Case report
Sarcoidosis and breast cancer: A retrospective case series

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ABSTRACT

Background: Sarcoidosis and breast cancer co-incidence is reported in the literature in the form of case reports.

Aim: To describe our experience from a single large sarcoidosis clinic.

Methods: Retrospective chart review of 1000 sarcoidosis cases seen in our clinic from 2003 to 2008.

Results: 429/1000 female sarcoidosis cases were identified. Among them 20/429 had a history of sarcoidosis and breast cancer. In 12/20 breast cancer preceded sarcoidosis by 52 months, in 4/20 sarcoidosis preceded breast cancer by 200 months and in 4/20 they presented concurrently. Mean age of sarcoidosis diagnosis was 53.9 (±12.4) years. Majority were of European decent (16/20), 3 were African-Americans and 1 Asian. Scadding radiography stages distribution was (n) 4/11/3/2/0 for stages 0/I/II/III/IV respectively. They had 3.4 (±1.3) organs involved, mainly with intrathoracic involvement. 10/20 were asymptomatic and 11/20 received chronic treatment. Compared to 409 cases of sarcoidosis sine breast cancer (mean age 46.7 ± 13.1), sarcoidosis-breast cancer cases had sarcoidosis diagnosed at a significantly later age (p = 0.01). Histological diagnosis applied in all co-incidence cases, in 5 via mediastinoscopy.

Conclusions: Older females with breast cancer may develop sarcoidosis, with features indistinguishable from stand-alone sarcoidosis. When sarcoidosis is suspected histological diagnosis is mandatory.

1. Introduction

Sarcoidosis is a granulomatous disease that can affect any organ system. The granulomas appear to occur from an altered immune response directed toward an antigen(s) that is yet to be identified. Since the original report by Brincker describing an increased prevalence of various malignancies in the context of sarcoidosis, investigators sought to characterize a causal relationship based on the hypothesis that the altered immune response in sarcoidosis may predispose patients to cancer [1,2]. Malignancies linked with sarcoidosis include both hematologic and solid malignancies, including breast cancer [1,3]. Sarcoidosis and breast cancer coincidence is described in the form of case reports [4].

We conducted this study in order to provide our experience from a single large sarcoidosis clinic; to record any such coincidence cases (sarcoidosis and breast cancer) and to describe the clinical characteristics and course of sarcoidosis when coexists with breast cancer in the same patient.

2. Materials and methods

2.1. Study design and subjects

We performed a retrospective chart review of all patients with biopsy proven sarcoidosis seen from year 2003–2008 in the sarcoidosis clinic at the University of Southern California-University Hospital at Keck School of Medicine, Los Angeles. This retrospective study was Institutional Review Board approved with a consent waiver. Start and end dates of the study were defined arbitrarily, in order to include a large sum of patients (start date) and influenced by the affiliation of principal investigators to the institution (end date). Diagnosis of sarcoidosis was based on ATS/ERS/WASOG criteria [5]. The subjects were included into the study if they had proven sarcoidosis, if they were female and if there was a history of breast cancer (S + BC). To better study demographics and disease characteristics, S + BC subjects were further classified in three groups; group A where diagnosis of BC preceded sarcoidosis, group B where sarcoidosis preceded BC and group C, where the two diseases were diagnosed simultaneously (within one year). S + BC subjects were...
comparing for age and race to rest sarcoidosis sine breast cancer cases (S-BC).

2.2. Statistical analysis

We performed column statistics to calculate means (± Standard Deviation, SD), non-parametric two-tailed test to compare measured variables (age) and chi-square test for categorical variables (race). We used Graphpadprism 8 (USA). Statistically significant was a p value < 0.05.

3. Results

Of 1000 sarcoidosis subjects screened from 2003 to 2008, we identified 429 females with sarcoidosis. Among them, 20 were found to have a history of breast cancer. All of them were alive by January 01, 2009. The complete % prevalence of female breast cancer in our sarcoidosis population was 4.6% (20/429). 4 cases were diagnosed inside the study period, therefore crude incidence rate was 155 new cases per year per 100,000.

Demographics of all subjects are shown in Table 1. When coinciding with breast cancer, sarcoidosis was diagnosed at an older age (t-test, p = 0.01). Fig. 1 shows the age distribution of sarcoidosis subjects in ACCESS study and in our clinic population. A shift to the right representing older age is noted in our sarcoidosis with breast cancer cases. Breast cancer was diagnosed at 51 (±10.8) years of age.

In 12/20 cases BC preceded sarcoidosis by 52 months (SD ± 31) (group A). In 4/20 cases sarcoidosis preceded BC by 200 months (SD ± 140) (group B). In 4/20 cases diseases presented concurrently (group C) (Table 1).

Detailed clinical presentation along with breast cancer treatments is shown in Table 2. 10/20 cases were asymptomatic and were detected incidentally. Interestingly, 3 cases had sarcoidosis that was in remission, recur after the diagnosis of breast cancer. Most common organs involved were lungs and central lymph nodes. Mediastinoscopy was the diagnostic procedure in 5 cases. 11/20 cases received treatment to achieve and maintain sarcoidosis control.

4. Discussion

We presented 20 cases of female sarcoidosis patients with breast cancer. In the majority, breast cancer preceded sarcoidosis, the latter presenting rather shortly after and at an older age than usual. Sarcoidosis affected mainly lungs and central lymph nodes, was multi-systemic and not always needed treatment. Compared to our sarcoidosis sine breast cancer patients, co-existence patients developed sarcoidosis with similar disease characteristics but at a later age.

Recently, Chen et al. reported 5 cases of sarcoidosis and breast cancer median age of whom was 49 years old when sarcoidosis was diagnosed. The authors suggested that an association between two diseases is uncommon and should be confirmed histologically [6]. Schweitzer et al. reported 10 such cases, where sarcoidosis was diagnosed at 61 years old females, on average 4 years after breast cancer diagnosis. The authors concluded that patients with breast cancer may be at risk for developing sarcoidosis [7]. Further, Grados et al. reported 4 cases of sarcoidosis diagnosed 3 years after breast cancer. Sarcoidosis was diagnosed at 55 years of age, was often asymptomatic and necessitated treatment at half of cases. The authors conclude that sarcoidosis should be considered at the differential diagnosis of breast cancer patients presenting on computed tomography or positron emission tomography scans with lymphadenopathy or pulmonary opacities [8].

Our findings agree with the published above studies. In our series sarcoidosis usually followed breast cancer by 4.3 years and was diagnosed at 54 years, was often asymptomatic, detected on follow-up and was diagnosed histologically. However, we were able to further compare our S + BC cases to our S-BC cases (n = 409) as well as historic ASSSESS population, showing that significant proportion of co-existence patients (>40%) present with sarcoidosis over 55th year of age [9].

The retrospective of our study does not allow firm epidemiological conclusions. However, prevalence of breast cancer is reported 14% between 40 and 49 years of age and 23% between 50 and 59 years; as well incidence rates of 538/100,000 population [10]. The rates we observed in our population are substantially lower, in a way that our data may not preclude but definitely do not support a causal association between sarcoidosis and breast cancer.

Other authors suggest an increased incidence of sarcoidosis in the event of malignancy and its treatment [11]. Malignancy itself or immunosuppressant chemotherapy might down-regulated sarcoidosis, which evolved upon immune reconstitution, as was proposed by Israel [12]. He also proposed that an infection acquired during chemotherapy might lead to sarcoidosis activation. Wittington et al. concluded that chemotherapy drugs might be responsible for inducing sarcoidosis in their 2 cases [13]. Such doxorubicin based chemotherapy was administered in certain of our study subjects (cases 1, 3, 4, 5, 7, 13, 14, 15, 16) (Table 2). Doxorubicin is reported to induce granulomas in hematologic malignancies [14]. A tumor antigen(s) might be triggering an oligoclonal T-cell hyperreactivity towards granulomatous disease, as Bassler et al. postulated in a histology study [15]. Such antigens could theoretically be implicated in our simultaneously manifested cases that had not received systemic chemotherapy (cases 6, 8, 10, 17) (Table 2). Short intervals between breast cancer and sarcoidosis could support the above hypotheses. However, these might well be attributed to the close follow-up of these patients for their primary malignancy, involving frequent computed tomography and positron emission tomography scans. Whatever the cause, as we showed too, sarcoidosis may complicate breast cancer.

Sarcoidosis and breast cancer both occur commonly in women, and their co-existence has certain clinical implications. In a young female with sarcoidosis and evidence of breast disease by symptoms or radiology tests, malignancy should be excluded as in non-sarcoidosis females, given in addition that breast sarcoidosis is a rare manifestation of the disease. On the other hand, when an older female with breast cancer develops new pulmonary infiltrates and/or mediastinal/hilar lymphadenopathy clinicians should suspect sarcoidosis. In such cases, histological diagnosis is mandatory. Instead of mediastinoscopy used frequently in our case series, endobronchial ultrasound (EBUS) guided lymph node biopsy has a diagnostic accuracy up to 90%, for both malignant and benign conditions [16]. When sarcoidosis is suspected and scans reveal mediastinal/hilar lymphadenopathy, endobronchial ultrasound (EBUS) guided lymph node sampling is the procedure of choice [17].

In the largest sarcoidosis and breast cancer case series published, to our knowledge, to date, sarcoidosis mainly occurs shortly after breast cancer diagnosis and treatment, with the classical disease features of chest involvement, but at a significantly older age, as compared to our sarcoidosis sine breast cancer patients. Our study does not allow conclusions on a possible association between two diseases, whereas large epidemiological registry-based studies yield contradictory results on the association of sarcoidosis with malignancies [18,19]. Another limitation of our study is the lack of data on chemotherapy regimens administered
in these patients. Last, our data are over 10 years old. In the advent of EBUS-TBNA and recently published studies on two diseases association, we believe our data may be of use for the clinicians involved in the diagnosis and management of sarcoidosis and breast cancer.

### Table 2: Clinical presentation of 20 sarcoidosis + breast cancer cases.

| No | R  | Dx Age BC/S | Interval (months) | Symptoms | Organ involvement | Diagnosis/BC staging-intervention | Treatment |
|----|----|-------------|-------------------|----------|-------------------|-----------------------------------|-----------|
| 1  | C  | 63/65       | 24                | No       | Lungs, CLN, hypercalcemia, kidney disease, spleen | Mediastinoscopy/III-surgery + DCP + RT | HCQ       |
| 2  | C  | 37/25       | 144               | PET/CT positive Systemic Shortness of breath | Liver, eye, skin disease. 30 years later sarcoidosis recurrence (Lungs, CLN) | Skin biopsy/1 | Prednisone, HCQ |
| 3  | C  | 69/74       | 60                | No       | Lungs, CLN       | Lung biopsy/II-surgery + DCD | MTX       |
| 4  | C  | 61/61       | 15                | PET/CT positive Uveitis Chest pain | Eye, lungs, CLN | Lung biopsy/III-surgery + DC + RT | No        |
| 5  | C  | 52/52       | 15                | No CT positive | Lungs, CLN, Hypercalcemia | Lung biopsy/1-surgery + DCP | Prednisone, MTX, Aza |
| 6  | C  | 50/50       | 1                 | Cough, shortness of breath jaundice | Lungs, submandibular glands. 6 years later bone sarcoidosis. | Liver biopsy/II-mastectomy, no chemotherapy | Prednisone, HCQ |
| 7  | A  | 62/66       | 4                   | CXR positive | Liver, GI system | Liver biopsy/II-surgery + DCP | Prednisone, MTX |
| 8  | C  | 54/54       | 1                 | No | CLN, cervical nodes, parotid glands, SURT, hypercalcemia | Nodes/potiod biopsy/III-mastectomy, no chemotherapy | No |
| 9  | C  | 80/50       | 360               | Parotid fever | Parotid, CLN | Parotid biopsy/III | No |
| 10 | C  | 47/47       | 9                 | No | Lungs, CLN | Lung biopsy/1-mastectomy, no chemotherapy | No |
| 11 | C  | 39/46       | 84                | CT positive | Lungs, CLN, Spleen disease | Mediastinoscopy/I-mastectomy | No |
| 12 | C  | 46/38       | 96                | Systemic | Lungs, CLN, neurosarcoidosis. 24 years later sarcoidosis recurrence | Lung biopsy/II | Pentoxifylline |
| 13 | C  | 62/65       | 39                | No CT positive | Lungs, submandibular adenopathy | Submandibular biopsy/III-surgery + DCP + RT | No |
| 14 | AA | 52/58       | 72                | No CT positive | CLN | Mediastinoscopy/II-surgery + DCP | No |
| 15 | AA | 49/51       | 16                | No CT positive | CLN, bones | Bone biopsy/II-surgery + DCP | HCQ |
| 16 | C  | 40/45       | 60                | Systemic | Lungs, liver, spleen | Lung biopsy/1-surgery + DCP | HCQ |
| 17 | A  | 53/53       | 2                 | Uveitis | Eye, parotids, lacrimal gland, lungs | Lung biopsy/II-mastectomy, no chemotherapy | No |
| 18 | C  | 38/46       | 96                | No CT positive | CLN | Mediastinoscopy/I-surgery | Prednisone |
| 19 | C  | 55/51       | 48                | Systemic, cough | Lungs, bone, liver, neurosarcoidosis | Lung biopsy/1 | MTX |
| 20 | C  | 55/56       | 12                | No CT positive | CLN, eye, lungs | Mediastinoscopy/II-surgery | No |

Abbreviations: R: Race; C: Caucasian; AA: African-American; A: Asian; Dx Age BC/S: Age at diagnosis for Breast Cancer/Sarcoidosis; CXR, chest x-ray; CT, computed tomography; PET, positron emission tomography; CLN: central lymph nodes; GE: gastrointestinal; SURT: sarcoidosis upper respiratory tract; Diagnosis: modality establishing sarcoidosis; BC TNM Stage; RT: radiotherapy; DCP: doxorubicin, cyclophosphamide, paclitaxel; DCD: doxorubicin, cyclophosphamide, docetaxel; HCQ: hydroxychloroquine; MTX: methotrexate; AZA: azathioprine.

5. Conclusion

In conclusion, this is the largest series of patients with co-existence of sarcoidosis and breast cancer. Sarcoidosis occurs usually after breast cancer at a later than usual age, is mainly located intrathoracically and in 50% of cases is asymptomatic. Pulmonologists should be aware that
sarcoidosis may benignly complicate the course of malignancy patients and pursue histological diagnosis.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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