Clinical and Medical Case Reports

Tran et al., Clin Med Case Rep 2019, 3:1

Case Report Open Access

Treatment of Aggressive Metastatic Breast Cancers with Signet-Ring Cell Features

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Received Date: 23 March, 2018; **Accepted Date:** 13 February, 2019; **Published Date:** 20 February, 2019

Abstract

Signet-ring carcinoma of the breast (SRCC) is a rare form of breast cancer with high rates of axillary and distant metastases. Most prior case reports focused on the clinicopathologic features rather than management of SRCC.

Case Report: Hereby, we report a 39-year-old women who had distant recurrent of estrogen receptor positive, progesterone receptor negative and Her-2 positive signet-ring carcinoma of the breast to the lungs, liver, bones and brain. Since no standard guidelines existed, we directed her treatments according to hormonal and Her-2 receptor status and optimized supportive care. She had resolution of pulmonary lymphangitis and diffuse liver metastases on computerized tomography scan and lived for 4 years after recurrence.

Conclusion: Despite its aggressive biology, our case suggests that signet-ring carcinoma of the breast should be treated similarly to other invasive breast cancers based on hormonal and Her-2 receptor status.

Keywords Breast cancer; Chemotherapy; Invasive lobular carcinoma; Signet-ring carcinoma; Trastuzumab

Introduction

Signet-ring carcinoma can arise from the stomach, colon, lung, ovaries, prostate and breast [1]. Signet-ring carcinoma of the breast (SRCC) was first identified by Steinbrecher et al as a variant of infiltrating lobular carcinoma but was later classified by World Health Organization as a distinct clinicopathologic entity under 'mucinous carcinomas and other tumors with abundant mucin' in 2003 [2,3]. The prevalence of SRCC features varies between 2 to 4.5% of breast cancers [4]. Among 24 cases with breast SRCC, 12 cases were associated with ductal carcinoma, 9 with lobular carcinoma, 1 with colloid carcinoma, and 4 were pure signet-ring cell carcinoma [4]. Breast SRCC exhibits aggressive clinical behavior with high rates of axillary lymph node and distant metastases and a higher mortality rate when compared with other forms of breast cancer [4,5]. Breasts SRCC tumors are more aggressive than mucinous carcinoma, invasive ductal carcinoma of no special type and invasive lobular carcinoma with higher risk of metastasis [6]. The prognosis of SRCC is poor with a reported 5 year overall survival of 45-60% [7].

Most case reports in literature mainly focus on the histopathological aspect of SRCC rather than therapeutic management. Hereby, we report a 39-year-old women who had distant recurrence of her breast SRCC to the lung, liver, central nervous system (CNS) and bone.

Case Report

A 39-year-old Caucasian women with no personal or family history of cancer who was first diagnosed with stage T2N1M0 right invasive lobular breast cancer (ILC) with signet ring features in 2009. Immunohistochemical (IHC) stains of the right breast biopsy were significant for ER+ (83% on IHC stain), PR - and Her-2 + (3 + by IHC). Her-2 FISH was strongly positive with 9.3.

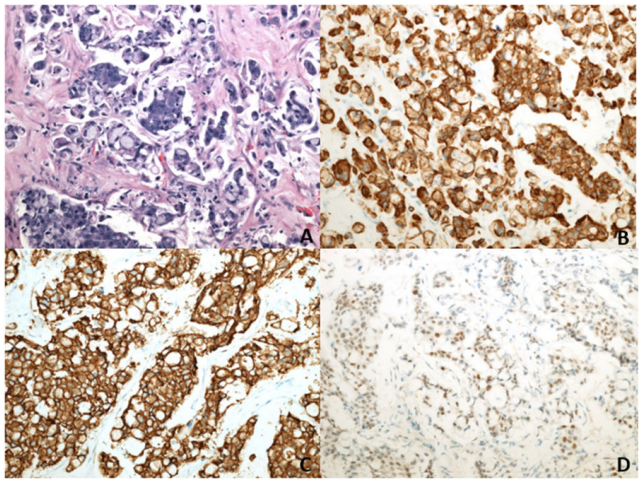

Figure 1: Histological findings of resected brain tumor. The tumor demonstrated invasive lobular carcinoma with SRCs. (A) H&E stain, magnification X 20. (B) CK7, magnification X20. (C) Her-2 stain, magnification X 20. (D) ER stain, magnification X 20.

She underwent neoadjuvant chemotherapy with dose-dense cyclophosphamide and doxorubicin followed by bilateral radical mastectomies. Then she received 3 cycles of adjuvant paclitaxel and 1 year of trastuzumab (Genetech, San Francisco USA) in addition to

tamoxifen (AstraZeneca, Cambridge UK). She subsequently underwent adjuvant chest wall radiotherapy in May 2009. Three years later she presented with headache, weakness and dyspnea at an outside hospital. Work-up revealed a dominant occipital mass measuring 2 cm and multiple infracentimetric lesions in the cerebrum and cerebellum. She underwent emergent sub-occipital craniotomy with resection of the dominant lesion, which resulted in improvement of her weakness. Pathology revealed an infiltrating lobular carcinoma with SRCs comprising most of the tumor mass. Immunostains were positive for CK7, ER and Her-2 but negative for PR (Figure 1). These IHC features were consistent with the prior breast biopsy.

Her spine MRI revealed widespread osseous metastasis disease with no spinal metastasis. CT chest revealed bilateral pleural effusion with associated progressive diffuse irregular septal thickening, concerning for lymphangitis carcinomatosis. CT abdomen and pelvis demonstrated multiple metastatic hepatic lesions. She was subsequently transferred to our hospital for hypoxic respiratory failure. She received docetaxel, trastuzumab and pertuzumab with improvement of her pulmonary lymphangitis carcinomatosis and disappearance of her hepatic lesions in July 2012 (Figure 2). Later in December 2012, we discontinued docetaxel and started her on tamoxifen, trastuzumab and pertuzumab.

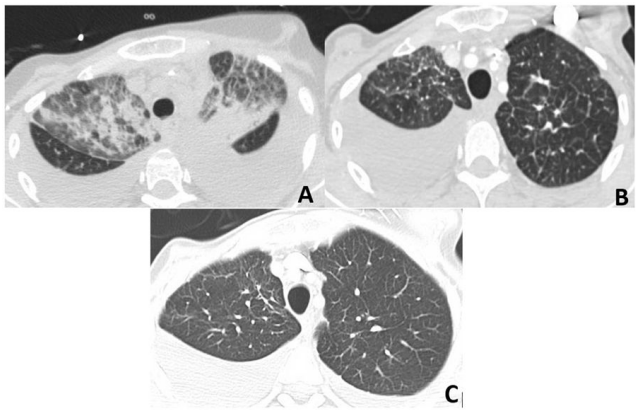

Figure 2: CT scan of the chest demonstrated clinical improvement of pulmonary lymphangitis from July 2012 to October 2013 after initiation of docetaxel, trastuzumab and pertuzumab.

In December 2014, she presented with urinary incontinence and paralysis of lower extremities. Spine MRI showed T2 intramedullary lesion with cord edema. There was also dural enhancement along her spine on MRI consistent with leptomeningeal carcinomatosis. Neurosurgery determined that the thoracic lesion was inoperable. She received 20 Gy in 5 fractions of palliative radiation to the T2 lesion. Given her progressive disease, we switched her to ado-trastuzumab from trastuzumab and pertuzumab. Repeat MRI spine in March 2014 showed evolutionary cystic changes and decreased lesion size and enhancement at the T2 level of the spinal cord. Clinically, her motor strength was 4/5 in both upper and lower extremities. She was able to stand and ambulate with assistance. She was also treated with intrathecal cytarabine and trastuzumab from December 2014 to March 2015. Subsequently she was enrolled on the ANG 1005 clinical trial with systemic ANG1005, a peptide-drug conjugate containing paclitaxel covalently linked to a peptide (Angiopep-2) designed to cross the blood-brain barrier, in March 2015. She continued to experience stable disease for almost one year. In February 2016, patient presented to the hospital for septic shock secondary to urinary tract infection and pneumonia and subsequently died.

Discussion

There are two histological types of SRCC. The first type is characterized by large vacuoles secondary to mucin accumulation and a compressed nucleus at the periphery. When SRCC is associated with ILC, its invasive component may demonstrate targetoid pattern of classical lobular carcinoma as seen in our case [3]. The second type of SRCC appears similar to gastric cancer, diffuse-subtype, where the cell cytoplasm is filled with mucosubstances and the nucleus is dislodged to one pole of the cell [3]. This type of signet ring cell carcinoma is associated with ductal neoplasia. Although controversial, most authors agree that breast SRC tumors should contain at least 20% of the signet ring cells [5]. Some tumors may contain up to 99% of SRCC, which are called pure SRCC. The proportion of SRC in the tumor appears to correlate with prognosis. One study suggested that patients with Stage I breast tumor containing more than 10% signet ring cells had higher risk of recurrence and distant metastasis [8]. SRCCs frequently metastasize to unusual sites such as gastrointestinal tract, genital tract, urinary tract and spleen [8,9].

In our case, the patient's SRCC was associated with ILC and had ER +, PR-, and Her-2 +. Her-2 signal was 9.3 by FISH, which implicated high degree of amplification and likely drove the tumor's aggressive biology.

The hormonal and Her-2 receptor profiles were the same for her original breast tumor and the metastatic brain tumor. A prior observational study found that 70% of metastatic ER/PR positive receptor tumors retained the original ER/PR positivity. However, about 50% of the original Her-2 positive tumor became Her-2 negative at the metastatic site [10]. Her-2 amplification was known to be strongly associated with distant metastasis [HR 7.80 (1.55 – 39.3)] and inferior overall survival [HR 6.9 (1.42 – 33.5)] compared with Luminal A ILC [11]. To our knowledge, no studies have reported the frequency of hormonal and Her-2 receptor status in SRCC. However, the rate of ER and PR positivity in ILC is around 94 and 81%, respectively [12]. The rate of ERBB2/Her-2 alteration is about 10% in ILC in most reports [13,14]. Genomic data of 413 ILC tumors suggested that SRCC, which was grouped into mixed non-classic ILC, might be enriched with HER-2 alteration, TP53 mutations and chromosome 1p36.22 loss [15].

Expression of hormonal and Her-2 receptors guided our therapeutic decisions in this case. The patient presented with aggressive metastatic breast cancer with SRC features at recurrence which prompted initiation of docetaxel, trastuzumab and pertuzumab. The rationale for this regimen was based on the CLEOPATRA trial, which demonstrated an improvement in median overall survival by 15.7 months and median progression free survival by 6.3 months in the treatment (docetaxel, trastuzumab and pertuzumab) group compared with the control group (docetaxel, trastuzumab and placebo) [16]. This combination led to rapid improvement of pulmonary lymphangitis and liver metastasis and maintained systemic control for 2 years. Additionally, whole brain radiotherapy was also very effective in maintaining CNS disease control in this case. After completion of docetaxel, we started her on tamoxifen given her pre-menopausal status with pertuzumab and trastuzumab. Two years later, the patient had a new symptomatic thoracic intramedullary lesion causing cord edema and associated leptomeningeal carcinomatosis, without

recurrence of pulmonary lymphangitis or hepatic metastases. Palliative radiotherapy to the T2 intramedullary lesion led to partial response, re-demonstrating the radiosensitivity of breast SRCC. Sanctuary site tumor progression on trastuzumab and pertuzumab led us to switch her on ado-trastuzumab. We also enrolled her on the Phase II study of ANG1005 (Angiochem, Montreal, Canada), which targets both intracranial and extracranial metastatic breast cancer. Recent published data demonstrated that ANG1005 led to intracranial disease control rate (DCR) in 41/58 (71%) and extracranial DCR in 27/30 (90%) of the patients [17]. Although most patients had SD, the estimated median OS was 34.6 weeks (95% CI 24.1 – 40.9) [17]. Importantly, 93% of these patients were exposed to prior taxane therapy as in our case.

In conclusion, we report successful treatment of metastatic recurrence of ILC with SRC features. Consistent with prior observations, SRCCs exhibited aggressive clinical behavior that spread to the brain, liver, and lungs. In addition to chemotherapy, hormonal modulation and Her-2 blockade rapidly led to rapid systemic disease control. Surgical resection of CNS mass and WBRT also improved CNS control. Based on our clinical experience, treatment of SRCC of the breast is similar to other types of breast cancer despite its aggressive clinical course.

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