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Case Study

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# Breast sarcoidosis: 3 cases and literature review

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## Abstract

Breast involvement in sarcoidosis is rare, reported in less than 1% of cases. We report 3 new cases of breast sarcoidosis and analyzed the 22 previously published cases. Breast involvement was the only manifestation of sarcoidosis in only three cases while breast sarcoidosis was the site of sarcoidosis at presentation in 12 cases. Sarcoidosis was multi-systemic in 45% of the 25 cases. Except in one case, physical examination revealed multiple breast masses without skin/nipple changes or lymphadenopathy. X-ray, ultrasound of the breasts showed multiple irregular and/or spiculated hypoechoic masses without micro calcifications. MRI showed mass with gadolinium enhancement. Treatments, rarely given for BS rather than sarcoidosis, included steroids and immunosuppressant therapy, usually showed, a good efficacy in these series.

## Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology which can affect any tissue in the body. Sarcoidosis mostly occurs in young adults, especially between 20 and 40 years [1]. This inflammatory disease is caused by alteration of cellular immune response after multiple factors i.e. environmental, occupational, and genetic and/or infections [2]. The most frequent organs involved are lungs, lymph nodes, skin, eyes and liver. Sarcoidosis breast involvement is reported in less than 1% of cases although it is probably an under-estimation due to non-systematic performance of mammography [3,4]. Malignancy must always be considered [5-7]. Breast sarcoidosis can be diagnosed during the follow up of carcinoma [3,6] or both diseases can be diagnosed concomitantly [8,9]. We herein report 3 new cases of breast sarcoidosis and review in depth 22 cases previously published in literature with English abstract [4-7,10-26].

## Case report

### Case 1

A 44-year-old Caribbean female with a multi-systemic sarcoidosis (peripheral, thoracic and abdominal lymphadenopathy; pulmonary involvement; myelopathy and intracranial involvement) was successfully treated by both prednisone (0.5 mg/kg/d) and subcutaneous methotrexate (0.3 mg/kg/week). Immunosuppressive therapy was progressively reduced to obtain in 2010 a maintenance dose regimen (prednisone 5 mg/d; hydroxychloroquine 400 mg/d). In June 2015, CT scan showed stable pulmonary changes. FDG PET scan demonstrated hypermetabolic activity of mediastinal (SUV max 3.7) and axillary (SUV max 3.7) lymphadenopathy and bilateral pulmonary condensation (SUV max 7.4). Of note, there was no breast hypermetabolism. A systematic mammography revealed cystic lesions of inferior quadrants of the left breast. Breast ultrasound showed bilateral ectasia of mammary duct associated with a left dense nodular lesion which was suggestive of bilateral breast cancer (ACR4 classification). Pathology results of bilateral core biopsy showed a bilateral granulomatous inflammation consistent with sarcoidosis, without associated malignancy. The persistent pulmonary sarcoidosis activity was treated by prednisone (5 mg/d) and methotrexate (0.2 mg/week). In 2017, a clinical and morphologic relapse of sarcoidosis (central nervous system, pulmonary) was noted. FDG-PET-scan showed persisting bilateral breast hyper activity and abnormal pictures on echography (left hypoechoic lesion) / mammography (ill-defined mass with irregular contour) (right: ACR2; left ACR4) and MRI (breast hamartoma) (right: ACR2; left ACR3). She received for six months pulses of cyclophosphamide with no response. Then, she was treated by infliximab until March, 2018 (5 mg/kg) when sarcoidosis remained quiescent with neither neurological nor pulmonary signs.

### Case 2

In 1997, a 42-year-old Caribbean female presented, a severe multi-systemic sarcoidosis with erythema nodosum, uveitis, severe lung infiltration, lymphadenopathy and liver involvement. Compliance to treatment revealed very poor for more than 5 years. In 2005, she started a combination with prednisone (0.5 mg/kg/d), mycophenolate mofetil (3 gr/d), and monthly intravenous pulses of cyclophosphamide. A partial pulmonary and hepatic response was observed. After stopping cyclophosphamide, she was treated by infliximab (5mg/kg/8 weeks). Six months later, infliximab was withdrawn because of a paradoxical reaction (sarcoid lesions, biological inflammatory process, more severe hepatic disorders) and the patient status worsened. FDG-PET-scan showed diffuse, severe, hypermetabolic activity on thoracic, abdominal and pelvic nodes (SUX max 5.5 to 15.8), liver (SUV max 6), lymphoid facial structure (SUV max 10.5), bones (SUV max 8.1) and left breast (SUV max 5.5). Mammography was normal. Due to the discovery of that breast hypermetabolism along a multisystemic and severe sarcoidosis relapse, without any mammographic abnormality, we did not consider adequate to request a breast biopsy and supposed that the breast hyper metabolism corresponded to BS. She was treated

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successfully by cyclophosphamide pulses with prednisone. Three years later, FDG-PET-scan showed a good persistent response on nodes, bones, and nasal localization; there was no more breast hypermetabolic activity.

### Case 3

A 57-year-old Maghrebian female was admitted for multi-systemic sarcoidosis with skin (sarcoid lesion), nasal (nasal obstruction), salivary gland, joints (arthralgia), cervical nodes, stage II thoracic involvement and neurological signs (migraines). Cerebral MRI revealed meningeal gadolinium enhancement. Physical exam revealed a non-inflammatory tumefaction in the upper outer quadrant of the left breast, without skin change. The echography/mammography revealed a lesion with irregular borders. Breast MRI showed a T2 enhancement with T1 hyposignal, associated with enhancement on gadolinium images. Breast biopsy showed non-caseating giant cell granulomas without element of breast cancer. She received prednisone (0.5 mg/kg/d) associated with methotrexate (0.2 mg/kg/week). After 10 years-follow-up period, she presented a neurological relapse of the sarcoidosis; however, there was no relapse of breast granuloma and no appearance of breast cancer.

## Literature review and discussion

Sarcoidosis is a multi-systemic granulomatous disease of unknown etiology [1]. Breast sarcoid involvement is rarely reported and always in women [4-7,10-26]. In our sarcoidosis' series including 382 females, we observed 7 breast cancers (1.8%) and 3 breast sarcoidosis (0.8%), rates similar to those of the Lower's series [3]. Main characteristics of our three cases and twenty-two cases found in the literature are detailed in Tables 1 and 2 [4-7,10-26]. For the present study, we excluded cases with history of breast carcinoma and/or incidental finding of regional sarcoidosis-like reaction to the cancer in a breast removed for carcinoma as well as all differential diagnoses (Table 3). Of note, the comparative analysis revealed difficult to perform as cases were analyzed through either a pathological or radiological approach rather than clinical.

After review (Table 1) [4-7,10-26], BS appears exceptional under 30 years, mean age at BS diagnosis is 47.84 years (29-67) and in 59% (10/17) in black women [5,6,11,12,16,22,23,26] (Cases 1 and 2). Breast involvement was the sole manifestation of sarcoidosis in only three cases [9,17,18], and BS revealed sarcoidosis in 50% of cases [4,17,23].The most frequent sarcoidosis localizations associated with BS in 22 cases

**Table 1.** Main characteristics of patients with breast sarcoidosis

| | Ethnicity | Age SS* (years) | Age BS* (years) | Manifestations of systemic sarcoidosis | Positive biopsies for sarcoidosis | ACE at BS* | Treatment for sarcoidosis | Follow up of BS (months) |
|---|---|---|---|---|---|---|---|---|
| Ridgen B [4] | White | 22 | 29 | Unilateral linear shadowing, negative tuberculin test | Breast | ND | 0 | 48 |
| Ross MJ [5] | Black | 25 | 29 | Stage I thoracic | Kweim test | ND | Prednisone | 48 |
| Gansler TS [6] Case 1 | Black | 31 | 31 | Stage II, lymph nodes, ocular | Lymph node Pulmonary Breast | ND | ND | ND |
| Fitzgibbons PL [7] Case 1 | White | 70 | 65 | Stage I thoracic | Lymph node | ND | 0 | 120 |
| Fitzgibbons PL [7] Case 2 | White | 49 | 49 | None | Breast | ND | 0 | ND |
| Banik S [10] | White | 28 | 29 | Stage I thoracic, negative tuberculin test | Kweim test | high | ND | ND |
| Mc Pherson [11] | Black | 54 | 64 | Cutaneous, superior vena cava syndrome | Kweim test, Cutaneous, Lymph node, Breast | ND | 0 | 60 |
| Donaldson BA [12] | Caribbean | 44 | 44 | Stage II thoracic, hypercalcemia | Kweim test | high | Steroids | ND |
| Kenzel PP [13] | ND | 55 | 61 | Stage III thoracic, negative tuberculin test | Bronchial | normal | prednisone | 24 |
| Gisvold JJ [14] | ND | 57 | 67 | Cutaneous, cardiac | Cutaneous | ND | ND | ND |
| Harris KP [15] | ND | 53 | 53 | None | Breast | normal | 0 | 12 |
| Ojeda H [15] | Black | 43 | 43 | None | Breast | ND | ND | ND |
| Takahashi R [17] | Japanese | 48 | 48 | Stage I thoracic | Breast | high | ND | 25 |
| Ishimaru K [18] | ND | 26 | 31 | Stage I thoracic, cutaneous, negative tuberculin test | Breast | normal | 0 | 0 |
| El Khoury M [19] | ND | 50 | 50 | Stage III thoracic | Breast | ND | 0 | 0 |
| Fiorucci F [20] | White | 50 | 51 | Stage II thoracic, uveitis | Breast | high | Prednisone 0.5 mg/kg/d | 20 |
| Nicholson BT [21] | ND | ? | 58 | Stage III thoracic, pituitary | Breast | ND | ND | ND |
| Hermann G [22] | Black | 31 | 41 | Cutaneous | Breast | ND | 0 | ND |
| Rishi M [23] | Black | 31 | 39 | Stage I thoracic Liver | Breast | ND | Prednisone | 12 months |
| Panzacchi R [24] | ND | 57 | 57 | Stage II thoracic | Trans bronchial biopsy | high | Steroids | 15 |
| Zujic PV [25] | ND | 54 | 54 | Stage II thoracic High calcium level | Breast | high | Prednisone | 24 |
| Mason C [26] | Black | 37 | 37 | Stage II thoracic | Breast | ND | 0 | ND |
| Case 1 | Caribbean | 44 | 51 | Stage II thoracic, central nervous system, salivary glands, diffuse lymphadenopathy | Bronchial Lymphadenopathy Salivary glands, Nervous system | high | Prednisone: 5 mg/d + MTX 0.2 mg/kg/wk; cyclophosphamide; infliximab | 24 |

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|---|---|---|---|---|---|---|---|---|
| Case 2 | Caribbean | 42 | 58 | Stage III thoracic, liver, ocular, cutaneous, nasal diffuse lymphadenopathy, poor general condition | Bronchial, liver, Osteo-medullar Lymph node | high | Cyclophosphamide, Prednisone: 15 mg/d | 12 |
| Case 3 | Maghrebian | 57 | 57 | Stage II thoracic, central nervous system, ocular, nasal, salivary glands, joint | Nasal | high | Prednisone: 50 mg/d + MTX 20 mg/wk | 108 |

*SS: Systemic Sarcoidosis, BS: Breast Sarcoidosis, ACE: Angiotensin Converting Enzyme, MTX: Methotrexate, ND: Not Determined

**Table 2.** Main characteristics of breast sarcoidosis

| | Age at BS* (years) | BS detection | Echography | Mammography | CT-scan/MRI | Fine needle aspiration cytology | Core biopsy/ excision |
|---|---|---|---|---|---|---|---|
| Ridgen B [4] | 29 | Right breast nodule | ND | ND | ND | ND | ND/+ |
| Ross MJ [5] | 29 | Two irregular non tender breast masses | ND | ND | ND | ND | ND/+ |
| Gansler TS [6] Case 1 | 31 | Palpable nodule | ND | ND | ND | ND | ND/+ |
| Fitzgibbons PL [7] Case 1 | 65 | Palpable nodule | ND | ND | ND | ND | ND/+ |
| Fitzgibbons PL [7] Case 2 | 49 | Mass | ND | ND | ND | ND | ND/+ |
| Banik S [10] | 29 | Smooth mobile lesion | Normal | Normal | ND | ND | ND/+ |
| Mc Pherson [11] | 64 | Firm breast left mass | ND | ND | ND | ND | ND/+ |
| Donaldson BA [12] | 44 | Painless left breast masses, soft, non-tender, movable | ND | ND | ND | ND | ND/+ |
| Kenzel PP [13] | 61 | Mass | Hypoechoic lesion, sharply outlined contours | Ill-defined mass | Hyper intense, inhomogeneous tissue, irregular contours early washout phase | ND | ND/+ |
| Gisvold JJ [14] | 67 | Systematic mammography | ND | Multiple non-calcified spiculated bilateral nodules | ND | ND | +/ND |
| Harris KP [15] | 53 | Breast discomfort Localized nodule | Normal | Pronounced nodularity and architectural distortion | ND | ND | +/+ |
| Ojeda H [15] | 43 | Mass | ND | ND | ND | - | ND/+ |
| Takahashi R [17] | 48 | Painless right breast mass, soft movable mass | ND | Ill-defined mass without calcification | ND | + | ND/+ |
| Ishimaru K [18] | 31 | Mass | Small, irregular hypoechoic lesion surrounded by echogenic rim | Spiculated mass without calcifications | Hyper intense with irregular border after gadolinium | ND | ND/+ |
| El Khoury M [19] | 50 | Palpable painless mass | Hypoechoic lesion | Mass with speculated margins. | Intensely enhancing speculated mass | ND | +/ND |
| Fiorucci F [20] | 51 | Palpable nodule | Hypoechoic lesion | Speculated left lesion | ND | ND | ND/+ |
| Nicholson BT [21] | 58 | Mammography | Multiple bilateral round ill-defined hypoechoic mass with hyperechoic rims | Bilateral, round, ill-defined equal density | ND | ND | +/ND |
| Hermann G [22] | 41 | Chest discomfort | ND | Asymmetric left breast density | ND | ND | +/ND |
| Rishi M [23] | 39 | Mammography | ND | Left breast micro-calcifications | ND | ND | ND/+ |
| Panzacchi R [24] | 57 | Mammography | ND | Suspicious eft breast nodule | ND | + | +/+ |
| Zujic PV [25] | 54 | Extensive skin lesion of left breast; palpable induration; pigmentation; axillary lymphadenopathy | Hypoechoic lesion with thickened skin | Parenchymal blurring fused within the pectoral muscle | Extensive inflammatory changes of left breast; infiltration of pectoral muscle; enlarged left axillary lymph | ND | +/ND |
| Mason C [26] | 37 | Mammography | Ill-defined hypoechoic lesion | Single dilated duct of right breast | ND | + | ND/ND |
| Case 1 | 51 | Echography | Bilateral ectasia of mammary ducts and dense nodular lesion | Cystic lesions | ND | ND | +/ND |
| Case 2 | 58 | FDG- PET scan: intense hypermetabolic activity (SUV 10.5) | ND | Normal | ND | ND | ND/ND |
| Case 3 | 57 | Noninflammatory palpable tumefaction | Hypoechoic lesion | Nodular lesion | T2 enhancement, Hyposignal T1, gadolinium enhancement | ND | +/ND |

*BS: Breast Sarcoidosis, MRI: Magnetic Resonance Imaging, ND: Not Determined

**Table 3.** Breast mass in sarcoidosis patients: differential diagnosis.

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| • Tuberculosis |
| • Leprosy |
| • Brucellosis |
| • Typhoid |
| • Blastomycosis |
| • Coccidioidomycosis |
| • Sporothrichosis |
| • Histoplasmosis |
| • Hydatid disease |
| • Cysticercosis |
| • Filariasis or oxyuris infestation |
| • Granulomatous mastitis |
| • Foreign-body |
| • Reaction from surgical procedures or substances introduced for cosmetic reasons |

were thoracic in 81% of cases (stage I: 6 cases; stage II: 8 cases; stage III: 4 cases) [5-7,10,12,13,17-21,23-26] (Cases 1, 2 and 3), skin (23%) [11,14,18,22] (Case 2) and eyes (18%) [6,20] (Cases 2 and 3). Sarcoidosis was multi-systemic (≥ to 2 organs and/or hypercalcemia) in 45% of cases. Nodules, masses, and discomfort of breast revealed BS in 60% of cases with normal skin appearance [4-7,10-13,15,16-22,25] (Case 3). Usually, physical examination revealed multiple unilateral or bilateral breast masses without skin/nipple changes or lymphadenopathy. Only 1 patient had extensive skin lesion with palpable induration of left breast [25].

BS could also be discovered on systematic echo/mammography (6 cases) [14,21,23,24,26] (Case 1), or FDG-pet scan (Case 2). The echographic lesion appears as an irregular hypoechoic mass (8/9 cases) [13,18-21,25,26] (Case 3), or shows ectasia of mammary duct and dense nodular lesion [26] (Case 1). Bilateral mammography performed in 17 cases was normal in 2 cases [12], (case 2), or demonstrate abnormal pictures in 10 cases such as unique [13,15,17-20,22-25] or multiple irregular and/or spiculated masses [14,21]. Of note, micro calcifications are exceptional [23] as well as dilated duct [26]. MRI was rarely reported but it was always abnormal (4/4), showing irregular mass with gadolinium enhancement [13,18,19,25] (Case 3). FDG-PET-scan can show hypermetabolic breast lesion (as in our Case 2), sometimes associated to sarcoidosis typical butterfly distribution pattern of hypermetabolic mediastinal and hilar lymphadenopathy [27] (Case 2). As all imaging suggest malignancy, breast biopsies are mandatory to eliminate all differential diagnoses including carcinoma (Table 3). In our case 2, once having eliminated differential diagnosis, we estimated appropriate to evoke a breast localization of sarcoidosis as breast hypermetabolism appeared simultaneously to a severe multisystemic flare up of the disease. Regression of hypermetabolism following immunosuppressive treatment confirmed our diagnosis.

In 2 cases, fine needle aspiration cytology demonstrates lymphocytes, epithelioid-like cells, aggregate histiocytes or/and reticulocytes without necrosis [17,24] and/ or core biopsy (10/10 cases) [14,15,19,21,22,24,25] (Cases 1 and 3), and/or excision (16/16 cases) [4-7,10,13,15-18,20,23,24]. In order to eliminate sarcoid-like reaction, clinical, laboratory and morphological investigations (Chest X ray, CT scan, FDG PET scan) must be consistent with a diagnosis of sarcoidosis. Typical histological pattern of sarcoidosis was noted in other organs than breast in 12 cases [5,6,7,11,13,14,24] (Cases 1, 2 and 3) or Kweim test alone [10,11]. Based on 14 cases with sufficient details, the mean follow up was 39.42 months (12 to 120). Among the 7 published cases who received steroids for their sarcoidosis, none relapsed from BS. However, in our 3 cases, despite immunosuppressive therapy, we did not observe regression of mammography abnormalities in two cases while we found a normalization of FDG-PET-scan in one case. In other published cases, BS was asymptomatic, with an indolent course and no therapy was required except excision. Breast localization of sarcoidosis was not an indication to immunosuppressive treatment. The latter was indicated for extra-breast severe localization of sarcoidosis which might compromise vital or functional prognosis. In those cases, corticosteroids were usually able to induce clinical and imaging improvement of BS [5,12,13,20,23,24,25] (Cases 1, 2 and 3). When BS is diagnosed, it is necessary to have regular follow up due to the possibility of coexisting BS and breast malignancy [3,5,10,30-32]. Nevertheless, previous reports did not demonstrated any association between sarcoidosis and breast cancer [9,30].

Our three cases report and 22 previously published cases emphasize the possibility to observed BS, independently of breast carcinoma. Breast sarcoidosis remains a rare localization of sarcoidosis with diverse and nonspecific characteristics. Imaging features frequently mimic a breast cancer. Core biopsies are mandatory to confirm sarcoidosis and eliminate other diagnoses. In cases with localized BS, breast mass excision seems to be sufficient with no relapse of BS. Nevertheless, a prolonged breast follow-up is necessary in all cases.

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