

Original Article

Inflammatory breast cancer of triple-negative subtype during lactation: a case report and review of the literature

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Abstract: Here we describe a breast cancer case from a 36-year-old female 4 months after delivery. During lactation, she had a painful large lump in the left breast, accompanied by erythema and edema of the 1/3 skin of the breast. Surgical biopsy confirmed that it was a case of invasive breast cancer without special type, grade 3, triple-negative/basal-like subtype (ER-, PR-, HER2-, CK5&6+, EGFR+) and no dermal lymphatic involvement was observed. Although inflammatory breast cancer was diagnosed, the clinical evidence of metastasis was not found. After neoadjuvant chemotherapy, the patient underwent mastectomy with dissection of the axillary lymph nodes. The tumor did not invade her chest wall and skin. The tumor showed mild response to chemotherapy. No metastasis was identified in the axillary lymph nodes. The patient developed lung metastasis 8 months after mastectomy.

Keywords: Breast, inflammatory breast cancer, lactation, triple-negative subtype, prognosis

Introduction

Inflammatory breast cancer is a very aggressive type of locally advanced breast cancer with a poor prognosis, which is often associated with early metastasis and frequent resistance to conventional therapies. Patients present with rapid onset of erythema and edema of the breast skin (i.e., peauorange) [1, 2].

Pregnancy-associated breast cancer is termed as the breast cancers occurring during pregnancy or within a year (or a number of years) post-partum [3, 4]. Contrary to popular point, pregnancy-associated breast cancer is not a rare disease and have affected up to 40,000 women in 2009 [4]. Two distinct subtypes of pregnancy-associated breast cancer were the breast cancer during pregnancy and that of post-partum (with or without lactation). Emerging epidemiologic data highlights worsened outcomes specific to post-partum cases. The studies from Norway indicated that the patients with breast cancer diagnosed during lactation had the increased risk of cause-spe-

cific death [4]. The effect of worsened prognosis in the post-partum period is time-dependent and diminishes as the time increases between parturition and breast cancer diagnosis. Post-partum breast involution was also responsible for the increased metastatic potential of post-partum pregnancy-associated breast cancer [4, 5]. However, the diagnosis of breast cancer during pregnancy and lactation is difficult both clinically and radiologically because of the striking hormone-induced changes in breast tissue during this period. So, it is difficult to manage breast cancer occurs during pregnancy and lactation [6].

One point has been proposed that no direct relationship between inflammatory breast cancer and pregnancy or lactation [7]. Other studies showed the same conclusion that inflammatory breast cancer occurs in pregnant/lactating women have the same rate as that in non-pregnant women of the same age [3]. However, Tabbane et al. reported that nearly all the cases of breast cancer associated with pregnancy or lactation increased rapidly and most of inflam-

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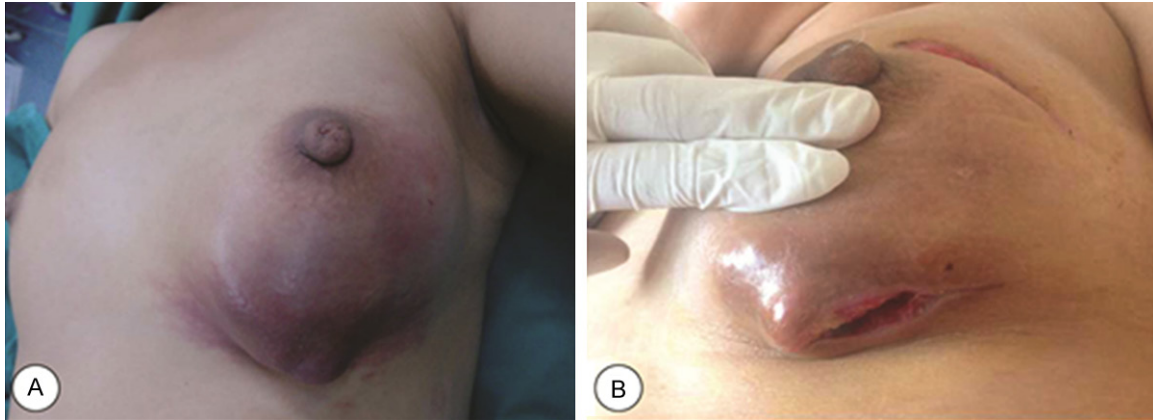


Figure 1. A. Significant enlargement of the left breast, a huge irregular, firm mass in the lower outer quadrant, and erythema, edema and warmth of the 1/3 skin of the breast. B. The surgeon performed incision and drainage with biopsy. The mass had a granular and firm appearance on the cut surface.

matory breast cancer occurred in the Tunisian breast cancer patients under the age of 30 [8]. The breast cancer with pregnancy or lactation in patients under the age of 30 reached 40% of the cases. This association has an aggravating role on the course of the breast cancer, as is shown by the high rate of early metastases [8].

In triple-negative inflammatory breast cancers, 29% of the inflammatory breast cancers were accounted to ER and HER2 status, and the triple-negative subtype was found to be the worst overall survival and high recurrence rates [9]. Inflammatory breast cancer shows a prominent geographic pattern, being more common in North Africa, including Egypt and Tunisia. Incidence of inflammatory breast cancer is low in Asian population. However, few inflammatory breast cancers during pregnancy or lactation and triple-negative inflammatory breast cancers have been reported in Asians. Here we reported a 36-year-old lactating Chinese female with inflammatory breast cancer of triple-negative subtype.

Case report

The 36-year-old Chinese woman was presented to the Chengde Central Hospital 4 months after delivery of the second child and during lactation. In Outpatient Department, the woman complains a painful lump in her left breast, accompanied by erythema and edema of the breast skin which was detected a month prior to presentation. There was no history of nipple discharge and fever. She had her first child at

her 23 years old, with lactation period lasting for one and a half years. She did not have the history of breast trauma, prior local irradiation, surgery, or any other tumor history. The patient denied using any hormonal therapy and had no family history of breast disease. Considering acute mastitis before admission, the patient was treated with hot compress and intravenous cefazolin, but without any effect. The patient had to use analgesics because of severe pain.

A breast examination showed a 10×8×6 cm irregular gelosis in the lower outer quadrant of her left breast. The mass was poorly mobile and adherent to the skin and chest wall. Erythema, edema and warmth of the 1/3 skin of the breast were observed as shown in **Figure 1A**. No axillary and supraclavicular lymphadenopathy was detected upon physical examination. No abnormality was found in the right breast. Patient had a temperature of 36.8 centigrade. Her white blood cell count was $11.1 \times 10^9/L$ (reference values: $3.5-9.5 \times 10^9/L$).

11.1×7.0×8.8 cm mass with clusters of mixed signal imaging was observed in axial T1 MR imaging, with clusters of equal and high signal imaging (a honeycomb change) in axial T2. Irregular clusters of mixed signal imaging were present with unclear border in sagittal T2 images (**Figure 2A-C**). So, abscess could not rule out carcinoma from the MR results. The result from fine needle aspiration cytology failed to detect tumor cells. The surgeon was performed with surgical incision and drainage with biopsy. The

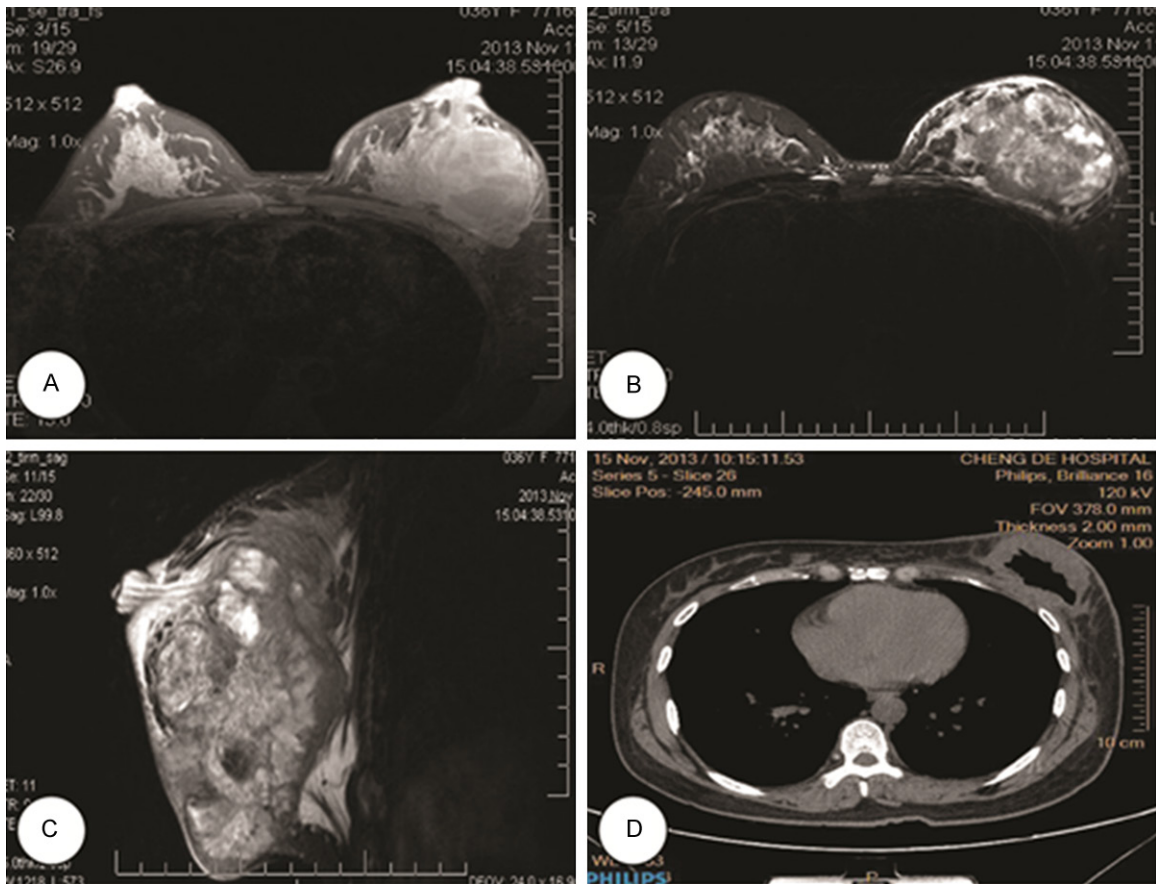


Figure 2. A. MRI axial T1: A huge mass with clusters of mixed signal imaging, relatively well-circumscribed, in the left breast. B. MRI axial T2: The mass with clusters of equal and high signal imaging (a honeycomb change). C. MRI sagittal T2: Irregular clusters of mixed signal imaging, the border is not clear, and the surface skin thicker. D. Axial CT scan: Irregular soft tissue mass in the left breast, with necrosis or abscess in the center. Subcutaneous space disappears, the surface skin is thicker, and the border between the mass and chest wall is not clear.

mass was found to have a granular and firm appearance on the cut surface (**Figure 1B**).

Surgical biopsy confirmed that it is grade 3 invasive breast cancer, no special type, triple negative/basal-like subtype (ER-, PR-, HER2-, CK5&6+, EGFR+), but dermal lymphatic involvement was not observed. The dermal lymph vessels were dilated and filled with monocytes. Immunohistochemistry result showed AE1/AE3 negative in the lymph vessels. Geographic necrosis was observed (**Figure 3**). According to the clinical features, inflammatory breast cancer was therefore diagnosed. CT scan also showed that a huge mass was poorly-circumscribed and adherent to the skin and chest wall (**Figure 2D**). ECT bone scintigraphy showed no evidence of metastasis.

The patient underwent neoadjuvant chemotherapy with AT (Paclitaxel+Pirarubicin) for 3

cycles at first. Assessment was SD (better) at first cycle, and PD (progress) at third cycle, with TTP=2.5 months. The mass progressed rapidly, while dark mass was observed to protrude out of the skin with ulceration on the surface. Then the patient underwent neoadjuvant chemotherapy with NX (Vinorelbine+Capecitabine) for 1 cycle. Assessment was PD, with TTP=1 month (**Figure 4A-C**).

After neoadjuvant chemotherapy, the patient underwent mastectomy with dissection of the axillary lymph nodes. The tumor size became 12×9×6.5 cm, and did not invade the chest wall and skin. Microscopically, the tumor was similar to biopsy specimen in morphology and immunohistochemistry (ER-, PR-, HER2-, CK5&6+, EGFR+). The tumor showed mild response to chemotherapy. No metastasis was identified in the axillary lymph nodes (0/38).

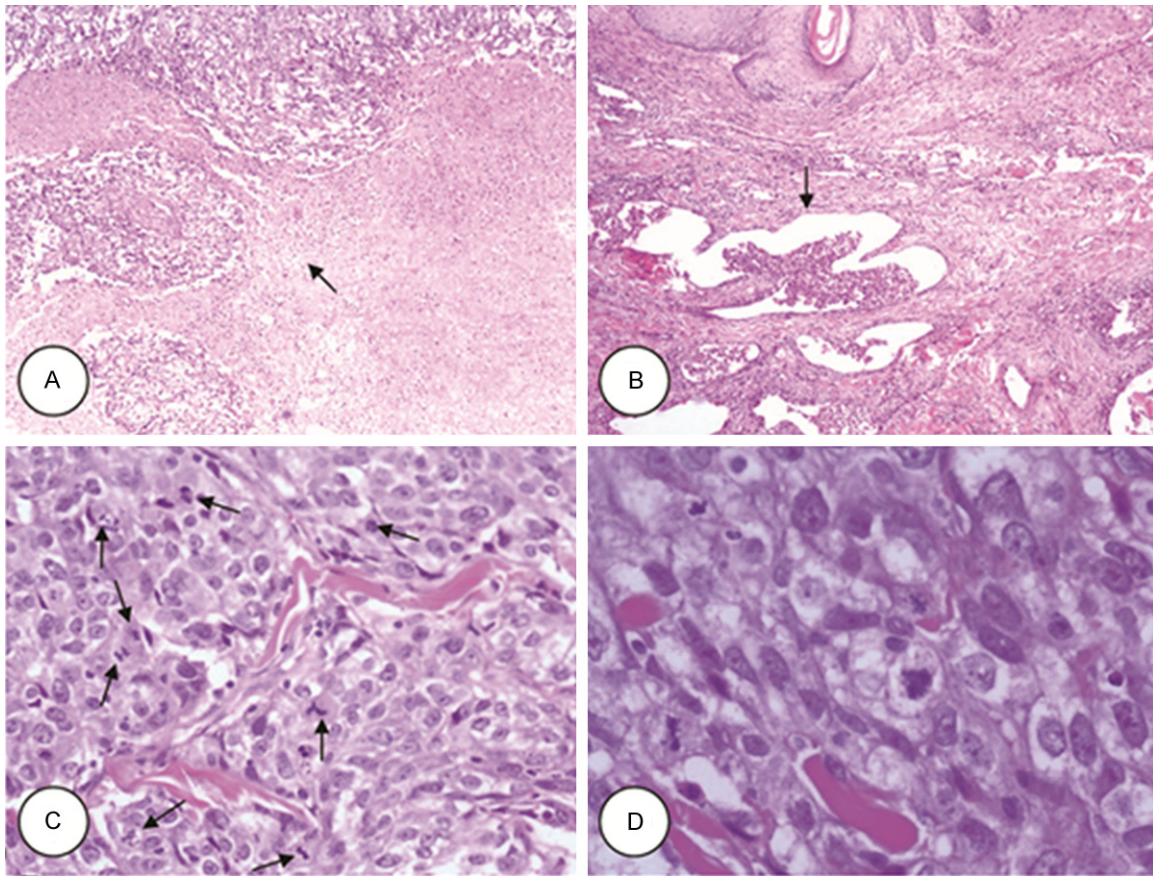


Figure 3. A. Geographic necrosis (arrow) in the central portion of the tumor ($\times 40$). B. The dermal lymph vessels (arrow) were dilated and filled with monocytes ($\times 40$). C. Invasive breast cancer, no special type, grade 3 with a lot of mitosis (arrows) ($\times 200$). D. High power field of the tumor ($\times 400$).

Finally, the patient received post-operative adjuvant chemotherapy with Gemcitabine+ Cisplatin for 6 cycles and no adjuvant radiation therapy was carried out. The wound healed well and no locoregional recurrence was observed (**Figure 4D**). The patient had lung metastasis at 8 months post-mastectomy. Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

Discussion

Inflammatory breast cancer is a rare and aggressive malignancy, so the etiology and risk factors are still insufficiently documented, especially in Asia. Inflammatory breast cancer patients were reported to have a significantly higher body mass index (BMI) than both the non-inflammatory breast cancer patients and the non-breast cancer patients. Le et al. reported that breast-feeding was associated with the

inflammatory breast cancer status in the multivariate analysis, and the general risk of breast cancer was shown to decrease as the duration of breastfeeding increased [10]. They presumed that a longer breast-feeding period led to mechanistic abnormalities in the breast tissue, such as dilatation of arterial and lymphatic breast vessels, which could increase the probability of inflammatory changes. An earlier return of menstruation in breast-feeding women allowed a more rapid subsequent pregnancy and relatively lower postnatal progesterone levels. Some hormonal factors were therefore involved in the occurrence of inflammatory breast cancer [10]. It has been reported that aggressive breast cancer occurs more likely than non-inflammatory breast cancer patients when women have their first child at a younger age [11]. The present patient had her first child at 23 years old, with lactation period of one and a half years.

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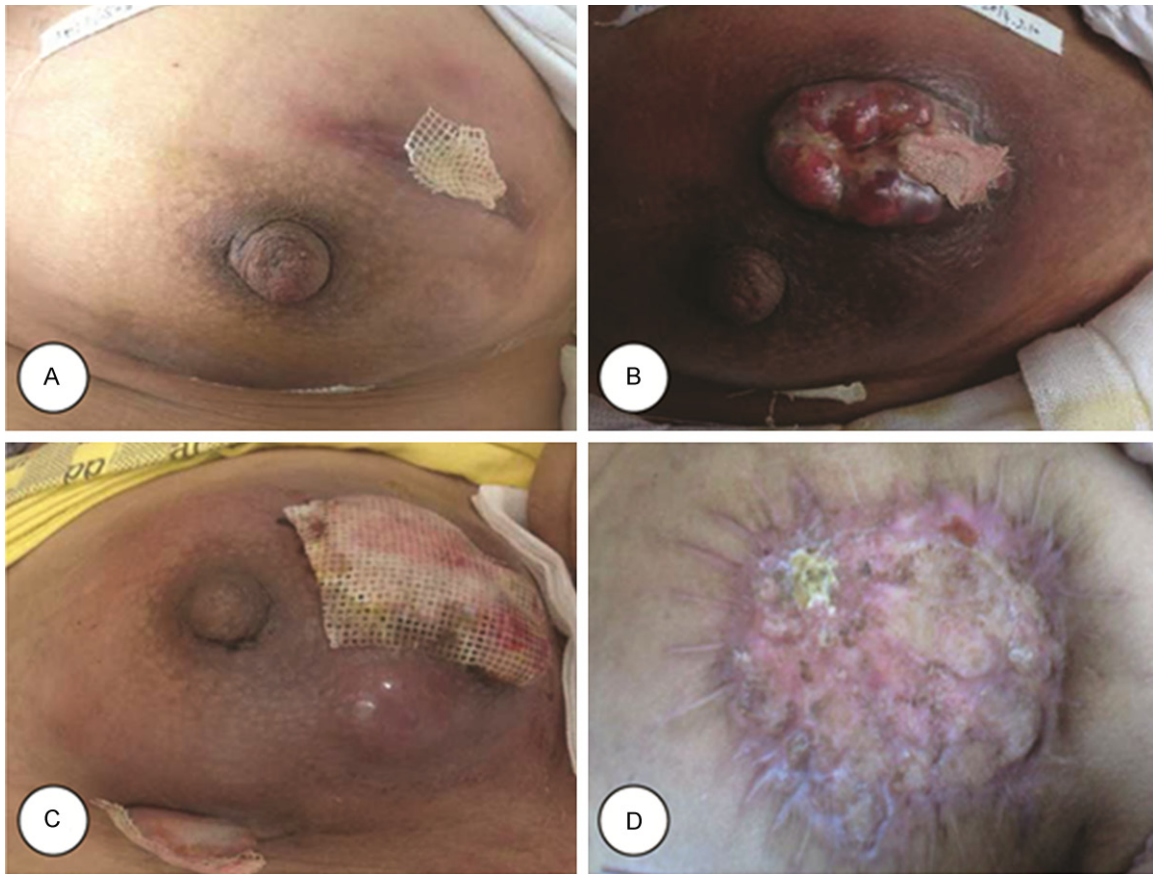


Figure 4. A. The mass was smaller and the skin turned nearly normal after 1 cycle of neoadjuvant chemotherapy with AT (Paclitaxel + Pirarubicin). B. But after 3 cycles, the mass progressed rapidly, with dark mass protruding out of the skin and ulceration on the surface. C. Then the patient underwent neoadjuvant chemotherapy with NX (Vinorelbine + Capecitabine) for 1 cycle. No significant effect. D. After post-operative adjuvant chemotherapy with Gemcitabine + Cisplatin for 6 cycles, the wound healed well and no locoregional recurrence was present.

Currently, there are no definitive molecular or pathological diagnostic criteria for inflammatory breast cancer, but current consensus is that clinical criteria are important for the diagnosis of inflammatory breast cancer. Signs and symptoms are required for a diagnosis of inflammatory breast cancer include erythema observed at least one third of the breast; other evidence included edema and/or peau d'orange of the breast, and/or a warm breast, and an underlying palpable mass. History of flattening, crusting, or retraction of the nipple may also be observed. Patients may have been diagnosed with mastitis and not responding to at least 1 week of antibiotics treatment. The onset of these signs and symptoms should be rapid; the duration of signs and symptoms at initial presentation should be less than 6 months. Inflammatory breast cancer is not an infectious process, so it generally does not cause fever

and leukocytosis [1, 12]. Importantly, although the diagnosis of inflammatory breast cancer or non-inflammatory breast cancer can be made based on clinical signs even without pathologic evidence of dermal lymphatic involvement, pathologic confirmation of breast cancer is required to distinguish inflammatory breast cancer from benign disease.

Inflammatory breast cancer is not considered to be a specific histological subtype of breast carcinoma, so it does not have special pathological diagnostic criteria. However, the combination of pertinent histopathological result in the breast and the overlying skin in conjunction with characteristic clinical findings can be used to suggest the diagnosis of inflammatory breast cancer. Patients with inflammatory breast cancer often have the ductal tumors with high histological grades with or without a distinct mass.

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Our present case was invasive cancer, no special type, grade 3, consistent with previous reports [12].

The most striking histopathologic finding in the patients of inflammatory breast cancer is the presence of lymphovascular tumor emboli in the papillary and reticular dermis overlying the breast. Although skin emboli are sometimes observed in the skin of patients with non-inflammatory breast cancer, emboli in patients with non-inflammatory breast cancer are usually less numerous and smaller than that in the patients with inflammatory breast cancer. There is no direct correlation between the presence, number, or size of emboli and the degree of skin redness in the patients of inflammatory breast cancer. Although pathological evidence of dermal lymphatic involvement is not considered as a definitive diagnostic criterion for inflammatory breast cancer, a skin punch biopsy is recommended in cases of suspected inflammatory breast cancer to aid to diagnosis. However, as previously noted, even with adequate sampling and pathological evaluation of the skin with punch biopsies, dermal lymphovascular involvement is observed in less than 75% of patients with inflammatory breast cancer. Currently, dermal lymphatic involvement is not required for the diagnosis of inflammatory breast cancer [1, 12, 13]. Woodward et al. developed an orthotopic human xenograft for MDA-inflammatory breast cancer [11]. Although it is presumed that the failure to identify tumor emboli in the dermal lymphatics is clinically simply a sampling error in the biopsy, this xenograft can manifest significant skin erythema as expected in inflammatory breast cancer. Only the evidence of rare tumor emboli suggested that other factors may mediate skin change in addition to congested lymphatic emboli [11]. So, our present case did not have dermal lymphatic involvement, but showed the typical clinical features of inflammatory breast cancer.

The diagnosis of breast cancer during pregnancy and lactation is difficult both clinically and radiologically because of the striking hormone-induced changes in breast tissue [6]. Differentiation of inflammatory breast cancer from acute mastitis, especially during lactation, may be difficult on initial diagnosis. Infection often occurs during breast-feeding from the nursing infant's nose and throat. The infection

is due to disruption of the epithelial interface of the nipple-areola complex with retrograde dissemination of the micro-organisms. Usually, the patient has a history of a cracked nipple or a skin abrasion. Milk stasis is an important risk factor, since stagnated milk is an excellent culture medium of micro-organisms. Antibiotic therapy given at an early stage usually controls the infection and stops abscess formation. In severe mastitis, skin and trabecular thickening from breast edema can be depicted. Abscesses can manifest as suspicious, ill-defined mass. In our present case, the necrosis on MR images was considered to be abscess. It was reported that nearly all the cases with associated pregnancy or lactation display necrosis histologically [8]. Inflammatory breast cancer should be suspected and rapidly excluded in patients whose condition does not improve by the use of antibiotic therapy. Fine-needle aspiration cytologic analysis or core biopsy is mandatory in this clinical setting.

Distinguishing some cases of locally advanced breast cancer from inflammatory breast cancer is problematic because of overlapping clinical and pathological findings. Direct extension of the invasive tumor to the overlying skin in some patients with locally advanced breast cancer can result in localized erythema, the same as the clinical presentation of inflammatory breast cancer. In such cases, however, the skin does not show extensive edema or as much dermal emboli as are usually observed in inflammatory breast cancer [13].

Patients with pregnancy-associated breast cancer tend to have larger, more advanced neoplasms at diagnosis and a poorer outcome than do other women of the same age with breast carcinoma. More than 50% of patients have high-grade tumors. High rates of inflammatory tumors have also been reported. In addition, more than 50% of patients have lymph node involvement. The high prevalence of hormone-receptor negative and HER2 positive tumors supports their aggressive biologic growth pattern. Prognosis is poor; it is a fact to partly explain by the tendency of pregnant patients to present at a more advanced stage than non-pregnant women. However, some studies have found that pregnancy itself may be an independent predictor of worse prognosis. Worse prognosis is likely the results from

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the combination of delayed diagnosis and a more aggressive growth pattern because of the biological effects of pregnancy. Recurrences are common and usually appear within 2-3 years of diagnosis [6].

The diagnosis of inflammatory breast cancer has a consensus guideline that recommends at minimum a core biopsy to enable detection of invasive carcinoma and to allow marker study (hormone receptors and HER2). The frequency of hormone receptor positivity is lower in inflammatory breast cancer than in non-inflammatory breast cancer; patients with estrogen receptor-negative inflammatory breast cancer have a poorer prognosis than patients with estrogen receptor-positive inflammatory breast cancer [12].

Several studies have reported a higher frequency of negative hormone receptors status in inflammatory breast cancers. Lack of expression of hormone receptors has been associated with a more aggressive clinical course. A higher incidence of HER2 overexpression has been reported among inflammatory breast cancer tumors, which is also associated with the poor outcome [1, 11]. In a retrospective analysis, 316 inflammatory breast cancer patients were assigned into four groups according to estrogen receptor and HER2 status: estrogen receptor positive (33%), estrogen receptor positive/HER2 positive (12%), HER2 positive (26%), and triple negative (29%). The triple-negative subtype was found to predict the worst overall survival and high recurrence rates [9]. Another study also reported that the triple-negative inflammatory breast cancer had the worst survival rate [14]. So, most pregnancy associated breast cancers are hormone-receptor negative [3]. Our present case was triple-negative subtype/basal cell subtype. The patient had no axillary lymph node metastasis at surgery and no locoregional recurrence, but she developed lung metastasis at 8 months post-surgery, suggesting aggressive behavior.

Today, the general consensus is that patients with inflammatory breast cancer without evidence of distant metastases at the time of diagnosis should receive systemic chemotherapy followed by surgery and radiation therapy. For patients with HER2-positive disease, treatment with trastuzumab (an antibody targeting HER-2) is recommended. For patients with hor-

none receptor-positive disease, hormonal therapy is administered.

It was recommended that patients with inflammatory breast cancer should receive a primary systemic regimen consisting of an anthracycline and taxane. A minimum of six cycles of preoperative treatment should be administered over a course of 4-6 months before proceeding to definitive surgery. However, this treatment may be modified in cases where disease progression is observed [1]. Our present patient initially responded to the first cycle of preoperative treatment, but then progressed rapidly.

The only method of definitive surgery is a modified radical mastectomy for the women with inflammatory breast cancer following preoperative systemic treatment [1, 12].

The level of pathological response to neoadjuvant chemotherapy is a very strong prognostic factor for survival rate [15, 16]. In the presence of residual cancer, hormone receptors and HER2 status should be repeated on the post-mastectomy specimen [1]. Our present case showed only mild response to chemotherapy.

When mastectomy is feasible after neoadjuvant chemotherapy, the standard approach for patients with inflammatory breast cancer is to deliver postmastectomy radiation therapy. Treatment fields are designed to target the chest wall and any dissected draining lymphatics, including the infraclavicular, supraclavicular, and internal mammary lymphatics [1, 12]. Our present case had not received post-mastectomy adjuvant radiation therapy and during follow-up developed lung metastasis without locoregional recurrence.

In conclusion, inflammatory breast cancer, especially during lactation, should be suspected and rapidly excluded for the patients if their condition does not improve with antibiotic therapy. Combination of neoadjuvant systemic chemotherapy, surgery, and radiation therapy has led to an improved prognosis. However, the overall 5-year survival rate for patients with inflammatory breast cancer is still very low, especially for patients of the triple negative subtype. The ongoing molecular studies of inflammatory breast cancer are becoming promising to identify molecular targets for treatment of this disease. Correspondingly, the

development of targeted inflammatory breast cancer therapy will be hastened and the overall survival for this aggressive disease could be increased [12].

Disclosure of conflict of interest

None.

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