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# Single-Institute Review of HER-2/Neu-Positive Invasive Lobular Breast Carcinoma in an Arab Population

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Statistical Analysis C  
Data Interpretation D  
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**Conflict of interest:** None declared

## Case series

**Patients:** Female, 54-year-old • Female, 67-year-old • Female, 58-year-old • Female, 63-year-old • Female, 61-year-old • Female, 60-year-old • Female, 63-year-old • Female, 60-year-old • Female, 40-year-old

**Final Diagnosis:** Invasive lobular carcinoma HER-2/neu-positive

**Symptoms:** Breast lump

**Medication:** —

**Clinical Procedure:** —

**Specialty:** Oncology

**Objective:** Rare disease

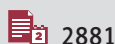
**Background:** Invasive lobular carcinoma is special subtype of breast cancer that has clinical behavior and morphology distinct from other breast cancer subtypes. It accounts for 5-15% of breast cancer. Overall, HER-2 gene amplification occurs at a significantly lower rate in ILC, but also has been linked to adverse outcomes. Most cases of ILCs with HER-2 overexpression and or amplification generally have the pleomorphic variant. We report the first series of cases from Saudi Arabia for this rare cancer in an Arab population.

**Case Reports:** Nine patients retrospectively were evaluated with HER-2/neu-positive ILC of the breast that were diagnosed and managed from 2003 to 2020. Four patients were diagnosed as early breast cancer, 3 had metastatic disease and 2 were locally advanced at their initial presentation. The mean age was 58 years; 30% were classic ILC and another 60% were of mixed non-classic variants (histologic pattern represented by nuclear pleomorphism). Management of patients with HER-2-positive ILC was performed according to standard multimodality breast cancer guidelines, consisting of surgery, chemotherapy with anti-HER-2/neu blockade, radiation, and endocrine therapy, based on stage and hormone status.

**Conclusions:** In conclusion, HER-2-positive invasive lobular carcinoma of the breast is uncommon in the Arab population, which has not been previously reported in the literature. Further studies are warranted to explore the biology, molecular characteristics, and clinical course in this group of patients.

**Keywords:** Carcinoma, Lobular • Receptor, erbB-2 • Receptors, Progesterone

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/928012>



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## Background

Invasive lobular carcinoma is a special subtype of breast cancer that presents with a distinct clinical behavior and morphology from other breast cancer subtypes. It accounts for 5-15% of invasive breast cancer [1]. Its clinical and biological characteristics have been extensively described in the medical literature [2]. They are frequently hormone receptor-positive, and demonstrate a higher incidence of contralateral primary tumors, present more frequently with multi-centric disease, and tends to metastasize to distinct sites.

Most patients with ILC express estrogen and progesterone receptor but lack HER-2 overexpression or amplification, and thus are categorized as “luminal” molecular classes [3]. Most cases of ILCs with HER-2 overexpression and/or amplification generally represent the pleomorphic variant. However, it is observed in series of classical-type ILC with HER-2/neu-positive status over several years and until recently reported an individual case of classical-type ILC with extracellular mucin production with strong HER-2/neu expression [4]. Overall, HER-2 gene amplification occurs at a significantly lower rate in ILC (10%), but has also been linked to adverse outcome. In a large series of classic ILC tumors, HER-2/neu-positivity was observed in 4.6% of all cases [5].

Breast cancer among Arab populations has specific morphological and molecular characteristics, including poorly differentiated pathological features and increased HER-2 overexpression [6]. To the best of our knowledge, ILCs with HER-2 overexpression among Arab populations has not been published in any medical literature. Management of patients with HER-2-positive ILC is according to standard multimodality breast cancer guidelines, consisting of surgery, chemotherapy with anti-HER-2/neu blockade, radiation, and endocrine therapy, based on stage and hormone status. Due to its rarity, it is seldom reported in the literature.

Herein, we report the first series of cases from Saudi Arabia of this rare cancer in an Arab population.

## Case Reports

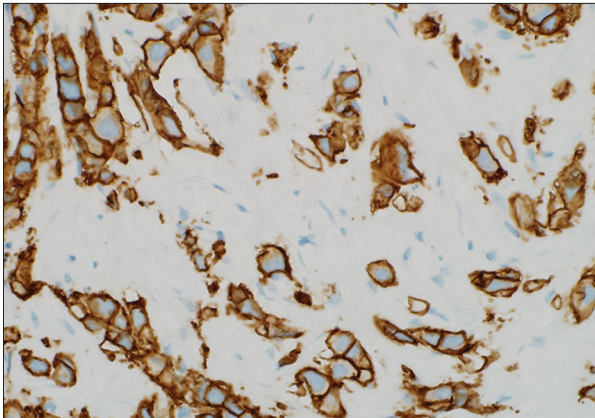
We retrospectively evaluated the charts of patients, including pathological diagnosis and management of 9 rare cases of HER-2/neu-positive ILC of breast that were diagnosed and managed from 2003 to 2020 at the King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia.

### Case 1

A 54-year-old woman who had no family history of cancer and had survived acute myeloid leukemia (M-2) underwent post-allogeneic stem cell transplant in remission from sibling donor sister 17 years ago. She was later diagnosed with refractory ITP after splenectomy and chronic viral hepatitis C. She presented with progressive left breast mass that appeared 4 months previously, diagnosed as ILC, positive for estrogen receptor and progesterone receptor, and HER-2/neu overexpression. She underwent modified radical mastectomy with pT1 N1 disease. Following surgery, she received 4 cycles of weekly chemotherapy adjuvant paclitaxel and trastuzumab. She had difficulty tolerating the weekly paclitaxel, so she was continued on trastuzumab for 1 year and letrozole after completion of adjuvant radiation. After 4 years, she presented to an internist with vague right hypochondria pain. An MRI abdomen demonstrated a cirrhotic liver with a new hepatic segment 8 lesion measuring 2 cm, and hypervascular washout with enhancing capsule on delayed phase, consistent with hepatocellular carcinoma, along with multiple sclerotic bone metastases. She received radio-frequency ablation for the hepatic lesion. She was clinically asymptomatic, but a bone scan showed multiple bone metastases. She underwent left iliac bone biopsy, which revealed bone fragments from primary breast cancer had weak hormone receptor positive for ER and showed HER-2 overexpression. She was not a candidate for chemotherapy as she had poor tolerance of weekly paclitaxel. She was started on dual anti-HER-2 blockade with pertuzumab and trastuzumab, along with hormonal treatment, letrozole, and zoledronic acid as part of her treatment for metastatic disease. So far, she has completed 14 cycles dual anti-HER-2/neu blockade treatment with sustained serological responses and will continue to receive the same therapy until disease progression or major adverse events.

### Case 2

A 67-year-old woman, with no family history of cancer, who had left early breast cancer in 2004, underwent left breast conserving surgery and left axillary lymph node dissection, with histopathology consistent with invasive ductal carcinoma. She was started on adjuvant anthracyclines and cyclophosphamides chemotherapy, followed by radiation and 5 years of hormonal treatment with tamoxifen as adjuvant treatment. After 15 years, she presented to a breast clinic with self-discovered bilateral breast lumps. Bilateral breast biopsies from the right breast showed invasive lobular carcinoma grade 1, pleomorphic type, both strongly positive 100% for ER and PR, and negative for HER-2/neu, Ki-67 20%, and left breast mass invasive lobular carcinoma, classic type, grade 2 (tubule formation 3, Nuclear pleomorphism 3, mitotic activity 1). She was also estrogen receptor (ER) strong positive 90%, progesterone receptor (PR)



**Figure 1.** HER-2 immunostain demonstrates intense complete membrane staining of tumor cells indicating HER-2 overexpression (original magnification 40x).

weak positive 5%, with presence of HER-2/neu overexpression (**Figure 1**) and Ki-67 60%. Staging workup did not reveal any distant metastases. She underwent a right breast simple skin-sparing mastectomy with right sentinel lymph node biopsy, which was negative, pT1b, Nsn0, and left simple mastectomy invasive lobular carcinoma, pleomorphic type pT1c, N0. Currently, she is receiving adjuvant chemotherapy followed by adjuvant trastuzumab and hormonal treatment.

### Case 3

A 58-year-old woman, with no family history of cancer, was diagnosed with right breast cancer. She presented with progressively increasing right breast and axillary masses. In the past she had been taking oral contraceptive pills. According to the patient, the mass has been progressing in size for the past few months with some skin changes but no nipple discharge. Further evaluation with bone scan was consistent with multiple bone metastases. A biopsy of the breast mass was consistent with ILC positive for estrogen, progesterone receptors, and HER-2/neu. She was started on 4 cycles of docetaxel, trastuzumab, and trastuzumab, with durable responses. She developed grade 2 peripheral neuropathy; therefore, she declined further chemotherapy and was continue on maintenance trastuzumab, pertuzumab, and letrozole, along with denosumab. She has completed 43 cycles of maintenance trastuzumab, pertuzumab and letrozole, with sustained stable responses.

### Case 4

A 63-year-old patient, with no family history of cancer, presented bilateral breast nodules on breast imaging. A systemic workup including CT scan and bone scan revealed multiple bone metastases and no visceral metastases. Histopathology of the right breast showed invasive lobular carcinoma classic type grade 2, positive for estrogen receptor 90% and progesterone

receptor positive 30%, along with positive HER-2/neu and Ki-67 10% (Tubule 3, Nuclear 2, Mitotic 1). She received palliative radiation to vertebral metastasis from T11 to L2 for symptomatic pain control. She is receiving hormonal treatment with letrozole with anti-HER-2/neu therapy as part of systemic treatment protocol and will continue to receive it until disease progression.

### Case 5

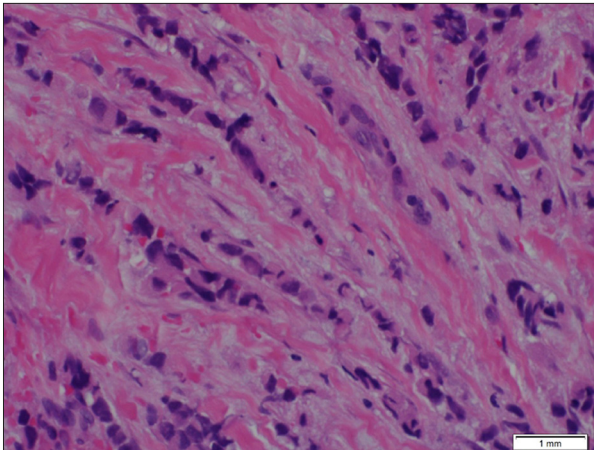
A 61-year-old postmenopausal woman, with a family history of a sister having metastatic breast cancer, presented with a left breast mass for 2 months. She initially ignored it and refused to seek medical care, but after the mass grew further, she underwent biopsy, which revealed invasive lobular carcinoma positive for estrogen receptor, and HER-2/neu. She underwent left modified radical mastectomy and was staged as stage T1 N0. Later, she was started on 4 cycles of docetaxel, cyclophosphamide, and trastuzumab, then adjuvant trastuzumab for 1 year, along with adjuvant hormonal treatment and letrozole for a total of 5 years. She completed adjuvant hormonal treatment and continues to be on surveillance.

### Case 6

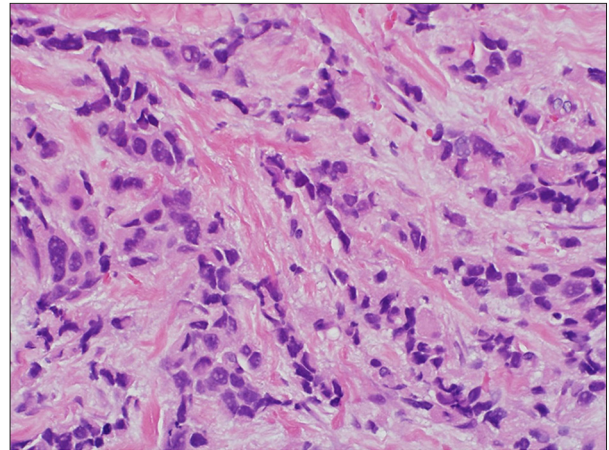
A 60-year-old postmenopausal woman with no family of cancer was diagnosed with left breast cancer. Her tumor upon biopsy was found to be invasive lobular carcinoma classical-type, grade 2, estrogen receptor (ER)-positive 90%, progesterone receptor (PR)-positive 5%, and HER-2/neu-positive on FISH amplification. The tumor was located in the upper outer quadrant at 4 o'clock in the left breast. The baseline biopsy from the left axilla was also positive for tumor metastasis, clinically staged as T4N1. She was started on neoadjuvant chemotherapy with docetaxel, trastuzumab, and pertuzumab. Following that, she underwent left modified radical mastectomy. The histopathology revealed multifocal residual lobular carcinoma in situ with no invasive component. Single lymph nodes were positive for tumor metastasis, and 10 additional lymph nodes were negative for tumor metastasis, ypTisN1Mx. Later, she received adjuvant radiation in addition to hormonal therapy and trastuzumab. She completed adjuvant trastuzumab and continued on adjuvant letrozole and has no evidence of recurrence or metastatic disease. It has been for more than 3 years from the time of initial diagnosis and she is doing well, tolerating the treatment, and the systemic disease is well controlled on maintenance therapy.

### Case 7

A 63-year-old postmenopausal woman with no family history of cancer was diagnosed 3 years ago with early right breast carcinoma, invasive lobular subtype. She underwent right skin-sparing mastectomy and sentinel lymph node biopsy.



**Figure 2.** The neoplastic cells infiltrate the stroma singly or in linear strands in pleomorphic variant (hematoxylin-eosin, original magnification 40×).



**Figure 3.** The neoplastic cells exhibit nuclear variation (hematoxylin-eosin, original magnification 40×).

The tumor biology revealed invasive lobular carcinoma grade 3, size 2 cm, node negative, and ER strongly positive for estrogen (ER) and progesterone receptor (PR) and HER-2 positive by immunohistochemical staining and by cytogenetic technique. After surgery, she was started on treatment with 12 weekly doses of paclitaxel and trastuzumab as part of her adjuvant treatment. Accordingly, she completed trastuzumab for 1 year along with adjuvant hormonal treatment with letrozole. She has completed 2 years of hormonal treatment and is planned to receive it for 3 more years.

### Case 8

A 60-year-old postmenopausal woman with family history of endometrial cancer in her mother and sister presented with bilateral breast heaviness and mild pain but no palpable mass. She was reviewed in a breast clinic with a mammogram which showed development of new focal area of dense asymmetry in the central part of the left breast, with a degree of progression in the nodules in both breasts. Ultrasound scans of the breasts revealed several cysts in the left breast. At 5 o'clock position there was a suspicious irregular hypoechoic area measuring 9×15×20 mm. No axillary lymphadenopathy was on ultrasound criteria, with a 10-mm septated cyst with internal echoes in the right breast in addition to a suspicious lobulated mass measuring 9×15×20 mm in the left breast. Left breast biopsy revealed invasive lobular carcinoma, pleomorphic type grade 2 (tubular formation 3, nuclear pleomorphism 2, mitotic rate 2), estrogen receptor-positive (ER) (strong, 90%), progesterone receptor-positive (PR) (strong, 80%), positive for HER-2/neu overexpression (3+) and Ki-67: 30% (Figures 2, 3). She underwent simple mastectomy and sentinel lymph node biopsy, pT1cN0. She is planned for adjuvant treatment with standard treatment protocols for HER-2/neu-positive early breast cancer.

### Case 9

A 40-year-old premenopausal woman presented with a progressive right breast mass which was later diagnosed to be locally advanced right breast cancer in January 2003. She was started on neoadjuvant chemotherapy along with trastuzumab followed by right modified radical mastectomy. Histopathology was consistent with invasive lobular carcinoma, tumor size 2 cm, and 6 out of 36 lymph nodes positive, positive for estrogen receptor (ER), positive for progesterone receptor (PR), and HER-2/neu-positive. Later, she was subjected to adjuvant radiation and was subsequently treated with tamoxifen as adjuvant hormonal treatment. She remained disease free on hormonal treatment for 4 years, but later she complained had swelling of her right arm due to lymph edema, along with chest wall recurrence confirmed to be recurrent breast cancer by histopathology. There was no metastatic disease on further work-up. For that reason, the patient was initially managed with palliative chemotherapy for a few months, but later was lost to follow-up by our institution.

### Discussion

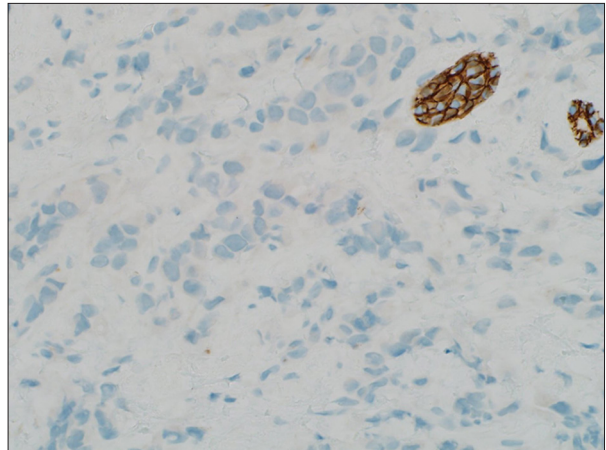
Overall, breast cancer is the most frequently diagnosed malignancy among Arab women, representing an estimated 17.7% to 19% of all new cancers in 2018 [7,8]. HER-2/neu-positive breast carcinomas constitute around one-fifth of breast cancers [9]. Considering its aggressive biology and adverse overall outcomes, HER-2 status has become an important predictive and prognostic factor in cancer of the breast. HER-2 testing is considered a standard of care in assessment of patients with breast cancer, and it serves an important role in assessing patients for further treatment.

ILBCs display a relatively low rate of HER-2/neu overexpression or amplification (3-13% in recent series) [10]. Most invasive lobular carcinomas express the estrogen receptor and progesterone receptor but lack (HER-2) amplification. Consistent with the rarity of this histopathological entity, only 9 cases were identified in almost 2 decades among our patient population. Most of the patients were diagnosed at about age 60 years, which is consistent with a previous case series study [2], but another report found the patient population was relatively younger [11].

Our first case is unique; she had history of AML (M2) after allogenic stem cell transplant almost 17 years ago, followed by refractory idiopathic thrombocytopenic purpura that resolved after splenectomy, and she was later diagnosed with HER-2-positive invasive lobular breast carcinoma. To the best of our knowledge, this is the first such case to be reported. However, the occurrence of breast cancer after completion of AML has been mentioned in previous 2 cases, but with a different histology [12,13]. The risk for developing a solid tumor increases over time and is highest among patients who underwent allogenic transplantation as post-remission therapy [12]. Patients who survive cancer, especially hematological and lymphoid malignancies after successful treatment, are at high risk for having secondary malignant neoplasms. As the survival times have increased, secondary solid tumors are emerging as a serious long-term complication. However, not all secondary malignancies are due to cancer-related treatment.

Our second case is of a patient with early left breast cancer, histopathology consistent with hormone-positive and HER-2/neu-negative invasive ductal cancer, who completed adjuvant treatment and developed bilateral early breast cancer after 15 years. This time, histopathology of the right breast was consistent with invasive lobular carcinoma, pleomorphic type, strongly positive for hormone receptors and negative for HER-2/neu, and the left breast had mass invasive lobular carcinoma, classic type, strongly positive for hormone status along with presence of HER-2/neu overexpression. As presented in the literature, synchronous bilateral breast cancer is still an uncommon diagnosis. In a case series, the incidence of synchronous bilateral breast cancer was reported to be 2.1% [14]. To the best of our knowledge, this case with unique presentation and diverse histology has never been published before.

Among the ILC HER-2-positive subtypes, 30% were classic ILC with loss of E-Cadherin expression (Figure 4) and another 60% of patients were of mixed non-classic variants (histologic pattern represented by nuclear pleomorphism) (Figure 3). Consistent with the published literature, HER-2 overexpression is often considered to occur in the pleomorphic variant [5]. HER-2 positivity is linked exclusively to a pleomorphic variant of ILC and is not encountered in classic ILC according to other published data [15].



**Figure 4.** E-cadherin immunostain showing loss of expression in the tumor cells, while the cells of the benign duct show strong membrane staining (original magnification 40 $\times$ ).

In our analysis, we found higher rates of ER positivity in HER-2-positive ILC. The higher rate of hormone receptor positivity was also observed in patients in the cohort of ILC in the HERA trial, which is likely to have contributed to the observed pattern of HER-2 overexpression, but the limited number of patients in this small subgroup prohibits us from making any strong conclusions [11]. Our finding provided another clue to the inverse correlation between ER/PR expression and HER-2 overexpression. Furthermore, even though ER expression levels decreased in the HER-2+ ILC group, the majority of cases were still positive for ER compared to PR. In the past, many studies have shown the association between HER-2 amplification or overexpression and reduced or absent PR expression [9]. However, in a recent study among Jordanian Arabs, HER-2/neu-positivity was significantly associated with both progesterone receptor status and tumor size [16]. Evaluation of the proliferation index showed that Ki-67 was not significantly different in HER-2+ patients with hormonal status.

In our series, 2 cases had a family history of cancer. In a recent study, 1 in 5 hereditary breast and ovarian cancers patients in the Arab world have BRCA mutations, although its association with HER-2-positive ILC remains unknown due to its rarity [17], and may need further studies. One patient initially neglected her symptoms and presented late for care. A recent review concludes that the experiences of Arab women with breast cancer are strongly influenced by their family, social, religious, and healthcare contexts. Many of these experiences have a negative impact [18]. The patients presented in our study were generally early-stage, but since it is a small series, we cannot generalize this.

Management of HER-2-positive invasive lobular cancer requires a multimodality approach in treating local disease, and systemic therapy plays an important role. Following diagnosis,

and due to axillary lymph nodes metastases, treatment options include surgical removal and combination chemotherapy before or after surgery followed by IFRT, and a continuation of the targeted therapy with trastuzumab to complete 1 year of treatment with or without hormonal treatment based on hormonal status [11]. However, in patients with metastatic disease and good performance status, the therapeutic approach requires treatment by dual anti-HER-2/neu blockade in combination with taxanes as the first-line therapy, which provides a significant survival advantage [19]. Subsequently, patients responding well are treated with maintenance dual anti-HER-2/neu therapy until disease progression [20].

Overall, HER-2 positivity is an independent prognostic factor which is associated with undesired survival outcomes in patients diagnosed with ILC [5]. Eight patients in our patient population were alive and well at last follow-up, while 1 patient

was lost to follow-up. However, the surveillance time was too short to evaluate long-term clinical outcome and to predict the benefits of anti-HER-2/neu therapy for patients with both early-stage and metastatic HER-2-positive ILC.

## Conclusions

In conclusion, HER-2-positive invasive lobular carcinoma of the breast is a rare entity among Arab populations, which is not represented before in literature. Further studies are warranted to explore the biology, molecular characteristics, and clinical course in this group of patients.

## Conflict of Interests

None.

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