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.

(Medicine 94(28):e928)

Abbreviations: 18FDG-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 genetic1 and environmental factors with the highest prevalence in Northern European countries2 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.4,5,5 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 al10 in a national French retrospective study. In the present study, we aim
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 (18FDG-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 18FDG-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 18FDG-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 18FDG-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
| Case | Sex | Age at Cancer/Sarcoidosis Onset | Interval to Sarcoidosis, months | Type/Stage of Cancer | Clinical Manifestations at Diagnosis | Treatment, Duration, months | Follow-up After Cancer Diagnosis, months | Clinical Response | Radiation Therapy, Duration, months | Relapse | Follow-up After Sarcoidosis Diagnosis, months | Clinical Response | Relapse |
|------|-----|-------------------------------|-------------------------------|----------------------|--------------------------------------|-----------------------------|------------------------------------------|------------------|--------------------------------------|---------|------------------------------------------|------------------|---------|
| 1 | M | 54/55 | 7 | Localized Melanoma | None | Surgery | No | 92 | Asymptomatic, weight loss, Lymphadenopathy | None | CR/NR | No | 86 |
| 2 | F | 48/54 | 72 | Rectal Carcinoma T2N3M0 | None | Surgery, RT, CT | No | 112 | None | None | CR/PR | No | 41 |
| 3 | F | 40/44 | 48 | Thyroid Carcinoma | None | Surgery, RT, CT | No | 84 | Asthenia, weight loss, Lymphadenopathy | None | CR/NR | No | 38 |
| 4 | F | 43/47 | 42 | Breast Carcinoma T2NOM0 | None | Surgery, RT, CT | No | 77 | None | None | CR/PR | No | 47 |
| 5 | F | 57/58 | 8 | Breast Carcinoma T2NOM0 | None | Surgery, RT, CT | No | 70 | Cough | None | CR/PR | No | 40 |
| 6 | M | 66/67 | 8 | Rectal Carcinoma T2NOM0 | None | Surgery, RT, CT | No | 47 | None | None | CR/PR | No | 13 |
| 7 | F | 36/62 | 57 | Breast Carcinoma | None | Surgery, RT, CT | No | 89 | None | Skin Lesion | CR/PR | No | 4 |
| 8 | M | 73/67 | 11 | Rectal Carcinoma T2NOM0 | None | Surgery | No | 39 | None | None | CR/PR | No | 15 |
| 9 | F | 53/43 | 30 | Colorectal Carcinoma | None | Surgery, CT | No | 89 | None | None | CR/PR | None | 5 |
| 10 | M | 53/55 | 12 | Rectal Carcinoma | None | Surgery, RT, CT | No | 57 | None | None | CR/PR | No | 25 |
| 11 | F | 54/60 | 48 | Prostatic ADK T2NOM0 | None | Surgery, RT, CT | No | 96 | Asthenia, fever, arthralgia, myalgia, Papillitis | None | CR/PR | No | 4 |
| 12 | F | 64/59 | 8 | Colon Carcinoma | None | Surgery, CT | No | 68 | None | None | CR/PR | No | 9 |

**ADK** = adenocarcinoma, **CR** = complete response, **CS** = corticosteroids, **CT** = chemotherapy, **LN** = lymph nodes, **NA** = not available, **NR** = non response, **NSAID** = nonsteroidal anti-inflammatory drugs, **PI** = pulmonary infiltrates, **PR** = partial response, **RT** = radiotherapy, **Trt** = treatment.
### 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                   | 0 (0)                     | 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)                     |
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/mm³).

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, because thoracic lymph nodes or pulmonary infiltrates at the time of cancer diagnosis and 3 because they were in induction chemotherapy at the time of sarcoidosis diagnosis. Three series of cases presented outcomes of 11, 7 and 30 patients, respectively. Two of the patients corresponded to case reports. All characteristics of solid cancer and sarcoidosis, treatment and follow-up are reported in Tables 2 and 3. Because of absence of individual data, 30 patients from the study of Butt et al were not included in Table 2.
| Reference          | Sex | Age at Cancer/sarcoidosis Onset | Interval to Sarcoidosis, months | Type/Stage                                      | Trt | Follow-up After Cancer Diagnosis, months | Clinical Manifestations at Diagnosis | 18FET/CT findings | Trt/Duration, months | Clinical/Radiological Response | Follow-up After Sarcoidosis Diagnosis, months |
|--------------------|-----|---------------------------------|---------------------------------|-------------------------------------------------|-----|------------------------------------------|-------------------------------------|-------------------|---------------------|-----------------------------------|---------------------------------------------|
| Karapetis et al1   | M   | 31/33                           | 24                              | Localized testicular carcinoma and seminoma     | Surgery, CT | Yes* 42 | None                      | Hypermetabolic mediastinal LN and PI | None               | CR/CR               | None                             | 18                                          |
| Halluska et al12   | F   | 63/64                           | 10                              | Localized melanoma                              | Surgery | No 322 | None                      | Hypermetabolic mediastinal LN and hilar LN, PI, bone | None               | CR/NA               | None                             | 12                                          |
| Yao et al13        | M   | 49/49                           | 5                               | Tongue carcinoma T3N2cM0 osteosarcoma           | RT, CT  | No 65 | None                      | Hypermetabolic mediastinal and hilar LN | NA                | NA/NA/NA  | NA                               | NA                                          |
| Yao et al13        | F   | 30/35                           | 60                              |                                                  | Surgery, CT | No 63 | None                      | Hypermetabolic mediastinal and hilar LN | None               | CR/NA               | 9                                | NA                                          |
| Tanizawa et al14   | M   | 32/36                           | 54                              | Stage I seminoma                                | Surgery, CT for relapse | Yes* 96 | None                      | Hypermetabolic mediastinal and hilar LN | None               | CR/CR               | 57                              | NA                                          |
| Biglino et al15     | M   | 32/33                           | 10                              | Leydig cell tumor Ileocecal ADK                  | Surgery, CT | No 30 | None                      | Fever, dyspnea Thoracic pain             | CS/10             | PR/PR                | No                                | 20                                          |
| Fiorelli et al16    | F   | 62/67                           | 60                              |                                                  | Surgery, CT | No NA  | None                      | Hypermetabolic mediastinal and hilar LN | CS/NA             | CR/CR                | No                                | NA                                          |
| Kim et al17        | F   | 52/52                           | 11                              | Stage III ovarian cancer                         | Surgery, CT | No 14 | None                      | Cough and subcutaneous nodules            | Hypermetabolic diffuse LN and subcutaneous nodules | None               | CR/PR               | Yes NA                          | NA                                          |
| Dick et al18       | M   | 29/30                           | 12                              | Stage 2B seminoma                               | Surgery, CT | No 72 | Night sweats, arthralgia, erythema nodosum | Hypermetabolic hilar LN | CS/NA             | NA/PR               | No                                | 60                                          |
| Parra et al19      | 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 al19      | F   | 48/50                           | 26                              | Gastric leiomyosarcoma T3N0M0                    | Surgery | No 42 | Dyspnea                   | NR (x-ray CT: paratracheal LN and PI) | CS/NA             | CR/CR                | No                                | 16                                          |
| Rayson et al20      | M   | 29/53                           | 288                             | Localized seminoma                              | Surgery, RT | No 288 | None                      | NA: Thoracic LN                          | None               | NA/NA                | No                                | 0                                           |
| Rayson et al20      | M   | 23/28                           | 59                              | Localized seminoma                              | Surgery, RT | Yes 273 | None                      | NA: thoracic LN                          | None               | CR/CR                | No                                | 214                                         |
| Rayson et al20      | M   | 22/29                           | 80                              | Seminoma with RP LN                              | Surgery, CT, RT | No 161 | None                      | NA: thoracic LN                          | None               | CR/CR                | No                                | 81                                          |
| Rayson et al20      | M   | 28/32                           | 66                              | Localized testicular teratoma                   | Surgery | No 60 | None                      | NA: thoracic LN                          | None               | CR/CR                | No                                | 6                                           |
| Rayson et al20      | M   | 37/49                           | 144                             | Localized testicular cancer Seminoma with RP LN | Surgery | No 144 | Skin rash                 | NA: extrapulmonaryinvolvements           | None               | NA/NA                | NA                                | 0                                           |
| Rayson et al20      | M   | 27/35                           | 91                              | Seminoma with RP LN                              | Surgery, CT | No 104 | Hypercalcaemia            | NA: thoracic LN                          | CS and BP/NA | NA/NR                | No                                | 13                                          |
| Reference          | Sex | Age at Cancer/sarcoidosis Onset | Interval to Sarcoidosis, months | Type/Stage                                      | Cancer Characteristics | Sarcoidosis Characteristics | Follow-up After Cancer Diagnosis, months | Follow-up After Sarcoidosis Diagnosis, months |
|-------------------|-----|---------------------------------|---------------------------------|------------------------------------------------|------------------------|----------------------------|-------------------------------------------|---------------------------------------------|
| Rayson et al20     | M   | 34/36                           | 24                             | Localized seminoma                              | Surgery, RT            | No                         | 24                                        | NA: thoracic LN and PI                   |
| Rayson et al20     | M   | 34/37                           | 36                             | Localized seminoma                              | Surgery, RT            | No                         | 48                                        | None                                        |
| Rayson et al20     | M   | 18/20                           | 24                             | Embryonal testicular cancer with RP LN          | Surgery, CT            | No                         | 204                                       | Skin rash and eye pain                   |
| Rayson et al20     | M   | 43/45                           | 30                             | Seminoma with RP LN                             | Surgery, RT            | Yes*                       | 30                                        | None                                        |
| Rayson et al20     | M   | 29/38                           | 108                            | Localized testicular teratoma                   | Surgery                | No                         | 420                                       | Skin rash                                 |
| Inoue et al21      | F   | 54/56                           | 24                             | Oral floor carcinoma TseN2M0                    | Surgery, CT, RT        | No                         | 24                                        | Hypermetabolic thoracic LN, PI and spleen |
| Inoue et al21      | F   | 54/58                           | 48                             | Localized breast carcinoma                      | Surgery, CT            | No                         | 72                                        | Hypermetabolic diffuse LN                |
| Martella et al22   | F   | 56/59                           | 36                             | Breast carcinoma T1N0M0                         | Surgery, CT            | No                         | 109                                       | Hypermetabolic mediastinal LN             |
| Martella et al22   | F   | 55/59                           | 48                             | Breast carcinoma T1N0M0                         | Surgery, RT, HMT       | No                         | 97                                        | NA                                         |
| Martella et al22   | F   | 53/56                           | 34                             | Breastcarcinoma T1N0M0                         | Surgery, CT, RT, HMT   | No                         | 87                                        | Hypermetabolic mediastinal LN             |
| Martella et al22   | F   | 38/40                           | 26                             | Breast carcinoma T2N1M0                         | Surgery, CT, RT, HMT   | No                         | 143                                       | Hypermetabolic mediastinal LN             |
| Martella et al22   | F   | 69/70                           | 10                             | Breast carcinoma TisN0M0                        | Surgery                | No                         | 93                                        | Hypermetabolic mediastinal LN             |
| Martella et al22   | F   | 61/62                           | 11                             | Breast carcinoma T1N0M0                         | Surgery, RT, HMT       | No                         | 86                                        | Hypermetabolic mediastinal LN             |
| Martella et al22   | F   | 53/61                           | 82                             | Breast carcinoma T2N0M0                         | Surgery, HMT           | No                         | 116                                       | Hypermetabolic axillary LN               |

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, NT = 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. 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. 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 and lymphoma. 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 diagnosis is an average of 57 years, which is similar to what was described in literature.

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. It has also been hypothesized that certain chemotherapies, particularly α-interferon and bleomycin, may predispose to the development of sarcoidosis. 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. Those who were exposed to chemotherapy received many different drugs, so the development of sarcoidosis in these patients cannot be explained by chemotherapy alone.

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. In our study, 91% of patients were suspected of cancer relapse on 18F-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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