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Original Article

Low-intensity focused ultrasound versus conventional corticosteroid therapy for idiopathic granulomatous mastitis: improved pain relief, quality of life, and favorable safety profile

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Abstract: Purpose: Idiopathic Granulomatous mastitis (IGM) is a chronic inflammatory breast disease for which conventional corticosteroid therapy is limited by substantial adverse effects. This study aimed to compare the analgesic efficacy, quality-of-life improvement, and safety of low-intensity focused ultrasound (LIFU) monotherapy versus intralesional corticosteroid injections in patients with IGM. Methods: This retrospective study included individuals diagnosed with IGM between September 2021 and December 2025. Patients received either intralesional corticosteroid injections (hormone group, n = 124) or low-intensity focused ultrasound monotherapy (LIFU group, n = 117). Primary outcomes were pain intensity on the 10-cm Visual Analog Scale (VAS) and health-related quality of life using the 36-Item Short Form Health Survey (SF-36). Secondary outcomes included overall clinical response, inflammatory markers, ultrasound lesion characteristics and volume reduction rate, adverse events, and recurrence. Results: At week 12, the LIFU group had significantly lower VAS pain scores (2.86 ± 0.74 vs. 3.52 ± 0.86, P < 0.001). Improvements were also observed across other SF-36 domains, with six of eight domains remaining significant after correction for multiple comparisons. The overall response rate (ORR) in LIFU group was 94.02%, which was significantly higher than the 83.87% observed in the corticosteroid group (P = 0.013). Inflammatory markers were markedly lower with LIFU (CRP: 7.12 ± 2.37 vs. 8.96 ± 2.98 mg/L, P < 0.001; ESR: 16.92 ± 5.61 vs. 19.34 ± 6.44 mm/h, P = 0.002), and lesion volume reduction was greater (60.12 ± 11.95% vs. 55.26 ± 12.48%, P = 0.002). Adverse event rates (10.26% vs. 25.00%, P = 0.003) and recurrence rates (7.89% vs. 29.03%, P = 0.001) were both significantly lower in the LIFU group. Conclusion: Low-intensity focused ultrasound monotherapy is associated with superior pain relief, greater improvement in quality of life, higher clinical response rates, and a more favorable safety profile than corticosteroid injections in patients with IGM.

Keywords: Idiopathic granulomatous mastitis, low-intensity focused ultrasound, ultrasonic therapy, glucocorticoids, pain measurement, quality of life, retrospective studies

Introduction

Idiopathic Granulomatous Mastitis (IGM) is a chronic inflammatory breast disease that primarily affects women of childbearing age [1]. It is characterized histopathologically by non-caseating granulomas centered on lobules and clinically by painful, often progressive breast masses, abscess formation, and sinus tract development [2]. Although the exact etiology remains uncertain, the pathological hallmark is a sterile inflammatory infiltrate suggesting a dysregulated local immune response. The persistent pain, recurrent drainage, and breast deformity impose a substantial physical and psychological burden, markedly impairing health-related quality of life [3]. Despite the non-malignant nature of the disease, patients frequently endure prolonged morbidity due to the paucity of targeted and well-tolerated therapeutic options. Consequently, identifying treatments that combine effective inflammation

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control with a favorable impact on pain and daily functioning represents an urgent clinical priority.

Intralesional corticosteroid injections are currently regarded as the first-line pharmacological intervention for IGM, suppressing the aberrant inflammatory cascade and inducing remission in a considerable proportion of cases [4]. However, the high doses and prolonged courses required for disease control are invariably accompanied by dose- and time-dependent adverse effects, including cushingoid features, weight gain, hyperglycemia, and insomnia, which themselves undermine quality of life [5]. Furthermore, a substantial subset of patients experience relapse during tapering or after discontinuation, often necessitating repeated treatment cycles and accumulating toxicity [6]. Pain relief with corticosteroids is gradual, and some patients continue to report clinically significant pain even while on therapy [7]. These realities underscore the limitations of conventional hormone therapy and motivate the search for alternative strategies that uncouple anti-inflammatory efficacy from systemic toxicity.

Low-intensity focused ultrasound (LIFU) has emerged as a non-invasive physical modality capable of modulating tissue inflammation [8]. Preclinical evidence indicates that LIFU can attenuate pro-inflammatory signaling pathways, downregulate cytokines such as interleukin-6, and promote tissue repair by enhancing microcirculation and clearing inflammatory debris. In clinical settings, LIFU has been explored in various musculoskeletal and soft-tissue inflammatory conditions, where it reduced pain and improved function with an excellent safety profile [9]. The biological rationale for applying LIFU to IGM is compelling: the focused ultrasound energy, which generates both localized hyperthermia and mechanical effects, can be precisely delivered to the inflamed breast parenchyma, potentially alleviating pain through heat-induced modulation of sensory nerve endings and acceleration of inflammatory resolution, while avoiding the hormonal and metabolic disturbances inherent to systemic glucocorticoids [10]. Nevertheless, clinical data directly comparing LIFU monotherapy with standard corticosteroid regimens are lacking, and whether LIFU provides comparable or superior relief of pain and quality-of-life impairment remains unknown.

The present study was therefore designed to compare low-intensity focused ultrasound monotherapy with intralesional corticosteroid therapy in patients with histopathologically confirmed IGM, specifically focusing on the trajectory of pain relief and health-related quality-of-life outcomes.

Methods

Patients

Approval for this retrospective cohort investigation was obtained from the institutional ethics committee of the Fourth Hospital of Shijiazhuang (No.20220135). Given the retrospective nature of the research, the need to obtain written informed consent was waived. We retrospectively reviewed the medical records of patients diagnosed with Idiopathic granulomatous mastitis (IGM) at the Fourth Hospital of Shijiazhuang between September 2021 and December 2025. A total of 241 patients met the following inclusion criteria: (1) Histopathologically confirmed diagnosis of IGM by core needle biopsy; (2) Absence of specific infectious causes (tuberculosis, fungal infection, etc.); (3) No prior corticosteroid or focused ultrasound treatment before enrollment; (4) Complete clinical records available for the 12-month follow-up period. Exclusion criteria were: (1) Concomitant breast malignancy; (2) Pregnancy or lactation; (3) History of autoimmune diseases requiring concurrent systemic immunosuppressive therapy; (4) Active systemic infection. Based on the treatment they received, patients were assigned to the hormone group (n = 124, treated with intralesional corticosteroid injections) or the ultrasound group (n = 117, treated with low-intensity focused ultrasound monotherapy) (**Figure 1**).

Diagnostic evaluation and baseline assessment

All patients underwent comprehensive baseline assessment, including breast ultrasound examination and core needle biopsy for histopathological confirmation. B-mode ultrasound imaging was performed using a dedicated automated breast ultrasound system (ACUSON Oxana2; Siemens Medical Solutions USA, Mountain View, CA, USA). Lesions were classified according to a standardized B-mode ultrasound typing system: Type I: ill-defined hypoechoic mass without internal fluid or sinus

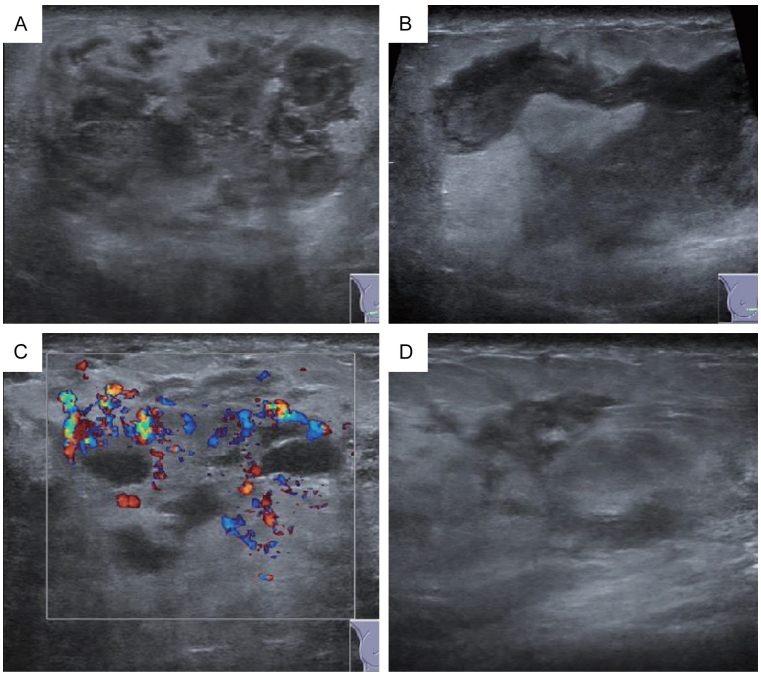

Figure 1. Representative B-mode ultrasound images at baseline and week 12 in both treatment groups. A. Hormone group at baseline; B. LIFU group at baseline; C. Hormone group at week 12; D. LIFU group at week 12.

tract; Type II: irregular hypoechoic lesion with internal fluid collections (abscess formation); Type III: complex lesion with multiple sinus tracts extending to the skin or ductal system [11]. Maximum lesion diameter was measured in the plane showing the largest extent of the mass, with values averaged across two independent sonographer assessments. Lesion number was categorized as solitary (single lesion) or multiple (two or more distinct lesions).

Demographic and clinical data collected at baseline included age, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), disease duration (months from symptom onset to diagnosis), affected side (left, right, or bilateral), clinical presentation (palpable mass, abscess, ulceration, sinus tract formation), history of pregnancy, smoking history, and alcohol consumption.

Pain assessment

Pain severity was assessed using the Visual Analog Scale (VAS) [12]. Patients were instructed to mark their current pain level on a standard 10-cm horizontal line, anchored by "0" (no pain) on the left and "10" (worst imaginable pain) on the right. The distance (in cm) from the left anchor to the patient's mark was measured as the VAS score. VAS assessments were conducted at baseline and at weeks 2, 4, 8 and 12 post-treatment initiation. Pain relief rate was calculated as (baseline VAS - post-treatment VAS)/baseline VAS × 100%.

Quality of life assessment

Health-related quality of life was evaluated using the 36-Item Short Form Health Survey (SF-36) Chinese version [13, 14]. This validated instrument assesses eight dimensions of health. Its dimensions and item counts are as follows: physical functioning (PF), with 10 items; role limitations due to physical health (RP), with 4 items; bodily pain (BP), with 2 items; general health (GH), with 5 items; vitality (VT), with 4 items; social functioning (SF), with 2 items; role limitations due to emotional problems (RE), with 3 items; and mental health (MH), with 5 items. Each dimension score ranges from 0 (worst possible health state) to 100 (best possible health state). Chinese version of SF-36 has been previously validated in Chinese populations with satisfactory reliability and validity. The questionnaire was administered at baseline and at the 12-week follow-up (week 12) by trained interviewers using a standardized protocol.

Laboratory measurements

Blood samples were collected from all patients at baseline and at week 12 following an overnight fast. Samples were centrifuged at 3,000 rpm for 10 minutes, and serum was separated for immediate analysis or stored at -80°C for batched analysis within two weeks. C-reactive protein (CRP) and interleukin-6 (IL-6) levels were measured using a fluorescence immunochromatography assay kit (IL-6/CRP Triple Detection Kit; Shenzhen Jinzhun Bio-Medical Engineering Co., Ltd., Shenzhen, China; 20172401870). The lower limits of detection for CRP and IL-6 were 0.5 mg/L and 1.0 pg/mL, respectively. Erythrocyte sedimentation rate

(ESR) was determined using the Westergren method on whole blood samples collected in sodium citrate tubes (3.2% citrate). All laboratory measurements were performed in duplicate, and the mean values were recorded.

Therapeutic methods

Hormone group: Patients received local injections of triamcinolone acetonide (Chongqing Federal Pharmaceutical Co., Ltd., Chongqing, China; approval No. H20119867) at a dose of 40 mg per lesion. The injection was prepared by drawing 1 mL of triamcinolone acetonide into a 10 mL syringe and diluting it with 2 mL of 0.9% sodium chloride injection. Injections were administered into the hard and firm areas of the mass, directed towards different directions, in the periareolar region. The treatment was given twice weekly for a total course of 8 weeks, with follow-up assessments conducted up to week 12 per protocol.

Ultrasound group: Patients received low-intensity focused ultrasound (LIFU) monotherapy using a JC-focused ultrasound tumor therapeutic system (Chongqing Haifu Medical Technology Co., Ltd., Chongqing, China). Before the procedure, the skin overlying the lesion was prepared as follows: the treatment area was defatted with 75% alcohol gauze extending at least 8 cm beyond the lesion margin. Degassed water was then applied using a negative pressure aspirator connected to a degassing disc, with negative pressure maintained at -0.01 to -0.04 MPa for 3-8 seconds per spot until skin indentation was observed. The patient was placed in the prone position, and treatment was performed under conscious sedation analgesia. A dedicated ultrasound diagnostic system (DC-80S; Mindray Medical International Co., Ltd., Shenzhen, China) was used for real-time imaging guidance.

The focused ultrasound transducer operated at a frequency of 0.98 MHz with a focal length of 151 mm. The electrical driving power was set between 50 and 80 W (corresponding to a spatial-peak temporal-average intensity, ISPTA, of 1.2-2.8 W/cm^2, as calibrated by the manufacturer and verified by our institutional physics measurements). The ultrasound was generated with a pulse repetition frequency (PRF) of 100 Hz and a duty cycle of 10% (i.e., 10 ms on and 90 ms off within each cycle). A "point-by-point" irradiation strategy was applied following a duty cycle of 1 second on and 2 seconds off, repeated for 3 cycles at each focal point, before the transducer was moved to the next target. The total sonication time (net ultrasound emission time) ranged from 800 to 1500 seconds per session. The total energy density delivered per session was approximately 120-240 J/cm^2. The adopted parameters are well within the range commonly defined as low-intensity focused ultrasound (ISPTA < 10 W/cm^2) and are consistent with previous preclinical and clinical studies using LIFU for inflammatory and pain conditions, where the primary mechanisms are mild thermal and non-thermal mechanical effects rather than ablative thermal necrosis. The estimated focal temperature range (38-42°C) under these settings is based on manufacturer-provided theoretical calculations, verified by our institutional physics team using a hydrophone and thermocouple measurements in tissue-mimicking phantoms. Although the device is named as a tumor therapeutic system, in this study it was configured and operated in a dedicated low-power, non-ablative mode, which is distinct from its high-intensity ablation mode. All patients received one focused ultrasound session per month for three months, totaling three sessions. No concurrent systemic corticosteroid therapy was administered in the ultrasound group.

Follow-up and outcome measures

All patients were followed for 12 months after treatment initiation. The primary and secondary efficacy endpoints (VAS, SF-36, clinical response, inflammatory markers, and lesion characteristics) were evaluated at baseline and at week 12. The extended 12-month follow-up was specifically designed to capture late recurrences and long-term safety outcomes.

Primary outcomes. (1) Pain intensity, assessed using VAS at all scheduled visits. (2) Health-related quality of life, assessed using SF-36 at baseline and week 12.

Secondary outcomes. (1) Clinical efficacy evaluated at week 12 according to predefined criteria: complete remission (CR) defined as complete resolution of all clinical symptoms and ultrasound findings; partial remission (PR) defined as ≥ 50% reduction in lesion diameter or clinical improvement without complete reso-

lution; stable disease (SD) defined as < 50% reduction in lesion diameter or no change in clinical symptoms; progressive disease (PD) defined as increase in lesion diameter or any disease progression requiring treatment adjustment. Overall response rate (ORR) was calculated as CR+PR. (2) Inflammatory markers (CRP, ESR, IL-6) measured at baseline and week 12. (3) Ultrasound lesion characteristics, including maximum lesion diameter and lesion volume reduction rate, assessed at baseline and week 12. Lesion volume was calculated using the ellipsoid formula: volume = π × (width × height × depth)/6, where width, height, and depth were measured in orthogonal planes on ultrasound. Volume reduction rate was calculated as (baseline volume-week 12 volume)/baseline volume × 100%. (4) Adverse events (AEs), including corticosteroid-related systemic AEs (cushingoid features, weight gain, hyperglycemia, epigastric discomfort, arthralgia, insomnia) and LIFU-related local AEs (skin reactions at the treatment site). All AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). Attribution of adverse events was determined by two independent investigators based on temporal association and known pharmacological/physical profiles, using categories of "related", "possibly related", "unlikely related", and "unrelated". Serious adverse events (SAEs) were defined as any event leading to hospitalization, prolonged hospitalization, or life-threatening complications. (5) Recurrence was defined as the reappearance of IGM lesions (clinically or ultrasound-confirmed) on the ipsilateral or contralateral breast after initial complete remission (CR). For patients who achieved only partial remission (PR), subsequent disease progression was not classified as recurrence but as progressive disease, and was analyzed separately. Recurrences requiring retreatment were also recorded.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as frequencies and percentages. Comparisons between the two groups were performed using independent-samples t-test for continuous variables and chi-square test (or Fisher's exact test when expected cell counts < 5) for categorical variables. Normality of continuous variables was assessed using the Shapiro-Wilk test. For comparisons of the eight SF-36 domain scores between groups at week 12, we applied a Bonferroni correction to control the family-wise error rate; a $P < 0.00625$ (0.05/8) was therefore considered statistically significant for these specific analyses. For longitudinal data involving multiple time points (e.g., VAS scores at weeks 0, 2, 4, 8, and 12), repeated-measures ANOVA with Bonferroni post-hoc tests was used for between-group comparisons over time. For each group, changes from pre- to post-treatment were examined using paired-samples t tests. To identify independent factors associated with the primary efficacy outcomes while adjusting for potential confounding, multivariable logistic regression analyses were performed. Two separate binary outcomes were modeled: (1) overall response (ORR, defined as complete remission plus partial remission) at week 12, and (2) any recurrence during follow-up period. Given the limited number of recurrence events, a parsimonious model was employed for recurrence analysis, retaining only the most clinically relevant covariates (treatment group, baseline maximum lesion diameter, lesion number, and sinus tract formation) to minimize overfitting. For the ORR analysis, which had a larger number of events, a more comprehensive set of covariates (including age, BMI, disease duration, lesion diameter, lesion number, abscess, and sinus tract) was included. Baseline maximum lesion diameter was dichotomized at ≥ 5 cm versus < 5 cm. This cutoff was selected based on previous studies in idiopathic granulomatous mastitis, which have identified 5 cm as a clinically meaningful threshold associated with worse treatment outcomes and higher recurrence risk [15]. Results are reported as adjusted odds ratios (aOR) with 95% confidence intervals (CI). A two-tailed $P < 0.05$ was considered statistically significant for all analyses. Statistical analyses were conducted using SPSS version 29.0 (IBM Corp., Armonk, NY, USA) with guidance from a professional medical statistician.

Results

Baseline demographic and lesion characteristics of all patients

The hormone and ultrasound groups did not differ significantly with respect to demographic or lesion characteristics at baseline (all $P > 0.05$, **Table 1**). Age, BMI, disease duration, dis-

Table 1. Comparison of baseline demographic and lesion characteristics between the two groups

Parameters	Hormone group (n = 124)	Ultrasound group (n = 117)	t/χ^2	P
Age (years)	33.45 ± 5.02	34.12 ± 5.51	0.995	0.321
BMI (kg/m^2)	23.68 ± 2.35	23.91 ± 2.48	0.742	0.459
Disease duration (months)	3.52 ± 0.96	3.48 ± 0.92	0.383	0.702
Affected side [n (%)]			0.006	0.997
Left	54 (43.55)	51 (43.59)		
Right	58 (46.77)	55 (47.01)		
Bilateral	12 (9.68)	11 (9.40)		
Lesion number [n (%)]			0.071	0.790
Solitary	71 (57.26)	65 (55.56)		
Multiple	53 (42.74)	52 (44.44)		
Maximum lesion diameter (cm)	4.12 ± 1.02	4.05 ± 0.98	0.600	0.549
Clinical presentation [n (%)]				
Palpable mass	102 (82.26)	97 (82.91)	0.018	0.895
Abscess	38 (30.65)	35 (29.91)	0.015	0.902
Ulceration	21 (16.94)	18 (15.38)	0.107	0.744
Sinus tract formation	15 (12.10)	13 (11.11)	0.057	0.811
B-mode ultrasound classification [n (%)]			0.002	0.999
I	31 (25.00)	29 (24.79)		
II	57 (45.97)	54 (46.15)		
III	36 (29.03)	34 (29.06)		
History of pregnancy [n (%)]	86 (69.35)	80 (68.38)	0.027	0.870
Smoke history [n (%)]	8 (6.45)	6 (5.13)	0.193	0.661
Alcohol consumption [n (%)]	15 (12.10)	13 (11.11)	0.057	0.811

Abbreviation: BMI, Body Mass Index.

Table 2. Repeated measures ANOVA results for VAS pain scores over 12 weeks

Source	SS	df	MS	F	P
Group	156.42	1	156.42	12.873	< 0.001
Time	892.56	4	223.14	18.367	< 0.001
Group × Time	97.38	4	24.35	8.724	< 0.001
Error (within)	116.28	956	0.122		

Abbreviations: SS, sum of squares; df, degrees of freedom; MS, mean square.

tribution of affected side, lesion number, maximum lesion diameter, clinical presentation, B-mode ultrasound classification, history of pregnancy, smoking status, and alcohol consumption were all comparable between the two cohorts.

Changes in pain VAS score

Pain scores on the visual analog scale were similar at baseline (P = 0.761). Repeated measures ANOVA revealed a significant group × time interaction (F = 8.724, P < 0.001), indicating that the two groups exhibited different trajectories of pain reduction over the 12-week period (**Table 2**). A significant between-group difference emerged as early as week 2 and was maintained at every subsequent assessment, with patients in the ultrasound group consistently reporting lower pain levels (week 2: t = 4.527, P < 0.001; week 4: t = 5.375, P < 0.001; week 8: t = 6.257, P < 0.001; week 12: t = 6.380, P < 0.001) (Bonferroni post-hoc tests; **Figure 2**).

Health-related quality of life

Baseline SF-36 scores across all eight domains were comparable between the groups (all P > 0.05). At week 12, the ultrasound group demonstrated better health-related quality of life than the hormone group across all eight SF-36 domains. After Bonferroni correction for multiple comparisons (threshold P < 0.00625), the differences remained statistically significant

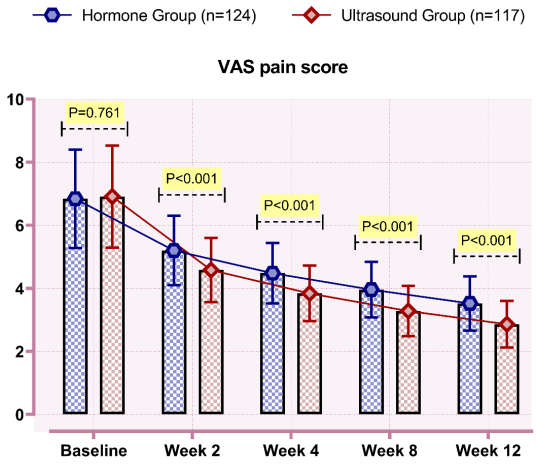

Figure 2. Comparison of VAS pain score before and after therapy between two groups. Abbreviation: VAS, Visual Analog Scale.

(all P < 0.001) for Physical Functioning (t = 5.470), Role-Physical (t = 6.473), Bodily Pain (t = 9.874), Vitality (t = 4.017), Social Functioning (t = 4.318), and Role-Emotional (t = 4.270). The differences for General Health (P = 0.042) and Mental Health (P = 0.013) did not reach the corrected significance threshold, though they showed a consistent trend favoring the LIFU group (**Table 3**).

Inflammatory markers

Pretreatment concentrations of CRP, ESR, and IL-6 did not differ between the groups (CRP: P = 0.548; ESR: P = 0.612; IL-6: P = 0.770). After 12 weeks, the ultrasound group exhibited significantly greater reductions in all three markers (CRP: t = 5.336, P < 0.001; ESR: t = 3.106, P = 0.002; IL-6: t = 3.262, P = 0.001) (**Table 4**).

Clinical efficacy

The pattern of clinical response differed significantly between the two treatments (χ^2 = 8.329, P = 0.040). The overall response rate (complete plus partial remission) was significantly higher with low-intensity focused ultrasound than with hormone therapy (χ^2 = 6.229, P = 0.013). Disease progression was observed in both groups but was less frequent in the ultrasound cohort (**Table 5**).

Lesion characteristics on ultrasound

Maximum lesion diameter was similar at baseline (P = 0.549). By week 12, patients treated with ultrasound had a significantly smaller residual lesion diameter (t = 3.022, P = 0.003) and a greater lesion volume reduction rate (t = 3.088, P = 0.002) compared with those receiving corticosteroids (**Figure 3**).

Adverse events

Adverse events were significantly less common in the ultrasound group (χ^2 = 8.927, P = 0.003). Specifically, cushingoid features (χ^2 = 9.937, P = 0.002), hyperglycemia (P = 0.046), and arthralgia (χ^2 = 4.701, P = 0.030) occurred more frequently in the hormone group, whereas self-limited skin reactions at the treatment site were observed only in ultrasound group (P = 0.032). No notable between-group differences were observed for weight gain ≥ 5%, epigastric discomfort, and insomnia (all P > 0.05). Serious adverse events were rare and occurred at similar rates in both groups (P = 0.960) (**Table 6**). All AEs were Grade 1-2 according to CTCAE v5.0; no Grade 3 or higher events were observed. Systemic adverse reactions in the corticosteroid group (e.g., hyperglycemia, cushingoid features) were considered treatment-related based on the known systemic absorption profile of locally injected triamcinolone acetonide. Skin reactions in the LIFU group were mild erythema or transient local warmth (Grade 1), all of which resolved spontaneously without intervention.

Analysis of recurrence between the two groups

Over the follow-up period, the ultrasound group had a significantly lower overall recurrence rate than the hormone group (χ^2 = 10.619, P = 0.001). This advantage was evident for ipsilateral recurrence (χ^2 = 7.364, P = 0.007), while contralateral recurrence was infrequent and did not differ between groups (P = 0.251). Retreatment for recurrent disease was required significantly less often in the ultrasound cohort (χ^2 = 5.397, P = 0.020) (**Table 7**).

Multivariable analysis of factors associated with ORR and recurrence

Multivariable logistic regression was performed to examine variables independently associated with ORR and disease recurrence after adjusting for potential confounders (**Tables 8** and **9**). As shown in **Table 8**, LIFU treatment remained significantly linked to higher odds of achieving

Table 3. Comparison of SF-36 domain scores before and after therapy between the two groups

Parameters	Hormone group (n = 124)	Ultrasound group (n = 117)	t/χ^2	P
PF				
Baseline	62.35 ± 8.96	61.97 ± 9.12	0.327	0.744
Week 12	76.48 ± 6.85	81.23 ± 6.60	5.470	< 0.001**
RP				
Baseline	47.28 ± 7.85	46.94 ± 7.91	0.326	0.745
Week 12	65.32 ± 6.37	70.56 ± 6.18	6.473	< 0.001**
BP				
Baseline	41.76 ± 6.94	41.32 ± 7.03	0.485	0.628
Week 12	62.45 ± 5.98	69.84 ± 5.63	9.874	< 0.001**
GH				
Baseline	58.46 ± 7.42	58.12 ± 7.51	0.356	0.722
Week 12	68.72 ± 6.25	70.35 ± 6.12	2.044	0.042
VT				
Baseline	53.12 ± 6.85	52.86 ± 6.92	0.285	0.776
Week 12	64.38 ± 5.94	67.42 ± 5.81	4.017	< 0.001**
SF				
Baseline	59.84 ± 7.23	59.56 ± 7.31	0.305	0.761
Week 12	70.52 ± 6.08	73.86 ± 5.92	4.318	< 0.001**
RE				
Baseline	51.08 ± 7.44	50.74 ± 7.49	0.359	0.720
Week 12	67.96 ± 6.10	71.28 ± 5.96	4.270	< 0.001**
MH				
Baseline	56.92 ± 6.73	56.68 ± 6.79	0.280	0.780
Week 12	68.25 ± 5.85	70.12 ± 5.72	2.515	0.013

Abbreviations: SF-36, 36-Item Short Form Health Survey; PF, Physical Functioning; RP, Role-Physical; BP, Bodily Pain; GH, General Health; VT, Vitality; SF, Social Functioning; RE, Role-Emotional; MH, Mental Health. **p-values remained significant after Bonferroni correction (threshold P < 0.00625) for all domains except GH (P = 0.042) and MH (P = 0.013).

Table 4. Comparison of inflammatory markers before and after therapy between the two groups

Parameters	Hormone group (n = 124)	Ultrasound group (n = 117)	t/χ^2	P
CRP (mg/L)				
Baseline	24.56 ± 7.32	25.13 ± 7.45	0.601	0.548
Week 12	8.96 ± 2.98	7.12 ± 2.37	5.336	< 0.001
ESR (mm/h)				
Baseline	38.42 ± 11.06	39.15 ± 11.21	0.507	0.612
Week 12	19.34 ± 6.44	16.92 ± 5.61	3.106	0.002
IL-6 (pg/mL)				
Baseline	15.87 ± 4.43	16.04 ± 4.51	0.293	0.770
Week 12	6.73 ± 2.22	5.85 ± 1.94	3.262	0.001

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6.

ORR (aOR = 3.24, 95% CI: 1.50-7.01, P = 0.003) after controlling for age, BMI, disease duration, baseline lesion diameter, lesion number, abscess, and sinus tract. Baseline maximum lesion diameter ≥ 5 cm (aOR = 0.48, 95% CI: 0.25-0.92, P = 0.027) and the presence of sinus tracts (aOR = 0.38, 95% CI: 0.17-0.85, P = 0.019) were independently linked to reduced overall response.

For recurrence analysis (**Table 9**), given the limited number of events, only four core covariates were included. LIFU treatment was independently linked to reduced odds of recurrence (aOR = 0.29, 95% CI: 0.11-0.76, P = 0.012). Other covariates did not reach statistical significance in this parsimonious model.

Discussion

This study compared low-intensity focused ultrasound monotherapy with intralesional corticosteroid treatment in patients with IGM, revealing consistent advantages of LIFU across the dimensions of pain control, health-related quality of life, inflammatory burden, clinical response, safety, and recurrence. The findings suggest that LIFU may represent a promising alternative that provides effective disease modulation while circumventing the systemic toxicity inherent to prolonged corticosteroid exposure.

Pain relief occurred earlier and was more pronounced with LIFU than with corticosteroids. The between-group difference in pain intensity emerged as early as the second week and

Table 5. Comparison of clinical efficacy at week 12 between the two groups

Parameters	Hormone Group (n = 124)	Ultrasound Group (n = 117)	χ^2	P
Overall clinical response [n (%)]			8.329	0.040
CR	62 (50.00)	76 (64.96)		
PR	42 (33.87)	34 (29.06)		
SD	14 (11.29)	5 (4.27)		
PD	6 (4.84)	2 (1.71)		
ORR [n (%)]	104 (83.87)	110 (94.02)	6.229	0.013

Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; ORR, overall response rate (CR+PR).

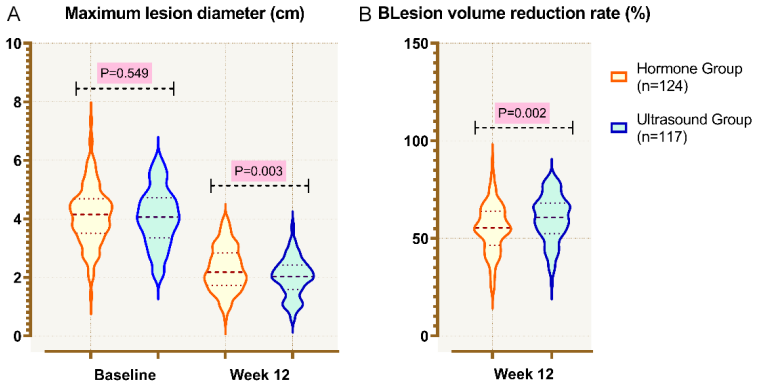

Figure 3. Comparison of lesion characteristics on ultrasound at week 12 between two groups. A. Maximum lesion diameter (cm); B. Lesion volume reduction rate (%).

persisted throughout the 12-week observation period. This rapid analgesic effect likely reflects the combined biophysical actions of LIFU. The mild thermal effect generated by low-intensity focused ultrasound can raise local tissue temperature to a range that is sufficient to modulate sensory nerve conduction and suppress the release of pro-inflammatory and algogenic mediators (e.g., prostaglandin E2, substance P) from activated immune cells, without causing wholesale coagulative necrosis [16, 17]. In parallel, non-thermal mechanical effects-including acoustic streaming and stable cavitation-may directly disrupt inflammatory cell aggregates and facilitate the clearance of necrotic debris and bacterial antigens [18]. This dual mechanism explains the prompt pain relief observed as early as week 2. In clinical series of tendinopathy and arthritis, similar ultrasound protocols were associated with prompt pain reduction, consistent with the trajectory observed here [19, 20]. Corticosteroids, by contrast, require time to reach intracellular glucocorticoid receptors and alter gene transcription, which may account for the relatively slower onset of analgesia [21]. Moreover, the persistent nociceptive input from residual abscess collections or sinus tracts - which respond poorly to systemic immunosuppression alone - may continue to drive pain in corticosteroid-treated patients, whereas the thermal and mechanical actions of LIFU can physically open abscess cavities and sinus tracts, facilitating drainage and decompressing inflamed tissue planes [18].

At the 12-week follow-up, LIFU recipients showed uniformly better health-related quality-of-life gains, as evidenced by superior scores on each of the eight SF-36 subscales. Notably, six of the eight domains (PF, RP, BP, VT, SF, RE) reached statistical significance after correction for multiple comparisons. The advantages were particularly striking in bodily pain, physical role functioning, and social functioning. This pattern corresponds to the effective pain relief and the avoidance of corticosteroid-related adverse effects that compromise daily activities and emotional well-being. Corticosteroid therapy, even when anti-inflammatory, frequently leads to cushingoid appearance, weight gain, sleep disturbance, and mood lability, all of which are known to erode quality-of-life scores independently of the primary disease [22, 23]. The LIFU cohort was spared these systemic burdens, which plausibly explains the superior performance in vitality, mental health, and emotional role domains. Previous quality-of-life assessments in women with non-malignant breast conditions have indicated that body image and psychological distress are prominent concerns; the absence of metabolic and cosmetic side effects makes physical modalities particularly attractive in this population [24].

Table 6. Comparison of adverse events between the two groups [n (%)]

Parameters	Hormone Group (n = 124)	Ultrasound Group (n = 117)	χ^2	P
Any adverse event	31 (25.00)	12 (10.26)	8.927	0.003
Cushingoid features	12 (9.68)	0 (0.00)	9.937	0.002
Weight gain ≥ 5%	10 (8.06)	3 (2.56)	3.569	0.059
Hyperglycemia	6 (4.84)	0 (0.00)	Fisher's	0.046
Epigastric pain	6 (4.84)	2 (1.71)	Fisher's	0.319
Arthralgia	9 (7.25)	1 (0.85)	4.701	0.030
Insomnia	8 (6.45)	2 (1.71)	2.316	0.128
Skin reactions at treatment site	0 (0.00)	6 (5.12)	Fisher's	0.032
Serious adverse events	2 (1.61)	1 (0.85)	Fisher's	0.960

"Any adverse event" represents the number of patients who experienced at least one adverse event, not the sum of individual event frequencies (as one patient may have multiple events). Fisher's exact test was used for 2×2 comparisons where expected cell count < 5.

Table 7. Comparison of recurrence between the two groups

Parameters	Hormone Group (n = 124)	Ultrasound Group (n = 117)	t/χ^2	P
Recurrence	CR (n = 62)	CR (n = 76)		
Any recurrence [n (%)]	18 (29.03)	6 (7.89)	10.619	0.001
Ipsilateral recurrence [n (%)]	14 (22.58)	5 (6.58)	7.364	0.007
Contralateral recurrence [n (%)]	4 (6.45)	1 (1.32)	Fisher's	0.251
Recurrence requiring retreatment [n (%)]	14 (11.29%)	4 (3.42%)	5.397	0.020

Abbreviations: CR, complete remission. Recurrence rates were calculated with the number of patients who achieved CR as the denominator, as recurrence was defined only after initial complete remission. Retreatment rates were calculated with the total number of patients in each group as the denominator, as retreatment could be required regardless of initial response status. Fisher's exact test was used for 2×2 comparisons where expected cell count < 5.

Table 8. Multivariable logistic regression analysis of factors associated with ORR

Variables	Category/Unit	aOR (95% CI)	P
Treatment group	LIFU vs. Hormone	3.24 (1.50-7.01)	0.003
Age	Per 1-year increase	0.98 (0.93-1.04)	0.512
BMI	Per 1 kg/m^2 increase	0.97 (0.88-1.06)	0.489
Disease duration	Per 1-month increase	0.92 (0.70-1.21)	0.552
Max lesion diameter	≥ 5 cm vs. < 5 cm	0.48 (0.25-0.92)	0.027
Lesion number	Multiple vs. Solitary	0.74 (0.38-1.42)	0.365
Abscess	Present vs. Absent	0.67 (0.34-1.32)	0.252
Sinus tract	Present vs. Absent	0.38 (0.17-0.85)	0.019

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; LIFU, low-intensity focused ultrasound; ORR, overall response rate (CR+PR).

Table 9. Multivariable logistic regression analysis of factors associated with recurrence

Variables	Category/Unit	aOR (95% CI)	P
Treatment group	LIFU vs. Hormone	0.29 (0.11-0.76)	0.012
Max lesion diameter	≥ 5 cm vs. < 5 cm	1.67 (0.78-3.57)	0.187
Lesion number	Multiple vs. Solitary	1.42 (0.63-3.19)	0.399
Sinus tract	Present vs. Absent	2.11 (0.82-5.42)	0.122

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; BMI, body mass index; LIFU, low-intensity focused ultrasound.

The greater reductions in circulating CPR, ESR, and IL-6 in the LIFU group indicate that localized ultrasound application exerts a measurable systemic anti-inflammatory effect. As discussed above, the thermal and non-thermal effects of LIFU contribute to the modulation of inflammatory responses [25, 26]. These laboratory findings align with the sonographic evidence of greater lesion volume reduction and smaller residual diameters in the LIFU group, supporting the notion that focused ultrasound treatment can remodel granulomatous tissue without pharmacological immunosuppression [27].

Clinical response rates further distinguished the two approaches, with a higher proportion of complete remis-

sions and a lower likelihood of disease progression among LIFU-treated patients. The modest proportion of stable or progressive disease despite corticosteroid therapy mirrors reports from other retrospective cohorts, where response heterogeneity has been attributed to variable drug penetration into fibrotic lesions, poor adherence due to side effects, and inherent glucocorticoid resistance in certain inflammatory cell subsets [28, 29]. Ultrasound, by delivering energy directly to the lesion margin, may overcome some of these barriers and interrupt the cycle of fistula formation that perpetuates the disease [30].

The safety profile of LIFU proved favorable: fewer patients experienced any adverse event, and the hormonal-metabolic complications typical of corticosteroids-hyperglycemia, cushingoid features, and arthralgia-were markedly less frequent [31]. Mild skin reactions at the transducer site were the only LIFU-specific events and resolved spontaneously, consistent with the safety record of therapeutic ultrasound when applied within recommended intensity limits. The rate of serious adverse events did not differ meaningfully between groups, underscoring the overall tolerability of both treatments in appropriately selected patients [32, 33].

Recurrence rates were lower after LIFU, and fewer patients in the ultrasound group required retreatment for relapsing disease [3]. This observation carries clinical importance, given that recurrent episodes compound psychological distress, prolong medical management, and increase the risk of breast deformity. The durability of the LIFU treatment effect might stem from a more thorough resolution of the local inflammatory microenvironment, as opposed to the suppressive rather than curative effect of corticosteroids, where disease activity frequently rebounds upon dose tapering [34]. The lower rate of ipsilateral recurrence is particularly notable, and the comparable contralateral recurrence rates argue against a merely constitutional predisposition toward granulomatous inflammation in one treatment arm.

It should be noted that while the LIFU parameters used in this study (50-80 W, 0.98 MHz) are lower than those employed for conventional tumor ablation, they still generate a measurable temperature rise (estimated focal temperature 38-42°C) that contributes to the therapeutic effect without causing widespread coagulative necrosis. Thus, the mechanism of action is best characterized as a low-power thermal therapy with adjunctive mechanical effects, rather than classical thermal ablation.

A few caveats should be considered. The single-center, retrospective design could have given rise to selection bias, and because randomization was not employed, unmeasured factors such as lesion duration, patient preferences, and physician experience could have influenced treatment allocation and outcomes. Follow-up was limited to 12 months, which may be insufficient to capture late recurrences or long-term sequelae such as breast atrophy and chronic sinus tract formation. Pain and quality-of-life assessments relied on patient-reported instruments that, while validated, remain subjective and susceptible to recall bias. The LIFU protocol involved one treatment session per month for three months; however, data on protocol standardization and healthcare resource utilization were not evaluated. Future research employing prospective randomized designs is warranted to verify these observations, establish optimal ultrasound parameters including frequency, intensity, and session duration, and determine whether combining LIFU with a short, low-dose corticosteroid course could achieve synergistic benefits while further minimizing toxicity. Longer surveillance and inclusion of patient-centered outcomes such as breast cosmesis and return to usual activities will refine the clinical role of LIFU in the management of IGM.

Conclusion

In this retrospective cohort investigation involving IGM patients, low-intensity focused ultrasound monotherapy was associated with more rapid and substantial pain relief, greater improvements across multiple domains of health-related quality of life, more favorable reductions in systemic inflammatory markers, higher clinical response rates, and lower rates of adverse events and recurrence when compared with intralesional corticosteroid therapy. These findings suggest that localized, low-intensity focused ultrasound energy, acting through a combination of mild thermal and non-thermal effects, can effectively control the inflammatory process underlying IGM while

eliminating the metabolic, hormonal, and psychological burdens that accompany prolonged corticosteroid exposure. The durable response and favorable safety profile support low-intensity focused ultrasound as a promising first-line alternative that may shift the therapeutic paradigm away from immunosuppressive pharmacotherapy toward targeted physical modulation. Future Randomized controlled studies with extended follow-up are needed to corroborate these findings, determine optimal treatment parameters, and evaluate the potential role of combination strategies.

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Disclosure of conflict of interest

None.

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