Journal of Case Reports in Medicine

Case Report ISSN:2090-5351

A Case of Hormone Receptor Positive Chest Wall Metastatic Breast Cancer Effectively Treated with Anti-Angiogenesis Combined with Endocrine Therapy

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Abstract

Objective: To verify the efficacy and safety of anti-angiogenesis therapy combined with endocrine therapy (ET) in a case of young hormone receptor (HR) positive advanced breast cancer (ABC) involving chest wall metastasis (CWM).

Method: We described a recent case of HR positive ABC receiving anti-angiogenesis therapy combined with ET and reviewed relevant literature regarding the efficacy and safety.

Results: Complete resolution of the CWM was perceived over the course of two months after initiation of treatment, with grade 2 proteinuria and grade 2 intracranial hemorrhage that was resolved with symptomatic and supportive treatment.

Conclusion: Anti-angiogenesis therapy combined with ET was highly effective for the breast cancer patient with CWM. However, adverse events deemed inevitable and vigilant monitoring from the beginning of treatment proved beneficial.

Case Presentation and History

In July 2020, a 43-year old Chinese female presented with a huge mass on her chest wall. She reported she first noticed it raised as a tiny spot seven years ago, which she neglected until it grew bulky and compounded with profound ulceration (**Figure 1A**). Core biopsy was performed on bilateral palpable axillary nodules. Pathology consistently revealed an invasive ductal carcinoma, grade II by the Bloom-Richardson system. The immunohistochemical staining was positive for markers E-cad, P120 and GATA3, but negative for markers p63, CK5/6 and calponin, while testing for estrogen receptor (ER) was positive (>80%), progesterone receptor (PR) was positive (>80%), human epithelial growth factor receptor-2 (HER2) was negative (score 1+), with a low proliferative index Ki-67 10%, corroborating with breast carcinoma. Physical exam revealed firm nodules in the bilateral supraclavicular regions, as well as a smooth semi-spherical mass on her right chest, for which biopsy was performed and pathology showed hyalinized collagen fibers, with no evidence of malignancy. Cross-sectional imaging of the chest by computed tomography (CT) showed asymmetric soft-tissue density measuring 10.9cm x 5.4cm with spiculated margins and heterogeneous enhancement at the left anterior

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Keywords: anti-angiogenesis therapy; advanced breast cancer; chest wall metastasis

Received: 02 June 2021; **Accepted:** 08 June 2021; **Published:** 10 June 2021

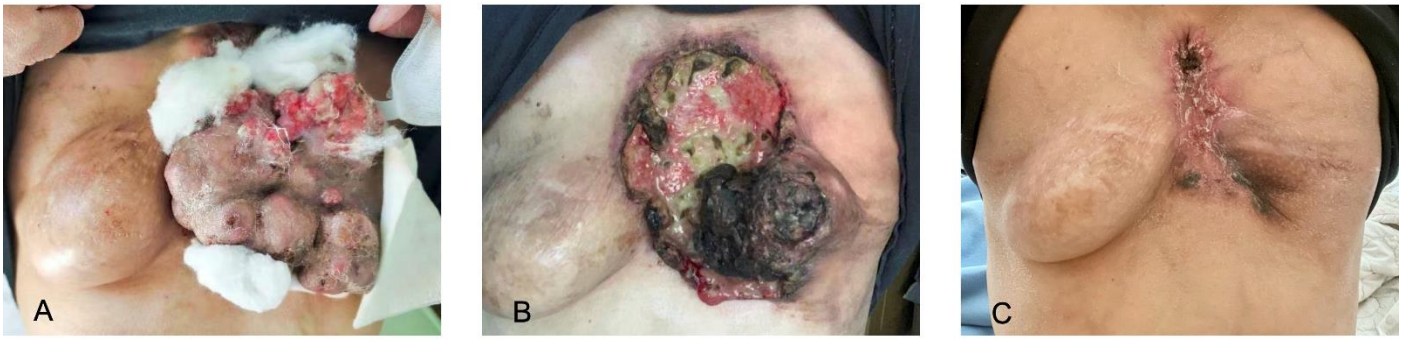

Figure 1: (A) Cauliflower-like purplish-red lesion 20 cm x 20 cm x 6 cm on the left chest wall with profound ulceration. (B) Chest wall lesion subsided six weeks after the initiation of treatment. (C) Complete resolution of the chest wall lesion.

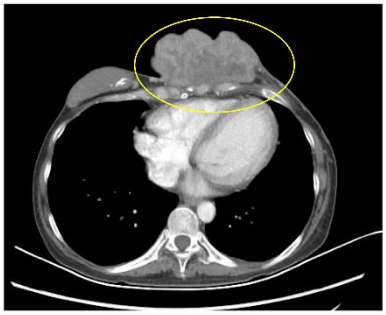

Figure 2: Soft-tissue density 10.9 cm x 5.4 cm with spiculated margin and heterogeneous enhancement at the left anterior chest wall.

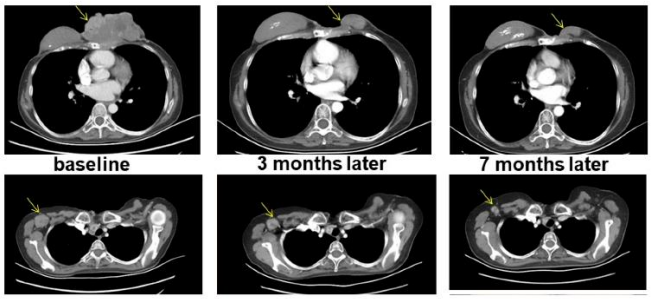

Figure 3: The chest wall lesion successively subsided, and the axillary nodules diminished (highlighted in yellow arrows).

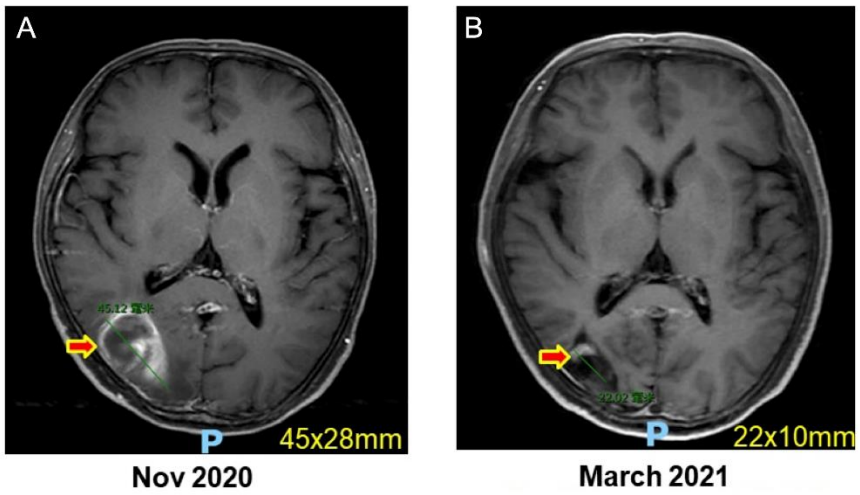

Figure 4: (A) Brain MRI showed right parietal-occipital hemorrhage suspicious from metastasis (Nov 2020). (B) The lesion remarkably subsided with very faint enhancement (March 2021).

chest wall (**Figure 2**); there were osteolytic lesions at the sternum; well circumscribed, rounded opaque lesions measuring up to 1.5cm x 1.2cm were noted in the periphery of the bilateral lungs; multiple lymphadenopathies were noted in the bilateral axillary regions, with the most prominent one measuring 3.1cm x 1.8cm. Baseline evaluation was conducted, with negative findings for abdominal and pelvic ultrasound. Bone scan showed a single lesion in the sternum. Her clinical staging was cTxN3M1, stage IV.

Past medical history was significant for intraductal breast masses status post bilateral mastectomy in 1993 (aged 16), for which the pathology was unknown. She received neither chemotherapy nor radiotherapy following the surgical

procedure, except intermittent intake of traditional Chinese medicine. There was no history of cigarette smoking, alcohol consumption, hypertension, or diabetes mellitus. She was single, premenopausal and nulliparous. Family history was negative for breast or ovarian malignancies.

Treatment and Response

She was noted to have an Eastern Cooperative Oncology Group performance status of 0. She all along expressed her preference to defer any chemotherapy. She received first line apatinib 500mg oral daily, toremifene 60mg oral daily, goserelin 3.6mg subcutaneous every 28 days, denosumab 120mg subcutaneous every 28 days, along with vitamin D 400 IU supplement and calcium carbonate 600mg. Six weeks after the initiation of treatment, her chest wall lesion subsided (**Figure 1B**), but a urine analysis showed protein 3+. Therapy was withheld and urine analysis was repeated before the immediate next cycle where proteinuria remained unchanged so apatinib was discontinued, replaced by a once-daily oral dose of 12 mg anlotinib on days 1-14 of a 21-day cycle. Two weeks after the initiation of anlotinib, she developed dizziness with loss of consciousness. She was taken to a local hospital, where brain CT indicated right parietal-occipital hematoma with intraventricular hemorrhage. Anlotinib was suspended. She received hemostatic therapy for ten days until her condition was stabilized. Meanwhile, tumor response was assessed using Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 and revealed partial response (PR) – her chest wall lesion and axillary nodules had significantly diminished, while her lung solid nodules remained static. Brain magnetic resonance imaging (MRI) showed hemorrhage suspicious from metastasis (**Figure 4A**), unfortunately there was no baseline for comparison. In view of her intolerance to both vascular endothelial growth factor (VEGF) inhibitors, her endocrine therapy was adjusted to palbociclib 125mg oral d1-21 every 28-day cycle, plus letrozole 2.5mg oral daily, along with ovarian function suppression (OFS) with goserelin. Most recent tumor response assessment was consistent with PR – her chest wall lesion further subsided, and her axillary nodules diminished (**Figure 3**), with complete clinical resolution of her chest wall lesion (**Figure 1C**). Brain MRI showed the previous right parietal-occipital lesion to have remarkably subsided with very faint enhancement (**Figure 4B**). Meanwhile, both tissue-based and liquid-based next generation sequencing was performed. There was no pathogenic variant of BRCA 1, BRCA 2, or PIK3CA. This patient was still receiving treatment at the time of writing this report.

Discussion

This patient was characterized with a young age at disease onset, being premenopausal, with stage IV breast cancer ab initio, luminal A subtype, with a cauliflower-like huge chest wall metastasis (CWM) with profound ulceration. There was no visceral crisis. She had an excellent response to anti-angiogenesis therapy combined with endocrine therapy (ET), with complete resolution of the chest wall mass. The question was, why anti-angiogenesis therapy? Could she tolerate the side effects of the therapy? One of the hallmarks of cancer is the evolution of a tumor microenvironment whereby the tumor constantly interacts with the surrounding blood vessels, immune cells, fibroblasts, signaling molecules and extracellular matrix. A thorough understanding of these cellular interactions may unveil novel targeted anti-tumor therapies [1]. VEGF signaling promotes vasculogenesis and angiogenesis and is critical to tumor-induced new vasculature formation, which is essential for tumor growth and metastasis [2]. Anti-angiogenic therapy has been a vital strategy for cancer therapy. Apatinib is a small-molecule tyrosine kinase inhibitor (TKI) that potently and selectively inhibits the activity of VEGF receptor 2 (VEGFR2) in vitro, it also inhibits the activities of VEGFR1, Kit, c-SRC, and RET tyrosine kinases and blocks downstream signaling inhibiting tumor angiogenesis [3]. This drug was approved by the Chinese Food and Drug Administration (CFDA) for the treatment of advanced gastric cancer in 2014 [4]. As breast cancer with a CWM has rich vascular distribution, whether apatinib is also effective for breast cancer with a CWM remains unknown previously. Literature review has been conducted. According to a recent multicenter phase II clinical study conducted by Li et al., in patients with HER2 negative advanced breast cancer (ABC) with CWM, anti-angiogenesis therapy with the TKI apatinib showed satisfactory efficacy and manageable adverse effects [5]. Adverse effects as recorded in Li's study included hypertension in up to half of the patient population, of which grade 3 accounted for 6.7%; 33% of patients had proteinuria, of which grade 3 amounted to 20% [5]. Another multicenter phase II clinical study conducted by Hu et al. showed that the VEGFR inhibitor

apatinib exhibited objective efficacy in patients with pretreated metastatic non-triple-negative breast cancer with manageable toxicity, with the most common grade 3/4 treatment-related adverse effects including hypertension (20.5%), hand-foot syndrome (10.3%), and proteinuria (5.1%) [6]. A randomized phase II study by Curigliano et al. also reported therapeutic effect of antiangiogenic therapy in advanced breast cancer with chest wall metastasis [7]. Patient education is important, paying attention to the possible side effects from the beginning of the treatment. Similarly, anlotinib is a small-molecule TKI that binds to VEGFR1, VEGFR2, VEGFR3, Kit, platelet-derived growth factor receptor (PDGFR)-α, and multiple fibroblast growth factor receptors (FGFR1, FGFR2, and FGFR3), with high selectivity inhibiting tumor angiogenesis [8]. This drug was approved by the CFDA for the treatment of advanced non-small cell lung cancer in 2018 [9]. The patient in our present study got started with apatinib, with PR reached as soon as after two cycles, but she developed proteinuria, so apatinib was switched to anlotinib, unfortunately she had intracranial hemorrhage, and VEGF inhibitor was suspended. According to NCCN, for premenopausal lady with hormone receptor positive (HR+) HER2 negative ABC, ovarian ablation or suppression plus ET plus a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor would be recommended with Level 1 evidence [10]. Indeed, CDK4/6 inhibitor combined with ET has shown substantial benefit for first line as well as for second line treatment, both with significantly improved PFS [11, 12]. This patient in our present study was no longer a good candidate for anti-angiogenesis therapy, despite the fact that she responded to the treatment really well. She had not been exposed to any CDK4/6 inhibitors. So it was reasonable to start her on a CDK4/6 inhibitor on top of ET [11, 12]. Second line treatment response assessment revealed PR. As for her brain lesion, an updated brain MRI was conducted, with right occipital lesion remarkably subsided, with very weak enhancement. Whether or not it was a true metastatic lesion from the beginning, it would be difficult to verify. Clinical and serial radiographic follow up would be warranted. In summary, we have learnt from this patient: (i) For HR+ breast cancer, anti-angiogenesis therapy combined with ET is a clinically worthwhile treatment option especially for patients who opted to defer chemotherapy. (ii) Giant chest wall metastatic lesions exhibited no significant hemorrhagic risk. (iii) Suspension of anti-angiogenesis therapy was not followed by any rebounce of disease progression. This patient was still receiving treatment at the time of writing this report. She has resumed her social functions, with a satisfying quality of life.

Conflict of Interest: The authors have no competing interests to declare.

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