

## Anti-Tuberculosis Treatment for Idiopathic Granulomatous Mastitis Mimicking Breast Cancer: A Retrospective Review of 36 Cases

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### Abstract

**Purpose:** This study aimed to share our experience with anti-tuberculosis (TB) therapy for the management of Idiopathic Granulomatous Mastitis (IGM).

**Methods:** A retrospective study was performed on 36 IGM cases treated with anti-TB therapy from Jan 2009 to Dec 2012 in our department. Clinical data, including on presentation, histopathology, and management, were analyzed by reviewing medical records.

**Results:** The diagnosis of IGM was based on histopathological evaluation. All patients had been excluded from tuberculosis mastitis by lab examinations. Fifteen relapsed IGM patients were switched to anti-TB treatment after surgery or when prednisolone failed. Another 21 patients accepted anti-TB drugs as their primary treatment. Among the 36 patients, 2 patients stopped treatment because of the side effects of the anti-TB drugs. In a 29.6-month follow-up of 34 patients who completed 6-12 months of therapy, a satisfactory result was obtained for 33 patients.

**Conclusions:** Our study demonstrates that treatment with anti-TB drugs is a safe and effective therapy for IGM patients, presenting a high cure rate for both initial and relapsed cases.

**Keywords:** Breast carcinoma; Inflammatory; Corticosteroid; Idiopathic granulomatous mastitis; Tuberculosis

### Introduction

Idiopathic Chronic Granulomatous Mastitis (IGM) is a rare and benign inflammatory breast disease that was first described by Kessler and Wolloch in 1972[1]. Clinically, IGM presents as an inflammatory process in the breast that can mimic an inflammatory cancer or an abscess. A common clinical finding is a palpable mass with erythematous skin changes, pain, sterile abscesses, fistulae, and/or nipple retraction[2]. The mechanisms of IGM have been proposed to be etiologic factors, including a chemical reaction associated with oral contraceptive pills, autoimmune phenomena, infection with yet-unidentified pathogens, and a localized immune response to extravasated secretions from lobules[3]. The pathophysiology of the disease remains unknown. Cer-

tain reports claim a relationship between corynebacterial infection and IGM[4,5]. To establish a diagnosis of IGM, other causes of Granulomatous Mastitis (GM), such as Tuberculosis (TB), sarcoidosis, foreign-body reaction, mycotic infection, ductal ectasia, Wegener's granuloma, and histoplasmosis, should be excluded.

Because the clinical findings of IGM are nonspecific, pathological evaluation usually plays a crucial role in the diagnosis of IGM. The treatment of IGM is still a challenge, as there is little awareness of this disease. Although surgical excision and steroid therapy are the most commonly used treatments, the optimal treatment remains unclear. The surgical treatment options vary widely, including drainage, wide excision, and mastectomy[6,7]. Although the recurrence rate ranges from 20% to 75% and although fistula formation has been reported after excision[2,7], surgical excision is still the most common treatment modality for IGM. Steroid use to treat IGM was first proposed by Dehetrogh et al in 1980[1]. Corti-

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costeroid therapy has previously been shown to be efficacious in IGM[8-10]. However, this treatment may not be appropriate in the presence of complications such as abscess formation, fistulae, and persistent wound infection[11]. Akbulut's study demonstrated that methotrexate(MTX) was effective in the treatment of 4 cases of IGM, especially in preventing complications, resolving the inflammatory process, and limiting the side effects of corticosteroids[12]. *Corynebacteria* have been identified in certain patients with IGM. Anti-TB drugs can be used to treat corynebacterial infection. Thus, we began to use anti-TB drugs to treat IGM in our clinical practice in 2009. In this study, we share our experience with anti-TB drugs for the treatment of IGM and describe the effectiveness of anti-TB drugs in treating IGM.

## Methods

We retrospectively reviewed the hospital records of 36 cases of IGM that were pathologically diagnosed between Jan 2009 to Dec 2012. We excluded 8 patients who were diagnosed with TB Mastitis (TM) and another 21 patients who were cured by surgery or prednisolone during the same time period. Clinical information regarding the 36 patients, aged between 19 and 56 years, is presented in Table 1. An ultrasound was performed on all patients. A mammogram was performed on 22 patients older than 35 years. The diagnosis of IGM was based on a core needle biopsy using a Bard® disposable 14-gauge needle or on a surgical sample. All tissue samples were stained immunohistochemically for pancytokeratin and epithelial cadherin. The pus was sent for microscopy analysis, culture, and antibiotic sensitivity testing. All patients underwent chest radiography, a tuberculin skin test, and a blood PCR test to exclude TB infection. No microorganisms were found in the pus or tissue-sample culture. Stains for acid-fast bacilli and fungus were negative in sections of cell and tissue blocks in all cases.

The prescriptions given to the patients were rifampicin (10mg/kg/d) and isoniazid (5mg/kg/d) plus ethambutol (15mg/kg/d) or pyrazinamide (20mg/kg/d). The medical treatment lasted for 6-12 months, based on the patient's disease response. The drugs were withdrawn when the patient achieved a final complete lesions relief by ultrasound.

## Results

This study describes 36 patients who presented a breast lump and were diagnosed with IGM at Sun Yat-Sen Memorial Hospital. The clinical characteristics of the patients were as follows: 32 patients presented a breast lump ranging from 3-10cm in size (mean size, 4.2cm). The lesions were unilateral. The right breast was affected in 19 patients, and the left breast was affected in 17 patients. A total of 22 (61.1%) patients presented painful swelling mimicking an inflammatory cancer. Ten (27.8%) patients had ulcerative skin lesions, and 8 (22.2%) patients formed a sinus (Figure 1 and 2). Six (16.7%) of the patients presented abscess, and 11 (30.6%) had nipple retraction (Figure 2).

All patients presented a mass during the ultrasonography of the breast, compared with only 3 (13.7%) patients showing an ill-defined mass during the mammography (Table 2). The ma-

ior ultrasonographic finding was a hypoechoic lobulated mass, with dotted blood flow signals around the mass (Figure 3). Mammography detected an asymmetric density or ill-defined mass in the affected breast (Figure 4). There were fourteen (38.9%) patients and six (27.2%) patients who were classified as Breast Imaging Reporting and Data System (BI-RADS) category 4-5 by ultrasound and mammography, respectively.

The diagnosis of IGM was based on histopathological evaluation by core needle biopsy or incisional biopsy of the affected breast tissues. The major pathological change was found to be a granulomatous inflammatory reaction centered on the lobules. Granulomas composed of epithelioid histiocytes, Langerhans giant cells accompanied by lymphocytes, and plasma cells were generally found within and around the dilated lobules (Figure 5). In this study, 15 patients relapsed, including 11 postoperative patients transferred from other hospital (4 cases of drainage and 7 cases of drainage and wide excision) and 4 patients for whom prednisolone treatment failed. Another 21 patients used anti-TB drugs as their primary treatment. Among the 36 patients, two patients stopped the anti-TB treatment two weeks or one month later because of the side effects of the drugs and switched to prednisolone treatment. There were 34 patients who finished 6-12 months of anti-TB treatment. One patient exhibited recurrence after 22 months of follow-up and then underwent mastectomy. During an average follow-up of 29.6 months, 33 patients were cured. The cure rate of anti-TB treatment for IGM was 91.7% (Table 3).

## Discussion

IGM is a chronic inflammatory, benign clinical condition involving the breast. IGM is an uncommon breast disease of unknown etiology, generally affecting women of reproductive age[13, 14]. This condition presents as a breast mass, with skin thickening, nipple retraction, and regional lymphadenopathy, and often mimics a breast carcinoma. Breast cancer is the most important differential diagnosis for IGM. In our study, approximately half of the patients with IGM had suspected malignancy based on clinical and radiological signs. Because radiology has limited value in the diagnosis of patients with IGM, pathological diagnosis is crucial in the planning of treatment for patients who have a similar presentation as in breast carcinoma. Cytologic analysis by fine needle aspiration biopsy is usually insufficient for definitive diagnosis and may be misleading, so histopathological examination by core needle biopsy has a significant role in obtaining a definitive diagnosis[15, 16]. Another uncommon breast inflammatory disease that should be differentiated from IGM is Tuberculosis Mastitis (TM) of the breast. In the published literature, most diagnoses of IGM are based on ruling out TB by histochemical staining and clinical evaluation[17]. There were 11 patients in our hospital who were diagnosed with TM in the same period. All of these patients had received anti-TB treatment for more than 9 months. However, anti-TB treatment alone may not be adequate to treat TM patients. 90% patients with TM may ultimately need surgical intervention coupled with anti-TB medication to eliminate draining sinuses, breast masses, or non-healing ulcers [18, 19].

The exact causes of IGM are still unknown, although an au-

Characteristics (n=36)	Positive	Negative
Breast lump	32 (88.9%)	4 (2.8%)
Painful swelling	22 (61.1%)	14 (38.9%)
Ulcerative skin lesions	10 (27.8%)	26 (72.2%)
Sinus formation	8 (22.2%)	28 (77.8%)
Nipple retraction	11 (30.6%)	25 (69.4%)
Abscess	6 (16.7%)	30 (83.3%)

**Table 1:** Clinical characteristics of patients with IGM

Imaging modality	No. (%)
Ultrasonography (n=36)	
Hypoechoic lobulated mass	16 (44.4%)
Mixed-echogenicity parenchymal mass	11 (31.6%)
Irregular tubular mass and parenchymal distortion	9 (25%)
Abscess	6 (16.7%)
Skin thickening	8 (22.2%)
Fistula tract	5 (13.9%)
Axillary lymph node enlargement	10 (27.8%)
BI-RADS category 4-5	14 (38.9%)
Mammography (n=22)	
Asymmetric increased density	10 (45.5%)
Ill-defined mass	3 (13.7%)
Calcification	1 (4.5%)
Axillary lymph node enlargement	7 (31.8%)
BI-RADS category 4-5	6 (27.2%)

**Table 2:** Ultrasonography and mammography findings in patients with IGM

No.	Age	Location	Diagnostic	Pre-treatment	Drugs	Duration	Outcome
1	33	L	Biopsy	Drainage and wide excision	R+I+E	6 months	Cured
2	42	L	Core needle biopsy	-	R+I+E	9 months	Cured
3	36	R	Core needle biopsy	-	R+I+P	6 months	Cured
4	40	R	Core needle biopsy	Drainage	R+I+E	6 months	Cured
5	44	L	Core needle biopsy	-	R+I+E	6 months	Cured
6	39	R	Core needle biopsy	-	R+I+P	6 months	Cured
7	37	L	Core needle biopsy	Drainage	R+I+E	9 months	Cured
8	28	R	Core needle biopsy	-	R+I+E	1 months	Prednisolone
9	30	R	Core needle biopsy	-	R+I+E	6 months	Cured
10	46	R	Core needle biopsy	Prednisolone	R+I+E	9 months	Cured
11	36	R	Core needle biopsy	-	R+I+P	6 months	Cured
12	26	R	Biopsy	Drainage and wide excision	R+I+P	12 months	Cured
13	31	L	Core needle biopsy	-	R+I+E	6 months	Cured
14	26	R	Core needle biopsy	-	R+I+E	6 months	Cured
15	19	L	Core needle biopsy	Drainage	R+I+E	6 months	Cured
16	47	R	Core needle biopsy	-	R+I+E	6 months	Cured
17	39	L	Core needle biopsy	-	R+I+E	6 months	Cured
18	45	R	Core needle biopsy	Prednisolone	R+I+P	9 months	Mastectomy
19	34	R	Biopsy	Drainage and wide excision	R+I+E	9 months	Cured
20	29	R	Core needle biopsy	-	R+I+E	6 months	Cured
21	33	L	Biopsy	Drainage and wide excision	R+I+P	6 months	Cured
22	45	L	Core needle biopsy	-	R+I+E	6 months	Cured
23	30	L	Core needle biopsy	Drainage	R+I+P	6 months	Cured
24	40	R	Core needle biopsy	-	R+I+E	7 months	Cured
25	38	R	Core needle biopsy	Prednisolone	R+I+E	6 months	Cured
26	42	L	Core needle biopsy	-	R+I+E	6 months	Cured
27	37	L	Biopsy	Drainage and wide excision	R+I+P	10 months	Cured
28	48	L	Core needle biopsy	-	R+I+P	2 weeks	Prednisolone
29	56	R	Core needle biopsy	-	R+I+E	6 months	Cured
30	31	L	Biopsy	Drainage and wide excision	R+I+E	8 months	Cured
31	26	R	Core needle biopsy	-	R+I+E	6 months	Cured
32	39	R	Biopsy	Drainage and wide excision	R+I+P	8 months	Cured
33	44	L	Core needle biopsy	-	R+I+E	6 months	Cured
34	37	R	Core needle biopsy	-	R+I+P	6 months	Cured
35	42	L	Core needle biopsy	-	R+I+E	6 months	Cured
36	25	L	Core needle biopsy	Prednisolone	R+I+E	6 months	Cured

**Table 3:** Clinical outcomes of 36 patients treated with anti-TB therapy

R+I+E, patients were treated with rifampicin plus isoniazid and ethambutol; R+I+P, patients were treated with rifampicin plus isoniazid and pyrazinamide.



Figure 1: Clinical symptoms of case 1

This was a 33 years old patient who had recurrence at the upper outer part of the left breast 3 months after wide surgical excision. A, the fistula was presented on the left breast before anti-tuberculosis treatment. B, the fistula was cured after 6 months of anti-TB treatment.

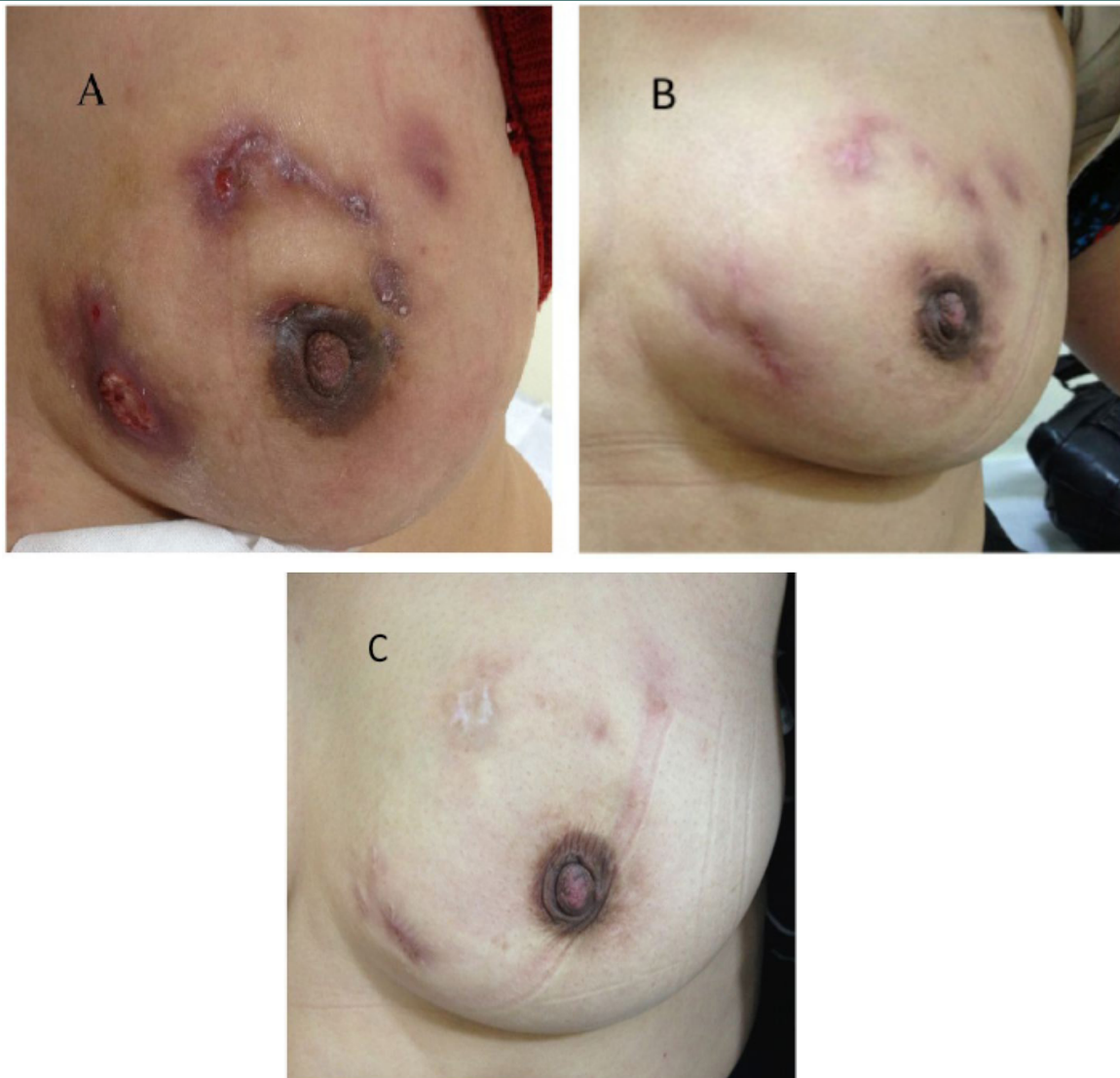
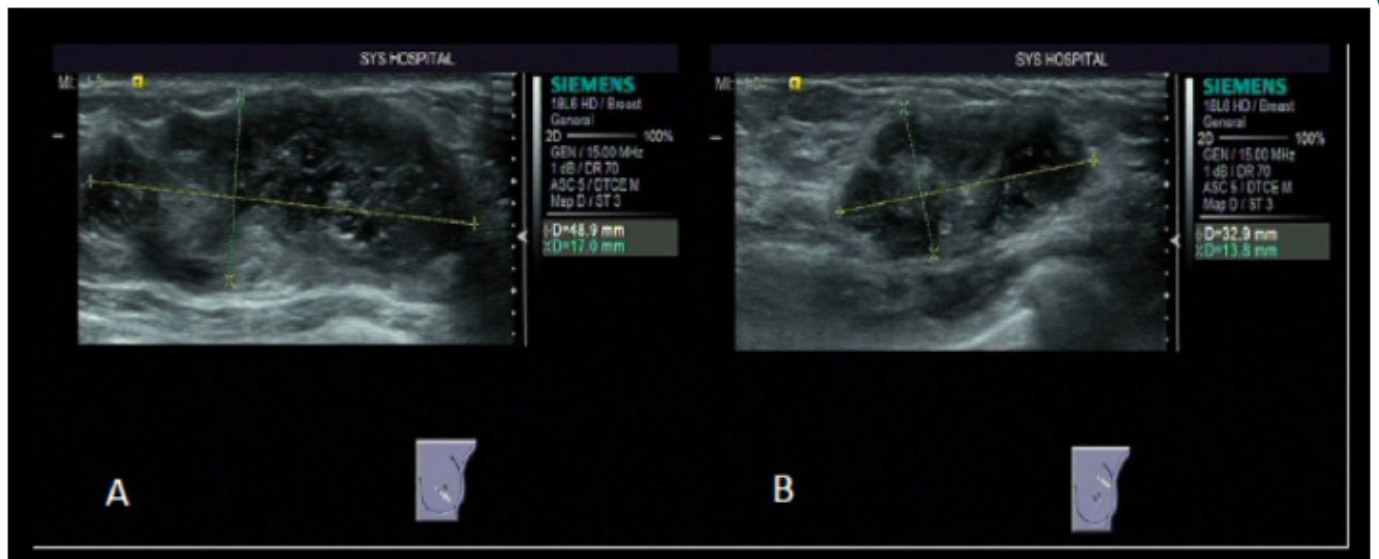
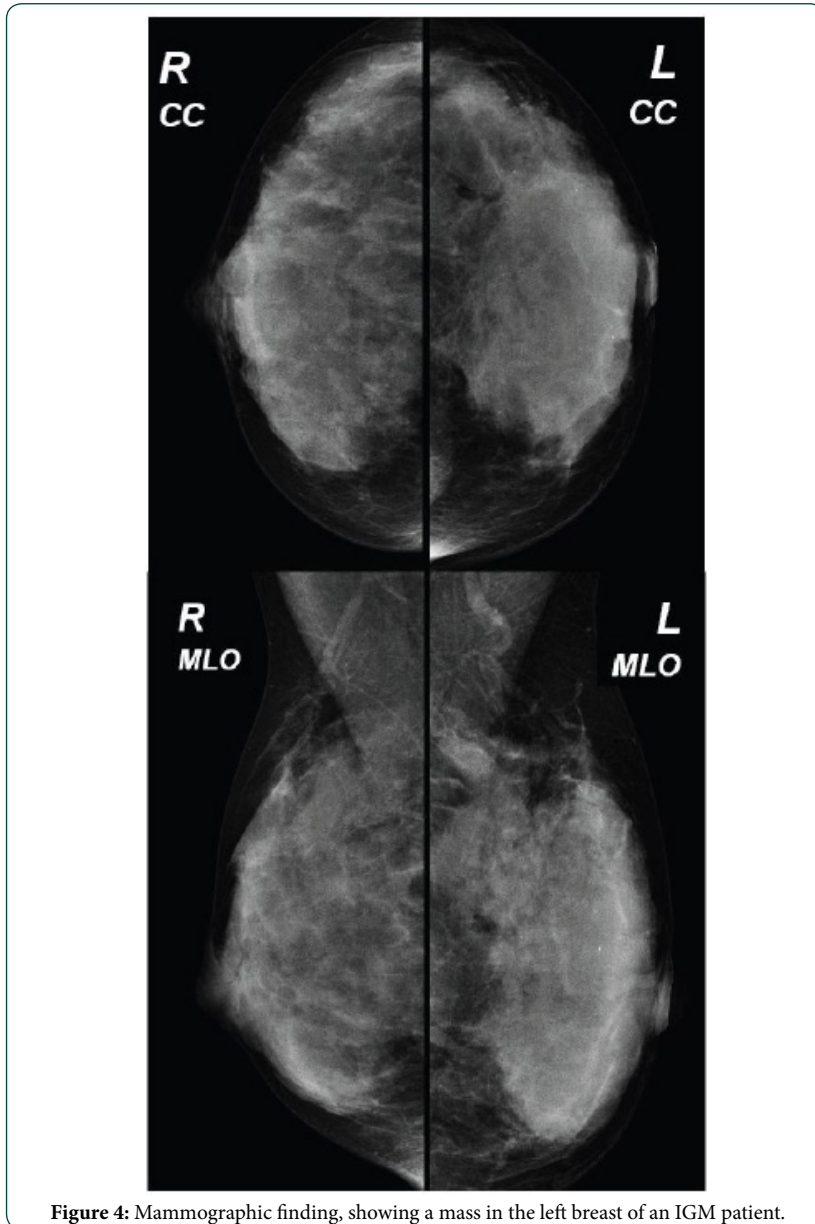


Figure 2: Clinical symptoms of case 2

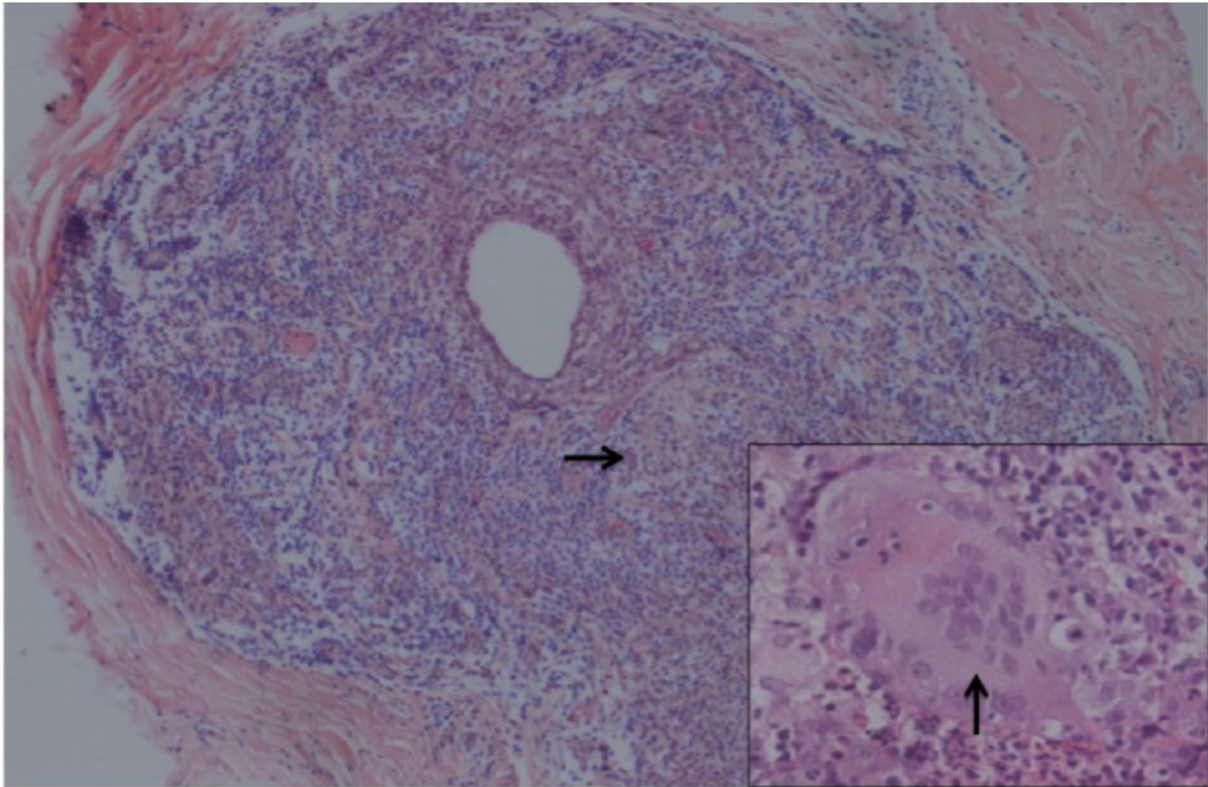
This was a 42 years old patient who accepted anti-TB treatment as primary therapy, who presented ulcerative skin lesions, sinus, abscess, and nipple retraction before treatment. A, ulcerative skin lesions were presented before anti-tuberculosis treatment. B, the ulcerative skin lesions were cured after 9 months of anti-tuberculosis treatment. C, the breast presented soft and normal 3 years later of follow up.



**Figure 3:** Multiple hypoechoic masses in the ultrasonographic evaluations of a patient with IGM. One lesion was located in the inner lower quadrant of the left breast (A), and another lesion was located in the outer upper quadrant (B).



**Figure 4:** Mammographic finding, showing a mass in the left breast of an IGM patient.



**Figure 5:** Microscopic findings for a core needle biopsy specimen, showing dilated ducts with a surrounding inflammatory infiltrate of lymphocytes, plasma cells, granuloma formation (→) and giant cells (↑). (H&E stain  $\times 100$  and inlet magnification  $\times 200$ ).

to immune reaction to protein secretions from the mammary ducts is one supposed causation[20]. There is a higher rate of IGM in women from developing countries than from developed countries because the largest series report came from developing countries[21]. This may suggest that some kinds of unidentified pathogens associated with environmental pollution may be related to IGM. Many studies have tried to find an infectious species in samples or tissues from IGM patients. Certain case reports claim a relationship between corynebacterial infection or mycobacterium and IGM[4, 22]. Although a lot of queries about whether these organisms are contaminants or pathogens exist, several lines of evidence suggest these bacteria are true pathogens. Contaminative bacteria are detected early in the disease process, while the consistent finding of *C. kroppenstedtii*, a rare and unusual species, suggests pathogenicity[23].

The management of choice for IGM has still not been established. The available treatment options include close follow-up; anti-biotherapy; limited or wide surgical excision; steroid and immunosuppressive drugs, such as MTX and azathioprine[24-26]. Surgical approaches varied from drainage to wide excision to mastectomy. And the most commonly used approach was wide excision[7]. The reoperation rate ranged from 21-75% either for completion of excision after surgical drainage or for recurrence[15, 27]. The high incidence of recurrence necessitates extensive resection to obtain disease-free margins, but wide local excision or repeated incisions often make the cosmetic outcome unacceptable. Additionally, mastectomy for benign disease is a challenging decision for both surgeons and patients. Mastectomy and breast reconstruction

techniques may be the last option for patients with a long history of recurrences[6]. In our study, 11 (31.4%) patients had recurrent disease after surgical treatment. All of these patients were cured after receiving anti-TB medication. Several studies have showed that systemic therapy is a safe and effective treatment for IGM, including steroids and MTX, used either alone or in combination. The full recovery rate with steroid treatment is 42-93.5%; the partial recovery rate, 6.4-58%; and non response, 6.5%[7, 16, 28]. Treating those IGM patients who have had no response to steroids or who have had recurrent disease when steroid treatment was stopped is still a challenge. Akbulut thought that MTX treatment should be considered in IGM patients who have no response to steroids to resolve the inflammatory process and to limit the side effects of corticosteroids[12]. Although these studies showed a good response of IGM to steroid treatment, most of the reports were based on a small number of cases. Long-term steroid therapy may induce severe side effects, including glucose intolerance and Cushingoid features[27]. If a patient fails to respond to systemic corticosteroid therapy, chronic pathogenic bacteria infections such as corynebacteria should be considered[4]. Because anti-TB medications can be used to treat corynebacteria infection according to the drug description, we tried to use anti-TB drugs to treat IGM patients beginning in 2009. Based on our observations, treatment with anti-TB drugs produced excellent responses and achieved a high cure rate for this type of disease. The IGM patients presented good adherence to anti-TB treatment and were satisfied with the therapeutic results. Among the 34 patients who completed 6-12 months of treatment, 33 patients were cured, without additional surgical intervention.

This is the first report demonstrating that anti-TB medication is another safe and effective systemic therapy for IGM patients, especially in those patients for whom steroid or surgical treatment has failed. Our study shows that anti-TB therapy may act as a compensatory treatment for IGM in addition to immunosuppressive therapy and surgical therapy.

## References

- 1) DeHertogh DA, Rossof AH, Harris AA, Economou SG (1980) Prednisone management of granulomatous mastitis. *N Engl J Med* 303: 799-800.
- 2) Akcan A, Akyildiz H, Deneme MA, Akgun H, Arıtas Y, et al. (2006) Granulomatous lobular mastitis: a complex diagnostic and therapeutic problem. *World J Surg* 30: 1403-1409.
- 3) Patel RA, Strickland P, Sankara IR, Pinkston G, Many W Jr, et al. (2010) Idiopathic granulomatous mastitis: case reports and review of literature. *J Gen Intern Med* 25: 270-273.
- 4) Mathelin C, Riegel P, Chenard MP, Tomasetto C, Brettes JP (2005) Granulomatous mastitis and corynebacteria: clinical and pathologic correlations. *Breast J* 11: 357.
- 5) Ang LM, Brown H (2007) *Corynebacterium accolens* Isolated from Breast Abscess: Possible Association with Granulomatous Mastitis. *J Clin Microbiol* 45: 1666-1668.
- 6) Hladik M, Schoeller T, Ensaf F, Wechselberger G (2011) Idiopathic granulomatous mastitis: successful treatment by mastectomy and immediate breast reconstruction. *J Plast Reconstr Aesthet Surg* 64: 1604-1607.
- 7) Wilson JP, Massoll N, Marshall J, Foss RM, Copeland EM, et al. (2007) Idiopathic granulomatous mastitis: in search of a therapeutic paradigm. *Am Surg* 73: 798-802.
- 8) Fletcher A, Magrath IM, Riddell RH, Talbot IC (1982) Granulomatous mastitis: a report of seven cases. *J Clin Pathol* 35: 941-945.
- 9) Jorgensen MB, Nielsen DM (1992) Diagnosis and treatment of granulomatous mastitis. *Am J Med* 93: 97-101.
- 10) Pathirana AA, Fernando A, de Silva MV (2007) Three patients with granulomatous mastitis showing good response to oral prednisolone. *Ceylon Med J* 52: 14-15.
- 11) Erozyen F, Ersoy YE, Akaydin M, Memmi N, Celik AS, et al. (2010) Corticosteroid treatment and timing of surgery in idiopathic granulomatous mastitis confusing with breast carcinoma. *Breast Cancer Res Treat* 123: 447-452.
- 12) Akbulut S, Yilmaz D, Bakir S (2011) Methotrexate in the management of idiopathic granulomatous mastitis: review of 108 published cases and report of four cases. *Breast J* 17: 661-668.
- 13) Goldberg J, Baute L, Storey L, Park P (2000) Granulomatous mastitis in pregnancy. *Obstet Gynecol* 96: 813-815.
- 14) Al-Khaffaf B, Knox F, Bundred NJ (2008) Idiopathic granulomatous mastitis: a 25-year experience. *J Am Coll Surg* 206: 269-273.
- 15) Kok KY, Telisinghe PU (2010) Granulomatous mastitis: presentation, treatment and outcome in 43 patients. *Surgeon* 8: 197-201.
- 16) Kuba S, Yamaguchi J, Ohtani H, Shimokawa I, Maeda S, et al. (2009) Vacuum-assisted biopsy and steroid therapy for granulomatous lobular mastitis: report of three cases. *Surg Today* 39: 695-699.
- 17) Tse GM1, Poon CS, Ramachandram K, Ma TK, Pang LM, et al. (2004) Granulomatous mastitis: a clinicopathological review of 26 cases. *Pathology* 36: 254-257.
- 18) Afridi SP, Memon A, Rehman SU, Memon A, Baig N (2009) Spectrum of breast tuberculosis. *J Coll Physicians Surg Pak* 19: 158-161.
- 19) Seo HR, Na KY, Yim HE, Kim TH, Kang DK, et al. (2012) Differential diagnosis in idiopathic granulomatous mastitis and tuberculous mastitis. *J Breast Cancer* 15: 111-118.
- 20) Han BK, Choe YH, Park JM, Moon WK, Ko YH, et al. (1999) Granulomatous mastitis: mammographic and sonographic appearances. *AJR Am J Roentgenol* 173: 317-320.
- 21) Bani-Hani KE, Yaghan RJ, Matalka II, Shatnawi NJ (2004) Idiopathic granulomatous mastitis: time to avoid unnecessary mastectomies. *Breast J* 10: 318-322.
- 22) Betal D, Macneill FA (2011) Chronic breast abscess due to *Mycobacterium fortuitum*: a case report. *J Med Case Rep* 5: 188.
- 23) Paviour S, Musaad S, Roberts S, Taylor G, Taylor S, et al. (2002) *Corynebacterium* species isolated from patients with mastitis. *Clin Infect Dis* 35: 1434-1440.
- 24) Kim J, Tymms KE, Buckingham JM (2003) Methotrexate in the management of granulomatous mastitis. *ANZ J Surg* 73: 247-249.
- 25) Asoglu O, Ozmen V, Karanlik H, Tunaci M, Cabioglu N, et al. (2005) Feasibility of surgical management in patients with granulomatous mastitis. *Breast J* 11: 108-114.
- 26) Yau FM, Macadam SA, Kuusk U, Nimmo M, Van Laeken N (2010) The surgical management of granulomatous mastitis. *Ann Plast Surg* 64: 9-16.
- 27) Ocal K, Dag A, Turkmenoglu O, Kara T, Seyit H, et al. (2010) Granulomatous mastitis: clinical, pathological features, and management. *Breast J* 16: 176-182.
- 28) Hovanessian Larsen LJ, Peyvandi B, Klipfel N, Grant E, Iyengar G (2009) Granulomatous lobular mastitis: imaging, diagnosis, and treatment. *AJR Am J Roentgenol* 193: 574-581.

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