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Original Research Article

WhyGM! – a prospective case-control study evaluating the etiology of idiopathic granulomatous mastitis

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ABSTRACT

Background: Idiopathic granulomatous mastitis (IGM) is a chronic inflammatory condition affecting mostly young women usually within 5 years of childbirth and lactation. The etio-pathogenesis of this disease is not well understood leading to mismanagement causing progressive inflammation and multiple recurrences.
Methods: It was a case-control study design with cases comprising patients with histopathological diagnosis of IGM and matched controls comprising women with benign breast disease other than IGM. All patients were interviewed with a structured questionnaire to determine potential risk factors. Serum sample was analysed for anti-nuclear antibody (ANA), prolactin, globulin and tissue from biopsy specimen was analysed in cases for microbial growth. Specific Autoantibody, Immunoglobulin assay was done in case of ANA positivity or elevated globulin levels
Results: There was a significantly longer period of lactation (p=0.0002) and previous history of nipple discharge (p=0.038) among the cases. There was no evidence of uncommon infections caused by bacteria, mycobacteria or fungi. Markers for systemic autoimmunity such as serum ANA, Immunoglobulin levels (p=0.9531) and prolactin levels (p=0.1086) did not show a significant increase in case
Conclusions: IGM was associated with a significantly longer period of lactation and nipple discharge. There was no significant correlation with systemic autoimmunity, hyperprolactinemia or infections. The aetiology of IGM remains elusive with potential for further research into localized autoimmune phenomenon.

Keywords: Granulomatous mastitis, Autoimmunity, Infections, Hyperprolactinemia

INTRODUCTION

Idiopathic granulomatous mastitis (IGM), a chronic inflammatory condition affecting the breasts, was first described by Kessler and Wolloch in 1972.[1]

It is characterised by peripherally-located lobulo-centric granulomatous inflammation with the presence of multinucleate giant cells, epithelioid histiocytes, and lymphocytes (Figure 1).

Etiological factors that have been proposed include hormonal imbalance, autoimmunity, infections, α1-antitrypsin deficiency, smoking, ethnicity, etc.[2,3] Its association with erythema nodosum, polyarthritis with positivity for serum markers such as rheumatoid factor (RF), anti-nuclear antibodies (ANA), anti-double stranded DNA (Anti-DsDNA), specific extractable nuclear antibodies as well as clinical response to immunosuppressants such as corticosteroids, methotrexate and azathioprine etc., has lent support to a probable systemic autoimmune phenomenon.[4-9]

The presence of signs of inflammation with multiple sinuses discharging pus raises the possibility of an infectious etiology (Figure 2). Bacterial organisms, especially *Corynebacterium* species,[10–12] atypical mycobacteria,[13] parasites such as Wuchereria bancrofti, and fungi such as blastomycosis, cryptococcosis, histoplasmosis, actinomycosis have been reported.[14-17]

Hormonal factors such as pregnancy, lactation, use of oral contraceptive pills (OCPs), hyperprolactinemia secondary to drugs or pituitary adenomas, have been postulated to increase breast secretions and alter the breast tissue, thereby making it prone to extravasation, resulting in a local autoimmune phenomenon causing granulomatous inflammation.[18,19] The high corelation of IGM with young women within 5 years of childbirth and a recent history of lactation also corroborates this hypothesis. Its increased prevalence in the Mediterranean and South East Asia gives rise to the possibility of ethnicity or common environmental exposure that may contribute to the causation.[2]

The etiology of IGM has not been fully understood and hence often is misdiagnosed as tuberculosis, periductal mastitis, or malignancy and therefore mismanaged. The increasing disease burden, the associated morbidity of this disease, and the paucity of literature, especially from South Asia, led to this study, which aims at analysing etiological factors that may be demographic, patient-related, or environment-related.

METHODS

A case-control study was conducted in the departments of general surgery and endocrine surgery at Christian Medical College, Vellore, Tamil Nadu, India, from October 2015 to October 2017. The study was conducted after obtaining approval from the institutional ethics committee (IRB min no. 9684 (observe) dt. 20.10.2015).

All patients in the case group were diagnosed with IGM based on histopathological confirmation (n=30). Women who presented to our outpatient clinic with non-inflammatory benign breast disease were group-matched with individual cases for age (age±5 years) and childbirth (Last childbirth <5 years) and were included as controls (n=30). Patients with histopathology other than IGM and those not consenting to be part of the study were excluded. Tissue taken at the time of core biopsy or excisional biopsy was sent for bacterial, fungal, MGIT culture, and Gene XPERT TB PCR. Based on initial growth, further subcultures on special media and MALDTI-TOF identification was performed to look for *Corynebacterium*.

Details of demographics, clinical profile, and risk factors were recorded amongst both case and control groups. Subsequently, the serum sample was analysed for serum ANA [Indirect immunofluorescence using fluorescein-coated antibodies to human IgG (EUROIMMUNE, Germany)], serum prolactin (Sandwich immunoassay), and serum globulin [derived from A/G ratio (Albumin measured by bromocresol green dye binding colorimetric assay and total protein measured by biuret method)].

If serum ANA was positive (indirect immunofluorescence showing fluorescence intensity >2+ at a dilution of 1:100), further specific autoantibody analysis (AntiSm, AntiRo, AntiLa) was done based on the pattern of immunofluorescence. If serum globulin was elevated (>3.5 gm/dl), further estimation of serum IgM, IgA, and IgG was done. Serum prolactin >25 mg/dl was considered as elevated.

Data collected from all cases and controls were entered using EpiData manager and EpiData entry client (v4.2.0.0). Analysis was done using STATA Data Analysis and Statistical software (v13.1). All demographic and clinical variables were summarised as counts and percentages for categorical variables, mean and standard deviation for symmetrically distributed continuous variables and median and range for skewed continuous variables. Chi square test was used to compare the proportions between categorical variables. The independent t test was used to compare the means between two groups for normally distributed continuous variables and the Mann-Whitney U test was used for skewed variables. For all data analysis, 5% level of significance was considered to be significant.

RESULTS

Demographics

There were 30 patients in the case and control group respectively. The demographics of the case and control group are detailed in the table below (Table 1). There were no significant differences in age, gender, menstrual status, parity or socioeconomic status between both groups.

Clinical features and management

There was no evidence of bilateral involvement in our series. The right breast was found to be involved more than the left (56.7% vs 43.3%), with single (Upper outer) quadrant involvement being more common (46.7%).

The most common presenting complaint was breast lumps (96.7%) and pain (93.3%) with signs of inflammation and skin changes being noted in the majority (76.67%). This included erythema (82.61%) warmth (73.91%), skin ulceration (39.13%), discharging sinuses (36.67%), skin tenderness (47.83%), skin oedema (34.78%) and abscess formation (39.13%). Axillary lymphadenopathy was noted in 50% of patients.

Fourteen patients in our series were managed with short course oral corticosteroid therapy only, whereas five patients required only surgical management. Ten patients underwent both surgical management as well as

corticosteroid therapy. One patient in our series defaulted treatment.

Autoimmunity

Only one patient amongst the cases was serum ANA positive whereas all controls were ANA negative. This patient however was previously diagnosed with rheumatoid arthritis and was on treatment. There was no evidence of significant elevation of serum globulin levels in the cases [n=13; mean (SD); 3.4 (0.67) g%] as compared to control group [n=7; Mean (SD); 3.3(0.62) g%] [student's t test, p=0.953].

Further serum immunoglobulin level analysis was done for these patients which showed elevated IgM levels in one control and no significant evidence of hypergammaglobulinemia amongst the case group.

Infections

Bacterial tissue culture showed growth in six patients [5 patients with coagulase negative *Staphylococcus aureus* (CONS) and 1 patient with methicillin resistant *Staphylococcus aureus* (MRSA)], whereas there was no evidence of fungal or mycobacterial growth on MGIT culture, XPERT TB PCR or Fungal culture. As there was no initial growth, further subculture for *Corynebacterium* was not performed.

Hormonal factors

Hyperprolactinemia was detected in three patients in the case group and one patient among the control population. This was however, not statistically significant different {[Median (IQR) cases]-9.06 (6.80, 15.50) vs [Median (IQR) controls]-7.40 (5.40,10.20); p=0.1086}.

On analysing breastfeeding practices, the average duration of lactation was found to be significantly longer among the case group [mean (SD); 25.74 (11.71) months] as compared to the controls [mean (SD);15.26 (8.37) months] (Student's t test, p=0.0002). The presence of pre-existing history of nipple discharge was also found to be significantly higher amongst cases (p=0.038). However, other benign breast diseases were not significantly different between both groups.

There was no significant association between the use of OCPs, hormonal IUCDs or any other hormonal therapy, smoking, consumption of tobacco or alcohol. There was no significant association with history of autoimmune symptoms such as joint pains, fever, eye symptoms, oral or genital ulcers, skin rashes etc. None of the cases or controls gave history of autoimmune disease in the family. Other risk factors such as clothing habits, local application of substances, trauma, dietary habits, hygiene practices, comorbid illnesses, immunization, environmental exposure to pets or animals did not show any significant correlation with IGM in cases as compared to controls.

Table 1: Patient demographics.

Patient demographics	Case (n=30)	Controls (n=30)	P value
Age (in years), mean (SD)	33.76 (7.68) (Range 23-62)	33.9 (9.2) (Range 21-65)	
Gender			
Female	30 (100)	30 (100)	0.96
Male	0	0	
Menstrual status			
Premenopausal	27 (90)	26 (86.7)	0.89
Postmenopausal	3 (10)	4 (13.3)	
Parity, mean (SD)	2.1 (0.9)	2.1 (0.9)	

Table 2: Clinical features.

Clinical presentation		N (%)
Breast involved	Right	17 (56.7)
	Left	13 (43.3)
	Bilateral	0
Number of quadrants involved	Single	20 (66.7)
	Multiple	10 (33.3)
Quadrants involved	UOQ	14 (46.7)
	UIQ	6 (20)
	LOQ	11 (36.7)
	LIQ	3 (10)
	Retroareolar	9 (30)
Breast lump		29 (96.7)
Pain		28 (93.3)
Nipple discharge		30 (100)
Skin changes	Overall	23 (76.7)
	Erythema	19 (82.6)
	Warmth	17 (73.9)
	Ulceration	9 (39.1)
	Sinus	11 (36.7)
	Tenderness	11 (47.8)
	Oedema	8 (34.8)
	Abscess	9 (39.1)
Axillary lymphadenopathy		15 (50)

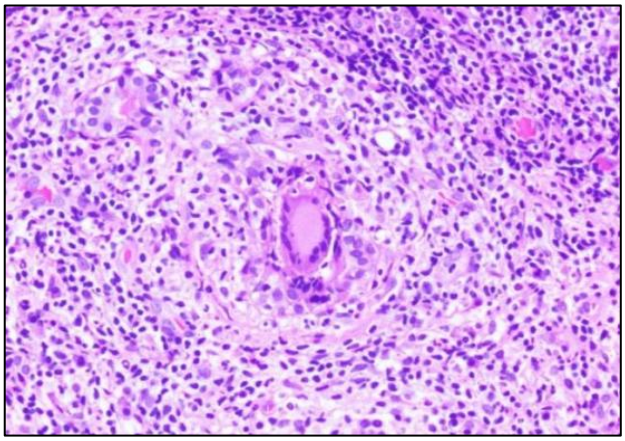

Figure 1: Perilobular inflammation characteristic of IGM.

Table 3: Hormonal factors and breastfeeding practices.

Variables		Case (n=30, mean±SD)	Controls (n=30, mean±SD)	P value
Serum prolactin level median (IQR)		9.06 (6.80, 15.50)	7.40 (5.40,10.20)	0.1086
Number of children breastfed		1.6±0.77	1.7±0.83	0.6319
Average duration of breastfeeding (All lactations)		25.74±11.71	15.26±8.37	0.0002
History of mastalgia		7 (23.33%)	8 (26.67%)	0.766
History of nipple discharge		4 (13.33%)	0	0.038
History of breast lumps		6 (20%)	3 (10%)	0.278
Regular usage of OCPs	Daily	4 (13.33%)	0	0.058
	Occasionally	3 (10%)	1 (3.33%)	
	Never	23 (76.67%)	29 (96.67%)	
Hormonal IUCD		0	0	-
Hormonal therapy for infertility		3 (10%)	0	0.076

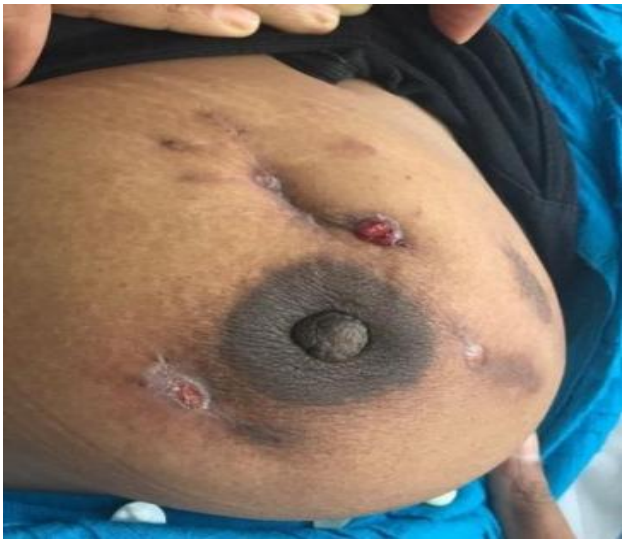

Figure 2: Clinical photograph of IGM with signs of inflammation and multiple sinus tracts.

DISCUSSION

Though IGM is a rare disease, its prevalence is higher in developing countries, especially in the Mediterranean and Asia.[2,20] In our study, IGM was found to occur predominantly amongst premenopausal women with a wide range of 23-65 years. Though IGM is found to be common in women of childbearing age, it has been reported to occur in males as well as older women.[20-22]

While testing for the presence of infections in our series, only six (20%) patients showed culture positivity for bacterial organisms, with no growth of fungi or mycobacteria. However, this was deemed to be a skin commensal (CONS) or hospital-acquired infection (Methicillin-resistant *Staphylococcus aureus*). The endogenous flora of the human breast has been found to predominantly contain coagulase-negative staphylococcus (53%) which has been postulated to colonise the deep breast tissue from the skin.[23]

Corynebacterium has garnered attention as being a potential etiological factor for IGM. Taylor et al showed the presence of *Corynebacterium*, especially *C. kroppenstedii* (54.8%) in 34 patients with IGM.[10] In a metagenomic analysis published by Yu et al 13 out of 19 patients grew *Corynebacterium*, the predominant being *C. kroppenstedtii*.[12] Recent studies have highlighted that *Corynebacterium* may not have a direct causative role, but a potentiating one, enabled by a novel glycoprotein that chelates iron, causing endogenous bacterial death and normal mammary cell death, resulting in increased cytokines and inflammation.[24] Our series, however, did not show any growth of *Corynebacterium*.

While there was no growth of *Mycobacterial* or fungal organisms in our series, it was notable that one patient, despite being diagnosed with active multi-drug resistant tuberculous pleural effusion, did not show the presence of tuberculous organisms in the breast tissue.

Various studies have lent support to the possible autoimmune mechanism behind the pathogenesis of IGM. The coexistence of inflammatory arthritis, Erythema nodosum, other systemic autoimmune diseases such as systemic lupus erythematosus (SLE), Sjogren's syndrome and response to immunosuppresants such as methotrexate and steroids have been pointers towards this autoimmune phenomenon. There was no significant difference in symptoms of autoimmune disease between the two groups in our study. Increase in cytotoxic T cells, Natural killer cells, natural killer T cells, plasma cells, neutrophil-to-lymphocyte ratio, cytokines (IL-33, IL-6, IL-8, IL-10, IL-17, IL-22, and IL-23), HLA (A10, A2403, B18 and DR17) and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) are thought to some of the factors causing systemic immune dysregulation.[25] While some authors were able to demonstrate seropositivity, some studies could not substantiate autoimmunity using ANA, RF and other extractable nuclear antibody levels.[8,9,26] Our study similarly could not substantiate any evidence of systemic autoimmunity. Despite two patients presenting with arthritis and one with erythema nodosum, they were

found to be ANA negative. The efficacy of intralesional corticosteroid injection has lent support to the role of localised autoimmune phenomenon, which needs to be studied further.[27]

Several factors, such as a history of prior breastfeeding, onset of symptoms within a short period (<5 years) from lactation, smoking, hyperprolactinaemia, hormone therapy, trauma, nipple discharge or inversion, and depression, have been identified as risk factors for IGM.[28,29] However, in our study, analysis of risk factors (breastfeeding practices, clothing habits, application of local substances, local trauma, dietary habits, hygiene practices, addictive habits, environmental exposure, hormonal factors, pregnancy-related factors, and other illness-related factors) showed a statistically significant difference only in the duration of breastfeeding and previous nipple discharge.

There has been a paradigm shift in the management of these patients from purely surgical therapy to combined therapy and even upfront medical treatment followed by reassessment and surgical intervention only in the setting of recurrence, relapse, or partial response. A thorough understanding of the etiopathogenesis of IGM will be instrumental in modifying treatment and preventing recurrence, thereby reducing morbidity of the disease.

The limitations of our study were that, though we were able to demonstrate the absence of systemic autoimmunity, we were unable to test for local autoimmune phenomena, and due to the rarity of the condition, the study had a relatively small sample size.

CONCLUSION

There was a significantly longer duration of lactation and previous nipple discharge in cases as compared to controls. There was no evidence of uncommon infections caused by bacterial, mycobacterial, or fungal pathogens. Markers for systemic autoimmunity, such as serum ANA, Immunoglobulin levels, and hormonal factors such as hyperprolactinemia, did not show any significantly higher positivity amongst our cases compared to controls. The role of other risk factors, such as breastfeeding practices, clothing habits, application of local substances, local trauma, dietary habits, hygiene practices, habitual substance usage, environmental exposure, hormonal factors, pregnancy-related factors, and other illness-related factors, were also not found to be significant. The aetiology of IGM continues to be elusive and needs further evaluation to assess a localized autoimmune process.

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REFERENCES

1. Kessler E, Wolloch Y. Granulomatous mastitis: a lesion clinically simulating carcinoma. Am J Clin Pathol. 1972;58(6):642-6.
2. Altintoprak F, Kivilcim T, Ozkan OV. Aetiology of idiopathic granulomatous mastitis. World J Clin Cases WJCC. 2014;2(12):852-8.
3. Sheybani F, Naderi HR, Gharib M, Sarvghad M, Mirfeizi Z. Idiopathic granulomatous mastitis: Long-discussed but yet-to-be-known. Autoimmunity. 2016;49(4):236-9.
4. Fruchter R, Castilla C, Ng E, Pomeranz MK, Femia AN. Erythema nodosum in association with idiopathic granulomatous mastitis: a case series and review of the literature. J Eur Acad Dermatol Venereol. 2017;31(9):e391-3.
5. Skandarajah A, Marley L. Idiopathic granulomatous mastitis: a medical or surgical disease of the breast? ANZ J Surg. 2015;85(12):979-82.
6. Salehi M, Salehi M, Kalbasi N, Hakamifard A, Salehi H, Salehi MM, et al. Corticosteroid and Azithromycin in Idiopathic Granulomatous Mastitis. Adv Biomed Res. 2017;6:8.
7. DeHertogh DA, Rossof AH, Harris AA, Economou SG. Prednisone management of granulomatous mastitis. N Engl J Med. 1980;303(14):799-800.
8. Ozel L, Unal A, Unal E, Kara M, Erdoğdu E, Krand O, et al. Granulomatous mastitis: is it an autoimmune disease? Diagnostic and therapeutic dilemmas. Surg Today. 2012;42(8):729-33.
9. Altintoprak F, Karakece E, Kivilcim T, Dikicier E, Cakmak G, Celebi F, et al. Idiopathic Granulomatous Mastitis: An Autoimmune Disease? de Bree E, De Luca M, editors. Sci World J. 2013;2013:148727.
10. Taylor GB, Paviour SD, Musaad S, Jones WO, Holland DJ. A clinicopathological review of 34 cases of inflammatory breast disease showing an association between corynebacteria infection and granulomatous mastitis. Pathology (Phila). 2003;35(2):109-19.
11. Paviour S, Musaad S, Roberts S, Taylor G, Taylor S, Shore K, et al. Corynebacterium species isolated from patients with mastitis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2002;35(11):1434-40.
12. Yu HJ, Deng H, Ma J, Huang SJ, Yang JM, Huang YF, et al. Clinical metagenomic analysis of bacterial communities in breast abscesses of granulomatous mastitis. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2016;53:30-3.
13. Thimmappa D, Mallikarjuna MN, Vijayakumar A. Breast Tuberculosis. Indian J Surg. 2015;77(3):1378-84.
14. Kapila K, Verma K. Diagnosis of parasites in fine needle breast aspirates. Acta Cytol. 1996;40(4):653-6.
15. Sangwan S, Singh SP. Filariasis of the breast. Med J Armed Forces India. 2015;71(1):S240-1.
16. Houn HY, Granger JK. Granulomatous mastitis secondary to histoplasmosis: report of a case

diagnosed by fine-needle aspiration biopsy. Diagn Cytopathol. 1991;7(3):282-5.
17. Osborne BM. Granulomatous mastitis caused by histoplasma and mimicking inflammatory breast carcinoma. Hum Pathol. 1989;20(1):47-52.
18. Omranipour R, Mohammadi SF, Samimi P. Idiopathic granulomatous lobular mastitis-report of 43 cases from iran; introducing a preliminary clinical practice guideline. Breast Care Basel Switz. 2013;8(6):439-43.
19. Erhan Y, Veral A, Kara E, Ozdemir N, Kapkac M, Ozdedeli E, et al. A clinicopthologic study of a rare clinical entity mimicking breast carcinoma: idiopathic granulomatous mastitis. Breast Edinb Scotl. 2000;9(1):52-6.
20. Baslaim MM, Khayat HA, Al-Amoudi SA. Idiopathic granulomatous mastitis: a heterogeneous disease with variable clinical presentation. World J Surg. 2007;31(8):1677-81.
21. Kawashima K, Yamamoto S, Narui K, Fujiwara Y, Adachi S, Sasamoto M, et al. Granulomatous mastitis in a male breast: A case report and review of literature. Clin Case Rep. 2023;11(3):e7048.
22. Akcan A, Akyıldız H, Deneme MA, Akgun H, Arıtas Y. Granulomatous Lobular Mastitis: A Complex Diagnostic and Therapeutic Problem. World J Surg. 2006;30(8):1536.
23. Thornton JW, Argenta LC, McClatchey KD, Marks MW. Studies on the endogenous flora of the human breast. Ann Plast Surg. 1988;20(1):39-42.
24. Liu R, Luo Z, Dai C, Wei Y, Yan S, Kuang X, et al. *Corynebacterium parakroppenstedtii* secretes a novel glycolipid to promote the development of granulomatous lobular mastitis. Signal Transduct Target Ther. 2024;9:292.
25. Wang X, He X, Liu J, Zhang H, Wan H, Luo J, et al. Immune pathogenesis of idiopathic granulomatous mastitis: from etiology toward therapeutic approaches. Front Immunol. 2024;15:1295759.
26. Koksal H. The Clinical Utility of Autoantibodies in Patients with Idiopathic Granulomatous Mastitis. J Investig Surg Off J Acad Surg Res. 2022;35(2):325-9.
27. Yuan QQ, Xiao SX, Farouk O, Du YT, Sheybani F, Tan QT, et al. Management of granulomatous lobular mastitis: an international multidisciplinary consensus (2021 edition). Mil Med Res. 2022;9:20.
28. Ramadan R, Koryem IM, Fayed H. Idiopathic granulomatous mastitis: Risk factors and management. Breast Dis. 2022;41(1):413-20.
29. Zeng R chao, Li Q, Lin K lu, Zhang W, Gao E li, Huang G li, et al. Predicting the factors of lateral lymph node metastasis in papillary microcarcinoma of the thyroid in eastern China. Clin Transl Oncol Off Publ Fed Span Oncol Soc Natl Cancer Inst Mex. 2012;14(11):842-7.

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