

GRANULOMATOUS MASTITIS IS NOT ALWAYS TUBERCULAR: ROLE OF FINE NEEDLE ASPIRATION CYTOLOGY IN EVALUATION OF GRANULOMATOUS MASTITIS

Ridhima¹, Sneha Singh², Prem Singh³, SP Khanna⁴, Aditi Gupta⁵

¹Assistant Professor, ²Assistant Professor, ³Professor, ⁴Associate Professor, ⁵Resident
^{1,2,3,4,5} Department of Pathology, MMIMSR, MMDU, Mullana

Article Info: Received 30 November 2019; Accepted 21 December 2019

DOI: <https://doi.org/10.32553/ijmbs.v3i12.810>

Corresponding author: Prem Singh

Conflict of interest: No conflict of interest.

Abstract

INTRODUCTION AND OBJECTIVES: Granulomatous mastitis is rare chronic inflammatory benign breast lesion, which clinically and radiologically resembles carcinoma breast thus creating a diagnostic dilemma. The term granulomatous mastitis includes two broad categories namely specific granulomatous mastitis for which aetiological factors can be defined such as infectious causes like Mycobacterium tuberculosis, blastomycosis, cryptococcosis, histoplasmosis, actinomycosis and filarial infection. Other factors include association with autoimmune diseases such as Wegner's granulomatosis and giant cell arteritis and there are other rare causes such as include duct ectasia, foreign body reaction and fat necrosis which also leads to granulomatous lesions of breast.

Cytological features of granulomatous mastitis (GM) have not been widely discussed and described in literature, so through this study we have made an attempt to thoroughly discuss cytological spectrum of granulomatous mastitis.

MATERIALS AND METHODS: A retrospective study was performed over a period of four years from 2016 to 2019. A total of 465 cases of breast lump reported to cytopathology section out of which 24 cases of GM diagnosed on FNAC were included in our study. Results of Erythrocyte sedimentation rate (ESR) and Mantoux test along with TB-PCR were recorded. FNAC slides were retrieved pertaining to study period.

Granulomatous lesions of breast were further categorized broadly into IGM/ NGM, granulomatous mastitis without caseous necrosis and tubercular mastitis where diagnosis were made definite on basis of demonstration of AFB or positive TB-PCR.

RESULTS: Patient age ranged from 23 years to 55 years with the mean age of 36.6 years with maximum of patients falling in second decade followed by third decade. *Granulomatous lesions were broadly categorized into Idiopathic/ Non specific granulomatous mastitis (11 cases, 45.8%), GM with caseous necrosis (8 cases, 33.3%) and tubercular mastitis (5 cases, 20.9%). Histopathology was available in 7 cases (29.2%). TB-PCR was sent in all cases of granulomatous mastitis diagnosed on cytology and was positive in 10 cases (41.7%).*

CONCLUSION: *Idiopathic granulomatous mastitis and tubercular mastitis are rare inflammatory diseases of breast which mimic malignancy clinically and radiologically. FNAC plays important role in diagnosis of granulomatous diseases of breast and also their differentiation from malignant tumors. Tubercular mastitis needs to be differentiated from IGM since treatment options are different in both the cases. Cytopathology plays an important role in differentiating both the diseases supplemented by radiological and microbiological investigations.*

The present study thus highlights the importance of FNAC as an infallible tool in diagnosis of granulomatous mastitis and its differentiation from neoplastic lesions of breast thus avoiding time consuming histopathological work up of cases.

Introduction

Granulomatous mastitis is rare chronic inflammatory benign breast lesion, which clinically and radiologically resembles carcinoma breast thus creating a diagnostic dilemma.¹ It was well discussed and described by Kessler and Wooloch in 1972 for the very first time.² The term granulomatous mastitis includes two broad categories namely specific granulomatous mastitis for which aetiological factors

can be defined such as infectious causes like Mycobacterium tuberculosis, blastomycosis, cryptococcosis, histoplasmosis, actinomycosis and filarial infection. Other factors include association with autoimmune diseases such as Wegner's granulomatosis and giant cell arteritis and there are other rare causes such as include duct ectasia, foreign body reaction and fat necrosis which also leads to granulomatous lesions of breast.³ Idiopathic

granulomatous mastitis/ Non specific granulomatous mastitis(IGM/ NGM) also called as granulomatous lobular mastitis is another entity for which aetiology is obscured.

Histopathology though is considered as gold standard for establishing correct diagnosis but Fine Needle Aspiration Cytology(FNAC) being a minimally invasive, simple and cost effective procedure plays crucial role in diagnosing granulomatous mastitis.

Cytology of Granulomatous mastitis(GM) generally shows presence of epithelioid granulomas, multinucleated giant cells, inflammatory cells with or without necrosis and benign ductal epithelial cells.⁴ However IGM includes any of above features along with polymorphs and absence of caseous necrosis.

Through this study we made an attempt to explain that all granulomatous mastitis are not tubercular, even in endemic countries like India. Tubercular mastitis(TBM) is one of rarest forms of extrapulmonary tuberculosis and accounts for < 0.1% of all breast lesions.⁵ TBM was first documented by Sir Astley Cooper in 1829 and he called it as scrofulous swelling of bosom(4). Demonstration of acid fast bacilli(AFB) by Zeihl Neelsen(ZN) staining, bacteriological culture aided by Tuberculosis Polymerase Chain Reaction (TB-PCR) remains gold standard for diagnosis of tubercular pathology.⁶ Cytological features of granulomatous mastitis(GM) have not been widely discussed and described in literature, so through this study we have made an attempt to thoroughly discuss cytological spectrum of granulomatous mastitis.

MATERIALS AND METHODS:

The present study was a retrospective study performed in department of pathology , Maharishi Markandeshwar University of Health Sciences and Research, Mullana Ambala(India) over a period of four years from 2016 to 2019. The cases were retrieved from cytopathology archives along with slides. All cases reported as granulomatous mastitis on fine needle aspiration cytology were included in the study. A total of 465 cases of breast lump reported to cytopathology section out of which 24 cases of GM diagnosed on FNAC were included in our study. The clinical details of patient including age, presenting symptoms, relevant past medical history, history of trauma, family history of tuberculosis(TB) and treatment history were collected from case files. Results of Erythrocyte sedimentation rate (ESR) and

Mantoux test along with TB-PCR were recorded. FNACs slides were retrieved pertaining to study period.

In all cases, cytological parameters such as presence of granulomas, type of multinucleated giant cells, relative proportion of cells including epithelioid histiocytes, polymorphs, lymphocytes, background necrosis were evaluated. Histopathology was available in 7 cases, slides of which were also retrieved.

RESULTS:

A total of 24 cases of granulomatous mastitis were reported during period of 4 years. Mainly granulomatous lesions of breast were categorized broadly into IGM/ NGM, granulomatous mastitis without caseous necrosis and tubercular mastitis where diagnosis were made definite on basis of demonstration of AFB or positive TB-PCR . Patient age ranged from 23 years to 55 years with the mean age of 36.6 years with maximum of patients falling in second decade followed by third decade(Table 1).

Table 1:

AGE GROUP	NO. OF PATIENTS
0-10	0
11-20	0
21-30	12
31-40	6
41-50	4
51-60	2

Duration of symptoms such as palpable breast lump ranged between 2 days to 4 years. Out of 24 cases, breast lump was palpable in 22 cases (91.7%) while two patients only had history of mastalgia and lump was discovered on Ultrasonography(USG). USG guided FNAC was performed in these 2 cases(9.3%). Tender breast lump was present in about 18 cases(75%). History of pulmonary tuberculosis was present in 2cases (8.3%). A single case presented with breast abscess which persisted after incision and drainage. No case suggestive of history of sarcoidosis, fungal infections, connective tissue disorders and autoimmune disease was reported. History of lactation was present in single case(4.2%). (Table 2)

Table 2:

CLINICAL PRESENTATION	NO. OF CASES(n= 24)
Breast lump	22, 2 cases revealed lump on USG
Painful lump	18
Fever	11
History of TB	02
History of lactation	01
Lymphadenopathy	05
Breast abscess	01
Sinus formation	01

Radiological diagnosis was available in 15 cases (62.5%) in form of USG breast and mammography. Radiologically, mastitis was diagnosed in 6 cases(25%) , fibroadenoma and BIRADS(Breast Imaging Reporting and Data System) II each in 2 cases(8.3%) while single case each of duct ectasia, residual abscess, hematoma, fibroadenosis and galactocele. The wide range of radiological diagnosis had created a diagnostic dilemma. Besides imaging studies, clinical suspicion of malignancy was observed in 5 cases(20.8%).

Routine hematological tests like ESR were correlated in 20 cases. Mantoux test was available in 13 cases(54.2%) which was positive in 11 cases(45.8%)(Table 3)

Table 3:

MANTOUX TEST	No. of cases available (n= 13)	Positive in 11 cases	Negative in 2 cases
ERYTHROCYTE SEDIMENTATION RATE	No. of cases available (n=20)	Raised in 15 cases	Normal in 5 cases

Mantoux test was considered positive in an induration of 15 mm or above while 4 cases have induration between 10-15 mm, but still considered positive as they were exposed to high risk environment and two cases had positive family history of tuberculosis(TB). A single case(4.2%) was observed with concomitant pulmonary tuberculosis. On cytology, various cytomorphological features were evaluated such as presence or absence of epithelioid cell granulomas, caseous necrosis, giant cells of langhans or foreign body giant type, inflammatory cell population of polymorphs, lymphocytes or histiocytes and epithelioid cell granulomas containing lymphocytes and plasma cells (Fig.1,a-c).

Based on the above mentioned features granulomatous lesions were broadly categorized into Idiopathic/ Non specific granulomatous mastitis(11 cases,45.8%), GM with caseous necrosis(8 cases, 33.3%) and tubercular mastitis(5 cases, 20.9%) .(Table 4)

Table 4:

Type of Granulomatous Mastitis	No of cases (n=24)
Idiopathic GM	11
GM with caseous necrosis	8
Tubercular mastitis	5

Last two categories were sub classified on the basis of their acid fast positivity on ZN stain. IGM is diagnosis of exclusion and often requires biopsy for definitive diagnosis. Histopathology was available in 7 cases(29.2%). TB-PCR was sent in all cases of granulomatous mastitis diagnosed on cytology and was positive in 10 cases(41.7%) (Table 5)

Table 5:

DIAGNOSIS	NO. OF CASES(n=24)	TB-PCR positivity	ZN Stain positivity
Idiopathic/ Non specific Granulomatous Mastitis	11	Nil	Nil
Granulomatous mastitis with caseous necrosis	8	5	Nil
Tubercular Mastitis(TBM)	5	5	All 5 cases were positive

Among total of 24 cases encountered of granulomatous mastitis, 5 cases were given definitive diagnosis of TBM based on positive AFB staining. TB – PCR was done in all 24 cases. Out of which 8 cases of granulomatous mastitis with caseous necrosis 5 cases(62.5%) were positive for TB-PCR while 3 cases(37.5%) turned out to be negative. Remaining 3 cases which were negative for TB-PCR and ZN stain were given Anti tubercular treatment(ATT) and on follow up showed good response to ATT because of caseous necrosis and positive history of TB.

Periodic acid-Schiff(PAS) stain slides were available in cases diagnosed as IGM and were non contributory.

On fine needle aspiration, blood mixed aspirates were obtained in all cases, barring 7 cases where pus was aspirated. On cytological smears, in idiopathic GM, out of 11 cases, 8 cases showed presence of granulomas and 10 cases showed singly scattered epithelioid cells. 7 cases showed presence of ductal epithelial cells (Fig.1,d) revealing mild reactive atypia. Foreign body giant cells were present in 7 cases. Almost all the cases (10 out of 11) showed presence of histiocytes while lymphocytes and polymorphs were present in background 9 and 2 cases respectively. Plasma cells were also noted in 7 cases

In TBM, all 10 cases showed presence of granulomas along with singly scattered epithelioid cells. Caseous necrosis was seen in 6 cases out of 10 while Langhans' and foreign body giant cells were seen in 4 and 6 cases respectively. Background showed inflammatory cells such as histiocytes in 8 cases, polymorphs in 7 cases while lymphocytes were seen in all 10 cases.

Among 3 cases of granulomatous mastitis with caseous necrosis, granulomas were present in all the cases. Langhans giant cells were there in 2 cases while background lymphocytes, polymorphs were present in all 3 cases and histiocytes in single case. (Table 6)

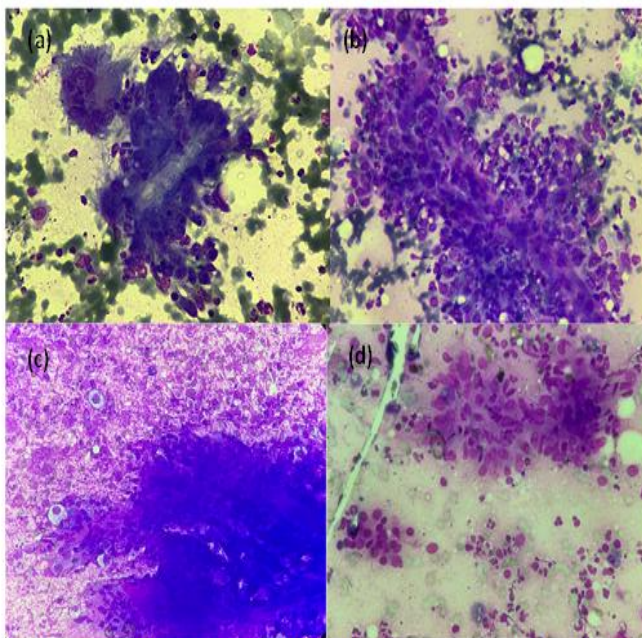


Fig 1: Photomicrograph showing granulomatous mastitis showing a) Epithelioid granulomas with langhans giant cells (MGG x400); b) Epithelioid granulomas with surrounding singly dispersed epithelioid cells (MGG x400); c) caseous necrosis along with foam cells admixed with neutrophils and apoptotic cells surrounding epithelioid cell granuloma: TBM (MGG x200); d) epithelioid cell granulomas along with few ductal cells IGM.

Table 6:

CYTOMORPHOLOGY	DIAGNOSIS		
	Non specific/ Idiopathic GM (n=11)	Tubercular mastitis (n= 10)	GM with caseous necrosis (n= 3)
Ductal cells	7	6	2
Granulomas	8	10	3
Caseous necrosis	0	6	3
Foreign body giant cells	7	4	2
Langhan's giant cells	0	6	1
Epithelioid cells	10	7	1
Histiocytes	10	8	1
Lymphocytes	9	10	3
Polymorphs	2	7	3
Plasma cells	7	5	0

DISCUSSION:

Granulomatous mastitis is an uncommon breast lesion representing approximately 0.025-3 % of surgical treated breast lesions.⁷ It is known for its worrisome presentation as a hard breast lump in younger women and clinically and on imaging studies cannot be distinguished from breast carcinoma.⁸ The etiology in most cases is idiopathic however there are specific granulomatous diseases ranging from infectious causes like tuberculosis, histoplasmosis, cryptococcosis, actinomycosis and autoimmune diseases like sarcoidosis. The diagnosis of idiopathic granulomatous mastitis is still unknown however Kessler and Woolloch proposed an autoimmune pathogenesis.²

GM occurs by and large in reproductive age group and presents in early thirties and may be associated with lactation or post partum period. Our study included all patients in reproductive age group (mainly 21-40 years). One patient (4.2%) was associated with lactation. The common presentation is firm, unilateral, discrete breast mass which is tender with inflammation of overlying skin and sometimes axillary lymphadenopathy. Lump can be associated with pain and skin ulceration.

In our study, axillary lymph node involvement was seen in 5 cases (20.8%). Sometimes the mass mimics carcinoma clinically and radiologically. The course of disease depends upon the etiology and infective causes like tuberculosis leads to abscess formation or discharging sinus as seen in our study. In our study 2 patients had history of mastalgia, their revealed

breast lump was revealed on USG examination and there USG guided FNAC was done.

FNAC is primary investigation for breast lesion but role of FNAC in granulomatous mastitis has been debated with some authors describing the usefulness of FNAC as an important tool.^{9,10} However some authors concluded that various types of granulomatous diseases can be differentiated by FNAC.¹¹ It cannot be overemphasized that cause of worry for clinician is overlapping features and resemblance to malignancy and reported pretreatment diagnosis of malignancy is 51%.^{12,13}

The common etiological features that have been evaluated include necrosis, giant cells, epithelioid cells, histiocytes, granulomas, neutrophils and lymphocytes in background.

NGM/IGM is a rare cause of granulomatous disease of breast. The aetiology of this form of mastitis is usually idiopathic and has to be distinguished from other rare specific granulomatous conditions like tuberculosis, sarcoidosis and Wegner's granulomatosis.² Study by Divya Achuthya Ail et al revealed 1.8 % cases of granulomatous mastitis of total breast lesions were diagnosed on FNAC.³ However our study revealed much higher percentage of granulomatous lesions of breast i.e 5.2%(24 out of total 465 breast lesions) which is in close concordance(4.4%) to the study done by Munemane A et al.¹⁴ It is proved beyond doubt that IGM is a diagnosis of exclusion where no cause is identified.¹⁴ It is also to be noted that there is no place for surgical intervention in diagnosis of GM and biopsy would be unnecessary procedure with its scar and other cosmetic complications.¹⁵ FNAC is simple and non invasive method and is infallible tool to differentiate between granulomatous mastitis from malignancy.¹⁶ However FNAC may not always differentiate between IGM and other granulomatous lesions of breast and may require histological sampling. Other conditions that may cause granulomatous inflammation is fat necrosis, granulomas associated with malignancy and are not included in our study. Our study revealed concordant results of granulomatous mastitis(5.2%) with that of study done by Munemane A et al, 4.4%.¹⁴ Study by Achuthya DA Ail et al revealed the incidence of IGM and TBM as 76.2 % and 23.8% respectively while our study showed higher incidence of tubercular mastitis as 41.7%. This high frequency over other cases is due to fact that patients being referred here to our tertiary care hospital were from western part of

Uttar Pradesh and northern part of Haryana (India) where tuberculosis is more prevalent.³

Tuberculosis requires demonstration of acid fast bacillus(AFB) which on smears requires bacterial load of 10,000 to 1,00,000/ ml of pus material and culture which is positive in 25% of cases(4, 16). Overall sensitivity of TB-PCR is 78.3% and for pulmonary and extra-pulmonary specimens is 82.3% and 72.0% as quoted by Cheng VCC et al and in our study it came out to be 76.9%.¹⁷

Patient of GM present with lump in breast in one of the quadrants, firm to hard in consistency may be associated with periodic abscess formation and mimics infective mastitis and breast cancer.¹⁸ History of breast feeding have been reported by few authors,¹⁹ but in our study only one patient of tubercular mastitis gave history of breast feeding. Patients usually present in reproductive age group due to hormonal changes in breast parenchyma and susceptibility to trauma and infections.²⁰

Cytomorphology of all the cases revealed presence of granulomas along with number of granulomas is directly proportional to singly scattered epithelioid cells. IGM generally showed presence of foreign body giant cells while tubercular mastitis revealed presence of langhans giant cells (60%) along with predominance of polymorphs (70%) and lymphocytes (100%). These results were different from the study done by Achuthya Ail et al where polymorphs and lymphocytes were 20% and 40% respectively.³

The surgical intervention thus has no role in the management of GM and biopsy would be a futile exercise in both forms of GM and moreover it is mandatory to differentiate between idiopathic GM from those of tubercular mastitis as both have different lines of treatment.¹

FNAC being simple and non invasive method plays a significant role in differentiating GM from neoplastic lesions of breast.

CONCLUSION:

Idiopathic granulomatous mastitis and tubercular mastitis are rare inflammatory diseases of breast which mimic malignancy clinically and radiologically. FNAC plays important role in diagnosis of granulomatous diseases of breast and also their differentiation from malignant tumors. Tubercular mastitis needs to be differentiated from IGM since treatment options are different in both the cases.

Cytopathology plays an important role in differentiating both the diseases supplemented by radiological and microbiological investigations. . Also it plays a significant role in evaluation of cytological details in granulomatous lesions of breast. Epithelioid cell granulomas being common in both TBM and IGM whereas singly scattered epithelioid cells are more common in IGM/NGM. Langhans type of giant cells are more common in TBM as compared to foreign body giant cells which are more common in IGM. Presence of neutrophils and lymphocytes favour TBM. AFB stain positivity on FNAC material and TB-PCR favours TBM.

The present study thus highlights the importance of FNAC as an infallible tool in diagnosis of granulomatous mastitis and its differentiation from neoplastic lesions of breast thus avoiding time consuming histopathological work up of cases.

REFERENCES:

1. Bakaris S, Yuksel M, Ciragil P, Guven MA, Ezberci F, Bulbuloglu E. Granulomatous mastitis including breast tuberculosis and idiopathic lobular granulomatous mastitis. *Can J Surg.* 2006;49:427-30
2. Kessler E, Woolloch Y. Granulomatous mastitis: A lesion clinically simulating carcinoma. *Am J Clin Pathol.* 1972;58:642-6.
3. Achutya D, Bhayekar P, Joshi A, Pandya N, Nasare A, Lengare P et al. Clinical and cytological spectrum of granulomatous mastitis and utility of FNAC in picking up Tubercular Mastitis: An eight year study. *J Clin Diagn Res.* 2017 Mar; 11(3): EC45–EC49.
4. Kishore B, Khare P, Gupta RJ, Bisht SP. Fine needle aspiration cytology in the diagnosis of inflammatory lesions of the breast with emphasis on tuberculous mastitis. *J Cytol.* 2007;24(3):155-56.
5. Seo HR, Na KY, Yim HE, Kim TH, Kang DK, Oh KK, et al. Differential diagnosis in idiopathic granulomatous mastitis and tuberculous mastitis. *J Breast Cancer.* 2012;15(1):111-18.
6. Baharoon S. Tuberculosis of the breast. *Ann Thorac Med.* 2008;3(3):110–14.
7. Nemenqani D, Yaqoob N, Hafiz M. Fine needle aspiration cytology of granulomatous mastitis with special emphasis on microbiologic correlation. *Acta Cytol.* 2009;53:667-71.
8. Tse GMK, Poon CSP, Law BKB, Pang LM, Chu WCW, Ma TKF. Fine needle aspiration cytology of granulomatous mastitis. *J Clin Pathol* 2003; 56: 519-21.
9. Kumarasinghe MP. Cytology of granulomatous mastitis. *Acta Cytol* 1997; 41: 727-30.
10. Yip CH, Jayaram G, Swain M. The value of cytology in granulomatous mastitis: a report of 16 cases from Malayasia. *Aust N Z J Surg.* 2000; 70: 103-5.
11. 11. Martinez-Parra D, Nevado-Santos M, Melendez-Guerrero B, García- Solano J, Hierro- Guilmain CC, Pérez-Guillermo M. Utility of fine needle aspiration in the diagnosis of granulomatous lesions of the breast. *Diagn Cytopathol* 1997; 17: 108-14.
12. Kuba S, Yamaguchi J, Ohtani H, Shimokawa I, Maeda S, Kanematsu T. Vacuum-assisted biopsy and steroid therapy for granulomatous lobular mastitis: report of three cases. *Surg Today* 2009;39:695-699.
13. Munemane A, Torane K, Karle R. *Indian Journal of Basic and Applied Medical Research*; September 2017: Vol.-6, Issue- 4, P. 598-601
14. Rizvi G, Pandey HS, Khetan H, Negi M. Granulomatous mastitis-Can fine needle aspiration cytology avoids unnecessary biopsy. *Sch J App Med Sci.* 2016;4(8A):2746-49.
15. Baharoon S. Tuberculosis of the breast. *Ann Thorac Med.* 2008;3(3):110–14.
16. Cheng, Yam, Hung et al. Clinical evaluation of polymerase chain reaction for rapid diagnosis of tuberculosis *J Clin Pathol* 2004; 57:281-285.
17. Kamra HT et al. Cytological Features of Granulomatous Mastitis- A study of ten cases. *Indian Journal of Pathology and oncology*, January-March 2016;3(1); 129-132.
18. Seo HR, Na KY, Yim HE, Kim TH, Kang DK, Oh KK, et al. Differential diagnosis in idiopathic granulomatous mastitis and tuberculous mastitis. *J Breast Cancer.* 2012;15(1):111-18.
19. Baharoon S. Tuberculosis of the breast. *Ann Thorac Med.* 2008;3(3):110-14.