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Clinical, Diagnostic And Therapeutic Management Of Patients With Breast Tuberculosis: Retrospective Analysis Of 16 Cases

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ABSTRACT

Background: Breast tuberculosis is a rare form of extrapulmonary tubercular infection. Very little data available about the clinical presentations, diagnostic difficulties and therapeutic ap poach of breast tuberculosis. **Aim and Objective:** To highlight the nonspecific clinical presentations, diagnostic difficulties and therapeutic approach of breast tuberculosis. **Patients and Methods:** Sixteen patients diagnosed with breast tuberculosis between 2016 and 2019, who were attended OPD and admitted to indoor of MKCG Medical college and Hospital, Berhampur, Ganjam, Odisha India were reviewed retrospectively. Clinical features, all diagnostic methods, and the outcomes of treatment were analysed. **Results:** All cases were female with a mean age of 36.4 years. Breast mass and pain were the most common complaints. While 31.2% of the cases had a physical examination with suspicions for malignancy, 43.5% of the patients had Breast Imaging Reporting and Data System (BIRADS) 3 lesions suggested malignancy radiologically. Definitive diagnosis was based on histopathologic examination through core needle biopsy (*n* =10), excisional biopsy (*n* =04), and open biopsy (*n* =02) taken from the abscess wall during drainage. Standard antiTB therapy for 6 months was given to all cases. Thirteen patients recovered with standard 6-month therapy while extended treatment for 9 to12 months was needed in 3 (18.8%) cases. Surgery was carried out in 6 cases. Two patients developed recurrence. **Conclusion:** Breast tuberculosis can be easily confused with breast cancer, suppurative abscess, and other causes of granulomatous mastitis, both clinically and radiologically. A multidisciplinary approach is

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required to prevent diagnostic delays and unnecessary surgical interventions. Although antiTB therapy is the mainstay treatment of breast TB, surgery is usually indicated in patient's refractory to medical treatment.

Keywords: Tuberculosis, Acid-fast bacilli, Z-N staining, Montoux, Granuloma, Caseous Necrosis

INTRODUCTION:

Although Tuberculosis (TB) remains a major public health problem with 1.3 million/year deaths globally [1], breast TB, first described by Sir Astley Cooper in the 1800s [2], is a rare clinical entity with an estimated rate of 0.025% to 1.04% of all breast pathologies [3]. Breast TB is usually classified as primary and secondary forms. Among these, the secondary form is seen more frequently, and usually associated with various primary tubercular foci such as from the lungs, pleura, or lymph nodes. Due to its rarity and variable clinical presentations, breast TB can be confused with other breast diseases such as breast carcinoma and pyogenic breast abscess, both clinically and radiologically [4]. Therefore, correct diagnosis of this uncommon disease is usually based on high index of clinical suspicion. In this paper, we aimed to analyse the clinical features, diagnostic difficulties, and therapeutic outcomes of breast TB.

AIM AND OBJECTIVE OF THE STUDY:

1. To highlight the nonspecific clinical presentations, diagnostic difficulties and therapeutic approach of breast tuberculosis.

MATERIALS:

Inclusion criteria:

1. All diagnosed cases of Breast Tuberculosis in women who were attended OPD and admitted to indoor of MKCG Medical college and Hospital, Berhampur, Ganjam,Odisha India between 2016 to 2019.

Exclusion criteria:

1. Cases with other co morbid conditions like dearranged Liver Function test, cardiac problems, psychiatric illness etc
2. Cases having known history of allergy to drugs.
3. Cases who were pregnant and lactational period.

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METHODS:

Patients

The medical records of 16 breast TB patients who were treated between 2016 and 2019 at MKCG medical College and Hospital Berhampur Odisha India were reviewed retrospectively. Informed consents of the patients were waived due to the retrospective nature of the study. Patients' demographic data such as age, gender, marital status, employment status, educational status, past and contact history of TB, comorbid diseases, the initial clinical findings, radiological investigations including breast ultrasonography (US) and mammography (MM) were recorded. All patients were also evaluated in terms of coexisting pulmonary TB, with chest x-ray and culture of respiratory secretion.

Diagnosis

The breast TB diagnosis was mainly made based on histopathological findings from core needle biopsy, excisional biopsy of the abscess wall during drainage. Smear and culture of breast tissue or discharge were also other methods in the diagnostic workup. The histopathological findings of epithelioid cell granulomas, Langhans' giant cells, and lymphohistiocytic aggregates confirmed the diagnosis.

Treatment and follow-up

All patients were treated with isoniazid (5 mg/kg day, max. 300 mg/day) and rifampicin [10 mg/kg day, maximum (max) 600 mg/day] for 6 months. In the first 2-month period, pyrazinamide (20 to 30 mg/kg day, max. 2 g/day) and streptomycin (15 mg/kg day, max. 1 g/day) or ethambutol (15 to 20 mg/kg day, max. 1.5 g/day) were administered. All patients were evaluated at the end of the therapy, and if there was no full resolution of symptoms and *Mycobacterium tuberculosis* was still present in any specimen, a treatment of 3 months was added. Patients were invited at regular intervals after the end of the treatment. All complications during the follow up period were recorded.

Statistical assessment

The statistical package for social science (SPSS 21.0 IL, Chicago, USA) standard version was used for data analyses. Descriptive analysis was done for demographic, clinical, and radiographic features. The results are presented as mean SD/percentages for continuous variables and number/percentage for categorical variables. Chi-square (c2) test, Fisher's Exact test, and ManneWhitney U-test were used to test for the significance of association between the two antiTB treatment groups (patients who healed with standard antiTB therapy for 6 months and those who needed extended therapy of 9 to 12 months). A significance level was accepted as $p < 0.05$.

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DATA ANALYSIS AND RESULTS:

All cases were female with a mean age of 36.4 years. All demographic and clinical data of the patients are presented in (Table 1). The mean duration of symptoms prior to admission was 35.5 days (range 0 to 180). The most common presenting symptoms were breast lump (14, 87.5%) and pain (2,12.5%). Clinically apparent breast abscess was the initial presentation in two (12.5%) cases. The left breast was more frequently affected than the right breast (Table 2).

Breast Ultrasound was the first step radiological investigation in all patients while mammography could be performed in 4 (25%) cases due to the limitation of age. Sonographic examination of the breast revealed abnormal findings in the majority of patients (91.3%). All the radiological findings are presented in (Table 3).

Definitive diagnosis was mainly based on histopathological examination in all patients. Core needle biopsy (n = 10) was the most frequently used diagnostic tool, with an accuracy rate of 93.5%. In cases of inconclusive core needle biopsy small nonpalpable masses (n =4), excisional biopsy with wide margins was performed for the diagnosis. Open biopsy taken from the abscess wall during drainage was carried out in two patients. Epitheloid cell granulomas with or without caseous necrosis and multinucleated giant cells were the leading histopathological findings. All specimens were also subjected to culture and Ziehl Nelsen staining for identifying *M. tuberculosis*. Culture of breast tissue and acid-fast bacilli (AFB) staining were positive in 56.2% (9/16) and 25% (4/16) patients, respectively. In addition, nine patients had smear examination of discharge (from nipple or fistula), and pos itive Ziehl Nelsen staining was obtained in five of those. Polymerase chain reaction (PCR) analysis could be done in only four patients with 50% positivity.

Table 1 Baseline characteristics of patients (n = 16). Patient characteristics n (%)

Patients Characteristics	n (%)
Age (y)	36.4, (24 to 62)
Marital status	
Single	2 (12.5%)
Married	13(81.3%)
Divorced	1 (6.2%)
Employment status	
Housewife	15 (93.7%)
Employed	1 (6.2%)
Educational status	
Primary/secondary school	13(81.3%)
High school	02 (12.5%)
University	1 (6.2%)

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Menopausal status	
Premenopausal	14(87.5%)
Postmenopausal	2(12.5%)
Location	
Rural	13(81.3%)
Urban	3(18.7%)
Coexisting pulmonary TB	3 (18.7%)
Past history of TB	5 (31.2%)
Contact history of TB	7 (43.7%)
Presence of BCG vaccination	15 (93.7%)
PPD positivity	14(87.5%)

BCG- Bacillus Calmettee Guerin, TB- Tuberculosis
PPD- Purified protein derivative

All patients received standard antiTB therapy for 6 months. Thirteen patients healed with standard 6- month therapy while extended treatment for 9 to12 months was needed in 3(18.7%) who had discontinued drug therapy and had persistent symptoms and signs. There were no statistical differences between the patients who healed with standard 6-month antiTB therapy and the patients who had discontinued drug therapy and had persistent symptoms and signs. There were no statistical differences between the patients who healed with standard 6-month antiTB therapy and the patients who needed extended treatment, in terms of clinicopathological features ($p > 0.05$). Surgery was carried out in 4 cases, including total excision of mass for 3 patients and repeated aspirations of abscess in one patient. Two of the 16 patients developed recurrence during the follow up period. Recurrent lesions were in mass formations in both patients, and were totally excised. Then, these two patients were treated with antiTB therapy for 8 months ($2H_3R_3Z_3E_3S_3$ $1H_3R_3Z_3E_3$ $5H_3R_3E_3$). No recurrence was observed during their follow-up periods.

Table 2 : Presenting symptoms and signs of the patients with breast TB.

Clinical findings	n (%)
Presenting symptoms and findings	
Breast lump with sinuses	2 (12.5%)
Breast lump without sinuses	8 (50%)
Breast pain with nodularity	1(6.2%)
Breast pain without nodularity	1 (6.2%)
Sinus formation	2 (12.5%)
Nipple discharge	8 (50%)

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Axillary lymphadenopathy	4 (25%)
Fever	3 (18.5%)
Incidental	1 (6.2%)
Side of the disease	
Left	10 (62.5%)
Right	6 (37.5%)
Quadrant of the disease	
Upper-outer	10 (62.5%)
Upper-inner	2 (12.5%)
Lower-outer	2 (12.5%)
Lower-inner	2 (12.5%)
Clinical suspicion of malignancy	5 (31.2%)

Table 3 Radiological findings of the patients with breast TB.

Radiologic findings	n (%)
Chest x-ray (n = 16)	
Sequelae findings of past TB	3(18.5%)
Radioopacity	2(12.5%)
Pleural effusion	1(6.2%)
Normal	10(62.2%)
Ultrasonographic findings (n = 16)	
Hypoechoic mass with irregular border	4(25%)
Nonspecific inflammatory changes	2(12.5%)
Axillary lymphadenopathy	1(6.2%)
Abscess	2(12.5%)
Well-defined mass	5(31.2%)
Normal	2(12.5%)
Mammographic findings (n = 4)	
Asymmetric density or poorly defined mass	1(6.2%)
Distortion	1(6.2%)
Spiculated mass	1(6.2%)

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Circumscribed mass	1(6.2%)
Radiological suspicion of malignancy	
(BI-RADS 4-5)	3(18.7%)

DISCUSSION:

Breast TB generally affects women of reproductive age group; however, it can be also seen in young girls, elderly women, and males [5]. Our study population completely consisted of female patients with a mean age of 36.4 years, and only two cases were in their postmenopausal periods. Although secondary form of breast TB has been more frequently reported than primary form [6], 31.2% of the patients had coexisting pulmonary TB, past or contact history of TB in the present study. However, it should be noted here that the primary focus cannot be usually detected radiologically or clinically [7]. In our opinion, presence of coexisting pulmonary TB, past and contact history of TB should be always investigated in the initial evaluation of patients with breast TB. While the primary form of the disease occurs via infection through skin abrasions or openings of the lacrimal ducts at the nipple, secondary form develops through three ways, including direct extension, hematogenously from the lung TB, and retrograde lymphatic dissemination from the affected axillary lymph nodes.

Various risk factors such as multiparity, lactation, and pregnancy have been reported in the etiopathogenesis of breast TB [7-9]. Among those, presence of lactation seems to be more associated with the development of breast TB, with a reported incidence rate of up to 30% [10]. This condition may be explained by increased vascularity of the breasts during lactation and lacerations at the areola, which make the breast more vulnerable to tubercular infection.

Breast TB usually has unilateral involvement, and both sides seem to be affected equally [4,11]. In the present study, the majority of the patients had left breast lesion, and bilateral involvement was observed in no patient. Additionally, upper outer quadrant of the breast is the most common location in our patients, consistent with the pre vious studies [12,13]. Multicentric presentation was also frequent in the study population.

The patients with breast TB are often symptomatic prior to diagnosis for several weeks or months. The mean duration of symptoms in the present study was similar to other many case series [6,8,10].

According to the clinical, radiological, and pathological findings, breast TB can be classified as nodular, disseminated, and sclerosing forms [14]. Sclerosing type, characterized by extensive fibrosis, is rare and often found in elderly women [15]. While the disseminated form is characterized by multiple lesions associated with sinus forma- tion, nodular form is reported to be the principal clinical manifestation that is characterized by a well-defined,

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painless, slow growing breast mass [16]. Similarly, breast mass and pain were the most common physical findings in our case series. However, physical examination of the breast was consistent with malignancy in a significant number of patients. Multiple sinuses with or without discharge, ulcers, nipple or skin retraction, and discharge from the nipple can be accompanied with the breast lump. Ipsilateral axillary lymph node involvement is found in approximately one-third of patients with breast TB [15,17]. In our work, approximately one-sixteenth of the patients had ipsilateral enlarged axillary lymph nodes, differ with these previous reports. Abscess formation may be the initial clinical presentation in a small number of patients [17]. In accordance, 12.5% of our study population presented with a fluctuated breast abscess as initial complaint. Due to the variable presentations, breast TB is often confused with malignancy and pyogenic breast abscess clinically.

Breast TB has also nonspecific radiological findings. US is often used as the first step imaging method which shows heterogeneous hypoechoic lesion with irregular borders and internal echoes in most of the cases with breast TB. However, nonspecific stromal coarsening, asymmetric density, and ill-defined nodules are among the most common mammographic findings, which are not specific to breast TB. Additionally, both mammogram and Ultrasound are of limited value as the findings are often indistinguishable from other differential diagnoses such as breast carcinoma [6]. In our work, Ultrasound was used in all patients; however, Mammogram was the choice of imaging modality only for 4 cases > 35 years of age. The radio- logical findings of our study population were also in parallel with the data in the literature, and approximately half of the cases had radiologically suspected lesions.

Mantoux test is often positive in patients from endemic areas for TB, therefore may not be helpful in the diagnosis of breast TB [18]. Additionally, high false positivity rate of this test in BCG-vaccinated people due to cross reaction with bacillus CalmetteeGue´rin (BCG) limits its widespread use. In the present study, most of the patients had positive Mantoux test, and almost all of those patients had previously been vaccinated. Therefore, this test did not provide any significant diagnostic value in our work.

Although detection of tuberculous bacille by Ziehl Neelsen staining or culture is accepted as the gold standard diagnostic method in breast TB [19], these tests have some limitations. It is well known that culture of M. tuberculosis requires a lot of time and frequently gives negative results [7,20]. Similarly, low positivity rates of AFB staining have been reported in previous studies [3,11]. Our results of AFB staining and culture were also similar to these previous reports. The other method, PCR, is known as a rapid diagnostic test, but its low sensitivity and high costs are the disadvantages for its general use. However, it can be considered in cases with negative culture results or for differential diagnosis between other forms of granulomatous mastitis. In the present study, PCR was used in only four patients, and positive results were obtained from two. As a result, definitive diagnosis was mainly based on his- topathology by core biopsy and open (incisional or excisional) biopsy in our study population. Although fine needle aspiration cytology (FNAC) has been reported as a

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method with high diagnostic yield, some authors concluded that definitive diagnosis of breast TB may need a histological confirmation by larger tissue samples because granuloma- tous inflammation cannot be confidently differentiated by FNAC [21]. In accordance, we usually used core needle biopsy in the diagnostic algorithm, and obtained high diagnostic yield. It should be noted here that the recognition of tuberculosis does not exclude concomitant cancer. In our study, biopsy specimens revealed no cancer diagnosis.Standard antiTB therapy for 6 months is accepted as a main treatment modality with reported very high success rates [15,22]. This standard regimen was also administered all the patients in the present study. Extended therapy of 9 to 12 months was needed in 3 cases due to the incomplete resolution of the symptoms. Surgical intervention is generally indicated for drainage of breast abscess, diagnosis of the lesion, and excision of residual sinuses or masses. Segmental or total mastectomy may be indicated in patients with extensive disease or poor response to antiTB therapy [23]. In our study, the number of patients who received extended antiTB therapy may be considered as high. Incompatibility of the patients in drug intake may have led to this situation because, there was no significant differences between the patients who healed with standard 6-month antiTB therapy and the patients who received extended treatment, in terms of all clinicopathological characteristics.

CONCLUSION:

Isolated breast TB is an uncommon entity, even in TB endemic areas. Diagnosis is usually based on high degree of clinical suspicion. A multidisciplinary approach is important to prevent diagnostic delays and unnecessary surgical interventions. The principal differential diagnosis is that of breast carcinoma. Other breast diseases such as fat necrosis, suppurative abscess, and idiopathic granulomatous mastitis may be confused with breast TB, both clinically and radiologically. Although antiTB therapy is the main stay treatment of breast TB, surgery may be required for patient’s refractory to medical treatment.

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