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Management of granulomatous mastitis

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【Abstract】 Granulomatous mastitis can be a disturbing disease. More patients have been affected in recent years. Clinicians need to understand the etiology and course of disease before they can formulate a useful treatment strategy. This paper aims to review the literature and the local experience on the management of the disease.

【Key words】 Granulomatous mastitis; Therapeutics; Inflammation

Mastitis commonly occurs during breast feeding. But non-puerperal mastitis, especially granulomatous mastitis, can be a diagnostic challenge, as its clinical features can mimic breast cancer.

Kessler and Wolloch[1] firstly described granulomatous mastitis as a lesion clinically simulating carcinoma in 1972. They reviewed five cases of mastitis which were suspicious of cancer but characterized by granulomas and abscess formation. They reported this lesion as a well-defined entity which was different from other types of mastitis previously described.

Granulomatous mastitis may be idiopathic or secondary to microbial infection, sarcoidosis or reactionary to foreign body. Idiopathic granulomatous mastitis is not a common disease. It accounts for less than 1% of women undergoing breast biopsy[2]. It occurs predominantly in premenopausal women between 20 and 40 years of age, shortly after childbirth or occurs years after the last delivery[2]. It is mostly seen in Asia and Mediterranean region. Besides posing a diagnostic challenge mimicking breast cancer, granulomatous mastitis can be difficult to treat, especially when they develop fistula and abscess. An optimal treatment is yet to be found. There are various reports recently studying this disease entity and this review aims to discuss the latest findings on its etiology and management.

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1. Clinical features and course

Idiopathic granulomatous mastitis is usually unilateral and only 5% of cases occurred bilaterally[3-4].

Patients firstly present acute inflammation of the breast, associated with erythema, fever and painful mass, like other common forms of mastitis. If left untreated, the disease will progress into abscess formation, leading to chronic inflammation with skin ulcerations and fistula[5]. Wang et al[6] described in detail the different forms of the disease when it progresses through the different phases: (1) the phlegmon phase when the inflammation is at its early stage; (2) the abscess phase when there is frank abscess within the affected area; (3) the difficult-to-treat phase when skin complications occur.

It may be confused as cancer when it develops into its full form, presenting with additional features of nipple retraction and even peau d'orange. Because of its inflammatory nature, ipsilateral axillary lymph nodes are commonly enlarged. It is at this stage that the disease may be misinterpreted as inflammatory breast cancer.

2. Pathogenesis and etiology

The diagnosis of the disease is usually made by core needle biopsy or open biopsy. Histologically, there are lobular non-caseating granuloma, giant cells, epithelioid cells, macrophages and abscesses besides chronic inflammatory cells; sarcoidosis, Wegener's granulomatosis and breast cancer should be excluded. Microbiological evaluation includes gram staining, Ziehl-Neelson and periodic acid-Schiff (PAS) staining to exclude bacterial, mycobacterial and fungal

infection. Bacterial culture is usually negative[7-11].

The etiology is unclear. It has been postulated that granulomatous mastitis may arise from autoimmune response, infectious disease or hormonal disruption[12-16]. In certain occasions, the disease has been shown to be correlated with breast-feeding or the use of oral contraceptives. But most patients do not have such history, which that leads to the belief that it could be an autoimmune disease. Other factors include cigarette smoking, α1-antitrypsin deficiency, diabetes mellitus, breast trauma and obesity [17]. But none could be substantiated.

There are reports that associate granulomatous mastitis with Sjögren syndrome, erythema nodosum, arthritis or Hashimoto's thyroiditis which are autoimmune diseases[18]. In addition, intraductal proteinosis secretion and ductal ectasia leading to lymphocyte T-cell-mediated activities and intraductal inflammation and galactophoritis are thought to be the trigger of the autoimmune reaction [17,19]. But the autoimmune serologic tests are inconclusive and thus it is still controversial whether granulomatous mastitis is an autoimmune disease.

Wong et al[20] reported a series of patients infected by corynebacterium kroppenstedtii and the authors suggested that this could be an emerging cause of granulomatous mastitis. Interestingly, psychiatric illness was seen in 37% of patients with corynebacterium kroppenstedtii-related mastitis/abscesses, an incidence significantly higher than the local prevalence of mixed anxiety and depressive disorders and psychotic disorders in the local population. They thought that some cases of granulomatous mastitis were corynebacterium kroppenstedtii-related but were misdiagnosed as idiopathic because routine culture methods did not reliably isolate this slow-growing organism. The authors further suspected that antipsychotic-induced hyperprolactinemia may be a leading cause. Prolactin induces ductal ectasia and milk stagnation as well as pro-inflammatory effect through induction of nuclear factor κ-light-chain enhancer of activated B-cell signaling pathway. Li et al[21] reported a patient with idiopathic granulomatous mastitis associated with risperidone induced hyperprolactinemia, who was successfully treated with a dopamine agonist, bromocriptine with complete resolution, without surgical intervention.

Destek et al [22] reported the genetic study of a patient. They found mutations in methylenetetrahydrofolate reductase C677TT, β-fibrinogen-455G > A, plasminogen activator inhibitor-1 5G/5G, angiotensin-converting enzyme I/D. As these genetic changes have been reported to be closely related with inflammatory, autoimmune events and breast cancer, the authors suggested that genetic polymorphism may have implications on the development of granulomatous mastitis.

3. Investigation and diagnosis

The diagnosis of granulomatous mastitis should be confirmed by histology. Typically, there are lobular non-caseating granuloma, giant cells, and chronic inflammation. The biopsied materials should also be sent for gram staining and culture with special attention on identifying corynebacterium kroppenstedtii. Tuberculosis and fungal infection should be excluded by Ziehl-Neelsen and PAS staining.

Blood should be tested particularly on prolactin level. Besides, the usual complete blood picture on total while cells and neutrophil counts, other inflammatory parameters such as c-reactive protein, nuclear antibody, anti-ds DNA antibody, anti-microsomal antibody, anti-thyroglobulin antibody could also be tested if available.

The radiological features are non-specific and it is common that they mimic breast cancer. Mammography shows focal asymmetric densities whereas there are usually irregular nodular opacities and heterogenous hypoechoic nodules on sonography. MRI may show type 2 or 3 enhancement curves on kinetic studies.

4. Management

The management will depend on the different phases of the disease. In general, surgery can be done but it is not usually recommended as the first treatment of choice when it is at the beginning or at the late phase. However, the medical treatment of the disease is controversial. If there is history of anti-psychotic therapy, the disease will abate with the switch of medications. Patients with raised serum prolactin level can be treated successfully with bromocriptine.

As the etiology of the disease is unknown and commonly thought to be autoimmune in origin, patients without recognizable causes are commonly treated by

oral steroid therapy, especially during the acute phase. However, it is common for patients to experience recurrence, especially when only short-course steroid is used. The complete response rate is reported to be 63%–80% and 23%–30% of patients will experience recurrence[16,23]. It has been suggested that steroid therapy can be used against recurrences and for prolonged duration, especially for patients with partial response[24]. The other strategy is to use methotrexate, as for other autoimmune disease. The dose is usually 7.5–15.0 mg per week, even up to 20.0 mg per week[24-25]. The dose can be gradually reduced when the disease responds to treatment and the drug can be maintained for a year or even longer. The response rate is usually good and is reported to be about 83%[26].

We have been using non-steroidal anti-inflammatory drug (NSAID) to treat granulomatous mastitis. The disease in early phase responds very well, with almost complete resolution within 1 month. But maintenance therapy is required. The usual duration of therapy including the treatment at the acute phase is 3 months. It may take longer for more extensive disease. The sonographic resolution takes a bit longer but mostly not more than 3 months. NSAID is also used for patients with more advanced or extensive disease after drainage of pus. This usually follows the antibiotic treatment of corynebactrium. The majority of patients will require the treatment no less than 6 months.

During the abscess phase, the infected materials can be drained. If formal drainage is to be carried out, all pockets of pus should be drained and the abscess wall taken for histology to exclude cancer. It is customary to leave the wound open for packing and dressing. But on occasions when the skin is healthy and not inflamed, a suction drain can be inserted and the wound can be closed. Wang et al[6] suggested alternate drainage method with needle aspiration of the abscess, which can be done repeatedly. The skin can be left intact and avoid prolonged cumbersome dressing procedures.

Surgery can also be performed when the disease is stabilized. In patients with residual disease after medical therapy, surgery can be offered. It is necessary to remove all lesions including sinuses and chronically inflamed tissues. The principle of surgery is similar to that of cancer surgery and in most patients, wide local resection may be necessary. It is common to see patients with recurrence if the disease is not resected completely and some have been operated on for two to three times without cleaning up of the disease. The extent of surgery will depend on the experience of the surgeon. In difficult cases, frozen section to ensure clean margin can be considered. Once the disease is judged to be resected clean, cosmesis can be restored with rearrangement of the breast tissue as in oncoplastic procedure for breast cancer.

5. Conclusion

Granulomatous mastitis can be a difficult disease to diagnose and treat. Particular attention should be paid to look out for corynebacterial infaction and hyperprolactinemia. Medical treatment can be prolonged to reduce recurrence. Drainage of pus is necessary in case of abscess. Resection should be reserved for the disease in chronic phase and should be performed widely to remove all the chronically inflamed tissue.

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