

Breast Cancer and Sarcoidosis: Case Series and Review of the Literature

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Established Facts

- The presence of sarcoidosis and breast cancer in the same patient is uncommon but sarcoidosis can mimic breast cancer.
- The differential diagnosis between breast involvement of sarcoidosis and malignancy is difficult clinically and radiologically, and histologic study is necessary when this association is suspected.

Novel Insights

- We report the first case series of Jewish females affected by both sarcoidosis and breast cancer.
- Based on our clinical cases and literature review, a histologic study is highly recommended over imaging if sarcoidosis or breast cancer is suspected in a Jewish female.

Keywords

Sarcoidosis · Breast cancer · Sarcoid-like reaction

Summary

Background: Sarcoidosis is a chronic inflammatory disease of unknown etiology, which can involve different organs and systems. Accordingly, sarcoidosis can mimic breast cancer, making the differential diagnosis very difficult. **Case Report:** 5 patients with a diagnosis of both sarcoidosis and breast cancer followed by the Rabin Medical Center between January 1993 and June 2012 were enrolled in this study. Additionally, a comprehensive literature review which identified 104 patients diagnosed with breast cancer and sarcoidosis was carried out. In both populations reviewed, the average age at diagnosis of sarcoidosis and breast cancer was 57 years. Among the 66 patients with both sarcoidosis and breast

cancer, sarcoidosis preceded breast cancer in 31 cases, followed it in 23 cases, and appeared concurrently in 10 cases. **Conclusion:** Based on our clinical cases and literature review, a histological study is recommended over imaging if sarcoidosis or breast cancer may be present. Furthermore, breast cancer is rarely associated with sarcoidosis or sarcoidosis-like reaction.

Introduction

Sarcoidosis is a granulomatous inflammatory disease whose exact pathogenesis is not known [1]. It is caused by alteration of the cellular immune response after exposure to an environmental, occupational, or infectious hazard [2, 3], and can involve multiple

tissues and organs, including breast tissue. Accordingly, sarcoidosis can mimic breast cancer, making the differential diagnosis very difficult.

Although sarcoidosis is considered to be a rare manifestation in breast cancer, it is conceivable that this may be an under-representation. Despite similar clinical manifestations, very little is known about the incidence of breast cancer with a subsequent diagnosis of sarcoidosis within a short (2–4 years) period. Much of what is known about the clinical diagnosis and chronological connection between breast cancer and sarcoidosis, is based on a few published series [4–21].

The shared characteristics of the 2 diseases suggest that breast cancer and sarcoidosis may have a similar pathogenesis. Therefore, the present study examined all known cases from the Rabin Medical Center and those previously reported in the medical literature with the overall goal of improving patient outcomes and understanding the mechanisms that may be involved in the pathogenesis of sarcoidosis developing in patients with breast cancer. Additionally, it should be noted that this is the first report of such cases in the Jewish population.

Case Description and Methodology

Clinical Cases

We evaluated the medical records of all patients who were admitted to the Rabin Medical Center, Israel from 1993 to 2012 and had a confirmed diagnosis of both breast cancer and sarcoidosis or sarcoid-like reaction. Data extraction from the medical records included: medical history, medical images, and histological and pathological reports from breast tissue biopsies. All clinical classifications were according to the American College of Radiology (ACR) Lexicon for Mammography [22]. Pathological specimens were evaluated for the presence of non-caseating granulomas consistent with sarcoidosis and for the manifestation of proliferative breast disease.

Literature Review

Focusing on the English and French literature, we conducted a systematic PubMed search of articles published between 1951 and 2013; sarcoidosis was cross-referenced with the following search terms: sarcoid-like reaction, breast cancer, breast carcinoma, and mammary carcinoma. Our review of the literature identified 104 patients diagnosed with breast cancer and sarcoidosis ($n = 66$) or sarcoid-like reaction ($n = 38$) [1, 8, 13, 14, 18–21, 23–53].

Since this was a review of the literature and not a meta-analysis, no data extraction occurred. However, we recorded needed information from each source such as age, preoperative diagnosis, pathological evaluation, and treatment plan. The chronological connection of the diseases was assessed as follows: i) breast cancer 1 year prior to sarcoidosis; ii) sarcoidosis 1 year prior to breast cancer; or iii) diagnosis of both conditions within 1 year.

Results

Summary of Clinical Cases

We report 5 cases with histologically confirmed sarcoidosis and breast cancer diagnosed and treated at the Rabin Medical Center. Demographic and clinical data are summarized in table 1 (online supplemental, www.karger.com/?DOI=381324). All patients were Caucasian females with a mean age of 49.2 years (range 26–69

years) at diagnosis of sarcoidosis and 61.2 years (range 50–77 years) at diagnosis of breast cancer. All patients underwent curative surgical procedures and recovered without complications. At the time of conclusion of this study, all of these women were cancer survivors and free of breast malignancy, with a median follow-up of 6 years (range 1–18 years).

Literature Review

In 23 (22%) patients the breast cancer diagnosis preceded the identification of sarcoidosis; in 32 (31%) patients sarcoidosis preceded the diagnosis of breast cancer; and in 10 (10%) patients both diseases developed in parallel (table 2; online supplemental, www.karger.com/?DOI=381324). The average interval between the diagnosis of sarcoidosis and breast cancer was 9 years and 6 months. When breast cancer preceded sarcoidosis, the average interval was 4 years and 8 months. Table 2 displays the findings for all of patients with both breast cancer and sarcoidosis. Median age at the time of breast cancer diagnosis was 50 years (range 28–77 years), and median age at the time of sarcoidosis diagnosis was 49 years (20–70 years). Only 1 of 66 patients was male.

The patient's race, reported in 29 patients, was Caucasian in 21 (72%), Black in 6 (21%), and Asian in 2 (7%). Signs and symptoms of the malignancy at presentation were reported in detail in 26 patients, of whom 24 (92%) had a self-detected mass, and 1 (4%) had nipple retraction and a peau d'orange appearance; in 1 (4%) patient the mass was detected during routine gynecologic examination.

Reported in 34 patients, mass size at presentation ranged from 1 to 7 cm. The mass was located in the left breast in 21 (57%) patients and in the right breast in 15 (40%) patients; 1 (3%) patient had bilateral breast masses. The lesions were located in the upper quadrants in 19 patients (upper outer quadrant in 10, upper inner quadrant in 5, not specified in 4), and in the lower quadrants in 3 patients; in the remaining 12 patients the location of the mass was not specified.

Diagnostic evaluation for breast cancer included mammography, ultrasound, fine-needle aspiration, and excisional biopsy. Of the 35 patients in whom mammography findings were reported, 34 had abnormalities. We assume, based on common clinical practice, that more mammograms and biopsies were performed than specified in the reviewed literature. The same is true for other diagnostic studies.

Discussion

Sarcoidosis has a tendency to present between the ages of 20 and 49 years [44]. The incidence rates vary by race and geography, being higher among African Americans [44] and populations in Northern Europe [54]. Female gender is associated with a relative risk of 1.3 [44]. Among patients with breast cancer, the female predominance appears to be higher. Only 1 of the patients with breast cancer and sarcoidosis identified in the present review was male. Our report presents the first case series among the Jewish population, in particular Ashkenazi Jewish females, where the incidence

rate for breast cancer is higher. In US publications, the Jewish population is categorized as white or Caucasian, which could represent a potential limitation of our report.

There are several possible chronological associations that exist between breast cancer and sarcoidosis. As previously reported, breast cancer may develop in patients with sarcoidosis, sarcoidosis may develop in patients with breast cancer, the 2 diseases may develop in tandem, or breast cancer may induce a sarcoidosis-like granulomatous response [55].

Data from our medical center showed that sarcoidosis preceded breast cancer in 50% of the cases, appeared after breast cancer in 25%, and occurred in tandem in 25%. All breast cancer cases were managed according to common clinical practice. In all our patients, the physical findings of a mass and palpable axillary node (in 1 patient) could be attributed to either a malignancy or an inflammatory granulomatous process.

Sarcoidosis usually presents in the lungs, and is often accompanied by mediastinal or hilar lymphadenopathy [56]. One of the most frequent extrapulmonary manifestations is peripheral lymph node involvement, reportedly found in 8–15% of patients [56–58]. The possibility of axillary lymph node involvement in sarcoidosis poses a diagnostic challenge in the differentiation of sarcoidosis from suspected breast mass metastasis to the lymphatic system and warrants nodal tissue sampling in all cases.

Local inflammatory effects of sarcoidosis and sarcoid-like reaction could potentially cause technical difficulties during sentinel lymph node or axillary lymph node dissection. However, we did not encounter these problems nor were such scenarios reported in the literature.

Breast involvement is not common in sarcoidosis [55, 59], and the diagnostic and physical findings resemble those of breast cancer. Sarcoidosis and breast masses have similar features upon palpation. Imaging is also of little value in differentiating breast involvement in sarcoidosis from breast malignancy. Although most of the patients reported in the literature may be assumed to have undergone mammography or ultrasound, the majority of publications did not mention the results of imaging studies. Hence, we cannot reach conclusions regarding the effectiveness of various imaging techniques in the differential diagnosis of sarcoidosis with breast involvement and breast cancer. It is noteworthy that sarcoidosis has been reported to increase levels of CA 15-3 in some cases [60], so the presence of this biomarker might be misleading.

In our review of the literature, about one-third of patients presented with sarcoidosis before cancer and one-third had a regional

sarcoid-like reaction to the cancer; in 22% the cancer presented first, and in 10% both diseases occurred within less than 1 year of each other. The interval between the diagnosis of sarcoidosis and breast cancer was considerably longer (9 years and 6 months) than the interval between the diagnosis of breast cancer and sarcoidosis (4 years and 8 months). This finding may suggest a lack of chronological association between the 2 pathologies, especially when malignancy precedes sarcoidosis. This is consistent with previous reports which failed to demonstrate any clear association between breast cancer and sarcoidosis [24, 25, 61]. As for other malignancies, some authors described an increased incidence of lymphoma, lung cancer, and skin cancers in patients with sarcoidosis [14, 24, 62] whereas others did not [26, 63].

The exact nature of sarcoid-like reaction is unknown. It is usually found in proximity to the primary tumor or in its lymphatic drainage basins [13]. As sarcoid-like granulomas are histologically identical to sarcoidosis [31, 64], the diagnosis of sarcoid-like reaction should be based on the absence of other features of sarcoidosis. The high rate of sarcoid-like reaction among breast cancer patients in the literature highlights the importance of a thorough clinical investigation when sarcoid-like granulomas are found in the context of known breast cancer to detect the possible presence of sarcoidosis. Furthermore, sarcoid-like reaction in regional lymph nodes can conceal a metastasis and needs to be carefully evaluated [65].

In conclusion, the presence of sarcoidosis and breast cancer in the same patient is uncommon. The differentiation between breast involvement of sarcoidosis and malignancy is difficult clinically and radiologically, and histological study is necessary when this association is suspected.

Online Supplementary Material

Table 1. Rabin Medical Center case series: patients with breast cancer and sarcoidosis

Table 2. Summary of reports in the English literature of sarcoidosis and breast cancer cases (by sequence of appearance), and sarcoid-like reaction in breast cancer cases

To access the online supplemental tables, please refer to www.karger.com/?DOI=381324.

Disclosure Statement

The authors declare that they have no conflict of interest.

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