

# Discussion of pathogen and potential therapeutic strategy for triple negative breast cancer based on a rare case study

## Abstract

Triple Negative Breast Cancer (TNBC) accounts for 10-22% of all breast cancer patients. Here we report a rare case of TNBC patient with metastasis to opposite chest organs, left abdomen is rectus muscle, eventually to brain. According to course of disease and gene expression profile in this case, we discuss the pathogen and potential therapeutic strategy for TNBC: DNA methylation may be the main cause for the negative expression and mutations of breast cancer biomarkers. Hormone therapy is dangerous for TNBC patients. Immunomodulators and anti-neovascularization may bring the breakthrough for increasing survival rate of TNBC patients.

**Keywords:** triple negative breast cancer (TNBC), distant metastases, blood-brain barrier (BBB), DNA methylation, neovascularization, hormone therapy

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**Abbreviations:** TNBC, triple negative breast cancer, distant metastases, BBB, blood-brain barrier; BC, breast cancer; ER, estrogen receptor; PR, progesterone receptor; MGMT, O-methylguanine-DNA methyl transferase

## Introduction

The most aggressive subtype of Breast Cancer (BC) is Triple Negative Breast Cancer (TNBC) that accounting for 10-22% of all breast cancer patients.<sup>1,2</sup> The most deadly factors of TNBC are early relapse and distant metastases, especially brain metastases, currently lacking of effective treatment targets.<sup>3,4</sup> Here, we report a rare case of TNBC patient with metastasis to opposite chest organs, left abdomen rectus muscle, eventually to brain. According to gene expression profile in this case, we discuss the pathogen and potential therapeutic strategy for TNBC.

## Case report

A 46years old female patient self-palpated a lump in upper quadrant of the left breast in June, 2012. The Mammogram suggested a round one centimeter nodule, mastectomy resected the tumor with 2.2centimeter with unclear margin at the local Breast Diseases Hospital and pathological diagnosis was phyllodes tumor. The patient chose to closely follow-up with no any treatment.

In December, 2012, the patient self-palpated again a mass in the left breast. Ultrasound revealed multiple low hypoechoic nodules in upper outer quadrant of the left breast with sizes from 0.5 to 2centimeter in diameter. Simple left breast mastectomy was carried out with sentinel lymph node biopsy. Pathologists in Beijing Cancer Center diagnosed as spindle cell sarcoma from high-grade phyllodes tumor origin with high expression of Vimentin (+++). Physicians considered its bad efficacy and suggested to take herb Chinese medicine without aggressive therapies like chemo- and Radio- therapies. The patient took two months Chinese medicine and was closely followed up.

One year later in December, 2013, Follow-up PET-CT and CT revealed two nodules shadow in the right lower lobe of lung. Right local lobectomy with thoracoscopy was performed with wedge resection of right lower lobe (3x6centimeter). Two masses

were intraoperatively noted between the dorsal and posterior basal segment that were pathological misdiagnosed as high possibility of inflammatory pseudotumor in local hospital. The patient took two months' Chinese medicine until pathologists in USA FCCC gave the clear diagnosis as spindle cell tumor with mild to moderate atypia cells and small numbers of giant tumor cells. The patient started to administer Epirubicin 100mg/m<sup>2</sup> over 72h for 4 weeks in March through May, 2014.

The follow-up CT in July, 2014 revealed again a 4.5x1.9cm pleural mass in the right middle lobe. With considering a metastatic tumor, the partial resection of diaphragm, right middle lobe, chest wall soft tissue and rib wedge resection were conducted. The pathology revealed metastatic spindle cell neoplasm involving parietal pleura lining the diaphragm, chest wall and rib consistent with metastatic malignant phyllodes tumor from breast primary cancer. At the end of October, 2014, one more time the follow-up CT revealed small nodules in the right chest wall and irregular thickening in the right pleural wall and longitudinal diaphragmatic pleura. MRI and CT also revealed metastatic lesion in the left rectus abdomens muscle. The patient refused to undergo operation any longer, but accepted chemotherapy with dacarbazine and nedaplatin, intravenous perfusion a cycle; gemtine/recombinant Human Ad-p53 local injection and thermotherapy to the lesion localized in the rectus muscle according to the result of mutational analysis by next generation sequencing on the specimens collected in latest resections from CARIS Life Sciences, which showed TP53 mutant L194R with 73% frequency.

In order to participating PD-1 clinical trial according to the suggestion from CARIS Life Sciences, the patient came to MD Anderson in December, 2014. Pathological analysis was repeated with the specimens that the patient brought in. With the same pathological diagnosis, the oncologist let the patient signed the informed consent form for phase I trial of pazopanib plus crizotinib because no PD-1 trials were currently available to breast cancer in MD Anderson. The patient continued home medication.

Based on the notes written by patient's husband, the patient complained headache and vomiting during taking Pazopanib. In February, 2015, CT scan and Multiplanar MR images of brain revealed multiple intracranial metastasis foci. The patient had radiotherapy in

MD Anderson for 10times, and gamma knife to treat the metastatic lesions in brain. Depending on talking with the husband of patient, patient took hormones (no detailed information) in March, which rapidly accelerated medical condition getting worsen. The patient passed away in April, 2015 after she returned China.

## Special examination

The most significant and consistent results of immunohistochemistry analysis of surgical specimens conducted by multi-medical institutes of China are ER and PR negative, her2 were not determined but with diffuse expression of Vimentin, SMA and BCL2. Molecular profiling at CARIS Life Sciences confirmed that expression of ER, PR and Her 2 are negative, RRM1 (50%), TUBB3(35%), PTEN(90%) and PD-L1(25%) are positive, No MGMT expression was detected. The next generation sequencing shows TP53 L194R and ATM T615I mutants frequency 73% and 23% respectively in the specimens of breast tumor and metastatic chest wall soft tissue.

## Discussion

TNBC is defined by negative expression of three important biomarkers for breast cancer, estrogen receptor (ER), progesterone receptor (PR) and HER2. Owing to lacking of effective treatment targets, and early relapse, distant metastases, TNBC is the most aggressive subtype of breast cancer. However, up to date, metastasis to muscle tissue has not been reported to our knowledge. Here we report this rare TNBC case and look into its gene expression profiles for discussion of pathogene and potential therapeutic strategy for TNBC.

There is emerging evidence that DNA methylation is involved in outbreak and metastases of cancer. Barekati et al.,<sup>5</sup> recently studied methylation signature of lymph node metastases of breast cancer and found the heterogeneity of DNA methylation between primary tumor and metastatic lesion. The<sup>6</sup> O-methylguanine-DNA methyltransferase (MGMT) is enzyme play important role in DNA repair. MGMT methylation correlates with the loss of MGMT expression that leads cells transform to cancer cells. MGMT methylation had been found in 22% breast cancer patients.<sup>6</sup> In our case, no MGMT expression was detected in specimens from TNBC tumor, which suggests that DNA methylation may be involved in the specific gene profile of the rare phenotype of the patient. On the other hand, TP53 polymorphism has shown modulator function in DNA methylation of carcinoma.<sup>7</sup> ATM is another gene mediating DNA methylation.<sup>8</sup> ATM inactivating mutant had been shown its resistant to those DNA damaging drugs probably through the immune system, which affected efficacy of chemotherapy to leukemia.<sup>9</sup> Taken together, we believe that Immunomodulating drugs maybe the promising treatment for TNBC patients.

Tumor Metastases to brain must have disruption of Blood-Brain Barrier (BBB). The brain metastases is the most major cause for mortality of TNBC patients.<sup>10</sup> BBB is a typical structure that type 1 astrocytes surrounding capillaries that formed by brain endothelial cells and pericytes. In our case, SMA positive pericytes significantly increased in the tumor. Our previous study had shown perocytes' roles in formation of neovascularization.<sup>11</sup> Recent study had shown that Angiopoietin2 mediating impairment of BBB and initiating metastases to brain in TNBC patients. Addressing to angiopoietin2 is a potential therapy for reducing mortality for TNBC.<sup>12</sup> TUBB3 is Class III beta-Tubulin that structuring cytoskeleton for microtubules that function in cells mobility. ALDH overexpression had been found in cancer stem cells isolated from TNBC.<sup>13</sup> The gene profile in this case may suggest that low ER expression, high Vimentin expression, along with ALDH featuring stem cells favored to distant lung and

brain metastases. Therefore, targeting Angiopoietin2, IL17 and VEGFR, ALDH are potential therapeutic strategies to decrease distant and brain metastases of TNBC patients.

Ribonucleotide reductase subunit M1(RRM1) is a component of ribonucleotide reductase holoenzyme involved in metabolism of cells. One of the enzyme of Ribonucleotide reductase had been used to reverse the cardiac dysfunction through myotoin activation.<sup>14</sup> Although the overexpression of RRM1 in this case may contribute to the muscle metastases, we may use RRM1 pathway members to treat heart failure or other vascular diseases with cardiac muscle dysfunction. Finally, there is evidence that heart may be adversely influenced by primitive or metastatic thoracic tumors as well as some types of anticancer therapy.<sup>15</sup>

Accelerated worsen of medical condition for this patient after the administration of hormone suggests that hormone therapy is dangerous for TNBC patient. Taken together, although TNBC is a very aggressive sub-style of breast cancer, immunomodulators and anti-neovascularization may bring the breakthrough for increasing survival rate of TMBC patients.

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## Conflicts of interest

Author declares there are no conflicts of interest.

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