CASE REPORTS

Diagnosis and treatment of inflammatory breast cancer

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Abstract

Inflammatory breast cancer (IBC) is a rare disease in clinic, with rapid progression and poor prognosis. It is easy to be misdiagnosed in cases of atypical clinical symptoms and imaging findings. Combined with the medical record of IBC in our hospital, the author explores the causes of misdiagnosis of inflammatory breast cancer, based on clinical manifestations, diagnosis, imaging examination, treatment and so on, so as to improve the clinical physicians understanding and diagnosis of this disease.

Key Words: Inflammatory, Breast cancer, Diagnosis, Treatment

1 Medical record

1.1 General information

A 58-year-old female was admitted to our hospital due to red and swollen breast at the right side for one week duration. The right breast gave off heat since onset of the disease, accompanied by the signs of fever, slight pain, without fever or chills. Specialized examination: the skin at the right side of the breast was red and swollen (occuping 4/5 of the whole breast), without texture resembling the peel of an orange (peau d'orange). A mass about 7 cm $\times$ 5 cm in size above the nipple together with several enlarged lymph nodes was palpable, but no lymph nodes were touched on the right clavicle. Results of auxiliary examination were introduced as follows. Mammography examination indicated change in the inflammatory breast cancer. Ultrasound examination demonstrated multiple lymph node metastasis in right breast cancer, right arm and right supraclavicular (or subclavicular) area. Chest CT examinations showed multiple right breast cancer and right axillary lymph node metastasis.

Figure 1: Inflammatory breast cancer

1.2 Primary diagnosis

Inflammatory breast cancer

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1.3 Diagnosis and treatment

Further biopsy was performed in the right breast and pathological diagnosis confirmed right breast infiltrating ductal carcinoma and right axillary metastasis of poorly differentiated adenocarcinoma. Immunohistochemistry examination detected Er (-), PR (-), HER-2 (++) and FISH found HER-2 gene amplification. In that case, she received 6 cycles of docetaxel combined with cyclophosphamide as neoadjuvant chemotherapy, with the effect of partial remission. Later she underwent right breast modified radical surgery plus right supraclavicular lymph node dissection. Postoperative pathology report specified right breast infiltrating ductal carcinoma and lymph node metastasis (15/26), ER (-), PR (-), HER-2 (+++). Postoperative radiotherapy for chest wall and clavicle area was completed. 6 months after the surgery, the patient suffered from recurrence on the chest wall, and the follow-up treatment of paclitaxel liposome combined with doxorubicin for 2 courses, and paclitaxel liposomal, doxorubicin combined with bevacizumab for 1 course to achieve stable condition. The patient was also treated with trastuzumab in combination with vinorelbine and carboplatin as HER-2 reached (+++). She remains in a stable condition for 15 months.

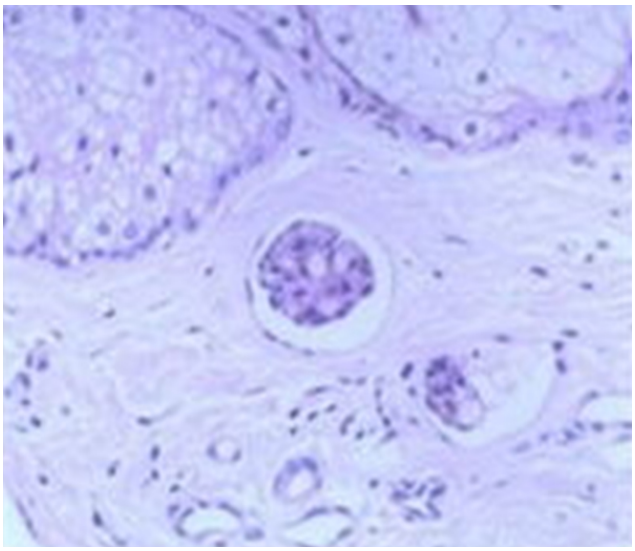

Figure 2: Tumor emboli in the dermal lymphatic channels (HE stain, 200×)

2 Discussion

2.1 Dr. Jin Zhao

Dr. Jin Zhao is the Associate Chief Physician of General Surgery Department at the Third Affiliated Hospital of Inner Mongolia Medical University, specializing in Diagnosis and treatment of gastrointestinal diseases and malignant tumors.

Inflammatory breast cancer (IBC) is a rare form of breast cancer with generally poor prognosis, accounting for 2.5 percentages.[1] It presents acute onset, rapid progress, low 5 years' survival rate, and its clinical symptoms are similar to acute mastitis. IBC is characterized by a various clinical signs, such as diffuse erythema, reddened area with texture resembling the peel of an orange (peau d'orange) in more than two-thirds of the cases, harder or firmer in the breast and unusual warmth of the affected breast. Nearly all women have lymph node involvement at the time of diagnosis, and approximately 30% have gross distant metastases. Lymph node metastasis also occurred in our case.

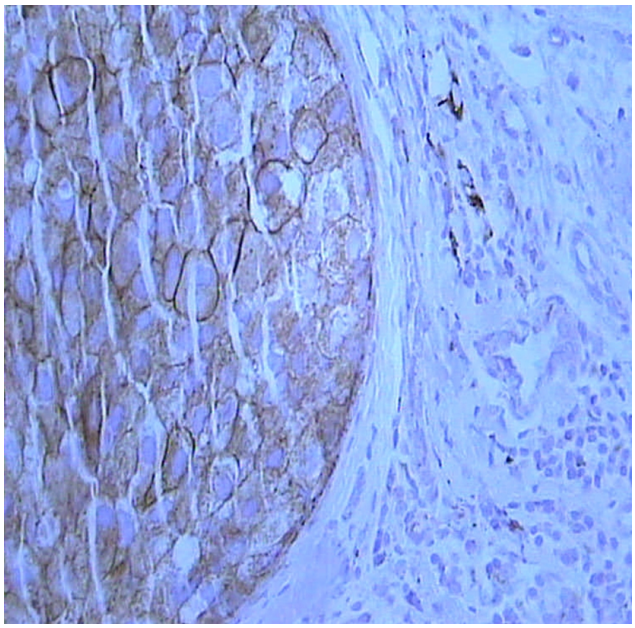

Figure 3: Her-2 immune complex protein on the cell (400×)

Usually, IBC is mistakenly recognized as acute mastitis (AM) since it is mainly manifested as redness, swelling, warmth and pain, initially resembles mastitis. Therefore, it is necessary to differentiate IBC from AM according to the following aspects: 1) The symptoms of local pain and tenderness are more obvious in AM than those in IBC. 2) The syndrome of redness and swelling in AM is either limited or wide, and its color is bright red. While skin changes in IBC is extensive, with involvement of the entire breast, and its color is dark red and aubergine. On the other hand, the skin for patients with AM is generally characterized by pitting edema; while it showed "cellulite" in most IBC cases. 3) Infectious systemic poisoning symptoms are not apparent in IBC, and there is no significant increase of blood cell count and classification. Chills, fever and other systemic inflammatory response are distinct in AM. 4) Direct signs of breast cancer could also be visualized in IBC through X-ray examination, such as spiculation or malignant calcification. 5) The clinical symptoms of acute masti-

tis will be relieved after short-term anti-inflammatory treatment, which remains invalid in IBC.[2] 6) Local abscess formation presents with touch sense of fluctuation one week after the incidence of acute mastitis, and puncture examination demonstrates the existence of purulent fluid. Cancer cells were observed then in IBC. 7) Axillary lymph node enlargement was involved in both AM and IBC. Axillary lymph node enlarged, firm but inactive by palpation, with the skin and the surrounding tissue adhesion. It is relatively soft in AM, with the surrounding tissue adhesion, and good activity. In addition, some literatures[3] reported that ovarian cancer and other breast metastases also presented clinical performance of IBC. Lingcheng Wang[4] reported that the clinical manifestations of bilateral breast swelling, orange dermoid change, with axillary lymph node enlargement caused by hydatidiform mole may be misrecognized as IBC. Therefore, fine needle aspiration cytology is particularly important in the diagnosis of IBC. The patient underwent right breast tumor biopsy, and her pathological diagnosis is right breast invasive ductal carcinoma, right axillary metastatic poorly differentiated adenocarcinoma.

2.2 Dr. Guoyu Li

Dr. Guoyu Li is the Chief Physician of General Surgery Department at the Third Affiliated Hospital of Inner Mongolia Medical University, specializing in breast disease.

Foreign literatures reported that the incidence of IBC had certain relevance with menstruation, fertility, body mass, blood type and immune factor, yet the relationship remained to be discovered.[5] The disease is more common in young women, especially among 28 to 60 years old, the median age is 48 years old, of which 1/3 of the cases occurred before and after menopause, about 1% occurred in the pregnancy lactation, very rare in male patients.[6] The typical clinical manifestations of IBC are red, swollen, hot and painful. Generally, patients are not with fever. Compared with the other normal breast, the affected breast is found to be large, red and swollen through visual examination. Palpation of breast is generally solid, often associated with axillary lymph nodes, breast thickening of the skin, nipple depression, orange peel appearance or satellite nodules but lacks of obvious palpable masses. Some patients were unaware of the fact that symptoms described above may be potentially caused by IBC so that no special attention was paid to it, which led to delay in diagnosis and treatment. It is generally believed that IBC inflammation performance due to the extensive lymph duct tumor thrombus caused by lymphatic obstruction. Pathological diagnosis of intradermal and subcutaneous lymph tube often discovered cancer cells, with vascular or lymphatic invasion. The incidence of IBC is explosive, and its clinical performance resembles those caused by acute mastitis with tendency of distant metastasis. The disease occurs mostly in the early stage of menopause, the course lasts for a few weeks or months. About one in three patients experienced inflammatory change in skin with involvement of the entire breast when IBC was initially diagnosed. Nearly 30%-65% of patients had palpable mass in the breast. Ipsilateral axillary or supraclavicular lymph node metastasis occurred in more than 70 % and distant metastasis in 20 percentages.[7] The patient in our case is 58 years old, an easily affected age of the disease, characterized by acute onset and duration of one week. In addition, she was with typical performances of breast redness, swelling, heat, pain and lymph node metastasis in right axillary, supraclavicular (or down) area, which were consistent with the diagnosis of inflammatory breast cancer.

2.3 Dr. Bing Li

Dr. Bing Li is the Attending Physician of General Surgery Department at the Third Affiliated Hospital of Inner Mongolia Medical University, specializing in breast disease.

The necessary imaging examination of IBC includes:

2.3.1 Mammography

Mammography is the first choice in the diagnosis of breast disease. Typical X-ray manifestations of IBC are burr or lobulated mass associated with or without malignant calcification, increased breast density, glandular disorder, thickening of the skin (especially under the skin), subcutaneous fat layer opacity with dense shadow of line strip- or fishing net-shape and axillary lymph nodes. Yaping Lv et al[8] believed that IBC was suspected if mass was with or without malignant calcification, extensive thickening of the skin, gland disorders were examined and breast density generally increased via X-ray in non-clinical pregnancy or breastfeeding women with mastitis performance. The X-ray manifestations of IBC often cross each other, so it is important to grasp the performance of IBC in early diagnosis.

2.3.2 Breast ultrasound examination

Breast ultrasound examination is widely accepted examing method among patients due to its fast, safe and flexible characteristics, and it owns obvious advantages over other technique in terms of cystic and solid tumors . Color Doppler ultrasound examination results of IBC include echo of an uneven mass or dense infiltrative nodules in breast tissue, thickening of the skin, breast subcutaneous effusion and so on. Foreign literatures reported that 55% 85% of IBC cases were discovered to have axillary or supraclavicular lymph node metastasis.[9] In that case, axillary and supraclavicular lymph node ultrasonography is helpful for early diagnosis of suspected IBC during clinical practice.

Ultrasound, mammography, CT, and magnetic resonance imaging (MRI) examination show images of different changes, but they are not qualitatively significant in the diagnosis of IBC, for which highly relies on cytology or pathology. Fine needle aspiration cytology is generally recognized as the primary examination method of suspected cases of IBC. The results of mammography and CT in this patient were in accordance with the imaging changes of inflammatory breast cancer, and fine needle aspiration cytology confirmed the diagnosis.

2.4 Dr. Zhijian Zhang

Dr.Zhijian Zhang is the Chief Physician of Pathology Department at the Third Affiliated Hospital of Inner Mongolia Medical University, specializing in clinical pathological diagnosis of all tissues.

IBC is a clinical diagnosis rather than a pathological diagnosis, characterized by rapid progression, high degree of malignancy, short survival time and poor prognosis.[10] Pathological studies on IBC proposed that IBC could also be termed as carcinoma mastitoides due to the similar reaction between the two. Its pathological features include: 1) The pathology of IBC does not belong to a specific histological type, due to high malignancy, simple scirrhous carcinoma and invasive carcinoma in infiltrating growth, complicated by wide cancer cell infiltration in gland and skin, which leads to obstruction and regional lymph nodes metastasis. Most cases are poorly differentiated invasive ductal carcinoma. 2) Compared with non-inflammatory breast cancer, IBC is characterized by lymph nodes metastasis, and axillary lymph nodes and distant metastasis in the early stage, and it carries the most severe prognosis of locally advanced breast cancers. (3) Estrogen receptor (ER) and progesterone receptor (PR) are mostly negative, HER-2 and epidermal growth factor receptor (EGFR) protein is over expressed and gene is amplified.[11] There is no uniform diagnosis standard of IBC and investigator's views vary greatly in present stage. However most of them believed that specific pathological feature of IBC was lymphatic tube tumor thrombus forming in breast and skin tissue.[12] Fine needle aspiration cytology is a simple, quick and effective diagnosis method. It has a higher value in the diagnosis of IBC and its coincidence rate is up to 95% with pathological diagnosis.[13] At the same time, the method has less tissue damage and it is easy to be accepted by the patients. But needle aspiration cytology has a certain false positive, so clinicians should pay attention to the identification.

2.5 Dr.Nan Kang

Dr. Nan Kang is the associate Chief Physician of General Surgery Department at the Third Affiliated Hospital of Inner Mongolia Medical University, specializing in breast disease.

In the past, IBC was generally treated with chemotherapy, surgery or radiation therapy alone, which failed to improve the prognosis of the disease. Preoperative neoadjuvant chemotherapy, postoperative chemotherapy or radiotherapy as the comprehensive treatment of IBC has been widely recognized nowadays,[12] and it can significantly enhance efficacy and prognosis.

2.5.1 Neoadjuvant chemotherapy

Neoadjuvant chemotherapy (NEO) can decrease the size of primary tumor, reduce tumor dissemination caused by operation and cut down postoperative recurrence, exterminate subclinical micrometastases and show sensitivity to chemotherapy in tumor. In most cases, IBC is of multi differentiation, and relatively sensitive to chemotherapy so that the role of NEO in treating with IBC has been affirmed. At present, many chemotherapy regimens include anthracycline and gemcitabine. Horváth et al[14] made retrospective study and found that complete remission rate of chemotherapy containing doxorubicin regimen and combined chemotherapy containing docetaxel and epirubicin were 54.2% and 54.5% respectively. Doxorubicin and cyclophosphamide treatment for 5 weeks and sequential paclitaxel for 12 weeks are effective towards candidate patient for treatment with surgical method.[15] It was even reported that primary tumor disappeared in 87.5 percentages of IBC patients without distant metastasis undergoing chemotherapy combined with radiotherapy, and they also had breast conserved.[16]

2.5.2 Surgical treatment

Singletary[17] proposed that surgery was feasible only if outcome of preoperative chemotherapy was good. On the contrary, the patient should receive additional radiotherapy prior to surgical treatment when preoperative chemotherapy effect is not good or invalid. Surgery is advisable in most IBC cases so that more care is required over the choice of surgical timing. The primary tumor was significantly reduced, local skin redness and swelling reduced or disappeared after 3 4 cycles of neoadjuvant chemotherapy, which permits more choices of surgical approach. Modified radical mastectomy for breast cancer is recommended of all surgical approaches, and the resection range should include at least 3 mm of the negative resection margin.[18] In principle, the scope of breast skin resection should be large enough to avoid the remnants of skin cancer and local recurrence.

2.5.3 Radiotherapy

Radiotherapy. International inflammatory breast cancer experts proposed the active implement of local radiotherapy. Radiotherapy not only reduces the potential occurrence of lymph node metastases, but also prevents cancer recurrence. It has been reported that alternate treatment of chemotherapy and radiotherapy was practical when IBC patients without distant metastasis, and whose curative effects are similar to those of surgical treatment.[19] Radiotherapy alone could control the local recurrence, but it has little significance to improve the survival rate of patients.[20] Local radiotherapy is suggested in those patients, who are 45 years old, the sum of resection margin or positive axillary lymph node metastasis is more than or equal to 4, and the effect of neoadjuvant chemotherapy is not obvious.

2.5.4 Endocrinotherapy

Endocrinotherapy could effectively improve the prognosis of patients with ER or PR positive breast cancer. The most widely used endocrine drugs for breast cancer include anti estrogen, progesterone and luteinizing hormone luteinizing hormone releasing hormone analogues and aromatase inhibitors. The vast majority of ER or PR in IBC was negative therefore endocrine therapy is advisable for ER or PR positive IBC patients. GPR30 is a newly discovered G protein coupled estrogen receptor, which is much associated with breast cancer metastasis and overall survival rate, and the expression of GPR30 were reported as high as 69% in IBC.[21] Tamoxifen is widely used in clinic as the role of estrogen receptor inhibitor. It can stimulate the GPR30 expression, and further stimulate the epidermal growth factor receptor (EGFR) signal pathway to improve the prognosis of the patients. Lapatinib is a tyrosine kinase inhibitor, mainly affecting EGFR. Its single drug treatment is an effective method for relapsed or refractory HER-2 overexpression in IBC.[22] Goldfarb et al.[23] retrospectively analyzed 51 patients of IBC who had received neoadjuvant chemotherapy, surgery, chemotherapy or radiotherapy and endocrine therapy, and revealed that the 5-year survival rate was 63%.

2.5.5 Molecular targeted therapy

Usually, tumor molecular targeted therapy is feasible when specific target molecules are confirmed. In the current research, Her-2 is discovered to serves as a target molecule in IBC. In addition, the use of trastuzumab for HER-2 IBC postoperative adjuvant therapy could reduce risk of recurrence to some extent, improve disease-free survival, and impose relief effect on reoccurrence.[24] Foreign scholars discovered that early preoperative application of trastuzumab combined with neoadjuvant chemotherapy brought pathological complete response rate to be 62.5% in 16 cases, significantly improving the prognosis of patients.[25] Sportès et al[26] found that 6- year survival rate for non-metastatic IBC patients pretreated with high-dose melphalan or etoposide plus autologous stem cell transplantation was 69%, but the method is difficult to promote clinically.[26]

We finally chosde the classical targeted drug chemotherapy in combination with surgery and radiotherapy based on the pathological examination results. Systemic chemotherapy for the reoccurrence of the disease was carried out six months later, and the clinical control methods turned to be effective. According to metastasis breast cancer treatment guideline recommended by European Society of Medical Oncology, our next plan is to have some attempt at some other targeted drugs, such as Lapatinib, T—DM1 or Pertuzumab, which not only targets HER-2 gene but also blocks other HER family members. In addition, the use of chemotherapy drugs such as docetaxel, gemcitabine and VP16 are worthy of consideration. It should be strongly emphasized that treatment alone is often unable to obtain the expected effect due to the high degree of malignancy, and prone to distant metastasis so that systemic individualized treatment should be based on the specific circumstances of the patients.

3 Conclusions

In short, IBC is a type of poorly differentiated adenocarcinoma, characterized by fast progression, short term invasion of the entire breast, presence of distant metastasis in early phase (transfer rate is as high as 30% - 40%), and misdiagnosis may cause a huge difference in prognosis within a short time. Therefore, clinicians should grasp a sufficient understanding of the clinical manifestations of IBC, timely and effective diagnosis and treatment is particularly important. It is difficult to identify inflammatory breast cancer and acute mastitis in the early stage, while their differences are gradually becoming clear with the development of the diseases. Hence, the patients should see seek professional help in the hospital when they have breast swelling and heat pain so as not to cause delay in timely treatment. Fine needle biopsy should be carried out for suspected cases of IBC as early as possible to confirm the diagnosis. Neoadjuvant chemotherapy, surgery, postoperative chemotherapy and radiotherapy and endocrine therapy, molecular targeted therapy and other comprehensive treatment should be fully employed, in order to further improve the prognosis of IBC patients.

Conflicts of Interest Disclosure

The authors have no conflict of interest related to this article.

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