Treatment Protocol for Idiopathic Granulomatous Mastitis - an Approach to Settle an Unsettled Issue in Clinical Practice

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Idiopathic granulomatous mastitis is a chronic non-caseating granulomatous disease of unknown aetiology usually affects women of child bearing age. It is a rare disease and there is considerable uncertainty about incidence. We conducted a longitudinal study among all the patients of histologically diagnosed cases of granulomatous mastitis admitted in Khulna Medical College Hospital, AG Breast Care Center and from clinical practice in private clinics in Bangladesh from January, 1999 to December, 2011. Convenient type of purposive sampling was used for selection of study population. A total of 121 patients were included in our study. Most of the patient presented with unilateral painful lump with erythema and features of inflammation. Diagnosis was established histologically, 35 patients were treated with steroid and methotraxate and 86 patients needed surgical treatment and steroids. All patients responded but 12 patients relapsed within 6 months of completion of primary treatment. Despite of successful treatment, the recurrence rate of IGM found indeed high (> 10%). So follow up evaluation is essential in every case. No single modality of treatment yet found to be effective nor is any definite treatment protocol well established for IGM. In this research study, the primary aim was to evaluation this scenario in our clinical setup and to establish a definite treatment protocol in our clinical practice using IGM scoring system. Breast surgeon will sure be benefited if they follow our submitted protocol of this study

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Key words: Idiopathic granulomatous mastitis (IGM), surgical management, non-surgical management

Introduction

Granulomatous diseases of the breast can result from a variety of causes like tuberculosis, sarcoidosis, fungal infections, Wegner's granulomatosis. Granulomatous mastitis may occur as a complication of diabetes. Use of hormonal contraceptives, prolactin raising medications and hyperprolactaminemia has been implicated in pathogenesis or as predisposing factor. We consider the granulomatous mastitis as idiopathic (IGM) when there is non-caseating granulomatous disease of unknown aetiology. Treatment of secondary granulomatous disease depends upon its underlying cause, but treatment of IGM is non-specific. In this research study, the primary aim was to evaluation this scenario in our clinical setup and to establish a definite treatment protocol in our clinical practice using IGM scoring system.

Granulomatous mastitis (GM) is a chronic inflammatory disease of the mammary gland, characterized by recurrent inflammatory breast tumors of varying sizes, usually unilateral, and without nipple retraction.[1] These tumors can fistulize with subsequent infection. GMs were studied by Kessler and Wolloch in 1972.[2] Only a few hundred cases have been reported worldwide,[3,4] reflecting

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the low incidence of this disease. The images obtained with mammography, ultrasound and magnetic resonance imaging (MRI) are nonspecific and correspond to heterogeneous masses of variable sizes with irregular shapes, sometimes confluent, and without atypical micro-calcifications allowing for diagnosis confirmation.[5,6]

Histological examination (micro-biopsy or surgical specimen) is required to obtain a definitive diagnosis. Within these nodules there is generally a breast inflammatory infiltrate rich in lymphocytes (B and T), plasma cells, neutrophils and histocytes. Interestingly, there is sometimes a diffuse infiltration of immunoglobulin (Ig) G4 + cell type, associated with high serum IgG4 concentration[5]. Sometimes an invasion of the lobules by giant cells associated with micro-abscesses can be observed, and outbreaks of non-caseating necrosis in acini and intra-lobular ducts can be associated with the cellular inflammatory infiltrate.[7] Most of the time, the GM is considered idiopathic but there are cases of GMs secondary to infection or systemic diseases. A wide range of microorganisms have been implicated, and fungi, parasites, as well as bacteria have all been reported to be causal in GM. However, involved microorganisms are mainly corynebacteria and specifically Corynebacterium kroppenstedtii,[8] and Propionibacterium acnes,[8] Mycobacterium tuberculosis[9] and Brucella melitensis.[10] Thus, a higher prevalence of secondary GMs has been observed in Mediterranean and Asian countries (China and Malaysia),[11] probably because of endemic tuberculosis or brucellosis in these regions.

Secondary GMs have also been reported in association with sarcoidosis,[12] Wegener's disease,[13] systemic lupus erythematosus,[11] erythema nodosum[14] and isolated oligoarthritis.[15] Such GMs that are secondary to connectivity have usually a favorable outcome when on corticosteroids.[1] Secondary GMs occur at different ages depending on the underlying disease with extremes ranging from 11 to 83 years. Idiopathic GMs are more common in women of childbearing age, taking oral contraceptives or close to a period of childbirth or breastfeeding, which raises the question of hormonal influence, though it has never been proven.[1] Idopathic granulomatous mastitis (IGM) is benign, chronic non-caseating granulomatous disease of unknown aetiology usually affects women of child bearing age (17 to 42 yrs). It is a rare disease and there is considerable uncertainty about incidence. IGM is thought to be an autoimmune reaction to extravasated fat and protein rich luminal fluid (denaturized milk).[1,2,3]

The most common presentations of IGM are unilateral painful breast lump with or without nipple inversion and axillary lymphadenopathy. The best method to diagnose granulomatous mastitis (IGM) is by core biopsy. Characteristic histologic features of IGM are non-caseating granuloma containing multinucleated giant cells epithelioid histiocytes, plasma cells and eosinophils. IGM is usually diagnosed only after exclusion of cause or secondary complication of other diseases. Lighter cases may resolve spontaneously or alter symptomatic treatment and thus never be diagnosed. No definite treatment protocol is well established. Medical treatment like corticosteroids and methotrexate alone or in combination with surgical treatment is effective. Risk of recurrence is high.[1]

Methods

This study was conducted as a longitudinal study with joined collaboration of AG breast care Centre among all the patients of histologically diagnosed case of granulomatous mastitis except the patients associated with tuberculous and Wegmer's granulomatous mastitis admitted in Khulna Medical College Hospital, AG Breast Care center and from clinical practice in private

clinics in Bangladesh from January, 1999 to December, 2011. Convenient type of purposive sampling was used as the method of sampling for selection of study population. In this study a total number of 121 patients were selected based on inclusion criteria among which 116 women were of child bearing age and 5 women were above 55 years.

All selected patients underwent a clinical examination to identify the lump in breast and to evaluate associated findings like skin changes, axillary lymphadenopathy. HRUS was done in all selected patients. Mammography was done in women older than 35 years. Definitive diagnostic tests like FNAB, ultrasound-guided core biopsy or incision biopsy were done on demand in selected patients.

Results

In this cross sectional study, among the total number of 121 patients (age distribution is shown in table I), 116 (95.9%) women were of child bearing age and 5 (4.1%) women were non child bearing age (all above 55 years) which is depicted in figure 1. (Mean ± SD) age was (35.3 ± 1.7) years (table I).

Table I: Age distribution of study population

Age in years	No of patients	%	Mean±SD (years)	P
< 25	27	22.3		
26 - 35	43	35.5		
36 - 45	32	26.4	35±1.7	0.05
46 - 55	14	11.6		
> 55	5	4.1		
Total	121	100		

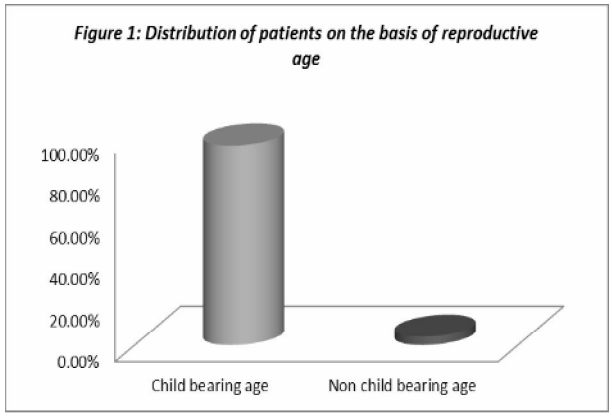


Table II represents the common clinical presentations of idiopathic granulomatous mastitis among the study population. Most common presenting symptoms were painful mass in the breast, erythema and feature of inflammation (100%). Associated other features were draining sinus (21 patients out of total 121), nipple discharge (32 patients), axillary lymphadenopathy (6 patients) and fever (5 patients).

Table II: Clinical presentations of idiopathic granulomatous mastitis

Findings	No. of patient	%	P value
Painful breast lump with erythema	121	100	
Draining sinus	21	17.4	0.05
Nipple discharge	32	26.4	
Axillary lymphadenopathy	06	05	
Fever	05	4.1	

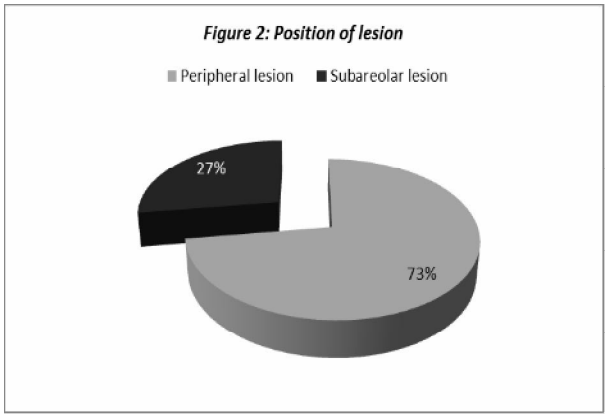
Lumps in breast were variable size – clinically measured 2.5 cm to 12 cm. Most were firm to hard in consistency. Few were partly firm and partly soft and fluctuant. Ultrasound examination was done in all patients. Large single but irregular hypoechoic mass with multiple tubular extensions was seen in 85 (70.2%) patients followed by sonographic skin thickening were in 75 (62%) patients. Multiple lobulated hypoechoic mass were detected in 36 (29.8%) patients.

Parenchymal distortion was in 12 (10%) patients (table II).

Table III: Ultrasound findings of IGM

Findings	No. of patient	%	P value
Single irregular hypoechoic mass	85	70.2	0.05
Multiple lobulated heterogeneously hypoechoic mass	36	29.8	
Skin thickening	75	62	
Parenchymal distortion	12	10	

Another important finding (figure 2) of this study was that most of the lesions (73%) were located in the periphery (in 88 patients) and few (27%) were located in subareolar region (in 33 patients).

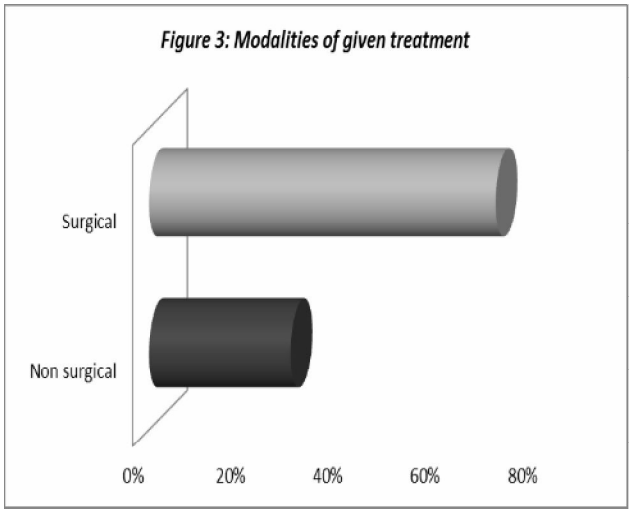


Among 121 patients, mammography was done in 50 patients. All patients were above 35 years. Mammography showed a heterogeneously dense parenchymal breast pattern, or focal asymmetric density. Few reveal skin thickening or axillary adenopathy. Initially FNAB was performed in all patients and was diagnosed as granulomatous mastitis in 96 patients. Ultrasound (USG) guided core biopsy done in 100 patients of which 98 were diagnostic for granulomatous lobular mastitis. Remaining patients were underwent surgical excision and subsequently confirmed as granulomatous lobular mastitic by histopathology of resected specimen (table IV). Confirmation of granulomatous lobular mastitic was done by histopathology of resected specimen.

Table IV: Types of intervention for diagnosis

Interventions	No of patients	Positive cases	P value
Mammography	50	37	
FNAB	100	96	0.01
USG guided core biopsy	100	98	
Excisional histopathology	86	86	

Non-surgical treatment including antibiotic and steroid selected for smaller lesion having no evidence of central liquefaction or collection and less inflammatory sign 35 patients (29%) underwent non-surgical treatment (figure 3). All patients responded but 5 patients relapsed within six months of stopping steroid. Those patients needed excision of granulomatous tissue and continuation of steroid for three months or more. Figure 3 suggests that surgical treatment with excision of granulomatous dead and devitalized tissue was performed for other 86 patients (71%). Following surgery steroid was given in all patients. After 3 to 8 weeks secondary closure was done. All the patients responded well but 7 patients relapsed within 6 months of treatment. Four responded to steroid and one patient needed methotraxate. Post-operative follow up was maintained by clinical examination and ultrasound scanning.



Discussion

Granulomatous lobular mastitis is a rare and benign inflammatory disease of the breast that was first described in 1972.[1] No single modality of treatment yet found to be effective nor any definite treatment protocol is well established for IGM. In the research study, the primary aim was to evaluation this scenario in our clinical setup and to establish a management protocol for IGM. In this cross sectional study, among the total number of 121 patients, 116 (95.9%) women were of child bearing age [majority of them (35.5%) were in 26 – 35 years age group followed by 26.4% were in 36-45 years age group] and 5 (4.1%) women were non child bearing age (all above 55 years). (Mean ± SD) age was (35.3 ± 1.7) years (table 1). Another retrospective study suggests that granulomatous mastitis usually affects women of child-bearing age, and this was reflected in that particular study (mean age of patients was 33.1 years).[5]

Women with granulomatous lobular mastitis typically present with a breast mass that may be associated with pain, skin thickening, sinus formation, or axillary adenopathy.[7] Many women in the previous mentioned study were initially thought to have carcinoma because most presented with a unilateral mass (89%) and regional adenopathy (28%) and did not have a history or clinical findings suggestive of inflammation.[5] But the most common presenting symptoms found in this cross sectional study were painful mass in the breast, erythema and feature of inflammation (table 2). Associated other features were draining sinus (21 patients out of total 121), nipple discharge (32 patients), axillary lymphadenopathy (6 patients) and fever (5 patients). Lumps in breast were variable size – clinically measured 2.5 cm to 12 cm. Most were firm to hard in consistency. Few were partly firm and partly soft and fluctuant. Ultrasound examination was done in all patients. Large single but irregular hypoechoic mass with multiple tubular extensions was seen in 85 (70.2%) patients followed by sonographic skin thickening were in 75 (62%) patients. Multiple lobulated hypoechoic mass were detected in 36 (29.8%) patients. Parenchymal distortion was in 12 (10%) patients (table 3). Another important finding (figure 2) of this study was that most of the lesions (73%) were located in the periphery (in 88 patients) and few (27%) were located in subareolar region (in 33 patients).

Imaging features of granulomatous lobular mastitis have not been described frequently in the literature and currently are found only in reports of small series. Mammographic findings are considered nonspecific in granulomatous lobular mastitis. Han et al.[16] described multiple small masses or a large focal asymmetric density. Yilmaz et al.[17] and Memis et al.[18] identified a focal asymmetric density as the most frequent pattern. More recently, a study of 11 women by Lee et al.[19] showed an irregular ill-defined mass to be the most common finding. Similar to the findings shown by Yilmaz et al. and Memis et al., our study showed that the most common mammographic presentation in granulomatous lobular mastitis was a focal asymmetric density with no distinct margins (20/45) and was most easily identified when compared with the

contralateral breast. Granulomatous lobular mastitis was mainly unilateral and most often seen in the periphery of the breast. Less common mammographic findings included a lobulated or irregular mass (7/45) and diffusely increased density (3/45) in the affected breast. Lesions were mammographically occult in 15 of 45 women, possibly because of an overlying dense breast pattern seen in most women (36/45). Abnormal lymph nodes or skin thickening was identified in 20% of the women[5]. Because clinical and imaging studies of granulomatous lobular mastitis are nonspecific, definitive diagnosis is made by histopathology.[20] FNA is still an option for tissue sampling because it is more easily available and provides faster results than core biopsy.[21] FNA may be helpful in differentiating malignancy from an inflammatory condition even though it may not be as specific as core biopsy. Because the findings in granulomatous lobular mastitis may mimic an abscess, FNA for fluid aspiration and culture can be attempted. In our study, we found ultrasoundguided core biopsy to be more accurate because it showed the tissue architecture. Core biopsy was diagnostic in 96% of patients who underwent ultrasound-guided biopsy, whereas only four of 19 FNA procedures were diagnostic. Common causes for failure of FNA include insufficient material and nonspecific findings (e.g., fat necrosis, abscess).[5]

Among 121 patients in this study, mammography was done in 50 patients. All patients were above 35 years. Mammography showed a heterogeneously dense parenchymal breast pattern, or focal asymmetric density. Few reveal skin thickening or axillary adenopathy. Initially FNAB was performed in all patients and was diagnosed as granulomatous mastitis in 96 patients. Ultrasound (USG) guided core biopsy done in 100 patients of which 98 were diagnostic for granulomatous lobular mastitis. Remaining patients were underwent surgical excision and subsequently confirmed as granulomatous lobular mastitic by histopathology of resected specimen (table IV). Confirmation of granulomatous lobular mastitic was done by histopathology of resected specimen. Final diagnosis of granulomatous mastitis was characterized microscopically by non-necrotizing granuloma, presence of lymphocytes, plasma cells, neutrophils and giant cells. Before planning treatment all clinical imaging and pathological finding were correlated.

Few articles have described treatment protocols for granulomatous lobular mastitis,[20, 22, 23] and the optimal treatment has not yet been established. Before treatment, other causes of granulomatous lesions in the breast, such as tuberculosis, fungal infection, and sarcoidosis, must be excluded. Non-surgical treatment including antibiotic and steroid selected for smaller lesion having no evidence of central liquefaction or collection and less inflammatory sign 35 patients (29%) underwent non-surgical treatment (figure 3) in this study. All patients responded but 5 patients relapsed within six months of stopping steroid. Those patients needed excision of granulomatous tissue and continuation of steroid for three months or more. Figure 3 suggests that surgical treatment with excision of granulomatous dead and devitalized tissue was performed for other 86 patients (71%). Following surgery steroid was given in all patients. After 3 to 8 weeks secondary closure was done. All the patients responded well but 5 patients relapsed within 6 months of treatment. Four responded to steroid and one patient needed methotraxate. Post-operative follow up was maintained by clinical examination and ultrasound scanning.

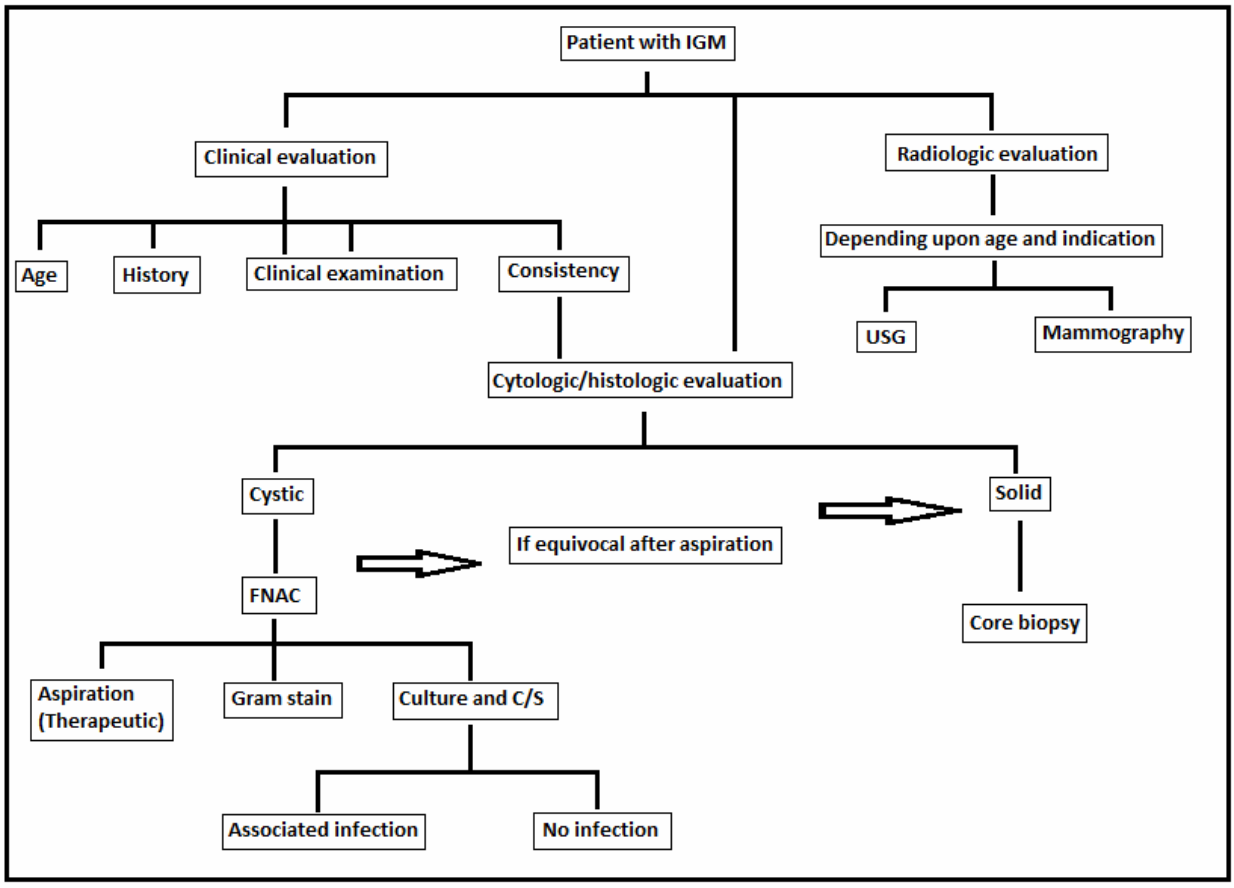


Figure 4. Pathway of triple evaluation of IGM

Table V: IGM Evaluation Scoring System

Assessment factors		Score	Highest score	Lowest score
• Size of lesion				
	> 6 cm	5	5	0
	3 – 6 cm	2		
	< 3 cm	1		
	No lesion	0		
• Number of lesions				
	3	5	5	0
	2 – 3	2		
	1	1		
	No lesion	0		
• Rate of growth				
	> 1cm per month	5	5	0
	0.5 – 1 cm per month	2		
	< 0.5 cm per month	1		
	No lesion	0		
• Sign of inflammation				
	Severe	5	5	0
	Moderate	2		
	Mild	1		
	Nil	0		
• Evidence of liquefaction and necrosis				
	Extensive	5	5	0
	Moderate	2		
	Mild	1		
	Nil	0		
	Total		25	0

Table VI: follow up schedule

Score	Significance	Intervention
> 10	Specific (S)	Surgical along with steroids
5 – 10	Equivocal (E)	Non surgical and follow up
<5	Non specific (NS)	• Counseling • Supportive treatment • Symptomatic treatment • Exclusion of carcinoma • Exclusion of other causes • Elimination of anxiety of the patient

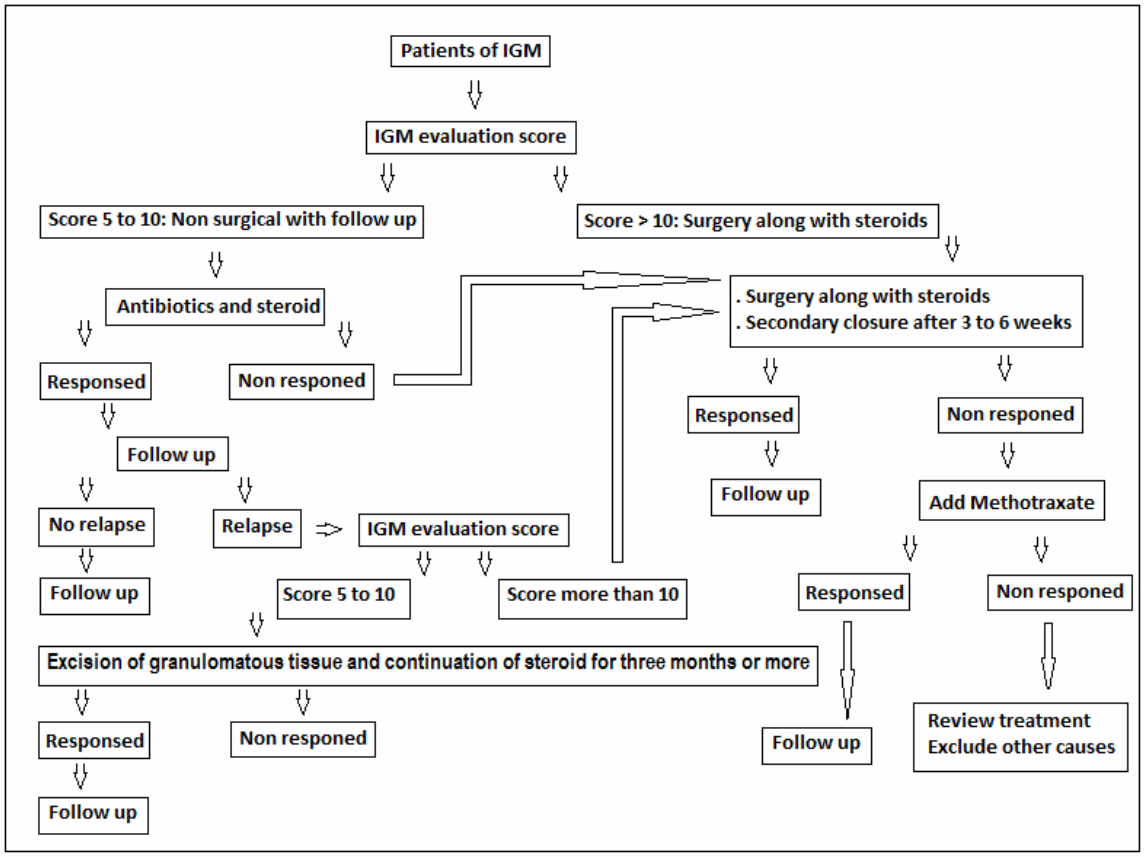


Figure 5. Algorithm of management

Recommendation

In this study, we basically try to follow a definitive treatment protocol to evaluate its effectiveness as a management tool in clinical practice with a desire to establish it as the treatment protocol for IGM. For diagnosis, we propose the specific pathway of triple evaluation (figure 4).

For the management, we specifically suggest and recommend the following IGM Evaluation Scoring System (table V) with follow up (table VI) and the algorithm of management (figure 5).

Conclusion

Granulomatous lobular mastitis has clinical and imaging characteristics similar to breast carcinoma. However, the mammographic finding of a focal asymmetric density and appearance of an irregular hypoechoic mass with multiple tubular extensions on sonography suggest granulomatous lobular mastitis. Final diagnosis relies on exclusion of other causes of granulomatous mastitis and specific pathologic findings on biopsy. No definite treatment protocol is well established yet for IGM. Steroid and methotraxate alone or in combination with surgical treatment is found effective in this study. Patient needed follow-up with periodic clinical examination and sonographic scan, because risk of recurrence is high.

References

1. Vinayagam R, Cox J, Webb L: Granulomatous mastitis: a spectrum of disease. Breast Care (Basel) 2009, 4:251–254

2. Kessler E, Wolloch Y: Granulomatous mastitis: a lesion clinically simulating carcinoma. Am J Clin Pathol 1972, 58:642–646
3. Tse GM, Poon CS, Ramachandram K, Ma TK, Pang LM, Law BK, Chu WC, Tang AP, Cheung HS: Granulomatous mastitis: a clinicopathological review of 26 cases. Pathology 2004, 36:254–257
4. Wilson JP, Massoll N, Marshall J, Foss RM, Copeland EM, Grobmyer SR: Idiopathic granulomatous mastitis: in search of a therapeutic paradigm. Am Surg 2007, 73:798–802
5. Hovanessian Larsen LJ, Peyvandi B, Klipfel N, Grant E, Iyengar G: Granulomatous lobular mastitis: imaging, diagnosis, and treatment. AJR Am J Roentgenol 2009, 193:574–581
6. Dursun M, Yilmaz S, Yahyayev A, Salmaslioglu A, Yavuz E, Igci A, Acunas G, Tunaci M: Multimodality imaging features of idiopathic granulomatous mastitis: outcome of 12 years of experience. Radiol Med 2012, 117:529–538
7. Olsen ML, Dilaveri CA: Idiopathic granulomatous mastitis: a case report of breast abscess. BMJ Case Rep 2011. doi: 10.1136/bcr.05.2011.4271
8. Mathelin C, Riegel P, Chenard MP, Brettes JP: Association of corynebacteria with granulomatous mastitis. Eur J Obstet Gynecol Reprod Biol 2005, 119:260–261
9. Banerjee A, Green B, Burke M: Tuberculous and granulomatous mastitis. Practitioner 1989, 233:756–757. 754
10. Nemenqani D, Yaqoob N, Hafiz M: Fine needle aspiration cytology of granulomatous mastitis with special emphasis on microbiologic correlation. Acta Cytol 2009, 53:667–671
11. Yip CH, Jayaram G, Swain M: The value of cytology in granulomatous mastitis: a report of 16 cases from Malaysia. Aust N Z J Surg 2000, 70:103–105
12. DeHertogh DA, Rossof AH, Harris AA, Economou SG: Prednisone management of granulomatous mastitis. N Engl J Med 1980, 303:799–800
13. Stappaerts I, Colpaert C, Verbraecken J, Van Marck E, Vermeire P: Granulomatous mastitis as presenting sign of Wegener's granulomatosis. Acta Clin Belg 1999, 54:207–210
14. Adams DH, Hubscher SG, Scott DG: Granulomatous mastitis-a rare cause of erythema nodosum. Postgrad Med J 1987, 63:581–582
15. Gregoir C, Hilliquin P, Acar F, Lessana-Leibowitch M, Renoux M, Menkes CJ: [Acute mastitis in rheumatoid polyarthritis with Gougerot-Sjogren syndrome treated with tiopronin (Acadione)]. Rev Rhum Mal Osteoartic 1991, 58:203–206
16. Han BK, Choe YH, Park JM, et al. Granulomatous mastitis: mammographic and sonographic appearances. AJR 1999; 173:317–320
17. Yilmaz E, Lebe B, Usal C, Balci P. Mammographic and sonographic findings in the diagnosis of idiopathic granulomatous mastitis. Eur Radiol 2001; 11:2236–2240
18. Memis A, Bilgen I, Ustun EE, Ozdemir N, Erhan Y, Kapkac M. Granulomatous mastitis: imaging findings with histopathologic correlation. Clin Radiol 2002; 57:1001–1006
19. Lee JH, Oh KK, Kim EK, Kwack KS, Jung WH, Lee HK. Radiologic and clinical features of idiopathic granulomatous lobular mastitis mimicking advanced breast cancer. Yonsei Med J 2006; 47:78–84
20. Imoto S, Kitaya T, Kodama T, Hasabe T, Mukai K. Idiopathic granulomatous mastitis: case report and review of the literature. Jpn J Clin Oncol 1997; 27:274–277
21. Martinez-Parra D, Nevado-Santos M, Melendez- Guerrero B, Garcia-Solano J, Hierro-Guillermain CC, Perez-Guillermo M. Utility of fine-needle aspiration in the diagnosis of granulomatous lesion of the breast. Diagn Cytopathol 1997; 17:108–114
22. Dixon JM, Chetty U. Diagnosis and treatment of granulomatous mastitis. Br J Surg 1995; 82:1143–1144
23. Wilson JP, Massoll N, Marshall J, Foss RM, Copeland EM, Grobmyer SR. Idiopathic granulomatous mastitis: in search of a therapeutic paradigm. Am Surg 2007; 73:798–802