Metastatic Triple-Negative Breast Cancer; Unusual Presentation

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Abstract

Triple-negative breast cancer (TNBC) which does not over-express HER-2 (human epidermal growth factor receptor 2), estrogen receptor, or progesterone receptor creates the biggest challenge in the treatment of metastatic breast disease. Patients diagnosed with TNBC have shown an inferior prognosis with the increased likelihood of distant recurrence including brain metastases within five years of diagnosis. We present an interesting case of a 37-year-old female diagnosed with invasive high-grade triple-negative breast cancer, who presented with right breast mass and multiple cervical and axillary LNs. Restaging work up document no visceral metastasis. She was treated was multiple lines of chemotherapy with complete response (CR), but unfortunately with rapid relapse after each one. The unusual is that all relapses were in cervical area only without any visceral involvement or local recurrences which resembles lymphomas or head and neck tumors.

Introduction

Breast Cancer (BC) is by far the most frequent Cancer of women worldwide. The American Cancer Society estimates that 234,580 Americans will be diagnosed with breast cancer and 40,030 will die of the disease in the United States in 2013[1]. BC is second only to lung cancer as a cause of cancer death and its incidence has increased steadily over the past few decades but the mortality appears to be declining, suggesting a benefit from early detection and more effective treatment [2, 3]. Among Saudi patients, there is a significant increase in the incidence of breast cancer, which occurs at an earlier age than in western countries [4].

Due to advances both in early detection and in adjuvant treatment, mortality rates from breast cancer have been decreasing steadily in most countries since the early 1990s. However, it is still the leading cause of cancer mortality in women. Approximately 4–6% of breast cancers are metastatic at diagnosis; of those approximately one-fifth will survive 5 years. Depending on prognostic factors, in the worst-case scenario, up to 30% of node-negative and up to 70% of node-positive breast cancers will relapse. The prevalence of metastatic disease is high because many women live with the disease for several years [5]. Triple negative breast cancers (TNBC), defined by the lack of estrogen receptor (ER), progesterone receptor (PR) and epidermal growth factor receptor 2 (Her2/ cerbB2/ EGFR2) expression, account for 10 to 20% of all breast carcinomas in Asian and Western populations ,but occur at much higher frequencies in individuals of African descent. These tumors are usually of higher histological grade (Grade 3) and are associated with distinctive metastatic patterns, shorter time to recurrence and earlier mortality [6].

TNBC is highly proliferative and sensitive to systemic chemo-therapies. However, despite its relative sensitivity to chemotherapy, patients outcome are poor compared with other subtypes of breast cancer (HER2+ or ER+). The cause of death of patients with TNBC is often recurrence (30–40% of TNBC cases), which presents as distant metastasis.

Case report

37 years old female patient started to complain about one year ago from right axillary painless mass that appeared gradually and increased in size progressively, but she ignored to seek medical advice, nine months later there were two new masses; one in right breast and the other in right cervical region, at that time she attended to her local hospital where biopsy was taken and revealed invasive duct carcinoma grade III, triple negative with high ki 67. Biopsy from right cervical mass showed metastasis from breast origin, but unfortunately she lost follow up. 6 weeks later the patient had extreme edema of the right upper limb, enlarged right breast with diffuse swelling of right upper limb. At that time, the patient was transferred to our center (King Abdullah Medical City) for further work up.

On examination the patient had performance status 1 according to ECOG, the whole right breast was edematous, tender, enlarged, hot with upper outer quadrant mass 3 x 5 cm with nipple retraction and peau d' orange. Hard fixed right axillary mass about 2 x 3 cm, right hard fixed cervical mass 5x4cm with extreme edema of the right upper limb, multiple scattered left cervical lymph nodes the largest 2x2cm . The contra lateral left axillary lymph node (LN) 1x2 cm, with no other finding. She was a premenopausal with gynecological histories of 3 pregnancies; the first when she was 18 years old, and no history of

abortion was noted. She had positive family history of cancer as her mother had lymphoma. She denied the use of an oral contraceptive pills.

Slide review showed the same pathology and the same phenotype (figure 1a, b, c , d).Staging work up was done in form MRI of breasts, CT chest, abdomen, pelvis; brain and bone scan with no evidence of visceral metastatic. Doppler U/S of right upper limb revealed DVT of subclavian, axillary and proximal brachial vein. Laboratory investigations were in normal ranges, with CA15.3 = 25 u/ml. The patient was diagnosed as stage IV (T4a N2 M1); and started chemotherapy in the form of paclitaxel /carboplatin (paclitaxel 175 mg/m ^{2} / carboplatin AUC=5) with therapeutic dose of enoxaparin. At the time of the second cycle; the right breast showed decrease in size with no palpable LN in the right axilla, multiple right cervical LNs the largest was 1 cm in size, the right upper limb swelling improved with no hotness or tenderness, normal left breast and left axillary hard mobile LN 1x1.5 cm. CBC showed neutropenia with TLC 3.6, ANC 0.8, where second cycle of chemotherapy was postponed. After one week CBC recovered and the second cycle was given and continued for total four cycles with G-CSF support. Re-evaluation by C T chest & Doppler U/S after the fourth cycle of chemotherapy showed only skin thickening, edema of the right breast with disappearance of the previously reported right outer aspect breast mass ,with regression of the right axillary LN 1.5X1 cm (previously 3.4x2cm), regression of the bilateral cervical LN largest was 1.3x0.8cm, with patent right jugular, subclacvian, axillary and brachial veins. Then the patient completed 8 cycles of chemotherapy and started follow up. Two months post the eighth cycle, the patient presented to ER with fever and right submandibular hard fixed swelling (4.76x2.05cm), FNA was taken that revealed metastatic cancer most likely of breast origin, CT head, neck, chest, abdomen and pelvis was done revealed multiple enlarged right submandibular LNs (figure 3) with features suggestive of infection with no other findings suggestive of metastasis. True-cut biopsy was taken from the mass revealed metastatic adenocarcinoma of breast origin with negative ER, PR, HER-2/neu, CT brain was done with no evidence of metastasis (figure 2a.2b).

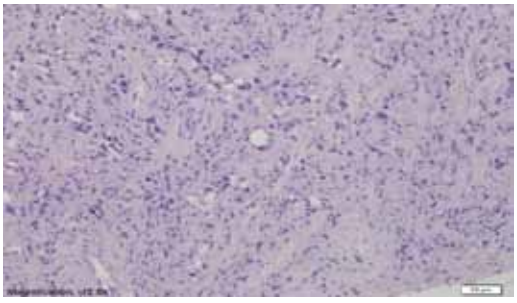

Fig 1a: IDC GIII right breast, core biopsy.

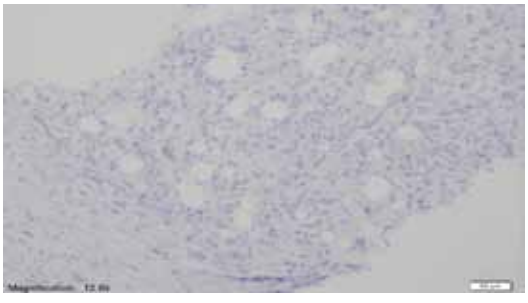

Fig 1b: Negative PR right breast biopsy.

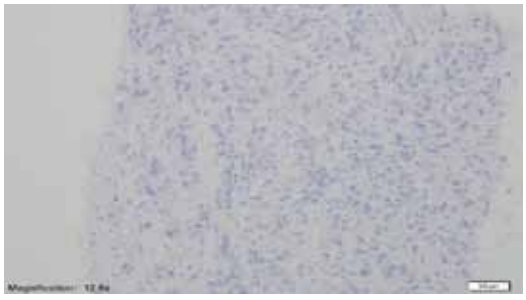

Fig 1c: Negative ER right breast, HP, core biopsy.

Fig 1d: Negative Her-2 right breast, core biopsy.

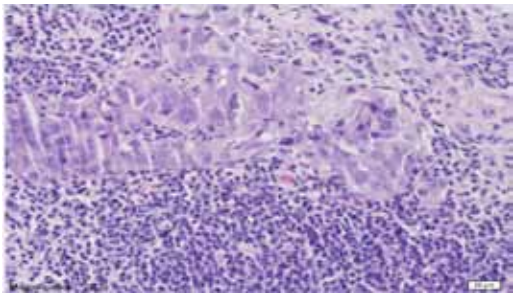

Fig 2a: Microscopic picture of cervical lymph node metastasis high power

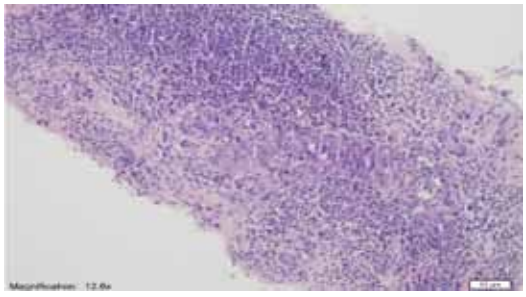

Fig 2b: Microscopic picture of cervical lymph node metastasis low power.

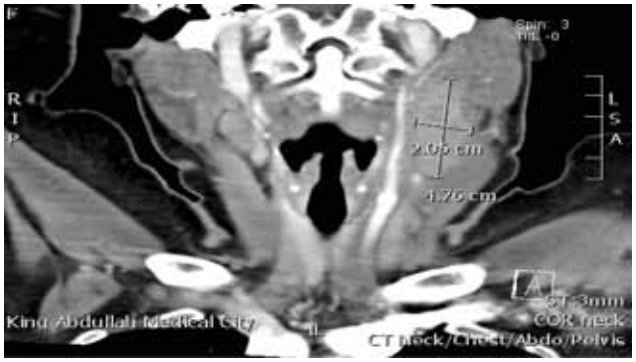

Fig 3: CT Neck (relapse post 8 cycles of paclitaxel/carboplatin)

Second line chemotherapy AC (Adriamycin 60 mg/m^2– cyclophosphamide 600mg/m^2) was started, patient received two cycles with delay between them caused by neutropenia, at the time of the third cycle clinical examination revealed regression of the right submandibular mass to 1x1cm, and this mass disappeared after the third cycle. Patient received the fourth cycle with 25% reduction because of the neutropenia post chemotherapy. Re-evaluation (Figure 4) was done with CT neck, chest, abdomen, pelvis and bilateral mammography showed only thickening of the right breast skin.

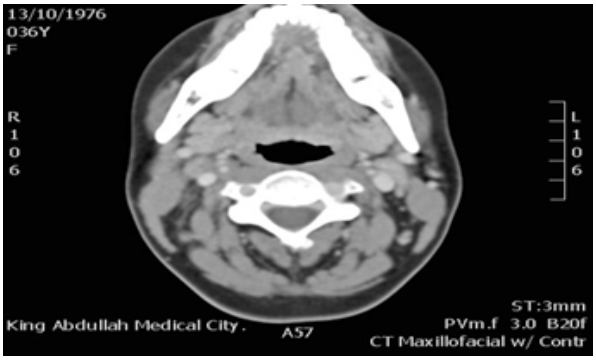

Fig 4: Complete response after Adriamycin /cyclophosphamide

Then due to bone marrow exhausion from repeated chemotherapy and poor tolerance even with G-CSF support, we shifted to capecitabin, which is FDA-approved for such condition and recommended for TNBC [7]. Capecitabine was started and continued for 6 cycles, re-evaluation was done by CT neck, chest, abdomen &pelvis showed progressive enlargement of cervical LNs bilaterally with largest 2.8x2.2cm in left upper deep cervical LN. Figure 5

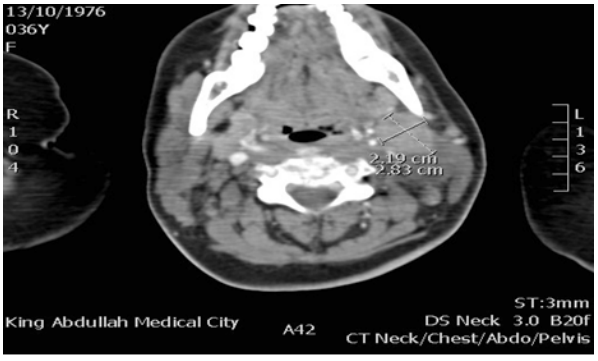

Fig 5: Disease progression after Capecitabine

Chemotherapy was changed to weekly paclitaxel 80 mg/m 2 as a fourth line, patient received 6 weeks of weekly paclitaxel. Re-evaluation with CT neck, chest, abdomen &pelvis there was significant reduction in the size of the previously noted bilateral deep cervical lymph nodes, largest on left side measures 1.19 x 0.84 cm with no evidence of other metastasis. Figure 6

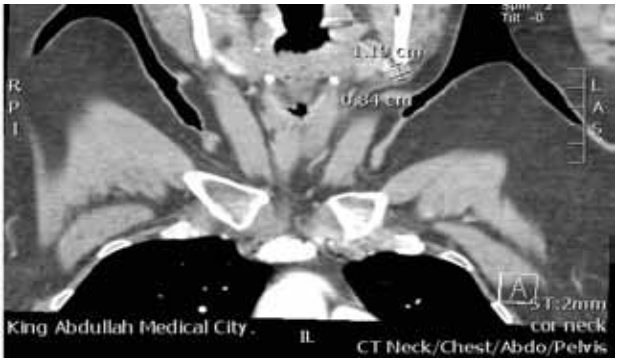

Fig 6: CT Neck (response post 6 cycles of paclitaxel)

Discussion

TNBC is defined by the absence of ER, PR, and HER-2 Over expression. It accounts for 15–20% of all breast cancer cases [8, 9], and occurs at a higher frequency in young premenopausal women with African Ancestry (AA) [10]. High body mass index (BMI) and high parity, instead of low parity in other types of breast cancer, have been associated with increased risk for TNBC [11–13]. TNBC is associated with an overall poor prognosis as exemplified by a higher rate of early recurrence and distant metastasis to brain and lungs compared to other breast cancer subtypes [14, 15].The unfavorable clinical outcome is partly explained by its aggressive pathologic features including a higher histology grade and mitotic index [16].

Chemotherapy is the only systemic therapy currently available for TNBC and is curative in a subset of patients with chemotherapy-sensitive disease. A higher rate of pathologic complete response (pCR) to standard chemotherapy has been observed in patients with TNBC compared to ER+ disease. A pCR rate of 22% in TNBC versus 11% in ER+ disease was reported in a study of over 1 000 patients treated with neoadjuvant anthracycline and taxane based chemotherapy regimens [17]. The excellent outcome associated with the pCR, however, is in contrast to the high risk of recurrence and cancer-related deaths in those with residue disease. Although alternative agents such as platinum compounds have demonstrated promising activity, up to 70– 80% of patients have residual cancer following neoadjuvant cisplatin [18]. In the metastatic setting, TNBC is typically associated with an initially higher response rate, but in a shorter time to progression following treatment with existing chemotherapy agents, resulting a shorter overall survival compared to ER+ breast cancer in multiple studies [19].The underlying molecular mechanism for this paradox is yet to be elucidated, although one could hypothesize that the inherent genomic instability of TNBC renders the possibility of a faster adaptation to the cytotoxic effect of chemotherapy.

Our patient was diagnosed as stage IV and started on chemotherapy; paclitaxel /carboplatin, she received 8 cycles with good response after 4 cycles and complete response after 8 cycles with recanalization of all thrombotic veins but unfortunately after two months, she relapsed by submandibualr lymph nodes which proved to be metastatic from breast origin with the same pathology and the same phenotype. We started AC protocol with complete response after 4 cycles but due to exhaustion of bone marrow and neutropenic fever after third cycle, the fourth cycle was with 25 % reduction and then she was shifted to capcitabine but after 6 cycles there was disease progression, at this time she was shifted to weekly paclitaxel with CR after 6 weeks.

As usual Triple-negative breast cancer is highly proliferative and sensitive to systemic chemo-therapies. However, despite its relative sensitivity to chemotherapy, patient outcomes are poor. This means that chemosensitivity of TNBC does not reflect whether the cancer will metastasize. Therefore, the mechanism of metastasis needs to be studied separately from that of tumorigenicity. But the unusual in this case is the presentation and in the multiple relapse in non visceral organs; all in cervical and submandibular lymph nodes.

The treatment options for chemotherapy-resistant TNBC are limited. The established targeted therapies, including endocrine treatment and HER2-targeted agents, are ineffective. Although several small molecule inhibitors and monoclonal antibodies against important cellular pathways have been tested in clinical trials, none has entered clinical practice due to limited efficacy. A better understanding of the underlying biology of TNBC is therefore needed to identify new therapeutic targets and to pinpoint which TNBC patients may benefit from them. Recent advances in microarray and DNA sequencing technologies have made it possible to analyze the tumor at the genomic level for therapeutic target discovery. These studies indicate that TNBC is a molecularly heterogeneous group of diseases with highly complex genomic aberrations. A further classification at the molecular level may be possible to facilitate drug development. In the seminal paper by Sørlie et al. breast cancer was subdivided into five intrinsic molecular subtypes, including luminal A, luminal B, HER-2 enriched, normal like, and basal like, based on hierarchical clustering analysis of approximately 500 genes (termed the intrinsic gene set because expression was not modulated by treatment) on a cDNA microarray study of 65 breast tumors obtained from 42 different individuals, Which will be reflected on future clinical trials [15]. The search for new therapeutic targets is complicated by the tremendous complexity of this disease, as demonstrated by the recent report of the first completed genome of a basal-like breast cancer. At the level of gene expression, the TNBC group also is actually comprised of distinct subtypes with very different biological signatures. All these subtypes would benefit from comprehensive analysis at the genomic, epigenomic, and proteomic levels and the results of the cancer genome atlas project are awaited with great interest. So, potential targeted therapy can be applied to TNBC depending on the subtype. However, most of the current trials are conducted in otherwise unselected patients and not directed by predictive biomarkers or mechanistic hypotheses. If this relatively large number of trials does not produce a breakthrough, we must rethink our investigational approach for this highly heterogeneous group of breast cancers.

Conclusion

TNBC is a heterogeneous disease with different types depends on molecular classification, so molecular diagnostic methods appear to be more important for selection of potential prospective patients with triple negative breast cancers who may benefit from many target therapy. Chemotherapy-resistant triple negative breast cancer remains a major cause of mortality and currently lacks any proven targeted therapy.

The development of "genome-first approaches" where patients are stratified upfront and prospectively placed into clinical trials designed to address the therapeutic hypotheses generated by analysis of individual tumor profiles is surely the most logical approach to consider.

Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest: The authors certify that is no potential or actual conflict of interest related to this article.

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