Granulomatous Mastitis Complicated by Arthralgia and Erythema Nodosum Successfully Treated with Prednisolone and Methotrexate

Tomoyuki Nakamura¹, Katsunobu Yoshioka², Tomoko Miyashita¹, Katsumi Ikeda³, Yoshinari Ogawa³, Takeshi Inoue⁴ and Keiko Yamagami¹

Abstract

A 23-year-old woman was admitted with complaints of swelling and pain in the left breast, fever, polyarthritis and erythema nodosum. A fine-needle biopsy of the mass in the left breast revealed non-caseous granulomatous lobulitis. A diagnosis of granulomatous mastitis was thus made. The administration of prednisolone 40 mg/day resulted in the resolution of the patient’s symptoms, and the breast mass thereafter decreased in size. The mass relapsed during the subsequent prednisolone taper. Additional therapy with methotrexate resulted in complete remission. Granulomatous mastitis should therefore be included in the differential diagnosis of polyarthritis.

Key words: granulomatous mastitis, erythema nodosum, polyarthralgia, glucocorticoids, methotrexate


Introduction

Granulomatous mastitis is a rare, benign and chronic inflammatory breast disease first described by Kessler and Wolloch in 1972 (1). It is clinically characterized by hard breast lumps with local inflammation and histologically by the presence of non-caseous granulomatous lobulitis. Polyarthritis and erythema nodosum, as opposed to fever, are rare systemic manifestations of granulomatous mastitis. As far as we know, only three such cases have so far been reported (2-4).

The etiology of granulomatous mastitis remains unknown. However, the histological findings and responsiveness to systemic glucocorticoid therapy suggest that the disease is caused by immune-mediated mechanisms.

We herein report the case of a patient with granulomatous mastitis complicated by severe polyarthritis and erythema nodosum who was successfully treated with systemic glucocorticoid and methotrexate (MTX) therapy. Additionally, the rationale for using such treatment strategies is discussed.

Case Report

A 23-year-old woman was admitted to our hospital in August of 2009 complaining of swelling and pain in the left breast, fever, an erythematous lesion on her leg and severe polyarthritis. She had been in good health until one month prior when she noticed swelling and pain in her left breast. She had no history of parturition, galactorrhea or breast injury and was taking no medications. She presented with a high fever and severe symmetrical polyarthritis and was evaluated at the breast surgery department of our hospital. Due to the fact that she had chills and could not move as a result of the severe polyarthritis, she was referred to our department and admitted to the hospital.

On admission, the patient was 163 cm in height and weighed 60 kg. Her temperature was 38°C, her pulse was 76 beats/min and her blood pressure was 100/60 mmHg. On physical examination, pain in the entire left breast accompa-
A mass was observed, as well as erythema nodosum of the left lower extremity (Fig. 1). The remainder of the physical examination was unremarkable. Laboratory tests on admission revealed elevated C-reactive protein levels and leukocytosis (Table). Ultrasonography revealed multiple abscesses in the left breast (Fig. 2). Computed tomography (CT) revealed multiple abscesses in the left breast and left axillary lymph node (Fig. 3). A diagnosis of arthritis and erythema nodosum caused by bacterial infection was initially suspected. After draining the contents of the abscess, the patient was started on antibiotic therapy with cefazolin. However, the symptoms and inflammation did not improve. Bacterial cultures of the blood and aspiration specimens were negative. Because a diagnosis of granulomatous mastitis was suspected at this point, a fine-needle biopsy of the mass was performed. Microscopic features showed a non-caseating granuloma composed of epithelioid cells. Multinu-
cleated giant cells were also present; however, no microorganisms were detected (Fig. 4). A diagnosis of sarcoidosis and Wegener’s granulomatosis was thus suspected. However, a diagnosis of sarcoidosis was thought to be unlikely because both angiotensin converting enzyme and the lysozyme levels were normal, and also because the granulomatous lesion was confined to the breast. Wegener’s granulomatosis was ruled out because tests for auto-antibodies, including proteinase 3 ANCA, were negative. After tuberculosis was also ruled out by normal chest X-rays and histological findings, a diagnosis of granulomatous mastitis was thus confirmed.

Since this patient had arthralgia and systemic inflammation, prednisolone 40 mg/day was administered starting on the 8th day of hospitalization according to the standard medical treatment of systemic granulomatous disease. The following day, this treatment regimen led to the resolution of the fever, erythema nodosum and arthralgia, and the patient regained the ability to walk independently. During the second week of treatment, the pain in the patient’s left breast improved and the CRP level normalized. Prednisolone was tapered by 5 mg every two weeks, and the abscess in the left breast became smaller on CT (Fig. 5). Two months later, while the patient was taking 15 mg/day of prednisolone, the swelling and pain in the left breast recurred. The dose of prednisolone was then increased to 50 mg/day; however, the symptoms did not improve. Surgery was contraindicated due to fistula formation. MTX 4 mg/week was added based on reports that it may be effective in patients that show a lack of response to steroids (5). One month after adding MTX, the patient’s symptoms improved. The dose of prednisolone was gradually tapered to 5 mg/day over eight months, and 4 mg/week of MTX was continued for one year. During the 5-month course of prednisolone administration, no disease recurrence was observed. Thereafter, the prednisolone dose was tapered to 1.25 mg/day over three months. Two years later, the abscess was found to have disappeared and MTX was therefore discontinued. The patient is now being treated with prednisolone 1.25 mg/day and has not experienced any further recurrence of the disease.

Discussion

Granulomatous mastitis usually presents with a unilateral breast lump, breast pain, nipple inversion and axillary lymphadenopathy. Because these symptoms are also seen in breast cancer and because granulomatous mastitis has no specific radiological appearance (6), it is difficult to clinically distinguish granulomatous mastitis from breast cancer. A histological examination is therefore essential for a proper diagnosis (7). The characteristic histological findings are lobular non-caseating granulomas with epithelioid histiocytes, giant cells and neutrophils and a negative microbiological investigation.

Due to histological similarities between the diseases, the differential diagnosis of granulomatous mastitis also includes tuberculosis, sarcoidosis, Wegener’s granulomatosis, fungal infection and aseptic abscesses syndrome (8). Aseptic abscesses syndrome, a clinicopathological entity first described in 1995, is characterized by recurrent manifestations of abscess-like areas that respond to corticosteroid therapy but not to antibiotics. Patients with aseptic abscesses syndrome also present with arthritis as well as pyoderma gangreno-
sum. Histologically, the abscess-like lesions contain mature neutrophils, epithelioid cells and giant cells (9). Therefore, clinical and histological similarities exist between granulomatous mastitis and aseptic abscesses syndrome. However, the typical presentation of patients with aseptic abscesses syndrome is characterized by the presence of aseptic lesions that are usually located in the spleen, liver and abdominal lymph nodes. In contrast, the abscess in the present case was localized to the breast and the skin lesion was typical of erythema nodosum. Therefore, the possibility of aseptic abscesses syndrome was considered to be low. It is necessary to distinguish these diseases based on both histological and clinical findings. The present case was diagnosed with granulomatous mastitis based on both findings, as described above.

Polyarthritis and erythema nodosum, as opposed to fever, are rare systemic manifestations of granulomatous mastitis. In 1987, Adams et al. reported the first case of granulomatous mastitis complicated by arthritis and erythema nodosum (2). Although cases of granulomatous mastitis complicated solely by erythema nodosum are occasionally reported, as far as we know, only two other cases of granulomatous mastitis complicated by both arthritis and erythema nodosum have been previously reported (3, 4). Because granulomatous mastitis usually develops in association with lactation, hyperprolactinemia or breast injury, an immune response to extravasated secretions from lobules has been proposed as an underlying mechanism. However, the present patient had no history of parturition, galactorrhea or breast injury. Therefore, this mechanism was unlikely. The presence of a microabscess implies an infective cause of granulomatous mastitis. However, no infectious agents were identified, despite extensive investigation. Therefore, the etiology of granulomatous mastitis in this case is unknown. However, the complications of polyarthritis and erythema nodosum and the responsiveness to glucocorticoid therapy suggest that the granulomatous mastitis in this case was caused by immune-mediated mechanisms. However, both auto-antibodies and auto-antigen-specific T cells are absent in patients with granulomatous mastitis. Therefore, granulomatous mastitis may be a form of autoinflammatory disease.

No consensus exists concerning the optimal treatment modality for patients with granulomatous mastitis. The treatment used in the present report consisted of corticosteroids and surgical excision. Patients without symptoms may be observed without treatment. It has been reported that 50% of granulomatous mastitis cases resolve spontaneously without treatment and a complete resolution occurs at a mean of 14.5 months (range: 2-24 months) (10). It was reported in 1980 that treatment with systemic corticosteroids is an effective therapy for granulomatous mastitis (11). However, an optimal dose of corticosteroid therapy has not yet been established, and the disease can recur when corticosteroids are tapered. Considering that the present case was complicated by severe arthralgia and erythema nodosum and an immune-mediated mechanism was suspected, corticosteroids were administered. In the present case, the initial response to prednisolone was excellent. However, the granulomatous mastitis relapsed when the dose of prednisolone was tapered to 15 mg/day. It has been reported that a low weekly dose of MTX may be effective in cases with resistance to corticosteroids (5, 12). Therefore, MTX was added to the patient’s therapy. Thereafter, the dose of prednisolone was reduced, leading to complete remission. The patient’s symptoms did not improve with increases in prednisolone; however, they did improve with the addition of low-dose MTX. The success of the clinical course of the present case was thought to be attributable to the efficiency of MTX plus prednisolone, not to the natural course of the disease.

In summary, we herein reported a rare case of granulomatous mastitis complicated by symmetrical arthralgia and erythema nodosum. MTX was used to reduce the dose of prednisolone, which resulted in complete remission. Physicians should therefore be aware of the existence of granulomatous mastitis in order to properly treat patients presenting with polyarthritis.

The authors state that they have no Conflict of Interest (COI).

References