

Case Series

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 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 here in 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 one chography (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 (5mg/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 (3gr/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 multi systemic 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 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.

A 57-year-old Maghrebien 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] (case 1-2-3), BS appears exceptional under 30 years, mean age at BS diagnosis is 47.84years (29-67) and in 59% (10/17) in black women [5,6,11,12,16,22,23,26](case 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 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] (case 1, 2 and 3), skin (23%) [11,14,18,22] (Case 2) and eyes (18%) [6,20] (case 2 and 3). Sarcoidosis was multi-systemic (\geq 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 in duration 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 speculated 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 showed hyper metabolic 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 hyper metabolism appeared simultaneously to a severe multi systemic flare up of the disease. Regression of hyper metabolism 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] (case 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] (case 1, 2 and 3) or Kveim 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

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 (2) 1978	White	22	29	Unilateral linear shadowing, negative tuberculin test	Breast	ND	0	48
Ross MJ (3) 1983	Black	25	29	Stage I thoracic	Kweim test	ND	Prednisone	48
Gansler TS (4) 1984, Case 1	Black	31	31	Stage II, lymph nodes, ocular	Lymph node Pulmonary Breast	ND	ND	ND
Fitzgibbons PL (5) 1985, Case 1	White	70	65	Stage I thoracic	Lymph node	ND	0	120
Fitzgibbons PL (5) 1985, Case 2	White	49	49	None	Breast	ND	0	ND
Banik S (8) 1986	White	28	29	Stage I thoracic, negative tuberculin test	Kweim test	high	ND	ND
McPherson (9) 1993	Black	54	64	Cutaneous, superior vena cava syndrome	Kweim test, Cutaneous, Lymph node, Breast	ND	0	60
Donaldson BA (10) 1995	Caribbean	44	44	Stage II thoracic, hypercalcemia	Kweim test	high	Steroids	ND
Kenzel PP (11) 1997	ND	55	61	Stage III thoracic, negative tuberculin test	Bronchial	normal	prednisone	24
Gisvold JJ (12) 2000	ND	57	67	Cutaneous, cardiac	Cutaneous	ND	ND	ND
Harris KP (13) 2000	ND	53	53	None	Breast	normal	0	12
Ojeda H (14) 2000	Black	43	43	None	Breast	ND	ND	ND
Takahashi R (14) 2001	Japanese	48	48	Stage I thoracic	Breast	high	ND	25
Ishimaru K (16) 2002	ND	26	31	Stage I thoracic, cutaneous, negative tuberculin test	Breast	normal	0	0
El Khoury M (17) 2005	ND	50	50	Stage III thoracic	Breast	ND	0	0
Fiorucci F (18) 2006	White	50	51	Stage II thoracic, uveitis	Breast	high	Prednisone 0.5 mg/kg/d	20
Nicholson BT (19) 2007	ND	?	58	Stage III thoracic, pituitary	Breast	ND	ND	ND
Hermann G (20) 2008	Black	31	41	Cutaneous	Breast	ND	0	ND
Rishi MA (21) 2009	Black	31	39	Stage I thoracic Liver	Breast	ND	Prednisone	12
Panzacchi R (22) 2010	ND	57	57	Stage II thoracic	Trans bronchial biopsy	high	Steroids	15
ZujicPV (23) 2015	ND	54	54	Stage II thoracic High calcium level	Breast	high	Prednisone	24
Mason C (24) 2017	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

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
*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 (2) 1978	29	Right breast nodule	ND	ND	ND	ND	ND/+
Ross MJ (3) 1983	29	Two irregular non tender breast masses	ND	ND	ND	ND	ND/+
Gansler TS (4) 1984, Case 1	31	Palpable nodule	ND	ND	ND	ND	ND/+
Fitzgibbons PL (5) 1985, Case 1	65	Palpable nodule	ND	ND	ND	ND	ND/+
Fitzgibbons PL (5) 1985, Case 2	49	Mass	ND	ND	ND	ND	ND/+
Banik S (8) 1986	29	Smooth mobile lesion	Normal	Normal	ND	ND	ND/+
McPherson (9) 1993	64	Firm breast left mass	ND	ND	ND	ND	ND/+
Donaldson BA (10) 1995	44	Painless left breast masses, soft, non-tender, movable	ND	ND	ND	ND	ND/+
Kenzel PP (11) 1997	61	Mass	Hypoechoic lesion, sharply outlined contours	Ill-defined mass	Hyper intense, inhomogeneous tissue, irregular contours early washout phase	ND	ND/+
Gisvold JJ (12) 2000	67	Systematic mammography	ND	Multiple non calcified spiculated bilateral nodules	ND	ND	+ /ND
Harris KP (13) 2000	53	Breast discomfort Localized nodule	Normal	Pronounced nodularity and architectural distortion	ND	ND	+ /+
Ojeda H (14) 2000	43	Mass	ND	ND	ND	-	ND/+
Takahashi R (15) 2001	48	Painless right breast mass, soft movable mass	ND	Ill-defined mass without calcification	ND	+	ND/+
Ishimaru K (16) 2002	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 (17) 2005	50	Palpable painless mass	Hypoechoic lesion	Mass with speculated margins.	Intensely enhancing speculated mass	ND	+ /ND
Fiorucci F (18) 2006	51	Palpable nodule	Hypoechoic lesion	Speculated left lesion	ND	ND	ND/+
Nicholson BT (19) 2007	58	Mammography	Multiple bilateral round ill-defined hypoechoic mass with hyperechoic rims	Bilateral, round, ill-defined equal density	ND	ND	+ /ND

Hermann G (20) 2008	41	Chest discomfort	ND	Asymmetric left breast density	ND	ND	+ /ND
Rishi M (21) 2009	39	Mammography	ND	Left breast micro-calcifications	ND	ND	ND/+
Panzacchi R (22) 2010	57	Mammography	ND	Suspicious left breast nodule	ND	+	+ /+
ZujicPV (23) 2015	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 (24) 2017	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	Non inflammatory palpable tumefaction	Hypoechoic lesion	Nodular lesion	T2 enhancement, Hypo-signal T1, gadolinium-enhancement	ND	+ /ND

*BS, breast sarcoidosis; MRI, magnetic resonance imaging; ND, not determined;

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

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

compromise vital or functional prognosis. In those cases, corticosteroids were usually able to induce clinical and imaging improvement of BS [5,12,13,20,23-25] (case 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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