

Internal Medicine
Section

Case Series of Primary Breast Tuberculosis Presenting as a Lump: A Diagnostic Challenge

SHOBITHA RAO¹, S ANEESHA²



ABSTRACT

Tuberculosis of the breast is rare, even in countries where the disease is endemic. Breast tuberculosis usually occurs secondary to infection elsewhere. Less commonly, it may be the primary site with no demonstrable focus elsewhere. It is mainly encountered in immunosuppressed individuals, those with a history of trauma and suppurative mastitis. It commonly presents as a lump in the breast, but other presentations such as breast abscess, dull aching pain, nipple discharge, etc., have been reported. Multiparous and lactating women in their second to fourth decade are commonly affected. Studies have shown that microbiological diagnosis is limited to a few cases, and histopathology is the mainstay in diagnosing cases of breast tuberculosis. In the present case series, two cases (44-year-old and 40-year-old females) presented with a painless, ill-defined lump in the left breast. Another case (33-year-old female) presented with a lump in the left breast with dull aching pain. Constitutional symptoms were absent in all of the present case series patients. Microbiological positivity in the form of Cartridge-based Nucleic Acid Amplification Test (CBNAAT) positivity was seen in only one of the patients. Biopsy of all these cases showed non caseating granuloma. All the patients had primary breast tuberculosis with no other organ involvement. All the patients were started on standard antitubercular therapy with a fixed drug combination, following an initial delay due to the non caseating nature of the granuloma. All of them responded well to the therapy. The present case series compared the characteristics and delved deeply into the current data and research on breast tuberculosis to understand the same.

Keywords: Biopsy, Endemic, Granuloma, Mastitis

INTRODUCTION

Breast tuberculosis is a rare diagnosis, even in countries where tuberculosis is highly prevalent [1]. It accounts for less than 0.1% of extrapulmonary cases in Western countries. However, in places of high prevalence, like India and Africa, the incidence is reported to be as high as 3-4% of extrapulmonary cases [2]. The prevalence of tuberculosis in India is estimated to be 312 per 100,000 population with a crude prevalence of 31.3% in those aged 15 years and above [3]. Sir Astley Cooper first described it in 1829, where he described it as a scrofulous swelling in the bosom of a young woman [4]. Tuberculosis of the breast can be difficult to diagnose because of the low frequency of incidence and its ability to mimic other common conditions like malignancy or breast abscess. It commonly affects young lactating women. The usual site of occurrence is the upper outer quadrant, but other sites of occurrence within the breast are also reported, which include central or multiple lumps within the same breast [5]. Hereby, the authors report three cases of breast tuberculosis which put forward a diagnostic challenge due to inconclusive histopathological and atypical microbiological findings [Table/Fig-1].

Case 1

A 44-year-old non lactating female presented with complaints of a left breast lump that she noticed one month ago. It had gradually increased in size but was painless, and there was no discharge from the nipples. The skin above the lump appeared normal. She had no history of fever, weight loss, loss of appetite, joint pains, cough, rhinitis, haematuria, or other systemic symptoms. There

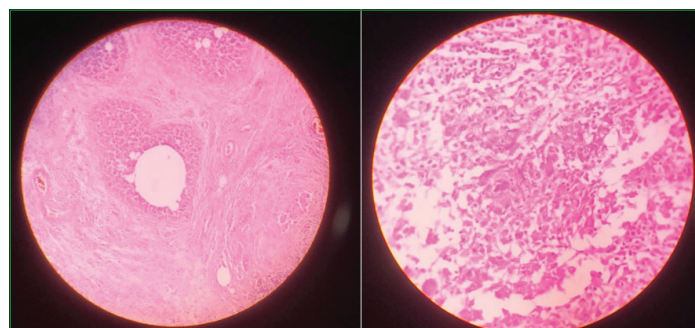
Characteristics	Case 1	Case 2	Case 3
Clinical symptoms	44-year-old, female, non lactating. Lump in left breast for 1 month. No pain, skin changes or constitutional symptoms.	33-year-old, female, non lactating. Dull aching pain in left breast for 1 month. Lump in the breast for 15 days. No pain, skin changes or constitutional symptoms.	40-year-old, female, non lactating. Lump in the left breast for 1 month. No pain, skin changes or constitutional symptoms.
Past medical or surgical history or co-morbidities	None.	History of caesarean section.	None.
Examination of breast	Painless, poorly defined, hard mass in the lower and outer quadrant of the breast. On follow-up, postsurgery patient developed an abscess.	Retracted nipple with normal skin. A 5x4 cm firm, well-defined mass was felt over the left breast in the upper inner quadrant. A local rise in temperature and tenderness was present. There was no fluctuation.	Painless, well-defined, hard mass measuring 6x4 cm in the lower and outer quadrant of the breast.
Ultrasonography	Ill-defined, spiculated, heterogenous, hypoechoic and antiparallel lesion measuring 6x2.8 cm in lower outer quadrant.	-	Ill-defined, spiculated, heterogenous, hypoechoic, antiparallel lesion measuring 6x4 cm in lower outer quadrant.
Histopathology	Non caseating granuloma.	Non caseating granuloma.	Non caseating granuloma.
Microbiological findings	AFB smear, CBNAAT for <i>M.tuberculosis</i> was negative from tissue sample. CBNAAT from recurced abscess was positive for <i>M.tuberculosis</i> .	AFB smear, CBNAAT for <i>M.tuberculosis</i> , gram stain was negative.	AFB smear, CBNAAT for <i>M.tuberculosis</i> , gram stain was negative.

[Table/Fig-1]: Summary of findings of the present case series with breast tuberculosis.
AFB: Acid-fast bacilli; CBNAAT: Cartridge-based nucleic acid amplification test; M: Mycobacterium

were no similar complaints among other family members, and had no significant medical or surgical history in the past.

On physical examination, a painless, poorly defined, hard lump was found in the lower outer quadrant of the breast. Ultrasonography revealed an ill-defined spiculated heterogeneously hypoechoic antiparallel lesion measuring 6x2.8 cm with posterior acoustic shadowing noted at 3 to 5 o'clock position in the lower outer quadrant of the left breast, which received a Breast Imaging Reporting and Data System (BI-RADS) score 4 [6]. Additionally, a few left axillary lymph nodes were noted, the largest measuring 9 mm in short axis with atypical cortical thickening. Chest radiography and ultrasound of the abdomen with pelvis did not show any other organ involvement.

A biopsy of the lump revealed a lobulocentric mixed inflammatory infiltrate composed of lymphocytes, plasma cells, macrophages, neutrophils and scattered multinucleated giant cells. Round to oval cystic spaces (lipid vacuoles) were seen rimmed by neutrophils, forming microabscesses. These were surrounded by epithelioid histiocytes and multinucleated giant cells, without the presence of caseous necrosis. Stains for Acid-fast Bacilli (AFB), gram stain, Periodic Acid-Schiff stain (PAS) and CBNAAT for *Mycobacterium tuberculosis* were negative. Granulomatous Mastitis (GM) secondary to non tubercular infection was considered given the non caseating nature of the granuloma and the absence of tubercle bacilli on microbiology examination [Table/Fig-2,3]. She was prescribed doxycycline 100 mg twice daily for two weeks. However, patient returned after two weeks with a repeat abscess. The patient then underwent repeat aspiration, which was sent for CBNAAT again. This was found to be positive for *Mycobacterium tuberculosis* (*M. tuberculosis*). Consequently, patient was started on antitubercular treatment, which led to complete resolution of the breast lesion after one month of starting therapy. She was put on follow-up for six months, with no recurrence thereafter.



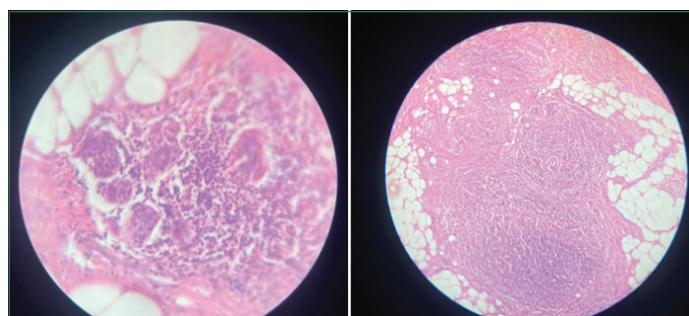
[Table/Fig-2]: Haematoxylin and Eosin staining of the lesion (H&E, 100X).
[Table/Fig-3]: Inflammatory cell infiltrate, non caseating granulomas and lipid vacuole in the breast tissue (H&E, 400X). (Images from left to right)

Case 2

A 33-year-old non lactating female presented with a complaint of left breast pain persisting for one and a half months. The pain was described as dull aching, non radiating, and not associated with any discharge, with no exacerbating factors. She noticed a swelling in the breast approximately, 15 days prior. No history of fever, loss of appetite, or weight loss, and no other other medical co-morbidities or similar complaints among family members. Patient had undergone caesarean sections for two pregnancies in the past.

Upon examination, the nipple was retracted, but the skin over the swelling was normal with no discharge. A 5x4 cm mass was palpable over the left breast in the upper inner quadrant. There was tenderness with local rise in temperature. The consistency was firm, the margins were well-defined and the lump was not attached to the underlying structures. The lump was non fluctuant. An excision biopsy was performed, and the fibrocystic lesion was excised and sent for histopathology, AFB smear and CBNAAT. The histopathology revealed the presence of a lobulocentric mixed inflammatory infiltrate

composed of non caseating granuloma containing multinucleate giant cells and macrophages [Table/Fig-4,5]. Microabscesses were also observed. Acid-fast staining and CBNAAT were negative. Antitubercular drugs were initiated since other causes were ruled out. The patient showed complete resolution of the lesion within a month of therapy and experienced no recurrence after completing six months of treatment.



[Table/Fig-4]: Mixed inflammatory infiltrate, neutrophils, lymphocytes, and giant cells forming a non caseating granuloma in the excised breast tissue (H&E, 400X).
[Table/Fig-5]: Breast tissue with mixed inflammatory infiltrate, neutrophils, lymphocytes and giant cells forming a non caseating granuloma (H&E, 100X). (Images from left to right)

Case 3

A 40-year-old non lactating female presented with complaints of a left breast lump, which she noticed one month prior. It had gradually increased in size but was painless, and there was no discharge from the nipples. The skin above the lump appeared normal. No history of fever, weight loss or loss of appetite. Additionally, she had no significant co-morbidities, nor any family history of similar complaints.

Physical examination revealed a painless, well-defined, hard lump in the lower outer quadrant of the breast. Ultrasonography of the bilateral breast and axilla showed an ill-defined, spiculated, heterogeneously hypoechoic antiparallel lesion measuring 6x4 cm with posterior acoustic shadowing in the left breast's lower outer quadrant. A biopsy of the lump revealed a lobulocentric mixed inflammatory infiltrate composed of lymphocytes, plasma cells, macrophages, neutrophils, and scattered multinucleated giant cells and epithelioid cells. Microabscesses were present. Acid-fast stain, gram stain, and CBNAAT for *M. tuberculosis* were negative.

The patient was initially treated with Doxycycline 100 mg twice daily for 14 days. However, the lesions recurred. Subsequently, she was started on antitubercular treatment, as other cause work-up was negative. Following the initiation of antitubercular therapy, the breast disease completely resolved in six weeks with no recurrence six month follow-up.

These cases are being reported here as a series highlighting the diagnostic challenge posed by the non caseating granulomas caused by tubercle bacilli. These lesions, due to their non caseating nature, mimicked other cases of GM. The differentials included infection by fungi/corynebacterium, sarcoidosis, wegenger's granulomatosis, duct ectasia, granulomatous reaction to tumours/foreign bodies, and rarely idiopathic. Work-up required sending fungal culture, bacterial culture, autoimmune panel, acid-fast staining and nucleic acid testing for *M. tuberculosis*.

DISCUSSION

Tuberculosis of the breast is rare because breast tissue is more resistant to infection, making the survival and multiplication of the tubercle bacilli very difficult [2]. It is considered primary when there is no other focus of infection elsewhere, and the breast is the only organ affected. It is considered secondary when there is a pre-existing focus elsewhere. Primary breast tuberculosis can occur due to direct inoculation through skin abrasion or hematogenous spread from a pulmonary focus, or through retrograde lymphatic flow [7]. In all of three current cases, there was no obvious focus elsewhere, and hence, it was diagnosed as a case of primary breast tuberculosis.

A breast lump is a common presentation of breast tuberculosis. The overlying skin may be normal, ulcerated, or can form a sinus. The upper outer quadrant is commonly involved, and constitutional symptoms are present in less than 20% of cases [8]. In all of the present case series, the left breast was involved. Two of them had involvement in the lower outer quadrant, while others had involvement in the upper inner quadrant. Few studies have reported that the left and right breasts are equally involved. However, Sen M et al., reported that right breast involvement was more common in their case series than the left [7].

Radiologically, breast tuberculosis can present in three forms: nodular, diffuse and sclerosing types. The nodular type is well-defined and usually mimics malignancy. The diffuse form is poorly defined and can form multiple lesions. The sclerosing type is commonly seen in the elderly and is associated with fibrosis [8,9].

All of the present case series patients presented with a breast lump. One of the cases involved pain, and one patient developed an abscess postsurgical lump excision. In their case series, Ghaleb M et al., also found that a lump in the breast was the most common presentation of breast tuberculosis, seen in 50% of their cases. 33% of the cases had breast tenderness. Other findings included a breast abscess, discharge from the nipple, erythema of the skin and axillary lymphadenopathy [10].

Two patients in the present case series, were in the age group of 30-40 years, while one was above 40 years of age. Breast tuberculosis is reported mostly in multiparous and lactating women who are in their second to fourth decade [1]. The fifth decade is slightly older than in most other case reports [7,8,11]. However, Oucharqui S et al., and Marinopoulos S et al., also reported their cases to be slightly older [1,2]. Other risk factors include trauma, a history of suppurative mastitis, Acquired Immunodeficiency Syndrome (AIDS), and other immunosuppressive conditions [12]. The present case series patients had none of these risk factors.

The definitive diagnosis of tuberculous mastitis is made by microbiological confirmation and/or histopathological demonstration of characteristic caseating granulomas [8,11]. Diagnostic challenges can be posed by other granulomatous inflammatory conditions of the breast, including Granulomatous Mastitis (GM) secondary to non-tubercular infections such as fungi/corynebacterium, sarcoidosis, Wegener's granulomatosis, duct ectasia, granulomatous reaction to tumors/foreign bodies and rarely idiopathic conditions [13]. GM caused by the corynebacterium genus also affects individuals in the reproductive age group. However, they typically tend to present with unilateral painful swelling which may later progress to abscess formation. It is also commonly implicated in recurrent mastitis. The organism is fastidious and hence difficult to isolate. However, it generally responds well to a course of doxycycline [14].

Jairajpuri ZS et al., who presented a series of cases of patients with breast tuberculosis, also noted that none of their cases were initially suspected to have tuberculosis. Most of their cases were clinically mistaken for malignancy or fibroadenoma. However, most of their cases showed caseating necrosis and/or AFB positivity [15]. Ghaleb M et al., noted that though microbiological diagnosis is the gold standard, it is not always achieved. Only 12% of their cases had AFB positivity on staining. Studies have shown that *M.tuberculosis* can be isolated in only one-fifth of the cases of breast tuberculosis, and hence histopathological diagnosis becomes the mainstay in most cases [10]. All the present case series patients had non caseating granuloma with failed microbiological isolation of any bacteria, prompting us to consider other causes for GM. Studies have shown that non caseating granulomas can be seen in tuberculosis. Altered immune response and paucibacillary disease may contribute to non caseating necrosis in some patients [16,17].

The diagnostic challenges posed by the present case series of breast tuberculosis are numerous. As discussed previously, they can present as a lump, breast abscess, nipple discharge, erythema of the skin, and/or axillary lymphadenopathy. None of these findings are specific to breast tuberculosis. They mimic other diseases of the breast, which are much more common than breast tuberculosis. Unlike radiological imaging for pulmonary or other forms of tuberculosis, mammography and ultrasonography findings also overlap with other conditions. As highlighted in the previous paragraph, very few cases allow the isolation of mycobacterium from the lesion. Hence, biopsy becomes the only definitive mode of diagnosis. In the present cases, since the biopsy did not show the hallmark histopathology of tuberculous infection, there was a delay in diagnosis in the cases. Clinicians dealing with tuberculosis must be aware of all other causes of granulomatous mastitis, and evidence for them should be sought clinically and through investigations, if required.

CONCLUSION(S)

The clinical features and radiological findings in breast tuberculosis are not specific, and microbiological isolation may not always be possible. Histopathology becomes the mainstay in diagnosing breast tuberculosis in most cases. Challenges may arise when the histopathology is also not definitive, as in the present case series. Clinicians dealing with tuberculosis must be aware of all causes of granulomatous mastitis, including tuberculosis. However, a cautious approach may be required in endemic countries before an alternative diagnosis is made. A high index of suspicion is required in cases that present as a lump or breast abscess showing granulomas on Fine Needle Aspiration Cytology (FNAC) and biopsy.

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PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Respiratory Medicine, Srinivas Institute of Medical Sciences and Research Centre, Mangaluru, Karnataka, India.
2. Junior Resident, Department of Respiratory Medicine, Srinivas Institute of Medical Sciences and Research Centre, Mangaluru, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Shobitha Rao,
Associate Professor, Department of Respiratory Medicine, Srinivas Institute of
Medical Sciences and Research Centre, Mangaluru-574146, Karnataka, India.
E-mail: shobitha.rao@gmail.com

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