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Sarcoidosis Occurring After Solid Cancer: A Nonfortuitous Association

Report of 12 Cases and Review of the Literature

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Abstract: The association between cancer and sarcoidosis is controversial. Some epidemiological studies show an increase of the incidence of cancer in patients with sarcoidosis but only few cases of sarcoidosis following cancer treatment have been reported.

We conducted a retrospective case study from internal medicine and oncology departments for patients presenting sarcoidosis after solid cancer treatment. We also performed a literature review to search for patients who developed sarcoidosis after solid cancer. We describe the clinical, biological, and radiological characteristics and outcome of these patients.

Twelve patients were included in our study. Various cancers were observed with a predominance of breast cancer. Development of sarcoidosis appeared in the 3 years following cancer and was asymptomatic in half of the patients. The disease was frequently identified after a follow-up positron emission tomography computerized tomography evaluation. Various manifestations were observed but all patients presented lymph node involvement. Half of the patients required systemic therapy. With a median follow-up of 73 months, no patient developed cancer relapse. Review of the literature identified 61 other patients for which the characteristics of both solid cancer and sarcoidosis were similar to those observed in our series.

This report demonstrates that sarcoidosis must be considered in the differential diagnosis of patients with a history of malignancy who have developed lymphadenopathy or other lesions on positron emission tomography computerized tomography. Histological confirmation of cancer relapse is mandatory in order to avoid unjustified treatments. This association should be consider as a protective factor against cancer relapse.

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Abbreviations: ^{18}FDG-PET/CT = positron emission tomography computerized tomography, ACE = angiotensin-converting enzyme, ADK = adenocarcinoma, BP = bisphosphonate, CR = complete response, CS = corticosteroids, CT = chemotherapy, HMT = hormonal therapy, IS = in situ, LN = lymph nodes, NA = not available, NR = not realized, non response, NSAID = nonsteroidal anti-inflammatory drug, PI = pulmonary infiltrate, PR = partial response, RP = retroperitoneal, RT = radiotherapy, TLD = thalidomide, Trt = treatment, x-ray CT = x-ray computed-tomography.

INTRODUCTION

Sarcoidosis is a benign multisystem granulomatous disease of unknown origin and seems to correspond to an aberrant immune response in a susceptible host. The incidence is dependent on genetic[1] and environmental factors with the highest prevalence in Northern European countries[2] and black Africans.[3] It is most frequently observed in young adults and commonly affects thoracic lymph nodes and lung. The diagnosis is established on the basis of compatible clinical and radiological findings, supported by histological evidence in 1 or more organs of noncaseating epithelioid-cell granulomas in the absence of organisms or particles.

Relationships between granulomatosis and cancer have been described for a long time.[4–7] Aside from granulomatosis due to infectious disease in immunocompromised cancer patients, granulomas can be observed in mainly 2 situations. First, granulomas may be found as a sarcoid reaction, observed in the lymph nodes draining the cancer, the organ of the tumor origin, or distant tissue sites such as the spleen, bone marrow, and skin. This reaction has been observed in patients with either hematological malignancies or solid tumors.[8] Second, patients may present typical sarcoidosis occurring before, during or after the diagnosis of cancer. The first association is the most established.[4,5,9] Sarcoidosis occurring after cancer has also been reported in the literature but rarely. These descriptions corresponded most of the time to clinical reports, in patients with a history of hematological malignancies or solid tumors.[10–23]

The description of patients presenting sarcoidosis after lymphoma has recently been reported by London et al[10] in a national French retrospective study. In the present study, we aim

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to describe the clinical characteristics and outcomes of patients presenting with sarcoidosis occurring after solid cancer.

PATIENTS AND METHODS

Our Case Series

We performed a retrospective study, conducted from 3 internal medicine French departments and 1 oncology department between 2009 and 2014. We included patients who developed sarcoidosis after solid cancer. Sarcoidosis was defined by the association of clinical and radiological findings suggestive of sarcoidosis, histological confirmation and exclusion of other specific granulomatous disorders. Patients who had a history of granulomatous disease before cancer, thoracic lymph nodes or pulmonary infiltrates at the time of cancer diagnosis and those who developed sarcoidosis during cancer treatment were excluded.

Demographic informations (including gender, age at diagnosis of solid cancer and sarcoidosis), clinical history of cancer and sarcoidosis (including clinical features at diagnosis and over the course of the disease, treatment received for each pathology and outcomes), were collected.

Imaging findings including x-ray computed-tomography (x-ray CT) and/or positron emission tomography computerized tomography (^{18}FDG-PET/CT) and biological data such as serum protein electrophoresis, calcium, angiotensin-converting enzyme (ACE), or C-reactive protein were noted when available.

Cancers were classified according to stage grouping, based on TNM classifications: stage I and II corresponded to limited cancer, with tumor localized to 1 part of the body but could reach regional lymph nodes, and stages III and IV corresponded to advanced cancer that has spread to distant lymph nodes or other organs.

Response to treatment of sarcoidosis was classified as follows: clinical complete response was defined as the total disappearance of clinical symptoms, partial clinical response as improvement of these symptoms, without onset of new symptoms; radiological complete response was characterized by normalization of x-ray CT and/or ^{18}FDG-PET/CT and partial radiological response by decrease of number or size of initial lesions without any new lesions related to sarcoidosis.

The research was conducted in compliance with the Declaration of Helsinki and the protocol of Good Clinical Practices. In accordance with French law, formal approval from an ethics committee was not required for this type of study.

Literature Review of Cases

We reviewed other reported cases with a literature search conducted in the PubMed database using the following terms: ''sarcoidosis,'' ''granulomatous reaction,'' ''cancer,'' and ''solid malignant tumor.'' The search was performed restricted to English and French language. The same inclusion and exclusion criteria as for our series were used. Only reports published with enough clinical, radiological, histological data were included.

Statistical Analysis

Descriptive statistics included the mean and/or median with minimum and maximum values as appropriate for continuous variables and frequency with percentage for categorical variables.

RESULTS

Our Case Series

In our series, we identified 13 patients presenting sarcoidosis after solid cancers, 8 women and 5 men. One patient was excluded because a history of granulomatous hepatitis before cancer diagnosis.

All characteristics of the patients are shown in Tables 1 and 2.

Characteristics of Solid Cancers

Median age at cancer diagnosis was 54 years (range, 33–73 years). Cancers most frequently observed affected breast with carcinoma (n = 4) and colorectal tract with carcinoma or adenocarcinoma (n = 3). The other cancers observed were thyroid and renal carcinomas, prostatic adenocarcinoma, melanoma, and osteosarcoma. One patient had a history of thyroid and breast cancer with an interval of 2 years. Among these patients, none presented metastatic locations. At the time of diagnosis, cancer was limited in 8 patients (stage I or II) and advanced in 2 patients (stage III). All but 2 patients had an x-ray computer tomography or ^{18}FDG-PET/CT analysis at cancer diagnosis that did not show neither distant lymphadenopathy nor interstitial lung infiltration. The 2 patients without imaging examination had localized melanoma and intracapsular prostatic adenocarcinoma.

Treatment of these cancers consisted to surgery for eleven patients, radiotherapy for 6 patients and chemotherapy for 8 patients. Single surgery was used for 4 patients who had melanoma, osteosarcoma, prostatic adenocarcinoma, or renal carcinoma. Seven other patients received radiotherapy and/or chemotherapy in addition to surgery. Finally, 1 patient was treated with radiotherapy and chemotherapy without surgery. Chemotherapy agents were alkylating agents (n = 6), antimetabolites (n = 4), mitotic inhibitors (n = 3) and topoisomerase inhibitors (n = 2). They were used during a median of 6 months (range, 2–11 months).

All patients had initial response to treatment. One patient had relapse of breast carcinoma, 3 years after the first diagnosis of cancer and before sarcoidosis flare, treated successfully by a second line therapy. With a median follow-up of 73 months (range, 15–124 months), all patients achieved sustained remission.

Characteristics of Sarcoidosis

The diagnosis of sarcoidosis was made at median of 34.5 months following the diagnosis of cancer (range, 7–82 months) with a median age at sarcoidosis diagnosis of 55 years (range, 42–76 years).

Sarcoidosis was identified after a systematic x-ray computer tomography or ^{18}FDG-PET/CT follow-up evaluation in asymptomatic patients in half of cases. The diagnosis was made because of clinical manifestations in the other half of patients. These manifestations included constitutional symptoms with asthenia (n = 4), weight loss (n = 3) or fever (n = 1), arthralgia or myalgia (n = 3), cough (n = 1), lymph node tumefaction (n = 1), or skin lesion (n = 1). In all cases, clinical and radiological findings were suggestive of cancer recurrence.

Among these 12 patients, 4 had single-area involvement, corresponding to lymph node involvement localized in thorax (n = 2) or diffuse (n = 2). The remaining patients had multiple organ involvements, with 4 having 2 organs involved, 1 having 3 organs involved, 1 having 4 organs involved, and 2 having 5 or

TABLE 1. Characteristics of Our 12 Patients

				Cancer Characteristics				Sarcoidosis Characteristics					
Case No.	Sex	Age at Cancer/ Sarcoidosis Onset	Interval to Sarcoidosis, months	Type/ Stage	Trt	Relapse	Follow-Up After Cancer Diagnosis, months)	Clinical Manifestations at Diagnosis	^{18}PET/CT findings	Trt/ Duration, months	Clinical/ Radiological Response	Relapse	Follow-up After Sarcoidosis Diagnosis, months
1	M	54/55	7	Localized Melanoma	Surgery	No	92	Asthenia, weight loss, LN	Hypermetabolic medaist-inal and abdominal LN, spleen, bone	None	CR/NR	No	86
2	F	48/54	72	Rectal carcinoma T2N+M0	RT, CT	No	112	None	Hypermetabolic mediast-inal LN and PI	None	CR/PR	No	41
3	F	40/44	48	Thyroid carcinoma Breast carcinoma T2NxM0	Surgery, RT, CT	No	84	Asthenia, weight loss, arthralgia	Diffuse hypermetabolic LN, bone	CS/28	PR/NR	No	38
4	F	43/47	42	Rectal ADK T2N0M0	Surgery, RT, CT	No	77	None	Diffuse hypermetabolic LN, spleen, PI, bone	CS/36	CR/NR	No	47
5	F	57/58	23	Breast carcinoma T2N3M0	Surgery, RT, CT	No	70	Cough	Diffuse hypermetabolic LN, skin	CS/14	CR/PR	Yes	47
6	F	66/67	8	Breast carcinoma	Surgery, RT, CT	No	47	None	Diffuse hypermetabolic LN	CS/15	CR/NR	No	40
7	F	36/42	82	Breast carcinoma T2N0M0	Surgery, RT, CT	Yes*	89	None	Hypermetabolic mediast-inal and subclavian LN	None	CR/PR	No	13
8	M	73/76	27	Renal carcinoma T3N0M0	Surgery	No	39	None	NR	None	CR/NA	No	4
9	F	53/54	11	Ovarian carcinoma s tage III	Surgery, CT	No	15	Skin lesions	Hypermetabolic hilar and mediastinal LN	None	CR/PR	No	5
10	M	54/55	12	Chondrosarcoma grade 1–2	Surgery	No	37	Asthenia, fever, Arthralgia	Hypermetabolic hilar LN and PI	CS/10 MTX/4	PR/NR	No	25
11	M	64/68	48	Prostatic ADK T2N0M0	Surgery	No	96	Asthenia, weight loss, arthralgia, myalgia, Papillitis	Hypermetabolic hilar and mediastinal LN	CS/41 MTX/5	PR/NR	Yes	48
12	F	64/69	58	Colon ADK T3N1M0	Surgery, CT	No	68	None	Diffuse hypermetabolic LN	None	CR/NA	No	9

ADK = adenocarcinoma, CR = complete response, CS = corticosteroids, CT = Chemotherapy, LN = lymph nodes, NA = not available, NR = non response, NR = not realized, NSAID = nonsteroidal anti-inflammatory drugs, PI = pulmonary infiltrates, PR = partial response, RT = Radiotherapy, Trt = treatment.

* Relapse of cancer before sarcoidosis.

TABLE 2. Summary of Baseline Characteristics of Our Patients and Literature Review

	Our Patients No. (n = 12)	Literature Review No. (n = 61)
Female/Male, n (%)	8 (66.7)/4 (33.3)	35 (57.4)/26 (42.6)
Age at cancer diagnosis,mean/median, years	54/54	48.9/NA
Underlying cancer, n (%)		
Breast carcinoma	4 (33.3)	18 (29.5)
Colorectal cancer	3 (25)	3 (4.9)
Thyroid carcinoma	1 (8.3)	0 (0)
Renal carcinoma	1 (8.3)	0 (0)
Melanoma	1 (8.3)	3 (4.9)
Osteosarcoma	1 (8.3)	1 (1.6)
Prostatic ADK	1 (8.3)	3 (4.9)
Lung cancer	0 (0)	5 (8.2)
Testicular cancer	0 (0)	16 (26.2)
Ovarian cancer	0 (0)	2 (3.3)
Head and neck cancer	0 (0)	7 (11.5)
Others*	0 (0)	3 (4.9)
Cancer stage at diagnosis, n (%)		
Limited	8 (66.7)	43 (70.5)
Advanced	2 (16.7)	15 (24.6)
Not available	2 (16.7)	3 (4.9)
Cancer treatment, n (%)		
Surgery	11 (91.7)	45 (73.8)
Radiotherapy	6 (50)	18 (29.5)
Chemotherapy	8 (66.7)	32 (52.4)
Recurrence of cancer, n (%)		
Prior sarcoidosis	1 (8.3)	3 (4.9)
After sarcoidosis	0 (0)	3 (4.9)
Point unavailable	0 (0)	1 (1.6)
Age at sarcoidosis diagnosis, mean/median, years	57/55	52/NA
Interval between cancer and sarcoidosis, mean/median, months	36.5/34.5	39/NA
Revealing sarcoidosis signs, n (%)		
Constitutional symptoms	4 (33.3)	2 (8.6)*
Pain	3 (25)	1 (4.2)*
Lymph node tumefactions	1 (8.3)	0 (0)*
Pulmonary manifestations	1 (8.3)	5 (20.8)*
Skin manifestations	1 (8.3)	5 (20.8)*
Eye manifestations	1 (8.3)	1 (4.2)*
Hypercalcemia	0 (0)	1 (4.2)*
Asymptomatic	6 (50)	14 (58.3)*
Not available	0 (0)	32 (52.4)
Organ involvement, n (%)		
LN	12 (100)	58 (95)
Thoracic LN	12 (100)	56 (91.8)
Extra-thoracic LN	7 (58.3)	9 (14.7)
Pulmonary infiltrates	6 (50)	25 (41)
Skin	2 (16.7)	6 9.8)
Bone/Joint	5 (41.7)	1 (4.2)
Eye	2 (16.7)	1 (4.2)
Spleen	3 (25)	1 (4.2)
Liver	1 (8.3)	1 (4.2)
Hypercalcemia	0 (0)	1 (4.2)
Treatment of sarcoidosis, n (%)		
None	6 (50)	54 (91.5)*
Prednisone	6 (50)	12 (20.3)*
Others**	2 (16.7)	4 (6.8)*
Not available	0 (0)	2 (3.3)
Clinical sarcoidosis response at last follow-up, n (%)		
Complete response	9 (75)	13 (81.2)*
Partial response	3 (25)	2 (12.5)*
No response	0 (0)	1 (6.3)*
Not available	0 (0)	45 (73.8)
Radiological sarcoidosis response at last follow-up, n (%)		
Complete response	0 (0)*	7 (43.7)*
Partial response	4 (40)*	637.5)*
No response	6 (60)*	3 (18.8)*
Not available	2 (16.7)	45 (73.8)

	Our Patients No. (n = 12)	Literature Review No. (n = 61)
Relapse of sarcoidosis, n (%)		
Yes	2 (16.7)	2 (7.4)*
No	10 (83.3)	24 (88.9)*
Not available	0 (0)	34 (55.7)
Follow-up, mean,mean/median (months)		
Total follow-up	67.7/73	80.8/NA
Follow-up after sarcoidosis diagnosis	28.4/24.5	45.8/NA

* Others: Thymoma, Gastric leiomyosarcoma, endometrial cancer, 1 patient each.
** Others: Methotrexate, Topical steroid, Bisphosphonate, Thalidomide, NA: not available,*: percentage were calculed from available data.

more organs involved. All patients had thoracic involvement with hilar or mediastinal lymph nodes associated in half of cases to pulmonary involvement. When pulmonary involvement was present, there were no infiltrative pneumonia and no pulmonary dysfunction. Other manifestations involved peripheral lymph node (n = 7), bone and joints (n = 5), spleen (n = 3), skin (n = 2), and eyes (n = 2). Lofgren and Heerfordt's syndromes were not observed.

No patient had hypercalcemia. Elevated C-reactive protein was observed in 2 of 11 patients analyzed. ACE level was elevated (>70 U/L) in 4 of 10 patients analyzed. Serum protein electrophoresis was available in 8 patients: normal in 6 patients, hypergammaglobulinemia in 1 patient and hypogammaglobulinemia in 1 patient. Finally, 4 patients had lymphopenia (defined by lymphocytes $<1500/mm^3$).

All patients underwent diagnosis procedures to exclude cancer relapse. Histological confirmation was obtained from lymph node biopsy in 11 patients, skin biopsy in 2 patients and bone biopsy (vertebra) in 1 patient. Infectious causes of granulomatous disease were excluded by negative stains and cultures for fungi and mycobacteria.

Half of patients did not require systemic therapy. The other half of patients received oral steroids as first line treatment. Decisions to provide treatment were persistent constitutional symptoms, pulmonary involvement, spleen involvement and joint involvement. Median duration of corticosteroids was 21.5 months (range, 10–41 months) with 2 patients still treated at the last visit. Two of the 6 treated patients experienced clinical complete response; the other 3 patients had partial clinical response, explained by persistent arthralgia. One patient obtained partial radiological response, the other patients showed unchanged imaging findings during the follow-up. In patients without treatment, 2 had spontaneous clinical symptoms regression. Partial radiological response was obtained for 1 case, whereas no imaging modifications were observed in 3 cases.

With median follow-up after sarcoidosis diagnosis of 24.5 months (range, 4–86 months), 2 patients experimented a relapse during the decrease or after discontinuation of steroid. These relapses affected, for the 2 cases eyes, with uveitis and papillitis. These patients did not presented with eye involvement at the first flare. They were treated by steroids. Methotrexate was added in 2 patients because of corticosteroid resistance or dependence, 43 and 21 months after the first flare of the disease respectively. No death was observed.

Literature Review of Cases

Review of the literature identified 22 studies, including 110 patients presenting with sarcoidosis occurring after cancer diagnosis. Thirty-nine patients were excluded for lack of data,[24–26] 7 were excluded because of thoracic lymph nodes or pulmonary infiltrates at the time of cancer diagnosis[20,21,27–29] and 3 because they were in induction chemotherapy at the time of sarcoidosis diagnosis.[27,30,31] Three series of cases presented outcomes of 11, 7 and 30 patients, respectively.[20,22,23] The other patients corresponded to case reports.[11–19,21]

All characteristics of solid cancer and sarcoidosis, treatment and follow-up are reported in Tables 2 and 3.[11–22] Because of absence of individual data, 30 patients from the study of Butt et al were not included in Table 2.[23]

Results are similar to our series. Most of patients were women, with a median age at cancer diagnosis of 48.9 years and sarcoidosis of 52 years. The 2 cancers most represented were breast and testicular cancers (18 and 16 patients, respectively). As in our series, limited stage of cancer was more frequent than advanced form. Data of clinical manifestations of sarcoidosis were not available for all patients but in 29 cases. Half of the patients presented symptoms (frequently pulmonary or skin manifestations) whereas the other half were non symptomatic. Organ involvements were predominantly lymph nodes, lung (with infiltrates) and skin. Most of patients (91.5%) did not receive any treatment for sarcoidosis. With a median follow-up after sarcoidosis diagnosis of 45.8 months, 2 of 28 evaluable patients experimented a sarcoidosis relapse. Only 3 cancer relapses were observed.

DISCUSSION

Even if no definite causal relationship has been identified, several case reports and studies conducted over the past 4 decades have described the association between malignancy and sarcoidosis. Previous epidemiological studies showed an increased incidence of cancer in patients with sarcoidosis.[4,5,9] In 1974, Brincker and Wilbek found for the first time, from 2544 cases of sarcoidosis in a Danish registry, that lymphoma occurred 11 times more frequently and lung cancer occurred 3 times more frequently than in the general population.[5] In 1999, Askling et al showed, from cohorts of 9015 Swedish patients with sarcoidosis, that the risk for cancer of the lung, liver, and skin were elevated.[4] Subsequently, the development of sarcoidosis in patients with cancer has been described in several small series and case reports.[11–23] This association seems not be cancer specific, the spectrum of underlying cancers being wide, including a variety of solid and hematological malignancies. In solid tumors, cancers the most described are testicular and breast cancers. Indeed, Rayson et al[20] found, from the Mayo Clinic database between 1950 and 1996, 14 patients who had a diagnosis of a malignant testicular tumor and sarcoidosis. Twelve of them had carcinoma diagnosed before sarcoidosis. In a retrospective chart review of all patients with a diagnosis of sarcoidosis or mediastinal adenopathy who underwent mediastinoscopy at the Swedish Medical Center and Cancer Institute from 2004 to 2008, Hunt

TABLE 3. Characteristics of 31 Patients From the Literature Review

				Cancer Characteristics				Sarcoidosis Characteristics					
Reference	Sex	Age at Cancer/ sarcoidosis Onset	Interval to Sarcoidosis, months	Type/Stage	Trt	Relapse	Follow-up After Cancer Diagnosis, months	Clinical Manifestations at Diagnosis	^{18}PET/CT findings	Trt/ Duration, months	Cmlinical/ Radiological Response	Relapse	Follow-up After Sarcoidosis Diagnosis, months
Karapetis et al[11]	M	31/33	24	Localized testicular carcinoma and seminoma	Surgery, CT	Yes*	42	None	Hypermetabolic mediastinal LN and PI	None	CR/CR	No	18
Haluska et al[12]	F	63/64	≈10	Localized melanoma	Surgery	No	≈22	None	Hypermetabolic mediastinal and hilar LN, PI, bone	None	CR/NA	No	≈12
Yao et al[13]	M	49/49	5	Tongue carcinoma T3N2cM0	RT, CT	No	≈5	None	Hypermetabolic mediastinal and hilar LN	NA	NA/NA	NA	NA
Yao et al[13]	F	30/35	60	osteosarcoma	Surgery, CT	No	63	None	NR (x-ray CT: bilateral hilar and paratracheal LN)	None	CR/NR	No	9
Tanizawa et al[14]	M	32/36	≈54	Stage I seminoma	Surgery, CT for relaspe	Yes*	≈96	None	NR (x-ray CT: mediastinal and hilar LN)	None	CR/CR	No	57
Biglino et al[15]	M	32/33	≈10	Leydig cell tumor	Surgery, CT	No	≈30	Fever, dyspnea	NR (x-ray CT: PI)	CS/10	PR/PR	No	20
Fiorelli et al[16]	F	62/67	60	Ileocecal ADK	Surgery, CT	No	NA	Thoracic pain	Hypermetabolic mediastinal and hilar LN	CS/NA	CR/CR	No	NA
Kim et al[17]	F	52/52	11	Stage III ovarian cancer	Surgery, CT	No	≈14	Cough and subcutaneous nodules	Hypermetabolic diffuse LN and subcutaneous nodules	None	CR/PR	Yes	NA
Dick et al[18]	M	29/30	12	Stage 2B seminoma	Surgery, CT	No	72	Night sweats, arthralgia, erythema nodosum	Hypermetabolichilar LN	CS/NA	NA/PR	No	60
Parra et al[19]	M	72/74	24	Lung carcinoma T3N0M0	Surgery	No	≈36	Dyspnea	Hypermetabolic mediastinal and hilar LN and PI	CS/NA	CR/PR	No	≈12
Parra et al[19]	F	48/50	26	Gastric leiomyosarcoma TxN0M0	Surgery	No	42	Dyspnea	NR (x-ray CT: paratracheal LN and PI)	CS/NA	CR/CR	No	16
Rayson et al[20]	M	29/53	288	Localized seminoma	Surgery, RT	No	288	None	NA: Thoracic LN	None	NA/NA	No	0
Rayson et al[20]	M	23/28	59	Localized seminoma	Surgery, RT	Yes	273	None	NA: thoracic LN	None	CR/CR	No	214
Rayson et al[20]	M	22/29	80	Seminoma with RP LN	Surgery, CT, RT	No	161	None	NA: thoracic LN	None	CR/CR	No	81
Rayson et al[20]	M	28/32	66	Localized testicular teratoma	Surgery	No	60	None	NA: thoracic LN	None	CR/CR	No	6
Rayson et al[20]	M	37/49	144	Localized testicular cancer	Surgery	No	144	Skin rash	NA: extrapulmonaryinvolvments	None	NA/NA	NA	0
Rayson et al[20]	M	27/35	91	Seminoma with RP LN	Surgery, CT	No	104	Hypercalcemia	NA: thoracic LN	CS and BP/NA	NA/NR	No	13

					Cancer Characteristics			Sarcoidosis Characteristics					
Reference	Sex	Age at Cancer/ sarcoidosis Onset	Interval to Sarcoidosis, months	Type/Stage	Trt	Relapse	Follow-up After Cancer Diagnosis, months	Clinical Manifestations at Diagnosis	^{18}PET/CT findings	Trt/ Duration, months	Cmlinical/ Radiological Response	Relapse	Follow-up After Sarcoidosis Diagnosis, months
Rayson et al[20]	M	34/36	24	Localized seminoma	Surgery, RT	No	24	None	NA: thoracic LN and PI	None	NA/NA	NA	NA
Rayson et al[20]	M	34/37	36	Localized seminoma	Surgery, RT	No	48	None	NA: thoracic LN and PI	None	CR/PR	No	12
Rayson et al[20]	M	18/20	24	Embrynal testicular cancer with RP LN	Surgery, CT	No	204	Skin rash and eye pain	NA: thoracic LN	Topical CS/NA	PR/PR	No	184
Rayson et al[20]	M	43/45	30	Seminoma with RP LN	Surgery, RT	Yes*	30	None	NA: thoracic LN	None	NA/NA	NA	0
Rayson et al[20]	M	29/38	108	Localized testicular teratoma	Surgery	No	420	Skin rash	NA: thoracic LN	Topical CS/NA	NR/NA	Yes	312
Inoue et al[21]	F	54/56	24	Oral floor carcinoma TxN2M0	Surgery, CT, RT	No	24	None	Hypermetabolic thoracic LN, PI and spleen	NA	NA/NA	NA	NA
Inoue et al[21]	F	54/58	48	Localized breast carcinoma	Surgery, CT	No	72	None	Hypermetabolic diffuse LN	None	CR/NR	No	24
Martella et al[22]	F	56/59	36	Breast carcinoma T1N0M0	Surgery, CT	No	109	NA	Hypermetabolic mediastinal LN	None	NA/NA	No	73
Martella et al[22]	F	55/59	48	Breast carcinoma T1N0M0	Surgery, RT, HMT	No	97	NA	NR (x-ray CT: mediastinal LN and PI)	TLD/24	NA/NA	No	49
Martella et al[22]	F	53/56	34	Breastcar cinoma T1N0M0	Surgery, CT, RT, HMT	No	87	NA	Hypermetabolic mediastinal LN	None	NA/NA	No	53
Martella et al[22]	F	38/40	26	Breast carcinoma T2N1M0	Surgery, CT, RT, HMT	No	143	NA	NR (x-ray CT: mediastinal LN)	None	NA:NA	No	117
Martella et al[22]	F	69/70	10	Breast carcinoma TisN0M0	Surgery	No	93	NA	NR (x-ray CT: mediastinal LN)	None	NA/NA	No	83
Martella et al[22]	F	61/62	11	Breast carcinoma T1N0M0	Surgery, RT, HMT	No	86	NA	NR (x-ray CT: PI)	None	NA/NA	No	75
Martella et al[22]	F	53/61	82	Breast carcinoma T2N0M0	Surgery, HMT	No	116	NA	Hypermetabolic axillary LN	None	NA/NA	No	34

ADK = adenocarcinoma, BP = Bisphosphonate, CR = complete response, CS = corticosteroids, CT = Chemotherapy, HMT = Hormonal therapy, is = in situ, LN = lymph nodes, NA = not available, NR = non response, NR = not realized, PI = pulmonary infiltrates, PR = partial response, RP = Retroperitoneal, RT = Radiotherapy, TLD = Thalidomide, Trt = treatment, x-ray CT = x-ray computed-tomography.

* Relapse of cancer before sarcoidosis.

et al[24] described 21 patients presenting with sarcoidosis after cancer, including 10 breast cancers. Finally, a study conducted at the urban medical center in Detroit from 2001 to 2010 identified 30 other patients, including also 10 breast cancers.[23] In our study, 4 breast cancers but no testicular cancers were observed. The other cancers were lung, colorectal, and head and neck cancers.

Sarcoid reactions refer to the development of noncaseating epithelioid cell granulomas in patients who do not fulfill the criteria for systemic sarcoidosis. In ''oncologic'' patients, this sarcoid-like reaction has been most commonly observed in the lymph nodes draining the cancer. It is particularly prevalent in testicular cancer[32] and lymphoma.[8] However, the distinction between sarcoidosis occurring in an ''oncologic'' patient and sarcoid reactions is difficult. In our study, we included patients in cancer remission at the time of sarcoidosis diagnosis, with a median interval between these 2 diagnoses of 34.5 months. Some of patients developed general symptoms, joint, and eye involvements that are not usual in sarcoid reaction. These data are consistent with systemic sarcoidosis. Nevertheless, patients who developed sarcoidosis following cancer have clinical features that may differ from classic sarcoidosis in the general population. The age of the patients in our study at sarcoidosis diagnosis is an average of 57 years, which is similar to what was described in literature. This age is older than the peak age of onset of sarcoidosis in the general population that is evaluated to 20 to 39 years.[33] This can probably be explained by the fact that cancer develops in older age. Location of granulomatous reaction is sometimes atypical with especially bone involvement observed in 41.7% of our patients versus 0.5% in classic sarcoidosis.[34] Hypergammaglobulinemia or hypogammaglobulinemia are not classically observed in our patients, unlike that which occurs in classic sarcoidosis or common variable immunodeficiency. Finally, most often, sarcoidosis occurring after cancer has not serious organ involvement and has a good prognosis. Of the 73 patients described, 82% of patients do not require treatment. Clinical response is good with disappearance, improvement or absence of new symptoms of sarcoidosis in the majority of cases and only 3 cancer relapses among all of cases have been observed.

The pathogenic mechanism of this association remains incompletely understood. Development of sarcoidosis might be the consequence of an excessive systemic immune response against antigen or factors produced by the tumor itself. This hypothesis is not consistent with the relative large interval between the end of cancer treatment and the suspicion of sarcoidosis but could explain the absence of cancer recurrence in most of these patients, as in our study where all patients remain in sustained remission after a median follow-up of 73 months. This immune reaction seems to correspond to sarcoid like reaction that has been shown to have a positive prognostic significance in patients with Hodgkin disease and gastric cancer.[35,36] It has also been hypothesized that certain chemotherapies, particularly α-interferon and bleomycin, may predispose to the development of sarcoidosis.[37,38] However, chemotherapy is not systematically used in all patients: in our study, 33.3% of our patients did not receive any chemotherapy; the same rates are observed in the literature review.[23,24,39] Those who were exposed to chemotherapy received many different drugs, so the development of sarcoidosis in these patients cannot be explained by chemotherapy alone.

^{18}FDG-PET/CT is a technique widely used for managing a malignancy and also to assess the extent of organ involvement, and response to treatment, in sarcoidosis.[40,41] Symmetrical hilar FDG uptake is typically associated with a benign etiology, in particular when the level of uptake is low (SUV max, 3) and limited to the hila, whereas the presence of elevated asymmetric uptake in hilar and other mediastinal nodes that appear enlarged on CT corresponded most of the time to a malignant process.[42] In our study, 91% of patients were suspected of cancer relapse on ^{18}FDG-PET/CT. Results were not typical for diagnosis of sarcoidosis because high level of uptake for 3 patients or unusual location for 2 patients (bone involvement). For these reasons, a biopsy for pathological examination in patient with a history of cancer and the presence of FDG avid lesions is mandatory to distinguish between a cancer relapse and a sarcoidosis.

CONCLUSIONS

This case series and review of literature shows the characteristics and outcomes of patients who develop sarcoidosis following cancer. The major limitation of our study is the retrospective nature of the analysis. Nevertheless, this report demonstrates that sarcoidosis must be considered in the differential diagnosis of patients with a history of malignancy who have developed hypermetabolic lesions during follow-up. All cancer types can be observed. Sarcoidosis appears most of the time within 3 years after cancer, may have atypical location but not serious complications. This association could be considered as a protective factor against cancer relapse because of the very low rate of cancer relapse reported in these patients. Consequently, biopsy is mandatory to avoid unjustified treatment of cancer relapse in cases of sarcoidosis occurring during cancer follow-up. Future prospective studies are needed to clarify the relation of cancer and sarcoidosis and the prognostic value of this finding.

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