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ORIGINAL ARTICLE / ÖZGÜN MAKALE

A CHALLENGING ENTITY IN THE DIFFERENTIAL DIAGNOSIS OF BREAST CANCER: A RETROSPECTIVE ANALYSIS OF 17 CASES WITH GRANULOMATOUS LOBULAR MASTITIS

MEME KANSERİNİN AYIRICI TANISINDA ZOR BİR DURUM: GRANULOMATOZ LOBULER MASTİTLİ 17 OLGUNUN RETROSPEKTİF ANALİZİ

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ABSTRACT

Objective: Granulomatous lobular mastitis (GLM) is a rare and benign disorder of the breast, of unknown etiology. Differential diagnosis by radiological and clinical evaluation remains uncertain. There is no optimal treatment for this disorder. In this study, we aimed to analyze 17 cases with GLM retrospectively with the help of clinical and radiologic studies and to give detailed information about outcomes.

Materials and Methods: A retrospective chart review of 17 consecutive patients with granulomatous lobular mastitis (GLM), who were treated in Kartal Education and Research Hospital between March, 2004 and January, 2011,was carried out in our study.

Results: All the cases were women of childbearing age, who had given birth and breastfed at least once. The most common causes for admission were; breast mass in 12 patients (70.6%) and pain in 12 (70.6%) cases. Five (29.4%) cases developed a fistula and four (23.5%) had abscess requiring drainage. Mammography was used for 10 (58.8%) cases, 12 (70.6%) were examined by MRI and all the patients were evaluated with ultrasound. Five (29.4%) cases were suspicious for malignancy prior to biopsies. Diagnoses of sixteen (94.1%) cases were established with tru-cut biopsy. Fourteen (82.3%) cases underwent wide local excision (WLE) following antibiotic therapy and/or drainage and 3 (17.6%) cases with diffuse disease also underwent wide local excision following therapy with antibiotics and/or drainage and steroids (prednisolone 32 mg bid). Complete remission was observed in one patient with diffuse disease who was referred to our clinic with excisional biopsy after steroid therapy (prednisolone 32 mg bid). Relapse developed in two (11.7%) cases in the end of thirty-six months of median follow-up. Both patients were treated with steroids (prednisolone 32 mg bid).

Conclusion: GLM is a benign disorder and has no widely accepted treatment. Wide local excision may be performed successfully in the management of GLM alone or following a steroid therapy in those patients with diffuse involvement.

Key words: Breast, granulomatous, lobular, mastitis, breast cancer

ÖZET

Amaç: Granulomatöz lobüler mastit (GLM) memenin etiolojisi bilinmeyen selim bir hastalığıdır. Klinik ve radyolojik olarak ayırıcı tanısı zordur. Optimal bir tedavisi yoktur. Bu çalışmada klinik ve radyolojik çalışmaların ışığında granulomatöz lobüler mastit tanısı ile tedavi edilen 17 olgu retrospektif olarak incelendi.

Yöntem ve Gereçler: Mart 2004-0cak 2011 tarihleri arasında genel cerrahi kliniğinde GLM tanısı ile tedavi edilen ardışık 17 hastanın dosyalarının retrospektif incelenmesi ile elde edilen bilgiler değerlendirildi.

Bulgular: Tüm hastalar daha önce doğum yapmış, emzirmiş ve doğurganlık çağında olan kadınlardı. En sık başvuru şikayeti 12 hastada (%70,6) memede kitle ve 12 hastada (%70,6) meme ağrısı idi. Beş (%29,4) hastada fistül ve 4 (%23,5) hastada drenaj gerektiren apse gelişti. On (%58,8) hastaya mamografi, 12 (%70,6) hastaya manyetik rezonans görüntüleme ve tüm hastalara ultrasonografik inceleme yapıldı. Beş (%29,4) hastanın biyopsi öncesi tanısı meme kanseri şüpesi idi. 16 hastanın (%94,1) tanısı tru-cut biyopsi ile kondu. Üç (%17,6) hasta yaygın tutulum nedeni ile antibiyotik ve/veya drenaj ve steroid (prednizolon 32 mg bid) tedavisi sonrası, 14 (%82,3) hasta antibioterapi ve/veya drenaj sonrası Geniş Local Eksizyon (GLE) ile tedavi edildiler. Kliniğimize eksizyonal biyopsi yapılarak gönderilen bir hastada steroid (prednizolon 32 mg bid) tedavisi sonrası tam remisyon gözlendi. Otuz altı aylık median takip sonunda nüks gelişen iki (%11,7) olgu steroid ile tedavi edildiler.

Sonuç: GLM zor tanı konulabilen ve yaygın kabul görmüş bir tedavisi olmayan selim bir meme hastalığıdır. Geniş local eksizyon uygun olgularda tek başına, yaygın tutulumu olan olgularda ise steroid tedavisi sonrası başarı ile uygulanabilir.

Anahtar sözcükler: Meme, granulomatöz, lobüler, mastit, meme kanseri

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Two types of granulomatous mastitis (GM) have been defined; specific and idiopathic. Specific granulomatous mastitis arises as a result of tuberculosis, sarcoidosis, and mycotic and parasitic infections of the breast. Idiopathic granulomatous mastitis (IGM) or granulomatous lobular mastitis (GLM) is a rare chronic inflammatory disorder of the breast of unknown etiology. GLM can mimic the clinical and radiologic characteristics of breast cancer, although it generally presents with findings including sinus formation and abscesses (1-5). Most of the patients are premenopausal women of childbearing age (1, 5). Pregnancy, lactation and use of oral contraceptives are predisposing factors (6-8). Alpha-1-antitrypsin deficiency and high levels of prolactin are reported in some patients diagnosed with GLM (9). It is discomforting for the patient and the physician with recurrent attacks up to a rate of 16-50% even under long term medical treatment (9-11). GLM generally affects only one breast, with involvement of all four quadrants (7, 12). It is generally characterized by chronic necrotizing granulomatous lobulitis around the ducts and lobules of the breast and formation of abscesses (8, 13, 14).

For management, drainage of abscesses, antibiotics, non-steroidal anti-inflammatory drugs, colchicine, methotrexate, steroids, wide local excision, and even mastectomy are recommended (1, 11, 15, 16). In this article, we wished to present our experiences regarding the treatment of GLM accompanied by the literature.

Materials and Methods

A retrospective chart review of consecutive patients with granulomatous lobular mastitis (GLM), who had been treated in our surgical department between March, 2004 and January, 2011, were conducted in this study. Medical histories of the cases were obtained by an inquiry including age, systemic concomitant disease, family history of breast disease, marital status, parity, time elapsed from the last delivery, duration of lactation, use of oral contraceptives, smoking history and presence of familial autoimmune diseases.

Clinicopathological data of the patients (symptoms and physical examination, diameter and location of the mass, complete blood count, sedimentation rate, C-reactive protein (CRP), ultrasound (US), mammography and magnetic resonance imaging (MRI) results, culture antibiogram, PPD skin test, chest radiograph, microscopic examination of the leakage and results of tru-cut or excisional biopsy) were retrospectively evaluated. Treatment modalities and their outcomes (antibiotics, anti-inflammatory agents, steroids, drainage of abscesses and surgical excision) were also retrospectively evaluated. All the cases with specific granulomatous mastitis (tuberculosis, sarcoidosis or parasitic and mycotic infections) were excluded from the study.

Written informed consent was obtained from the patients for publication of scientific material including patient pictures.

Results

Median age was 35 years (range, 17-46) in our study. All the cases were married, having given birth and breastfed at least once. Median number of live parity was 2 (range, 1-4), and the median time elapsed since the last delivery was 5 (range, 2-11) years. Median total lactation period was 14 months (range, 0-67). One case had been taking oral contraceptives regularly for 7 months. Four cases (23.5%) were smokers. One (5.9%) case had diabetes mellitus (DM) type II. One (5.9%) case had undergone drainage and antibiotic therapy 3 years previously in another center for non-puerperal breast abscess. Family history revealed breast cancer of the aunt (5.9%).

Most common reasons for admission were mass in the breast, pain, redness, leakage, and retraction of the areola in 12 (70.6%), 12 (70.6%), 8 (47.1%), 4 (23.5%), and 2 (12.3%) of the cases, respectively. Involvement of the breast was on the left in 9 (52.9%), and on the right in 8 (47.1%) of the cases. The opposite breast was not affected at all for any of the cases. The mean diameter of the mass in the breast was 4.2±2.6 cm (range 2-10 cm). Hyperemia and edema of the skin were present in nine (52.9%) cases (Figure 1A, B). Enlarged axillary lymph nodes were found in five (30%) cases. Areolar retraction was present in four (23.5%) cases. Four (23.5%) cases had fistula formation . Fluctuating masses consistent with an abscess were palpated and drained in four (23.5%) cases. Initial diagnosis before histopathologic examination was breast cancer in five (29.4%) of the patients in whom findings of physical examination and imaging were consistent with malignancy.

Ten (59%) of the cases over 35 years of age underwent mammography, while twelve (70.6%) were examined with MRI and US was performed for all cases in our study (Table 2).

The findings of mammography primarily indicated asymmetric density (Figure 2), mass with irregular margins, thickening of the skin, and enlarged axillary lymph nodes. Mammographic findings were considered as BIRADS 4 and BIRADS 5 in six and 2 cases, respectively (Table 2). A hypoechoic irregular mass, multiple adjacent abscess focuses with irregular hypoechoic masses, fistulized abscesses in the skin, enlarged axillary lymph nodes, and thickening of the skin were found in breast US (Table 2). Contrast enhancements in MRI studies were consistent with Type I (malignancy), borderline, and Type III (benign) in 5, 1, and 7 of the cases, respectively (Figure 3). Chest x-ray was normal in all the cases (Table 2).

Microbiological research was performed including studies for tuberculosis bacillus, fungi, aerobic and anaerobic organisms in the leakage material in the fistula orifice or in the drained abscess material. Coagulase-negative staphylococci were reproduced in five cases. No bacilli or fungi were detected in the specific staining (Gram, Ziehl-Neelsen, periodic acid-Schiff) for microorganisms. Tuberculin skin tests were inconsistent with tuberculosis for all cases.

Histopathologic diagnosis was established with tru-cut biopsy in 16 (94.1%) cases. One of the cases with masses comprising multiple cystic components had received GLM diagnosis 4 months previously in another center after an excisional biopsy. The diagnosis was confirmed by consulting the pathology material with the pathology clinic in our hospital and no further intervention was made for the histopathologic diagnosis.

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Histopathologic diagnosis was established by detecting no specific reasons except obliteration of the whole structure with a lobular core which shows the characteristics of non-caseous granulomatous inflammation. Epithelioid histiocytes, lymphocytes, plasma cells, leucocytes with polymorphic nuclei, and Langhans-type giant cells not accompanied by caseous necrosis were detected in all cases.

With regard totreatment results, most of the cases had received various doses of antibiotics for different durations before admittance to our outpatient clinic. Medical treatment including antibiotic therapy with amoxicillin, clavulonic acid or ampicillin sulbactam plus non-steroidal anti-inflammatory drugs (i.e., naproxen, diclofenac, ibuprofen) was administered for 14 days to 10 (58.8%) cases who had fistulas and findings of inflammation in the skin after drainage of existing abscesses. Eleven (64.7%) of the cases who had localized disease suitable for excision underwent excision, and oral prednisolone 32 mg/day was administered to two cases who were not suitable for basic cosmetic excision where at least two quadrants of the breast were affected and to 3 (17.6%) cases with masses larger than 8 cm. Complete remission was achieved with 6 months of steroid therapy in a case with diffuse

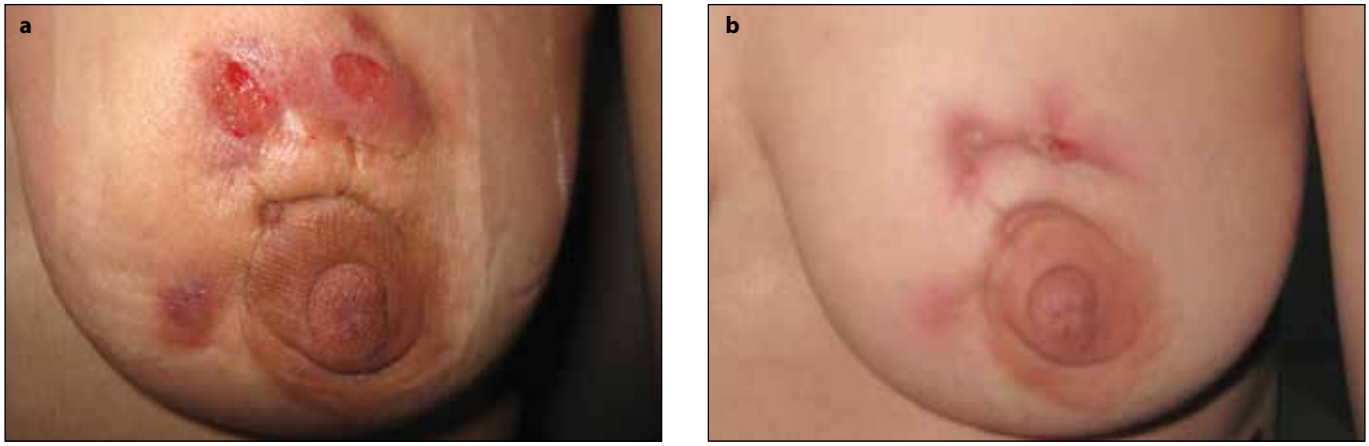

Figure 1. a) Appearance of the breast before treatment. **b)** Appearance of the breast after treatment

Table 1. Patient characteristics.

Age	*Number of pregnancy*	*Total breast feeding duration (months)*	*Oral contraceptives use*	*Complain*	*Pre-diagnosis*	*Management*	*Recurrens*
30	2	12	No	Discharge	Abscess/ GM	Drainage+wide excision	Yes
37	4	30	No	Mass	Malignancy?	Steroid+Wide excision	No
33	1	14	Yes	Painful mass	Mastitis/GM	Wide excision	Yes
41	3	28	in the past	Discharge	Malignancy	Steroid+Wide excision	No
35	0	0	in the past	Discharge	Abscess	Drainage+wide excision	No
29	1	7	No	Painful mass	Mastitis	Wide excision	No
42	3	28	No	Mass	Malignancy?	Wide excision	No
28	1	5	Yes	Discharge	Abscess	Drainage+wide excision	No
17	0	0	No	Painful mass	Mastitis	Wide excision	No
39	5	67	in the past	Painful mass	Mastitis	Wide excision	No
30	1	10	No	Mass	Malignancy?	Steroid+Wide excision	No
35	2	14	No	Painful mass	Mastitis	Wide excision	No
46	4	42	in the past	Painful mass	Mastitis	Wide excision	No
42	3	18	No	Painful mass	Abscess	Wide excision	No
38	3	44	No	Mass	Malignancy?	Wide excision	No
24	1	0	No	Painful mass	Mastitis	Wide excision	No
28	1	7	No	Pain, discharge	Abscess	Drainage+ Wide excision	No

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Table 2. Radiological findings of the patients.

Radiological Findings	*n*
Mammographic Findings:	10
Very dense breast tissue	3
Asymmetric density	4
Mass with irregular borders	2
Lobulated mass	1
Skin thickening	2
Axillary lymphadenomegaly	4
Ultrasound Findings:	16
Irregular hypoechoic mass	7
Multiple abscess foci and adjacent, irregular, hypoechoic masses	6
Abscesses adjacent to each other	2
Skin abscesses and fistulous	1
Axillary lymphadenomegaly	5
Skin thickening	7
Magnetic Resonance Findings:	12
Boundaries clearly cannot be selected mass-like enhancement	7
Enchancing heterogeneous contrast-enhancing lesions in the style of the round in areas	3
Enhancing heterogeneous areas	2
Nodular enchancement	2
Skin thickening	5
Axillary lymphadenomegaly	9
Retraction of nipple	2
Contrast Involvement:	
Type I (malignant)	5
Type II (borderline)	1
Type III (benign)	6

disease whose diagnosis was established in another center with excisional biopsy. Steroid could only be used for 3 weeks in a case who developed epigastric and joint pain. This case underwent wide local excision when a cosmetic excision was considered possible after detection of 40% regression through physical examination and US evaluations. Wide local excision is employed for another 3 (17.6%) cases in whom the extent of the disease and diameter of the mass became suitable for cosmetic excision after 6 to 8 weeks of steroid therapy. All the cases considered the appearance of their breasts cosmetically satisfactory after surgery. No further intervention was made in any patient for cosmetic reasons.

Median follow up time was 36 months (range, 5-56). No relapses were observed in those cases who were treated with steroids. Relapse developed in one case who underwent excision approximately at 5 months. Re-excision was made for this patient who rejected steroids treatment. This case is in the 11th month of follow up and has no problems. Persistent serous leakage developed in one case in the incision area after 2 months of excision. Edema and fluid was identified in the excision area in US. This case was considered as a relapse and the leakage was stopped after aspiration of the fluid and 3 weeks of prednisolone therapy. The case is in the 9th month of follow up and has no problems so far. The total ratio of relapse was estimated as 12%.

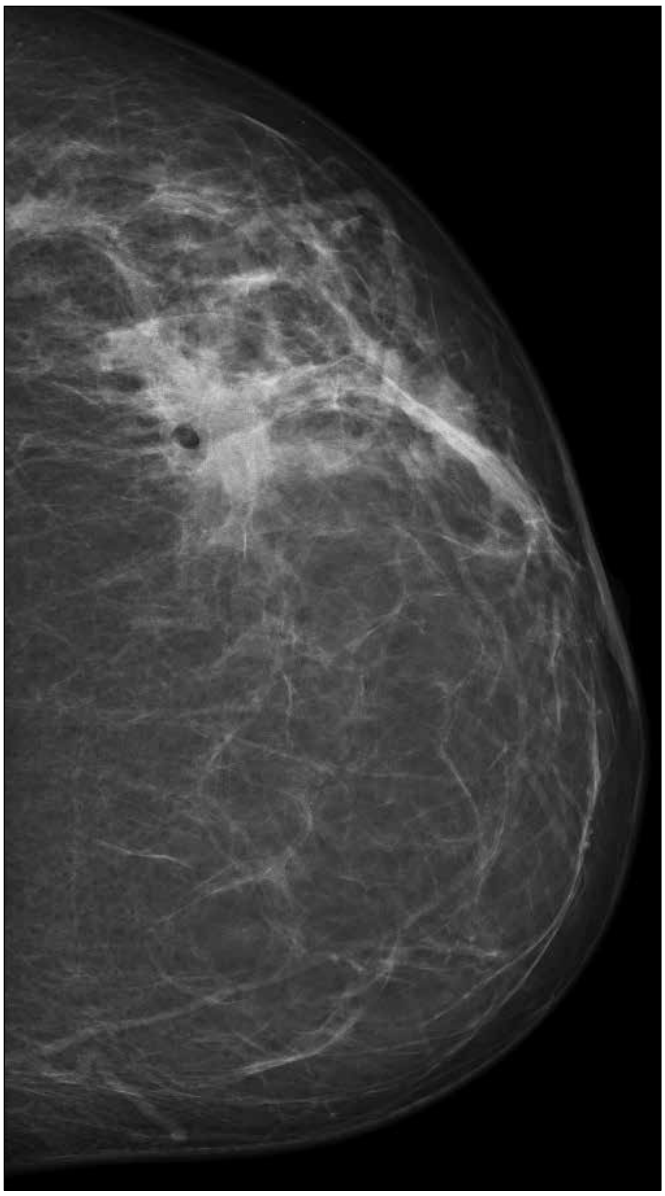

Figure 2. Mammographic imaging of the breast before treatment (cc)

Discussion and Conclusion

Granulomatous mastitis has two types called idiopathic (granulomatous lobular mastitis-GLM) and specific granulomatous mastitis (SGM). The SGM rate in Asian and African countries is 0.025%. Tuberculosis inflammation is established by histopathologic examination as well as bacterial and culture studies (17, 18). Sarcoidosis should be distinguished from GLM when seen in the breast. In addition, fungi infections including actinomycosis, histoplasmosis, blastomycosis, and parasitic infections such as filariasis and schistosomiasis are also associated

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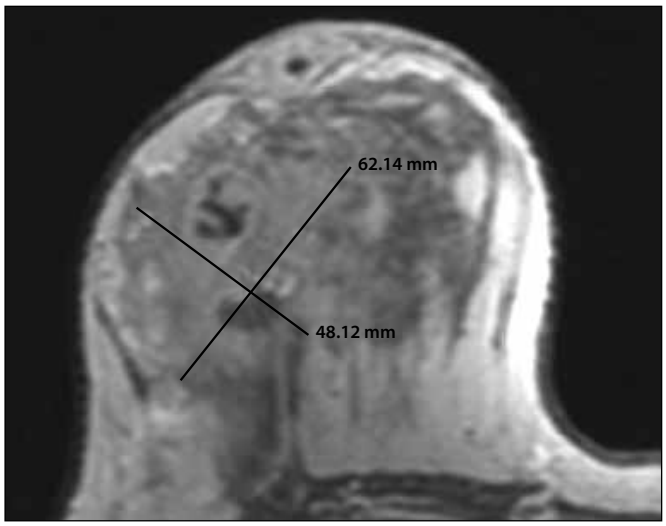

Figure 3. Magnetic resonance imaging of the breast before treatment

with granulomatous mastitis (19). Differential diagnosis should necessarily be made between GLM and SGM and the underlying agent should be treated in SGM. In this study, we assessed the diagnostic and treatment characteristics of our cases who were diagnosed with GLM, where the cases with SGM were excluded.

GLM is a rare, chronic, and benign disorder of the breast which can mimic the clinical and radiologic characteristics of breast cancer (2-4, 7). More than half of the patients are diagnosed with breast cancer until the histopathologic examination (1, 20). Indeed, some patients had been exposed to mastectomy following an incorrect diagnose of malignancy as a result of false positive FNAB (7, 21). Generally single breast involvement is seen, although bilateral breast involvement has been reported, and all four quadrants can be affected (4, 7, 8, 21, 22). In our study, single breast involvement was identified in all cases.

Though GLM is generally found in young women of childbearing age, the youngest patient in the literature is 11 years old, the oldest one is 83 years old, and it can also be seen in men (7, 23, 24). Our youngest case was 17 and the oldest was 46 years old, where the mean age was 33.8 years.

The etiology of granulomatous mastitis is unknown, though possible factors are identified after the comments and opinions of some authors. One third of the patients with granulomatous mastitis have a history of oral contraceptive use in some publications (7). Two (17%) of our cases were on oral contraceptives at the time of diagnosis (4, 8, 22, 25-27). The infectious agents were implicated in the etiology of GLM, but they have not been isolated and proven so far (9). Autoimmunity was generally held responsible for the etiology. Leakage of intraluminal fluids into the lobular connective tissue as a result of damage in the ductal epithelium following local trauma, local chemical irritation or infection were thought to trigger granulomatous response by lymphocyte and macrophage migration (7, 22). However, serologic tests such as Anti Nuclear Antibody (ANA) and Rheumatoid Factor (RF), which demonstrate the presence of autoimmunity, are generally negative. GLM is reported to be found together with some autoimmune disorders including erythema nodosum, polyarteritis nodosa, Wegener granulomatosis, and lymphatic alveolitis (9, 28).

While its frequency is equal in both breasts, GLM can sometimes penetrate the skin and pectoral fascias and muscles located behind as a painful or painless mass. It can cause peau d'orange, ulcerations and retraction of the areola. Hyperemia, local heat increase and local sensitivity can develop due to inflammation. Nonspecific flux of the areola can be seen (28). Retraction of the areola, sinus formations and enlarged axillary lymph nodes can be present (2, 4, 7, 28, 29). Cases accompanied by pituitary hyperprolactinemia, blunt trauma, and use of medications (metaclopramide, ranitidine) are reported (30, 31).

Ultrasound and mammography are used in general to diagnose GLM, though use of MRI has become more common recently. There are very few papers on this topic. Both ultrasound and mammography have no specific radiologic findings for GLM. Ultrasound carries the advantage of cost effectiveness. A substantial proportion of patients are of younger ages, which curtails the sensitivity of mammography. Mammography had no contribution to establish the diagnosis due to the dense structure of the breasts in 3 patients who had mammographic examination.

The most common findings in mammography were asymmetric density reported in 44-66% of the cases, while the second most common finding was a mass with ambiguous margins seen in 15.5-33% (4, 32-34). Nodular opacity, thickening of the skin, retraction of the areola, and enlarged axillary lymph nodes were less common findings. None of these findings alone are specific for GLM. The most common findings were asymmetric density (40%) and axillary lymphadenopathy (LAP) (40%) in 10 of our cases who had mammography. Masses with indefinite borders were detected in two (20%) cases, where two cases (20%) showed thickening of the skin and lobulated cyst was found in one (10%) case. Mammography findings were considered as BIRADS 4 and BIRADS 5 in 5 and 2 cases, respectively.

Findings from ultrasound are better defined in GLM. The most frequently identified findings are single or multiple heterogeneous, hypoechoic structures with irregular borders and tubular enlargements; focal or segmental parenchymal heterogeneity; mass(es) accompanied by cystic components/abscess cavities; and sinus tracts (12, 35, 36). Hypoechoic irregular mass/masses were identified in 13 (81%) of our cases. Six (32%) of these were accompanied by cystic components/abscess.

There are very few studies investigating the MRI findings in GLM. MRI findings may appear both as areas with heterogeneous contrast enhancement without any masses or nodular structures or as nodular structures or mass-like enhancements showing various contrast enhancement patterns. Contrast enhancement patterns may show diversity even between the nodular structures or abscess formations in the same area in a particular case (37). MRI indications for GLM are not clear. We should consider MRI usage for each patient. We believe MRI should be applied in case of malignancy suspicion. In the literature review, it can be noted that MRI is rather chosen for the difficulty of differential diagnosis between the disease and breast cancer. However, MRI is not

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sufficiently satisfactory to distinguish between breast cancer and GLM (14, 16, 32, 38).

We performed MRI for 13 cases and observed that findings were consistent with malignancy in 5 of these cases and that MRI is not specific enough in GLM. Final diagnosis can be established by fine needle aspiration biopsy, tru-cut or surgical biopsy. Fine needle aspiration biopsy (FNAB) is easy to implement, but less accurate compared with tru-cut or surgical biopsy. There are cases in the literature who underwent mastectomy as a result of incorrect assessment for malignancy upon fine needle biopsy (7, 9). Therefore, tru-cut or surgical biopsies are more reliable in the diagnosis of granulomatous mastitis. Diagnostic accuracy rate is reported to be 21-50% with (FNAB) (28, 34). 16 of our cases were diagnosed with tru-cut biopsy. A case who had masses with multiple cystic components had been diagnosed by excisional biopsy in another center.

Clinical findings of the patient and size of the mass in the breast are crucial in the management of idiopathic mastitis. While being unilateral in general, rare cases of bilateral involvement have been reported (8, 21, 22). The location and dimensions, and the volume of the breast are important in unilateral cases. Antibiotic therapy should be started in cases where there is inflammation alone with clinically relevant findings including redness, pain, and high temperature, while drainage should be performed when findings of abscess are present and culture should be taken in the same session. Empiric antibiotic therapy should be started and changing to another agent should be considered if the culture shows a positive result. Steroid (prednisolone) therapy is recommended for GLM cases in whom remission cannot be achieved by antibiotic therapy or adequate shrinkage for surgical treatment is not achieved (11, 28).

Drainage is to be performed before steroid therapy if there is abscess formation, and then prednisolone 30 mg twice a day should be continued for 6 weeks, even until complete remission (11). Some authors promote drainage of the pus with puncture only instead of surgical drainage of the abscess; we, however, prefer to drain the abscess through a mini incision (39).

A period of 6 weeks to 11 months is considered to be sufficient for complete remission (11). Concomitant low-dose (10-15 mg/week) methotrexate for 12 to 24 months is recommended in persistent cases (40). The rate of recurrence is reported as 50% after steroid therapy (11, 28). The target of steroid therapy is not only complete remission and prevention of recurrence, but also achieving an adequate decrease in the skin findings and mass diameter allowing a large cosmetic excision in whom complete response is failed (28, 34). There are studies reporting a complete regression with high doses of steroids for 3 weeks after establishing the diagnosis by fine needle aspiration biopsy (23). We believe the steroid regimen has the advantage of a low rate of side effects. Despite GLM has no optimal management, there are publications of recent studies reporting that large surgical excision following or without a steroid therapy is a favorable treatment of choice (2, 9, 23, 26, 27, 41). Asoglu et al. (23) reported that, among 18 cases who had undergone large local excision, recurrence was observed only in one case during 36 months of follow-up, who was treated with re-excision. In a study by Bani-Hani KE et al. (9), 23 cases out of 24 underwent local excision, and among these, 15 underwent large excision, and mastectomy was performed for one case due to an incorrect diagnosis of carcinoma upon FNAB. Four cases among these showed relapse. None of the cases received pre-operative steroids before excision. Steroid was chosen for relapse cases in principle (6). Oral amoxicillin/clavulonic acid or ampicillin/sulbactam was used for 14 days in 10 of our cases. Surgical drainage was made in four cases. For 4 cases in whom adequate response failed, prednisolone 32 mg/day was used for 3-8 weeks. At least 40% regression was achieved in these cases, who then underwent wide local excision after being considered suitable for cosmetic surgical excision.

Relapse rates after wide local excision are reported to be 6-83% (23, 42). The diversity of these rates can be explained by the absence of a standard surgical procedure and the scantiness of follow-up periods and number of cases. Steroid can be preferred as well as re-excision in relapses after surgical excisions (23). We detected relapse in two cases during 32 months of follow-up and estimated our relapse rate as 12%. We treated one of these cases with steroids, and the other who rejected steroid therapy with re-excision.

GLM is a benign breast disorder causing difficulty for physician and requiring patient treatment. Clinical and radiologic findings are not specific and can be deceptive. The diagnosis may be established only by excluding agents of specific granulomatous mastitis and malignancy by histopathologic examination. Malignancy should be strictly excluded; diagnostic value of tru-cut biopsy is high. Large surgical excision is the first treatment of choice in which a good cosmetic result can be achieved. Steroid therapy can help a surgical intervention with better cosmetic results by decreasing the size of larger masses.

Conflict of interest

No conflict of interest was declared by the authors.

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