Chapter

Sarcoid Involvement of the Mammary Gland

Patricia López Arribas, Elena Martínez Gómez and Álvaro Zapico Goñi

Abstract

Sarcoidosis is a systemic granulomatous disease of unknown cause. Mammary involvement is rare, less than 1% of all cases. In addition, it makes necessary an appropriate differential diagnosis in order to rule out malignant pathology as the main diagnosis. Therefore, it is necessary to carry out different tests as mammography, ultrasound, and histological confirmation if necessary. When the diagnosis of mammary sarcoidosis is suspected by fine needle aspiration cytology, exceptional procedures should be also considered to examine for the possibility of a coexisting carcinoma. In such cases, excisional biopsy or resection is strongly recommended. There are some cases of mammary sarcoidosis associated with breast cancer. Breast cancer may develop in patients with sarcoidosis, sarcoidosis may develop in patients with breast cancer, the two diseases may develop in tandem, or breast cancer may induce a sarcoidosis-like granulomatous response. Sarcoidosis is possibly linked to silicone gel breast implants. The silicone might cause a sarcoidlike reaction as the result of an acceleration of an already existing hypersensitivity response, resulting in mammary sarcoidosis. The management of sarcoidosis in the breast usually is an excisional biopsy. At the same time, we confirm diagnosis and the treatment is done. The prognosis of mammary sarcoidosis remains unknown.

Keywords: breast sarcoidosis, granulomatous disease, mammary gland, granuloma, breast mass

1. Introduction

Sarcoidosis is a multisystemic granulomatous disorder of unknown etiology [1]. Our understanding of the pathogenesis of sarcoidosis has advanced and provided new insights into potential causes of this disease. It is important to remember that any etiologic agent of sarcoidosis must be capable of causing the pathologic hallmark of systemic noncaseating granulomas and the heterogeneous clinical features of sarcoidosis [2]. It is caused by alteration of the cellular immune response after exposure to an environmental, occupational, or infectious hazard and can involve multiple tissues and organs, including breast tissue [3].

About 80–90% of patients present lung or hiliar lymph nodes affected. These are the most common systems involved. However, the involvement of skin, eyes,

nervous system, locomotor system, lacrimal and salivary glands, heart, and kidney in sarcoidosis has also been described [1].

Sarcoid involvement of the breast parenchyma has been extremely rare in patients with sarcoidosis, less than 1% of the overall diagnosed patients. It is more common in African American, Afro-Caribbean, Swedish, and Danish individuals. It typically presents in women in their third and fourth decade of life and can often mimic breast carcinoma [4].

The descriptions of breast sarcoid vary in the literature from masses with ill-defined margins or spiculated as seen in cancer, negative imaging, or other non-specific appearances [3]. The most common presentation is a palpable breast mass. Because sarcoidosis can mimic breast cancer, it makes the differential diagnosis very difficult [3].

2. Etiology

Since sarcoidosis was first described more than a century ago, the etiologic determinants causing this disease remain uncertain. Studies suggest that genetic, host immunologic, and environmental factors interact together to cause sarcoidosis. Immunologic characteristics of sarcoidosis include noncaseating granulomas, enhanced local expression of T helper-1 (and often Th17) cytokines and chemokines, dysfunctional regulatory T-cell responses, dysregulated Toll-like receptor signaling, and oligoclonal expansion of CD4+ T cells consistent with chronic antigenic stimulation. Multiple environmental agents have been suggested to cause sarcoidosis. Studies from several groups implicate mycobacterial or propionibacterial organisms in the etiology of sarcoidosis based on tissue analyses and immunologic responses in sarcoidosis patients. Despite these studies, there is no consensus on the nature of a microbial pathogenesis of sarcoidosis. Some groups postulate sarcoidosis is caused by an active viable replicating infection, while other groups contend there is no clinical, pathologic, or microbiologic evidence for such a pathogenic mechanism [2]. The authors posit a novel hypothesis that proposes that sarcoidosis is triggered by a hyperimmune Th1 response to pathogenic microbial and tissue antigens associated with the aberrant aggregation of serum amyloid A within granulomas, which promotes progressive chronic granulomatous inflammation in the absence of ongoing infection.

3. Clinical manifestations

In the breast, the clinical presentation is a breast mass that could be isolated or multiple and unilateral or bilateral. Most of the patients do not present infectious or inflammatory symptoms. Moreover the nodules are not painful. It is very important to be alert of the possible systemic symptoms that our patient may present. Sometimes breast sarcoidosis is the first diagnosis disease, but most times, the diagnosis is already done.

4. Diagnosis

The clinical impact of sarcoidosis is directly related to the extent of granulomatous inflammation and its effect on the function of vital organs.

In each patient, the sites and the severity of granulomatous involvement throughout the body must be assessed to determine the impact of sarcoidosis on

systems that most greatly affect the patient's activities and quality of life or that may lead to premature death.

In the breast, the most common symptom is a breast mass. It could be only one or multiple tumors. Therefore it is very important to make a correct differential diagnosis.

First of all, the physical examination probably discloses a non-tender, firm, and mobile lesion, with no nipple abnormalities. The patient could or not present axillary lymph nodes. But in some cases the lesions were fixed or tender, clinically resembling a carcinoma.

Then, we should perform some image techniques.

Mammography, most of the time, is the first test and usually shows a nonspecific, ill-defined mass with low density, poorly outlined with no microcalcification.

We have the same problem with ultrasound examination that does not support an unequivocal diagnosis, but we are able to point out the irregularity of the contours, hypoechoic spiculation, and nonhomogeneous internal echostructure of the nodule [5] (**Figure 1**).

The next step is the high-field system MR but always complementary to the previous ones.

Images can reveal the lesion to be a solitary signal-intensive inhomogeneous tumor with irregular contours, fast contrast enhancement, and an early "wash-out" phenomenon often observed in carcinomas or in inflammatory lesions of the breast.

After that, it is important not to forget that the imaging techniques do not offer a definitive diagnosis and we must correlate it with pathological diagnosis.

To rule out infection origin, we should perform microbiologic test as stains for fungi and acid-fast bacilli.

Biopsy of the breast demonstrates chronic granulomatous inflammatory process, with epithelioid granulomas and non-necrotizing giant cells (**Figure 2**).

Breast sarcoidosis is very uncommon; most of the times, a fine needle biopsy is not enough, so an excisional biopsy is necessary.

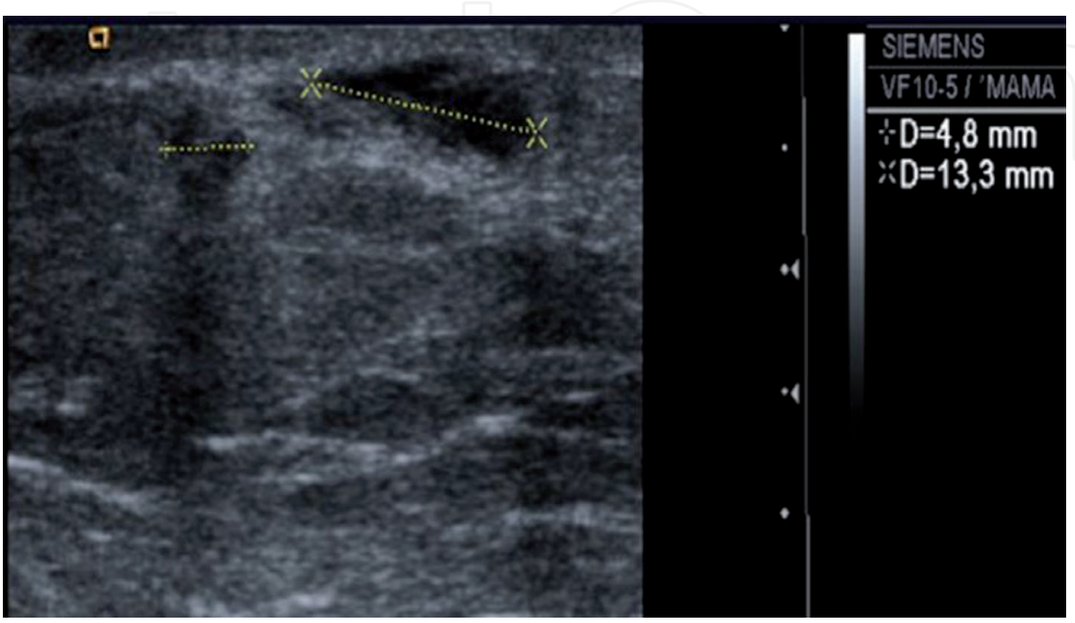

Figure 1.
Ultrasound examination with two nonspecific hypoechoic masses.

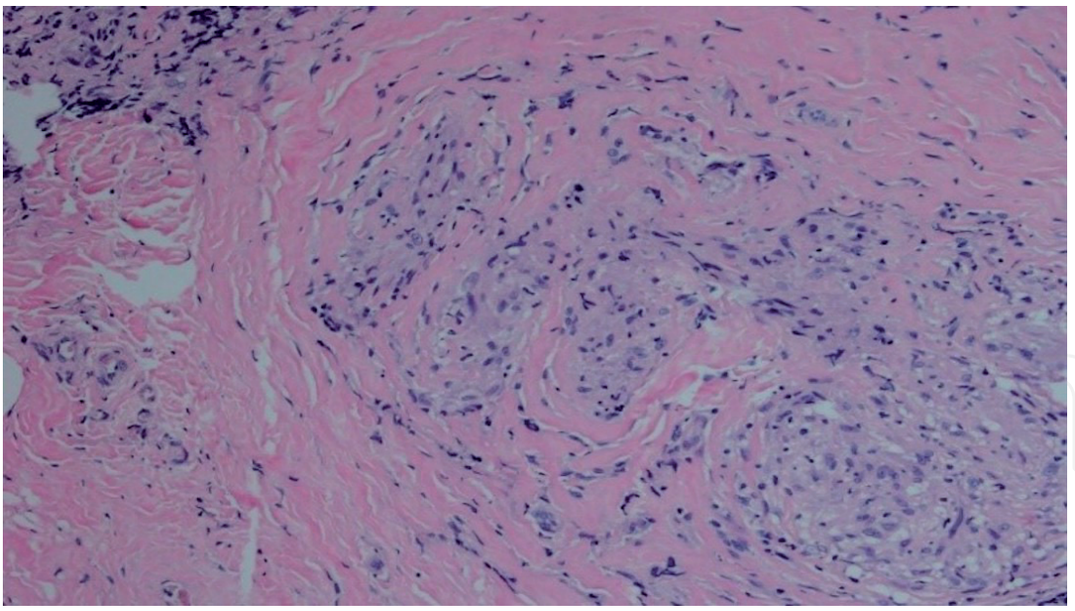

Figure 2.
Chronic granulomatous inflammatory process, with epithelioid granulomas and non-necrotizing giant cells.

The diagnosis is based on typical radiologic manifestations supported by histologic evidence of noncaseating granulomas in the absence of infection and exclusion of other types of granulomatous affections [6].

5. Differential diagnosis

There are some diseases that we should rule out when we are thinking about the diagnosis of sarcoidosis in the breast. Then, we break down each one of them.

5.1 Malignant pathology

First of all, the most important and the most frequent is malignant pathology of the breast. The American Cancer Society (ACS) estimates that 268,600 women will receive a diagnosis of invasive breast cancer and 62,930 people will receive a diagnosis of noninvasive cancer in one year. When we diagnose a breast mass, we suspect breast cancer. The initial test is mammography, ultrasound, and sometimes MRI. As we have previously objectified, there are no defined patterns in the imaging test for sarcoidosis in the breast, and we have the same problem with cancer. Therefore, we obtain a suspicious diagnosis that we need to confirm. After those techniques, we perform further tests like pathological test and immunohistochemistry to establish the definitive diagnosis, prognosis parameters, and correct therapy.

5.2 Idiopathic granulomatous mastitis (IGM)

Idiopathic granulomatous mastitis is a rare, chronic benign breast disease, which may mimic a breast abscess, malignancy, or other granulomatous pathologies. Most patients present in the third or fourth decade of life, and it typically is seen in women of childbearing potential from 6 months to 6 years postpartum. It is a diagnosis of exclusion and requires a high index of suspicion [7, 8].

Early misdiagnosis as bacterial mastitis is common, prompting multiple antibiotic regimens. When antibiotics fail, patients are worked up for inflammatory

breast cancer, given the nonhealing breast nodules. Mammography, ultrasonography, and fine needle aspiration often are unable to rule out carcinoma, warranting excisional biopsies of nodules. After that, we exclude malignancy and suspect a potential sarcoidosis or IGM.

Idiopathic granulomatous mastitis is a diagnosis of exclusion, made after obtaining evidence of granulomatous inflammation on breast biopsy and ruling out other granulomatous disorders, such as tuberculosis and sarcoidosis.

Almost the totality of sarcoid patients (90%) has lung disease; when we suspect a sarcoidosis, a chest radiograph is needed to screen for hilar lymphadenopathy and sometimes an ophthalmology evaluation [8].

Many cases self-resolve, but more severe cases can persist for a long period before adequate symptomatic treatment is achieved by methotrexate, corticosteroids, or surgical excision.

5.3 Tuberculosis

Breast tuberculosis (TB) is another disease characterized by the presence of granulomas. This pathology is rare but increasingly reported in Western Europe, accounting for 4.5% of all breast lesions in TB-endemic areas and 0.1% in the developed world.

The presenting features may mimic other breast pathologies including bacterial abscess, idiopathic granulomatous mastitis, sarcoidosis, or carcinoma, making diagnosis challenging. Risk factors for the development of breast TB include immunosuppression, lactation, multiparty, and previous exposure to TB [9, 10].

The most frequent symptom is an isolated mass, with less evidence of inflammation or infection than in other types of infectious mastitis. To this, we must associate that they do not present systemic symptoms.

Diagnosis of breast TB is difficult, often necessitating multiple clinic consultations and tissue sampling procedures. This frequently results in delays in TB treatment.

5.4 Sarcoidosis-like reaction

A phenomenon known as autoimmune/inflammatory syndrome induced by adjuvants may underlie the association between silicone implants and sarcoidosis-like reaction with foreign body granulomatous reaction, in which silicone serves as an immunologic adjuvant to enhance antigen-specific immune response. This leads to enhanced production and activation of both B and T cells [11].

There are some case reports in the literature that describe this reaction, and it may take place in the breast skin, subcutaneous tissue, and also in axillary lymph nodes.

6. Treatment

The treatment of breast sarcoidosis is similar to systemic sarcoidosis, but most of the time, an excisional biopsy has to be done to confirm the diagnosis, and if the sarcoidosis is isolated in the breast, then other treatments is not necessary.

Conflict of interest

The authors declare no conflict of interest.

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