Metastatic serous borderline tumor with micro-invasive ovarian carcinoma presenting as a breast lump
A case report
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Abstract

Rationale: Breast metastasis from serous borderline tumor with micro-invasive carcinoma of ovary is a very rare condition. The breast lump as the only clinical presentation is rarely seen in ovarian carcinoma, which may lead to be misdiagnosed, and the mechanism of breast metastasis from ovarian tumors in early stage still needs to be explored. Differentiation from primary breast cancer and extramammary malignancy is crucial because the treatment and prognosis are significantly different.

Patient concerns: A 33-year-old female presented with a painless, movable, 1.0 × 1.0 cm lump in the upper outer quadrant of the right breast for a month.

Diagnoses: Breast metastasis of serous borderline tumor with micro-invasive ovarian carcinoma confirmed by pathology and immunohistochemistry.

Interventions: The patient underwent lumpectomy, bilateral ovarian tumor stripping operation and prophylactic chemotherapy.

Outcomes: No signs of recurrence have been detected in 1.5 years of follow-up.

Lessons: Distant metastasis may occur in early stage of ovarian carcinoma. It is important to determine the origin of the primary tumor and develop an effective treatment strategy for patients. Imaging findings and pathological diagnostic criteria are important to accurately differentiate between metastasis and primary breast lesions, which may improve the patient’s outcomes.

Abbreviations: CT = computed tomography, ER = estrogen receptor, GCDFP-15 = Gross cystic disease fluid protein 15, HER-2 = epidermal growth factor receptor-2, Ki-67 = proliferation marker Ki67, PAX8 = paired box 8, PET-CT = positron emission tomography/computed tomography, PR = progesterone receptor, WT-1 = Wilms’ tumor gene-1.

Keywords: breast cancer, metastasis, ovarian tumors

1. Introduction

Ovarian carcinoma is the most commonly disseminated intraperitoneally, but breast metastasis cannot be seen frequently in early stage. Metastasis of ovarian tumors to breast is a very rare condition.[1,2] Ascites, abdominal pain, abdominal distension are the most common symptom of ovary carcinoma,[3] however, the breast lump as the first clinical presentation for ovarian carcinoma is rarely seen. Breast metastasis from serous borderline tumor with micro-invasive carcinoma of ovary has never been reported in literature. Differentiation from primary breast cancer and extramammary malignancy is crucial because the treatment is significantly different.[4] In this report, a case of serous borderline tumor with micro-invasive carcinoma of ovary that metastasizes to breast is presented. Interestingly, the breast lump was the only clinical presentation and prior to this, the patient had no any systemic symptoms.

2. Case report

This study was approved by the Ethics Committee and the Institutional Review Board of the First Hospital of Jilin University.

In December 2017, a 33-year-old female, previously healthy female with a family history of breast cancer (aunt, sister of her father), who presented with a painless, movable lump in the upper outer quadrant of the right breast of one month duration. Ultrasound revealed a mixed echo lump containing cystic and solid components; the lump was 10.8 mm × 10.1 mm in size (Fig. 1). No suspicious axillary lymph nodes were involved. Mammography showed a slightly high-density lump in the upper...
outer quadrant of the right breast (Fig. 2). The patient underwent lumpectomy. Pathological result revealed papillary carcinoma with psammoma bodies (Fig. 3). Immunohistochemistry showed the following: estrogen receptor (ER, +60%), progesterone receptor (PR, +70%), epidermal growth factor receptor-2 (HER-2, 0), proliferation marker Ki67 (+60%), PAX8 (+) (Fig. 4) and WT-1 (+) (Fig. 5). Histological and immunohistochemistry analysis confirmed that the malignancy originated from extramammary tumor, which might originate from the ovary or lung.

A chest computed tomography (CT) scan showed normal and vaginal ultrasound revealed multiple lumps in bilateral ovaries. The maximum diameters of the lumps in the right and left ovaries were 46 mm x 34 mm and 46 mm x 29 mm respectively, which were also cystic and solid components (Fig. 6). Then, positron emission tomography/computed tomography (PET-CT) showed that there were no other metastatic lesions. Serum tumor markers such as CA125 were also normal.

In January 2018, the patient underwent laparotomy and bilateral ovarian tumor stripping operation. The laparotomy showed a multitude of papilliform excrescences in the bilateral ovary. Following specimen collection and pathology revealed the diagnosis of serous borderline tumor with micro-invasive carcinoma of ovary (Fig. 7). Immunohistochemistry showed the following results: ER (+); PR (+); HER-2 (0); Ki67 (approximately 30%+); Cytokeratin7 (+); PAX-8 (+); P53 (<30%+); WT-1 (+). Breast tumors were evaluated with the slides of primary ovarian carcinoma counterparts, which...
confirmed the ovary origin of the lesion. Then the patient received prophylactic chemotherapy every 3 weeks and completed 6 cycles (240mg of Paclitaxel and 500mg of Carboplatin). No signs of recurrence have been detected in 1.5 years of follow-up.

3. Discussion
In 2018, there are 2.1 million new cases of breast cancer among females. Breast cancer is not only the most commonly diagnosed cancer but also the leading cause of cancer deaths among women.[5] However, metastasis from extramammary malignancy to the breast is a rare condition, accounting for only 0.3% of all breast malignancies.[3] Furthermore, the patient in this case study is diagnosed with borderline tumor with micro-invasive carcinoma of ovary with low malignant potential, which appears to be even more rare. Breast metastatic lesions are typically described as appearing quite benign on both mammographic and clinical examinations. In addition, the lumps are usually superficial, rarely adhere to the surrounding tissues, and has no skin adhesion.[6]

The mechanism of breast metastasis from ovarian cancer is still unclear and may be related to dissemination, hematogenous or lymphatic. Sippo et al[4] considered that hematological disseminated metastases often developed as a circumscribed mass, whereas lymphatic dissemination often presented as diffuse breast edema and skin thickening. Tumors that blocked lymph vessel might lead to lymphedema and enlargement. Hence, lymphatic metastasis could be more similar to inflammatory breast cancer.

There are 35 published literatures of breast metastasis from ovarian carcinoma between 1981 and 2019, ranging from 14 to 81 years old (Table 1). Thirty cases of ovarian tumors metastasizing to breast were serous carcinoma,[2,7–29] 2 cases were carcinoid tumor,[30,31] 2 cases were clear-cell carcinoma,[32,33] 2 cases were borderline tumor,[20,34] 2 cases were small cell carcinoma,[35,36] 1 was mucinous tumor of low malignant potential,[37] 1 was dysgerminoma,[38] 1 was granulosa cell tumor[39] and 1 was endometrioid carcinoma.[40] Thirty-one cases (73.2%) of these patients with breast metastasis had the
history of ovarian carcinoma. Wadhwa et al[26] reported an asymptomatic patient who developed a breast lump 1 month after ovarian surgery. Panse et al[7] described a ovarian cancer patient who presented with a metastatic breast mass 8 year later. However, the outcome of the patient was not available. Seven cases had primary ovarian cancer and breast lumps concurrently.[9,12,13,15,27,36,40] This article reported a case of ovary borderline tumor with micro-invasive carcinoma presenting as the breast lump.

Imaging studies and pathological diagnostic criteria are important to accurately differentiate between metastatic and primary breast cancer because the treatment and prognosis are significantly different. Mammography is valuable for differential diagnosis of primary and secondary breast cancers. The typical X-ray picture of secondary breast malignancy shows a clear, dense mass without calcification, distortion or thickening of the skin.[28] There is a good correlation between imaging findings and physical examination in evaluating the size of lump. Primary breast tumors usually have significant pro-connective tissue hyperplasia reaction. Therefore, the size of the lump on imaging is smaller than those on physical examination while the metastatic lesions are usually consistent with clinical imaging.[41] Immuno-histochemical markers are also significant and the combined use of multiple markers can provide more sufficient diagnostic evidence.[3] WT-1, PAX-8, and GCDFP-15 play a major role in differentiation between primary breast tumors and breast metastasis from ovarian tumors. WT-1 is mainly expressed in ovarian cancer, and less than 10% of primary breast cancers are positive for WT-1, which are usually weakly expressed or focally expressed.[7,9,42] PAX8 is a pivotal transcription factor in ovary and regulates the expression of WT-1, which is admitted with higher sensitivity and specificity than WT-1. The positive rate of

### Table 1

Reported cases of breast metastasis from ovary carcinoma.

| References                | Age (yr) | Type of ovary carcinoma | Interval between primary and breast metastasis(m) | Survival after finding breast metastasis(m) | Follow-up information |
|---------------------------|----------|-------------------------|--------------------------------------------------|---------------------------------------------|-----------------------|
| Panse G[7]                | 76       | SC                      | 66                                               | NA                                          | NA                    |
| Panse G[7]                | 81       | (P)SC                   | 96                                               | NA                                          | NA                    |
| Mori R[8]                 | 59       | (P)SC                   | 28                                               | NA                                          | NA                    |
| Van Rompuy AS[8]          | 55       | SC                      | concurrent                                       | NA                                          | NA                    |
| Akturk G[10]              | 66       | SC                      | NA                                               | NA                                          | NA                    |
| Akturk G[10]              | 47       | SC                      | NA                                               | NA                                          | NA                    |
| Rossfeldt KH[11]          | 65       | SC                      | 8                                                | 60                                          | DOD                   |
| Rossfeldt KH[11]          | 56       | SC                      | 59                                               | 60                                          | DOD                   |
| Baltra S[12]              | 47       | SC                      | concurrent                                       | 18                                          | Alive                |
| Rohsbach D[13]            | 61       | SC                      | concurrent                                       | NA                                          | NA                    |
| Gayathri S[14]            | 28       | SC                      | 10                                               | NA                                          | NA                    |
| Kurabayashi T[30]         | 34       | Carcinoid tumor         | 42                                               | NA                                          | DOD                   |
| Chauhan A[39]             | 45       | Granulosa cell tumor    | 4                                                | >24                                         | NA                    |
| Schneuer SE[17]           | 72       | SC                      | 56                                               | 84                                          | DOD                   |
| Cheng Z[26]               | 14       | SCCOPT                  | concurrent                                       | NA                                          | NA                    |
| Derin B[16]               | 48       | (P)SC                   | 72                                               | >24                                         | Alive                |
| Satto T[20]               | 62       | Clear-cell carcinoma    | 22                                               | 10                                          | DOD                   |
| Kolvičk E[19]             | 18       | (P)SC                   | 4                                                | 28                                          | DOD                   |
| Michi S[15]               | 39       | (P)SC                   | 72                                               | NA                                          | NA                    |
| Michi S[15]               | 74       | (P)SC                   | 84                                               | NA                                          | NA                    |
| Michi S[15]               | 41       | Borderline tumor        | 12                                               | NA                                          | NA                    |
| Öksüzüoğlu B[21]         | 35       | (P)SC                   | 12                                               | NA                                          | NA                    |
| Öksüzüoğlu B[21]         | 51       | (P)SC                   | 7                                                | NA                                          | NA                    |
| Martel J[24]              | 69       | SC                      | 36                                               | 8                                           | DOD                   |
| Moreira AL[24]            | 29       | Borderline tumor        | 12                                               | NA                                          | NA                    |
| Kayişoğlu F[23]          | 35       | (P)SC                   | 18                                               | 36                                          | DOD                   |
| Cormio G[24]              | 43       | (P)SC                   | 3                                                | 17                                          | DOD                   |
| Gupta G[25]               | 42       | (P)SC                   | 12                                               | NA                                          | NA                    |
| Özşaran AA[21]            | 41       | (P)SC                   | 4                                                | NA                                          | NA                    |
| Tepedino G[27]            | 30       | MTOLMP                  | 3                                                | NA                                          | NA                    |
| Jiang H[28]               | 60       | Clear-cell carcinoma    | 44                                               | 24                                          | DOD                   |
| Wadhwa J[29]              | 45       | (P)SC                   | 1                                                | NA                                          | NA                    |
| Petersen BL[27]           | 44       | (P)SC                   | concurrent                                       | NA                                          | NA                    |
| Domanski HA[26]           | 43       | SC                      | 36                                               | 24                                          | DOD                   |
| Yamasaki H[29]            | 57       | (P)SC                   | concurrent                                       | >2 months                                    | NA                    |
| Kattan J[38]              | 16       | Dyggerminoma            | 1                                                | NA                                          | NA                    |
| Ron IG[41]                | 63       | Endometrioid carcinoma  | concurrent                                       | >25                                         | NA                    |
| Current case              | 33       | Serous borderline tumor with micro-invasive carcinoma | concurrent                                      | 19                                          | Alive                |

(P)SC = (papillary) serous carcinoma, DOD = died of disease, m = month, MTOLMP = mucinous tumor of low malignant potential, NA = not available, SCCO = small cell carcinoma of the ovary, SCCOPT = small-cell carcinoma of the ovary pulmonary type, Yr = year.
PAX-8 in serous ovarian carcinoma is as high as 79%, which is one of the reliable indicators to differentiate primary ovary cancer from breast cancer. GCDFP-15 is a highly sensitive and specific marker of breast carcinoma marker, which may help to identify the primary site of origin. In a recent immunohistochemical study, GATA 3 is more sensitive than GCDFP-15 in detecting the origin of primary breast cancer. GCDFP-15 and GATA 3 can be used to distinguish between primary and metastatic breast malignancy. The positive expression of WT-1, PAX8 and ER in breast specimens made us suspect that the primary carcinoma originated from the ovary. Then the pathology of ovarian neoplasms confirmed the ovary origin of the lesion. Comprehensive medical history and radiological findings are not sufficient to differentiate between primary or metastatic involvement of the breast. Pathology and immunohistochemistry are gold standard for diagnosis of metastasis.

There are no standard treatment guidelines for breast metastasis from ovarian cancer in early stage. Simple excisional biopsy and systemic therapy for the carcinoma constitute the preferred manner of follow-up information. Breast metastasis from ovarian carcinoma in early stage may reflect poor prognosis in patients. Survival has been observed to be between 2 and 84 months after the occurrence of breast metastasis.

To our knowledge, this is the first case of serous borderline tumor with micro-invasive carcinoma of ovary simultaneously metastasizes to the breast reported to date. We emphasize the accurate diagnosis of metastatic breast cancer and differentiation from primary breast cancer which are meaningful for patients’ management, avoiding misdiagnosis and developing appropriate systemic treatment protocols. However, the mechanism of serous borderline tumor with micro-invasive carcinoma of ovary metastasizing to breast in early stage still needs to be explored.

4. Conclusions

In conclusion, it is important to determine the origin of primary ovarian carcinoma and develop an effective treatment strategy for breast metastasis from ovarian tumors. Imaging findings and pathological diagnostic criteria are important to accurately differentiate between metastatic and primary breast lesions because of the treatment and prognosis are significantly different.

Author contributions

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References

[1] Ilhan B, Kilic H, Karanlık H. Ovarian cancer presenting as an axillary mass: case series and literature review. Curr Res Transl Med 2016;64:161–3.

[2] Özşarar AA, Diken Y, Terek MC, et al. Bilateral metastatic carcinoma of the breast from primary ovarian cancer. Curr Res Transl Med 2000;26:446–7.

[3] Tempfer CB, El Fizzazi N, Ergonem H, et al. Metastasis of ovarian cancer to the breast: a report of two cases and a review of the literature. Oncol Let 2016;11:9008–12.

[4] Sippo DA, Kulkarni K, Carlo PD, et al. Metastatic disease to the breast from extramammary malignancies: a multimodality pictorial review. Curr Probl Diagn Radiol 2016;45:225–32.

[5] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[6] Recine MA, Deavers MT, Middleton LP, et al. Serous carcinoma of the ovary and peritoneum with metastases to the breast and axillary lymph nodes. Am J Surg Pathol 2004;28:1466–71.

[7] Panse G, Bossuyt V, Ko CJ. Metastatic serous carcinoma presenting as inflammatory carcinoma over the breast-Report of two cases and literature review. J Cutan Pathol 2018;45:234–9.

[8] Mori R, Futamura M, Morimitsu K, et al. The diagnosis of a metastatic breast tumor from ovarian cancer by the succession of a p53 mutation: a case report. World J Surg Oncol 2017;15:117.

[9] Van Rompuy AS, Vanderstichele A, Vergote I, et al. Diffusely metastasized adenocarcinoma arising in a mucinous carcinoid of the ovary: a case report. Int J Gynecol Pathol 2018;37:290–5.

[10] Akturk G, Goray Durak M, Cakir Y, et al. Metastatic ovarian serous carcinoma of the breast. Breast J 2017;23:162–4.

[11] Rossfeld KK, Carson WE 3rd. Surgical management of ovarian carcinoma metastatic to the breast and axilla: A role for metastasectomy? J Surg Oncol 2015;112:581–4.

[12] Batra S, Vaid AK, Bhargava K, et al. Malignancy knows no boundaries. BMJ Case Rep 2013;2013.

[13] Rohsdbach D, Trilloch F, Regier M, et al. Malignant transformation of a serous borderline tumor and early metastasis of associated low-grade serous carcinoma detected on screening mammography. J Clin Oncol 2011;29:e763–5.

[14] Gayatnti S, Budve S, Matei D. Breast mass in a patient with ovarian cancer: a case report. J Reprod Med 2009;54:639–44.

[15] Gingell D, Samuel A, Haynik D, et al. Metastatic ovarian serous carcinoma presenting as inflammatory breast cancer: a case report. Int J Gynecol Pathol 2010;29:243–7.

[16] Balaji R, Ramachandran K, Anila KR. Ovarian carcinoma metastasis to the breast and imaging features with histopathologic correlation: a case report and review of the literature. Curr Breast Cancer Rep 2009;9:196–8.

[17] Schneuber S, Scholz HX, Reining P, et al. Breast metastasis 56 months before the diagnosis of primary ovarian cancer: a case study. Anticancer Res 2008;28:3047–50.

[18] Derin D, Eralp Y, Guney N, et al. Ovarian carcinoma with simultaneous breast and rectum metastases. Onkolologie 2008;31:205–2.

[19] Kolwijk E, Boss EA, van Altena AM, et al. Stage IV epithelial ovarian carcinoma in an 18 year old patient presenting with a Sister Mary Joseph’s nodule and metastasis in both breasts: a case report and review of the literature. Gynecol Oncol 2007;107:583–5.

[20] Micha JP, Goldstein BH, Epstein HD, et al. Ovarian carcinoma metastatic to the breast. Gynecol Oncol 2006;102:386–90.

[21] Öksüzoglu B, Güler Ni. Bilateral inflammatory breast involvement as the first site of relapse of ovarian carcinoma. Am J Clin Oncol 2001;24:211.

[22] Martel J, Roux JJ, Treilleux I, et al. Breast metastases of an ovarian adenocarcinoma. Ann Dermatol Venereol 2003;130:623–5.

[23] Kayikcioglu F, Boran N, Ayhan A, et al. Inflammatory breast metastases of ovarian cancer: a case report. Gynecol Oncol 2001;83:613–6.

[24] Cormio G, di Vagno G, Melilli GA, et al. Ovarian carcinoma metastatic to the breast. Gynecol Obstet Invest 2001;52:73–4.

[25] Gupta D, Merino MI, Farhood A, et al. Metastases to breast simulating inflammatory carcinoma. Int J Gynecol Cancer 2011;21:985–9.

[26] Wadhwa J, Dawar R, Kumar L. Ovarian carcinoma metastatic to the breast. Clin Oncol 1999;11:419–21.

[27] Petersen BL, Hög dall E, Kryger-Baggesen N. Metastasis to the breast from an ovarian carcinoma. Acta Obstet Gynecol Scand 1999;78:826–7.

[28] Oyamanski HA, Mav-Morillas A. Breast metastases from pancreatic and ovarian carcinoma. Diagn Cytopathol 1999;21:154–5.

[29] Yamasaki H, Saw D, Zdanowicz J, et al. Ovarian carcinoma metastasis to the breast case report and review of the literature. Am J Surg Pathol 1993;17:193–7.
[30] Kurabayashi T, Minamikawa T, Nishijima S, et al. Primary strumal carcinoid tumor of the ovary with multiple bone and breast metastases. J Obstet Gynaecol Res 2010;36:567–71.

[31] Adams RF, Parulekar V, Hughes C, et al. Radiologic characteristics and management of screen-detected metastatic carcinoid tumor of the breast: a case report. Clin Breast Cancer 2009;9:189–92.

[32] Sato T, Muto I, Fushiki M, et al. Metastatic breast cancer from gastric and ovarian cancer, mimicking inflammatory breast cancer: report of two cases. Breast Cancer 2008;15:315–20.

[33] Jiang Q, Lai T. Ovarian malignant tumor metastatic to the breast. Zhonghua Fu Chan Ke Za Zhi 1998;33:184–5.

[34] Moreira AL, Yao J, Waisman J, et al. Metastatic “borderline” papillary ovarian tumor in an intramammary lymph node. Breast J 2002;8:309–10.

[35] Reckova M, Meg M, Rejekova K, et al. Small-cell carcinoma of the ovary with breast metastases: a case report. Klin Onkol 2010;23:43–5.

[36] Cheng Z, Yin H, Du J, et al. Bilateral breast metastasis from small-cell carcinoma of the ovary. J Clin Oncol 2008;26:5129–30.

[37] Tepedino GJ, Fusco EF, Del Priore G. Intra-mammary lymph node metastases in an early stage ovarian cancer of low malignant potential. Int J Gynaecol Obstet 2000;71:287–8.

[38] Kattan J, Droz J-P, Charpentier P, et al. Ovarian dysgerminoma metastatic to the breast. Gynecol Oncol 1992;46:104–6.

[39] Chauhan A, Dahya P, Singh H, et al. Isolated breast metastasis from granulosa cell tumor of the ovary. Arch Gynecol Obstet 2009;280:997–9.

[40] Ron I-G, Inbar M, Halpern M, et al. Endometrioid carcinoma of the ovary presenting as primary carcinoma of the breast: A case report and review of the literature. Acta Obstet Gynecol Scand 1992;71:81–3.

[41] Moore DH, Wilson DK, Hurteau JA, et al. Gynecologic cancers metastatic to the breast. J Am Coll Surg 1998;187:178–81.

[42] Tornos C, Soslow R, Chen S, et al. Expression of WT1, CA 125, and GCDFP-15 as useful markers in the differential diagnosis of primary ovarian carcinomas versus metastatic breast cancer to the ovary. Am J Surg Pathol 2003;27:1482–9.

[43] Gown AM, Fulton RS, Kandalaft PL. Markers of metastatic carcinoma of breast origin. Histopathology 2016;68:86–95.

[44] Ho GF, Chappell M, Robinson M. Invasive lobular carcinoma of the breast diagnosed from an ovarian tumour. Malays J Pathol 2008;30:121–4.

[45] Chan JK, Cheung MA, Teng NN, et al. Patterns and progress in ovarian cancer over 14 years. Obstet Gynecol 2006;108:521–8.