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Sarcoid in cancer patients: clinical characteristics and associated disease status

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Abstract. *Background:* The increased risk of cancer in patients with sarcoidosis is well established, but there is little information regarding sarcoid diagnosed during or following cancer. The purpose of this study is to describe and analyze the disease status and events associated with the diagnosis of sarcoid in cancer patients. *Methods:* At a large cancer center, we identified 64 patients with a pathologic diagnosis of sarcoid-like granuloma during or following a diagnosis of malignancy. Pathology specimens were re-examined by experts, and clinical and imaging information were reviewed. Disease-related events including recurrence, progression, death, and second malignancy were analyzed. *Results:* The most common primary malignancies were breast (17%), lymphoma (16%), lung (13%), and testicular cancer (11%). Thirty-six out of 64 patients (56%) were diagnosed with sarcoid within 10 months of their primary malignancy, whereas 28 (44%) were diagnosed with sarcoid in follow-up, including 15/28 without evidence of disease, 6 with associated diagnosis of recurrence, 5 with associated diagnosis of second malignancy, 1 with stable disease, and 1 with progressive disease. Sarcoid biopsy sites included mediastinal nodes (59%), hilar nodes (13%), lung (30%), and other nodes (17%), and the reason for biopsy was usually abnormal imaging (66%). Sarcoid and tumor were co-localized in 34%. Including long-term follow-up events, sarcoid was present in association with 10 of 19 recurrences (53%) and 8 of 12 second malignancies (67%). *Conclusion:* While sarcoid often presents at initial diagnosis or staging of cancer, in a significant number of patients, it appears in association with recurrence or second malignancy. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 200-207)*

Key words: neoplasm, malignancy, sarcoidosis, sarcoid, granuloma, recurrence

Introduction

The presence of sarcoid in patients with cancer often leads to diagnostic pitfalls due to nonspecific findings on computed tomography (CT) and positron emission tomography (PET) (1-3). Large sarcoidosis registry studies have demonstrated that patients with chronic active sarcoidosis have increased risk of cancer, particularly lymphoma and lung cancer (4-6). Conversely, a number of pathology studies have shown that patients with cancer (without sarcoidosis) may be found to have sarcoid-like non-caseating granulomas (7-9). For example, Laurberg et al. found non-caseating granulomas in 3.4% of mediastinal nodal specimens from patients with lung cancer (8) These sarcoid-like granulomas have been reported in lung cancer, Hodgkin lymphoma, breast cancer and testicular cancer, as well as many case reports (9-14).

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It is hypothesized that sarcoid-like granulomas may represent an inflammatory reaction to active malignancy, but there is a lack of large clinicopathologic studies to investigate the possible significance of sarcoid in cancer patients (14-16). This is particularly important in the follow-up setting, where an abnormal chest CT or PET scan may prompt a biopsy for suspected malignancy that reveals sarcoid. In this setting, it is unclear whether the diagnosis of sarcoid should prompt reassurance of disease-free status or further workup for active malignancy. The purpose of this clinicopathologic study is to correlate the diagnosis of sarcoid-like granuloma during or following malignancy with imaging and clinical events in 64 patients at a large cancer center.

Methods

Using an institutional Memorial Sloan-Kettering Cancer Center pathology database, we conducted a search of pathology reports between 1980 and 2011 containing the terms non-caseating granuloma, sarcoid, or sarcoidosis, yielding 93 patients. We then screened the clinical records and pathology reports for each patient to search for those who had a diagnosis of sarcoid after a diagnosis of malignancy (with no maximum time interval between diagnoses). We excluded 16 patients who had no clear pathologic diagnosis of malignancy. Most of these patients were seen in the pulmonary clinic for sarcoidosis without any history of cancer or suspected cancer. We also excluded 9 patients who had a history of sarcoid preceding malignancy. One patient was excluded due to a history of mycobacterial infection. For most patients (75%), granulomatous infection was ruled out by special stains and/or cultures. A total of 67 patients met these criteria.

Two expert pathologists (WDT, HW) independently re-examined all available pathology specimens in order to confirm the diagnosis of sarcoid-like granulomas, defined as nodular collections of epithelioid macrophages and multinucleated giant cells without central necrosis. Specimens were available for 49 patients. Three patients were excluded based on inconsistent pathology such as poorly formed granulomas. Eighteen patients without available specimens were included, as their reports described findings consistent with sarcoid. Therefore, a total of 64 patients were included. Notably, in this manuscript, the term 'sarcoid' is used to refer to pathologic findings rather than clinical sarcoidosis.

Patient charts were reviewed for clinical information regarding all malignancies including diagnosis, stage, treatment, and disease-related events. Stage was classified according to the American Joint Committee on Cancer 7th edition. Disease-related events, including recurrence, progression, death, and second malignancy, were analyzed from the date of cancer diagnosis as well as in relation to the diagnosis of sarcoid. The date of recurrence, progression, or second malignancy was defined as the date of confirmatory biopsy or surgery. In particular, clinical information and imaging were reviewed at the timepoint of sarcoid diagnosis, in order to assess possible significance of this diagnosis.

Results

Patient and tumor characteristics

This study included 64 patients who were diagnosed with sarcoid during or following a diagnosis of cancer. There were similar numbers of men and women, and most patients were Caucasian (92%; Table 1). The most common cancers were breast (17%), lymphoma (16%), lung (13%), testicular (11%), gynecologic (11%), bladder (6%), and colon cancers (6%; Table 1). Compared with the average proportions of these cancers in the United States, there were relatively more patients with lymphoma (especially Hodgkin), testicular, bladder, and gynecologic cancers (17). Conversely, there were relatively less patients with prostate, leukemia, pancreatic, and colon cancers.

The initial cancer stage was I in 38% of patients, II in 19%, III in 22%, and IV in 22%. Twenty-six patients (41%) received cytotoxic chemotherapy prior to the diagnosis of sarcoid, including 12 with anthracyclines, 11 with platinum agents, 9 with vinca alkaloids, 7 with etoposide, 7 with taxanes, and 5 with bleomycin. In addition, 32 patients (50%) underwent surgery and 14 (22%) received radiation therapy prior to the diagnosis of sarcoid.

Table 1. Primary malignancies in patients with diagnosis of sarcoid during or following malignancy (n = 64)

Primary malignancy	Number (%) of patients
Breast cancer	11 (17%)
Lymphoma	10 (16%)
Hodgkin lymphoma	5 (8%)
Non-Hodgkin lymphoma	5 (8%)
Non-small cell lung cancer	8 (13%)
Testicular cancer	7 (11%)
Seminoma	4 (6%)
Non-seminomatous germ cell tumor	3 (5%)
Bladder cancer	4 (6%)
Colon cancer	4 (6%)
Endometrial cancer	3 (5%)
Melanoma	3 (5%)
Ovarian cancer	2 (3%)
Cervical cancer	2 (3%)
Head and neck squamous cell carcinoma	2 (3%)
Thyroid cancer	2 (3%)
Sarcoma	2 (3%)
Renal cell carcinoma	1 (2%)
Esophageal cancer	1 (2%)
Mesothelioma	1 (2%)
Thymoma	1 (2%)

Table 2. Patient characteristics (n = 64)

Patient Characteristics	**No. (%)**
Female	33 (52%)
Male	31 (48%)
Race	
White	59 (92%)
Black	2 (3%)
Asian	3 (5%)
Median age (range)	51 (22-78) yrs
Site(s) of biopsy/surgery with sarcoid	
Mediastinal nodes	38 (59%)
Hilar nodes	8 (13%)
Other nodes	11 (17%)
Lung	19 (30%)
Bone marrow	4 (6%)
Liver/spleen	3 (5%)
Bladder	2 (3%)
Intestine	2 (3%)
Skin	1 (2%)
Breast	1 (2%)
Reason for biopsy/surgery with sarcoid	
Abnormal imaging for unrelated reason	4 (6%)
Abnormal imaging on initial cancer workup	19 (30%)
Biopsy for initial cancer staging	1 (2%)
Definitive surgery	15 (23%)
Abnormal imaging on cancer f/up	19 (30%)
Abnormal scope finding on cancer f/up	3 (5%)
Salvage surgery	2 (3%)
Unknown	1 (2%)
Cancer disease events associated with sarcoid	
First primary cancer diagnosis	36 (56%)
Follow-up	28 (44%)
No evidence of disease	15
Stable	1
Progression	1
Recurrence	6
Second primary cancer diagnosis	5

Diagnosis of sarcoid and associated imaging

Sarcoid was diagnosed in a variety of specimens, including mediastinal nodes in 59% of patients, hilar nodes in 13%, lung in 30% and other nodes in 17% (Table 2). Less frequent sites of sarcoid included bone marrow, liver/spleen, bladder, intestine, skin, and breast (Table 2). Thirty-one percent of patients had multiple specimens showing sarcoid. This anatomic distribution is similar to that seen with systemic sarcoidosis (18).

Forty-nine patients (77%) had confirmed active malignancy at the time of diagnosis of sarcoid (see Cancer Disease Status section below). Of these, 14 had confirmed cancer involvement of the lung, 7 of the mediastinal nodes, and 4 of the hilar nodes, based on pathology specimens (Table 3). Sarcoid and active malignancy were co-localized in 22 patients (34%), including primary, nodal, and metastatic sites of disease. In another 10 patients (16%), sarcoid was found alone but in the regional lymphatic bed of a site of active malignancy (e.g. in mediastinal nodes of a patient with stage I lung cancer). Seventeen patients (27%) had sarcoid at a site distant from active malignancy (e.g. in mediastinal nodes of a patient with stage I breast cancer).

In most patients (66%), the reason for biopsy showing sarcoid was abnormal imaging, including CT, PET, and/or chest X-ray (Tables 2 and 3). This occurred during initial workup in 30%, during routine follow-up in 30%, and for unrelated reasons in 6%. Imaging abnormalities were similar to those seen in systemic sarcoidosis, including lung nodules, lung interstitial markings, and mediastinal or hilar adenopathy (Table 3) (18, 19). There were also findings corresponding with other sites of sarcoid, including liver/spleen heterogeneity and other adenopathy.

Sarcoid was diagnosed incidentally on surgical pathology in 17 patients, including 15 who underwent definitive cancer surgery and 2 who underwent salvage surgery (Table 2). Notably, two of these cases showed no clear evidence of malignancy. One was a patient with a right lung nodule with biopsy suspi-

Table 3. Abnormal imaging findings and confirmed sites of cancer at the time of sarcoid diagnosis, in patients with a known diagnosis of cancer (n = 64)

Sites	CT Findings	%	PET Findings	%	Confirmed Cancer Sites	%
Total # of patients	51	80%	17	27%	49	77%
Lung	39	61%	10	16%	14	22%
Mediastinal nodes	36	56%	12	19%	7	11%
Hilar nodes	32	50%	12	19%	4	6%
Other nodes	14	22%	6	9%	8	13%
Liver/spleen	12	19%	3	5%	4	6%

CT = computed tomography. PET = positron emission tomography.

cious for lung cancer. She underwent a lobectomy and mediastinal node dissection showing sarcoid and no malignancy. She had a prior history of uterine cancer. Another patient had stage II testicular cancer. He was presumed to have recurrence based on abnormal imaging of the liver, spleen, and hilar nodes. He underwent chemotherapy followed by splenectomy and liver resection. Pathology showed sarcoid and no malignancy, so it is unclear whether he had a complete response to chemotherapy or no recurrence. These cases highlight the importance of biopsy in patients with suspected recurrence.

Cancer disease status in patients diagnosed with sarcoid after malignancy

Thirty-six out of 64 patients (56%) were diagnosed with sarcoid during initial cancer workup, within 10 months of their cancer diagnosis (Table 2, Figure 1). Twenty-eight patients (44%) were diagnosed with sarcoid in follow-up, defined as greater than 10 months after their cancer diagnosis or prompted by new symptoms. Of those diagnosed in follow-up, 15/28 (54%) had no evidence of concurrent active malignancy (within 6 months after diagnosis of sarcoid; see Cancer Outcomes section below for extended follow-up to median 5.1 yrs). One of 28 had stable disease. Surprisingly, 12/28 patients (43%) had cancer recurrence, progression, or a second malignancy within 6 months after diagnosis of sarcoid (Table 4). One patient (#7) had symptomatic progression of ovarian cancer in the pelvis and was simultaneously found to have thoracic sarcoid. Six patients (21%) had simultaneous recurrence of cancer, including four with lung metastases. As seen in Table 4, the elapsed time from cancer diagnosis to recurrence was variable (median 2.6 yrs, range 1.3-4.0 yrs). However, these recurrences occurred within 6 months of diagnosis of sarcoid. Notably, patient #6 had lung nodules at the time of sarcoid diagnosis but did not undergo lung biopsy until 7 months later. Five patients (18%) had simultaneous diagnoses of sarcoid and second malignancy (all lung cancer or lymphoma). Again, the elapsed time from the first cancer to the second cancer was usually quite long (median 5.2 yrs, range 0.5-21.7 yrs), but the second cancer was diagnosed within 6 months of sarcoid. Notably, patient #12 had a 6-month delay between her lung biopsy showing second malignancy and her definitive surgery that also showed sarcoid.

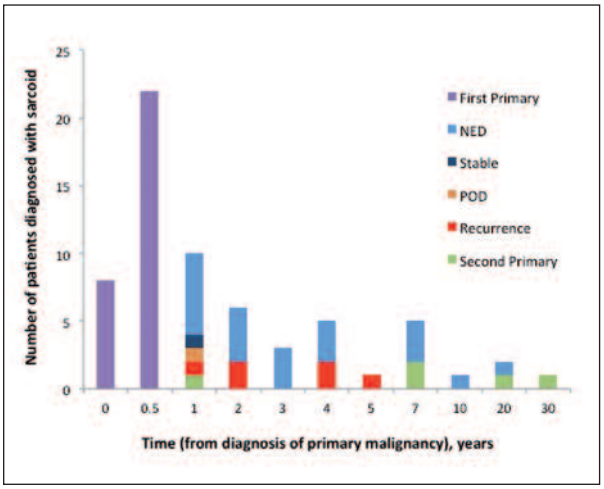

Fig. 1. Oncologic disease status at the time of diagnosis of sarcoid. Y axis of histogram shows the timing of diagnosis of sarcoid relative to diagnosis of first primary malignancy. NED = no evidence of disease. POD = progression of disease

Figure 2 shows an example of pathology and imaging from a patient (#4) with cancer recurrence associated with a diagnosis of sarcoid. This patient was diagnosed with stage III breast cancer in 1994 and underwent lumpectomy, adjuvant chemotherapy and radiation. In 1996, a routine chest X-ray showed inter-

Table 4. Characteristics of patients with cancer recurrence, progression, or second primary cancer associated with diagnosis of sarcoid in follow-up

ID	1st primary cancer diagnosis	Cancer event (sites)	Time from 1st primary to cancer event (yrs)	Time from 1st primary to sarcoid (yrs)	Site(s) of sarcoid biopsy
1	NSGCT	REC (lung, liver, spine)	4.0	4.0	Mediastinal LN
2	Tonsil cancer	REC (lung, hilar and mediastinal LN)	3.4	3.4	Mediastinal LN
3	Breast cancer	REC (internal mammary LN, sternum)	3.3	3.3	Lung
4	Breast cancer	REC (lung, liver, bone)	1.9	1.8	Lung
5	NHL	REC (nasopharynx, cervical LN)	1.3	1.3	Lung
6	Uterine sarcoma	REC (lung)	1.5	0.9	Mediastinal and hilar LN
7	Ovarian cancer	POD (pelvis)	0.5	0.5	Mediastinal and SCV LN
8	Breast cancer	2nd Primary (NHL)	21.7	21.3	Mediastinal and retroperitoneal LN
9	NSCLC	2nd Primary (SCLC)	13.7	13.5	Mediastinal LN
10	Seminoma	2nd Primary (NHL)	5.2	5.2	Mediastinal LN, BM
11	Bladder cancer	2nd Primary (NSCLC)	4.9	5.1	Lung, mediastinal LN
12	NSCLC	2nd Primary (NSCLC)	0.4	0.9	Mediastinal and hilar LN

REC = recurrence. POD = progression of disease. LN = lymph node. SCV = supraclavicular. NSGCT = non-seminomatous germ cell tumor of testis. NHL = non-Hodgkin lymphoma. NSCLC = non-small cell lung cancer. SCLC = small cell lung cancer. BM = bone marrow.

stitial lung markings and she underwent lung biopsies demonstrating extensive sarcoid but no tumor. Six weeks later, she was diagnosed with widespread breast cancer metastases in the lung, liver, and bone.

Clinical management of sarcoid

At the time of sarcoid diagnosis, 36% of patients had symptoms of cough or dyspnea, 41% saw a pulmonologist, and 47% underwent pulmonary function tests (PFTs). PFTs were normal in 25% and showed mild obstruction in 13%, moderate obstruction in 3%, and decreased diffusing capacity in 9%. In most cases, these findings were attributed to other (non-sarcoid) causes, including thoracic malignancy (14%), chronic pulmonary disease (7%), chemotherapy toxicity (5%), and acute infection (2%). Only 11 patients (17%) had evidence of chronic systemic sarcoidosis, and only 6 patients required treatment for sarcoidosis (with steroids and/or hydroxychloroquine).

Clinical cancer outcomes

From the date of cancer diagnosis, the median follow-up time was 5.1 yrs (range, 0.3-31.2 yrs). Of the 36 patients who were diagnosed with sarcoid during initial cancer workup, 11 (30%) later developed recurrence or progression, 5 (14%) developed a second malignancy, and 8 (22%) eventually died of cancer. Notably, 3 patients were again found to have sarcoid at the time of recurrence, and 3 had sarcoid at the time of second malignancy. Of the 28 patients who were diagnosed with sarcoid in follow-up, a total of 11 (40%) developed recurrence or progression, 7 (25%) developed a second malignancy, and 8 (29%) eventually died of cancer. As noted above, 12 patients developed these events in association with their diagnosis of sarcoid. In addition, one patient was found to have sarcoid both at the time of his second malignancy (#9 in Table 4) and when his first malignancy recurred 4 years later. Therefore, analyzing all 64 patients, sarcoid was present in association with 10 of 19 recurrences (53%) and 8 of 12 second malignancies (67%).

Discussion

These results from a large cancer center demonstrate that, in cancer patients, sarcoid-like granulomas are most often diagnosed in association with active malignancy. Out of 64 patients diagnosed with sarcoid during or after cancer, only 15 (23%) had no evidence of disease, whereas 49 (77%) had active malignancy. Most patients (56%) were diagnosed with sarcoid during initial cancer workup or staging, but another 20% were diagnosed with sarcoid in association with recurrence, progression, or second malignancy. Furthermore, analyzing all adverse cancer events during long-term follow-up (with a median follow-up time of 5.1 yrs), sarcoid was present in association with 10 of 19 recurrences (53%) and 8 of 12 second malignancies (67%).

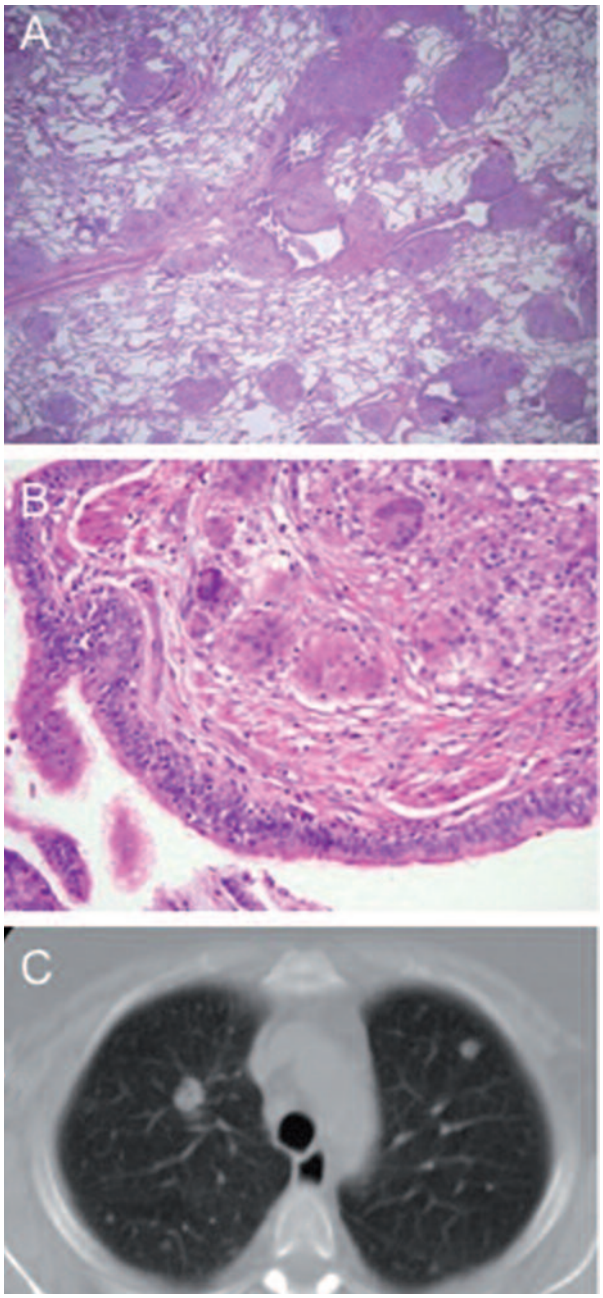

Fig. 2. Correlated pathology and imaging from a patient with sarcoid-like granulomas associated with cancer recurrence. This patient was diagnosed with stage III breast cancer 2 years earlier. Lung wedge biopsies were prompted by abnormal interstitial findings on CXR. The low-power view (A, 20x mag) demonstrates extensive lung involvement of non-caseating granulomas with a bronchovascular, septal and pleural distribution. The high-power view (B, 200x mag) demonstrates confluent tightly clustered non-caseating granulomas consisting of clusters of epithelioid histiocytes and multinucleated giant cells under the bronchiolar mucosa. Shortly after biopsy, the patient was diagnosed with metastases in the lungs, liver, and bone (C)

The most significant implication of this study is that a biopsy showing sarcoid in the follow-up setting may not be reassuring for a cancer-free disease status. Depending on the clinical circumstances, additional workup such as repeat biopsies or short interval imaging may be considered. To the authors' knowledge, this is the first study to demonstrate this association. Furthermore, it is the largest published series with clinicopathologic correlation of sarcoid and malignancy. Interestingly, another recent series of 30 patients with sarcoid and malignancy showed only 3 cancer recurrences, but all 3 occurred within 6 months of the diagnosis of sarcoid, consistent with our results (14).

The pathologic and imaging findings of this study build upon consistent data in previously published reports. Other studies have shown a high frequency of sarcoid in patients with lymphoma, lung, breast, and testicular cancers (7-14). Our study confirms this and also suggests a moderate frequency in patients with gynecologic and bladder cancers. We observed sarcoid most commonly in thoracic lymph nodes and lungs but also found it in many other tissues, as described in case reports of sarcoid and cancer (9, 10, 20-28). Our study is unique in reporting the distribution of sarcoid in relation to sites of active malignancy, showing that it occurs in locoregional proximity to malignancy in 50%, distant from malignancy in 27%, and without evidence of malignancy in 23%. As in other studies, nonspecific imaging findings were the most common indication for biopsy showing sarcoid (1-3). We found that PET/CT abnormalities usually involved the thoracic nodes and lungs, in agreement with previous studies by Chowdhury and Butt (1, 14). This pattern may be helpful to generate suspicion for sarcoid, but it is not sufficient to exclude malignancy.

Several studies of sarcoid and Hodgkin lymphoma suggest that patients diagnosed with sarcoid during initial lymphoma workup may have a better prognosis than those without sarcoid (20, 21). In the current study, we did not compare the outcomes of patients with sarcoid to those without sarcoid due the heterogeneity of the patient population. However, these studies are complementary, suggesting that if a patient with Hodgkin lymphoma is diagnosed with sarcoid during initial workup, they may have an improved prognosis, but if sarcoid is found in follow-up, it may raise suspicion for recurrence or second

malignancy. Further studies are needed to determine whether sarcoid diagnosed during initial workup has prognostic significance for other types of cancer.

The pathogenesis of sarcoid in cancer patients remains under significant debate and is likely multifactorial. Indeed, sarcoid may represent an immune or inflammatory reaction to malignancy (15), a side effect of chemotherapy (11, 22, 23) or previously undiagnosed systemic sarcoidosis. Some have suggested a mechanism of cell-mediated immune response to tumor antigens (15). Others have linked the cytokine tumor necrosis factor-α with development of sarcoid (24). Still others suspect a reaction to chemotherapies such as bleomycin that cause pulmonary toxicity (11, 22, 23). Finally, patients with chronic sarcoidosis have a well-established increased risk of cancer, and it is possible that the underlying immunologic disturbances of sarcoidosis may alter both susceptibility to, and response to, cancer (4-6).

The results of this study cannot elucidate the pathogenesis of sarcoid in cancer patients, but they seem most consistent with an immune or inflammatory reaction to malignancy. Only 41% of patients received chemotherapy prior to the diagnosis of sarcoid, and only 5 patients received bleomycin. Patients with prior evidence of sarcoidosis were excluded from the study, and the remaining patients rarely had evidence of chronic or systemic sarcoid (17%) or required treatment for sarcoid (9%). They were also much older than the typical sarcoidosis patient at diagnosis (18). Furthermore, the temporal association of the diagnosis of sarcoid with active malignancy in 77% seems consistent with an inflammatory or immune reaction to malignancy. The spatial association of sarcoid and active malignancy was variable, suggesting that a systemic reaction mechanism might be most likely.

The limitations of this study include its retrospective nature and small number of patients, though it is the largest clinicopathologic series describing sarcoid in cancer patients. Possible biases include a selection bias affecting patient and tumor characteristics, since the study was conducted at a single cancer center, as well as an observation bias affecting the temporal association of sarcoid with malignancy, as cancer patients have an increased rate of imaging and biopsy during initial workup and early follow-up. However, the presence of sarcoid in association with late follow-up events (up to 21 years) suggests that there was not a dominant observation bias. This investigation is also limited by the lack of control group, as matched controls were not possible in this heterogeneous population. In spite of these limitations, this study provides new important data for the practicing physician, suggesting that a biopsy showing sarcoid in the follow-up setting may warrant closer monitoring for cancer recurrence or second malignancy. The essential next step is a prospective study of patients undergoing biopsy for abnormal follow-up imaging, to test whether those with sarcoid are more likely to have adverse cancer events than those with non-sarcoid benign pathology.

Conclusion

This study of 64 patients at a large cancer center demonstrates that sarcoid is most likely to develop in cancer patients with active malignancy (77%) rather than those in remission (23%). Fifty-six percent were diagnosed with sarcoid during initial cancer workup, but another 20% were diagnosed with sarcoid in association with progression, recurrence, or second malignancy. These results suggest that the diagnosis of sarcoid in follow-up should possibly warrant closer monitoring. Though the pathogenesis of sarcoid in cancer patients remains unclear, these data are most consistent with the hypothesis that sarcoid represents an immune or inflammatory reaction to active malignancy. Prospective studies are needed to confirm these findings.

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