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Abscessed Breast Mastitis During Pregnancy Should Raise Suspicion Of Granulomatous Mastitis

S.Bouzid I.Kouri Dz.Lekmiti Z.Mechenane S.Kenfoud
Obstetrics And Gynecology Department Eph Hassen Badi
University Of Algiers 1 Ben Youcef Benkheda Faculty Of Medicine, Algiers - Algeria

Summary
Introduction : *Granulomatous mastitis is an inflammatory disease often erroneously considered as breast abscess, which is relatively rare, with few cases reported in the literature, mostly in the form of case reports.*
Materials and Methods : *In this article, we report six cases of granulomatous mastitis occurring during pregnancy, where different management approaches were applied. Clinical symptoms were dominated by swelling and pain, ultrasound was the main investigation, anatomopathological diagnosis was confirmed in 4 out of 6 cases, and the main therapeutic management was primarily surgical drainage.*
Discussion : *We conducted a literature review by using the databases pubmed, Google Scholar, clinicalkey, and EMC. This review allowed us to gain a better understanding of this condition, compare cases, and come to conclusions: the short-term prognosis is favorable, but recurrence is a concern.*
Conclusion : *Granulomatous mastitis is an inflammatory pathology with a clinically challenging diagnosis, often raising concerns of malignancy or erroneously considered as breast abscess. The evolution of the condition is unpredictable, making it difficult to establish a therapeutic consensus. Our objective is to draw attention to this pathology in order to minimize aesthetic damage and emphasize the necessity of long-term follow-up.*
Key word: *Mastitis, breast abscess, granulomatous mastitis, tuberculous mastitis, sarcoïdose.*

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I. Introduction

Granulomatous mastitis (GM) is a breast condition increasingly documented in the literature, often associated with unilateral or bilateral breast pain, presenting as an increase in breast volume or the palpation of a nodule. Although the pathogenesis of the disease remains unknown and debated, it appears to be a morphological entity distinct from ductal ectasia and plasma cell mastitis. GM was first described by Kessler in 1972 [1]. The description of the lesion raises concerns about carcinomatous mastitis, which should be investigated initially. Several clinical reports have linked GM to manifestations such as erythema nodosum, and sometimes arthritis and pregnancy. It has also been described in conditions such as sarcoidosis and Wegener's disease, suggesting an autoimmune background. GM also shares similarities with other infectious conditions, particularly tuberculosis. Characterized by the presence of inflammatory lesions limited to the lobules, often complicated by microabscesses [2], this entity poses challenges for positive diagnosis and differential diagnosis, with therapeutic implications.

II. Objectives

Our objective is to report and draw attention to mastitis cases occurring during pregnancy, which we managed between 2017 and 2022. Throughout this period, we adapted our approach to minimize aesthetic damage in young women. Additionally, we aimed to guide these women postpartum to specialized department for continued monitoring or necessary explorations, crucial for early diagnosis of highly probable autoimmune diseases in these contexts. We also emphasize the importance of directing our colleagues in pathology and radiology towards this specific entity, seeking relevant insights both in histology and radiological diagnosis. This raises questions regarding the concept of "idiopathic" mastitis. Early diagnosis plays a crucial role in minimizing aesthetic sequelae in young women. The challenge of radiological diagnosis is a genuine concern, as we strive not to overlook the possibility of carcinomatous mastitis. We present our experience with six cases of mastitis during pregnancy in young women, each one with slightly different clinical contexts, contributing to the enrichment of the data bank.

III. Materials and Methods

After managing two breast abscesses in 2017, which were drained with negative bacteriological results, we were motivated to perform breast tissue biopsies on subsequent patients in whom the diagnosis of granulomatous mastitis (GM) was established. Additionally, we conducted a literature review by using databases such as PubMed and ScienceDirect. Our patients were treated in the Obstetrics and Gynecology Department at Belfort between 2017 and 2022 for breast abscesses during pregnancy.

Cas n° I – 2017 S.A, a 21-year-old patient, G1P0, with no particular medical history, presented at the 5th month of pregnancy with a red swelling and induration in the left breast. Ultrasound revealed well-defined heterogeneous collections with an echogenic appearance in the adipose tissue measuring 57.7 × 59 mm. The diagnosis of breast abscess with mastitis of the left breast quadrant was established. The patient received outpatient antibiotic therapy, resulting in a reduction in the volume of the mass. However, there was a recurrence at 36 weeks of gestation, leading to hospitalization. Upon admission, the patient had a temperature of 38°C, an enlarged left breast with a warm, red swelling in the left upper outer quadrant without fistulization. Laboratory tests showed a white blood cell count of 30,000 and a CRP level of 24 mg/l. Ultrasound revealed a large intra-mammary collection in the left breast, occupying the outer quadrants, measuring 65 × 52 mm, with echogenic thickening of the skin overlay. The patient was administered Ceftizoxime 1g twice daily intravenously for 10 days, achieving afebrile status by day 3. However, on day 4, there was clinical worsening, fistulization to the skin, and the appearance of herpes zoster lesions on the left shoulder. Acyclovir 100mg/kg/day was initiated, and the white blood cell count was 11,900 with a CRP level of 96 mg/l. The patient was then treated with Pristinamycine 3g/day for 10 days, and drainage by incision was performed. The examination of the pus did not reveal any pathogenic bacteria. There was a good clinical evolution with a regression of inflammatory signs. Cervical maturation occurred at 38 weeks and 3 days for labor preparation, and there was no further follow-up mentioned.

Cas 2 - 2017: B.I, a 25-year-old patient, G2P1, with no particular medical history, consulted for a swelling in the right breast during the 18th week of pregnancy. She was initially treated with antibiotics (amoxicillin-clavulanic acid), but the symptoms persisted, accompanied by inflammatory signs (redness and warmth). Breast ultrasound revealed right mastitis, leading to a change in antibiotic therapy to cephalexin. Due to worsening clinical symptoms and the onset of fever, she was hospitalized. Upon admission, the patient had a temperature of 38°C, an enlarged right breast with palpation of a warm, red, hard mass in the upper outer quadrant. At 22 weeks of gestation, ultrasound revealed a focalized mastitis in the right upper outer quadrant, likely in the process of abscess formation. Laboratory tests showed a white blood cell count of 10,700, and CRP was negative.

The patient was treated with Ceftizoxime 1g twice a day intravenously for 10 days and Gentamicin 80 mg twice a day intramuscularly for 5 days. On the second day, clinical worsening occurred with the onset of joint pain and ecchymoses around the homolateral joints. The rheumatologist ordered an infectious and autoimmune panel. The patient was prescribed Medrol (methylprednisolone) 4 mg/day and Calcidose (calcium carbonate) once a day. She was discharged on the 12th day of hospitalization. Five days after discharge, she was readmitted for mastitis complicated by an abscess with periareolar fistulization and pus discharge. Ceftizoxime 1g twice a day was resumed. There was improvement, but the abscess persisted. At day 15, drainage by incision was performed, and Ceftizoxime was continued for 48 hours. Solupred (prednisolone) 3 tablets per day were prescribed along with directed wound healing.

Cas 3 - 2022: B.N, a 31-year-old patient, G3P2 (2 living children), with a personal history of hypothyroidism and no history of tuberculosis exposure, consulted during the 7th month of pregnancy due to the perception of a breast mass. Breast ultrasound revealed a hypoechoic area in the right upper outer quadrant, measuring 29×18 mm, with irregular contours associated with ductal dilation and wall thickening suggestive of galactophoritis and mastitis of the right breast. The patient was initially treated with antibiotics (cephalexin for 30 days) without improvement.

She was admitted due to worsening symptoms with therapeutic failure (Augmentin, Pyostacine for 30 days) at postpartum day 30 (no breastfeeding). On examination, the patient was afebrile, and the right breast showed a warm, red swelling with ulceration. Palpation revealed a painful, mobile, hard mass of 10 cm in the right upper outer and inner quadrants, along with painful right axillary lymphadenopathy. Breast ultrasound showed two collections communicating with the skin through a fistulous tract and significant subcutaneous fat infiltration. Laboratory tests revealed a white blood cell count of 5740 and CRP of 6 mg/l. Pus aspiration and a breast biopsy were performed, showing nonspecific inflammatory granulation tissue on histopathological examination. The patient received dual antibiotic therapy: Ceftizoxime 1g/12h and Gentamicin 80mg twice a day for 10 days.

At postpartum day 53, she was readmitted for recurrence. Surgical drainage was performed with a biopsy for histological examination. The histopathological examination revealed dense inflammatory infiltrates in the breast parenchyma, consisting of lymphoplasmacytic elements, histiocytes, epithelioid cells, Langhans multinucleated giant cells, and eosinophilic and neutrophilic polymorphonuclear cells. This suggested a tuberculoid granulomatous lesion of the breast. The patient was treated with first-generation cephalosporins

(cefadroxil, cephalexin). One month later, a follow-up breast ultrasound indicated galactophoritis with mastitis without collections. Echoguided fine-needle aspiration cytology showed a background with scanty blood, abundant nonspecific necrosis, lymphocytes, altered polymorphonuclear cells, epithelioid cell clusters, and multinucleated giant cells of Langhans, consistent with granulomatous mastitis. Pus culture on specific LJ medium was negative. The patient has been in clinical remission for 9 months (prescribed Solupred for 15 days in September).

Cas 4 - Novembre 2022: .R, a 27-year-old patient, G4 P3, with no significant medical or surgical history, **in the 28th week of gestation,** complicated by gestational diabetes managed with diet control, presented with a lump in the left breast accompanied by fever. On examination, there was a mass at the junction of the two outer quadrants, painful and inflamed. The patient was initially treated with amoxicillin and later with cephalosporins without improvement. Due to worsening symptoms, hospitalization was required. Upon admission, the patient was afebrile, with a warm red plaque. Palpation revealed a resilient mass of 5 cm, non-fistulized to the skin. Ultrasound showed a poorly defined collection in the same region, associated with fat infiltration, measuring 40×30 mm, consistent with a breast abscess, with no axillary lymphadenopathy. The patient was prescribed Pyostacine 1g/day, but the symptoms worsened, leading to the indication for incision drainage. Bacteriological examination of the pus was negative. The patient received dual antibiotic therapy: Pyostacine and cefadroxil. The histological results favored granulomatous mastitis. There was a good clinical and biological response, but the patient experienced a recurrence after a month, along with the development of erythema nodosum and joint pain. A second drainage was performed, followed by corticosteroid therapy. The patient was discharged and later returned for a cesarean section due to fetal anomalies of the external rotation of the fetal head (ERCF).

Case 5 - April 2022: B.F, a 26-year-old patient, G4 P0 C2 A1, with chronic hypertension, presenting a pregnancy at 21 weeks of gestation complicated by gestational diabetes requiring insulin. (History of exposure to tuberculosis reported during the interview) The patient developed a painful and inflammatory mass involving both outer quadrants of the left breast in a febrile context. She was initially treated with cephalosporins. Due to worsening symptoms, including an increase in breast volume and fistulization, surgical drainage was performed. One month later, the patient presented with a warm, red plaque involving both breasts with ulcerative lesions. Palpation revealed a painful, resilient mass of 7 cm, fistulized to the skin, discharging pus upon pressure. There was a left axillary lymph node of 2 cm, and red painful lesions appeared on the skin of the upper and lower limbs, accompanied by joint pain. The ultrasound examination reveals multiple communicating collections in the left breast extending throughout the upper quadrant. These collections have thickened walls with heterogeneous echogenic content. There is generalized edema of the left breast with subcutaneous fat densification, ductal dilation with echogenic content, regular thickening of the skin layer reaching 14mm, and left axillary lymphadenopathy.

Laboratory results show a white blood cell count of 21,680 and CRP of 96. The treatment includes Pyostacine 3g/day and Gentamicin 160 mg/day. Pus sampling with biopsy shows the absence of pathogenic bacteria, and the LJ medium culture is negative. Histopathological examination reveals significant inflammatory changes in the breast parenchyma organized into granulomas composed of epithelioid cells, lymphocytes, and giant cells, sometimes Langhans type and sometimes Muller type. Some tuberculoid-like granulomas are centered around microabscesses with polymorphonuclear cells without caseous necrosis. There are also foci of xanthogranulomatous lipophagic inflammation, morphologically consistent with granulomatous mastitis. Surgical drainage was performed 8 days later due to the persistence of the 41 mm collection, with continued antibiotic treatment (Pyostacine) and daily dressing changes. The histopathological report indicated a polymorphic inflammatory infiltrate rich in histiocytes and altered polymorphonuclear cells, followed by a favorable clinical and biological evolution with a white blood cell count of 11,480/mm3 and CRP of 96. The decision was made to discharge the patient, who was then referred to internal medicine for possible corticosteroid therapy after the infectious episode. She was prescribed Solupred 2mg tablets, 4 tablets daily for a month, followed by a gradual taper to 2.5 tablets per day. The Quantiferon test was negative, a chest CT scan showed no abnormalities, and the tuberculin skin test (IDR) was 14mm. Joint pain recurred on postpartum day 15 but improved under corticosteroid therapy.

Case 6 - June 2022: S.Z, a 34-year-old patient, G2P1, with no specific medical history, experienced mastodynia with an increase in the volume of the left breast during her pregnancy at 13 weeks gestation. She was initially treated with antibiotics (Augmentin for 15 days). One month later, she returned at 17 weeks and 1 day of gestation due to persistent symptoms and the onset of erythema nodosum, leading to her hospitalization. On clinical examination, the patient was in good general condition, afebrile, and presented with a reddish inflammatory plaque in the supero-external and infero-external quadrants of the left breast. Arthralgia and erythema nodosum also appeared on both lower limbs. Laboratory results showed a white blood cell count of 7000 and CRP of 94. The breast ultrasound reveals an abscessed collection with ill-defined borders in the infero-external and supero-external quadrants of the left breast. There is diffuse subcutaneous fat densification and ductal dilation **with thickened, thick content**. The patient was placed on dual antibiotic therapy: Cefizox 1g/8h

intravenously for 13 days and Pyostacine 500mg tablets, 2 tablets 3 times a day for 21 days. Dressing changes were performed twice daily, and needle aspiration yielded purulent fluid with predominantly leukocytic inflammatory cells. Microbiological culture of the pus showed no pathogenic germs. Four days later, there was a worsening of clinical signs with a decline in general condition and functional impairment of both lower limbs. An abscess had fistulized to the skin with ipsilateral axillary lymphadenopathy. Drainage was performed with a good subsequent outcome. However, a recurrence occurred one month later at 25 weeks of gestation. The patient was placed back on antibiotics (Pyostacine, 2 tablets twice a day for 15 days) followed by a third drainage. The histopathological study revealed breast tissue altered by a significant inflammatory reaction, sometimes organized into granulomas composed of epithelioid cells, occasionally centered by giant cells, and sometimes diffuse with polymorphic lymphoplasmacytic elements and neutrophils. There was no caseous necrosis, indicating a chronic granulomatous tuberculoid inflammatory reaction with superimposed infection and abscess formation (abscessed granulomatous mastitis). The patient did not receive corticosteroid therapy and is currently in remission.

IV. Discussion:

In terms of clinical symptoms, the most frequent among our patients were inflammatory signs (cutaneous signs (6/6), fistula (5/6), fever (4/5), pain (4/5), increased breast volume, mass (4/6), axillary lymphadenopathy (3/6), erythema nodosum, and arthralgia (4/6). Similarly, according to other reports, the most common symptom is a palpable painful mass that may be associated with erythema and inflammation. It typically presents with multiple peripheral abscesses or rare central abscesses, a sinus or cutaneous fistula, nipple retraction, and axillary lymphadenopathy.[3] Due to the lack of specific symptoms, the disease often takes months from the onset of symptoms to diagnosis. In terms of laboratory findings, generally reported in published reports, there is a biological inflammatory syndrome (increased CRP, leukocytosis, etc.). However, in our patients, the results were inconsistent; increased CRP was not present in all cases, and CRP elevation (4/6) and leukocytosis (4/6) varied regardless of clinical signs. Mammographic or ultrasound signs are generally not pathognomonic. Hypoechoic tubular lesions with irregular contours and a peripheral echogenic halo associated with galactophoric dilation, multiple abscesses, hypoechoic lobular masses, tissue distortion, cutaneous fistula, and axillary lymphadenopathy can be observed on ultrasound. Mammographic results show focal asymmetry, diffuse hyperdensity, mass, retraction, and tissue heterogeneity, similar to cancer. [4] In our patients, mammograms were not performed due to pregnancy. Ultrasound reports indicated heterogeneous collections (100%), galactophoric dilation (3/6), lymphadenopathy visible on ultrasound (1/6), and densification of breast fat (4/6). Mastitis granulomatosa (MG) presents a diagnostic challenge in conventional imaging (mammography and breast ultrasound), particularly with breast carcinoma (BC) [5]; hence, biopsy is necessary for diagnosis [6]. Elastography (UES) is an ultrasound technique for analyzing tissue hardness. Several previous studies have reported that combining ultrasound and elastography enhances the characterization of benign and malignant breast masses [7–8]. The differential diagnosis of different types of MG is not always straightforward. The pathology report reveals cells suggestive of breast tuberculosis with caseous necrosis, but Lacambra et al found caseous necrosis in 7% of MG cases in their series [9]. Some consider canalicular MG as a distinct entity with differences from plasmacytoid MG. We encountered similar clinical and radiological features, and the histology revealed dilatation of ducts and lymphoplasmacytic elements. Biopsy is the gold standard for diagnosing MG, and it is preferable to perform it with a core needle, offering a sensitivity of 96% [10]. MG is defined as a granulomatous inflammation involving epithelioid and giant cells in the breast parenchyma, which can be centered on the galactophoric ducts with ductal dilatation (plasmacytoid MG) or on the lobules with acinar dilatation (MG). The affected parenchyma generally loses its acinar structure, and the ducts are damaged [10].

In pathological samples, granulomatous lesions without necrosis are accompanied by infiltration of giant cells, histiocytes, lymphocytes, and plasma cells observed at the center of the breast lobules. Among our patients, we observed a tuberculoid appearance (3/6) with lymphoid cells, plasma cells, tuberculoid granulomas centered around abscesses with dissection of different glandular structures, and steatonecrosis with giant cell reaction (1/6). In the remaining two cases, where we only considered breast abscess, no biopsies were performed initially. In all patients, bacteriological samples were negative. It seems that secondary infection, especially by Corynebacterium (a bacterium often found on the skin surface), is possible and may exacerbate symptoms, giving a false impression of primary breast abscess. The infectious origin is poorly documented, although some cases associating MG with tuberculosis or Corynebacterium infections have been reported [11-12]. Recently, the hypothesis of a type IV hypersensitivity reaction induced by lipophilic corynebacteria has been suggested but needs confirmation. Taylor et al. found positive cultures of Corynebacterium (particularly Corynebacterium kroppenstedtii) in 34 out of 62 MG cultures [13].The tissue sample should be examined for acid-fast bacilli and fungi [14,15]. Several published reports have associated MG with erythema nodosum (EN) and sometimes arthritis, manifestations that have been linked to various autoimmune rheumatic diseases. This reinforces the hypothesis that MG could involve an immune-mediated process. EN is the most common type of panniculitis, an inflammatory condition of subcutaneous fat characterized by erythema and redness. It presents as erythematous, painful, and red nodules on

the anterior aspects of the lower extremities. EN has been associated with autoimmune diseases such as sarcoidosis and inflammatory bowel diseases, among others [18].The autoimmune hypothesis is notably considered in cases where there are high concentrations of lymphocytes in the tissues and an appropriate response to immunosuppressive treatments.[16] According to this hypothesis, there is an inflammatory response to the lesion of the epithelium of the mammary ducts that can occur following the penetration of secretions into the interstitial tissue.[17] The occurrence of erythema nodosum and arthralgia in our patients suggests a terrain overexpressed by pregnancy, which remains a period that reveals autoimmune conditions on which certain associated diseases with IGM [18] need to be explored. The occurrence of mastitis during pregnancy in our cases could suggest a relationship with prolactin, considering that MG has been described to occur with a prolactinoma. The occurrence of MG during pregnancy is rarely reported in the literature. Other theories propose that elevated levels of serum prolactin can cause ductal obstruction by milk. However, routine prolactin testing is not recommended for the diagnosis of IGM [19]. The occurrence of erythema nodosum and arthralgia in our patients suggests a terrain overexpressed by pregnancy, which remains a period that reveals autoimmune conditions. It will be necessary to explore certain described diseases associated with IGM [18].Erhan et al. found 2 patients with hyperprolactinemia [16]. The concept of MGI, in our opinion, remains to be defined. In our cases, we did not find this histological difference, even though we observed an association of both. Although various predisposing factors for MG have been mentioned, none of them have been proven. In this regard, the most common hypotheses are autoimmune, infectious, and hormonal factors [21]. While there are no specific treatment guidelines for MG, management includes expectant care, the use of glucocorticoids (GC), followed by the introduction of disease-modifying antirheumatic drugs (DMARDs), and surgical procedures in case of treatment failure [20].The recurrence rate for patients who were only monitored has been reported at 50% [22]. Yukawa et al., in their report on 13 patients,they only used deep pus drainage and followed them between 4 and 28 months. They considered this option to be shorter than the duration of corticosteroid use [22]. Bouton et al. reported 27 patients with IGM and showed that their condition improved after an average duration of 7.4 months without treatment [23]. The treatment with corticosteroids was first proposed by Herthogh et al. at a dose of 30 mg per day for two months, which reduced the size of the lesion but led to side effects such as weight gain, diabetes, and Cushing's syndrome [24]. Although glucocorticoids are the first-line treatment in most studies, the recurrence rate and side effects are high with these medications [25]. Methotrexate has been strongly recommended in previous research, especially in cases where corticosteroids have failed or are accompanied by complications. The recommended dose is 7.5 to 25 mg per week, in combination with daily or weekly folic acid [26]. The most common complications include stomatitis, leukopenia, abdominal pain, fatigue, fever and chills, dizziness, and infection [27]. Some researchers have recommended corticosteroids as the first-line treatment and MTX to reduce the corticosteroid dose and decrease complications or in case of treatment resistance [28]. The therapeutic response generally favored corticosteroid therapy [29]. In our cases, we observed two remissions without corticosteroid therapy. However, this does not necessarily predict a potential recurrence in the future. It is important to note that the majority of cases had superinfections on these mastitis (short-term response achieved with antibiotics). Published articles have proposed therapeutic strategies that seem practical for managing these mastitis [30]. This requires early diagnosis and intervention to reduce aesthetic damage (avoiding fistulization and repeated drainages by initiating corticosteroid therapy, with or without antibiotics, early on). Long-term follow-up of these patients is crucial, and exploration for diseases causing vasculopathies and autoimmune diseases is imperative [31], especially since this pathology occurs in young individuals. Referral to specialized services is recommended.

V. Conclusion

Granulomatous Mastitis (MG) remains a complex entity with a chronic course, posing significant challenges in positive diagnosis, differential diagnosis, etiology, and consequently in management, with significant aesthetic consequences. For individuals affected, specific exploration should be planned, and long-term follow-up organized. This is essential for tracking developments based on treatments and their doses, and for enhancing management protocols.

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