

## Breast Tuberculosis: Case report and review literature

Tuberculose Mamária: Relato de caso e revisão de literatura

Tuberculosis Mama: Reporte de un caso y revision de la literatura

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### **José de Ribamar Barroso Jucá Neto**

ORCID: <https://orcid.org/0000-0003-2750-7621>

Centro Universitário Christus, Brazil

E-mail: [juca.neto.medicina@gmail.com](mailto:juca.neto.medicina@gmail.com)

### **David Evangelista Barros de Oliveira**

ORCID: <https://orcid.org/0009-0000-4662-9224>

Centro Universitário Christus, Brazil

E-mail: [davidbarros.medicina@gmail.com](mailto:davidbarros.medicina@gmail.com)

### **Felipe Rabelo Costa**

ORCID: <https://orcid.org/0009-0004-4027-1697>

Centro Universitário Christus, Brazil

E-mail: [frabelocosta14@gmail.com](mailto:frabelocosta14@gmail.com)

### **Lívia Fontelles Brasil**

ORCID: <https://orcid.org/0000-0002-8173-7332>

Centro Universitário Christus, Brazil

E-mail: [liviafontellesbrasil@gmail.com](mailto:liviafontellesbrasil@gmail.com)

### **Olga Oliveira Machado**

ORCID: <https://orcid.org/0000-0002-8735-4631>

Centro Universitário Christus, Brazil

E-mail: [Omachado.olga@gmail.com](mailto:Omachado.olga@gmail.com)

### **Sara dos Santos Martins**

ORCID: <https://orcid.org/0009-0002-2289-5987>

Centro Universitário Christus, Brazil

E-mail: [saramartins\\_2009@hotmail.com](mailto:saramartins_2009@hotmail.com)

### **Vitor Teixeira Boscov**

ORCID: <https://orcid.org/0009-0005-0573-8324>

Centro Universitário Christus, Brazil

E-mail: [vitorboscov@gmail.com](mailto:vitorboscov@gmail.com)

### **Yasmim Cavalcante Sousa**

ORCID: <https://orcid.org/0009-0009-5738-7764>

Centro Universitário Christus, Brazil

E-mail: [yicsousa99@gmail.com](mailto:yicsousa99@gmail.com)

### **Abstract**

**Introduction:** Extrapulmonary manifestations of tuberculosis are well documented, however breast tuberculosis is a rare site of involvement, as it represents 0.1% of breast diseases in developed countries and 3%-4% in endemic countries. **Methodology:** The present study refers to a case report of Breast Tuberculosis and a literature review carried out in the PUBMED database with the keywords “Breast Tuberculosis” and “Young Adult” in the last 10 years. **Case Report:** A 32-year-old female patient complained of painful nodules in her right breast, in addition to the growth of axillary lymph nodes, associated with constitutional symptoms. Afterwards, a histopathological puncture of the lesion was requested, which showed the presence of active tuberculosis, and a regimen was initiated. of standard antibiotic therapy. **Discussion:** Breast tissue is extremely resistant to the presence of Mycobacterium tuberculosis, however these characteristics can change physiologically. The clinical presentation is not very specific with the possibility of breast nodulation being painful or painless, with fistulation or retraction of the breast and formation of a local abscess. Therefore, the gold standard for diagnosis is Fine Needle Aspiration Cytology (FNAC), which can be associated with additional tests. The basis of treatment for breast tuberculosis is antibiotic therapy, with emphasis on ethambutol, pyrazinamide, rifampicin and isoniazid. **Conclusion:** Breast tuberculosis is one of the differential diagnoses of breast nodulations, with investigation by Fine Needle Aspiration Cytology (FNAC) in addition to other tests that assist in clinical reasoning that leads to appropriate therapy.

**Keywords:** Tuberculosis; Breast; Young adult.

### **Resumo**

**Introdução:** As manifestações extrapulmonares da tuberculose são bem documentadas, porém a tuberculose de mama é um sítio raro de acometimento, visto que representa 0,1% das doenças da mama em países desenvolvidos e 3%-4%

em países endêmicos. Metodologia: O presente estudo refere-se a um relato de caso de Tuberculose Mamária e uma revisão de literatura realizada na base de dados PUBMED com as palavras-chave “*Breast Tuberculosis*” e “*Young Adult*” nos últimos 10 anos. Relato de Caso: Paciente do sexo feminino de 32 anos com queixa de nódulos doloridos em mama direita, além do crescimento de gânglios axilares, associados a sintomas constitucionais sendo em seguida solicitado punção histopatológica da lesão que evidenciou a presença de tuberculose ativa, sendo iniciado esquema de antibioticoterapia padrão. Discussão: O tecido mamário é extremamente resistente a presença do *Mycobacterium tuberculosis*, porém essas características podem se alterar fisiologicamente. A apresentação clínica é pouco específica com possibilidade de a nodulação mamária ser dolorosa ou indolor, com fistulação ou retração da mama e formação de abscesso local. Dessa forma, o padrão ouro para diagnóstico é a Citologia Aspirativa por Agulha Fina (CAAF), pode estar associada a exames complementares. A base do tratamento da tuberculose mamária é a terapia por antibióticos, destacando-se etambutol, pirazinamida, rifampicina e isoniazida. Conclusão: A tuberculose mamária é um dos diagnósticos diferenciais das nodulações de mama, com investigação por Citologia Aspirativa de Agulha Fina (CAAF) além de outros exames que auxiliam no raciocínio clínico que conduz a terapêutica adequada.

**Palavras-chave:** Tuberculose; Mama; Adulto jovem.

### Resumen

Introducción: Las manifestaciones extrapulmonares de la tuberculosis están bien documentadas, sin embargo la tuberculosis mamaria es un sitio raro de afectación, ya que representa el 0,1% de las enfermedades mamarias en los países desarrollados y el 3%-4% en los países endémicos. Metodología: El presente estudio se refiere a un reporte de caso de Tuberculosis Mamaria y una revisión de la literatura realizada en la base de datos PUBMED con las palabras clave “Tuberculosis Mamaria” y “Adulto Joven” en los últimos 10 años. Relato del Caso: Paciente femenina de 32 años refirió nódulos dolorosos en mama derecha, además de crecimiento de ganglios linfáticos axilares, asociados a síntomas constitucionales, posteriormente se solicitó punción histopatológica de la lesión, que demostró la presencia de tuberculosis activa, y se inició una pauta de terapia antibiótica estándar. Discusión: El tejido mamario es extremadamente resistente a la presencia de *Mycobacterium tuberculosis*, sin embargo estas características pueden cambiar fisiológicamente. La presentación clínica es poco específica existiendo la posibilidad de que la nodulación mamaria sea dolorosa o indolora, con fístula o retracción de la mama y formación de un absceso local. Por lo tanto, el estándar de oro para el diagnóstico es la citología por aspiración con aguja fina (CAAF), que puede asociarse con pruebas adicionales. La base del tratamiento de la tuberculosis mamaria es la terapia con antibióticos, con énfasis en etambutol, pirazinamida, rifampicina e isoniazida. Conclusión: La tuberculosis mamaria es uno de los diagnósticos diferenciales de las nodulaciones mamarias, siendo investigado por Citología Aspiración con Aguja Fina (CAAF) además de otras pruebas que ayudan en el razonamiento clínico que conduce a una terapia adecuada.

**Palabras clave:** Tuberculosis; Mama; Adulto joven.

## 1. Introduction

Tuberculosis (TB) is a very old transmissible pathology. However, its etiology remained unexplored until March 24, 1882, when the condition was discovered by Dr. Robert Koch, who announced the discovery of the bacillus later called *Mycobacterium tuberculosis* (MTB) (Sinha & Rahul, 2019; Adeiza et al, 2016). The MTB pathogen survives in the host's macrophages and can therefore harm any organ, most frequently the lungs. The TB epidemic is worsened by immunodeficiency, especially HIV, but recently, diabetes mellitus has been recognized as an important risk factor (Shrestha, A., 2019; Nalini, et al, 2015). As the rural social segment in developing countries adheres to the Western lifestyle and customs, eating habits change, it is predicted that 366 million people will have diabetes mellitus by 2030, with the majority living in Africa and in Asia (Khodabakhshi & Mehravar, 2014; Gupta et al., 2017).

The breast is a rare site of manifestation of extrapulmonary tuberculosis, especially as a primary manifestation, even in tuberculosis endemic countries (Sinha & Rahul, 2019; Bouziyane et al, 2020). Breast tuberculosis was first described by Sir Astley Cooper in 1829 as “scrofulous swelling in the breast of young women” and since then numerous important studies have emerged and everyone is unanimous about its rarity. Breast tuberculosis (TB) generally affects women of reproductive age, commonly between 21 and 30 years old, and is estimated to account for 0.1% of breast diseases in developed countries, but reaches 3% to 4% in countries where tuberculosis is endemic, such as India and Africa (Adeiza et al, 2016; Shrestha, 2019). TB has increasing clinical relevance in Western countries due to immigration, as a strong ally of lack of guidance will certainly delay diagnosis and may result in unnecessary surgeries (Gupta et al., 2017; Bhat, Gunasekaran et al., 2017).

Mammary Tuberculosis, a rare extrapulmonary form of Tuberculosis, can present in the form of an abscess or as a unilateral, painless breast mass. This condition has two primary and secondary subtypes (Bhat et al., 2017). The primary form involves a tuberculous infection located exclusively in the breast and is an extremely rare condition (Haitz et al., 2019). The secondary form is observed more frequently and is associated with several primary tuberculous foci such as lungs, pleura or lymph nodes (Murat Kılıç. et al 2016).

The nodule often exhibits irregular, ill-defined characteristics and a hard consistency, and may be painful, mobile or fixed to the underlying skin or muscle. Furthermore, the disease can present clinically as an isolated nodule, and normally, without the presence of constitutional symptoms typical of Tuberculosis (Shrestha et al, 2019; Nalini et al, 2015; Gupta et al., 2017). Therefore, clinical and radiological characteristics seen in breast TB can simulate other pathological conditions such as pyogenic breast abscess or breast neoplasms. Due to these characteristics, breast TB is often diagnosed late, which added to the low clinical suspicion and similarity with other diseases, makes the diagnosis challenging even in regions endemic for the disease (Bhat et al, 2019; Murat Kılıç et al, 2016; Hammami et al, 2021). The diagnosis of Breast Tuberculosis may include a triple evaluation by a specialized surgeon, a radiologist and a pathologist. Fine needle aspiration cytology (FNAC) is the most widely used initial invasive method for diagnosing breast tuberculosis, with the bacteriological culture examination of breast tissue being the gold standard for confirming the disease (Fatima & Naz, 2019; Aziz Slaoui. et al, 2019; Gon et al, 2013). Although this is the gold standard method of diagnosis, it has high false negative rates. Therefore, in endemic regions, even in the absence of culture, the presence of granuloma in the FNAC justifies empirical treatment for Tuberculosis. Furthermore, skin tests, interferon-gamma assay, imaging tests and biopsies, including the PCR-TB technique, can help to clarify the diagnosis (Zhong et al, 2015; Carolina et al, 2019).

Treatment includes administration of antibiotics for tuberculosis, and surgical excision and corticosteroid therapy are also commonly performed. Thus, Breast Tuberculosis is a rare condition that mimics other pathologies, making its diagnosis complex and challenging even in countries endemic for the disease (Hoang et al, 2022; Ail, 2017).

The present study aims to highlight a case report of Breast Tuberculosis, due to its rarity and atypical presentation within the clinical and laboratory investigation of breast nodules, together with a review of scientific literature that covers thematic axes from epidemiological and pathophysiological understanding to characterize the global understanding of the disease to then evolve with clinical and diagnostic reasoning, and finally, the appropriate therapeutic approach for the aforementioned pathological context.

## **2. Methodology**

The present study involves the presentation of a case report associated with a literature review on the same topic with the aim of deepening knowledge about a rare variant of a common pathology that is Tuberculosis. The case report about Breast Tuberculosis was acquired, according to care provided at an Outpatient Medical Clinic in Fortaleza-Ceará, Brazil in the Infectious Diseases service with approval from the ethics and research committee (CEP) with CAAE number 75945823.4.0000.5049 and Opinion Number 6,566 .301 and signing the Free and Informed Consent Form, respecting confidentiality and ethical principles. The descriptive and analytical literature review was carried out from the PUBMED database using the keywords “Breast Tuberculosis” and “Young Adult”, with the time filter in the last 10 years (2014-2023) which resulted in 88 articles, of which only 21 were used, the remaining 67 were discarded because they did not have a title or abstract directly related to the keywords or had online access restrictions.

### 3. Results and Discussion

#### 3.1 Case Report

The present case is a 32-year-old woman, born in Itaitinga, a respiratory therapist. She reported the appearance of slightly painful nodules in her right breast, seeking medical attention from a mastologist, in which the presence of axillary nodes on the right was also identified, and the hypothesis of breast carcinoma was raised. Thus, a breast ultrasound was performed, followed by mammography and histopathological puncture, but no examination demonstrated a definitive result. After the diagnosis was not clarified, the patient was referred to the infectious disease specialist, where it was discovered that associated with the breast condition there was a history of afternoon fever, adynamia, nocturnal awakenings with sweating and weight loss of 10kg. On physical examination, there was enlargement of the right breast with three hardened nodules with irregular contours, with skin drainage fistulas and lymph nodes in the right axilla. The patient has no comorbidities, has a complete vaccination schedule, a history of cesarean section eleven months prior to the condition with subsequent breastfeeding. The investigation continued with a request for a tuberculin skin test with a result of 12mm, an unremarkable chest x-ray, histological puncture with evidence of caseous granuloma, an unremarkable blood count and elevated inflammatory tests (erythrocyte sedimentation rate and C-reactive protein). Therefore, the diagnosis of breast tuberculosis was concluded, and antibiotic therapy was started with Rifampicin, Isoniazid, Pyrazinamide and Ethambutol, with subsequent improvement in symptoms and regression of breast nodules.

#### 3.2 Definition

Breast tissue is highly resistant to mycobacteria. Since it provides a sterile atmosphere for the survival and proliferation of bacilli, such as spleen and skeletal muscle, through the two immune modalities, innate by the macrophage that phagocytoses the bacilli and cell-mediated T4 lymphocytes through the cytokines they produce (Bouziyane et al, 2020; Haitz et al, 2019). This resistance explains the difficulty of diagnosis and the rarity that Breast Tuberculosis (BTB) presents, commonly affecting young, multiparous and lactating women (Hammami et al, 2021; Fatima & Naz, 2019). This may be due to physiological changes in the breast during the breastfeeding period, when the breast is susceptible to infections and trauma, i.e. due to increased blood supply, dilation of ducts during lactation and physiological stress of breastfeeding the susceptibility to Tuberculosis (TB) infection is increased (Sinha & Rahul., 2019; Hoang et al, 2022; Adeiza, 2016).

#### 3.3 Epidemiology

According to the World Health Organization (WHO), in 2014, 9.6 million new cases of TB were registered, of which 1.1 million were HIV-positive patients (Shrestha et al, 2019; Bouziyane et al, 2020). In the same year, 1.5 million deaths were recorded due to complications from this disease. Breast tuberculosis represents 2% of extra-pulmonary tuberculosis, 3.5% in a case series study (Darré et al., 2017). A study that included 65 cases of breast TB reported a rate of 10.6% of lactating patients (Hammami et al, 2021). From 1995 to 2016, 28 cases of breast tuberculosis were recorded, of these 28, 26 women and 2 men with an average age of  $34.2 \pm 0.3$  years and 63.9% were HIV positive (Sinha & Rahul, 2019). Among these cases, clinical signs were identified such as: nodule (84.1%), swelling (75%), abscess (63.6%) and swelling with cutaneous fistulization (59.1%) (Kiliç et al., 2016).

#### 3.4 Pathophysiology

Mckeown and Wilkinson, for the first time, in 1952, classified Mammary Tuberculosis (BTB) into 5 different types (I) Nodular Tuberculous Mastitis, (II) Disseminated or Confluent Tuberculous Mastitis, (III) Sclerosing Tuberculous Mastitis,

(IV) Tuberculous Mastitis Obliterans and (V) Acute Miliary Tuberculous Mastitis. However, Tewari, in 2005, suggested reclassifying breast tuberculosis into three categories, namely nodular, disseminated and abscess varieties. This most recent classification takes into account changes observed in the clinical presentation of tuberculosis over the last two decades. Sclerosing Tuberculous Mastitis, Obliterating Tuberculous Mastitis and Acute Miliary Tuberculous Mastitis are very rare nowadays, while Tuberculous Breast Abscess is more frequent (Carolina et al., 2019; Ail, 2017; Adeiza et al., 2016).

The rarity of Breast Tuberculosis is explained by the resistance of breast tissue to infection, such as skeletal muscles and the spleen, thus inhibiting the survival and multiplication of *Mycobacterium tuberculosis* (Hoang et al., 2022; Nalini et al., 2015). However, during lactation, the breast is highly vascularized and the ducts are dilated, which increases susceptibility to Tuberculosis (TB) infection in infants and multiparous women (Carolina et al., 2019; Ail, 2017). Furthermore, the pro-inflammatory T-helper response is suppressed during pregnancy, which may increase the predisposition to infection, as the history of symptom presentation in breast TB is generally less than a year, but varies from a few months to several years (Carolina et al., 2019; Ail, 2017; Adeiza et al., 2016).

The different modes of breast infection are the hematogenous route, the lymphatic route, spreading from contiguous structures such as infected ribs, costochondral cartilage, sternum, shoulder joint or direct inoculation by skin abrasion nipples or through the milk ducts and ductal infection (Khodabakhshi & Mehravar, 2014; Gupta et al., 2017). Breast TB was initially classified as primary when no other TB focus was detectable, and secondary when it was associated with another TB focus elsewhere in the body (Slaoui et al., 2019). Some authors, such as Vassilakos, 1973, debated that primary breast tuberculosis is, in a way, rare, and then considered that almost all cases of BTB were secondary, even if the primary location of the infection remains hidden clinically or radiologically (Slaoui et al., 2019). Rare cases of primary BTB are believed to be caused by infection from skin abrasions through the breast or main nipple ducts. The primary form is the result of an infection that spreads through cracks in the nipple, abrasions of the breast skin, or through the milk ducts. It can be transmitted directly through the infected palatine tonsils of breastfed babies. Breast trauma is considered another risk factor (Slaoui et al., 2019; Sabageh et al., 2015).

Although imaging resources should not be used alone as diagnostic tools, they confirm the presence of the three forms of the disease, found during the clinical examination. The nodular form appears on mammography as an ill-defined density, which mimics breast cancer. The disseminated form is characterized by sinus formation secondary to multiple TB foci. The sclerosing form is seen when there is extensive fibrosis rather than caseation, and the entire breast hardens with a retracted nipple (Gon et al., 2013; Bhat et al., 2017).

Regarding the differential diagnosis, the breast lump, being the most common manifestation, is often confused with a breast tumor. In advanced stages, when the condition manifests as a breast ulcer, it presents similarities with a fungal tumor (Gon et al., 2013; Ben Adib et al., 2015). A patient who has a developing abscess may be confused with conditions such as traumatic fat necrosis, plasma cell mastitis, periareolar abscess, or chronic pyogenic abscess. In the case of a patient with multiple breasts, the condition may mimic common fungal infections such as actinomycosis and blastomycosis (Gon et al., 2013; Ben Abid et al., 2018).

### 3.5 Clinical Condition

Breast tuberculosis (BTB) generally does not present specific clinical signs. The most common clinical picture is a mass in the breast, which may or may not be painful, mainly located in the central or upper external quadrant. Fistula formation, nipple or skin retraction may occur, but breast discharge is uncommon (Hoang et al., 2022; Haitz et al., 2017). Breast lump was the most common symptom, followed by lump with sinusitis and breast abscess. The presentation is usually a

hard, non-specific mass, with irregular boundaries and adherence to the surrounding tissue in 75% of cases. Breast abscess is the second most common symptom, present in 15% of cases, and may be associated with nipple retraction, sinus formation, fistulas and skin ulcerations (Ail 2017; Haitz et al., 2019).

Nipple discharge is rarely seen in breast tuberculosis. Axillary lymphadenopathy is not consistently found and may occur in 50 to 75% of cases. Breast pain unrelated to the menstrual cycle may be an occasional complaint (Gupta et al., 2017; Kiliç et al., 2016; Gon et al., 2013). Systemic symptoms are usually not reported. The average time until symptom onset varies from a few weeks to more than 7 months (Gupta et al., 2017; Kiliç et al., 2016).

Studies support the idea that, in most cases, the constitutional symptoms of tuberculosis (fever, weight loss, night sweats, or general deterioration) are rarely seen in BTB (Bouziyane et al., 2020; Fatima & Naz, 2019; Khodabakhshi & Mehravar, 2014). There is a clear predilection of breast tuberculosis lesions for the outer quadrants, probably due to the proximity to the axillary region from which retrograde lymphatic spread (Gupta et al., 2017).

### 3.6 Diagnosis

Breast tuberculosis is often misdiagnosed, being its main presentation through breast nodules in the early stages and, when advanced, through breast ulcers. The definitive diagnosis of tuberculosis is made through microbiological, cytopathological and histological investigation of bacilli. However, these tests often suggest a granulomatous infection that presents different diagnoses (Zhong et al., 2015; Carolina et al., 2019). Currently, the diagnosis is confirmed by the evaluation of mycobacterial culture, which, despite being one of the best tests, has several false negatives due to the pauci-bacillary nature of the disease (Naili et al., 2015).

More recent studies show that fine needle aspiration cytology (FNAC) has a good diagnostic rate, exceeding the 73% of patients actually diagnosed by this method. The other 27% required an incisional biopsy due to ulcers (Ail, 2017; Hammami et al., 2021; Kiliç et al., 2021).

Furthermore, there are some complementary tests that help in the diagnosis of breast TB, such as: 1) Mantoux test: It consists of the intradermal injection of the antigen, a purified protein derivative (PPD), found in cultures of *M. tuberculosis*. 2) Interferon-Gamma Release Assay (IGRA): A test that detects the interferon-gamma (IFN-g) response produced by T lymphocytes after stimulation by specific antigens (early secretion target antigen 6 - ESAT-6 and protein of culture filtrate 10 - CFP-10), encoded by a genomic segment exclusive to *M. tuberculosis*. 3) Breast tuberculosis, especially granulomatous mastitis and the nodular variant, can be identified through imaging and the triple approach (Physical Examination, Radiological Assessment - Ultrasonography, Mammography - and Cytology) (Zhong et al., 2015 ; Ail, 2017; Naili et al., 2015).

### 3.7 Treatment

The basis of treatment remains anti-tubercular therapy for a period of six months. To avoid recurrence, or when the cynical response is time-consuming, a prolonged duration of treatment has been reported, because the best medications for breast tuberculosis are: Etambutol 800 mg, Pirazinamide 1500mg, Rifampicin 450mg and Isoniazid 300mg (Hammami et al., 2021; Bouziyane et al., 2020). In addition, some clinical cases are reported that require prolongation of treatment up to 18 months, due to poor clinical response. Some reports pointed to the emergence of resistance to this regimen, therefore, the complementation of second-line therapy with Ethionamide, Canamycin, Ofloxacin and Para-aminosalicylic acid showed a good response (Hoang et al., 2022; Kiliç et al., 2016).

Furthermore, studies argue that surgical intervention is necessary in 15% to 40% of cases may be indispensable in patients who do not have an improvement in the clinical picture only to chemotherapy or with generalized disease. Breast conservation remains the objective of the treatment (Sinha & Rahul, 2019).

#### 4. Conclusion

Breast tuberculosis is one of the rare forms of extrapulmonary presentation of tuberculosis, which can present as an abscess or non-specific breast nodulation with an atypical clinical picture in relation to the classic presentation of pulmonary tuberculosis. Thus, even in regions endemic for Koch's bacillus, there are more prevalent differential diagnoses, but with similar clinical relevance that are only differentiated in histopathological examinations, which, despite being assertive, are often not very conclusive for the specific onset of the disease. therapeutic, requiring an empirical approach after analysis of the bacteriological culture of breast tissue collected by fine needle aspiration cytology (FNAC). Therefore, the diagnostic, propaedeutic and therapeutic challenge surrounding breast tuberculosis must be better addressed through more studies regarding its pathophysiology and histological understanding to facilitate effective and direct diagnosis, with the aim of allowing correct clinical reasoning and management for treatment.

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