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Cutaneous sarcoidosis and malignancy: An association between sarcoidosis with skin manifestations and systemic neoplasia

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Abstract

BACKGROUND: Whereas the association between multisystem and pulmonary sarcoidosis and malignancy has been documented, a relationship between cutaneous sarcoidosis and neoplasia has not yet been reported. Because cutaneous manifestations are seen in 20-25 percent of cases of sarcoidosis, this association deserves further investigation. METHODS: We reviewed the relevant literature, in addition to our case series, for a total of 110 cases of cutaneous and non-cutaneous sarcoidosis associated with malignancy with the aim of analyzing possible associations between cutaneous sarcoidosis and malignancy and to enhance the dermatologist's understanding of their critical role in the management of this disease. A search for consecutive cases, which were encountered during the past 20 years, identified 10 cases of confirmed cutaneous sarcoidosis. A review of the relevant literature was also conducted to identify cases of malignancy associated with cutaneous and non-cutaneous sarcoidosis. RESULTS: Cutaneous localization of sarcoidosis was identified in 58 of 100 patients with sarcoidosis and cancer found in the literature (58%) and in 4 of 10 patients in our series (40%). In our series, all cases manifested solid tumors, including breast (n=4 tumors), prostate cancer, colon cancer, kidney cancer, and squamous cell carcinoma of the skin (n=1 of each type). Among the 6 patients in our series with cancers and non-cutaneous sarcoidosis, the types of neoplasias encountered were renal cancer (n=1), mycosis fungoides (n=1), diffuse large B-cell lymphoma (n=1), colon cancer (n=1), and ADK of parotid (n=2). Neoplasias developed after an average of 7.14 years in the literature cases and eight years in our series, following the diagnosis of sarcoidosis. Among the 100 cases of cutaneous (n=58) and non-cutaneous (n=42) sarcoidosis associates with malignancy, which were extracted from the literature, hematologic malignancies accounted for 73 percent of cases and sarcoidosis preceded the detection of neoplasia in a majority (76%) of cases. Among 110 total cases analyzed in this paper, cutaneous sarcoidosis was confirmed in 56.4 percent of overall cases, a figure exceeding expected rates of cutaneous involvement (20-25%) in the general sarcoidosis population. CONCLUSIONS: Sarcoidosis with cutaneous manifestations appears to be associated with malignancy, possibly at a higher rate than other systemic forms of sarcoidosis. The predominant occurrence of sarcoidosis before the development of neoplasia may indicate that an immune dysregulation, such as impairment of cellular immunity mediated by sarcoidosis or the effects of treatment may contribute to an increased risk of malignancy in predisposed individuals. Physician recognition of this link between sarcoidosis and malignancy is critical. Dermatologists, in particular, play an important role, given that many of these associated cases manifest initially, or even solely, with cutaneous findings.

Introduction

Sarcoidosis is a chronic idiopathic systemic disease characterized by infiltration with non-caseating granulomas. Nearly any organ system can be involved in this disease, including the liver, spleen, parotid glands, bones, joints, and central nervous system. However, the lungs, lymphatic system, eyes, and skin are most frequently affected [**1**, **2**]. Pulmonary manifestations occur in a majority (90%) of cases [**3**]. Skin involvement is found in 20-25 percent of

cases and commonly emerges at the onset of disease [**1**, **2**, **4**, **5**]. However, cutaneous sarcoidosis may also occur in isolation in 9-30 percent of cases [**4**, **5**, **6**, **7**].

Skin findings can present at any stage of systemic sarcoidosis, especially at the onset of disease; oftentimes they represent the presenting symptom [**4**, **5**, **8**, **9**]. Dermatologists may be the first to evaluate the patient [**4**]. Therefore, any individual who presents with granulomatous skin lesions warrants a screening for systemic sarcoidosis, which should include a complete history and physical examination, chest x-rays, pulmonary function testing, electrocardiography, ophthalmologic assessment, and laboratory testing for baseline calcium, renal function, and hepatic function [**8**]. Subsequent screenings are critical, since isolated cutaneous sarcoidosis can develop into systemic disease in approximately one-third of patients within three years [**2**]. Sarcoidal skin involvement is diverse and lesions may present with many morphological varieties including: papules, plaques, nodules, lupus pernio, scar sarcoidosis, and more rare morphologies with nail involvement, ulceration, alopecia, hypopigmentation, lichenoid features, psoriasiform changes, and ichthyosis [**10**]. Skin lesions of cutaneous sarcoidosis are categorized into two general groups: specific and nonspecific. Nonspecific lesions lack histological evidence of non-caseating granulomas.

Erythema nodosum (EN) is most commonly seen [**9**], and classically presents as tender, subcutaneous nodules occurring on the anterior tibia, which are often, associated with systemic symptoms like fever, malaise, and polyarthralgias. EN is considered a hallmark of acute and benign disease [**2**, **11**] that may represent a hypersensitivity reaction to unidentified stimuli, including medications and infection. Specific cutaneous lesions are found in an estimated 9-37 percent of patients with sarcoidosis [**2**, **4**, **12**, **13**, **14**]. Although morphologically diverse, these lesions share histological evidence of non-caseating granulomas. Specific lesions include: maculopapular eruptions, infiltrated plaques, lupus pernio, and scar sarcoidosis [**2**, **9**, **12**, **15**, **16**]. Papules are most commonly seen [**2**, **16**, **17**].

Sarcoidosis has been observed in association with various entities, ranging from autoimmune disorders, Crohn disease, celiac disease, and amyloidosis, but its association with internal malignancies has been a particular focus of intense investigation. Cases of sarcoidosis diagnosed before, concomitant with, and after the detection of cancer are well documented in the literature, but the precise nature and strength of this association remains controversial. A link between sarcoidosis and malignancy was initially proposed over three decades ago in a seminal study by Brincker et al. Patient matching, between the Danish sarcoid registry (between 1962-1971) and the Danish Cancer Registry, showed a statistically significant, higher incidence of malignant tumors in patients with sarcoidosis ($P < 0.02$) [**18**]. Malignant lymphoma and lung cancer were shown to occur 11 times and 3 times more frequently, respectively, than expected. The authors speculated that immunologic deficiencies related to sarcoidosis may predispose patients to malignancy. More recently, several prospective cohort studies have investigated the sarcoidosis – malignancy link. In a large cohort study, linking hospitalized sarcoidosis patients from a Swedish hospital registry with a national cancer registry, Ji et al reported a 40 percent overall excess occurrence of malignancy among sarcoidosis patients (overall standardized incidence ratio 1.40), attributable largely to squamous cell carcinoma, non-Hodgkin lymphoma, and leukemia. Cancer risk was especially pronounced within the first year post-hospitalization (SIR 1.18 beyond the first year of follow-up) [**19**]. Linkage analysis, by Reich et al. on patients cross-matched between a large health maintenance organization tumor registry and sarcoidosis registry, suggests that sarcoidosis and malignancy may be related pathogenetically (etiologically) in about 25 percent of the cases in which both occur concomitantly. The authors proposed that the link between sarcoidosis and malignancy might be related to a generalized cell mediated response to tumor antigens which are dispersed in the setting of an underlying malignancy [**20**].

Given that cutaneous manifestations are present in about one-quarter of patients with sarcoidosis and, furthermore, that sarcoidal skin lesions may occur in isolation without internal organ involvement, further investigation to examine a possible relationship between cutaneous sarcoidosis and malignancy is warranted. We have sought to characterize the presence and clinical features of cutaneous sarcoidosis in relationship with cancer and with other systemic manifestations of this disease in patients who display the co-existence of sarcoidosis with cancer.

Materials and methods

We reviewed the relevant English medical literature published on PubMed using the search terms “sarcoidosis and cancer” and “sarcoidosis and neoplasia” in addition to the other search terms “lymphoma,” “Hodgkin’s,” “melanoma,” “adenocarcinoma,” and “sarcoma.” This literature search revealed 100 well-documented cases of sarcoidosis associated with cancer.

Our case series comprised 10 cases of sarcoidosis associated with diverse malignancies, seen in the Dermatology Clinic at Georgetown University in the past 20 years. (Tables 1 to 4, bottom). A total of 110 cases of cutaneous and

Clinic at Georgetown University in the past 20 years. (Tables 1 to 4, bottom). A total of 110 cases of cutaneous and non-cutaneous sarcoidosis associated with malignancy were found and were included in the present analysis.

Data was collected after ethical approval from the Institutional Review Board, and consisted of patient's age, gender, ethnicity, age and time of onset of sarcoidosis and malignancy, as well as histological documentation of sarcoidosis and the neoplasm(s).

Results

A review of the relevant medical literature identifies that both cutaneous sarcoidosis (**Table 1** and **Table 2**) and extracutaneous sarcoidosis (**Table 3** and **Table 4**) have been reported in patients who have also been diagnosed with malignancy. These associated neoplasms may occur either before, after, or concurrent with the diagnosis of sarcoidosis.

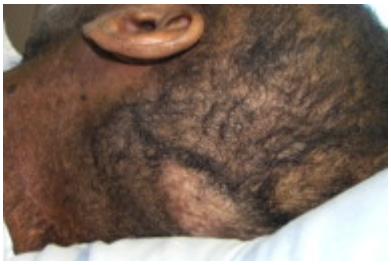

Figure 1a

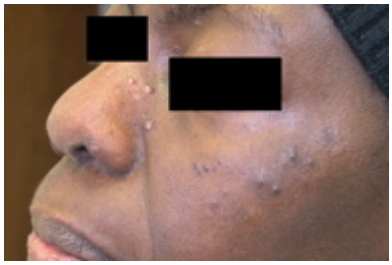

Figure 1b

Figure 1. Clinical aspects of cutaneous sarcoidosis in patients with associated cancer. Exemplified are cases of prostate cancer (1a) and breast cancer (1b).

We identified 100 cases reported in the literature of sarcoidosis associated with malignancy (Tables 1 through 4). This includes 58 cases of cutaneous sarcoidosis (58%); sarcoidosis preceded malignancy in 43 of these cases (74%). Furthermore, a total of 42 cases of non-cutaneous sarcoidosis associated with malignancy were retrieved. Among these, sarcoidosis preceded cancer in 33 cases (79%). Overall, with and without the presence of skin involvement, sarcoidosis was diagnosed before the detection of an associated neoplasm in a majority (76%) of cases, which is consistent with previous findings in the literature [18, 21-107]. Among these 100 cases of cutaneous (n=58) and non-cutaneous (n=42) sarcoidosis, hematologic malignancies accounted for 73 percent of cases, and sarcoidosis preceded the detection of neoplasia in a majority (76%) of cases.

We also present a novel series of 10 patients with sarcoidosis and associated malignancy who were evaluated in the past 20 years (Tables 1 through 4, bottom). Among these, 9 out of 10 were diagnosed with sarcoidosis prior to malignancy; the time between the two diagnoses ranged from 1 to 20 years. Four of these nine cases (44.4%) were cutaneous sarcoidosis (cutaneous sarcoidisis represented 40 percent of all sarcoidosis cases regardless of the timing of development of the neoplsia). Only one patient in our series developed non-cutaneous sarcoidosis and this occurred after the diagnosis of a colon cancer. In our series, all cases of cutaneous sarcoidosis preceding neoplasia presented solid tumors, including breast (n=4 tumors), prostate cancer, colon cancer, kidney cancer, and squamous cell carcinoma of the skin (n=1 of each type). The number of systemic malignancies for each patient with cutaneous sarcoidosis varied from 1 to 3, with an average of 2.0 cancers per patient. Two patients with cutaneous sarcoidosis developed three tumors each. Among the 6 patients in our series with cancers and non-cutaneous sarcoidosis, the types of neoplasias encountered were renal cancer (n=1), mycosis fungoides (n=1), diffuse large B-cell lymphoma (n=1), colon cancer (n=1), and ADK of parotid (n=2). The number of sarcoidosis cases seen during the time period when our 10 sarcoidosis-neoplasia cases occurred was approximately 300, corresponding to a significant 3.3 percent incidence of neoplasia in the overall sarcoidosis patient population.

Overall, among 110 total cases analyzed in this paper, cutaneous sarcoidosis was confirmed in 56.4 percent of cases, a figure exceeding expected rates of cutaneous involvement (20-25%) in the general sarcoidosis population. The majority of patients were young, with 80.4 percent of cases being 60 years of age or less.

Discussion

Physicians' ability to recognize the link between sarcoidosis and malignancy is important. Dermatologists, in particular, may play a critical role in the recognition of cancer in these patients because many cases of sarcoidosis

in association with cancer manifest initially, or even solely, with sarcoidal skin findings that may herald the development of cancer by several years (Tables 1-4). Therefore, patients who present with granulomatous skin lesions should be considered for screening for systemic sarcoidosis, as well as recommended for close follow-up (including age-appropriate cancer screening) to detect the emergence of associated disorders. Patients with sarcoidosis that is worsening, demonstrating new or evolving skin lesions, appear to be at the highest risk for malignancy. Although specific guidelines and risk-assessment tools for an early detection of malignancy have not yet been developed and validated, an increased physician awareness regarding the possible development and presence of systemic symptoms of cancer may contribute to better patient outcomes. Sarcoidosis skin findings provide both visible clues to the diagnosis and accessible tissue for histological examination.

Hematological malignancies remain most strongly linked with sarcoidosis compared to solid tumors. Since Brincker's initial investigation, several observational and epidemiological studies in the past thirty years have described associations between sarcoidosis and multiple hematological disorders, including: Hodgkin lymphoma [**99**, **108**], non-Hodgkin lymphoma (NHL) [**33**, **109**], Mycosis Fungoides [**21**, **24**], acute myeloid leukemia (AML) [**10**, **59**, **88**], chronic myelomonocytic leukemia (CMML) [**51**], hairy cell leukemia (HCL) [**49**], and multiple myeloma [**111**]. Among these, the link between sarcoidosis and lymphoma is best supported. The term sarcoidosis-lymphoma syndrome emerged in 1986 [**109**] to initially describe the development of lymphoma 1-2 years following a diagnosis of sarcoidosis. Patients associated with the sarcoidosis-lymphoma syndrome typically have a history of chronically active disease. It is estimated that patients with chronic sarcoidosis have a 5.5 times higher risk of developing a lymphoproliferative disorder [**109**].

The relationship between sarcoidosis and solid tumors is less extensively reported. The strongest association is described with adenocarcinoma of the lung [**44**], although other cancers have also been reported, including: small cell lung cancer [**112**], testicular cancer [**113**], carcinoid tumors [**114**], gastric adenocarcinoma [**48**], bladder cancer [**115**], adenocarcinoma of the colon [**116**], melanoma [**104**], Kaposi sarcoma [**117**], adenocarcinoma of the prostate [**57**], esophageal adenocarcinoma [**38**], hepatocellular carcinoma [**100**], papillary carcinoma of the thyroid [**60**], malignant lymphoplasmacytoid lymphoma (immunocytoma), squamous cell carcinoma of the uterine cervix [**73**], squamous cell carcinoma of the gingiva [**102**], and sweat gland carcinoma [**22**]. Whereas the individual incidences of lung cancer and sarcoidosis are relatively prevalent, their occurrence in the same patient is very rare. In Brincker's initial report [**18**], a threefold excess of lung cancers was noted in patients with sarcoidosis. Several case reports describe the coexistence of these two disorders [**93**]. In most instances, sarcoidosis preceded lung cancer by several years. Several hypotheses have emerged to explain this association. It is possible that the two diseases exist purely by chance. One premise is that the immune dysfunction related to sarcoidosis predisposes to later development of lung cancer. Alternatively, lung cancers in the setting of sarcoidosis may represent scar cancers, which develop in pre-existing fibrous tissue of sarcoid nodules [**118**]. Immune suppressive and mutagenic effects of the therapies used in sarcoidosis are other important factors to be considered for the development of secondary malignancies.

Whereas the association between sarcoidosis and malignancy is well documented, the mechanisms explaining these observations remain undetermined. Several theories related to immune dysregulation, impairment of cellular immunity, and other sequelae of chronic inflammation have been proposed (discussed in Dermatology Online Journal current issue, January 2011, Volume 17, Number 1, Commentary "**On the missing link between inflammation and cancer**"). The strength of the association is further enhanced by the development of neoplasias in relatively young patients, which is demonstrated in our analysis; less than 20 percent of patients were above the age of 60. Future therapies targeting inflammation will need to be tailored against the cellular pathways that also favor the development of cancers.

Because many instances of malignancies associated with sarcoidois are in fact not likely to be reported, it is probable that the risk of cancer in this setting remains under-estimated. Our results suggest that cutaneous sarcoidosis is present in a majority of cases of sarcoidosis associated with cancer (56.4%), more than the frequency of cutaneous involvement in the general population of sarcoidosis patients (20-25%). These findings support an etiological role of cutaneously located sarcoidosis, or, alternatively, may indicate that the skin disease represents a marker for a particular sarcoidosis phenotype associated with internal malignancy.

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