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Breast Cancer Associated with Pregnancy: Good or Bad Prognosis? A Case Report and Review of the Literature

Leticia Mendoza-Galindo[1,2], Jaime de la Garza-Salazar[3] and Claudia Arce-Salinas[1]*

[1]Medical Oncology Department, National Institute of Cancerology, Mexico City; [2]School of Medicine and Health Sciences, Instituto Tecnológico y de Estudios Superiores de Monterrey, Monterrey; [3]Clinical Research Department, National Institute of Cancerology, Mexico City

ABSTRACT

Introduction: There is consistent information that suggests the presence of unfavorable clinicopathological characteristics in patients with breast cancer associated with pregnancy that report frequent involvement of nodes, locally advanced disease, less presence of hormone-sensitive tumors and higher incidence of metastatic disease. **Case report**: A 26 year-old female that, immediately after delivery, developed arm pain associated with functional limitation during the breastfeeding of her son in 2010. After humerous pathological fracture was found, workup started and showed a left breast tumor (5 × 4 cm in largest diameter), without skin involvement, and clinically negative axillary nodes. Biopsy of the breast mass revealed an invasive ductal carcinoma, moderately differentiated, ER and PR positive, and HER2 negative. Bone scan showed bone metastases. The patient was treated with chemotherapy based on 5-fluorouracil/doxorubicin/cyclophosphamide followed by weekly paclitaxel. Partial response was achieved and she continued with tamoxifen, palliative radiotherapy at humerous and monthly zoledronic acid. In July 2014, she presented with back pain and limitation of her daily activities; workup demonstrated disease progression to pelvis and vertebrae. Exemestane and everolimus was started, achieving total pain relief within two weeks. After three months of treatment, partial response was shown in CAT scan. **Conclusions:** Pregnancy associated breast cancer women have poor outcomes, characterized by the

Correspondence to:
*Claudia Arce-Salinas
Servicio de Tumores Mamarios
Instituto Nacional de Cancerología (INCan)
Av. San Fernando, 22
Col. Sección XVI, Del. Tlalpan
14080 México, D.F., México
E-mail: haydee_arce96@yahoo.com.mx

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presence of unfavorable clinicopathological characteristics, delay and difficulties in diagnosis, and physiological changes involving pregnancy that affects hormonal status and mammary tissue. In the clinical case that we present, even when she was diagnosed with metastatic disease, after four years of follow-up she has had a good evolution. (J CANCEROL. 2014;1:73-9)
Corresponding author: Claudia Arce-Salinas, haydee_arce96@yahoo.com.mx

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INTRODUCTION

Pregnancy associated breast cancer (PABC) is defined as breast cancer that is diagnosed during pregnancy, in the first postpartum year or at any time during lactation[1]. Incidence is not well described; Anderson, et al.[2] did a population-based cohort study from Swedish registers, reporting an increased incidence from 16.0 to 37.4 per 100,000 deliveries from 1963 to 2002. Gogia, et al.[3] reported a prevalence of 0.7% (26 cases of 3,750 new breast cancer patients). Eight out 26 cases were diagnosed in stage IV. The prognosis of PABC is poor. Schedin[4] has mentioned that the increase in hormone exposure may not contribute only with the aggressiveness, but also with the increasing metastasis; another factor that has been proposed is the mammary microenvironment, which might become tumor-promoting after pregnancy because of remodeling of the mammary gland. This remodeling is associated with proinflammatory and wound-healing mechanisms, involved in tumor-cell dissemination. Clinically, Gogia, et al.[3] reported a median tumor size at diagnosis of 5.5 cm. Of the ER/PR negative tumors, 56 and 38% of them, respectively, were HER2 positive at three years of follow-up; the overall survival was 50%. We report a PABC case, diagnosed in stage IV, with multiple bone metastases. The patient has good response to endocrine therapy, and she is still alive four years after her diagnosis.

CASE REPORT

A 26-year-old female, without any relevant family or personal history. Her present illness started in 2010, immediately after delivery, during breast-feeding of her son, she developed arm pain associated with functional limitation. Humerous pathological fractures were found (Fig. 1 A). Workup started and showed left breast tumor, measuring 5 × 4 cm in largest diameter, without skin involvement, axillary nodes were negative at clinical examination. Biopsy of the breast mass revealed invasive ductal carcinoma, moderately differentiated, ER and PR positive, and HER2 negative. Bone scan showed bone metastases (Fig. 1 B). The patient was treated with chemotherapy based on four cycles of 5-fluorouracil/doxorubicin/cyclophosphamide (FAC) followed by weekly paclitaxel 12 times. With this treatment, partial response was achieved, and after chemotherapy was finished, she continued with tamoxifen. She also received palliative radiotherapy at humerous and monthly zoledronic acid. She remained asymptomatic until July 2013, when back pain was present, and magnetic resonance imaging (MRI) confirmed disease progression. Tamoxifen was changed to goserelin and anastrozole; accompanied with vertebroplasty, she continued on zoledronic acid every three months. One year later (July 2014), pain exacerbation was present and a new MRI demonstrated disease progression (Fig. 2 A, B and C). The pain was continuous and intense, associated with limitations in her daily activity, especially walking. Further workup included bone scan and CAT scan, which confirmed disease progression to pelvis and vertebrae. Exemestane and everolimus was started, achieving total pain relief within two weeks. After three months of treatment, partial response was showed in CAT scan (Fig. 2 D, E and F) and the treatment is ongoing.

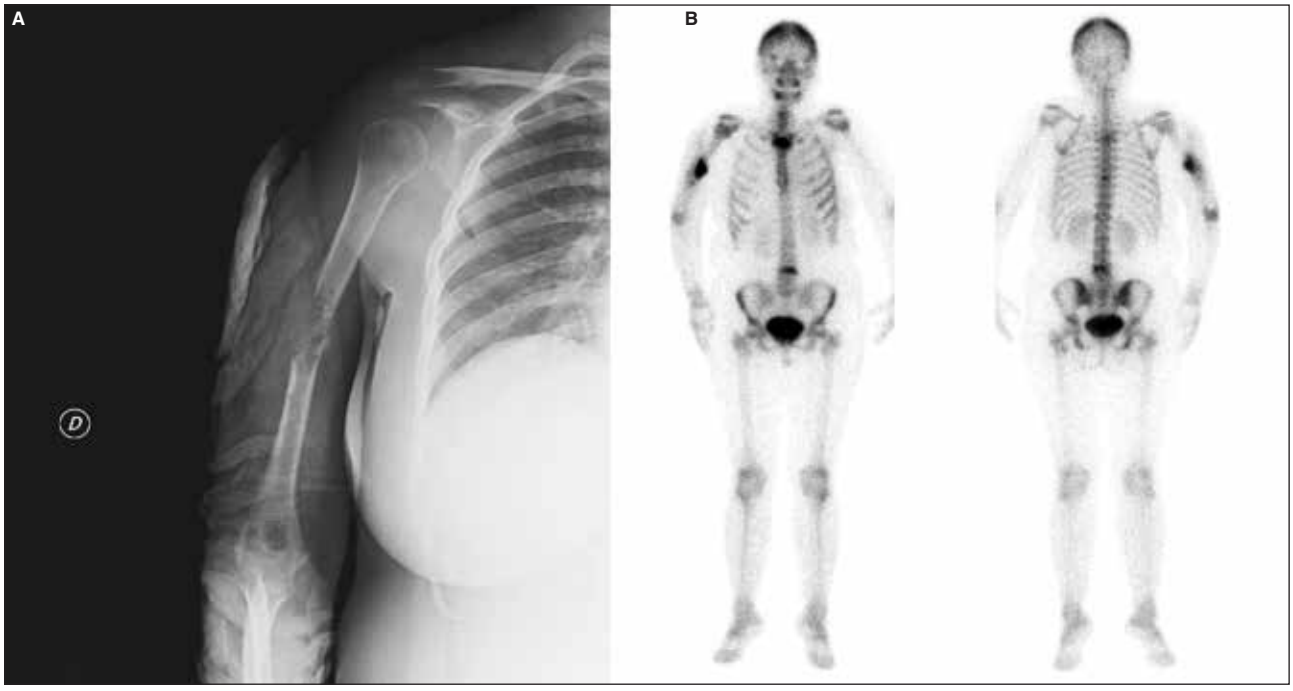


Figure 1. A: Pathological fracture of right humerus. Lytic lesion is observed with permeative pattern at the diaphysis, associated to a pathological fracture. **B:** Bone scan. After administration of the radiopharmaceutical tracer, suitable concentration is shown within the bone structures, with irregular distribution. Abnormal concentration zones at the manubrium, head and middle third of the right humerus, eighth thoracic vertebra and L4 is observed.

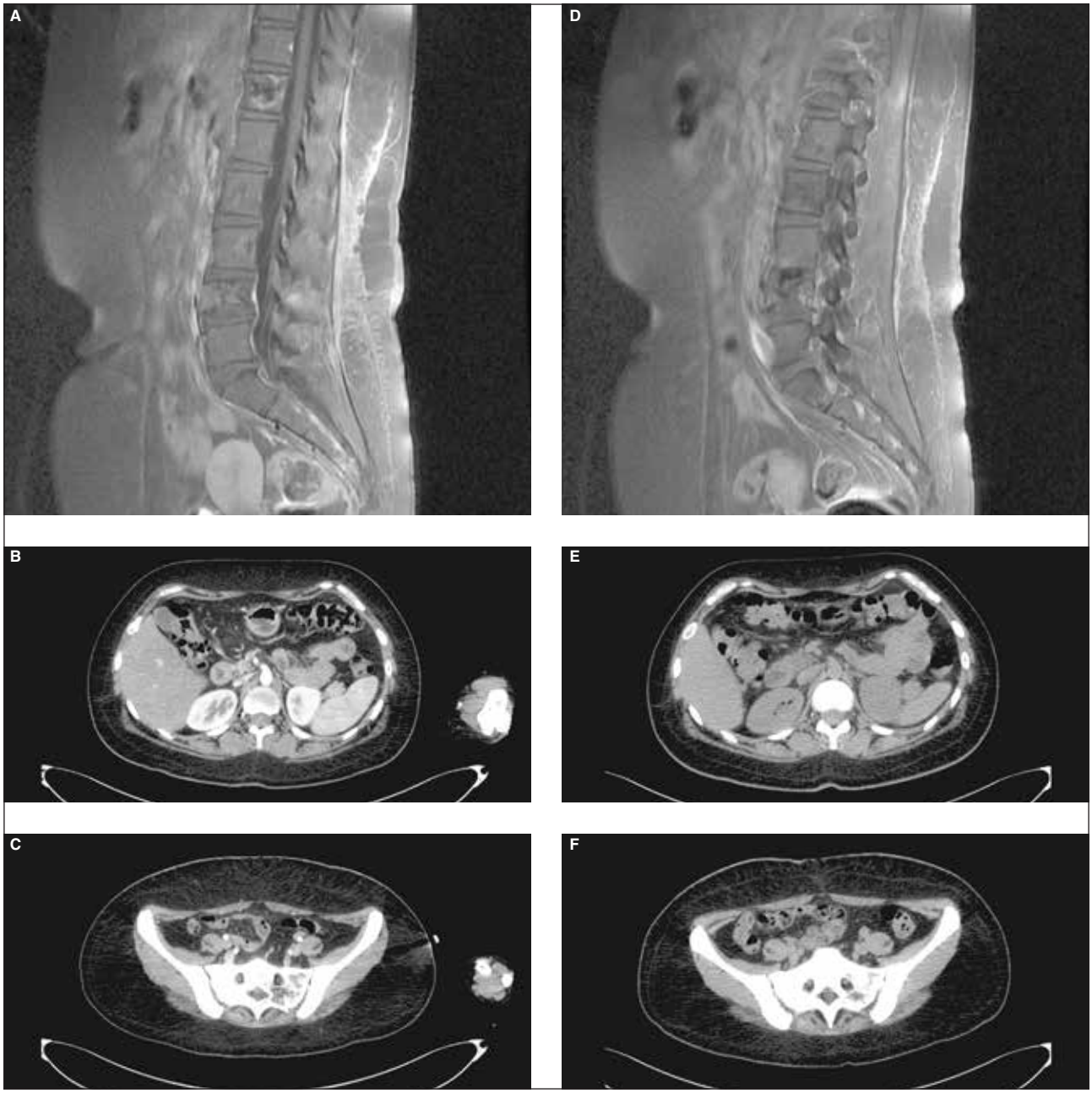
DISCUSSION

There is disparity between authors about the definition of PABC. Most of them define it as the development of breast cancer during pregnancy or within a year following delivery[1,5,6], but there are some that define this pathology considering postpartum periods ranging from six to 24 months[6]. It occurs in 1/3,000-10,000 pregnancies[1,5,6], so 10% of the patients with breast cancer younger than 40 years of age will be pregnant at diagnosis[6]. Although no specific risk factors for breast cancer in pregnancy are known[1], it is expected that this disease will become more frequent since there is an increasing trend for women to delay childbearing[7].

It is important to point out that 48% of women with an early onset of breast cancer have a positive family history and 9% are associated to BRCA1 or BRCA2 mutations[7]. A study involving more than 16,000 women shows the age of 35 as a crucial point. Pregnancy after this age was associated with a permanent increase in breast cancer risk (3.5% for every year that childbearing was delayed). A woman who had a baby at 35 years of age was found to have a 50% increased risk of developing breast cancer compared with a young mother of 20[8].

Regarding clinical characteristics, most cases present as a palpable mass and rarely are associated with nipple discharge[1,3,5-7]. Consistent information suggests the presence of unfavorable clinicopathological characteristics in this group of patients: frequent involvement of nodes, locally advanced disease, less presence of hormone sensible tumors, and higher incidence of metastatic disease.

A series of 117 cases of breast cancer during pregnancy between 1993-2009, in France, reported a mean age at diagnosis of 33.7 years with a



Figures 2. A, B and C: Disease progression in July 2014. In July 2014, spine MRI and CAT-scan showed multiple blastic lesions in almost all dorso-lumbar levels that showed diffuse enhancement of ring type after the contrast administration. **D, E and F:** Response after everolimus/exemestane was started. Performed in September 2014, revealed partial response after everolimus/exemestane was started, with improvement of blastic lesions in comparison with previous workup evaluation.

mean time to diagnosis of 5.8 months; 105 patients (89.7%) were diagnosed with a palpable mass and 95 (81.2%) were diagnosed after delivery, most of them (80 women) in the first 12 months after delivery. Prognostic factors were unfavorable: frequent lymph node involvement (51.8%), high-grade tumors (63.2%), hormone receptor negativity (45.9%), and HER2 positivity (38.7%)[5]. In a retrospective study in India, 26 women with this condition were found in an 11-year period; the

median age at diagnosis was 26 years and median duration of symptoms was 11.5 months. The median clinical tumor size was 5.5 cm, 17 patients were stage II-III, and eight patients (30.7%) had metastatic disease at the time of diagnosis; 12 women were ER negative (n = 23) and eight HER2 positive (n = 21)[3]. Gentalini, et al. did a retrospective study during seven years. They analyzed 21 Italian patients with breast cancer during pregnancy. The median age at diagnosis was 36 years, median tumor size was 2.4 cm, and 10 patients had positive axillary lymph nodes; regarding hormonal status, six patients had ER- and PR-negative tumors[9]. Even when breast cancer during pregnancy is characterized by more advanced disease stage, poorly differentiated tumors that tend to be non-endocrine responsive, and delays in diagnosis on the part of patient and physician, there is a breakthrough for research in this group of women because most reports have been retrospective in nature and have not included enough detail about patient and tumor characteristics to determine how generalizable the results are for routine clinical practice[10].

Most data available about treatment of breast cancer during pregnancy are limited and consist of case reports, case series, and retrospective registries. Nevertheless, the information is also consistent that chemotherapy can be safely administered to women during the second and third trimesters of pregnancy, and there are unlikely to be serious adverse long-term effects on the fetus[11]. Generally, these are the same indications as in a non-pregnant breast cancer patient, and chemotherapy is typically administered without dose modifications in the pregnant woman and adjusted and dosed per actual weight and body surface area[12]. The MD Anderson Cancer Center has a multidisciplinary prospective protocol since 1992, where patients with primary or recurrent breast cancer diagnosed during pregnancy are managed with locoregional therapy and FAC as a single-arm standard chemotherapy as clinically indicated, with a median of four cycles. Up to 2006, they reported 57 patients (32 in the adjuvant setting and 25 in neoadjuvant setting); all patients who delivered had live births, 40 are alive and disease-free, three have recurrent breast cancer, 12 died from breast cancer, one died from other causes, and one was lost to follow-up. Regarding women who received neoadjuvant FAC, 32% (six patients) had a pathologic complete response and four had no tumor response to chemotherapy. In this cohort, child outcomes reported one child with Down syndrome and two with congenital anomalies (club foot; congenital bilateral urethral reflux). The MD Anderson group concludes that PABC can be treated with FAC chemotherapy during the second and third trimesters without significant short-term complications for the majority of children exposed to chemotherapy *in utero*, but a future evaluation of the children is needed to assess late side effects such as impaired cardiac function and fertility[13]. A retrospective London series that includes five hospitals, during 18 years, identified 28 women who received chemotherapy during pregnancy: 16 of them were given doxorubicin/cyclophosphamide and 12 received cyclophosphamide/methotrexate/5-FU. Only one patient treated during the first trimester had a spontaneous abortion, and the rest of the women were treated during second and third trimesters and did not present serious adverse consequences for mothers and neonates[11]. There is little information about the use of taxanes during pregnancy, and most of this is as case reports; it has been shown that the use of chemotherapy based on taxanes after the first trimester has no significant risk to the mother and the fetus[14].

Biological agents have been poorly studied. Up to 2010, only 11 case reports had studied the use of trastuzumab during pregnancy: five of them were associated with oligohydramnios and two with anhydramnios. Given this concern, trastuzumab therapy should be delayed until after delivery[12]. Regarding endocrine therapy, tamoxifen is not recommended during pregnancy because it has been associated with congenital malformations in up to 20% of exposures, including Goldenhar's syndrome and ambiguous genitalia, and

also with pregnancy complications such as vaginal bleeding and spontaneous abortion[12-14].

Surgery is also considered a viable option treatment for PABC; the risks of this procedure are spontaneous abortion and preterm labor. Radiation therapy generally is not offered because of its teratogenic potential and induction of childhood malignancies and hematologic disorders[6].

The relationship between pregnancy and the outcome of breast cancer remains controversial[15]. Nevertheless, most authors demonstrated poor prognosis in this group of patients with breast cancer during pregnancy. Bonnier, et al. performed a comparative analysis of patients with or without PABC: 154 PABC patients versus 308 with non-pregnancy associated control patients. They found a major proportion of inflammatory breast cancer in PABC patients (26.0 vs. 9.1%; < 0.00001), and there were also more women with metastases at the time of diagnosis (10.6 vs. 4.9%; p = 0.025). With prognostic factors, they eliminated patients with inflammatory breast cancer (PABC [n = 114] vs. non-PABC without pregnancy [n = 280]), and they found a delay in diagnosis (2.16 vs. 1.18 months; p < 0.001), major median tumor size (4 vs. 3 cm; p = 0.024), more advanced clinical stage (p = 0.04), and major clinical node involvement (p = 0.0001). The probability of metastasis-free survival at five years was 0.50 in the PABC group vs. 0.70 in the non-PABC group (p < 0.007) and the overall probability of survival was 0.68 vs. 0.77 (p = 0.048). In the multivariate analysis, pregnancy was an independent risk factor for metastasis and poor overall survival[15]. A multicenter cohort that compared 311 patients with PABC versus 865 non-PABC found that pregnant women had worse prognosis for recurrence (HR 1.34 for disease-free survival; 95% CI: 0.93-1.91; p = 0.14) and for overall survival (HR 1.19; 95% CI: 0.73-1.93; p = 0.51). Cox regression estimated that the five-year disease-free rate for pregnant patients would have increased from 65 to 71% if these patients had not been pregnant, and the five-year overall survival rate would have increased from 78 to 81%[16].

In the French series, overall five-year survival was 81.8% (95% CI: 74.2-90.1), disease-free survival 56.5% (95% CI: 47.1-67.7), locoregional relapse-free survival 74.4% (95% CI: 65.7-84.3), and metastasis-free survival 72.5% (95% CI: 63.8-82.3). Metastatic events involved several sites in 53.3% of patients: bone only in 16.7%, liver only in 10%, and other sites in 20% of cases.[5] After a median follow-up of 25 months, the Italian group showed seven patients had developed distant metastases, with five deaths and two women alive with disease, with a median time to progression of 16.8 months[9]. In another study based in the Swedish Cancer Registry that includes 14,693 women, those who were diagnosed during pregnancy had a five-year survival rate of 52.1% (95% CI: 41.2-61.9) and a 10-year survival rate of 43.9% (95% CI: 33.1-54.2), compared with survival rates of 80.0% (95% CI: 79.6-81.4) and 68.6% (95% CI: 67.5-69.7) in women diagnosed more than 10 years since childbirth[17].

Worse outcomes have been related to the delay of diagnosis, difficulties in the examination and evaluation, promotional effects of pregnancy-associated hormones, tissue remodeling after pregnancy and lactation, and the rise of childbearing[4,5]. None of this information is currently conclusive.

It is common that neither the doctor nor the patient considers the possibility of an oncology diagnosis, especially during pregnancy, and tend to defer the investigations until after delivery. In clinical examination, breasts in pregnant women are more nodular and hypertrophied, and it can be difficult to confirm clinically the presence of a mass and even breast inflammation can be mistaken for puerperal mastitis[5]. Imaging studies also differ, some because of the difficulties with interpretation due the increase in mammary density, the fear of X-ray related risk, or the reluctance to request mammography in young women[5,15]. Breast ultrasound has a high sensitivity and specificity for the diagnosis of PABC[18]. This is the first diagnostic instrument when a breast mass and the axillary area need to be assessed in a pregnant woman[1] and

even if this method is not available, mammography has demonstrated to be a safe procedure during pregnancy as irradiation to the fetus is negligible[5].

There is a hypothesis about the effect of gestational hormones being responsible for the poor prognosis in this group of patients, principally associated with the increased concentrations of estrogen, insulin-like growth factor-1 (IGF-1), and progesterone. So, gestational hormones increase breast cancer risk and negatively affect prognosis by virtue of their growth-promoting effects on hormone-responsive breast tumor cells. This theory has been supported by some studies that indicate that preeclampsia (a condition involving placental breakdown and characterized by decreased concentrations of systemic estrogen and IGF-1) has a lower risk for PABC[4]. On the other hand, there is a change in mammary gland physiology: the process following lactation or even if the women do not nurse is known as involution. This process is characterized for a tissue-remodeling course that is similar to the programs that are activated during wound healing and inflammation. It has been suggested that this inflammatory microenvironment and its pro-oncogenic potential are associated with poor prognoses[4].

CONCLUSIONS

Pregnancy associated breast cancer women have poor outcomes characterized by the presence of unfavorable clinicopathological characteristics, delay and difficulties in diagnosis, and physiological changes involving pregnancy that affect hormonal status and mammary tissue. Every suspicious breast mass in pregnant women should be fully investigated with a complete diagnostic workup. It is recommended that a multidisciplinary assessment should to be made for this group of patients, including a medical oncologist, surgical oncologist, gynecologist, pediatrician, and geneticist. In the clinical case that we present, even when the patient was diagnosed with metastatic disease, after four years of follow-up she has had a good evolution. In June 2014 she developed progression and we started everolimus plus exemestane and one month after initiation of this treatment, pain was relieved 100% and even radiation was cancelled. Nowadays, she continues with the same therapy, no toxicity has developed, and she is asymptomatic.

DISCLOSURES

The authors disclose no potential conflicts of interest.

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