



# Metastatic, Triple-Negative, Androgen Receptor-Positive, Invasive Lobular Carcinoma of the Breast: A Case Report

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## Abstract

Triple-Negative Breast Cancer (TNBC) is one of the most aggressive subtypes of breast cancer and tends to be of invasive ductal carcinoma histopathology. Less commonly found are Invasive Lobular Carcinomas (ILC) that are triple-negative. Various biological types of breast cancer have been identified through techniques, such as immunohistochemistry and gene profiling, which have helped to guide prognosis and treatment. To date, there have been no cases described as triple-negative (estrogen receptor-negative, progesterone receptor-negative, and human epidermal growth factor receptor-negative), Androgen Receptor (AR) positive, ILC that metastasized to the stomach, small bowel, bones, and dura mater. There are a few studies that report proximal small bowel metastasis in the setting of triple-negative, ILC; however, the AR status was not reported. We report a case of a 58-year-old Caucasian female diagnosed with *de novo* metastatic, triple-negative, AR-positive, ILC with multi-organ distant metastasis.

**Keywords:** Triple-negative breast cancer; Invasive lobular carcinoma; Metastasis; Androgen receptor

## Introduction

It is estimated that in 2019, there will be 268,600 new cases of invasive breast cancer diagnosed in women residing in the United States, with about 6% of new cases having metastatic disease when first identified [1,2]. Invasive breast cancer can be subdivided into three main categories (depending on microscopic appearance): Invasive Ductal Carcinoma (IDC), Invasive Lobular Carcinoma (ILC), and Invasive Mammary Carcinoma (IMC), a mixture of both IDC and ILC. IDC is the most common type and accounts for approximately 75% percent of invasive breast cancers, followed by ILC, comprising about 5% to 15% of all invasive breast cancers [3].

In addition to their microscopic appearance, invasive breast cancers are further characterized based on immunohistochemical receptor expression. This includes the Estrogen Receptor (ER), Progesterone Receptor (PR), and over expression of Human Epidermal Growth Factor Receptor 2 (HER2/neu). In general, breast cancers that are either ER-positive or PR-positive tend to have a more favorable prognosis, mostly due to advancements in targeted hormonal therapy as compared to breast cancers that are not ER or PR positive. TNBC represents 15% to 20% of invasive breast cancers, tends to be poorly-differentiated, and confers a worse prognosis than hormone-positive breast cancers [4]. The mainstay of metastatic TNBC therapy consists of chemotherapy in which overall survival is 15 to 18 months [5]. Thus, novel targeted therapy for TNBC is an unmet need.

The incidence of ILC has increased over the years, while the incidence of IDC has been relatively stable [3]. ILC molecular subtypes are normally ER- and/or PR-positive, with a small percentage that is TNBC [6]. In addition, ILC of the breast can invade the bone, reproductive organs, peritoneum, retroperitoneum, gastrointestinal tract, and leptomeninges [7-11]. Here, we present the case of a 58-year-old Caucasian woman who was referred to our care and upon further evaluation was diagnosed with metastatic, triple-negative, Androgen Receptor (AR) positive, ILC of the breast.

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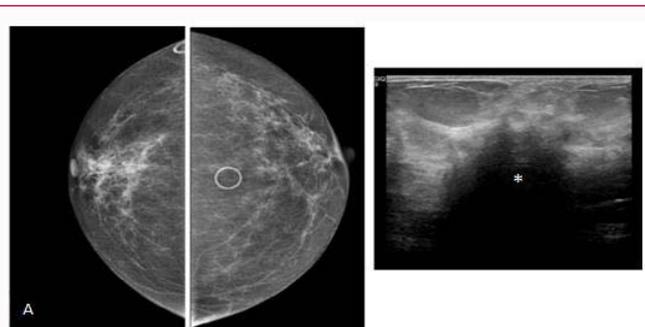
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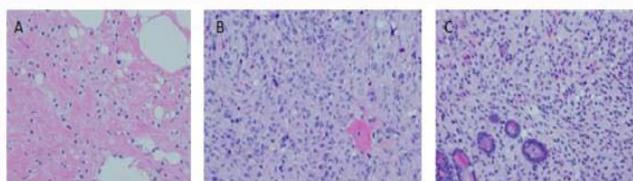
## Case Presentation

A 58-year-old female presented to urgent care in June 2015 complaining of uncontrolled back pain, bilateral shoulder pain, and neck stiffness without headache or numbness/tingling over the last 2 weeks. She originally attributed symptoms to her occupation as a valet parking attendant. She was diagnosed with muscle strain and given roboxin. Of note, her past medical history was significant for a rare autoimmune skin disorder, pemphigus vulgaris, which presented as a generalized erythematous blister-like skin rash on her face, mouth, and bilateral upper extremities, as well as the chest and trunk, diagnosed in April 2013. Since then, she has been treated with mycophenolate mofetil immunotherapy and daily oral steroids. In July 2015, she presented again to urgent care complaining of similar symptoms of back pain. A thoracic spine X-ray showed mild compression fractures at T6 vertebrae. Conservative management was done, because the fracture was thought to be due to osteoporosis. The patient declined bisphosphonate therapy. Over the next 2 months, the patient underwent physical therapy and took acetaminophen over the counter, as needed, however the back pain persisted. In October 2015, she was seen by her primary care physician who palpated a firm, non-tender, subareolar mass in the right breast on physical exam. Her last mammogram in 2013 did not demonstrate any abnormalities. Pertinent gynecologic history includes 2 full term pregnancies (first pregnancy at age 21) and no family history of breast or ovarian cancer. A subsequent diagnostic mammogram demonstrated a global asymmetry centered in the subareolar right breast, as well as right nipple retraction (Figure 1A). A right breast ultrasound confirmed an irregular hypoechoic mass corresponding to the palpable mass (Figure 1B). The patient then underwent a core needle biopsy of the mass demonstrating ILC, grade 2, ER-negative, PR-negative, and HER2-negative (Figure 2). She then had a bilateral breast MRI that demonstrated suspicious right axillary nodes, originally noted as probably benign on ultrasound (Figure 3). A core biopsy of the right axillary lymph node was proven to be metastatic disease.

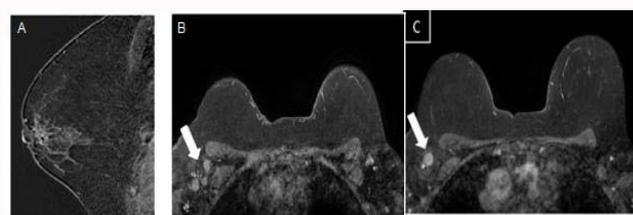
Further metastatic work-up included CT scans of the chest and abdomen, along with pelvis and bone scans (Figure 4), MRI of the spine (Figure 5), and MRI of the brain. She was found to have multiple lytic osseous lesions involving the skull, ribs, manubrium, spine, and a T-10 spinal canal encroachment by a metastatic soft tissue mass. The patient was hospitalized for T10/T11 cord compression (Figure 5B,5C) and treated with steroids, decompression, excision of a T10 mass, and T7-L2 posterolateral fusion using allograft. The T10 lesion was biopsy-proven TNBC (Figure 2B). MRI of the brain revealed enhancing extra-axial lesion along the right temporal lobe representing dural metastasis (Figure 6A). A month after cord decompression surgery, she had palliative radiation therapy to the cervical spine (30 Gy in 10 fractions) and to the thoracolumbar spine (30 Gy in 10 fractions) lesions. Two weeks later, she underwent stereotactic radiosurgery (15 Gy in a single fraction) of a single, right temporal dural lesion (Figure 6B,6C). After completing radiation therapy, she was started on capecitabine, 1500 mg, by mouth, twice daily, (2 weeks on, 1 week off) and monthly denosumab in January 2016. Of note, the patient was offered taxane chemotherapy with paclitaxel, but did not wish to undergo intravenous chemotherapy (standard of care in first line TNBC at the time). The combination of chemotherapy to treat her breast cancer and mycophenolate mofetil to treat her pemphigus vulgaris increased her fatigue and she weaned herself off mycophenolate mofetil. Skin lesions remained absent.



**Figure 1:** Craniocaudal A) mammographic views of the bilateral breasts show a global asymmetry centered in the subareolar right breast and right nipple retraction B) Ultrasound of right breast displays irregular hypoechoic mass (see asterisk).

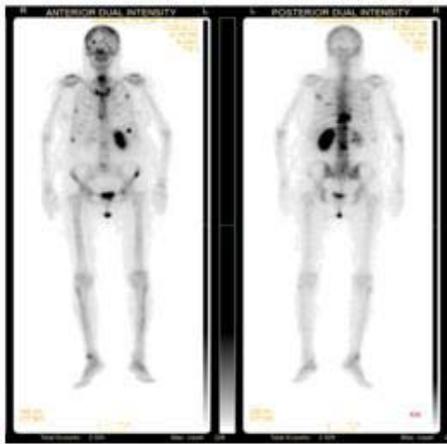


**Figure 2:** Invasive Lobular Carcinoma Core Biopsies: A) Breast biopsy: Invasive lobular carcinoma, modified Bloom-Richardson grade 2, B) Bone, and C) Duodenum show metastatic lobular carcinoma. Hematoxylin and eosin, original magnification x200.

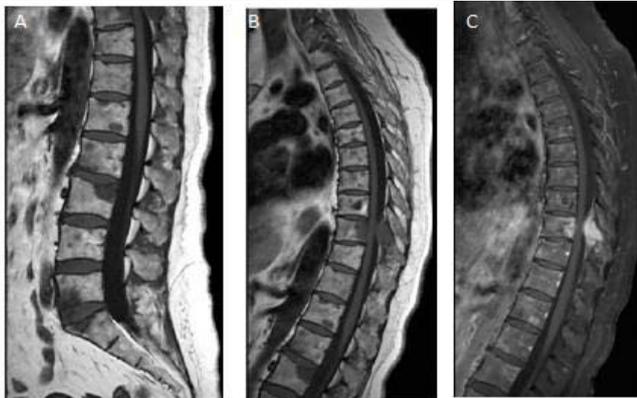


**Figure 3:** Sagittal T1 post-contrast subtraction MRI of the right breast A) shows a spiculated enhancing mass in the subareolar breast with associated nipple retraction. Additional non-mass enhancement extends beyond the mass with total enhancement measuring approximately 4 cm x 6 cm x 6 cm (AP x TV x CC dimensions). Axial T1 post-contrast images B and C) through the level of the axilla show at least 4 morphologically abnormal lymph nodes (arrows).

Approximately one year later, CT scans and bone scans showed new bone lesions; capecitabine was discontinued. With the aim of evaluating the patient for less toxic treatment options so that she could continue working, archival tissue from her previous breast biopsy was tested for androgen receptors which revealed overexpression. Thereafter, she enrolled in a phase 1/2 clinical trial to treat metastatic AR-positive breast cancer with a novel androgen blocker. After several months of androgen blockade, she complained of persistent nausea, vomiting, and severe abdominal pain for which she was admitted for inpatient evaluation. Labs showed new onset anemia and thrombocytopenia concerning for occult GI bleed. A CT scan of the abdomen and pelvis was done demonstrating findings suggestive of tumor involvement (Figure 7). An Esophagogastroduodenoscopy (EGD) showed a duodenal nodule, thickened duodenal wall, as well as thickened gastric folds in the body of the stomach; biopsies confirmed metastatic TNBC (Figure 2C). A colonoscopy was aborted due to inability to get past the sigmoid colon, secondary to stenosis. In addition, further images demonstrated progression of the osseous



**Figure 4:** Technetium 99m-methyl diphosphonate whole body bone scan shows multiple foci of radiotracer uptake consistent with bony metastases involving the ribs, sternum, spine, pelvis, and skull. Retained radiotracer was incidentally noted in the left.



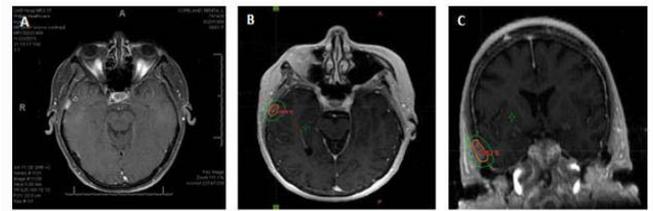
**Figure 5:** Sagittal T1 MRI through the lumbar A) and thoracic B) spine demonstrate numerous T1 hypointense lesions consistent with metastases. Sagittal T1 postcontrast imaging of the thoracic spine C) shows an enhancing lesion at T10 involving the posterior elements, resulting in moderate spine canal narrowing with cord compression.

metastases. With the findings of progression of disease, the decision was made to discontinue androgen therapy and initiate weekly paclitaxel. After two weeks of interrupted paclitaxel treatment, the patient decided to move forward with hospice care due to extreme fatigue, nausea, and poor appetite secondary to the treatment regimen and aggressive disease.

## Discussion

TNBC is known to be heterogeneous. Recently, Perou et al. [12] demonstrated that breast cancers could be further sub-classified by gene expression profiling [12,13]. Broadly, these subtypes include luminal ER-positive (luminal A and luminal B), HER2 enriched, and basal-like. Furthermore, molecular subtypes of TNBC are defined as Basal-Like 1 (BL1)-17%, Basal-Like 2 (BL2)-7%, Immunomodulatory (IM)-18%, Mesenchymal (M)-17%, Mesenchymal Stem Like (MSL)-14%, and Luminal Androgen Receptor (LAR)-12% [14,15]. Given the multiple TNBC subtypes, biologically-driven therapies may be an approach that could improve survival in this patient population.

The androgen receptor is a steroid receptor similar to estrogen and progesterone receptors. Seventy to ninety percent of breast



**Figure 6:** A) MRI of the brain demonstrating the single dural lesion (arrow). B and C) Radiation therapy to dural lesion (red outline: gross tumor volume, yellow outline: prescription dose, green outline: 50% prescription dose).



**Figure 7:** Axial CT images of the abdomen with oral and IV contrast show circumferential wall thickening of the ascending A) colon B) cecum and C) ileocecal junction. There is associated fat stranding surrounding the involved bowel. Findings are suspicious for tumor involvement.

cancers express AR. Typically, breast cancers that are AR-positive tend to be well-differentiated [16-18]. Well-differentiated tumors have a more indolent path than undifferentiated tumors. The application of androgen receptors in the treatment of prostate cancer is widely accepted, but developments are underway for breast cancer [19]. In preclinical models, LAR cell lines were uniquely sensitive to bicalutamide, an oral non-steroidal AR antagonist [15]. In women with LAR subtype, studies have demonstrated clinical benefits with response to AR inhibition. In Gucalp et al. [20] a single arm, non-randomized phase 2 trial of 26 patients revealed a Clinical Benefit Rate (CBR) at 24 weeks of 19% with a progression free survival of 12 weeks. No objective responses were noted. Additionally, another androgen blocker, enzalutamide, was used in a single-arm; non-randomized phase 2 trial of advanced TNBC which showed a CBR of 25% at 16 weeks and 20% at 24 weeks in patients whose tumors had AR expression of  $\geq 10\%$  [21]. It has been reported that triple-negative tumors which respond to AR inhibitors have more favorable tumor biology than those that are AR-negative [21]. Unlike hormone receptor positive tumors or tumors that over express HER2/neu, TNBC currently does not have targeted therapy and chemotherapy remains the mainstay of systemic therapy regimens. The findings above may confer that chemotherapy which targets fast growing; poorly-defined cells may not be the optimum therapy to treat LAR breast cancer subtypes.

Metastatic breast cancer may be observed on initial presentation (approximately 25% *de novo*) or can present as a breast cancer recurrence [22]. ILC tends to metastasize later than IDC and spreads to locations, such as the meninges, peritoneum, and rarely, the gastrointestinal tract [23]. A small, single-institutional retrospective study found that the rate of multiple metastases was higher in ILC (25%) than in IDC (15.8%) and may be related to the phenotypic trait of discohesive small cells which characterizes ILC [23]. There is limited research about gastrointestinal metastasis, but the few cases that are reported commonly indicate the importance of evaluating patients diagnosed with ILC for distant metastatic disease, especially those with gastrointestinal symptoms. In cases of metastasis to the

brain or dura, radiation therapy is the standard of care in treating those lesions, as systemic therapy has a limited role in crossing the blood brain barrier [24].

Traditionally, Whole Brain Radiation Therapy (WBRT) is used to treat patients with both identifiable brain metastases and prophylaxis for microscopic disease [24]. WBRT has been effective at palliation for those with brain metastases; however, it is associated with acute, early-delayed, or late toxicities. This includes, but is not limited to, nausea, vomiting, memory loss, cerebral edema (which is often treated with corticosteroids), and fatigue [24,25]. The factors contributing to the severity of these toxicities may involve the patient's age and size of the tumor-associated edema, as well as the number of brain lesions. Over the years, studies have been undertaken to determine ways to mitigate toxicities, while still offering equal or improved outcomes in treating brain metastases. A more recent technique is Stereotactic Radiosurgery (SRS) developed to treat brain metastases and other localized tumors [26]. SRS is the precise delivery of a high dose of radiation to a target with rapid dose drop-off to the surrounding tissues. This method is favorable, as it can reduce the side effect of cerebral edema to the surrounding tissue, which is associated with cognitive sequel [26]. Studies have demonstrated the effectiveness of combined SRS therapy and WBRT in the setting of 1 to 4 intracranial lesions [27]. In the current case presentation, the patient was treated with SRS for a single dural lesion, resulting in a prolonged response; she also maintained good cognition throughout her diagnosis.

With the knowledge that ILC tends more likely to be associated with multiple sites of metastasis, including the gastrointestinal tract, it is important for patients with related symptoms to be promptly evaluated. The development of targeted agents in TNBC is limited and continues to be an unmet need. In addition, studies have demonstrated that the LAR subtype of TNBC has a promising response to AR inhibition, which can lead us to pursue research that will perpetuate us finding an effective targeted therapy for this type of TNBC. Understanding the unusual patterns of ILC metastasis and the subtypes that respond to AR inhibition, as well as the effective therapy of SRS in cases of dural metastasis, can help to effectively treat patients with the unique tumor biology of triple-negative, AR-positive, ILC. Additional research in this area is warranted to help improve treatment options for patients with breast cancer presenting with this particular tumor biology, as well as pattern of metastasis.

## Conclusion

The median survival of patients diagnosed with advanced TNBC is 13 months [28]. Advanced treatment approaches are dependent upon further genomic profiling of these tumors. Systemic chemotherapy remains the standard of care for both lobular and ductal subtypes of TNBC, therefore, actionable receptors such as AR should be investigated to further refine prognosis and develop possible targeted therapeutics. There are only a few reported cases of ILC that metastasized to the stomach and small bowel [8,29]. Of those cases, the tumors were hormone receptor positive. To our knowledge, there is only one reported case of triple-negative, ILC with metastasis to the proximal small bowel; however AR expression was not reported [11]. Our case is unique in that we know the status of AR expression of the tumor, in the setting of a rare combination of triple-negative, ILC with synchronous metastasis to the gastrointestinal tract and dura conferring a poor prognosis, yet she survived almost 2 years with an aggressive disease. The biologic slow progression of her disease is most likely due to the LAR subtype. Patients with advanced

LAR breast cancer may benefit from using androgen inhibitors or other targets in the front line setting to improve progression-free survival and quality of life. Unfortunately, this was not afforded to our patient in the frontline setting and therefore, efficacy rate cannot be concluded. More data is needed to evaluate the clinical use of androgen blockade in LAR and TNBC, as well as other targeted agents in order to improve outcome of these patients.

## Declarations

### Authors' contributions

Stringer-Reasor E: Clinical case, writing, review, and editing.  
Ayre K: Clinical case, writing, review, and editing.

Wei S: Review, editing, and figures. Boggs D: Review, editing, and figures. Molony E: Review, editing, and figures.

Olariu E: Writing, review, and editing.

### Conflicts of interest

Dr. Stringer-Reasor discloses consulting fees with Breast Cancer Index, Immunomedics, and Lilly; honoraria with Lilly and ASCO; research support from Seattle Genetics, Tesaro, Cascadian Therapeutics, GSK, Pfizer, Susan G. Komen and V Foundation. Dr. Boggs discloses consulting fees and research support from Novocure, and Varian Medical Systems, Inc.

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