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A Case Report**

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Cystic Neutrophilic Granulomatous Mastitis during Pregnancy: A Case Report

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Abstract

Background: Granulomatous mastitis (GM) is a rare chronic inflammatory disease. The causes of GM have not been fully understood. The relationship between GM and *Corynebacterium* species has begun to be observed, but the culture of *Corynebacterium* species is very difficult. In recent years, cystic neutrophilic granulomatous mastitis (CNGM) has been pathologically observed and proposed as a cause of GM.

Case presentation: We present a woman in her 30s (25 weeks pregnant) who had redness and pain in her left breast. At first, she was diagnosed with mastitis and was given antibiotics, but the symptoms did not improve. After that, multiple erythematous lesions appeared on the front, lower part of both legs, and arthritis appeared in her legs. GM with erythema nodosum (EN) was suspected, and prednisolone (PSL) was administered. While the symptoms in the lower legs improved, her left breast symptoms persisted. A core needle biopsy was obtained from the left breast abscess, and it was diagnosed as GM. Because she was a pregnant woman, only PSL was administered without fat-soluble antibiotics such as tetracycline. As the breast symptoms gradually improved, the dose of PSL was gradually decreased and then discontinued. The period of treatment with PSL was 17 months. A review of the pathologic findings of breast biopsy specimens, including Gram staining, revealed the diagnosis of CNGM.

Conclusions: We present a case of CNGM during pregnancy. When hesitating to use fat-soluble antibiotics, such as tetracycline, PSL may be considered one of the treatments for CNGM.

Keywords: cystic neutrophilic granulomatous mastitis, pregnancy, *Corynebacterium* infection

Background

Granulomatous mastitis (GM) is a rare chronic inflammatory disease. The cause of GM has not been fully elucidated; however, some recent reports have shown that GM might be related to *Corynebacterium* infection¹⁾. Renshaw et al. reported the concept of cystic neutrophilic granulomatous mastitis (CNGM) in 2011, which suggests that there is a strong relationship between GM and *Corynebacterium* infection. It is known that GM sometimes accompanies erythema nodosum (EN). Both GM and EN occur frequently in women who are pregnant or have given birth (even years ago), but only three cases of GM with EN during pregnancy have been reported to date²⁻⁴⁾. Herein, we present a case of CNGM in a case of GM during pregnancy. In this case, complications with EN were also suspected.

Case presentation

Consent to publish the clinical data was obtained from the patient. We present a woman in her 30s (25 weeks pregnant) without any relevant past medical history who experienced redness and pain in her left breast. She visited a hospital and was diagnosed with mastitis. She was administered antibiotics (CFPN-PI) for a week; however, the symptoms did not improve. On the 20th day after the onset of symptoms, she visited another hospital, and incisional drainage was performed. Upon culturing the pus, neither aerobic nor anaerobic bacteria were found. On the 25th day, multiple painful erythematous lesions (maximum size, 6 cm) appeared on the front of both lower legs. On the 30th day, the erythema worsened, and she could not walk because of severe arthritis in her lower legs. GM with EN was suspected based on the clinical course, and prednisolone (PSL) treatment (20 mg/day) was started. The erythema and arthritis in her legs improved, while the symptoms involving her left breast did not. On the 48th day, a core needle biopsy was performed on a left breast abscess, and a diagnosis of GM was made based on the pathological findings (Figure 1).

On the 63rd day, she was admitted to the Department of Obstetrics in our hospital because of oligohydramnios. Then, she visited our department for treatment of the

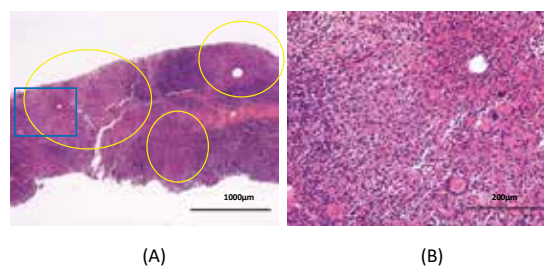


Figure 1. Pathological images of the abscess needle biopsy

A. Low power-field (H.E. stain $\times 40$)
Epithelioid granuloma formation with the appearance of multinucleated giant cells is widely observed, and the lobular structure is destroyed. (Granuloma in the yellow circle. The blue square is the image of B.)
B. High power field (H.E. stain $\times 200$)
In the granulomas, necrosis is not observed, and a small abscess is seen.



Figure 2. Clinical finding of the left breast

Mottled redness is seen over the inferior aspect of her left breast and a viscous yellowish-brown liquid drain from the reddened area.

abscess in the left breast. There was a mottled redness apparent on the inferior aspect of her left breast, and a viscous yellowish-brown liquid drained from a part of the reddened area (Figure 2). By that time, the erythematous lesions on her lower legs had disappeared. Ultrasonography revealed a mottled low echoic area over the inferior aspect of her left breast. The reddened areas of the skin were thin, and a fistula was partially observed between the low echoic area and the skin (Figure 3). The results of general bacterial culture were negative for both anaerobic bacteria and *Mycobacterium tuberculosis*. On the 82nd day, an emergency cesarean section was performed. Because she wanted to breastfeed, PSL administration was continued without incisional drainage or fat-soluble antibiotics, such as tetracycline. She was discharged on the 89th day, and the dose of PSL at this time was 15 mg/day. Thereafter, her symptoms gradually improved, and the dose of PSL was gradually reduced. She breastfed for 11 months, and treatment with PSL was discontinued three months after she stopped breastfeeding; the duration of treatment with PSL was 17 months. Her symptoms disappeared during the surveillance period of 14 months.

To determine the causative pathogens of GM, we

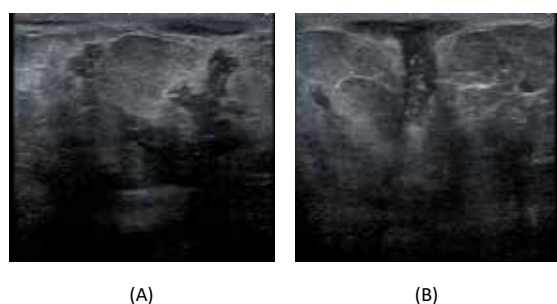


Figure 3. Images of the breast ultrasound examination

A. Over the inferior aspect of the left breast, immediately below the areola, mottled low echoic areas are observed.

B. Under the skin redness, the low echoic area penetrated to the skin.

performed Gram staining on the biopsy specimen. Subsequently, we identified small cystic spaces in the granuloma, aggregated neutrophils, and a small number of gram-positive bacilli (GPB) in the cystic spaces. Based on these findings, the patient was diagnosed with CNGM (Figure 4).

Discussion

GM is a rare, benign, and chronic inflammatory disease first reported by Wolloch and Kessler in 1972⁵. Although identified approximately 30 years ago, the etiology of this disease has not yet been fully elucidated. Therefore, a treatment strategy has not yet been established. The treatments for GM include antibiotics, steroids, immunosuppressants, and surgical resection². In recent years, there have been some reports suggesting that GM is caused by *Corynebacterium* infection. Paviour et al. reported that 9 of 12 cases of GM were associated with a *Corynebacterium* infection¹. Among the *Corynebacterium* species, *C. kroppenstedtii* was most frequently isolated⁶. *C. kroppenstedtii* is a rare lipophilic *Corynebacterium* that lacks the characteristic acid in its cell envelope. Due to its dependence on lipids, the breast is a favorable site for its growth and proliferation⁷. For the culture of *C. kroppenstedtii*, lipid-supplemented media containing 1% Tween 80⁶ is required. *C. kroppenstedtii* is sensitive to many antibacterial drugs, but water-soluble antibiotics are less effective in the mammary glands. Therefore, in such cases, it is necessary to administer fat-soluble antibiotics, such as tetracycline¹. Taylor et al. reported 34 cases of inflammatory breast disease in which microbiological

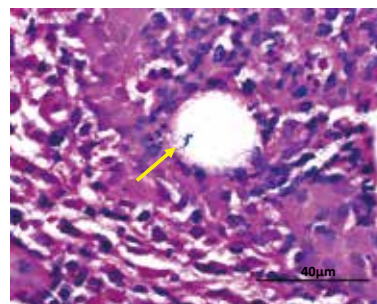


Figure 4. Pathological image of the abscess needle biopsy (Gram stain $\times 1000$)

Small cystic spaces are present in the granuloma, and neutrophils are aggregated. A small number of gram-positive bacilli are seen in the cystic space. (A yellow arrow indicates gram-positive bacillus).

specimens revealed the presence of *Corynebacterium* and/or histological specimens showed coryneform bacteria. Fourteen out of the 34 cases had coryneform bacteria on the histological sections, and the bacilli were confirmed to have empty spaces, consistent with dissolved lipids, and were surrounded by neutrophils⁶. In 2011, Renshaw et al. coined the term “cystic neutrophilic granulomatous mastitis” to draw attention to the distinct pattern of *Corynebacterium* infection in the breast that includes “enlarged vacuoles within neutrophilic inflammation” and the presence of GPB within the cystic spaces. Although all three cases reported by them showed GPB in single cystic spaces, they could not culture the bacteria in any of the cases⁸. This means that even if the causative bacterium of GM cannot be cultured, the bacteria may be present in the lesion of GM. The relationship with *Corynebacterium* species, which are GPB, has been strengthened. In 2020, Wu et al. summarized 141 cases of CNGM reported since 2002⁹. Epidemiological studies have revealed a relationship between CNGM and pregnancy (ranging from pregnancy to several years after birth). They pointed out that a review of the literatures clearly demonstrated the lack of a definitive all-encompassing definition of CNGM. Although there was no universal consensus on the definition of CNGM, morphological features suggestive of this evolving entity included lipid vacuoles rimmed by neutrophils and epithelioid histiocytes and contained GPB. They concluded that it was important to be aware of the association between CNGM and *Corynebacterium* species and pointed out the difficulties in detecting these organisms in tissue specimens by Gram staining and/or microbiological culture⁹.

EN has various causes. The most common causes are infections (28-48%), followed by sarcoidosis (11-25%), drugs (3-10%), pregnancy (2-5%) and enteropathies (1-4%). However, in many cases, it is impossible to determine the cause. The high incidence of EN in women suggests that it is related to sex hormones, and it may lead to the frequent occurrence during pregnancy or while using oral contraceptive pills. EN occurs in 4.6% of pregnant women. The role of sex hormones in the etiology of EN and their influence on the immunological system are not sufficiently known¹⁰. Some researchers have argued that EN is a self-limited disease and requires no treatment. They reported that the treatments should be directed at the underlying associated condition^{11,12}. EN is sometimes reported to be associated with GM. Metehan *et al.* insisted that we should keep in mind that EN can be caused by GM¹³. Ten cases of GM with EN have been reported to date, since the first report by Adams in 1987^{13,14}. Among them, 3 cases were associated with pregnancy²⁻⁴. Among these 3 cases, PSL alone was administered to 2 patients, and the other patient was administered PSL, colchicine, and azathioprine. The duration of treatment was not reported. Vural *et al.* reported that current knowledge could not definitely claim that EN, arthritis, and GM are autoimmune reactive processes; however, successful treatment using immunosuppressant agents and the lack of any other possible etiology may suggest an underlying autoimmune mechanism¹⁵. Our patient developed GM during pregnancy, and EN complications were also suspected based on the clinical course. We could not culture any bacteria in the pus of the lesion, but the diagnosis of CNGM was made based on the detection of GPB in tissue specimens by Gram staining and the pathological findings. We considered that the patient's EN-related symptoms, which may have occurred as an immune response to GM, were alleviated with PSL treatment. In this case, PSL rapidly improved the symptoms of EN and arthritis, while PSL took a long time to improve the symptoms of GM. We think that PSL might be useful for GM to some extent, and the discontinuation of breastfeeding might be one of the reasons for the improvement of the symptoms. If she was not a pregnant or breastfeeding woman and if it was known that the case was CNGM from the

beginning of treatment, it would have been possible to use antibiotics for radical treatment of GM, and the duration of treatment could have been reduced to less than 17 months. We hope that further case accumulation will define the pathogenesis of CNGM and establish a treatment.

Conclusion

We present the first case of CNGM during pregnancy. When hesitating to use fat-soluble antibiotics, such as tetracycline, PSL may be considered one of the treatments for CNGM.

COI Disclosure

The authors have no conflicts of interest to declare.

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