REVIEW ARTICLE

Outcome of Different Treatment Modalities in Non-caseating Granulomatous Mastitis: A Narrative Review

*S Nasrin[1], MRA Ovi[2], AS Arif[3], MJ Hasan[4]

ABSTRACT

Granulomatous mastitis (GM) is a benign inflammatory condition of breast disease that affects women of childbearing age with a history of breastfeeding. The rarity and complex pathophysiology make the diagnosis and management quite dilemmatic for clinicians. This review explored the available treatment options for the disease condition in light of the recent literature. Surgery alone, intervention with or without steroids, antibiotic therapy, abscess drainage, methotrexate therapy, and antibiotics are widely used in different settings. However, surgery (with or without steroids) showed a higher recovery rate along with a lower recurrence rate. Steroid therapy is promising, but its use is limited due to the higher number of recurrences. In addition, the use of methotrexate showed an increased remission rate, but the toxicity profile was still high. However, treatment outcome mostly depends on the severity of the disease and individual physical status, and therefore, a comprehensive evaluation of the patients is crucial. This review recommended the formulation of a standard guideline for uniform management of granulomatous mastitis conditions in our country.

Key words: Granulomatous mastitis, non-caseating,

Introduction

Granulomatous mastitis (GM) is a rare disease condition with complex pathophysiology that was first described by Kessler and Wolloch in 1972.[1] It is a chronic inflammatory pseudotumor characterized by noncaseating chronic granulomatous inflammation in breast lobules.[2,3] The etiology of GM is quite variable, and the pathophysiology is still hypothetical. The identified risk factors for GM include a history of pregnancy, breastfeeding, autoimmunity, tuberculosis, oral contraceptives, smoking, alpha-1 anti-trypsin deficiency, sarcoidosis, etc.[4,5] Diagnosis of the disease condition is quite challenging, as it mimics several types of mastitis.[4] Patients are often diagnosed with a late presentation, which makes management more difficult.[4] Moreover, consensus on standard treatment options for disease management is rarely available and impedes finding suitable treatment options.[6]

Available treatment options for granulomatous mastitis are surgical excision, curettage and drainage, use of corticosteroids, and earlier administration of antibiotics. The use of methotrexate (MTX) is also practiced in several centers. Additionally, close observation with symptomatic treatment and a combination of any of these were also chosen by the attending physicians.2,[7–9] However, the optimal treatment is variable and still contradictory10. Pandey et al. and Aghazandadeh et al. reported over two-thirds recovery by administration of steroids. The use of steroids can provide more than 70% recovery.[7,11] In patients with early detection of GM presenting mild symptoms, only observation with symptomatic medication showed excellent recovery rates.[12,13] A meta-analysis by Lei et al. observed that surgical management with and without steroid therapy was associated with a higher incidence of

[1]*Dr. Shamima Nasrin, Assistant professor, Department of Surgery, Anwer Khan Modern Medical College

[2]Dr. Mir Rasekh Alam Ovi, Consultant Surgery, General hospital Narayangonj,

[3]Prof. Abdus Salam Arif, Professor and Head, Department of Surgery, Anwer Khan Modern Medical College,

[4]Dr. Md. Jahid Hasan, Consultant, Pi Research Consultancy Center

*Corresponding author

Date of submission: 05.01.2022, Date of acceptance: 12.01.2022

AKMMC J 2022; 13(1) : 47-51

complete recovery of GM14, which was also supported by another review that emphasized surgical management only.[15] Risngsted and Friedmen also highlighted that due to the high frequency of systemic inflammation, patients with GM often need to be treated with methotrexate (MTX), and a multidisciplinary approach may require early and complete recovery.

GM mainly occurs in women of childbearing age, and mostly a history of breastfeeding was reported.[16] The disease usually develops approximately two years after breastfeeding, and the average age is 30 years[17]. Most patients with GM are diagnosed after progression of the disease process.16 The protracted course of the disease itself, along with the diagnostic dilemma and the complex treatment process, significantly affect the quality of life of the patients.[16] The present review was planned to summarize the current available treatment options for this chronic disabling disease with their alternatives.

Clinical presentation and diagnostic approach:

The disease most frequently appears in the 3rd or 4th decade of life, and reports have shown that the variable age of presentations ranged from 11 to 83 years. The main symptom of granulomatous mastitis (GM) is the presence of a tender and painful mass in the breast. It is primarily unilateral, but bilateral presentations are not rare. The most common quadrant in the posterior areola.[16] Almost half of the patients present with erythema and swelling along with redness, areola strictures, fistulas, and ulcers. One-third of the patients typically consult with physicians with an abscess at their first presentation.[6] Lymphadenopathy is variable and is not the only presenting feature of this patient group.[18] Signs of systemic inflammation, including erythema nodosum and arthritis, have also been reported at multiple frequencies.[10] A recent estimate suggests a lag period of months from the onset of symptoms and final diagnosis.[19]

Histopathology is the cornerstone step for the diagnosis of GM. The disease is characterized by a nonnecrotizing granuloma accompanied by limited infiltration of multinucleated giant cells, epithelioid histiocytes, lymphocytes, and plasma cells. With neutrophilic infiltrates, organized sterile microabscesses may form in fewer instances. In a severe form of the disease, inflammation may extend into adjacent lobules. Loss of acinar structures and damaged ducts are also observed in the parenchyma under the microscope.[20]

Although GM is a noninfectious disease, a study by Taylor et al. mentioned the presence of corynebacteria in the granuloma.[21] Studies by Emre et al. and Dobinson et al. also observed the presence of species of cornybacterium.[22,23] These cases also present granulomatous and neutrophilic inflammation along with cystic spaces in histopathology, which were defined as 'cystic neutrophilic granulomatous mastitis' in a study by Al-Mansara et al. [24] In contrast, some authors stated that the presence of corynebacteria in GM lesions is a contaminant from normal skin flora.[18]

The radiological evaluation of GM lesions showed nonspecific features that coincided with the characteristics of inflammatory carcinoma of the breast.[25] Multiple contiguous hypoechoic masses with posterior acoustic shadowing or enhancement are found on ultrasonography. The majority of cases have hypervascularity, which may be diagnosed by Doppler imaging.[26] The most common pattern on mammography is unilateral focal or regional asymmetry.[21] Depending on the intensity of the inflammation, MRI (magnetic resonance imaging) indicates heterogeneous ill-defined masses along with nonmass enhancement.[16]

Hence, the confirmatory diagnostic tool for GM is core needle biopsy, and correct diagnosis depends on the quality of biopsy tissue.[13] Laboratory findings of GM patients usually showed inconclusive results for rheumatoid factors, serum complements, c-reactive protein, carcinoembryonic antigen, and cancer antigen[20,21]

Management options of granulomatous mastitis:

For early diagnosed patients with granulomatous mastitis (GM), only observation was enough, as GM is sometimes a self-limiting condition.16 Pandey et al. and Buton et al. observed 100% complete remission among early diagnosed GM patients only after close

follow-up.[27,7] Hur et al. observed 87.5% complete remission following observation.[12] However, both conservative therapy and surgical management of GM are suggested in the literature.

Conservative management:

Conservative management mostly focused on symptomatic management of the patients and medical therapy. Each treatment option has its own merits and demerits.

Steroid therapy:

Steroid therapy is a widely practiced norm in chronic granulomatous mastitis patients. Initially, high-dose steroid therapy was proposed. DeHerthogh et al. first recommended corticosteroid therapy with prednisolone 30 mg/day for at least two months.[28] In general, this leads to a decrease in the diameter of the lesion but also to a variety of side effects, such as weight gain, hyperglycemia, and the risk of Cushing's syndrome. In recent years, a lower-dose regimen of steroids followed by slow tapering administration described by Freeman et al. has become more popular for the treatment of GM.[6] The recovery rate after steroid therapy varied greatly in different trials, ranging from 31% as described by Hur et al.[12] to 86% as described by Yabanglu et al., Neel et al.[29,30] The use of topical corticosteroids to minimize systematic adverse events was also under investigation.

Role of methotrexate:

Methotrexate (MTX) is a folate antagonist used as a disease-modifying agent in several rheumatologic diseases. However, the role of GM has also been tested and found to be promising. Ringsted and Friedmen, in their review, conclude with a stronger connection between inflammatory arthritis, erythema nodosum, and patients with GM.[10] Therefore, the drug was hypothesized to potentiate the action. They also observed a higher rate of relapse-free remission of GM following administration of methotrexate (MTX) in comparison to high steroid treatment and low steroid treatment. Sheybani et al. and Aghajanzadeh et al. also observed a higher remission rate from methotrexate.[8,11] Based on the supporting evidence, methotrexate is considered a treatment option for patients who have relapsed or who do not tolerate high-dose corticosteroid therapy or steroid-sparing agents.

Empirical antibiotics therapy:

Multiple infective and inflammatory conditions have been recognized, but recently, attention has been drawn to corynebacterial species as specific pathogens in this disease. However, in reality, most patients with granulomatous mastitis are prescribed blind antibiotic therapy without enough microbiological evidence due to the similarity of the presentation with bacteriological mastitis.[16] Even if microbiological evidence is sought, diagnosis can be challenging due to their particular growth requirements and prolonged incubation time. Consequently, current knowledge about antimicrobial options to treat Corynebacterium mastitis is still lacking. GM, as per definition, is a sterile inflammatory disease; therefore, blind antibiotic therapy usually fails in most cases.[31]

Surgical approach:

The choice of surgical management of GM varies depending on the progress of the disease and associated clinical presentations. Approximately one-third of GM patients present with abscesses. Therefore, abscess drainage has been considered a management option of GM for those patients. The decision of abscess puncture and drainage depends on the features of the presenting mass. However, the presenting mass might have necrotic tissue in the center, making the procedure difficult to conduct. The outcome is also often unsatisfactory due to the absence of bacterial causative agents.[16]

Surgical excision showed a satisfactory outcome in the management of GM. The success rate of surgical excision ranges from 61 to 100%, as reported in various trials. The inclusion of steroid therapy with surgery was described by some previous studies. The meta-analysis by Lei et al. described a 94.5% pooled incidence of complete recovery by the combination of oral steroids and surgical management. Surgical management showed 90.6%, and oral steroids showed a 71.8% complete remission rate14. A systematic review and meta-analysis by Ma et al. also showed that surgery significantly improved the rate of complete recovery (RR 1.22, 95% CI 1.10-1.36) compared to steroid-only therapy, whereas no difference was observed between only surgery and the combination of surgery and steroids (RR 0.78, 95%

CI 0.55-1.11). Steroid therapy requires a long time to achieve recovery. Surgery (with and without steroids) requires a relatively shorter period for recovery, which offers quicker rehabilitation to normal life. Other than a shorter recovery period, surgical management offered the highest incidence of recovery 7,11,21–23,25,26. A lower recurrence rate was observed with surgical management compared to oral steroids and other treatment options 29,30. Therefore, surgical management is the most effective management approach for GM.

However, steroid therapy was also observed as a recommendable therapy. Therefore, patients who are not comfortable with surgery and surgical scars and have any contraindication for surgery could be approached for steroid therapy. However, it requires a more extended period to achieve recovery and is associated with a high frequency of steroid side effects.[29,12] Moreover, a higher recurrence rate was also observed in steroid-only therapy.[29,30]

The available literature indicates variable findings regarding the therapeutic outcome and recurrence rate of GM. However, the overall results indicate the superiority of surgical management regarding a higher recovery rate, quicker recovery, and lower recurrence rate. Antibiotics and abscess drainage offer very low efficacy. However, early diagnosed cases showed a very good recovery only after observation. For patients with relapse who are not fit enough for high doses, steroids could be recommended as an additional methotrexate therapy, according to some studies.[10]

To measure the outcome of GM, no scale or scores have been established yet. Different trials have been conducted in different countries of the world, but a standard guideline has yet to be formed. The associated adverse effects due to the surgical approach and steroid therapy should be considered when recommending a complete treatment guideline for GM.

Conclusion:

Surgical procedures along with or without additional steroids seem to be the most efficient and recommended treatment option for patients with granulomatous mastitis. Steroid therapy in a dose-tapering manner has also shown a good recovery rate. Hence, the efficiency of certain management strategies varies from patient to patient due to their immunological status and associated comorbidities. Extensive trials should be conducted before concluding the best treatment approach, although the rarity of the disease is a significant obstacle to conducting a trial with a larger sample size.

Conflict of interest: none,

Acknowledgment: The authors must thank the entire team of the Pi Research Consultancy Center (www.pircc.org) for their constant support throughout the research work.

References:

1. Kessler E, Wolloch Y. Granulomatous Mastitis: A lesion Clinically Simulating Carcinoma. AM J Clin Pathol. 1972;58:642–6.
2. Gunduz Y, Altintoprak F, Tatli Ayhan L, Kivil- cim T, Celebi F. Effect of topical steroid treat- ment on idiopathic granulomatous mastitis: clinical and radiologic evaluation. Breast J. 2014;20(6):586–91.
3. Jeon JJ, Lee K, Kim Y, Yong SC, Park HK. Retrospective Analysis of Idiopathic Granulomatous Mastitis: Its Diagnosis and Treatment. J Breast Dis. 2017;5(2):82–8.
4. Uysal E, Soran A, Sezin E. Granulomatous Mastitis Study Group. Factors related to recur- rence of idiopathic granulomatous mastitis: what do we learn from a multicentre study? ANZ J Surg. 2018;88(6):635–9.
5. Gurleyik G, Aktekin A, Aker F, Karagulle H, Saglamse A. Medical and surgical treatment of idiopathic granulomatous lobular mastitis: a benign inflammatory disease mimicking inva- sive carcinoma. J Breast Cancer. 2012;J Breast C(15):119–23.
6. Freeman M, Lewis CD, Lower E. Refractory granulomas of breast: benign or malignant disease. J Clin Oncol. 2014;32(1):21.
7. Pandey TS, Mackinnon JC, Bressler L, Millar A, Marcus EE, et al. Idiopathic gran- ulomatous mastitis—a prospective study of 49 women and treatment outcomes with steroid therapy. Breast J. 2014;20(3):258–66.

8. Sheybani F, Sarvghad M, Naderi HR, Gharib M, Sarvghat MR. Treatment for and clinical characteristics of granulomatous mastitis. Obs Gynecol. 2015;125(4):801–7.

9. Li J. Diagnosis and Treatment of 75 Patients with Idiopathic Lobular Granulomatous Mastitis. J Invest Surg. 2018;1(1):1–7.

10. Ringsted S, Friedman M. A Rheumatologic Approach to Granulomatous Mastitis: a Case Series and Systematic Review. HHS Public Access. 2021;24(4):526–32.

11. Aghajanzadeh M, Hassanzadeh R, Alizadeh Sefat S, Alavi A, Hemmati H, Delshad M, et al. Granulomatous mastitis: Presentations, diagnosis, treatment and outcome in 206 patients from the north of Iran. Brest. 2015;24(4):456–60.

12. Hur SM, Cho DH, Lee SK, Choi MY, Bae SY, Koo MY. Experience of treatment of pa- tients with granulomatous lobular mastitis. J Korean Surg Soc. 2013;85(1):1–6.

13. Hovanessian Larsen LJ, Peyvandi B, Klipfel N, Grant E. Granulomatous lobular mastitis: imaging, diagnosis, and treatment. AJR Am J Roentgenol. 2009;193(2):574–81.

14. Lei X, Chen K, Zhu L, Song E, Su F, Li S. Treatments for Idiopathic Granulomatous Mastitis: Systematic Review and Meta-Analysis. BreastFeeding Medicine. 2017;12(7):1–7.

15. Ma X, Min X, Yao C. Different Treatments for Granulomatous Lobular Mastitis : A Systematic Review and Meta-Analysis. Brest Care. 2020;21000:60–6.

16. Wolfrum A, Kummel S, Reinisch M, Theuerkauf I, Pelz E. Granulomatous Mastitis: A Therapeutic and Diagnostic Challenge. Breast Care. 2018;13(6):413–8.

17. Johnstone KJ, Robson J, Cherian SG. Cystic neutrophilic granulomatous mastitis associated with Corynebacterium including Corynebacterium kroppenstedtii. Pathology. 2017;49:405–12.

18. Calis H, Karabeyoglu SM. Follow-up of granulomatous mastitis with monitoring versus surgery. Breast Dis. 2017;37:69–72.

19. Ozel L, Unal A, Unal E. Granulomatous mastitis: is it an autoimmune disease? Diagnostic and therapeu-tic dilemmas. Surg Today. 2012;42:729–33.

20. llman, JE, Terra SB, Clapp AJ. Granulomatous diseases of the breast and axilla. Radiological findings with pathological correlation. Insights Imaging. 2018;9:59–71.

21. Taylor GB, Paviour SD, Musaad S. A clinico-pathological review of 34 cases of inflammatory breast disease showing an association between corynebacteria infection and granulomatous mastitis. Pathol. 2003;35:109–19.

22. Emre A, Akbulut S, Sertakya M. Idiopathic granulomatous mastitis: overcoming this important clinical challenge. Int Surg. 2017.

23. Dobinson HC, Anderson TP, Chambers ST. Antimicrobial treatment options for granulomatous masti- tis caused by Corynebacterium species. J Clin Microbiol. 2015;53:2895–9.

24. Al Manasra AR, Al-Hurranu M. Granulomatous mastitis: a rare cause of male breast lump. Case Rep Oncol. 2016;9:516–9.

25. Fazzio RT, Shah SS, Shandhu NP. Idiopathic gran- ulomatous mastitis: imaging update and review. In sights Imaging. 2016;7:531–9.

26. Gumus M, Akkurt ZM, Gumus H. Is erythema nodo- sum coexisting with lesions of the breast a suggestive sign for idiopathic granulomatous mastitis? Turk J Surg. 2018;34:71–3.

27. Bouton ME, Jayaram L, O'neil PJ. Management of idiopathic granulomatous mastitis with observation. Am J Surg. 2015;210:258–61.

28. DeHertogh DA, Rossof AH, Harris AA. Prednisone management of granulomatous mastitis. N Engl J Med. 1980;303:799–800.

29. Yabanoglu H, Colakoglu T, Belli S. A comparative study of conservative versus surgical treatment protocols for 77 patients with idiopathic granulomatous mastitis. Breast J. 2015;21:363–9.

30. Neel A, Hello M, Cottereue A. Long-term outcome in idiopathic granulomatous mastitis: A western multicentre study. QJM. 2013;106:433–41.