

Triple Negative Breast Cancer In Young Pregnant Women – Three Proposed Cases

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ABSTRACT

Pregnancy-associated breast cancer (PABC) is malignant neoplasm of the breast diagnosed during pregnancy or up to one year after delivery. Triple negative breast cancer (TNBC) is more common in patients younger than 50 years and has a more aggressive character. The treatment of PABC should consider the type of tumor, the stage of the disease, the gestational age at the time of diagnosis and the wishes of the patient and family members. The first-line treatment, due to the contraindication to radiotherapy during pregnancy, is radical mastectomy. Chemotherapy drugs are contraindicated in the first trimester and outside this period, their use must be carefully and discussed. Breast tumors found in pregnant women, in addition to being diagnosed in more advanced stages, are often more aggressive, of the triple negative type, demonstrating the relevance of the association of both for discussion. For this reason, the present study aims to report 3 cases of young patients diagnosed with breast cancer associated with triple negative pregnancy.

Keywords

Breast cancer, Pregnancy, Triple negative.

Introduction

Breast cancer represents the most prevalent neoplasm among women in Brazil and in the world, except for non-melanoma skin cancer [1]. According to data from the National Cancer Institute (INCA), this neoplasm is responsible for 28% of new annual cases of cancer [2]. It is also estimated that in Brazil, one in every twelve women will develop this disease throughout their lives [3].

The definition of breast cancer according to the immunohistochemical profile is based on the evaluation of estrogen receptor (ER), progesterone receptor (PR), overexpression of human epidermal receptor-2 (HER-2) and cell proliferation index of the monoclonal antibody that detects a nuclear antigen, expressing cells entering the cell cycle and measuring the cell growth fraction (Ki67). Thus, the clinical-pathological subtypes

were classified as follows: luminal A: positive ER and/or RP, negative HER-2 and low Ki-67 (<14%); luminal B HER-2 negative: ER and/or RP positive, HER-2 negative, and high Ki-67 (≥14%); luminal B HER-2 positive: ER and/or RP positive and HER-2 positive; HER-2 overexpressed (non-luminal): ER and RP negative and HER-2 positive; triple-negative: absence of expression of ER, RP and HER-2.

Triple negative breast cancer (CMTN) is more common in young patients (under 50 years old) and accounts for about 15 to 20% of all types of breast tumors. This has a more aggressive character, higher rates of recurrence and lower overall survival in the metastatic condition [4].

By definition, pregnancy-associated breast cancer (PABC) is malignant neoplasm of the breast diagnosed during pregnancy or up to one year after delivery. Breast cancer is the gynecological neoplasm most associated with pregnancy and the puerperium

[5], with an estimated incidence between 0.02 and 3.8% of pregnancies, with approximately one in every 1,000 pregnancies arriving at term will be complicated by cancer.

Mammography is considered the screening test for breast cancer in women over 40 years old, however, the effectiveness of screening in young women is a controversial issue [6]. Thus, as pregnancy usually occurs in young women who are not part of screening programs, there is difficulty in the early diagnosis of PABC [7].

When the diagnosis is made in a pregnant woman, the gestational age and the characteristics of the tumor must be taken into account when choosing the best approach [8]. It is considered a delicate and challenging situation for the pregnant woman and the health professionals involved, as it brings with it the dilemma between the best treatment for the mother and the preservation of fetal well-being. [9].

Breast tumors found in pregnant women, in addition to being diagnosed in more advanced stages, are often more aggressive, of the triple negative type. Thus, the association of both constitutes an extremely relevant topic for discussion, aiming to strengthen the medical literature and promote improvements in the health of the population [9].

Cases Description

CASE 1

B.M.B., female, 21 years old, primiparous, complained of breast nodulation. Breast ultrasound showed nodulation in the right and left breasts classified as BIRADS 3, which after 6 months were reclassified as BIRADS 4A. On physical examination, there was a right breast with a 10 cm nodule occupying the union of the medial quadrants and a palpable 1.5 cm nodule in the right armpit. Core Biopsy was performed in the right breast with histopathological result (HPT) of Grade II Invasive Ductal Carcinoma (IDC). Immunohistochemistry (IHC) was negative for estrogen receptor, progesterone and HER 2 and positive for Ki-67 protein in 80%, configuring a triple negative breast cancer.

During follow-up, the patient reported menstrual delay and was diagnosed with a pregnancy of 7 weeks and 4 days. Screening for metastases performed with total abdominal ultrasonography did not show distant disease. The patient was hospitalized at 10 weeks and 5 days of gestation to perform a right mastectomy with axillary dissection. Anatomopathological evidenced IDC grade II and axillary lymph nodes with carcinoma metastasis for 1 of 16.

Two weeks after surgery, adjuvant chemotherapy was started. Twenty days after the end of chemotherapy, a cesarean delivery was performed at 37 weeks of gestation, with the newborn being born in good condition. Two months after delivery, extended radiotherapy was started in the region of the mastectomy plastron, axilla and supraclavicular fossa. Currently patient in exclusive clinical follow-up, without disease evolution. In breast reconstruction planning with plastic surgery team.

Case 2

F.B.S, female, 27 years old. She sought care 8 months after vaginal delivery complaining of increased volume in the right breast, local hyperemia and fever, which was treated as a breast abscess without success. On physical examination, an increased volume of the right breast, significant skin edema, heat, hyperemia in more than 50% of the mammary surface and a palpable lymph node in the right armpit were observed.

A breast ultrasonography showed evidence of a collection suggestive of an abscess and antibiotic therapy with Sulfamethoxazole + Trimethoprim was initiated. On the fifth day of antibiotics, a new ultrasound was performed due to the persistence of the condition. A large solid-cystic area was visualized, without the character of a breast abscess, in addition to an enlarged axillary lymph node and loss of the hilum. Core biopsy of the lesion was performed, which showed IDC grade 3 with estrogen receptor, progesterone and HER-2 negative, with Ki-67 positive in 80%, configuring triple negative breast cancer.

Tomographic screening showed secondary involvement of the liver and right axillary lymph nodes. Palliative chemotherapy was initiated, with an initial response almost complete in the breast and armpit and 80% in the liver. However, after the 3rd line of CT, she evolved with significant progression of locoregional disease in the right breast, right armpit and right supraclavicular lymph node. New CT scans also showed disease progression in the lung parenchyma and lymph node enlargement in the pre-vascular, pre-tracheal and para-aortic spaces.

Hygienic mastectomy was performed on the right breast with axillary dissection. After surgery, the 4th line of CT was started, associated with radiotherapy in the plastron and right supraclavicular fossa. After 3 cycles, she was diagnosed with decompensated heart failure profile B/C and palliative care was defined. After six days, he evolved with cardiorespiratory arrest and death.

Case 3

L.R.C.G, 34 years old, female, 7 weeks pregnant. She was admitted to the Mastology outpatient clinic 5 months after noticing a lump in her left breast. On physical examination, she had an enlarged left breast, nipple retraction, a lump occupying all breast quadrants, and a palpable axillary lymph node on the left. A core biopsy was performed that showed grade 3 pleomorphic/apocrine variant IDC with the presence of a high-grade intraductal component (DCIS). The immunohistochemical study showed positive estrogen and progesterone receptors in 1-10%, HER-2 negative and Ki-67 positive in 70%, configuring a triple negative breast cancer. Screening for metastases with abdominal ultrasonography did not show signs of distant disease.

Radical mastectomy and left axillary dissection were performed at 12 weeks and 5 days of gestation, which identified anaplastic IDC of the breast measuring 10 cm, grade 3, free surgical margins.

Table 1: Summary of cases.

	CASE 1	CASE 2	CASE 3
AGE	21 YEARS	27 YEARS	34 YEARS
Gestation	7 WEEKS AND 4 DAYS	9 MONTHS POSTPARTUM	7 WEEKS
Initial complaint	NODULE IN RIGHT BREAST	NODULE IN RIGHT BREAST	NODULE IN RIGHT BREAST
Ultrasound	NODULATION BIRADS 4A	ABSCESS SUGGESTIVE COLLECTION	NOT PERFORMED
HPT	ICD grade II	ICD grade III	Pleomorphic/Apocrine variant CDI
IHQ	Negative estrogen receptor Negative progesterone receptor HER-2 negative Ki-67 protein positive in 80%	Negative estrogen receptor Negative progesterone receptor HER-2 negative Ki-67 protein positive at 80%	Estrogen receptor positive 1-10% Progesterone receptor positive 1-10% HER-2 negative Ki-67 protein positive 70%
Surgery performed	Right mastectomy with axillary dissection	Hygienic mastectomy in the right breast with axillary dissection	Radical mastectomy and left axillary dissection
Chemotherapy	Adjuvant Chemotherapy Adriamycin, Cyclophosphamine and Paclitaxel + TDD	Palliative Chemotherapy Doxorubicin and Cyclophosphamine - 6 cycles Capecitabine - 5 cycles Paclitaxel - 5 cycles Doxil - 3 cycles	Adjuvant Chemotherapy Doxorubicin and Cyclophosphamide - 4 cycles + 1 cycle Paclitaxel Palliative Chemotherapy Capecitabine - 3 cycles Cisplatin and Gemcitabine - 3 cycles Taxane and Docetaxel - 3 cycles
Radiotherapy	Plastron of mastectomy, axilla and supraclavicular fossa.	Plastron and right supraclavicular fossa.	NOT PERFORMED
Evolution	In exclusive clinical follow-up, without disease evolution.	Cardiopulmonary arrest and death	COVID 19 and death

Source: Elaboration of the authors.

Infiltration of the nipple, blood vascular, lymphatic and perineural was detected, in addition to the presence of metastasis in 14 of the 18 dissected lymph nodes. Adjuvant chemotherapy was started and at 35 weeks of gestational age the patient underwent a cesarean delivery with the birth of a NB in good health conditions.

After delivery, tomographic staging was performed, which showed secondary involvement of the lungs, bones (sternum), liver and right axillary lymph nodes. Palliative chemotherapy was started, but the disease progressed with a high volume of bone, liver, lung and lymph node disease. The patient was diagnosed with COVID 19 and six days after admission she developed respiratory failure and death.

Discussion

The present study reports 3 cases of young patients diagnosed with breast cancer associated with triple negative pregnancy. Currently, there is a tendency for women to present lower parity and postpone pregnancy to the third or fourth decade of life. Considering that breast cancer is an estrogen- dependent disease and that there is a significant increase in the incidence of breast tumors in all age groups, the study of this topic is of great interest to the scientific community.

According to the literature, the incidence of breast cancer in women in general increases with age, being diagnosed mainly between 40 and 60 years. When it comes to pregnant women, there is a greater risk in women aged over 35 years, demonstrating a younger profile of involvement.

During the gestational period, the breasts undergo important changes, including increased volume and breast density, greater cellularity and number of mitoses, increased local vascularization and water retention. These changes are responsible for reducing the accuracy of mammography and physical examination, which compromises the workup of breast cancer in this period. Thus, physical examination and complementary imaging tests should be routinely included in pre-pregnancy examinations, especially in high-risk women.

When a palpable mass is identified on physical examination, the investigation should be continued in the usual way, similar to the conduct in a non-pregnant patient. Mammography presents a minimal fetal risk when performed with abdominal protection and in a retrospective study among women with breast cancer, it was able to visualize the mass in 90% of cases. Breast ultrasound, in turn, identified the mass in 100% of cases. After identifying the breast tumor, fine needle aspiration (FNA) or core needle biopsy should be performed for diagnostic conclusion, the latter being the preferred technique as it provides enough tissue for histological and immunohistochemical confirmation of breast cancer. breast.

The predominant histological type in PABC is the infiltrative ductal, which presents as undifferentiated tumors, of high nuclear grade, with vascular, perineural and lymphatic invasion, in addition to high diameters and negative hormone receptors. Despite this, the positivity of hormone receptors is debatable, due to the high endogenous levels of circulating hormones during pregnancy occupying cytoplasmic receptors, a condition that can lead to false- negative results.

The treatment of PABC should consider the type of tumor, the stage of the disease, the gestational age at the time of diagnosis and the wishes of the patient and family members. Its objective is based on the local control of the disease and the prevention of systemic metastases, in order to avoid potential adverse effects on the fetus. The first-line treatment, due to the contraindication to radiotherapy during pregnancy, is radical mastectomy. The safest time to perform surgery is in the second trimester, given the higher risk of miscarriage and premature birth in the first and third trimester, respectively.

Chemotherapy drugs are considered category D in pregnancy. They are contraindicated in the first trimester because they are associated with malformations in 10-20% of fetuses, such as micrognathia, hand and foot malformations, ventriculomegaly, neural tube defects, cleft lip and palate. Outside this period, its use should be carefully discussed, since recent evidence suggests the safety of several agents used in the treatment of breast cancer during pregnancy, especially if started after the first trimester. The most used regimen consists of 5-fluorouracil (F), doxorubicin (A) or epirubicin (E) and cyclophosphamide (C) or a combination of doxorubicin and cyclophosphamide (AC). In addition, delivery should be scheduled two to three weeks after the last cycle of chemotherapy to avoid maternal and/or fetal neutropenia.

As this is a profile of younger patients, the need for adjuvant chemotherapy is frequent, which aims to eliminate possible foci of micrometastases present at diagnosis. This can be performed within twelve weeks of breast surgery and should not be used in the 3 or 4 weeks preceding delivery due to the risk of transient fetal myelosuppression and septicemia.

Neoadjuvant treatment should be used in cases of locally advanced and metastatic carcinomas and local recurrence after conservative surgery.

Radiotherapy, in turn, should be postponed until postpartum whenever possible. Thus, this is reserved for after the end of systemic treatment, which on average lasts 6 months, no longer interfering with the gestational period.

The most common sites for metastases are the lungs, liver and bones. Thus, for staging the disease during pregnancy, chest X-rays with abdominal protection should be performed to assess the lung field, total abdomen ultrasound for liver assessment, and magnetic resonance imaging without contrast to assess the bone. Computed tomography, positron emission tomography (PET/CT) and bone scintigraphy are not recommended due to exposure of the fetus to radiation.

The main prognostic factors include the patient's age, tumor size, axillary lymph node involvement, HER-2 positivity or not, histological grade and increased proliferative activity markers. A meta-analysis of 30 studies showed a significantly higher risk of death from PABC compared to non-pregnancy-related breast cancer, and the trend towards a worse outcome was shown to be greater in women diagnosed in the postpartum period when compared to those diagnosed during pregnancy.

Conclusion

With the present study, it can be concluded that triple negative breast cancer is a condition diagnosed at an advanced stage in most cases and with a worse prognosis when associated with pregnancy. For this reason, its investigation and recognition are extremely important, aiming at the best treatment for the mother, taking into account the fetal well-being.

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