Int J Clin Exp Pathol 2020;13(7):1693-1697
www.ijcep.com /ISSN:1936-2625/IJCEP0111708

Original Article

Retroperitoneal metastasis synchronous with brain and mediastinal lymph nodes metastasis from breast invasive ductal carcinoma as the first site of distant metastasis: a case report and review of literature

Min-Long Chen[1], Zhao-Sheng Ma[1], Fei-Lin Cao[1], Xing-Qiang Yan[1], Liang-Min Zhang[2], Xiu-Bei Wang[3], Bo-Jian Xie[1]

Departments of [1]Surgical Oncology, [2]Pathology, [3]Radiology, Taizhou Hospital, Wenzhou Medical University, Linhai, Zhejiang Province, People's Republic of China

Received March 31, 2020; Accepted June 15, 2020; Epub July 1, 2020; Published July 15, 2020

Abstract: Breast carcinoma retroperitoneal metastasis is rare. The clinical symptoms of this disease are always non-specific. Laboratory tests are not always helpful for diagnosis and evaluation. We reported a case of a 52 year old Chinese patient who was diagnosed with retroperitoneal metastasis from breast invasive ductal carcinoma as the first site of distant metastasis synchronous with brain and mediastinal lymph nodes metastasis 4 years after modified radical mastectomy. Second-line chemotherapy of docetaxel and capecitabine was recommended. The response evaluation every two to three months was good. Unfortunately, the metastasis in the brain advanced. The patient was transferred to a radiotherapy department to receive radiotherapy and died 10 months later. We also review the related literature.

Keywords: Breast cancer retroperitoneal metastasis immunohistochemistry

Introduction

Breast carcinoma is the most common tumor in females, with variable morphology and behavior. It is a leading cause of female cancer death worldwide [1]. Invasive ductal carcinoma and invasive lobular carcinoma are the two most common histological types of invasive breast carcinoma, occupying approximately 71% and 5% of all cases in China, respectively [2]. The most common sites of breast carcinoma metastasis are lung, bone, liver, and brain. Because of the improvement of local and systemic treatments in recent decades, breast carcinoma metastasis patterns change, especially in patients with advanced breast carcinoma [3, 4].

Breast carcinoma retroperitoneal metastasis is rare. The clinical symptoms of this disease are always non-specific and laboratory tests, which are not always helpful for diagnosis and evaluation. There are no guidelines for treating, nor is there any reliable information on prognosis. Reports on this subject in literature are poor and mostly limited to case report [5, 6]. We reported a case of retroperitoneal metastasis from breast invasive ductal carcinoma as the first site of distant metastases synchronous with brain metastasis and mediastinal lymph nodes metastasis 4 years after modified radical mastectomy and we also reviewed the related literature.

Case presentation

A 47-year-old premenopausal Chinese women was confirmed with left breast carcinoma by frozen section during the operation of lumpectomy, followed by modified radical mastectomy in July 2011. Pathology showed a 6*4*1.5 cm breast mass, moderately-differentiated, invasive ductal carcinoma with partial ductal carcinoma in situ and 16 lymph node reactive hyperplasia, immunohistochemical (IHC) diagnosis showed the tumor cells to be estrogen-

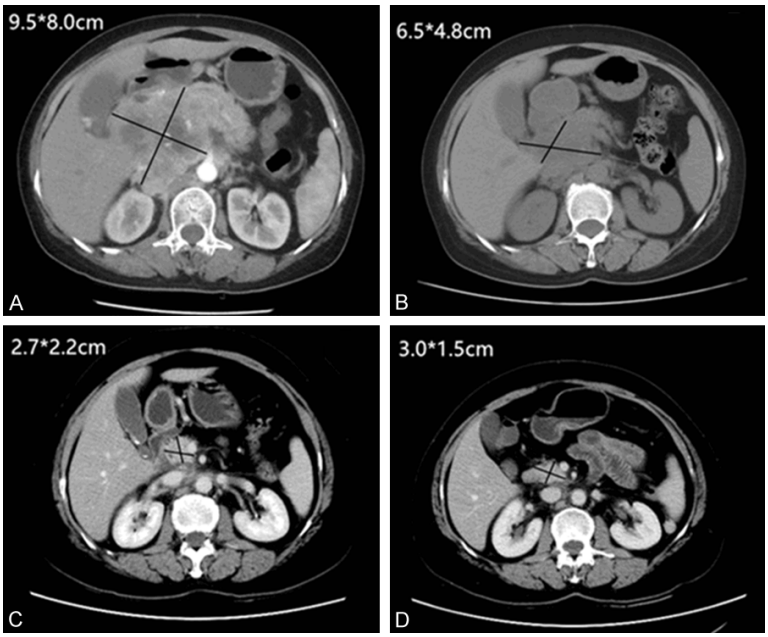

Figure 1. The biggest mass in retroperitoneum became smaller during evaluation every 2 to 3 months. Notes: A. June 1st, 2016; B. July 29th, 2016; C. October 28th, 2016; D. January 16th, 2017.

receptor (ER) positive, progesterone-receptor (PR) positive, human epidermal growth factor 2 (Her-2) negative, Ki-67 positive 15%, and no metastasis were found in the routine examination post-surgery, including CT scan of the lungs, brain MR, bone scan, and ultrasonic-b abdominal examination. She completed 6 cycles of cyclophosphamide/methotrexate/5-fluoracil (CMF), followed by radiotherapy on the left chest, supraclavicular area, and tamoxifen for endocrinotherapy.

In May 2015, the patient was aware of a palpable nodule of her supraclavicular region. At the time of presentation to our clinic, core needle biopsy was done and pathological examination, as well as other routine examinations. ICH analysis showed ER (80%+++), PR (-), Her-2 (1+), and protein-15 (GCDFP-15) positive, which was concordant with primary breast carcinoma. A routine examination showed no other organs involved. Endocrinotherapy was changed into anastrozole as advised since she was confirmed to be postmenopausal.

In May 2016, the patient came to our attention complaining of lacking in strength, her serum carcino-embryonic antigen (CEA) was 797.6 ng/ml (normal, <5.0 ng/ml), serum cancer antigen 15-3 (CA15-3) was 310 U/ml (normal, <31 U/ml), and serum cancer antigen 12-5 (CA12-5) was 63.3 U/ml (normal, <35 U/ml). PET-CT was then recommended and revealed multiple masses in retroperitoneum, mediastinum, and brain. An abdominal CT scan was used to further inspect and confirm the diagnose (**Figure 1A**). A core needle biopsy was then done for the biggest mass in the retroperitoneum. ICH revealed it to be ER (+), PR (-), Her-2 (-), Ki-67 positive (15%), GCDFP-15 (-), and PAX8 (-) (**Figure 2**). Second-line chemotherapy of docetaxel and capecitabine was recommended from then on. The patient received 14 cycles of chemotherapy during the next 10 months. Routine evaluations every 3 months showed that the masses in the retroperitoneum and mediastinum were becoming smaller (**Figure 1**). All tumor markers gradually decreased to a normal level (**Table 1**), indicating it to be effective. Unfortunately, the metastasis in the brain advanced in May 2017 and the patient was transferred to a radiotherapy department to receive radiotherapy and died 10 months later.

Discussion

Breast carcinoma metastasis can involve any organ of the body. Commonly, its sites are lymph nodes, bone, lung, liver, and brain. Breast carcinoma retroperitoneal metastasis is rare, compared with invasive ductal carcinoma. Invasive lobular carcinoma gives rise more often to distant unusual metastasis, such as gastrointestinal tract, peritoneum, and retroperitoneum [7]. Borst et. al. had compared metastatic rates between these two histological subtypes, showing statistically significant differences for metastases in the gastrointestinal tract (4.5% in ILC vs 0.2% in DC), gynecological organs (4.5% in ILC vs 0.8 in DC), and peritoneum/retroperitoneum (3.1% in ILC vs 0.6% in DC) in 2605 cases of breast carcinoma [6]. The case we reported was invasive ductal carcinoma, and the metastatic pattern was also scarce. Supraclavicular lymph

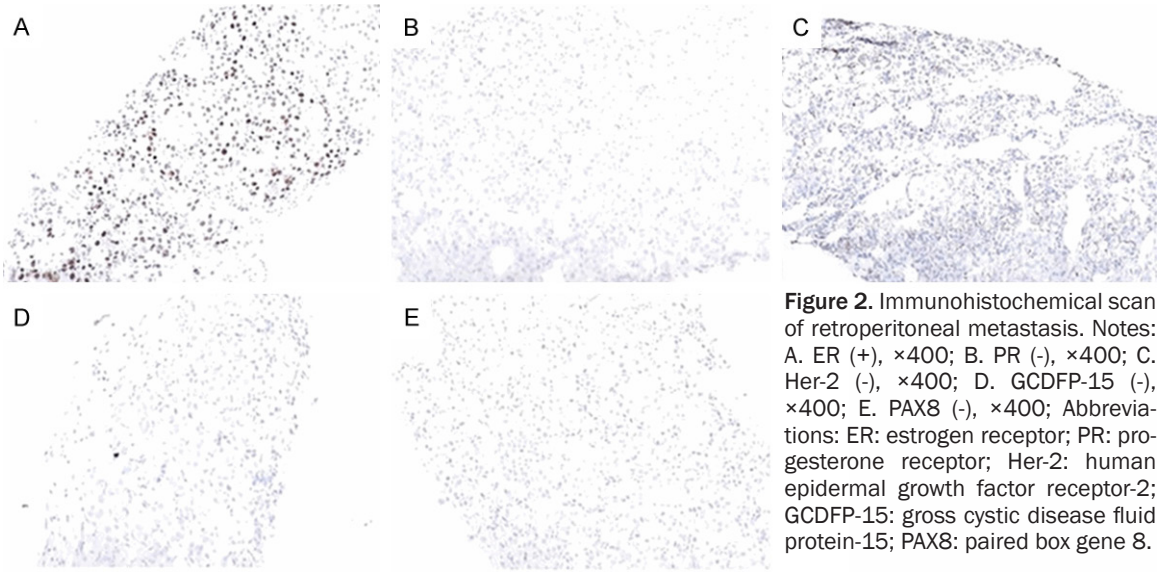

Figure 2. Immunohistochemical scan of retroperitoneal metastasis. Notes: A. ER (+), ×400; B. PR (-), ×400; C. Her-2 (-), ×400; D. GCDFP-15 (-), ×400; E. PAX8 (-), ×400; Abbreviations: ER: estrogen receptor; PR: progesterone receptor; Her-2: human epidermal growth factor receptor-2; GCDFP-15: gross cystic disease fluid protein-15; PAX8: paired box gene 8.

Table 1. Tumor makers during chemotherapy

	2016/5/1	2016/7/1	2016/10/1	2016/12/1	2017/3/1	2017/5/1	2015/8/1
CEA (ng/ml)	797.6	557.3	30.1	12.2	8.4	8.4	10.7
CA125 (U/ml)	63.3	57.2	25.1	21.3	18.9	17	15.8
CA153 (U/ml)	310	278.1	33.3	16.3	12	11	13.4

CEA: <5.0 ng/ml; CA123: <35.0 U/m; CA153: <31.0 U/ml.

nodes were first involved 4 years after the first treatment and then multiple metastatic nodes in the retroperitoneum and mediastinum were detected in synchronous with brain metastasis one year later.

The diagnosis of breast carcinoma retroperitoneal metastasis may be difficult. The clinical symptoms of this disease are always non-specific and laboratory tests, which are also not helpful for diagnosis and evaluation. Several case reports of breast carcinoma retroperitoneal metastasis were published in English literature, which manifested as retroperitoneal fibrosis, leading small bowel obstruction, ureteral obstruction, hydronephrosis, or back pain [8, 9]. As in this patient, she presented nothing, but lacking in strength. However, the history of breast cancer regional recurrence and abnormality of tumor makers arouse the surgeon the suspicion of a possibility of distant metastasis, so he recommended the patient to check for PET-CT, finally leading to an early diagnosis. Mediastinal nodes in this patient were not pathologically confirmed, but there was an abnormal FDG uptake in PET-CT and contraction during chemotherapy regimen, indicating these also to be metastatic. PET-CT scan was helpful for this patient in initial diagnosis.

Pathology and detailed IHC analysis are crucial for diagnosis and differentiation for breast carcinoma distant metastasis. As in this patient, we did the core needle biopsy the first time when the position and size of the mass in the retroperitoneum was confirmed by abdominal CT scan. ER and PR have been used as reliable markers to determine the breast origin. Metastatic breast carcinoma is usually positive for ER and PR.

Eitan Amir et. al. demonstrated that the discordance in ER and PR between the primary breast carcinoma and the metastasis was 16%, 40%, most included loss of ER and PR expression [10]. A possible explanation can be represented by the influence of systemic therapy and the dedifferentiation of tumor cells during disease progression. ER and PR can be present occasionally in other solid tumors, but a high level favors breast carcino-

ma metastasis. As in the present case, the ER and Her-2 status of retroperitoneal metastasis were accordant with the primary breast carcinoma, while PR expression lost after systematic treatment, but were concordant with supraclavicular lymphatic metastasis.

GCDFP-15 is another important IHC marker for the evaluation of a potential mammary origin of metastatic carcinoma of unknown primary sites. It was reported to be expressed by 38% of breast invasive micropapillary carcinoma [11]. While Carmen Tornos et. al. reported 14% of the primary breast carcinoma and 39% of metastatic breast carcinoma were positive for GCDFP [12]. PAX8, a transcription factor, was suggested to be a sensitive marker for tumors of the thyroid, kidney and thymus, and tumors derived from the Müllerian pipe organ [13, 14]. It was reported to be presented in 92-99% of serous ovarian carcinoma and absent in all breast carcinomas [14, 15]. In this case we reported, the PAX8 and GCDFP-15 were both negative. Therefore, every single ICH marker is not enough and may lead to misdiagnosis for some patients.

Data on treatment of breast carcinoma retroperitoneal metastasis are scarce. Since metastasis in the retroperitoneum represents evidence of systemic disease, systemic treatment is recommended as the first line of treatment. Surgery is reserved only for palliative surgical resection for obstruction and bleeding [16, 17]. On the other hand, local treatment, such as maximal cytoreduction and hyperthermic intraperitoneal chemotherapy was reported to be a promising approach to offer to highly selected patients [18]. In this case, the patient received chemotherapy of docetaxel and capecitabine for about 10 months. The assessment of therapeutic efficacy was stable. The data on prognosis of breast carcinoma retroperitoneal metastasis is limited, compared with a median survival of 20.5 months for metastatic breast carcinoma and 1.56 months for breast carcinoma metastatic peritoneal disease [19]. This patient received as long as 22 months survival, which is considered as an acceptable result.

Conclusion

Retroperitoneal metastasis from breast carcinoma is rare. With the improvement of local and systemic treatments of breast carcinoma, we believe treatment may occur more often in clinical practice in the future. Oncologists should be aware of such rare entities when faced with any complaints from patients with a history of breast carcinoma. PET-CT is helpful to detect the exact origin. Final diagnosis should be based on comprehensive analysis of history, clinical examinations, histology, IHC markers, and many other factors.

Acknowledgements

This work was supported by Science Research Fund of Taizhou (Grants No. 14SF03).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Bo-Jian Xie, Department of Surgical Oncology, Taizhou Hospital, Wenzhou Medical University, No. 150 Ximen Road, Linhai 317000, Zhejiang Province, People's Republic of China. Tel: +86-576-85199051; Fax: +86-576-85199876; E-mail: drxiebojian@163.com; drchenml@163.com

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Si W, Li Y, Han Y, Zhang F, Wang Y, Li Y, Linghu RX, Zhang X and Yang J. Epidemiological and clinicopathological trends of breast cancer in Chinese patients during 1993 to 2013: a retrospective study. Medicine (Baltimore) 2015; 94: e820.

[3] Saunders Y, Stebbing J, Broadley K and Johnston SR. Recurrent locally advanced breast cancer: the treatment of chest wall disease with further chemotherapy. Clin Oncol (R Coll Radiol) 2001; 13: 195-199.

[4] Lee B, Franklin I, Lewis JS, Coombes RC, Leonard R, Gishen P and Stebbing J. The efficacy of percutaneous vertebroplasty for vertebral metastases associated with solid malignancies. Eur J Cancer 2009; 45: 1597-1602.

[5] Yoneyama K, Takeshita T, Suzuki H, Morise M, Suzuki T, Kishi S, Tsutsui A and Matsumoto A. A case of possible retroperitoneal metastasis of breast cancer successfully treated with oral S-1 and cyclophosphamide therapy after TC therapy. Gan To Kagaku Ryoho 2011; 38: 435-437.

[6] Borst MJ and Ingold JA. Metastatic patterns of invasive lobular versus invasive ductal carci-

noma of the breast. Surgery 1993; 114: 637-41.
[7] Shakoor MT, Ayub S, Mohindra R, Ayub Z and Ahad A. Unique presentations of invasive lobular breast cancer: a case series. Int J Biomed Sci 2014; 10: 287-93.
[8] Kim J, Hwang JH, Nam BD, Park YW and Jeen YM. Mediastinal and retroperitoneal fibrosis as a manifestation of breast cancer metastasis: a case report and literature review. Medicine (Baltimore) 2018; 97: e11842.
[9] Carloss H and Saab G. Breast cancer and retroperitoneal metastasis. South Med J 1980; 73: 1570-1.
[10] Amir E, Miller N, Geddie W, Freedman O, Kassam F, Simmons C, Oldfield M, Dranitsaris G, Tomlinson G, Laupacis A, Tannock IF and Clemons M. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer. J Clin Oncol 2012; 30: 587-592.
[11] Moritani S, Ichihara S, Hasegawa M, Endo T, Oiwa M, Yoshikawa K, Sato Y, Aoyama H, Hayashi T and Kushima R. Serous papillary adenocarcinoma of the female genital organs and invasive micropapillary carcinoma of the breast. Are WT1, CA125, and GCDFP-15 useful in differential diagnosis? Hum Pathol 2008; 39: 666-671.
[12] Tornos C, Soslow R, Chen S, Akram M, Hummer AJ, Abu-Rustum N, Norton L and Tan LK. 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 2005; 29: 1482-9.
[13] Ozcan A, Shen SS, Hamilton C, Anjana K, Coffey D, Krishnan B and Truong LD. PAX 8 expression in non-neoplastic tissues, primary tumors, and metastatic tumors: a comprehensive immunohistochemical study. Mod Pathol 2011; 24: 751-764.
[14] Chai HJ, Ren Q, Fan Q, Ye L, Du GY, Du HW, Xu W, Li Y, Zhang L and Cheng ZP. PAX8 is a potential marker for the diagnosis of primary epithelial ovarian cancer. Oncol Lett 2017; 14: 5871-5875.
[15] Lotan TL, Ye H, Melamed J, Wu XR, Shih IeM and Epstein JI. Immunohistochemical panel to identify the primary site of invasive micropapillary carcinoma. Am J Surg Pathol 2009; 33: 1037-41.
[16] Schwarz RE, Klimstra DS and Turnbull AD. Metastatic breast cancer masquerading as gastrointestinal primary. Am J Gastroenterol 1998; 93: 111-4.
[17] Franceschini G, Manno A, Mulè A, Verbo A, Rizzo G, Sermoneta D, Petito L, D'Alba P, Maggiore C, Terribile D, Masetti R and Coco C. Gastro-intestinal symptoms as clinical manifestation of peritoneal and retroperitoneal spread of an invasive lobular breast cancer: report of a case and review of the literature. BMC Cancer 2006; 6: 193.
[18] Cardi M, Sammartino P, Framarino ML, Biacchi D, Cortesi E, Sibio S, Accarpio F, Luciani C, Palazzo A and di Giorgio A. Treatment of peritoneal carcinomatosis from breast cancer by maximal cytoreduction and HIPEC: a preliminary report on 5 cases. Breast 2013; 22: 845-849.
[19] Tuthill M, Pell R, Guiliani R, Lim A, Gudi M, Contractor KB, Lewis JS, Coombes RC and Stebbing J. Peritoneal disease in breast cancer: a specific entity with an extremely poor prognosis. Eur J Cancer 2009; 45: 2146-2149.