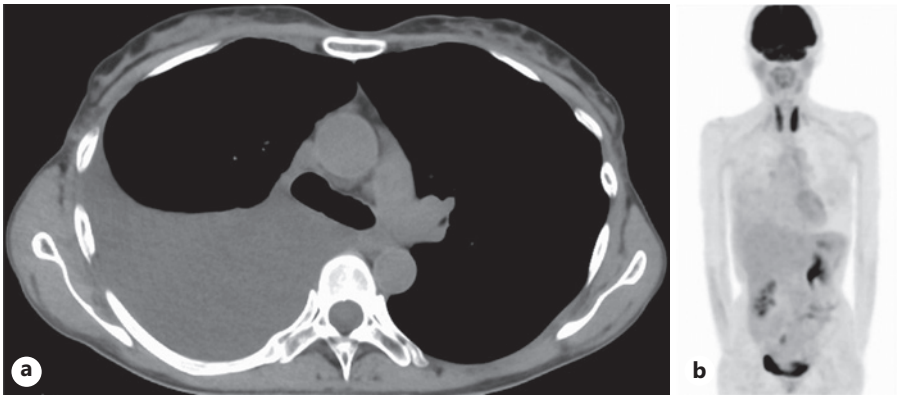

Fig. 2. Chest computed tomography (CT) and positron emission tomography (PET). **a** CT showed massive effusion in the right pleural cavity, neither with pulmonary nodules nor with pleural masses. **b** PET showed no avidity in the breasts.

the signet ring cells and the mucous lakes presumably led to the persistent time-signal intensity pattern [9]. Based on the fact that enhanced MRI clearly showed the target lesions in this case, enhanced MRI is judged to be very useful not only for the diagnosis of primary breast cancers but also for that of metastatic breast tumors, regardless of their phenotypes. On treating gastrointestinal malignancies, general surgeons should examine the newly appeared breast mass with enhanced MRI even when the standard image diagnoses do not show meaningful breast lesion(s).

By which mechanisms did this patient develop a metastatic breast tumor remain uncertain. It is well known that cancer cells metastasize or invade from the original site to the neighboring or distant organs through the mechanisms of hematogenous spread, lymphogenous spread, direct invasion, and dissemination. Direct invasion and dissemination can be easily ruled out as a metastatic mechanism in this case. Imaging evaluation of pulmonary metastases is somewhat difficult in this case due to the presence of pleural effusion, but the absence of overt pulmonary metastases after thoracentesis means that hematogenous spread to the breast is highly unlikely. Furthermore, hematogenous metastasis cannot explain the fact that metastatic breast tumor was observed only in the right breast in this case. Lymphatic spread, therefore, was the only possible mechanism of metastasis to the right breast. In this

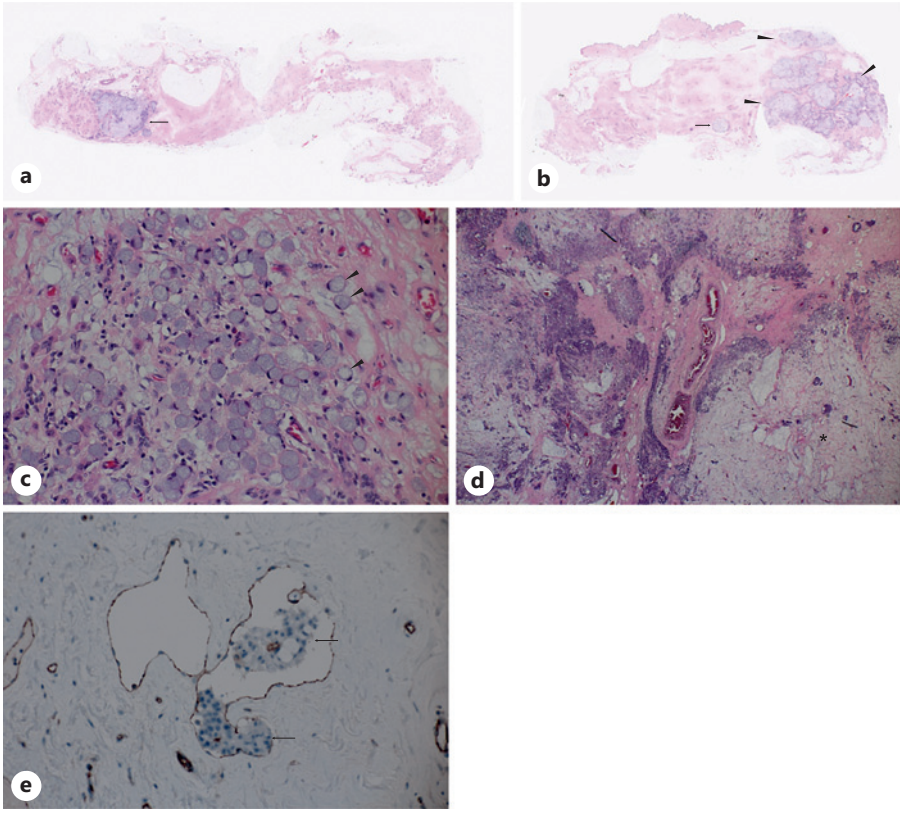

Fig. 3. Pathological findings. **a**, **b** Although the largest lesion (arrowheads) are distributed from the bottom to the top of the mammary gland, small nodules (arrows) are located deep in the mammary gland. **c** Typical signet ring cell carcinomas (arrowheads) formed a cluster. **d** A large mucous lake (asterisk) was observed in the mammary gland. **e** D2-40 immunostaining showed lymphovascular invasion (arrows).

case, right malignant pleural effusion preceded the breast event. Pleural metastasis due to lymphatic spread from the breast to the ipsilateral pleura, i.e., pleural metastasis, is very common in breast cancer oncology [10]. We cannot determine which lymphatic route(s) in the right breast contributed to this metastasis. It, however, is quite reasonable to assume that malignant cells in the pleural fluid reached the mammary gland through some lymphatic route(s). This hypothesis is well explained by the presence of evident lymphovascular invasion in the resected specimen and the fact that the breast lesions were mainly located at the chest wall side of the mammary gland.

It is naturally unclear what clinical implications simple mastectomy has in this case. Furthermore, the significance of multidisciplinary treatment including cytoreductive surgery and IP chemotherapy for pseudomyxoma peritonei has not yet been fully established. It, however, is very important for general surgeons treating pseudomyxoma peritonei to understand the presence of this type of metastasis and the difficulty of diagnosing metastatic breast tumors, especially from abdominal signet ring cell carcinomas. Multidisciplinary treatment using newly developed various anti-cancer agents should further accelerate the incidence of this type of metastatic phenotype due to the prolongation of survival of the patients with pseudomyxoma peritonei. Multidisciplinary treatment team, therefore, should include breast specialists to properly manage such patients.

In conclusion, we experienced an extremely rare metastatic breast tumor without abnormal findings in MMG and PET/CT originating from an appendiceal signet ring cell

carcinoma. The CARE Checklist has been completed by the authors for this case report, attached as the supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529672).

Statement of Ethics

The study was approved by the Kishiwada Tokushukai Hospital Ethics Committee (IRB #Case 22-12). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this research.

Author Contributions

Kenta Okumura contributed to the design of the report. Shoji Oura drafted the manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

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