CASE REPORT

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Advanced metastatic breast cancer in pregnancy: the imperative of physical breast examination in pregnancy

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Abstract

Breast cancer is the most frequent cancer diagnosed among women; its association with pregnancy is not encountered. As childbearing age is increasing, the diagnosis of breast cancer associated pregnancy tends to be more often than years ago. Here we report a case of a 37-year-old patient, gravida 7, para 7, diagnosed at 30 weeks gestation with metastatic breast cancer. The patient presented to hospital due to an altered performance status. Obstetrical evaluation was within normal range. A metastatic infiltrating breast cancer poorly differentiated (G3) with satellite skin lesions (T4b), ipsilateral axillary and supraclavicular lymph nodes (N3), lung metastasis bilateral with pleural effusion and hepatic metastasis (M1), were diagnosed. The tumor was positive for estrogen receptor (ER) and progesterone receptor (PR) status and negative for human epidermal receptor protein-2 (HER-2)/neu immunostaining. Due to a significant worsening of the patient's dyspnea, a Caesarean section was performed under spinal anesthesia, at 30 + 2 days; and a newborn weighing 1700 g was delivered without malformations. The unsuccessful management of the cancer was inevitable and the patient died two weeks later. Despite her hospitalizations for six prior deliveries (last birth was one year ago), the presence of a palpable tumor was never observed. We aim to highlight the importance of the clinical examination at any given point in pregnancy in order to detect, investigate and treat any suspect tumor of the breast.

Keywords: breast neoplasm, perineural invasion, pregnancy, lymph node metastasis, pleural effusion.

Introduction

The incidence of pregnancy associated breast cancer is one to 3000 pregnancies [1–3]. In Romania, breast cancer is the most frequent cancer diagnosed among women; in accordance with the *World Health Organization* (WHO), the mortality rate is estimated to be around 14.7 per 100 000 women per year [4]. As childbearing age is increasing, the diagnosis of breast cancer associated pregnancy tends to be more frequent than 20 years ago. Muenst *et al.* demonstrated the protective effect of pregnancy before of age of 20 on the appearance of breast cancer, a negligible protective effect of bearing first full term pregnancy in women between 30 and 34, and an increased risk in women with first full-term pregnancy occurring after the age of 35 [5].

Breast cancer is composed of a multitude of pathological subcategories which differ both, from a genetically and a molecular standpoint; breast cancer diagnosed during pregnancy may differ from that diagnosed in postpartum period [6].

The structure of the mammalian gland varies during physiological periods including puberty, onset of sexual activity, pregnancy, postpartum period and menopause, undergoing cellular division, differentiation and growth throughout the mentioned stages [7]. The number of mammalian stem cells varies under hormonal changes, thus adjusting to these physiological states. The raise of mammalian stem cell numbers was correlated with an increasing risk of breast cancer during pregnancy [8]. Prognostic differences and treatment options in patient outcomes are based on histological grade and estrogen receptor (ER) and progesterone receptor (PR) status, as well as the expression level of human epidermal growth factor receptor-2 (HER-2)/neu. Asztalos *et al.* demonstrated for human breast tumors that the normal breast environment following pregnancy is associated with up-regulation of inflammation related genes; the authors established a differential regulation of the same set of genes in breast tumors from nulliparous and multiparous women [9].

Studies conducted on human breast tissue showed that pregnancies in younger women reduce the number of receptors and intercellular reactions [10], therefore reducing the risk of developing breast cancer later in life.

Here we report a case of a 37-year-old multipara, with a metastatic breast cancer during her 7th pregnancy. Informed consent for the research and publication of the data was obtained from the patient, according to the *Declaration of Helsinki*, revised in 2000 in Edinburgh. Our principal aim was to highlight the importance of the clinical examination at any given point in pregnancy, in order to diagnose any tumor of the breast.

Case presentation

The study was performed according to the *European Communities Council Directive* of 24 November 1986 (86/609/EEC) and the treatment of the patient followed

the local Ethical Regulations, approved by the Ethical Committee. The patient has acknowledged and signed the Informed Consent for the treatment and for using this case for educational and scientific research purposes.

M.C., a 37-year-old pregnant female, unemployed, from a rural area, was referred to "Filantropia" Hospital in Bucharest, Romania, in October 2016 from a county hospital, at 30 weeks gestation of her 7th pregnancy, for a left breast cancer with cutaneous metastasis.

The patient presented on admission during routine physical examination with pallor and a poor performance status; she was capable of limited self-care and she was confined to bed more than 50% of waking hours, due mainly to a permanent dyspnea and tachypnea, with a slow onset since several weeks ago. The patient was O_2 therapy dependent, with moderate tachycardia and normal blood pressure, but no cardiac assessment (including left ventricular ejection fraction) had been performing. Her body mass index (BMI) was less than 18.5 kg/m^2 and she did not gain any weight during actual pregnancy. No follow-up or laboratory tests during pregnancies, only during the stay in hospital for giving birth.

From her medical records: a breast lump was noted from two years ago; and six registered live births with children aged between one and 15. The last birth took place one year ago, in a rural hospital setting; for all children, she has breastfeeded; no pathological or radiological exploration of the breast lump during their stays in hospital; one year ago, the patient considered the ulcerate lesion of the breast to be due to breastfeeding.

The patient was diagnosed two weeks ago, during her 7th pregnancy, in another hospital, with left breast cancer.

Clinical examination of the breast revealed a deep, yet palpable, adherent tumor, of about 4 cm, with skin alterations, which included an ulcerous necrotic area in the supero-external quadrant of the left breast, erythematous and tender patch (Figure 1). The tumor involved almost the whole left breast with satellite skin lesions (T4b), ipsilateral axillary and supraclavicular lymph nodes (N3) and lung metastasis and bilateral pleural effusion (M1) – on chest X-ray (Figure 2, a and b). The patient was screened for tuberculosis, due to respiratory symptoms.

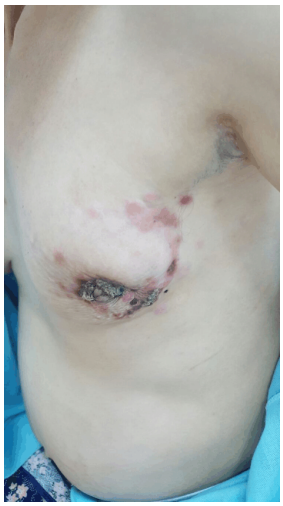

Figure 1 – ***Clinical examination of the breast demonstrates skin metastasis of the breast cancer.***

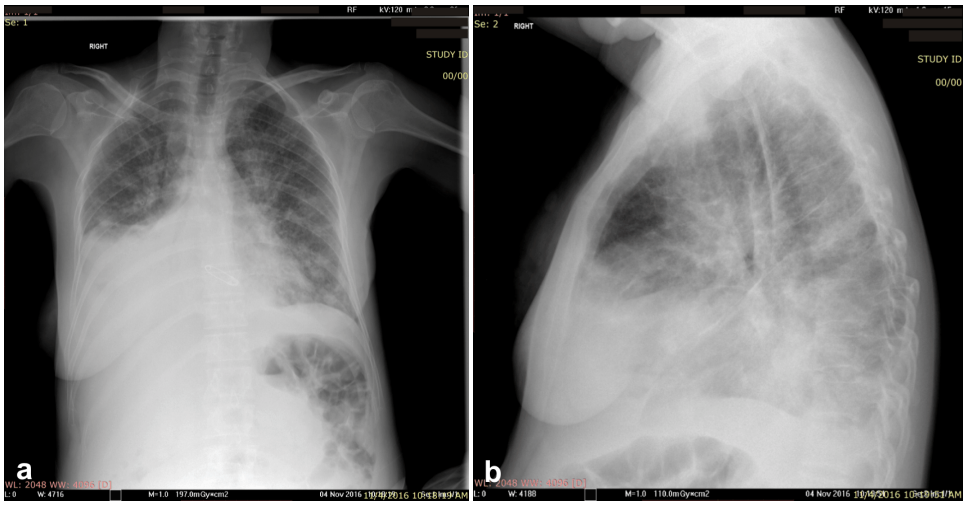

Figure 2 – ***Chest X-ray: (a) Depiction of upright postero-anterior view of the chest demonstrates canon-ball pulmonary metastases of breast cancer; (b) Depiction of lateral view of the chest demonstrates secondary pneumothorax of metastatic breast cancer.***

Pathology report showed an infiltrating (invasive) ductal breast carcinoma. Microscopically, an intraductal epithelial proliferation with irregularly extends through the stroma as cords and nests was seen (Figure 3a), atypical tumoral cells forming Indian file pattern (Figure 3b), rare tubular formations with central core, histological grade 3 (Figure 3c) and perineural invasion (Figure 3d). The tumoral cells are nuclei of high grade, markedly pleomorphic, with irregular contour and prominent nucleoli, eosinophilic cytoplasm and high mitotic rate.

A panel of commercially available antibodies was applied to formalin-fixed, paraffin-embedded tissue cross-sections: gross cystic disease fluid protein-15 [GCDFP-15, clone 23A3, Leica Biosystems, UK, ready to use (RTU), antigen retrieval in ethylenediaminetetraacetic acid (EDTA), 20 minutes], cytokeratin (CK) 7 (clone OV-TL 12/30, Dako Cytomation, Denmark, 1:200 dilution, antigen retrieval in EDTA, 15 minutes), E-cadherin (clone 36B5, Leica Biosystems, UK, RTU, antigen retrieval in EDTA, 15 minutes), HER-2/neu (clone SP3, Cell Marque, USA, 1:300 dilution, antigen retrieval in EDTA, 20 minutes), estrogen receptor (ER, clone 6F11, Leica Biosystems, UK, RTU, antigen retrieval in EDTA, 20 minutes), progesterone receptor (PR, clone 16, Leica Biosystems, UK, RTU, antigen retrieval in EDTA, 20 minutes) and Ki-67 (clone MM1, Leica Biosystems, UK, RTU, antigen retrieval in EDTA, 20 minutes).

The immunohistochemistry (IHC) confirms the breast origin of the carcinoma: GCDFP-15 and CK 7 were positive in the cytoplasm of tumor cells (Figure 4) and the ductal type of invasive carcinoma (E-cadherin was positive in the carcinomatous cells (Figure 5). The HER-2/neu immunostaining (Figure 6) revealed a negative tumor (score 0) but both hormone receptors (ER – Figure 7a

and PR – Figure 7b) were present in the tumor cells. The proliferative activity of the tumor was evaluated using Ki-67 immunostaining, and Ki-67 proliferative index was 50% (Figure 8).

A semiquantitative method for assessing the grade of differentiation of the tumor was used: each of the histological grading parameters (the percentage of tubule formation, the degree of nuclear pleomorphism and accurate mitotic count) were scored from 1 to 3. To obtain the overall tumor grade the scores for each category was added: 3 + 3 + 2 = 8; the invasive ductal carcinoma was poorly differentiated (G3).

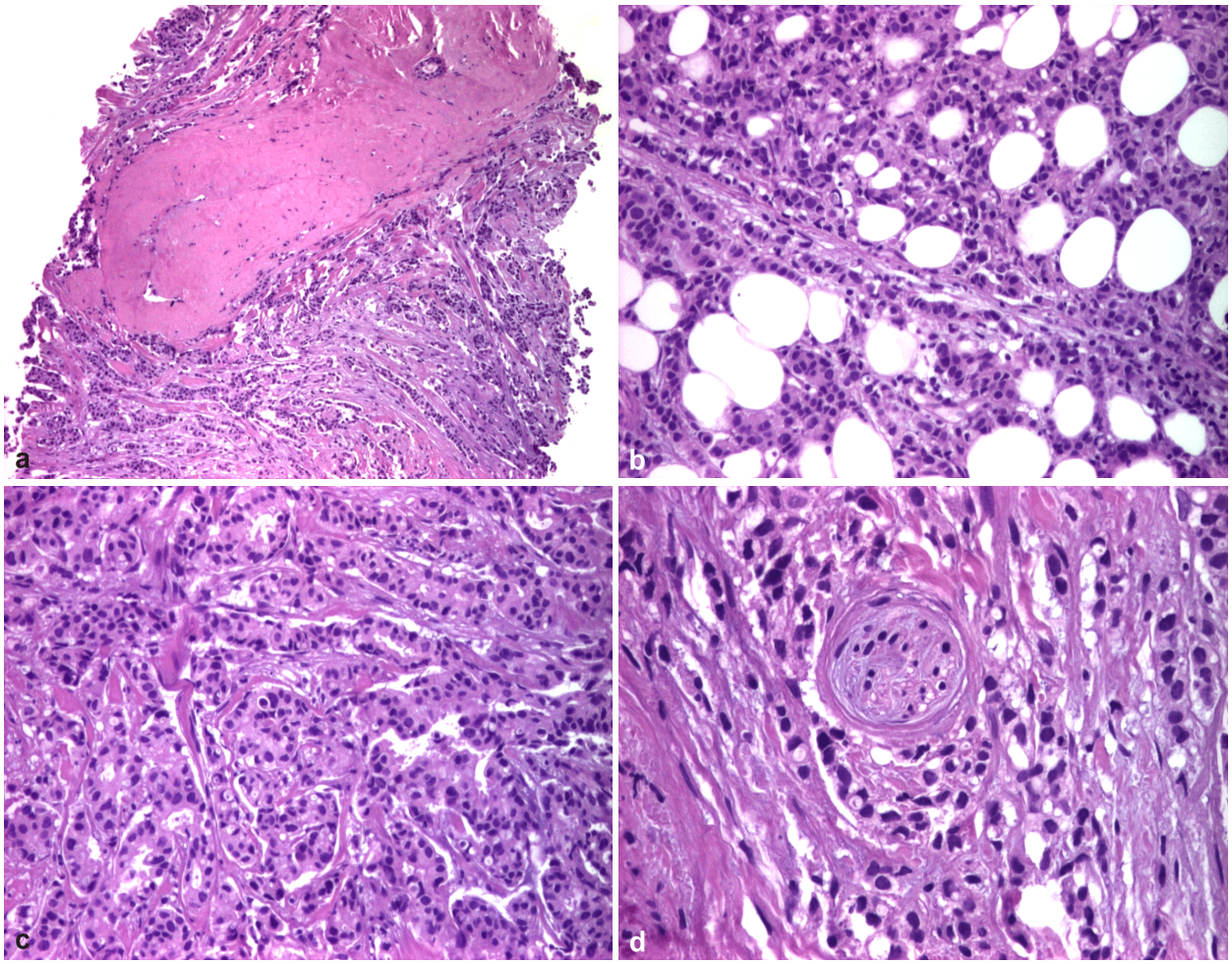

Figure 3 – ***Infiltrating ductal breast carcinoma: (a) A poorly differentiated (grade 3) tumor, periductal elastosis; (b) Malignant cells forming Indian file pattern invasion in the adipose tissue; (c) Histological grade 3 breast carcinoma, with a marked degree of cellular pleomorphism, frequent mitoses and no tubule formation; (d) Infiltrating ductal breast carcinoma, tumoral perineural invasion. Hematoxylin–Eosin (HE) staining: ×40 (a); ×100 (b and c); ×200 (c).***

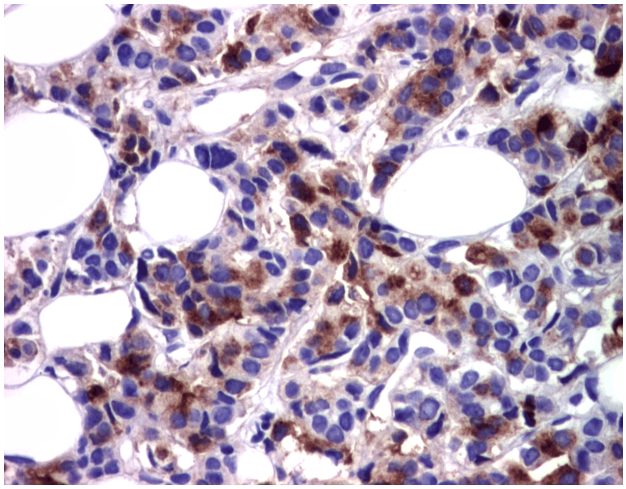

Figure 4 – ***GCDFP-15 expression by IHC was positive in the cytoplasm of tumor cells, ×200.***

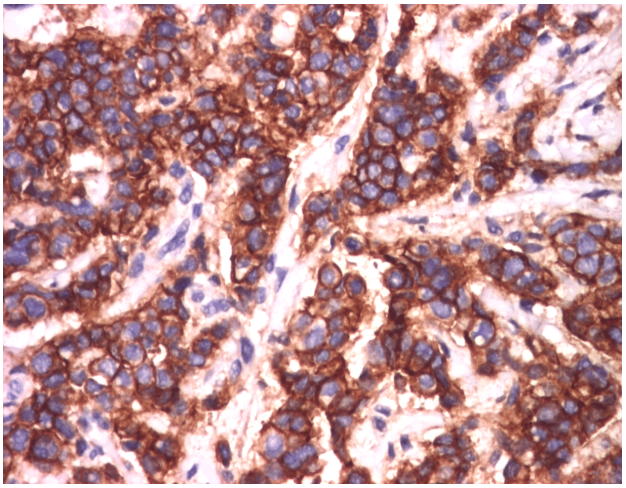

Figure 5 – ***E-cadherin expression by IHC was positive in tumor cells, ×200.***

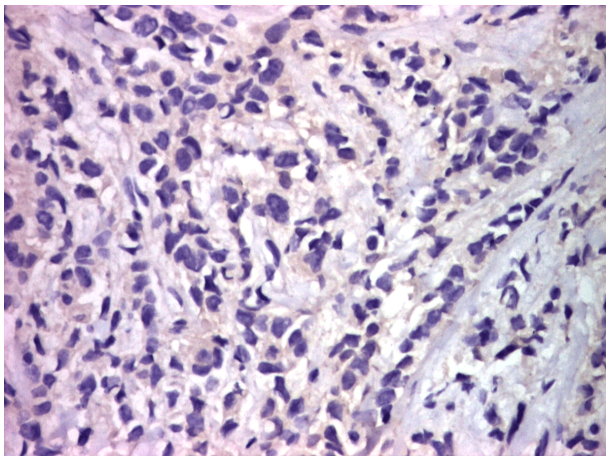

Figure 6 – ***HER-2/neu membrane staining status by IHC was negative, score 0, ×200.***

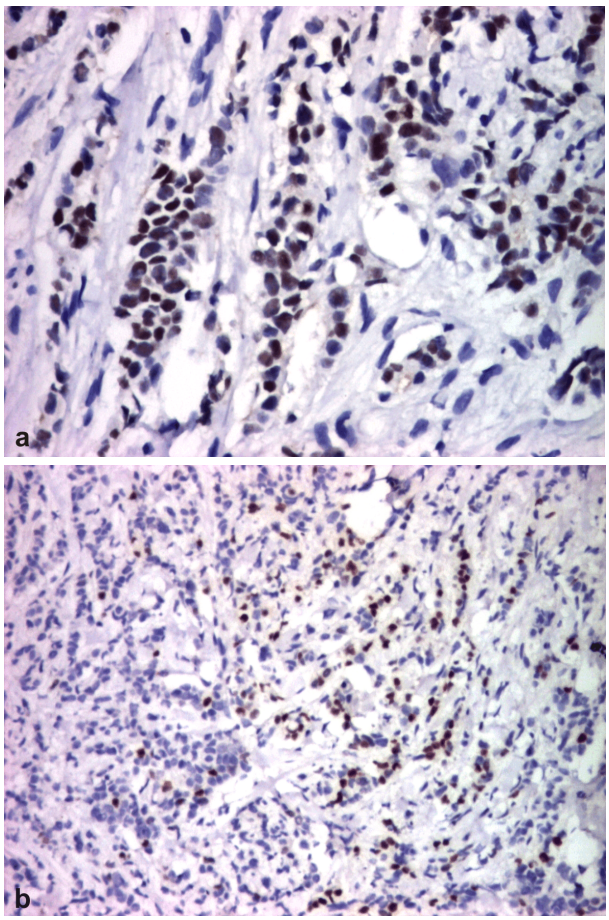

Figure 7 – ***(a) ER status was positive, ×200; (b) PR status was positive, ×100.***

External positive tissue controls were selected and undergone fixation and processing in a manner as closely similar as possible to the test tissue. As an external control, we used a breast cancer specimen with a known HER-2/neu score 2+, CK 7, E-cadherin and GCDFP-15. The same tissue was positive for ER and PR receptors and was used as an external positive control for hormonal receptors. As an external positive tissue control for Ki-67, we used a sample of a histological normal lymph node. Antigens internal to the patient sample may also be used for this purpose, if present. In order to evaluate the specificity of the IHC tests to identify false-positive staining reactions, we used negative reagent controls. This was represented by patient samples to which primary antibody was replaced with non-immune immunoglobulin serum same specie as primary antibody.

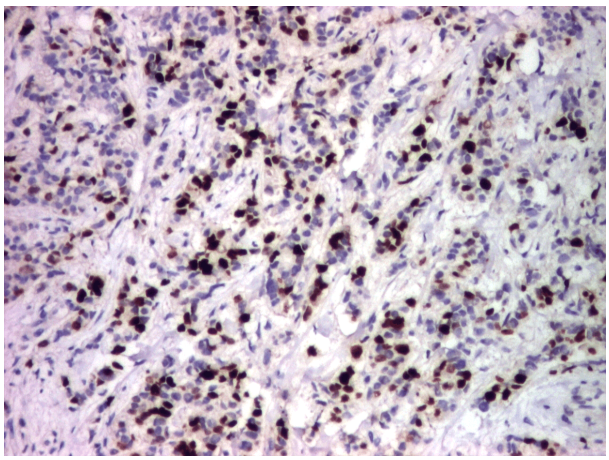

Figure 8 – ***Ki-67 immunostaining expression: Ki-67 proliferative index was 50%, ×100.***

The complete blood count (CBC) tests, biochemistry and coagulation panels were within normal ranges.

In our Institution, the multidisciplinary team proposed starting chemotherapy, in order to achieve a better quality of life and to avoid a premature delivery. The regimen proposed was Doxorubicin 60 mg/m^2 + Cyclophosphamide 600 mg/m^2. Chemotherapy was supposed to start following cardiac assessment and tuberculosis test results.

Due to a significant and unexpected worsening of patient's dyspnea, a Caesarean section was performed under spinal anesthesia, two days following presentation to our Clinic. A female newborn was delivered, weighting 1700 g, Apgar score 6/7/8. Postpartum obstetrical evolution was unremarkable.

Intraoperative findings included a tumor of about 1/0.5 cm situated in the right liver lobe.

The patient was referred the following day to the Department of Pulmonology for the treatment of acute respiratory failure. An imaging assessment was performed, demonstrating the existence of lung, liver and bone metastases, as well as an important pericardial effusion. The beginning of chemotherapy was postponed due to significant alteration of performance status. Two days later, the patient developed cardiac tamponade; a new surgical procedure taking place – a pericardial window. Unfortunately, no pathological exam of surgical pericardial specimen was obtained.

Although the hemodynamic parameters were stabilized, the patient was not considered a candidate for chemotherapy. Supportive care was initiated. One week later, the patient was transferred on request to the nearest palliative county hospital. Death was registered a few days later.

Discussion

This case emphasizes the importance of a complete physical examination upon each arrival at the doctor's office; it is of utmost importance to conduct these exams on patients with limited access to medical health care facilities. Increasing maternal age for childbearing over 32 and parity were associated with increased risk of breast

cancer; women in pre-symptomatic phase are free of palpable tumor. Reproductive factors and the number of live births was considered to exert protective effects due to the hormonal changes during pregnancy and lactation [11], but it is true for women giving birth less than 25. We now know that the cellular and molecular mechanisms underlying pregnancy and have hormonal negative influence on tumorigenesis [12].

In today's medical world, due to advancement in oncological treatment options and diagnostic techniques, such clinical presentations seem to be from ancient medical records. Breast cancer diagnosed during pregnancy was thought to be more aggressive, but more authors suggest no significant differences in disease-free or overall survival in patients with breast cancer diagnosed and imperative treated during pregnancy compared with non-pregnant comparison groups, when controlled for disease stage [13].

The major invasive breast tumor types were classified into anatomopathological subtypes: infiltrating ductal, invasive lobular, ductal/lobular, mucinous (colloid), and tubular, medullar and papillary carcinomas.

Assessment of histological grade is an important determinant of breast cancer prognostication and should be incorporated in algorithms to define management for patients with breast cancer [14].

Histological grade remained an independent prognostic factor for ER-positive tumors, even after the inclusion of gene signatures in a multivariate models [15].

There was a high correlation between histological grade (G3) and poor prognosis outcome.

In our case, we performed an IHC examination in order to confirm breast origin of the carcinoma, because the infiltrating breast cancer was poorly differentiated and no *in situ* carcinoma was seen (CK 7 and GCDFP-15 markers). Generally, ductal and lobular carcinomas, either invasive or *in situ* can be distinguished in HE-stained cross-sections; but, in our case, getting the accurate diagnosis was using IHC (E-cadherin marker). In our daily practice, all invasive breast cancers are tested for molecular markers such as ER, PR, HER-2/neu, Ki-67, in order to establish the optimal management.

A large study conducted over a 30-year period with more then 50 000 cases demonstrated that the ER and PR negativity, HER-2/neu and Ki-67 positivity, triple-negative status, and a basal-like phenotype were more frequently observed in clinically-detected breast cancers than in screen-detected breast cancers [16]. Maternal age, rather than pregnancy appears to determine the biological features of breast cancer [17].

In the present case, the ER and PR markers were positive, with HER-2/neu marker negative; the clinical appearance of breast cancer with cutaneous metastasis and supraclavicular and axillary adenopathies to a pregnant patient was remarkable. Cutaneous metastasis is considered by many authors to be more likely associated with breast cancer than with any other female related cancers [18]. The rate of cutaneous metastasis of breast cancer is 2.42% [19].

Similar to non-pregnant patient, the presence of a palpable tumor as well as nipple bleeding that can lead to further investigations in order not to overlook a breast cancer diagnosis. Our case confirms the fact that the pregnancy delayed the cancer diagnosis, despite the fact that pregnancy usually delays diagnosis with only about two month [20].

For this patient, the management of previous pregnancies omitted to initiate the necessary investigations to further the diagnosis.

Treatment options in breast cancer during pregnancy are similar to that of non-pregnant women including surgical treatment, chemotherapy, adapted to the clinical presentation and trimester of pregnancy, in order to protect the fetus from side effects [21].

Radiotherapy during pregnancy is controversy and contraindicate by our *Gynecology and Obstetrics National Guidelines* [22]. Some studies indicated that radiotherapy should be postponed until after birth in order to avoid maternal and fetal hematological complications [23].

Patient care should be composed of a multidisciplinary team comprised of an obstetrician, medical oncologist, oncological surgeon, neonatologist, anesthesiologist, psychologist and dedicated nurses. Couples should be counseled regarding treatment options, possible side effects both for mother and child, close surveillance is necessary after delivery. A comprehensive conversation about the prognosis of the disease should be mandatory.

For our patient, taking into consideration the gestational age of 30 weeks as well as the pathological exam provided by the rural hospital, the multidisciplinary team questioned if both corticoid therapy and chemotherapy are in the best interest for both mother and child. The laboratory investigations necessary for exclusion of pulmonary tuberculosis were performed. Shortly after, a Caesarean section under spinal anesthesia was performed due to respiratory failure and continuous oxygen flow dependency. Palliative care was initiated yet death occurred inevitably.

Conclusions

Our case report highlights the importance of performing a routine physical examination, including breast exam during pregnancy and even at birth. The delayed presentation of the patient, the metastatic infiltrating breast cancer poorly differentiated with ER and PR positive markers and HER-2/neu marker negative, made management unsuccessful. Histological grade remains an independent prognostic factor for ER-positive tumors.

Conflict of interests

The authors declare that they have no conflict of interests. All authors read and approved the final manuscript.

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