

## Decisions During Covid-19 Pandemic in A Middle-Income Country: A Case Report of Fast-Growing Breast Cancer in A Pregnant Woman

Meneghini AK<sup>1</sup>, Alessandra BADS<sup>2\*</sup>, Luiza MK<sup>1</sup>, Martina L<sup>3</sup>, Felipe Z<sup>2,4</sup> and Antonio F<sup>2,4</sup>

<sup>1</sup>Breast Surgeon fellow, Pontificia Universidade Católica do Rio Grande do Sul (PUCRS), Brasil

<sup>2</sup>Breast surgeon, Breast Cancer Center of Hospital São Lucas Pontificia Universidade Católica do Rio Grande do Sul, Brasil

<sup>3</sup>Colaborative Researcher, Breast Cancer Center of Hospital São Lucas Pontificia Universidade Católica do Rio Grande do Sul (PUCRS), Brasil

<sup>4</sup>Professor Medicine University at Pontificia Universidade Católica do Rio Grande do Sul (PUCRS)

### \*Corresponding author:

Alessandra Borba Anton de Souza,  
Breast surgeon, Breast Cancer Center of Hospital  
São Lucas Pontificia Universidade Católica do  
Rio Grande do Sul, Brasil,  
E-mail: [alessandra.masto@gmail.com](mailto:alessandra.masto@gmail.com)

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### Keywords:

Coronavirus Disease-19; Neoadjuvant Chemotherapy; Pandemic

### Abbreviations: BC: Breast Cancer

- Pregnancy at this moment also limited the MRI indication to define the extent of disease and identify additional disease
- pregnancy at this moment also limited the neoadjuvant chemotherapy with HER2 target therapy

### Author Contributions:

Alessandra BADS, Felipe PZ, Frasson AL. These authors are contributed equally to this work

## 1. Abstract

In this Brazilian breast cancer (BC) case report, we described a pregnant woman diagnosed with BC during the beginning of COVID-19 pandemic. The uniqueness of the case reported is related not only to the particularly fast-growing patient's situation but also to consider the consequences caused by the pandemic context. The COVID-19 pandemic worsened some difficulties in BC assessment and treatment that we already had previously in Brazil, a country with financially constrained healthcare system, like in other low-and-middle income countries. The pandemic's restrictions increased the complexity, in a scarce-resourced country, of cancer management decisions.

## 2. Background

On March 11, 2020, the World Health Organization (WHO) declared a pandemic due to more than 100,000 cases of a new respiratory disease, the Coronavirus Disease-19 (COVID-19) [1].

This context has affected health systems worldwide, forcing professionals to modify patient treatments preserving resources, and avoiding the risk of exposure by delaying elective surgeries. This scenario quickly changed cancer care, especially in Breast Cancer (BC). To address this challenge, institutions have proposed specific strategies for managing BC [2]. Based on priorities, surgeries must be performed in urgent oncological cases, according to available resources [3].

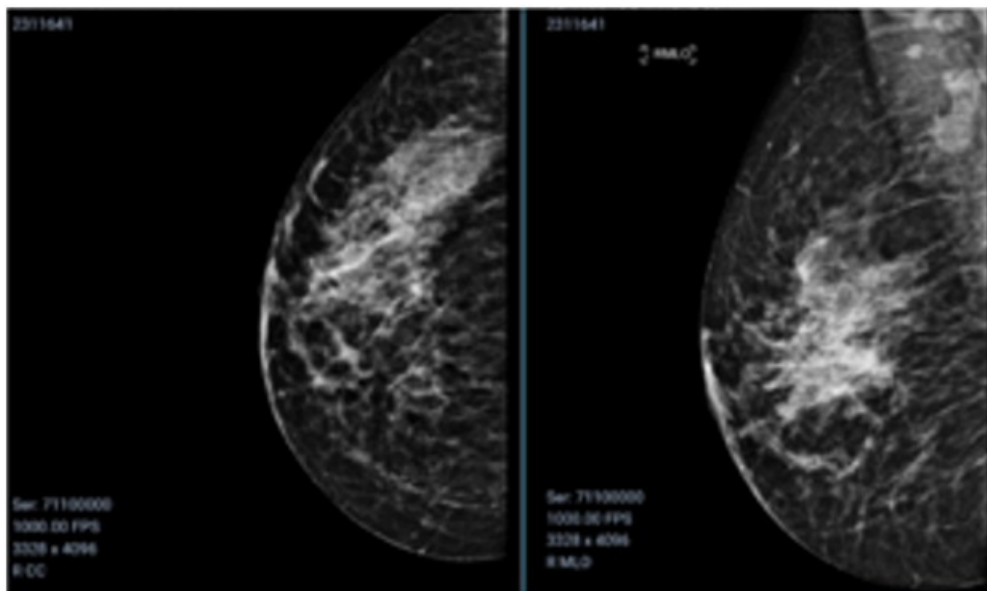
The decisions require a multidisciplinary collaboration and considerations, including stage, tumor biology, comorbidities, available hospital resources, and others factors [4]. Risks associated with delaying treatment or choosing less aggressive treatments with potential disease progression should be balanced. The limited health resources in a Middle-Income Country (MIC), such as Brazil, may potentialize the uncertain impacts of these changes in cancer treatment.

In this Brazilian case report, we described a pregnant woman diagnosed with BC during the COVID-19 pandemic and how the restrictions increased the complexity, in a scarce-resourced country, of cancer management decisions.

### 3. Case Report

A premenopausal 37-year-old white female with no family history of BC or ovarian cancer was evaluated at the dermatological department after a 4-month symptom of friable right nipple. The therapeutic test with topical corticosteroids showed no response. Later, at the BC department, the evaluation showed nipple erosion, and no breast lumps or axillary lymph nodes were palpable. Breast Ultra Sound (US) was negative, and Mammography (MMG) revealed microcalcifications, BIRADS 0. Both exams were performed outside our hospital.

Due to the persistent erosion in the nipple, an invasive diagnostic investigation was proposed with incisional biopsy in the sensitive nipple affected area under sedation. Preoperative exams and new breast images were requested. Magnetic Resonance Imaging (MRI) was not performed due to a first-trimester pregnancy identified during the preoperative evaluation (March 2020/ beginning of COVID-19 pandemic in Brazil). Surgical nipple biopsy disclosed Paget's disease diagnosis, the MMG showed an extensive area of 11cm pleomorphic microcalcifications in the right breast (Figure 1), and the US revealed no injuries. Vacuum-assisted breast biopsies are not available at our hospital through Brazil's Unified Health System (Sistema Único de Saúde - SUS); therefore, a stereotactic-guided biopsy of the microcalcifications was performed, resulting in negative for malignancy.

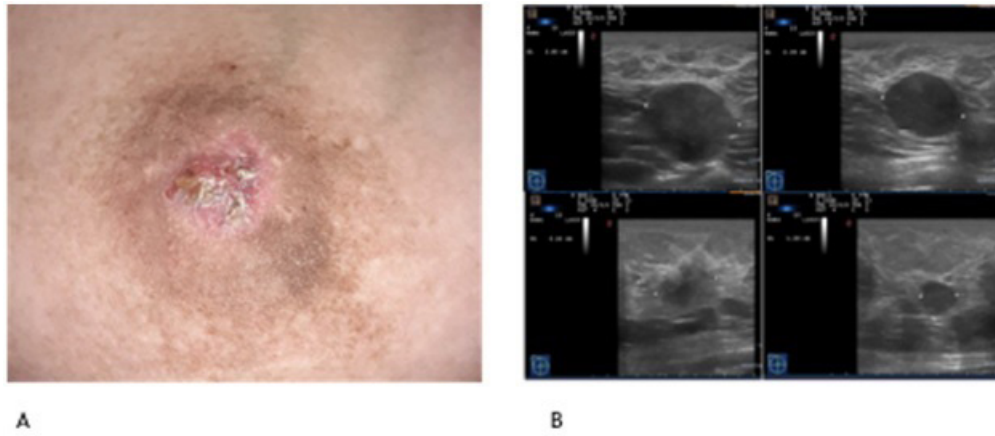


**Figure 1:** Mammography from our center - March 2020: extensive area of 11cm x 9cm pleomorphic microcalcifications in the right breast associated with skin thickening

Considering the pregnancy, the microcalcification negative biopsy result, and the unpredictable beginning of the COVID-19 pandemic situation in Brazil, the multidisciplinary group settled with the patient's consent to maintain follow-up for the following weeks. At that point (late March 2020), all elective surgeries were canceled at our hospital. The definitive treatment of Paget's disease and surgical investigation of microcalcifications would be performed posteriorly, according to available resources during the COVID-19 pandemic. We made the patient aware of all possibilities, including the chances of invasive disease with a false negative result from the stereotactic-guided biopsy, Ductal Carcinoma in Situ (DCIS), and the eventual fast progression for malignancy. We based our decision on current guidelines on BC treatment during COVID-19 and the high-risk pregnancy conditions during the pandemic. De-

isions were likely to be changed according to the lesion evolution or worsening at any moment.

In June 2020, after eight weeks, the patient at 26-week gestational age returned, referring a breast lump. The clinical exam showed a lesion healing in the nipple (Figure 2A), two palpable nodules in the breast, and a suspect lymph node in the ipsilateral axilla. The current US confirmed suspicious lymph nodes on the axilla and suspicious nodules in different quadrants of the right breast (Figure 2B). The biopsy of two lumps confirmed invasive carcinoma, grade 3, negative for hormonal receptors, Ki67 80%, and positive human epidermal growth factor receptor 2 (HER2) in both lesions. Axillary lymph nodes fine-needle aspiration resulted positive for malignancy. Systemic staging (chest x-ray and abdominal US) was negative.



**Figure 2A:** Right Nipple healing 7 weeks after the biopsy - May 27, 2020

**Figure 2B:** Ultrasound with new suspicious lumps and lymph nodes - June 1, 2020: two suspicious lymph nodes on the right axilla and three suspicious nodules of approximately 3cm, 2cm, and 1 cm in different quadrants of the right breast.

The patient started treatment with Neoadjuvant Chemotherapy (NAC) with cyclophosphamide and doxorubicin. After three cycles, she presented clinically local progression. Therefore, we decided to interrupt NAC treatment, and a pregnancy resolution at 36 gestational weeks was made. New systemic staging, with chest/abdominal tomography and bone scintigraphy, resulted negative. Posteriorly, surgical treatment with mastectomy and axillary dissection resulted in a 9cm invasive disease, grade 3, with clear surgical margins. The nipple was diagnosed with invasive and Paget disease with no areolar involvement. One positive from 18 lymph nodes resected. Following surgery, adjuvant paclitaxel and trastuzumab were started. In 2021, metastatic progression disease was detected after symptomatic bone lesion with back pain.

We must highlight some other limitations that we faced: pregnancy maintenance was desired by the patient, and abortion is illegal according to the Brazilian legislation. The pertuzumab is still not

approved for adjuvant treatment at SUS, and neither Trastuzumab-Emtansine (TDM-1) is available (for adjuvant or metastatic disease).

**4. Discussion**

The uniqueness of the case reported is related not only to the patient's circumstances but also to consider the pandemic context of COVID-19 and its consequences. In March 2020, we expected a chaotic future scenario in Brazil due to the pandemic, especially considering the financial resource limitations of our SUS, the only access to healthcare of approximately 70-80% of the Brazilian population [5]. The COVID-19 pandemic worsened some difficulties in BC assessment and treatment that we already had previously in Brazil. Our financially constrained healthcare system, like in other MIC, presented limited access to target HER2 therapy, for instance [6, 7]. The principal challenges faced in this case reported are summarized in (Table 1).

**Table 1:** Resumed Challenges in the decisions process of BC management in this case report: pregnancy, COVID-19 pandemic, and scarce resource in a middle-income country

Case report - Clinical Scenario	Ideal Management before COVID-19	Middle-Income Country limitations before COVID-19 (Brazil public health system)	Challenge after COVID-19 in Middle-Income Country
First-moment evaluation: Paget disease in the nipple (surgical biopsy) + ipsilateral suspicious microcalcifications in a pregnant woman with negative stereotaxic biopsy	Vacuum-assisted biopsy procedure of microcalcifications* Surgical treatment for Paget disease with conservative surgery + evaluation of extending surgery after vacuum biopsy result	No vacuum biopsy access Surgical excision is necessary for Paget disease treatment and microcalcification diagnosis	Possible overcrowding Hospitals Possible high risk of COVID-19 contamination hospital To postponed surgical management, especially in pregnant women without advanced BC
Second-moment evaluation: Newly diagnosed HER2 positive BC stage II-III in pregnant women with a fast-growing tumor	Neoadjuvant Chemotherapy without anti-HER2 target therapy, followed by surgery. After pregnancy, double blocked HER2 target therapy plus radiotherapy**	No access to double blocked HER2 target therapy Chemotherapy plus trastuzumab is the only option	The same before COVID-19

In March, the COVID-19 Pandemic BC Consortium published specific guidelines on BC management. In phase 1 of the guideline, named semi-urgent setting, there were few cases of COVID 19 patients, the hospital resources are not exhausted, and the COVID-19 trajectory is not in a rapid escalation. On April 10, the same consortium published more extensive guidelines dividing the cases into three priorities according to the case risk and severity [8]. Priorities A included urgent situations such as septic breast abscess, and prompt operation is recommended. Priority B cases included patients with no immediately life-threatening conditions, but for whom treatment should not be indefinitely postponed. Patients with triple-negative or HER2-positive lesions should be considered for NAC. Priorities C cases included patients for whom specific treatment, such as DCIS, could be postponed without adversely impacting their outcomes [3]. The moment the patient was referred, we were going through the Phase 1 scenario; therefore, surgery must be restricted to patients likely to have survivorship compromised if surgery is not performed within three months, and high-risk lesions should be deferred [2].

Paget's disease is rare (0.5-5% of all types of BC), and it is usually characterized by ulcerated lesions of the nipple. Some studies suggest that Paget's disease is associated in most cases (up to 85%) with underlying cancer, which is not necessarily adjacent to the nipple complex, and maybe DCIS or invasive disease. When a palpable mass is not present, the associated disease is more commonly DCIS8-10.

Following international guidelines, along with the patient consent on BC management during the pandemic, we opted to continue monitoring and not submitting the patient to surgical management of Paget's disease with suspicious (but not confirmed) extensive DCIS at the time. Both physicians and the patient were aware of the possibility of progression. However, the tumor's fast growth was not expected in 8 weeks, especially considering Paget's initial diagnosis without lumps.

Our case was influenced by some pregnancy peculiarities related to BC. The initial pregnancy in the pandemic context makes the patient's situation more delicate because of the potential contamination at the hospital during the surgery in an immunosuppression condition. Pregnant women seem to be at an increased risk for hospitalization and more severe COVID-19 illness [9]. Even though BC treatment in pregnancy after the first trimester does not differ much from non-pregnant cases, especially related to surgical treatment and NAC, the gestational changes on tissue structure make diagnosis more difficult. In our case, due to the pregnancy, MRI could not be performed, and an underlying carcinoma could have been more easily detected in the first moment with MRI. In this aggressive growing fast case report, initial HER2 target therapy, contraindicated in pregnancy, would probably have been beneficial [10,12].

This report emphasizes the multiple factors involved in the BC <http://www.acmcasereport.com/>

decision-making: an early-onset pregnant woman, diagnostic methods limitations, and the pandemic scenario. While science has come a long way in individualizing successful treatment, we will still face challenging circumstances. Although BC has a good prognosis, there will be cases out of the ordinary, and we cannot always predict them.

In conclusion, this report shows that the complications caused by postponing oncological treatments due to COVID-19 are not yet fully understood, leading us to face new ethical dilemmas. As breast surgeons, we focus on our patients' therapy precision focus on life and high cure rates; however, in the pandemic scenario, we must balance individual benefits and public health care [13].

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