CASE REPORT

Inflammatory breast cancer in a previously treated case of breast cancer: a diagnostic dilemma for the clinician

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SUMMARY

Inflammatory breast cancer (IBC) is a relatively rare and aggressive subtype, accounting for nearly 2.5% of all diagnosed breast cancers worldwide. It is usually characterised by an acute onset, rapid clinical progression, poor prognosis and micrometastasis at the time of presentation. Prompt recognition of clinical symptoms and identification of warning signs are vital in diagnosing and appropriately treating a patient with IBC.

BACKGROUND

In spite of improved understanding of the molecular biology, risk factors and management over the past few years, dilemmas still exist in diagnosing inflammatory breast cancers (IBCs).¹ A subgroup of IBC—secondary IBC—has been identified where pathologically identifiable IBC appears after surgical treatment of a primary non-IBC.² There is no clear understanding in order to identify potential ‘at-risk’ individuals developing secondary IBC.^{1 3} These are poorly understood and under diagnosed even to this day, due to a dearth of data mainly owing to its rarity.⁴

CASE PRESENTATION

A 60-year-old multiparous woman with no medical comorbidities, a tobacco chewer, hailing from a poor socioeconomic status, presented with a lump in the left breast, measuring around 4×4 cm, which was diagnosed as carcinoma of the left breast, stage cT2N1M0 (American Joint Committee on Cancer, AJCC 7th edition), in June 2014. She underwent left-sided modified radical mastectomy in the same month at a peripheral centre. Postoperative histopathology revealed a 4×3 cm tumour located beneath the nipple. Microscopically, a moderately differentiated infiltrative ductal carcinoma type (Modified Bloom Richardson Score—7) was noted in the studied specimen, with margins, skin, nipple and areola free of tumour cells. Ten lymph nodes were resected and all these nodes showed evidence of metastatic tumour deposits. The patient was staged as pT2N3aM0, group stage IIIC (American Joint Committee on Cancer, AJCC 7th edition). Immunohistochemistry performed on the resected tumour showed a negative oestrogen and progesterone receptor (ER/PR) status and a positive HER2/neu status with a score of 3. Three weeks after the surgery, the patient received adjuvant radiotherapy to the left chest wall, axilla and supraclavicular fossa to a dose of 50 Gy in 25 fractions, 5 fractions

per week, over 5 weeks. This was followed by five cycles of adjuvant chemotherapy with 5-fluorouracil, epirubicin and cyclophosphamide, administered every 3 weeks apart. Considering her negative ER/PR and HER2/neu enriched status, she was advised adjuvant anti-HER2/neu agent, trastuzumab, alone. However, owing to her financial condition, the patient was not keen on receiving the prescribed drug and was hence advised regular follow-up. Eight months after the completion of the entire treatment, she started to notice itching over the previously irradiated site. There was no associated fever and neither pain nor trauma was present at the area of concern. Unfortunately, the itching was ignored and medical attention was not sought for it initially, as it was not troublesome to the patient. However, over a period of 2 months, this progressed to involve the entire left chest wall, left axilla and anterior abdominal wall, crossing over to the right breast. She also started to develop ulceration of the left chest wall (figure 1). This worsening of symptoms at a rather alarming rate prompted her to seek medical help.

At presentation to our clinic, she was noted to have an ECOG (Eastern Cooperative Oncology Group) performance status of 2, along with anaemia. On local examination, she was found to have a 15×20 cm ulcerative lesion with everted margins occupying the entire left chest wall. This was associated with thickening of the skin over the medial half of the right breast as well. The surrounding erythema was seen to encroach onto the anterior abdominal wall, left axilla and left arm. A malodorous, serosanguinous discharge was noticed from the ulcerative lesion. On palpation, the lesion was acutely tender and associated with a marked

Figure 1 Clinical image showing extensive skin involvement with erythema in inflammatory breast cancer.

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rise in local temperature. Non-tender, matted right axillary lymph nodes measuring about 5×2 cm and hard in consistency were noted. Bilateral supraclavicular lymphadenopathy, measuring about 2×2 cm on either side, was also observed. Systemic examination was profoundly unremarkable. On completion of thorough clinical examination, relevant investigations were carried out to aid in the diagnosis and treatment.

INVESTIGATIONS

1. Routine blood investigations comprising of a complete blood count and renal and hepatic function tests were carried out. The complete blood count revealed grade 1 anaemia with no features of infection. Hepatic and renal function test was within normal limits.
2. Chest CT using intravenous contrast (figure 2) showed a plaque-like left chest wall thickening with associated thickening of the skin of the right breast. Also noted were soft tissue nodularity of the left pectoralis musculature, bulky right axillary, deep pectoral, internal mammary and bilateral lower cervical lymphadenopathy.
3. Ultrasound (US)-guided fine-needle aspiration cytology (FNAC) of the right axillary and left supraclavicular lymph nodes was performed, which showed evidence of malignancy with metastatic deposits.
4. US of the abdomen/pelvis reported evidence of neither hepatic nor lymph nodal metastases.
5. Bone scan performed using Technetium-99m had no definite scintigraphic evidence of skeletal metastases.

DIFFERENTIAL DIAGNOSIS

- ▶ On the basis of the aggressive clinical features with which the patient presented, differential diagnoses of recurrence of the primary breast carcinoma or carcinoma of the skin were considered.
- ▶ The possibility of occurrence of benign conditions such as chronic radiation dermatitis or cellulitis was also deliberated over.
- ▶ However, based on the rapid and aggressive progression of the characteristic symptoms in the postoperative irradiated chest wall and the opposite breast, along with axillary and supraclavicular lymphadenopathy and the presence of metastatic deposits, as evidenced by the cytological examination, a diagnosis of IBC was strongly contemplated.

TREATMENT

The patient was initially evaluated in a peripheral clinic, where a skin punch biopsy of the left chest wall lesion was performed.

Figure 2 CT scan of the thorax showing plaque-like left chest wall thickening and bulky right axillary lymphadenopathy.

This was reported to show epidermal hypertrophy, dermal vascular proliferation with very few inflammatory cells and no evidence of malignancy, suggestive of chronic radiation dermatitis. Hence the patient was started on steroids. However, in view of the progression of symptoms in spite of the medication, she decided to visit a tertiary care centre for an expert opinion, where she was evaluated with a thorough clinical examination, relevant blood investigations, imaging and cytology. On the basis of this information and the clinical features, a diagnosis of non-metastatic secondary inflammatory breast carcinoma was made and she was advised to start on second line chemotherapy agents consisting of single-agent paclitaxel, followed by lapatinib and capecitabine.

OUTCOME AND FOLLOW-UP

As the patient failed to report for her prescribed course of chemotherapy as scheduled, an enquiry was conducted. An ensuing telephone conversation with her relatives revealed that, owing to financial and logistical constraints, the patient continued receiving treatment from a hospital in the vicinity of her home.

DISCUSSION

The term IBC was first used by Lee and Tannenbaum⁵ in 1924, who described it thus: “the overlying skin is reddened and brawny and its blush may extend far beyond the limits of the mammary gland...the inflamed area presents a distinct raised periphery after the fashion of erysipelas and as the disease progresses, the skin becomes deep red or reddish-purple, and to the touch is brawny and infiltrated”.

In 1938, Taylor and Meltzer² identified two clinical varieties, primary IBC, where the inflammatory signs appear simultaneously with the carcinoma in a previously normal breast; and a secondary IBC, where the inflammatory manifestations appear suddenly in a previously invasive, non-IBC, or following mastectomy, either at the original site or in the opposite breast. However, an accurate case definition still remains controversial with various organisations and panels, setting forth their expert recommendations regarding the diagnostic criteria and management strategies.⁶

Though pathognomonic of IBC, dermal lymphatic invasion is not identified in all IBC tumours and is not mandatory for diagnosis. This is mainly considered to be due to sampling heterogeneity. Hence, being a clinicopathological entity, the diagnosis of IBC can be made based on clinical signs alone along with pathological confirmation of an invasive breast cancer.^{7–10}

In comparison to non-IBC tumours, IBCs tend to have a rather alarmingly aggressive clinical course, mainly affecting younger, obese women.^{11 12} Their natural history, pathology and response to treatment are also quite distinct, leading to speculation about differing molecular profiles between the two groups.¹³

Expression of aggressive biomarkers, such as high S phase, aneuploidy, negative ER and PR status and HER-2/neu amplification, has been noted more frequently in IBCs.¹⁴ This has paved the way for translational research being conducted in order to better understand the molecular characteristics of this entity, which could translate to better survival outcomes using appropriate therapies.⁴

In the case reported, the patient was an elderly woman with rapidly progressive secondary inflammatory carcinoma features occurring within a year of locoregional and systemic treatment for a non-inflammatory HER2/neu-enriched variant of invasive ductal carcinoma. However, when a patient presents with the

clinical picture mentioned, it often leads to a dilemma in establishing an accurate diagnosis as these are often misdiagnosed. A primary care physician's lack of exposure to IBCs clinically, mainly due to their rarity, often leads him/her to consider the differential diagnosis of cellulitis/mastitis, radiation dermatitis or a recurrent breast cancer. Approaching such cases with a high suspicion of IBC is of utmost importance as the diagnosis relies heavily on clinical features and could translate to timely management of this aggressive disease. Generally, positron emission tomographic-CT imaging is advised for diagnostic and metastatic workup along with histopathological confirmation in the form of biopsy or FNAC.¹⁵ The recommended treatment in this scenario would be to start the patient on chemotherapeutic agents such as taxanes, capecitabine and the targeted agent trastuzumab.^{1 16} Though it is the standard of care in HER2/neu-enriched cases, our patient could not receive the recommended trastuzumab owing to her financial constraints. Enrolment of such patients to clinical trials should be strongly considered.

Hashmi *et al* reported on four cases of secondary IBCs, postulating that the aetiology could be due to the phenomenon of accelerated tumour growth as a result of localised trauma and including surgery to treat the primary breast carcinoma. They hypothesise that angiogenesis in the postsurgical healing process could potentially stimulate the otherwise dormant micrometastases, leading to an aggressive malignancy.^{3 17} Also postulated is the phenomenon of possible hormonal pathogenesis, where it has been theorised that on surgically removing the primary tumour, there is a possibility of release of an inhibition of latent metastases.^{3 17 18} In spite of all these studies and theories, there are still no established indicators nor potential risk factors that could hint at the possibility or act as a predictor for a patient developing secondary IBC. The challenge remains in understanding and identifying such molecular markers or other factors, which could help in determining 'at risk' patients and what changes need to be undertaken in managing such cases.

Learning points

- ▶ Non-uniformity in diagnosing and managing inflammatory breast cancer (IBC) is a major hindrance to the development of further understanding and strategising management in these cases.
- ▶ IBC is one of the most virulent forms of breast cancer and has dismal survival outcomes.
- ▶ With several clinical features mimicking benign conditions, it is of utmost importance to carefully differentiate between the two in order to better manage such patients.
- ▶ Translational research could pave the way to profile the molecular type and aid in developing appropriate treatment strategies.

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