ORIGINAL ARTICLE

Tuberculous Mastitis in Females of South Punjab: A Clinicopathological Analysis of Ten Years from Pakistan

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ABSTRACT

Background and Objective: Extrapulmonary tuberculosis occurring in breast is a rare disorder in West but is still present in developing nations where tuberculosis is endemic. Tuberculous Mastitis (TM) is difficult to diagnose as it has vague clinical symptoms and insufficient radiological findings. The objective of this study was to determine the frequency of tuberculous mastitis by accessible modalities for early diagnosis.

Methods: After the Institutional Ethical Board approvals, Pathology laboratory archives and medical records of 5000 patients from Ibn-e-Sina Hospital Research Institute, Multan and Multi Test Laboratory, were retrieved from the year 2008 to 2018. A retrospective analysis of fine needle aspiration cytology (FNAC) results of patients who presented with breast lumps was carried out. The interpretation of cytological findings and Ziehl Neelsen stained smears was carried out by cytopathologists and microbiologists respectively. Mycobacterium DNA was detected using polymerase chain reaction (PCR) in selected cases.

Results: Out of 5000 patients, tuberculosis was diagnosed in 264 (5.28%) cases on FNAC. Acid fast bacilli (AFB) positive smears were found in 79.5%patients while 20.45% cases were AFB negative. Among AFB negative smears, 38 cases were further analyzed by PCR, among which 32 (84.2%) cases showed PCR positive results for TM. An increased frequency of TM among all inflammatory breast lesions from 18% in 2008 to 47.19% in 2018 was observed.

Conclusion: Tuberculous Mastitis is an uncommon form of extra-pulmonary tuberculosis. It has non-specific clinical, radiological and varied histological findings that often mimic breast abscess or carcinoma. FNAC is essential to guide the patient to further tests including histochemistry and PCR that can be used as more sensitive and time effective detection modalities.

KEYWORDS: Tuberculous mastitis, Fine needle aspiration cytology, Breast lump, Mycobacterium *tuberculosis*.

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INTRODUCTION

Tuberculosis (TB) is one of the most persistent human infections in the world. Pakistan ranked 6th in drug resistant tuberculosis, one among the highest tuberculosis burden.[1] While breast is a rare site of extrapulmonary infection but recently, there is an increase in incidence of tuberculous mastitis.[2] In endemic countries for tuberculosis like Indian subcontinent, incidence is 4% while it is 1% of all breast diseases in developed countries. It affects women of reproductive age. Risk factors associated with Tuberculous mastitis include lactation, multiparity or previous history of mastitis.[3]

The most reliable diagnostic tool to diagnose palpable breast masses is triple assessment that involves clinical evaluation and physical breast examination, breast imaging (mammography, ultrasound, and magnetic resonance imaging) and fine-needle aspiration cytology (FNAC).[4,5] It is thought to be the most uncommon disease of all breast pathologies but recent studies have revealed masquerading of TB as carcinoma or pyogenic breast abscess due to lack of well-defined clinical features.[6,7,8] High index of clinical suspicion is therefore the basis of its diagnosis.[9]

As tuberculous mastitis is a common disease in developing countries especially Pakistan, therefore the main aim of this study was to determine the frequency of TM diagnosed through cytological, histochemical and molecular methods in female population of South Punjab over a period of ten years.

METHODS

A retrospective cross sectional study was conducted at Ibn-e-Sina Hospital Research Institute, Multan and Multi Test Laboratory Multan, from 2008 to 2018 for a period of ten years where the medical records of FNAC of 5000 female patients presenting with breast lumps were reviewed. Females with previous confirmed diagnosis of malignancy, or female patients with tuberculosis involving any other organs were excluded. Relevant data including clinical presentation and laboratory findings was recorded in pre-set proformas. Ethical approval was obtained from Multi Test Lab vide Letter No. MTL/RES/ 05/18) and Ibn-e-Sina Hospital vide Letter No. C-22-220.

This study included patient's demographic data like age, gender, marital status and past or family history of TB. Erythrocyte sedimentation rate (ESR) and lymphocyte count was also screened. The diagnosis of TM was mainly based on microscopic cytological findings from FNAC. Ziehl Neelsen staining was also performed. The Polymerase chain reaction (PCR) analysis was carried out in selected cases after the year 2014. The investigators ensured that the study patients were receiving appropriate anti-tuberculous treatment.

STATISTICAL ANALYSIS

Data was collected and entered in Statistical Package for the Social Sciences (SPSS) version 20. Qualitative variables were analyzed by using frequency and percentages and quantitative variables were expressed as mean ± standard deviation. The *P-value* of *≤ 0.05* was considered significant.

RESULTS

The age of study population ranged from 16-65 years with mean age of 32.69 ± 7.36 years. All the patients revealed chronic history (2 – 3 months) of breast lump that was not responding to antibiotic treatment. Fever and nipple discharge was seen in 112 (42.4%) and 68 (25.7%) patients respectively. Majority of the patients in the present study had raised ESR with mean value 70 mm/hr ± 12.0 TB was diagnosed in 264 (5.2%) cases.

The sociodemographic and clinical profile of patients revealed that 83.3% females were in premenopausal age and 71% were multiparous. Almost 85.6% were BCG vaccinated (Table-1). The X-Ray chest detected opacities in 29 (10.9%) cases however ultrasound and mammography of the patients detected regular and irregular breast lumps (Table-2) (Fig:4&5). The occurrence of TB among all inflammatory breast lesions was 18% in the year 2008 while it had inclined to 47.19% in 2018 (Fig:2).

Table-1: Demographic Characteristics of TM Patients

Age	16 – 65
Marital status	
Single	29 (10.9%)
Married	235 (89%)
Work status	
Housewife	220 (83.3%)

Employed	44 (16.6%)
Educational qualification	
Primary/secondary school	200 (75.7%)
College	55 (20.8%)
University	09 (3.4%)
Menopausal state	
Premenopausal	250 (94.6%)
Postmenopausal	14 (5.3%)
History of pregnancy	
Multiparous	
Pregnancy at the time of diagnosis	189 (71%)
History of breastfeeding	15 (5.6%)
Active Lactation at the time of diagnosis	130 (49.2%)
Presence of BCG vaccination	255 (85.6%)

AFB in smears having caseous necrosis was detected in 210 patients (79.5%) (Fig:2). Cases that were negative for AFB on ZN staining were 52 (20.4%) of which 38 (73.1%) samples were processed by Rt-PCR (GeneXpert) after its availability in year 2014. Mycobacterial DNA was amplified in 32(84.2%) out of 38 cases (Fig:6).

All patients were given antituberculous drugs for 2-4 months (2 months of Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol and further 4-months of Isoniazid and Rifampicin). From the clinical record, it was revealed that nearly all patients recovered fully after completion of treatment.

Table-2: Clinical and Radiological Findings of TB Patients.

Clinical Findings	*N (%)*	*Radiological Findings*	*N (%)*
Breast lump sinuses	80 (30.3%)	Chest X-ray	
Breast lump without sinuses	120 (45.4%)	Normal	235 (89%)
Breast pain with nodules	99 (37.5%)	Radiopacity	29 (10.9%)
Breast pain without nodules	54 (19.6%)	***Ultrasonographic Findings***	
Fever	112 (42.4%)	Normal	05 (1.89%)
Nipple discharge	68 (25.7%)	Well-defined mass	8 (3%)
Side of Breast – Left	205 (77.6%)	Hypoechoic irregular bordered mass	164 (62.1%)
Side of Breast – Right	59 (22.3%)	Non-specific inflammatory changes	100 (37.8%)
		Abscess	03 (1.1%)
		Mammographic Findings	
		Poorly defined/ asymmetrical mass	65 (24.6%)
		Micro-calcification	15 (5.6%)
		Radiological findings mimicking malignancy	96 (36.3%)

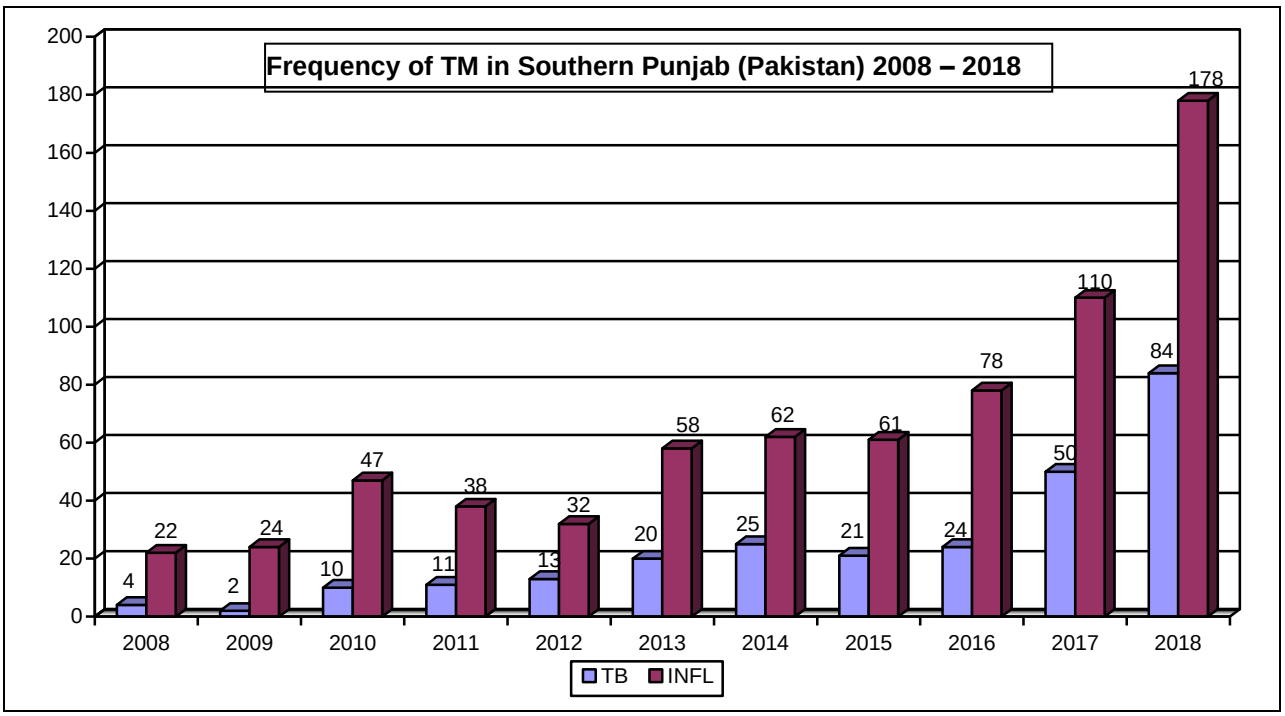

Fig.1: Frequency of TB over a decade since 2008-2018.

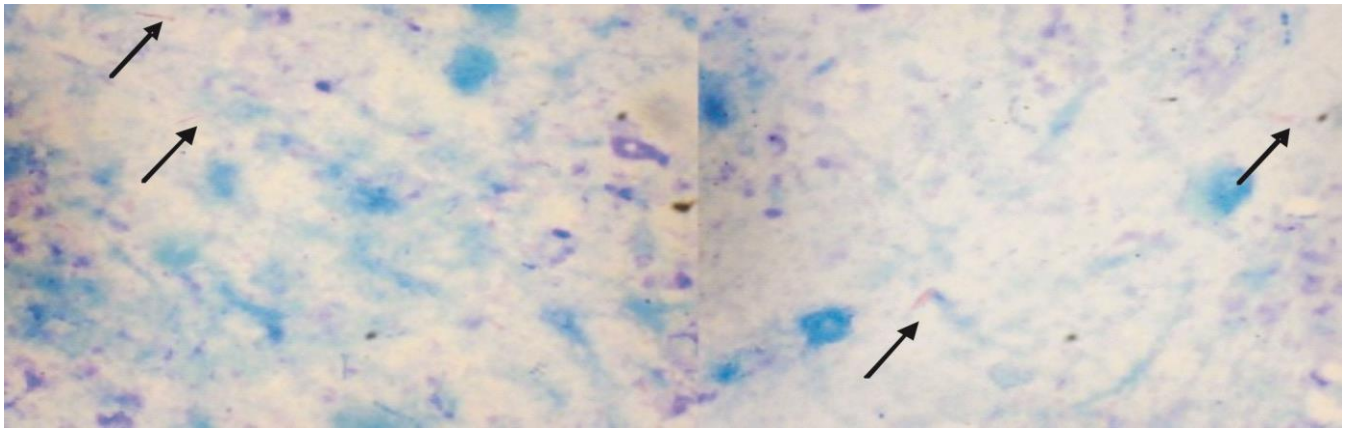

Fig.2: Photomicrograph showing FNA smear stained with ZN stain at oil emersion lens (100X). Acid fast bacilli are seen as pink to red rods (arrows).

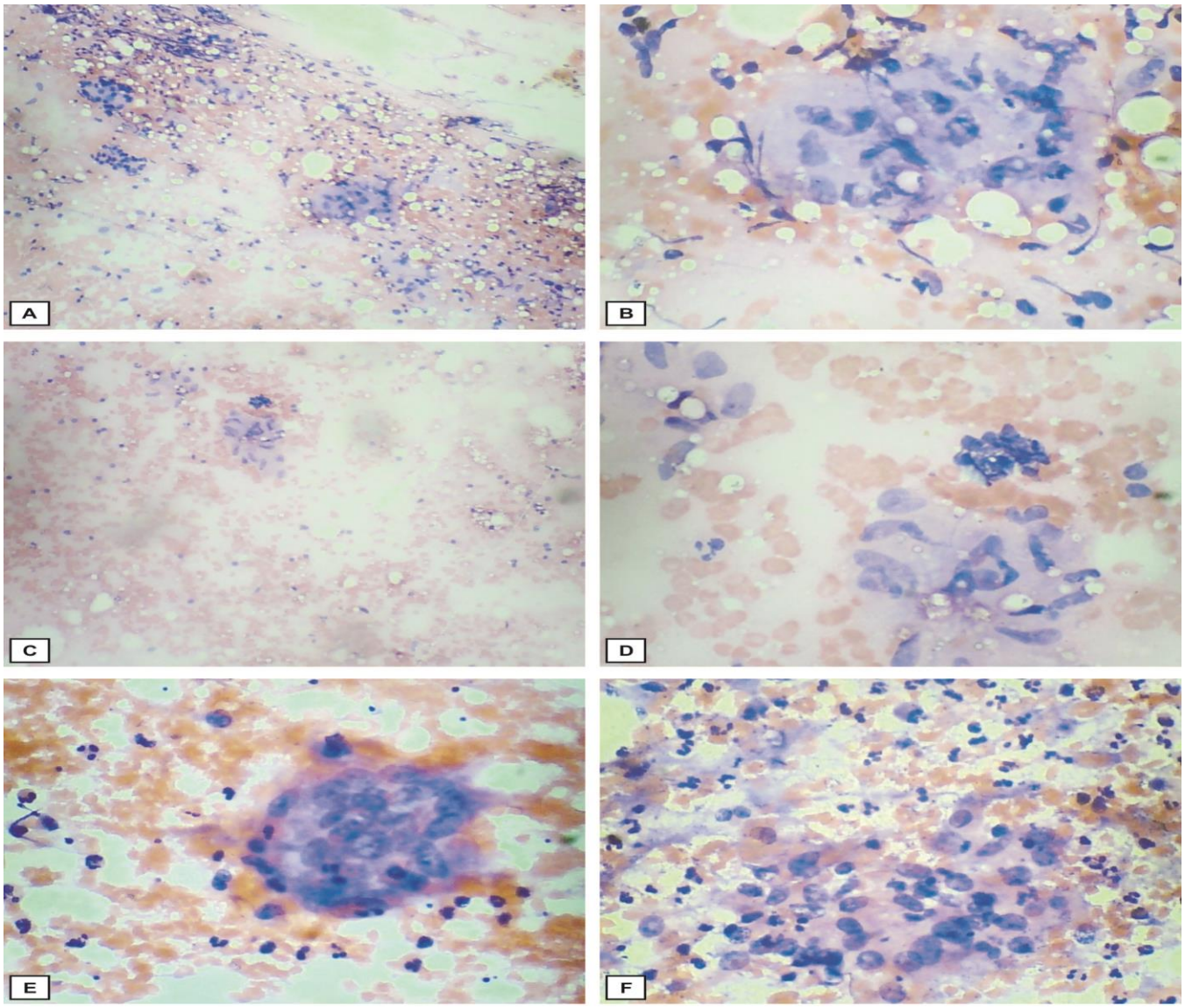

Fig.3: Photomicrographs showing smears of FNAC breast (A,C)at low magnification (100X) and at high magnification (400X) (B,D,E,F) showing granulomas

(B) of patients showing irregular breast lump.

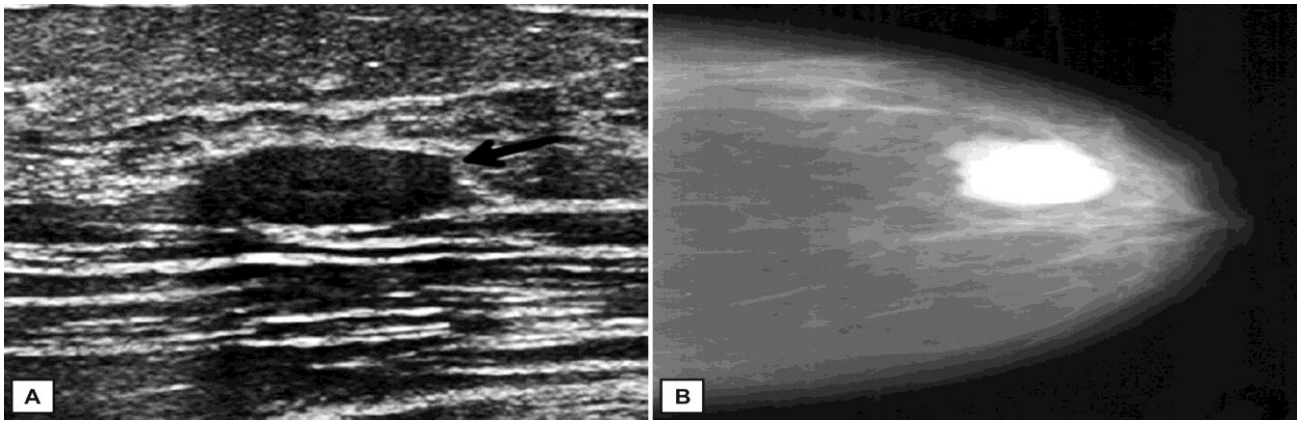

Fig.4: Radiographic image indicating ultrasonograph (A) and mammographic picture (B) of patients showing regular breast lump.

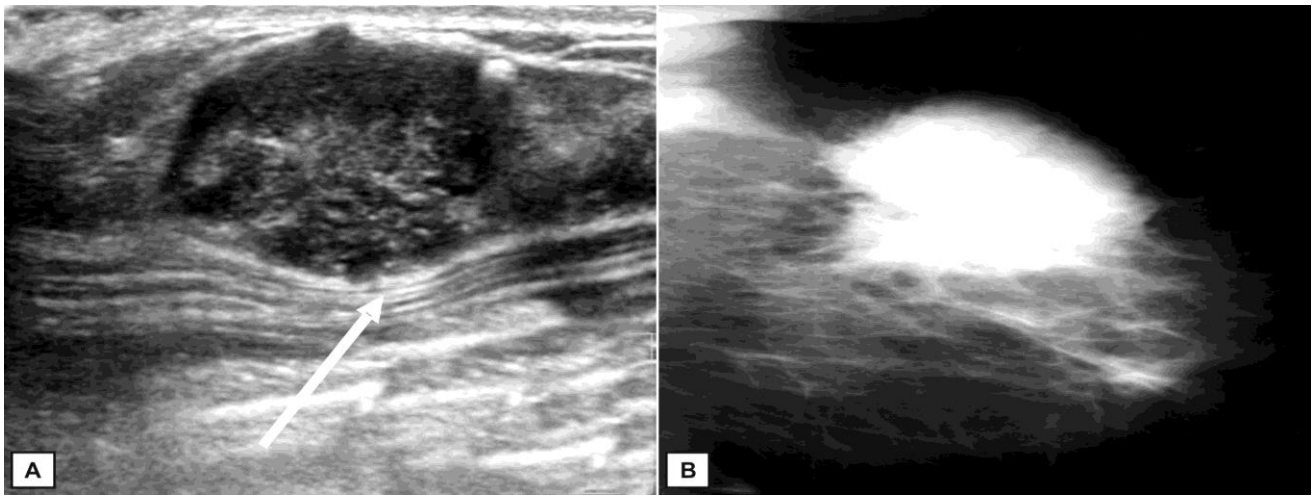

Fig.4: Radiographic image indicating ultrasonograph (A) and mammographic picture (B) of patients showing irregular breast lump.

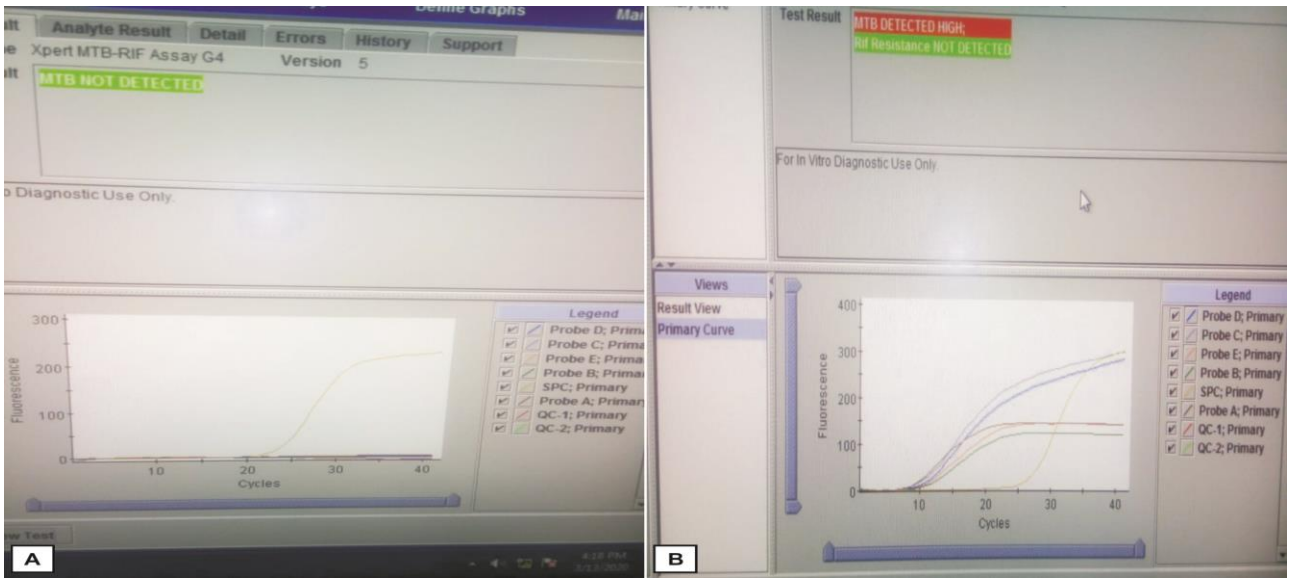

Fig.5: Negative (A) and Positive (B) results of GeneXpert for tuberculosis.

DISCUSSION

Tuberculous mastitis is a very rare modern disease in Western population with an incidence of 0.1% of breast lesions.[6] While a report from Bangladesh published 4% frequency, this retrospective analysis indicates 5.23% of TM cases in Pakistan.[3] Surveillance reports indicate Pakistan at number six among 22 most burdened countries with pulmonary and extrapulmonary TB.[10]

In this study most of the women were between the age group of 16-65 years where 3.03% (8/264) were under 20's while 5.3% (14/264) were found to be in post-menopausal state. Previous studies have shown that the females between the ages of 20-40 years are more effected by TM.[11] Shrestha et al.[12] has also reported similar findings stating that tuberculous mastitis is common in females of reproductive age group and rare in males. In another Indian frequency report, Tiwari et al. [13] reported 1.77% of tuberculous mastitis cases where 50% were in third decade of life.

Tuberculous breast lesions are classified into two categories: Primary and secondary forms. Cases with primary form are rare, as compared to secondary form, which is quite common.[14-16] Focus of this study was exclusively primary form of tuberculous breast lesions. Any case which showed indications of secondary TB were excluded from the study.

Wani et al.[17] finds various risk factors like lactation, pregnancy and multiparity contributing towards the etiopathogenesis of breast TB. In the current study, 49.2% of diagnosed patients gave history of lactation while Khanna (2002) observed that 30% of their patients were lactating when diagnosed. He also found that 2 (3.84%) out of 52 patients were pregnant. Current study shows that 15 (5.6%) and 189 (71%) females are pregnant and multiparous respectively.[18] This might be due to the fact that pregnancy and lactation increases the vascularity in the breast tissue, thereby facilitating colonization of the bacilli.[19]

Unilateral involvement is usually observed in tuberculous mastitis cases though both breasts maybe affected.[20,3] In present study 77.6% patients had left sided breast involvement while Sharif et al.[21] observed 100 breast lesions in his study and found 55% left sided involvement while 22.2% females had bilateral involvement.

Radiological findings usually do not give a clear picture of diagnosis though it defines the extent of lesion.[14,15] Radiography in early stages of disease can mimic fibroadenoma while in late stages of TM, it can mimic breast carcinoma because of irregular borders of the lesion.[22] In present study, X- ray data was extensively explored, but it turned out to be non-diagnostic for TM. Normal chest X-rays were found in 89% cases. Ultrasonographic findings showed 62% irregular masses (Fig:5) and 3% well-defined masses (Fig:4). Mammogram was unable to differentiate tuberculous mastitis from breast carcinoma which led to 36.3% cases mimicking malignancy. This is in accordance to Longman et al.[23] and Farrokh[24] (2019) who also reported that mammography has minimal value in giving a definitive diagnosis of TM. These undistinguished cases were the ill-defined, irregular lumps of breasts without sinuses. Radiologically and clinically, when TM mimics breast cancer, it raises diagnostic dilemmas.[25]

FNAC and histopathology are the golden tools for diagnosis of such inconclusive breast lesions.[14] Cytology comprising of epithelioid granuloma, Langhan giant cells and lymphohistiocytic aggregates is significant finding in tuberculous mastitis.[18] Sometimes, necrosis is also seen.[25] Nearly all cases in the present study revealed neutrophils, lymphocytes and mononuclear cells along with clusters of epithelioid cells in FNA smears. Therefore, almost all the cases in the present study were diagnosed of granulomatous inflammation (Fig:3). Further diagnosis was confirmed by traditional characteristic AFB under microscope with ZN staining (Fig:2). A total of 81% smears showed ZN positive results while 54 (20.4%) cases could not reveal acid fast bacilli (AFB) despite the presence of epithelioid cells. Culture of fine needle aspiration was not done for confirmation of TB. Since 2010, WHO recommended another highly sensitive and specific technique, Real time PCR (Gene Xpert) for reaching a conclusive for ZN negative specimens. From 2015-2018, due to availability of Gene Xpert in the laboratory where investigations were carried out, 38 samples were tested with Gene Xpert of which 32 cases turned out to be positive for mycobacterial DNA (Fig:6). This indicated 84.2% moderate sensitivity of Gene Xpert technique. Pandya et al.[26] also showed similar correlation where using

clinical and histopathological findings, 83.3% sensitivity of RT-PCR was noted. Therefore, this technique may be considered for analysis of for all suspicious cases of TM.

There is an approximately 2.5-fold inclining pattern for TM cases in the ten years, from 2008-2018 (Fig:1) which may be attributed to utilizations of more sensitive techniques for resolution of this therapeutic dilemma. Multidisciplinary assessment while diagnosing breast lesions (with clinical, radiological, histopathological and microbiological findings) to obtain high diagnostic accuracy is therefore indispensible.[27]

The treatment of TM consists of either anti–tuberculosis chemotherapy (ATT) or surgery with specific indications.[8] Majority of patients were completely cured in the current study as well. A total of 180 (68.1%) cases responded to initial therapy (administration of rifampicin, isoniazid, pyrazinamide and ethambutol) for the two months while 64 (24.2%) cases followed rifampicin and isoniazid for another four months. Twenty cases (7.5%) with slow clinical response were given extended anti-tuberculous therapy from 12 to 18 months and no surgical intervention was carried out in this study. Therefore, anti-tuberculous therapy is the standard treatment for resolution of TM and surgery is seldom required.[28]

CONCLUSION

Tuberculous mastitis is a rare disorder with a challenging diagnosis. FNAC is essential for reaching a conclusive diagnosis and to exclude malignancy. A multidisciplinary approach involving surgeons, radiologists, TB consultants, and microbiologists is required, coupled with a high index of clinical suspicion in order to aid timely diagnosis, and initiate prompt treatment to reduce complications.

LIMITATIONS OF STUDY

This study was not population based, as the data was collected from a single institution. Therefore, due to limited population, the results cannot be generalized. Culture of TM was not performed due to limited resources. Analysis at genetic level was performed in cases presenting after the year 2014. Due to non-availability of PCR, and not an easy access of this technique in earlier years, suspected cases remained unidentified.

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CONFLICT OF INTEREST

None to declare.

FINANCIAL DISCLOSURE

None to disclose.

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Author's Contribution

AS: Conception, collection and interpretation of data.
AAB: Interpretation of data and critical revision of the manuscript for intellectual content.
SS: Collection and interpretation of data and drafting of manuscript.
NF: Design and acquisition of data, drafting of manuscript and critical revision of the manuscript.
NA: Data interpretation and critical revision of the manuscript for intellectual content.
NN: Data interpretation and drafting of manuscript.
MEA: Critical revision of the manuscript for intellectual content.
MIA: Data interpretation, drafting of manuscript and critical revision of the manuscript for intellectual content.