

Relationship of post-treatment radiological findings with relapses in idiopathic granulomatous mastitis patients

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ABSTRACT

OBJECTIVE: The aim of this study is to investigate the relationship between post-treatment radiological findings and recurrences in idiopathic granulomatous mastitis (IGM).

METHODS: Clinical data, ultrasound (US) and magnetic resonance imaging (MRI) examinations of 160 patients with IGM (mean age 34.6±7 years; range 20–56 years) who received only steroid or steroid+surgical treatment were evaluated retrospectively. Patients were grouped as radiological complete response (RCR) or radiological incomplete response (RIR).

RESULTS: Only in the steroid group, 79 (54.1%) patients were in the RCR group and 67 (45.9%) patients were in the RIR group. Recurrence occurred in 42 (26.3%) patients, 27 (16.9%) in the same breast and 15 (9.4%) in the contralateral breast. Most of the recurrences in the same breast had residual lesions up to recurrence (74.1%).

CONCLUSION: Residual lesion after treatment is a risk factor for recurrence, and treatment can significantly reduce recurrences until the lesions disappear. The lesion size on MRI after treatment is not associated with recurrence.

Keywords: Granulomatous mastitis; magnetic resonance imaging; recurrence; ultrasonography.

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Idiopathic granulomatous mastitis (IGM) is a rare, benign, inflammatory disease of the breast [1]. Mostly seen in women of childbearing age and breastfeeding [2]. Its etiology is not clear. It has been suggested that an inflammatory response develops secondary to the disruption of the integrity of the ductal epithelial cells in the breast and the passage of intraluminal secretions into the breast stroma [3]. However, it has been suggested that it is associated with hyperprolactinemia [4] and corynebacterium [5–7]. Although it is most commonly presented as a painful, firm breast mass, inflammation, skin lesions, retraction of the skin and nipple, and fistulas

are also seen [2, 8]. Different degrees of clinical presentation are seen from mild to severe, and recurrences are common [9]. Among the imaging methods, MG, US and MRI are used. The most common radiological findings are asymmetrical density in MG, irregular hypoechoic mass showing tubular extension on US, rim or heterogeneously enhancing mass and non-mass enhancement (NME) on MRI [10]. Its clinical and radiological findings may mimic inflammatory breast cancer. Therefore, the definitive diagnosis is made by core needle biopsy and histopathological examination. Histopathological examination reveals non-causative granulomas [11].

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Treatment of IGM is long and difficult, and there is no established optimal treatment approach. Close regular follow-up, medical treatments and surgical treatments are applied. Among the medical treatments, antibiotics, corticosteroids, methotrexate, and azathioprine are used [12–14]. Recently, steroids have been used alone or in combination with surgery. Good results are obtained with the use of steroids plus surgical treatment [15–17]. Spontaneous resorption can be seen with only clinical and radiological follow-up, especially in patients with mild involvement [9].

Previously, the relationship between recurrences in IGM and clinical and pre-treatment radiological findings was investigated [2, 18–20]. However, the relationship between post-treatment imaging findings and recurrence was not investigated. Our aim in this study is to investigate the relationship between post-treatment radiological findings and recurrence in steroid-treated IGM patients.

MATERIALS AND METHODS

Ethics

This retrospective study was approved by the Kartal Dr. Lutfi Kirdar City Hospital Clinical Research Ethics Committee (date: 22.02.2023, number: 2023/514/244/14). The study was conducted in accordance with the Declaration of Helsinki.

Patients

Patients diagnosed with IGM by core-needle biopsy between January 2014 and September 2023 were included in the study. Gram, periodic acid-Schiff, Ziehl-Neelsen staining, mycobacterial cultures, Grocott-Gomori methenamine silver staining and purified protein derivative (PPD) skin test and QuantiFERON test were performed to differentiate from other mastitis.

Patients with a diagnosis of IGM, who received only steroid treatment or steroid+surgical treatment, who were compliant with the treatment and had regular check-ups were included in the study. Patients who could not comply with the treatment or who did not follow up regularly during the treatment were excluded from the study. Patients who did not receive steroid therapy and only underwent surgery were excluded. Patients who did not come to their follow-up visits after their treatment was completed or who did not come regularly were also excluded from the study.

Highlight key points

- A significant portion of recurrences in the same breast develop in patients with residual lesions after treatment.
- Continuing treatment until the lesions disappear completely can significantly reduce recurrences in the same breast.
- While no recurrence was observed in the same breast in the steroid+surgery group, most of the recurrences in the contralateral breast occur in this group.

Treatment and Follow-up Procedure

Clinical evaluation and follow-up of the patients were performed by two general surgeons with 10 and 28 years of experience in breast surgery. Patients were treated with 0.4 mg/kg methylprednisolone and 0.125% prednisolone ointment once a day on weekdays. While under treatment, patients were checked at 2-week intervals. Treatment was discontinued in patients who clinically recovered completely, developed steroid side effects or did not respond to treatment. A maximum of 6 months of treatment was applied to avoid the side effects of the steroid. Surgical treatment (wide local excision, mastectomy) was applied to patients who did not respond to steroid treatment. Fluctuating abscesses were drained. Healing of fistulas and ulcerations, absence of palpable lesions and inflammatory findings were accepted as complete clinical responses.

Of the patients with clinically complete responses, patients with radiological lesions were observed every 3 months, and those without lesions were observed clinically and radiologically every 6 months. After 2 years, patients without any complaints were followed up annually. Patients who did not respond to steroids underwent surgical treatment. Patients who had clinically complete recovery and later developed inflammatory symptoms were evaluated radiologically for recurrence. Patients with typical lesions in the same breast on US were considered relapsed. Patients whose lesions were not typical for IGM in the same breast were biopsied. In all patients who developed a lesion in the contralateral breast, recurrence was proven by core biopsy. Microbiological tests were performed again for the diagnosis of recurrences in the contralateral breast.

US and MRI Technique

MRI examinations of the patients were performed on a 1.5 T device (Philips Ingenia, Philips Healthcare, Best, The Netherlands). DCE series (three-dimensional fat-saturated ultrafast spoiled gradient echo) were obtained 90, 142, 194, 246 and 298 seconds after contrast agent

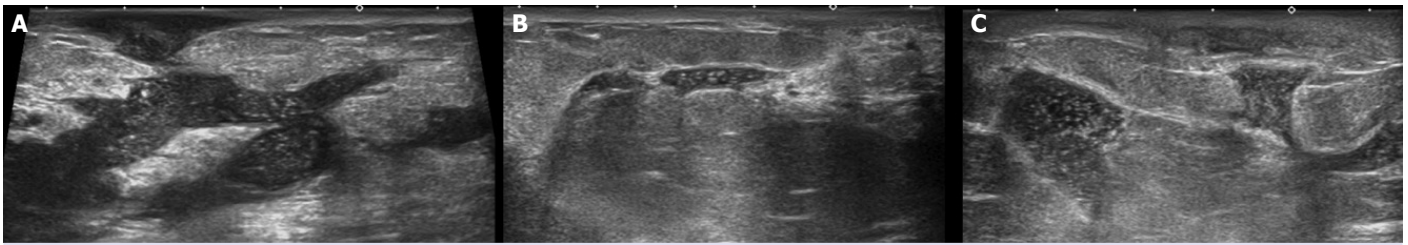


FIGURE 1. (A) Lesions consistent with mastitis on US before treatment. (B) Residual lesion after treatment. (C) Recurrence in the same breast after treatment is completed.

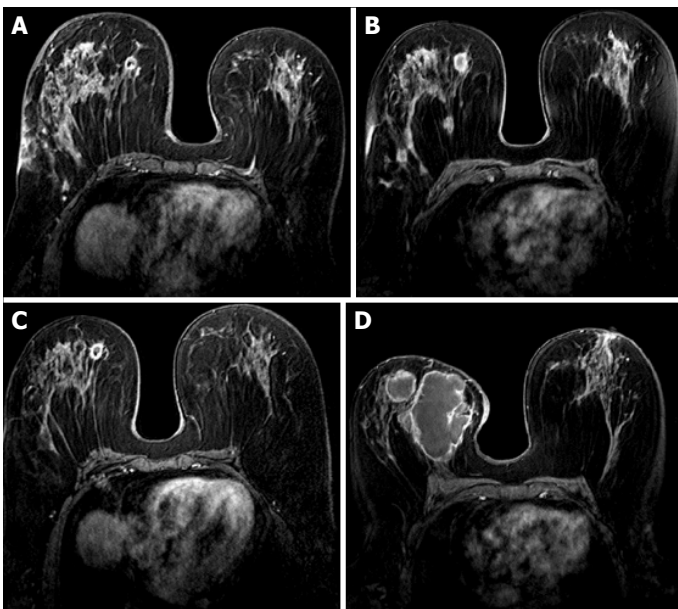


FIGURE 2. (A) Skin thickening, NME and abscess in the right breast in pre-treatment MRI. (B) Three abscess formations in the MRI 7 months later. (C) One residual abscess in MRI 13 months later. (D) Abscesses compatible with recurrence on MRI 26 months later.

injection. 0.1 mmol of gadolinium chelate (Dotarem 0.5 mmol/mL, Guerbet, Villepinte, France) per kilogram of body weight was administered by auto-injector. A dedicated 16-channel phased array breast coil (MammoTrak, Philips Healthcare, Amsterdam, The Netherlands) was used.

US examinations were performed with an Aplio™ 500 ultrasound machine (Toshiba Medical Systems Co. Ltd, Otawara, Japan) with linear 14.0 MHz transducer.

US and MRI Evaluation

MR and US analysis was performed on the image archiving and communication system (Infiniti Healthcare 3.0.11.4, Seoul, Republic of Korea) by two radiologists with 7 and

10 years of experience in breast imaging at the EIZO GS520 workstation (EIZO, Hakusan, Ishikawa, Japan).

The patients were divided into two groups as those who received steroid only and those who underwent steroid+surgery. Those who received only steroid treatment were divided into two groups according to the US and DCE-MRI examinations just after the treatment was stopped. Radiologically no lesions were classified as radiological complete response (RCR), and those with residual lesions as radiological incomplete response (RIR). Irregular hypoechoic mass and abscess formations with tubular extension were noted on US. The longest dimension of the lesions was measured on US examinations. Contrast-enhanced mass lesions and non-mass enhancement (NME) areas were noted. RCR and RIR groups were formed by evaluating the US and MRI examinations performed after the end of treatment in patients treated with only steroids. Patients who were given both steroids and surgery (wide local excision, mastectomy) were evaluated as the steroid+surgery group. All US and DCE-MRI examinations of the patients up to the last control were evaluated. It was checked whether the lesions of the patients disappeared or not. In patients whose lesions completely regressed, the date of disappearance of the lesion was noted. In patients who developed recurrence, the date of recurrence and the recurrence in which breast were evaluated. Relapses in the same breast, recurrences in the contralateral breast, and total recurrences as the sum of these two groups were recorded.

Images of some patients are presented as examples in Figures 1, 2 and 3. A 32-year-old female patient had a confluent tubular hypoechoic lesion in the lower outer quadrant at the time of diagnosis (A). After 1.5 months of steroid treatment, improvement in inflammatory findings and significant regression in lesions were detected. Residual lesion was always observed in US follow-ups (B). In the US examination of the patient who developed recurrence 7 months after the treatment was

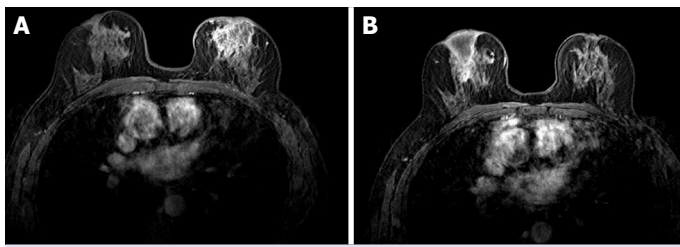


FIGURE 3. (A) A mass compatible with mastitis in the left breast on MRI before treatment. **(B)** While no lesion was observed in the left breast 18 months after the treatment, recurrence was detected in the right breast.

stopped, a residual lesion in the former mastitis area and newly developed lesions in the middle inner quadrant were detected (C) (Fig. 1).

In the pre-treatment MRI of a 37-year-old female patient, there was NME and skin thickening in the middle and lower outer quadrants of the right breast and an abscess in the lower inner quadrant (A). MRI performed 7 months later revealed peripherally enhanced abscesses in the lower outer, lower middle and lower inner quadrants of the right breast (B). In the MRI 13 months later, there was no lesion in the right breast, except for a peripherally enhanced 10 mm diameter abscess (C). Her treatment was discontinued and she was followed up. In the MRI of the patient who presented with symptoms of recurrence 10 months after the end of treatment, abscess formation was observed in the middle and lower inner quadrant of the right breast (D) (Fig. 2).

A 55-year-old female patient had a heterogeneously enhanced mass in the retroareolar region of the left breast on MRI at the time of diagnosis (A). MRI of the patient who had complaints in the contralateral breast 18 months later revealed an abscess and NME was diagnosed as IGM in the retroareolar region of the right breast. There was no lesion in the left breast (B) (Fig. 3).

Statistical Analysis

Data analysis was performed with Statistical Package for Social Sciences (SPSS) version 25.0.0.0 software (IBM Corp., Armonk, N.Y., USA). Descriptive data were given as percentage, mean and standard deviation. The one-sample sample Kolmogorov-Smirnov test was used to determine whether the groups were normally distributed. Normally distributed variables were presented as mean (\pm standard deviation [SD]), while non-normally distributed variables were presented as median (interquartile range [IQR]). Categorical variables were compared with the chi-square

TABLE 1. General characteristics of the patients

Features	Values
Premenopausal, n (%)	154 (96.2)
Postmenopausal, n (%)	6 (3.8)
Number of children (median Q1–Q3)	2 (2–4)
Breastfeeding time (median, Q1–Q3)	28 (24–57)
Oral contraceptive use, n (%)	32 (20)
Smoking, n (%)	26 (16.3)
Bilateral involvement (n, %)	2 (1.3)

test. Mann-Whitney U test was used to compare the numerical data between two independent groups. P-value <0.05 was considered statistically significant.

RESULTS

Clinical and radiological data of 239 IGM patients were evaluated. Ten patients who did not come to the control after the treatment started, 4 patients who did not comply with the treatment, 51 patients who did not come for the control after the treatment ended, 12 patients who did not want steroid treatment and only underwent surgery, and 2 patients whose MRI examination could not be evaluated due to artifacts were excluded from the study. US and MRI examinations of the remaining 160 patients (mean age 34.6 ± 7 years; range 20–56 years) were evaluated retrospectively. US examinations were performed in all patients at the time of discontinuation of treatment or in the subsequent follow-ups. At least one MRI was performed in the follow-up of 27 patients, apart from the MRI performed at the time of discontinuation of treatment.

All patients had a history of childbearing and breastfeeding. The characteristic features of the patients are presented in Table 1 in detail.

There were 146 (91.2%) patients in the steroid-only group and 14 (8.8%) patients in the steroid+surgery group. In the only steroid group, 79 (54.1%) patients were in the RCR group, and 67 (45.9%) patients were in the RIR group. The median duration of treatment was 4 (3–6) months. Total follow-up was median 2.7 (1.2–5.2) years. Relapse developed in 42 (26.3%) patients, median 4 (3–8) months after discontinuation of treatment. Recurrence occurred in the same breast in 27 (16.9%) patients and in the contralateral breast in 15 (9.4%) patients. Relapses in the same breast developed median 4

TABLE 2. Relationship between recurrences by groups

	Steroid+Surgery group (n=14)	Only steroid group (n=146)	p	RCR (n=79)	RIR (n=67)	p
Total recurrence (n=42)	4 (28.5%)	38	0.83	9 (11.4%)	29 (43.3%)	<0.001
Recurrence in the same breast (n=27)	0	30 (20.5%)	–	2 (1.3%)	25 (37.3%)	<0.001
Relapse in the contralateral breast n=15)	4 (28.5%)	9 (6.16%)	0.003	7 (10.1%)	4 (6%)	0.50

RCR: Radiological complete response; RIR: Radiological incomplete response.

TABLE 3. Presence of lesion up to the time of recurrence according to the recurrence groups

	Total recurrence (42) (%)	Recurrence in the same breast (27) (%)	Recurrence in the contralateral breast (15) (%)
Residual lesion	52.4	74.1	13.3
No lesion	47.6	3.7	86.7

(3–12) months after treatment was discontinued, and recurrences in the contralateral breast developed median 15 (4–20) months after treatment was discontinued.

There was no significant difference in total recurrences between the surgical and non-surgical groups ($p=0.83$). While there was recurrence in the same breast in 20.5% of the patients who received only steroid treatment, there was no recurrence in the same breast in the patients treated with steroid+surgery. Relapses in the contralateral breast were significantly higher in those who underwent steroid+surgery ($p=0.003$) (Table 2). Total recurrences and recurrences in the same breast were significantly higher in the RIR group than in the RCR group ($p<0.001$). There was no significant difference between the RCR and RIR groups in recurrences in the contralateral breast ($p=0.50$) (Table 2).

While 74.1% of the recurrences in the same breast had lesions in the radiological examinations until the development of recurrence, 13.3% of the recurrences in the contralateral breast had lesions up to recurrences (Table 3).

In the first post-treatment US, the median diameter of the residual lesions was 28 (18–35) mm. There was no significant difference between the residual lesion diameters in the relapsed and non-relapsed groups ($p=0.13$).

DISCUSSION

IGM is a disease with a recurrent and prolonged course, without optimal treatment. Recently, the use of steroids alone or in combination with surgery has been found to be successful [2, 15, 21]. The recurrence rates of patients who received surgical treatment and steroid treatment were controversial in studies. In some studies, surgical treatment was superior to steroid treatment with a lower recurrence rate [22]. It has previously been shown that IGM lesions shrink with steroids and less tissue is removed with surgery. It was reported that recurrences were less in patients who underwent steroid+surgery. [23, 24]. In a meta-analysis by Godazandeh et al. [16], the recurrence rate was found to be lower in patients treated with steroid+surgery.

Risk factors for recurrence in IGM have been investigated previously. Huang and Wu [25] suggested that obesity, FSH/LH, and prolactin levels are associated with relapse. Basim et al. [17] reported that recurrences were more common in patients with low B12 levels, multicentric lesions, severe involvement, accompanying fistula or erythema nodosum, rheumatologic diseases, and only medical therapy. Yilmaz et al. [26], using a scoring system based on clinical and radiological evaluation, observed that severe cases relapse more than mild cases. In a study conducted by Kayadibi et al. [20] in which the relationship between pre-treatment MRI findings and recurrence was investigated, it was suggested that high background enhancement and low ADC values may be risk factors for recurrence.

In our study, there was no significant difference in total recurrences between patients who received steroids only and those who underwent steroid+surgery. We did not observe any recurrences in the same breast in the steroid+surgery group. However, recurrences in the contralateral breast were significantly higher in the steroid+surgery group. According to the results of our study, steroid+surgical treatment is superior to only steroid treatment in recurrences in the same breast.

Total recurrence rates were significantly lower in the RCR group than in the RIR group in patients who received only steroids. Similarly, recurrences in the same breast were significantly less in the RCR group. According to the results of our study, residual lesion after treatment is an important risk factor in recurrences in the same breast. Even if patients achieve a complete clinical response, treatment until the lesions disappear completely radiologically can significantly reduce recurrences in the same breast.

There was no significant difference between the RCR and RIR groups in recurrences in the contralateral breast. We observed significantly higher recurrence rates in the contralateral breast in patients who received steroid+surgical treatment compared to those who only received steroids. Relapses in the contralateral breast may be seen more frequently in patients who are resistant to steroids and require surgery.

Relapses in the contralateral breast appeared after a longer time than recurrences in the same breast. Relapses in the same breast appear to be associated with ongoing disease, and recurrences in the contralateral breast occur long after the existing disease has healed. The majority of contralateral breast recurrences developed after the lesions in the breast disappeared. Relapses in the same breast appear to be associated with ongoing disease, and recurrences in the contralateral breast occur long after the existing disease has healed. The majority of contralateral breast recurrences developed after the lesions in the breast disappeared. We observed recurrence in the contralateral breast in 9.4% of all patients. Patients who have had IGM once may have an increased risk of recurrence in the contralateral breast. There is no information about contralateral breast recurrences in the literature. Since the follow-up period was longer in our study, we observed these recurrences more frequently.

Most of the relapses were in the RIR group. In this group, residual lesion size could not predict which of these patients would recur and which would regress spontaneously.

The retrospective nature and the small number of patients are limitations of our study.

Conclusion

In conclusion, despite the clinical complete response after treatment, residual lesion remaining is a risk factor for recurrence. The recurrence rates in the same breast were significantly lower in patients who underwent steroid+surgery compared to patients who received only steroids. The recurrence rate in the contralateral breast was higher in the steroid+surgery group than in the steroid group. The lesion size on MRI after treatment is not associated with recurrence.

Ethics Committee Approval: The Kartal Dr. Lutfi Kirdar City Hospital Clinical Research Ethics Committee granted approval for this study (date: 22.02.2023, number: 2023/514/244/14).

Authorship Contributions: Concept – GR, MA; Design – GR, MA; Supervision – GR, MA, KC, MFK; Fundings – GR, MA, KC, MFK; Materials – GR, MA, KC, MFK; Data collection and/or processing – GR, MA, KC, MFK; Analysis and/or interpretation – GR, MA; Literature review – GR, MA; Writing – GR, MA, KC, MFK; Critical review – GR, MA.

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