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Bilateral involvement in patients with granulomatous mastitis: Surgical treatment and case report

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ABSTRACT

Introduction: Granulomatous mastitis (GM) is a rare benign histopathologic lesion, associated with tissue inflammation, architectural distortions and heterogeneous parenchymal inflammation upon radiological evaluation. The treatment of GM is controversial, and currently, there is no consensus about the most appropriate therapy. Case Presentation: We presented a unique, atypical GM case with a prolonged disease course that ultimately led to a bilateral mastectomy. A conservative therapeutic approach and limited or wide surgical excisions have failed to prevent unfavorable outcomes in both the initial presentation and recurrent disease. Conclusions: There're no clear data in the literature delineating persistent recurrences of GM after conservative treatment and multiple surgeries. Obtaining a disease-free surgical margin might be an important prognostic factor for a lasting relapse-free clinical resolution.

Keywords: Granulomatous Mastitis; Medical Treatment; Breast Conserving Therapy; Surgical Margins

1. INTRODUCTION

Granulomatous mastitis (GM) is a rare benign histopathologic lesion associated with tissue inflammation, architectural distortions and heterogeneous parenchymal inflammation upon radiologic evaluation. Although an understanding of the etiology and association of GM with local trauma, autoimmunity, local chemical irritations or infection is needed, it is possible that damage to the ductal epithelium might represent the pathogenic cause for subsequent structural changes in the affected tissue [1]. The inflammatory infiltrate is generally confined to the breast lobules and comprises histiocytes, polymorphonuclear leukocytes, and multinucleated giant cells of the foreign body and Langhans type. GM typically presents with sinus formation or abscesses, suggesting carcinoma, but radiologic imaging is limited in distinguishing GM from malignancy. An awareness of this rare entity is important for the pathologist, as the definitive diagnosis of GM is microscopically determined through Core Needle Biopsy (CNB) or excisional biopsy of a tissue sample [2]. The treatment of GM is controversial, and there is no consensus about the most appropriate therapy. Patients receiving steroid therapy should be closely observed for side effects. Furthermore, the potential involvement of an infectious agent often challenges the use of steroids for GM treatment. The feasibility of surgical management represents an important choice modality for a shorter time required with fewer complications. The wide excision of the mass is typically performed, but the recurrence rate (RR) is reportedly higher than that observed with conservative treatment [3]. In the present study, we present a case of GM successfully treated with radical surgery for an aggressive disease with bilateral involvement and positive microbiological findings (**Table 1**), which has rarely been reported in the literature.

2. CASE REPORT

A 50-year-old Czech woman, was admitted to the hospital in October 2011 for recurrent inflammatory left breast disease, previously treated in a different hospital using antibiotics and local excision with no clinical re-

Table 1. Microbiological findings.

Microorganisms	Sample	Time	Site
Klebsiella pneumoniae spp. pneumoniae; *Escherichia coli*; *Enterococcus faecalis*	Wound swab	October 2011	Left breast
Stenotrophomonas maltophila	Pus drainage	November 2011	Left breast
Candida tropicalis	Wound swab	December 2011	Left breast
Klebsiella pneumoniae. spp. pneumoniae; *Enterococcus casseliflavus*; *Saccharomyces cerevisiae*	Surgical sample (mastectomy)	February 2012	Left breast
Escherichia coli; *Enterococcus faecium*; *Staphylococcus epidermidis*	Wound swab	March-April 2012	Surgical wound left breast
Enterococcus caselliflavus, *Klebsiella pneumoniae* spp. pneumoniae; *Candida parapsilosis*	Surgical sample (mastectomy)	February 2013	Right breast

sponse. The past medical history was characterized by one pregnancy without complication, nicotine addiction, positive familiar history for breast cancer and the surgical removal of a cardiac recorder (placed for syncopal episode), accidentally mobilized from the subclaveal side to the left breast in August 2010.

A physical examination revealed a hard, painful, hyperemic mass in the upper medial portion of the left breast with no palpable axillary lymphadenopathy. The skin overlying the mass and the contralateral breast was normal. The systems review was positive for low-grade fever. A mammogram revealed an ill-defined periareolar lesion extending into the upper quadrant with increased density and distortion. The ultrasound showed diffuse interstitial edema with fibro-glandular tissue consistent with inflammation and the presence of a mixed echostructure nodular alteration, measuring 1.6 cm × 1.8 cm × 0.9 cm, consistent with partially organized fluid collection. A breast MRI revealed thickening of the skin and subcutaneous tissue of the left breast, with an abnormal nodal enhancement pattern, lymphatic vasculature and abscessual fluid collections. Because of the worsening symptoms, a total body computerized tomography (CT) was performed, which showed no damage to other organs.

The results of seriated blood tests were within normal limits, but the index of inflammation was increased. Scant purulent fluid was collected using a fine needle stain, and after further examination, a presumptive diagnosis of spontaneous infectious mastitis was made. The wound cultures subsequently showed positivity for *Klebsiella pneumoniae*, *Escherichia coli* and *Enterococcus faecalis*.

As a first line of treatment, surgical drainage and targeted antibiotics with corticosteroids were conservatively administered for 2 weeks. After the completion of a 6-week course of therapy, the symptoms remained and appeared to worsen. Thus, the patient underwent an excisional biopsy of the lesion using a vacuum assisted closure therapy device. The pathology examination showed findings consistent with GM and no evidence of carcinoma or pathogenic organisms.

Four weeks later, the patient noticed a new growth in the site of the previous surgical resection, and subsequently a second surgical drainage of the breast abscess was performed. The microbiological examination was positive for *Stenotrophomonas maltophila*, and the new wound swab culture was positive for *Candida tropicalis*.

Because the symptoms worsened, despite targeted medical therapies, a modified mastectomy was performed, including all involved soft and breast glandular tissues. The histological examination revealed multiple foci of acute inflammation, with amorphous material fragments attributable to the previous electromedical device accidentally mobilized from the subclaveal side. The microbiological examination was positive for *Klebsiella pneumoniae*, *Enterococcus casseliflavus* and *Saccharomyces cerevisiae*. The slow healing of the surgical wound, with pus drainage, was observed, and the wound swabs were positive for *Escherichia coli*, *Enterococcus faecium* and *Staphylococcus epidermidis*. Hospitalization was long (96 days), and the patient showed complete resolution of the disease, without apparent recurrence.

After one year, the patient showed the same clinical presentation in the right breast. In addition, the tissue of right breast was painful and an eschar was observed (**Figure 1**).

Basing on the findings of previous microbiological examinations, an empirical antibiotic therapy using colimycin, caspofungin and teicoplanin was administered. After an initial improvement, the clinical presentation worsened. An additional eschar was observed upon palpation, with tenderness and diffuse swelling. In addition, two fistulas, which discharged pus when pressuring the breast, were also observed, and the breast was extremely painful.

Mammography revealed an asymmetric density increase with indistinct margins in the retroareolar region and upper outer quadrant of the right breast. No microcalcification was evident. The breast ultrasonography showed a loculated fluid alteration of 5 cm in the inner quadrants, associated with hypoechoic branching in cu-

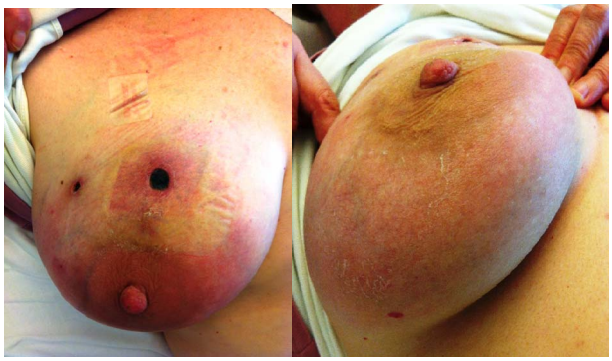

Figure 1. The right breast of a GM patient with several pus-filled fistulas and recurrence after a previous contralateral mastectomy for the same breast disease. The patient presented acute inflammatory symptoms, such as local temperature increase, hyperemia, and edema in the breast.

taneous fistulas. However, the mammary tissue was edematous. The breast magnetic resonance image (MRI) revealed thickening of the mammary skin of the right breast alongside nodular lesions and fluid collections in different locations and of various sizes with enhancing mass lesion (**Figure 2**).

Admission laboratory testing was significant for the detection of leukocytosis with bandemia. The ESR and CRP were 79 mm/h and 76.92 mg/L, respectively. Antinuclear antibodies, cytoplasmic antibodies, rheumatoid factor and anticyclic citrullinated peptide were negative. We attempted to identify immunologic, coagulation and chemical markers, as shown in **Table 2**, without evidence of diagnostic specificity.

The clinical symptoms and personal preference, associated with a prolonged disease course and multiple recurrences, ultimately led to radical mastectomy. Histological staining revealed acute and chronic xanthogranulomatous flogosis, consistent with GM (**Figure 3**). The microbiological examination was positive for *Enterococcus caselliflavus*, *Klebsiella pneumoniae* and *Candida parapsilosis*.

At 4 days post-operation, the patient was released in good status. The hospitalization lasted 8 days, with rapid patient rehabilitation and no apparent recurrence.

4. DISCUSSION

In this study, we evaluated patients with recurrent and bilateral GM, with a long history of failed multiple treatment modalities and permanent cure through radical surgery. The involvement was typically unilateral, as bilateral involvement had rarely been reported in the literature [4]. The primary problems of GM include the high rate of local relapse and the long duration required for the complete resolution of the disease symptoms. All treatment entities were associated with a recurrence rate of 16% - 50%, maintaining the patient under medical care

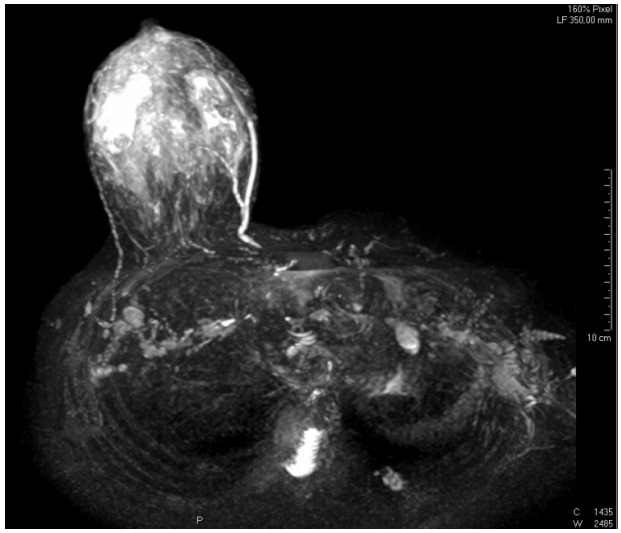

Figure 2. Post medical treatment image of right contralateral breast recurrence after a previous left mastectomy. The MRI shows diffuse enhancement in different areas. Mass lesions, non-suggestive of a specific diagnosis, parenchymal inflammation, and remarkable thickening in the mammary skin of the right breast were observed.

Table 2. Analysis of the immunological profile and coagulation blood tests during the second hospitalization.

Silica test	0.98 Negative
APTT test	Negative
Kaolin test	0.84 Negative
Russell Viper Venom test	1.02 Negative
dRVVT test	Negative
Lupus Anticoagulant test	Negative
Complement Factor C3	171.00 mg/dL Negative
Complement Factor C4	45.70 mg/dL Positive
Anti-cardiolipin antibodies IgM	11.68 UI/mL Negative
Anti-cardiolipin antibodies IgG	3.86 UI/mL Negative
Anti-dsDNA antibodies	<12.30 U/ml Negative
ENA screen test	4.7 Negative
Anti-Jo1 antibodies	Negative
Anti-SS-B antibodies	Negative
Anti-PM/Scl antibodies	Negative
Anti-Scl 70 antibodies	Negative
Anti-Sm antibodies	Negative
Anti-Sm/RNP antibodies	Negative
Anti-CENP-A/B antibodies	Negative
Anti-Ro (SS-A 60 kDa) antibodies	Negative
CD 19+	13%
CD 3+	74%
CD3+CD4+	41%
CD3+CD8+	29%
CD16+CD56+	8%
CD4/CD8	1.40

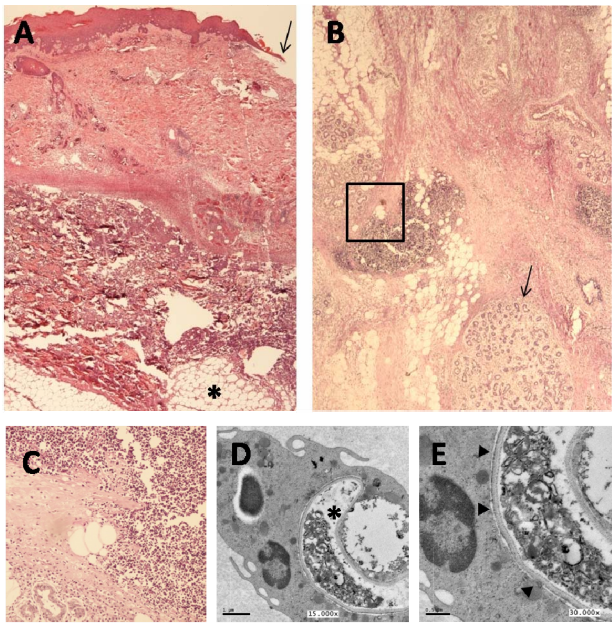

Figure 3. Morphological examination of right contralateral breast recurrence after a previous left mastectomy: Panel A (magnification 2×) shows that the breast tissue was almost completely substituted with necrotic tissue, surrounded by heavy polymorph nucleate infiltrate extending from the skin (arrow) to the adipose tissue (asterisk). Panel B (magnification 10×) shows that only a few islands of breast tissue were observed (arrow). Panel C (higher magnification of the insert in panel B) shows the results of an electron microscopy study demonstrating the presence of macrophages and Panel D) microorganisms (asterisk), namely, Candida albicans, characterized by a multilayered wall (arrow heads) surrounding a disorganized cytoplasm (asterisk).

for a prolonged period [5]. The overall trend among these patients is a long history of disease, accompanied by an enormous psychological burden, necessitating a reliable, safe and rapid solution. Currently, the most commonly applied treatment options are conservative modality through the administration of systemic antibiotics, corticosteroid therapy and surgical excision.

Often, medical treatment with corticosteroids significantly suppresses inflammation, facilitating more conservative surgery. However, prolonged steroid use generates local and systemic side effects and increases the potential to develop tolerance. In a retrospective analysis, none of the 19 patients with GM displayed a complete clinical response to the 8-week steroid treatment, and local excisions of the remaining lesions were performed with good cosmetic results in all patients [6]. Furthermore, the initiation of steroids is often limited by concerns related to the presence of an infectious etiology, as described above. Thus, steroids are primarily administered only in recurrent cases.

Although a variable percentage of cases of GM appear aseptic, case reports of documented co-infection with coexistent organisms have been reported in the UK, France and Italy. Follow-up examinations, after the excision of the mass, suggest that wound infection is a frequent problem [11]. However, a specific antibiotic therapy might be ineffective based on the anatomical and functional features of the breast and the disease extent. Further studies are needed to establish this hypothesis, suggesting that an initial pathogenic insult might be responsible for generating a subsequent autoimmune response, with further damage to lobular structures. In the present study, the results of the microbiological examinations, showing different germs at different times and an inefficacy of the targeted antibiotic therapy, suggest pathogenic colonization rather than infection. In addition, the presence of a local immunity deficit due to the anatomical structure of the mammary gland has also been suggested. However, in the context of a potential multifactorial etiology, the present study illustrates the controversial nature of an optimal treatment paradigm. There is no accepted management strategy for GM. Limited excision alone has little benefit, although this treatment plays an important role in the diagnostic pathway, there is a strong tendency of recurrence. A relapse rate of 5% to 50% was reported after surgical excision of the mass [7]. Furthermore, there is a high rate of poor wound healing and disfigurement after surgical intervention. Disease recurrence and fistula formation are known complications of GM, and in some cases, excision of the recurrence alone is not an adequate treatment, unless this procedure complies with the criteria of negative surgical margins in terms of inflammatory tissue [1]. In the case reported above, granulomatous deposits from the residual breast tissue were observed after previous excisions, potentially reflecting recurrence and emphasizing the necessity of mastectomy in patients with extensive structural alterations. Hladik *et al*. presented three patients, with a long history of recurrences, which were successfully treated with mastectomy and immediate breast reconstruction. However, in one case, skin-sparing mastectomy (SSM) and primary reconstruction with a transverse myocutaneous gracilis flap (TMGF) were ineffective because abscesses recurred from residual breast tissue [8]. In a retrospective review of cases observed over 25 years, Al-Khaffal *et al*. showed that regardless of the therapeutic intervention, which included steroids, antibiotics, and surgical intervention, alone or in combination, complete resolution took approximately 6 to 12 months. Consistently, the overall outcomes were not associated with any combination of treatment options [9]. In our experience, the patient had previously received multiple courses of oral and parenteral antibiotics, without improvement, and required bilateral mastectomy due to the severe and recurrent nature of the disease. We are aware of only eight other cases requiring complete mastectomy.

However, the contralateral recurrence that occurred almost 18 months after treatment, prompt surgical therapy improved the overall outcomes in the duration of clinical resolution compared with a conservative clinical approach. We reported an unusual presentation of IGM which had bilateral involvement and an unusual progression after radical treatment. Demolitive surgery represents a considerable burden for breast surgery specialists, but new oncoplastic strategies, with the support of biological and prosthetic materials, could achieve immediate reconstruction during a second operation [10]. Clearly effective feedback, in the context of a multidisciplinary team, is vital in these challenging cases. Indeed, multiple microhistological biopsies and a complex radiological definition of the disease extent might contribute to accurate diagnosis and adequate clinical management.

5. COMPETING INTEREST

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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ABBREVIATIONS

GM: Granulomatous Mastitis;
CNB: Core Needle Biopsy;
RR: Recurrence Rate;
MRI: Magnetic Resonance Imaging;
CT: Computerized Tomography;
ESR: Erythrocyte Sedimentation Rate;
CRP: C-Reactive Protein;
SSM: Skin-Sparing Mastectomy;
TMGF: Transverse Myocutaneous Gracilis flap.

