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Original Research Article

Cytological spectrum of granulomatous mastitis: diagnostic and treatment challenges

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ABSTRACT

Background: Granulomatous mastitis (GM) is an inflammatory disease of the breast which clinico- radiologically mimics both inflammatory and malignant lesions. This leads to diagnostic dilemmas and delay in treatment. The aim of the present study was to review the cases diagnosed as granulomatous mastitis on Fine Needle Aspiration Cytology (FNAC) with an objective to co-relate their clinico-radiological findings, histology review where available and follow up treatment received to establish etiology and study the treatment outcome.
Methods: Cytologically diagnosed cases of granulomatous mastitis were retrieved and reviewed from August 2015 - July 2017 records. Clinico-radiological co-relation, histology review where available and follow up treatment records were sought for.
Results: Around 31.7% (530/1670) cases were reported as malignant, 60.3% (1009/1670) as benign proliferative and 7.9% (131/1670) as inflammatory lesions by breast FNA. 3.1% (51/1670) cases were reported as GM of all breast FNAC and 38% (51/131) of all inflammatory lesions. Follow up was available for 47 cases. Of which 26 (55.3%) cases were diagnosed as Tubercular Granulomatous mastitis (TGM) and 21(44.7%) were idiopathic granulomatous mastitis (IGM).
Conclusions: Countries where tuberculosis is endemic, high degree of clinical suspicion and detailed work-up to rule out TGM is essential for all cases of granulomatous mastitis. Authors recommend a multidisciplinary workup with microbiological culture and molecular based tests on FNA material. This retrospective study illustrates that the cause of GM needs to be determined accurately for timely treatment, to avoid unnecessary delays and treatment dilemma in these patients.

Keywords: Breast cytology, Fine needle aspiration cytology, Granulomatous mastitis, Idiopathic granulomatous mastitis, Tuberculous granulomatous mastitis

INTRODUCTION

Granulomatous mastitis (GM) is an uncommon inflammatory lesion of the breast. It can be due to various etiologies like tuberculosis, fungal infections, connective tissue disorders, fat necrosis and sarcoidosis and when no attributable cause is detected it is termed idiopathic. Tuberculous granulomatous mastitis (TGM) is an infrequent disease but in endemic areas like India it is one of the common causes of granulomatous mastitis. The

incidence of breast tuberculosis is less than 0.1% of all breast lesions in Western countries and 4% of all breast lesions in endemic countries.[1] The other causes of GM are uncommon and when no cause is identified it is diagnosed as Idiopathic granulomatous mastitis (IGM). This condition was first described by Kessler and Wolloch in 1972.[2] IGM is a rare disease of unclear etiology although autoimmune diseases and immune reactions to breast tissue have been implicated.[3] The common clinical presentation of Granulomatous mastitis is a unilateral breast lump. The clinical and radiological features in GM can mimic both cancer and inflammatory conditions depending on the associate features, hence accurate diagnosis in these cases is essential to avoid unnecessary mastectomies.[4]

Incision and drainage along with open biopsies in these cases at times leads to non-healing ulcers with sinus formation. Fine needle aspiration cytology in breast lumps is an easy cost effective method with rapid diagnosis for initial triage of the patients.

The purpose of the study was to review the spectrum of granulomatous mastitis diagnosed on Fine Needle Aspiration Cytology (FNAC) with the objective to co-relate their clinico-radiological findings, diagnostic cyto-histological features and management course to establish etiology and study the treatment outcome.

METHODS

A retrospective study was conducted from August 2015-July 2017. A total of 1670 FNA breast cytology cases were retrieved from the Departmental archives and cases with inadequate cytology or inconclusive cytological diagnosis were not included. The cases with definite cytological diagnosis were classified into the inflammatory, benign proliferative and malignant. Those cases reported as inflammatory lesions were further classified as acute, chronic nongranulomatous and granulomatous mastitis.

Table 1: Etiological causes of granulomatous mastitis.

Etiological causes of granulomatous mastitis causes	Cytological picture	Diagnostic criteria
Bacterial: *Mycobacterium tuberculosis*	Epithelioid histiocytes forming cohesive clusters, MNGC of Langhans' type, caseous necrosis	Epithelioid histiocytes forming cohesive clusters, MNGC of Langhans' type against a background of caseous necrosis Demonstration of AFB on Ziehl Neelsen stain or microbiologic culture
Bacterial: *Corynebacterium kroppenstedtii*	Suppurative granulomas	Demonstration of bacteria on Gram's stain
Fungal: blastomycosis, histoplasmosis	Epithelioid granulomas with necrosis along with neutrophils, budding yeast forms	Epithelioid granulomas, MNGC foreign body type, demonstration of fungus on PAS/GMS
Parasitic: filaria	Mixed inflammation of neutrophils, eosinophils and lymphocytes	Presence of filarial adult worm or microfilaria
Autoimmune: Wegener granulomatosis	Epithelioid histiocytes, neutrophils, MNGC and necrotic collagen fragments	Necrotizing granulomas S. C-ANCA positivity
Foreign body reaction	Nonnecrotizing granulomas, loosely cohesive histiocytes with vacuoles, occasional intracytoplasmic refractile substance	Presence of foreign material and nonnecrotizing granulomas. Fibrous tissue fragment
Subareolar granuloma	Numerous anucleate squames, neutrophils, histiocytes, MNGC, granulation tissue	Subareolar lump, numerous anucleate squames, background mixed inflammation with MNGC
Hodgkin's lymphoma	Epithelioid cell clusters, neutrophils, lymphocytes, plasma cells and eosinophils and reed Sternberg cells	Mixed inflammatory cell population with Reed Sternberg cells
Fat necrosis	Dirty background with granular debris, fat droplets and fragments, foam cells, multinucleated GC, chronic inflammation, absence of epithelial cells	History of trauma/surgery Presence of fat, lipophages, altered adipocytes and multinucleated giant cells against a dirty background. Absence of epithelioid granulomas
Sarcoidosis	Noncaseating epithelioid cell granulomas in the absence of necrosis, GC asteroid bodies and Schaumann bodies	Noncaseating granulomas, negative for AFB and pas
Idiopathic	Noncaseating granulomas with mixed inflammatory cell infiltrate, abundance of neutrophils and GC	Exclude all above causes

Cytological review

Cytological criteria for GM was defined as presence of at least two clusters of epithelioid histiocytes with or without lymphocytes or plasma cells or Langhans' type of giant cells with the presence or absence of necrosis.5 The smears stained with H and E, MGG, Gram's and Ziehl Neelsen stains of all 51 cases reported as GM were reviewed for cytological features in all cases. PAS stained smears were also examined where fungal aetiology was suspected. The diagnostic criteria for the different causes of GM are defined in Table 1.

Clinical co-relation

The clinical presentation with detailed history was done in all cases and radiological features noted where available. Findings of microbiological cultures were also recorded where available. Further management received by patients reported as granulomatous mastitis on FNA were retrieved from clinical records and case files.

Follow-up information was analyzed in terms of management received (medical or surgical) and their outcomes. Those that underwent surgery, their histological features were noted.

RESULTS

Total 1670 breast FNAC were performed at our center during the study period. 31.7% (530/1670) cases were reported as malignant, 60.3% (1009/1670) as benign proliferative lesions and 7.9% (131/1670) as inflammatory by breast FNA. 3.1% (51/1670) cases were reported as GM of all breast FNAC and 38% (51/131) of all inflammatory lesions (Figure 1).

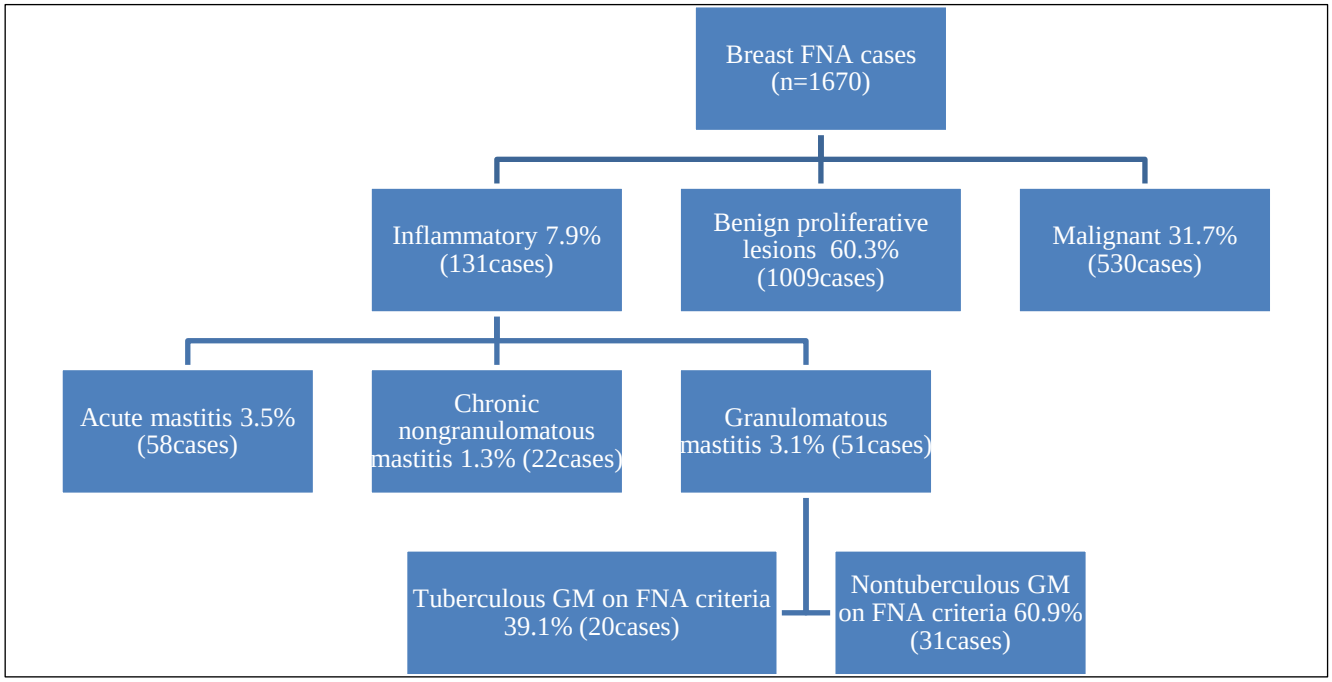

Figure 1: Schematic flowchart of breast FNA cases during the study period.

Clinical Findings

All 51 granulomatous mastitis cases were females. Age of presentation was predominant in the 3rd and 4th decade with a mean age of 34.5years. Unilateral lump was found on examination and 27 (53%) cases had it in the left breast and 23 (45%) were in the right breast. Only one (2%) lady had bilateral lumps. The site of occurrence of lump in the different quadrants of breast is shown in Table 2. All patients were parous except four who were nulliparous. Breast feeding was within last five years in 26 (51%) patients of which four were breast feeding at the time of FNA while the 21 had a history of more than five years. The most common ultrasound feature was an irregular hypoechoic lesion with size range 1.9-4.2cms.

Cyto-histological findings

Based on FNAC review of 51 GM cases, 20(39.2%) cases fulfilled the cytological criteria of GM with suggestion of tubercular etiology and revealed a caseous necrotic background with well-formed or ill formed epithelioid cell granulomas and presence of Langhans' type giant cells (Figure 2). Of these, only 7(13.7%) cases were positive for acid fast bacilli on Ziehl Neelsen stain, including the single case with bilateral breast lumps. In two cases PCR for Mycobaterium tuberculosis was

positive. The other 11 cases responded to standard antitubercular treatment based on other clinical and radiological findings. The remaining 31 (60.8%) cases which on cytological criteria were nontubercular GM and were negative for acid fast bacilli, had the cytological findings of epithelioid cell granulomas along with mixed inflammatory cell infiltrate and singly lying epithelioid histiocytes without a caseous necrotic background.

Table 2: Clinical presentation of patients.

Age of presentation		16-64yrs (Mean age:34.5yrs)
Laterality of breast lump	Left	27 (52.9%)
	Right	23 (45.2%)
	Bilateral	1 (1.9%)
History of breast feeding	<5yrs	22 (43.1%)
	>5yrs	21 (41.1%)
	Lactating	4 (7.8%)
	Absent	4 (7.8%)
Average size of lump		3.2cms (1.9-4.2)
Location of lesion	Upper outer quadrant	21 (41.1%)
	Central/Periareolar	15 (29.6%)
	Lower inner quadrant	6 (9.8%)
	Upper inner quadrant	5 (9.8%)
	Lower outer quadrant	4 (7.8%)

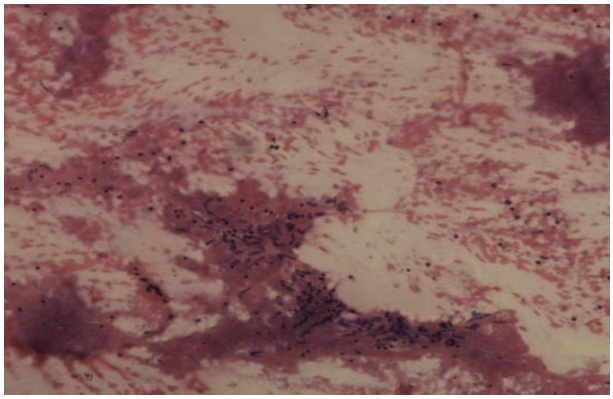

Figure 2: TGM with caseous necrosis in the background and epithelioid granulomas (H and E stain 10x).

Of these 31 cases follow-up was available in 27 cases. In these 27 cases the ultrasonographic findings were irregular heterogenous lesion in 13 (48.2%) patients, lobulated hypoechoic lesion in 6 (22.2%), abscess formation in 4 (14.8%), ill-defined heterogenous lesion with dilated ducts filled with material in 4 (14.8%). Associated findings were nipple retraction in 2 (7.4%) and axillary lymphadenopathy in 5 (18.5%) cases. Followup and treatment records of these patients were available. Five of the 27 (18.5%) patients were given antitubercular treatment on the basis of associated clinical findings and they responded to six-month therapy. Antibiotic treatment was given for short duration to the remaining 22 patients with partial response in two, however all underwent surgical intervention. Four (14.8%) of these patients underwent incision and drainage (I and D) and biopsy. 2 (7.4%) developed recurrence of lump and two were diagnosed as IGM as they were negative on ZN stain and on PCR for Mycobacterium tuberculosis. Hence 20 (74%) patients had surgical excisional biopsies, of these 2 patients had an earlier tru-cut biopsy. Of the 20 cases, one case on excision was diagnosed as TGM while the remaining 19 cases were IGM based on histological findings. FNA cytology of cases diagnosed as idiopathic granulomatous mastitis showed loose epithelioid cells with numerous neutrophils, histiocytes and Langhans' and foreign body type of giant cells in a background without caseous necrosis (Figure 3).

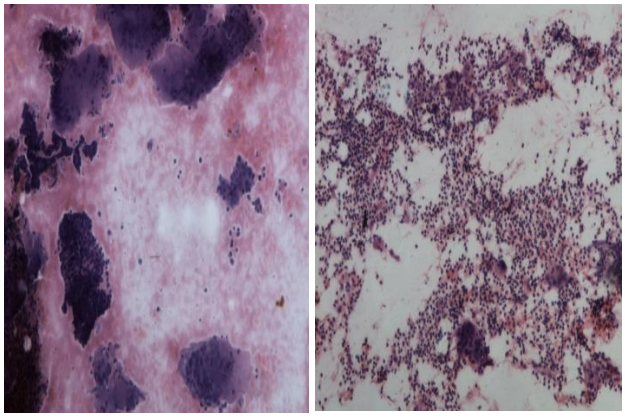

Figure 3: IGM: A) Clusters of ductal epithelial cells and numerous multinucleated giant cells. B) Mixed inflammatory cell background with numerous neutrophils (MGG stain 10x).

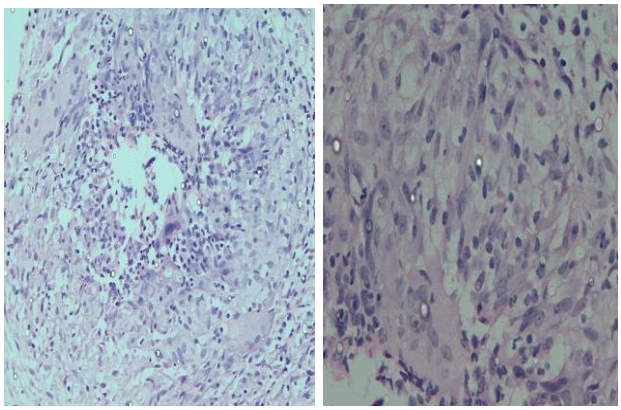

Figure 4: IGM Biopsy. A) Epithelioid granulomas with both Langhans' and foreign body type of giant cells around a central space (H and E stain, 10x). B) Epithelioid histiocytes admixed with lymphocytes, plasma cells, neutrophils and histiocytic giant cells (H and E stain, 20x).

The histological features in these cases showed lobulocentric presence of noncaseating granulomas around central space comprising of epithelioid histocytes, Langhans' type of giant cells and numerous mixed inflammatory cells in the background with predominance of neutrophils (Figure 4). 26 (55.3%) cases were of TGM, 21(44.7%) cases of IGM of the 47 cases where follow-up was available.

DISCUSSION

Granulomatous mastitis usually presents as a unilateral irregular firm to hard breast mass occurring in any quadrant of breast with restricted mobility, skin puckering and nipple retraction; thus mimicking malignancy both clinically and radiologically.[4] It also mimics inflammatory and infective lesions of the breast when presenting as a painful lump associated with skin inflammation (erythema), sinus formation or at times ulceration in advanced cases. Although an uncommon chronic inflammatory disease of the breast it has a tendency to persist and recur.[6] IGM usually occurs in young and parous females, within five years of childbirth.[7] 26 patients in our study were young parous with last child birth within five years and of these 4 patients were currently breast feeding. The age at presentation varied from 16-64 years in our study, with maximum number of patients in 3rd and 4th decade (17 (33.3%) each in both decades).

Granulomatous mastitis can be due to a specific etiology and in our hospital scenario tuberculosis is one of the commonest causes. TGM is a rare clinical entity as mammary gland tissue, like spleen and skeletal muscle, offers resistance to the survival and multiplication of the tubercle bacilli.[8] Yet among the granulomatous mastitis it is the most common cause. Other uncommon identifiable causes enumerated in Table 1 were excluded before a case is diagnosed as IGM. This is an uncommon diagnosis and the incidence varies in different populations. It has been postulated that racial factors may predispose to this condition.[9] Many etiological agents have been implicated for this condition like immune reaction to extravasated milk protein or fat, local irritants, increased secretions in ducts due to oral contraceptive pills, viruses, mycotic and parasitic infectious diseases, α_1 antitrypsin deficiency, hyperprolactinemia and diabetes mellitus, however none have been proven.[10-12] Autoimmune cause has also been postulated. Recently an association with local infection by Corynebacterium kroppenstedtii has been suggested and the condition is referred to as cystic neutrophilic granulomatous mastitis.[13] Histologically this condition resembles idiopathic granulomatous mastitis and differs from suppurative tubercular mastitis in being lobulocentric in distribution.

In granulomatous mastitis the radiological findings are non-specific and simulate a vast spectrum of diagnosis from mastitis, abscess to malignancy. Mammographically, GM can be differentiated as it shows architectural distortion without definitive lump as compared to malignant lesions. The ultrasonography usually reveals a hypoechoic lesion, some lesions filled with fluid are diagnosed as abscess or fibrocystic lesions and those with irregular or ill-defined lesions as malignant.[14] In this series irregular heterogeneous lesion (44.4%) was the commonest presentation, five (18.5%) cases where graded as BIRADS 4-5 with an irregular heterogeneous lesion with ill-defined margins and associated axillary lymph nodes in 5 (18.5%) cases. Upper outer quadrant (41.1%) had the maximum presentation followed by central quadrant.

The classical cytological features favoring Tubercular etiology on FNA include epithelioid cells, small lymphocytes, plasma cells and multinucleated Langhans' type of giant cells in a background of caseous necrosis. Numerous neutrophils along with singly lying epithelioid histiocytes without a background of caseous necrosis are highly suggestive of IGM. Tuberculosis being endemic in India, it is one of the commonest etiologies in granulomatous mastitis. Demonstration of acid fast bacilli and culture where possible are useful for confirmation and gold standard for diagnosis.[15] Presence of epithelioid granulomas was observed in only half the cases reported by Tse GM et al, in their series, suggesting that they are not pathognomic for GM. They opined that presence of these single epithelioid histiocytes in the absence of well-defined granulomas should alert the pathologist to the possibility of a granulomatous inflammation.[16] Cytological differential like sarcoidosis is difficult to diagnose on cytology and in fat necrosis epithelioid granulomas are not seen but numerous foamy macrophages against a dirty background are seen. FNA is an important preliminary diagnostic investigation as it helps to exclude malignancy from granulomatous mastitis and in the background milieu of caseous necrosis with epithelioid granulomas favors tuberculosis. However, not all cases of Tuberculous mastitis are positive for acid fast bacilli and not all cases have caseous necrotic background.[1] The gold standard diagnosis of Tuberculous mastitis is bacteriological culture or demonstration of acid fast bacilli by Ziehl Neelsen (ZN) stain.

However, demonstration of AFB in cytological smears requires the bacterial load to be 10,000 to 1,00,000/ml of the material and are identified in only 12% cases while culture isolates organism only in 25% of the cases.[17] Apart from the paucibacillary nature of the specimen, nonuniform distribution of bacteria and inadequate sample makes diagnosis difficult.[18] Hence studies have suggested that demonstration of caseating granulomas and involved lymph nodes maybe sufficient for diagnosis.[1,19,20] In this study, 16 such cases were treated as TBM.

However, for other conditions like IGM, at times a confident diagnosis cannot be made on FNAC, hence biopsy samples, microbiological tests to rule out other

causes and clinical correlation is required. Direct amplification tests should be done more frequently to get a definite diagnosis of tuberculosis especially in endemic countries as high numbers of cases are AFB negative. Antitubercular treatment per se can lead to complication due to drug therapy hence demonstration of Mycobacteria remains the gold standard.[21] A flareup of infection can occur in cases of TGM as IGM is treated with steroid or methotrexate which can be harmful to the patient. Hence histological findings in IGM have a lobular pattern of involvement of the breast parenchyma with central clear space surrounded by mixed inflammatory cells forming neutrophil microabscesses. The use of corticosteroids for this condition was first proposed by Dehetrogh et al.[22] Since then many case series have reported good response to use of steroids.[23]

Studies with large number of cases have shown that steroid treatment is a good alternative to surgical removal of breast tissue, however not all cases respond to the steroid treatment. Few require second line therapy of Methotrexate and still others require surgery.[13] Histopathological diagnosis is thus considered the gold standard, whether core or excisional biopsy. However, at times simple mastectomy has been done in large sized lesions.[24]

Granulomatous mastitis per se is an uncommon disease, comprising 3% in the present study with a clinical and radiological presentation mimicking malignancy. TGM is the commonest cause in the study while IGM being an uncommon cause of chronic granulomatous mastitis where the diagnosis is made by exclusion of other known causes. As discussed earlier, culture is not done routinely in all cases of granulomatous mastitis.

Hence, we recommend in cases of GM, tubercular etiology must be definitely ruled out with a repeat FNAC for detailed microbiological workup or tru-cut biopsy be done. The differentiation between these two conditions requires a multidisciplinary workup with increased awareness amongst surgeons, radiologists and pathologists. A high index of suspicion is required to prevent delayed diagnosis and unnecessary morbidity. Fine needle aspiration is important as an initial investigation as it helps in segregating benign and malignant cases and also provides material for microbiological and molecular workup. It is an economical, quick diagnostic technique and careful evaluation of smears also helps indicate the underlying etiology. All cases of nontuberculous granulomatous mastitis in this study underwent surgery, IGM was diagnosed on histology in majority patients.

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