***Original Research Article***

# Systemic granulomatosis in the context of solid tumors: a study of 10 cases


Abstract

Introduction. The association between solid cancers and sarcoidosis is well-known, however,we shouldn't quickly link a granulomatous lesion to sarcoidosis in a patient suffering from a solid tumor, hence, a granuloma in the context of a solid cancer presents a diagnostic and a therapeutic challenge.

Methods. It's a retrospective monocentric study of 10 cases, suffering from solid tumors, with granulomatous lesions. The type of cancer, the temporal relation between the granulomatous lesion and the cancer, the associated symptoms, the final diagnosis and the disease progression are reported. The patients were separated into three sub groups based on the time of appearance of the granulomatous lesions in relation to the solid tumor.

Results. Discovery of granulomatous lesions preceded the diagnosis of cancer in 1 case, discovered concomitantly with cancer in 5 cases and finally after the cancer in 4 cases. The main solid cancer in our study was breast invasive ductal carcinoma (40%), the other cancers were: squamous cell carcinoma of the breast, colorectal adenocarcinoma, ovarian epithelial cancer, esophageal squamous cell carcinoma, thyroid papillary carcinoma and uterine sarcoma.

Conclusion. A granuloma in the course of solid cancers maybe associated with multiple etiologies. Therefore, the clinician may face many difficulties, ranging from failing to diagnose a cancer to a wrong conclusion of treatment failure or a relapse. The biopsy is still the only guiding element.

## Introduction

The presence of granuloma, usually called “sarcoid reaction”, in the course of cancers is known since almost a century ago. In 1911, Wolbach was the first to describe a sarcoid-like reaction [1]. Not long after, Herxheimer reported a sarcoid reaction in patients with lung, rectal and urinary bladder cancers. Afterwards, Nickerson studied the differences between local granulomatous reaction and systemic sarcoidosis [2].

Later on, in 1986 Brinker described the sarcoid-lymphoma syndrome, which is defined as a lymphoma appearing at least 1 or 2 years after a diagnosis of sarcoidosis [3]. Then, he studied more specifically the association between granulomatous reactions and cancers [2].It seems that theses reactions are found in 5% of neoplastic diseases [4], and the association is particularly strong with germinal testicular cancer [5], Hodgkin disease and certain T-cell lymphomas [6].

In the course of cancers, the discovery of a granulomatous lesion may precede the diagnosis of a solid tumor, especially if the neoplastic cells are embedded in the middle of the granulomatous reaction, leading to a false diagnosis of sarcoidosis. In other cases, the two may be discovered at the same time. Hence, the diagnosis isn’t difficult, but in the case of persistent granulomatous lesions, assessing the response to treatment may be tricky. Finally, granulomatous lesions maybe discovered during the work-up of a patient suffering from cancer, and the challenge is to find out the etiology of the granuloma: the doctor should know how to track down a recurrent neoplastic disease or look for an opportunistic infection due to the immunosuppressed state. Therefore, the diagnosis of sarcoidosis should always be a diagnosis of exclusion.

The goal of this work was to study these different situations through a monocentric series of patients admitted in an internal medicine department for the work up of a systemic granulomatous disease, where the diagnosis of a solid cancer has been made.

## Patients and methods

It’s a retrospective monocentric study.

All of the patients were followed-up in the internal medicine department of Casablanca university hospital. Inclusion criteria were aconfirmed diagnosis of a solid tumor and the presence of granulomatous lesions in at least one biopsy. Then we have excluded all patients suffering from primary or secondary immunodeficiencies, tuberculosis and hypersensitivity reaction due to methotrexate use.

The patients were divided into three groups: in the 1st group the granuloma has preceded the cancer, in the 2nd group the granuloma discovery was concomitant with that of cancer which ishistologically confirmed and in the 3rd group the granuloma was discovered after the cancer (Table 1).

## Results

The detailed results are found in Table 1 and Table 2.

1. The study’s population

10 patients filled the inclusion criteria. The granulomas were diagnosed in the period between 2012 and 2020, and the cancer was diagnosed between 2008 and 2020, all of the patients were females, with a median age of 57 years old (42 – 86 years)

2. Sites and histology of the granulomas

Biopsy was performed on all patients, with presence of granulomas confirmed in each anatomopathological examination. The biopsy sites were variable: abdominal lymphadenopathies in four cases (40%), cervical lymphadenopathies in three cases (30%), mediastinal lymphadenopathies in two cases (20%), the liver in two cases (20%), and one case each in the cavum, the bone marrow and the bronchi.

The anatomopathological study has shown giant cells in four cases (40%) Accessory salivary gland biopsy was performed on six patients, with a normal histological aspect in each case.

3. Temporal relationships

The diagnosis of granulomatous disease has preceded the diagnosis of cancer in one patient (group no one), the time interval between the appearance of cancer after the discovery of granuloma was 13 months, five patients (50%) were diagnosed with granuloma and cancer at the same time (group no two), four patients (40%) were diagnosed with cancer before the granuloma (group no three), with a time interval varying between 11 and 48 months.

4. Clinical presentation

When the granuloma was diagnosed; four patients (40%) had a deterioration of their general state, seven patients (70%) had other symptoms: four cases had interstitial lung disease, three cases had articular manifestations, two cases had erythema nodosum, two cases had sicca and one patient had anterior uveitis.

5. Blood investigations

There was an inflammatory syndrome (CRP between 19 and 43 mg/l with a polyclonal hypergammaglobulinemia) in three patients of the second group. Angiotensin converting enzyme (ACE) was elevated in three patients, one in each group. Calcium and phosphorus levels were normal in all of the patients.

6. Granuloma treatment

Five patients (50%) received a treatment for their granulomatosis, of which four had received a full dose oral corticosteroid therapy indicated for the interstitial lung disease and a bilateral anterior uveitis, and one patient had received a small dose for a polyarthritis, azathioprine was administered to one patient in group three for recurrent uveitis.

7. Patients' evolution

In the course of the initial management, there was a single death (a patient in group two who suffered from esophageal squamous cell carcinoma associated with sever ILD and diffuse granulomatous cutaneous lesions). During follow-up there were two relapses of the granulomatous disease (colorectal adenocarcinoma and breast invasive ductal carcinoma)

8. Cancer

Five patients (50%) had breast cancer: an invasive ductal carcinoma in three patients of group three, in one patient in group two and a squamous cell carcinoma in one patient of group two, one case of uterine sarcoma in group

one, one case of thyroid papillary carcinoma, one case of esophageal squamous cell carcinoma and one case of colorectal adenocarcinoma in group two.

9. Chemotherapy treatment in group three

Three patients in group three had a breast invasive ductal carcinoma and had received adjuvant chemotherapy associating: cyclophosphamide and doxorubicin, cyclophosphamide doxorubicin and paclitaxel, anthracycline and paclitaxel. The fourth patient in group three who had an ovarian tumor received carboplatin .

## Discussion

A link between granulomatous disease and cancer was suspected a long time ago. The relationship between the two has become clearer nowadays due to epidemiological studies and the use of anti-cancerous immunotherapy [7], their coexistence covers different nosological situations: local granulomas, either due to a direct contact with a tumor, or found within the draining lymph nodes of the affected area or even at a distance from the cancerous tissue which appears to be the most common situation [8,9].

The possibility of a granulomatous adenitis in the draining territories (free from cancerous invasion) of epithelial tumors, digestif and mammary adenocarcinomas, melanomas and in the course of lymphoid hemopathies (Hodgkin disease and malignant non-Hodgkin lymphomas) must be known in order to avoid patient over treatment. The frequency of these granulomatous reactions at tumors' draining sites is estimated to be 14% in case of lymphomas and 4% in case of epithelial cancers[2,10]. It appears that it's associated with a better prognosis, especially in the case of Hodgkin's disease and adenocarcinomas of the stomach.

From a literature review done on April 2017, Spiekermann et al. have identified 24 observations with a simultaneous diagnosis of sarcoidosis and cancer; breast cancer (n = 7), endometrial cancer (n = 1), esophageal cancer (n = 1), ethmoid cancer (n = 1), lung squamous cell carcinoma or adenocarcinoma (n = 6), rectal cancer (n = 1), kidney cancer (n = 2), testicular cancer (n = 1) and thyroid cancer (n = 4) [11].

There are many hypotheses for explaining the appearance of a granulomatous reaction or systemic granulomatosis during neoplastic diseases. A granuloma represents an immune response against the neoplastic aggression. It's a hypersensitivity reaction mediated by activation of monoclonal T cells leading to stimulation of monocytes and the production of interferon gamma to form a granuloma [8,12].Other hypotheses are discussed as well, like the existence of an immune deficiency or an iatrogenic cause. Therefore, chemotherapy may provoke the development of granulomatous lesions, by inducing immunological perturbations [13].

When a granulomatous reaction precedes cancer, there's a risk of hastily diagnosinga sarcoidosis. Differentiating between sarcoidosis and a sarcoid reaction maybe difficult in certain patients, particularly, those who are mostly asymptomatic. The sarcoid reaction refers to the development of a non-caseous granuloma without fulfilling the criteria of a systemic sarcoidosis [14]. In our sub group of patients with prior and concomitant discovery of granuloma in relation to cancer, we noted atypical presentations which aren't found in a classic sarcoidosis, and these kinds of presentations must constitute signs of alert to the clinician. The atypical presentations of sarcoidosis were studied in 2007 by Bouvry et al. [15]. The disease affects many people in the third and fourth decade of life [16], in contrary to the median age of 57 years seen here. The mediastinal location is frequent in sarcoidosis [9],but in our series it's only present in 20% of cases, thus 80% of our patients have an extra mediastinal site of granuloma, specifically in the abdominal and cervical lymph nodes, in the skin, liver, bonne marrow and a nasopharyngeal location, without an associated mediastinal affection. A polyclonal hyper gammaglobulinemia is found in 20% to 80% of cases according to literature review [17].In our series the serum protein electrophoresis is normal in 70% of patients.

Seve et al have described the signs that should alert to the presence of a possible cancer in a patient where the diagnosis of sarcoidosis is suspected. Some are signs directly related to a cancer: bone pain, hemoptysis, signs of compression (e.g., superior vena cava obstruction) or a rapidly appearing mass or ulcer. Some general signs could be seen in the course of sarcoidosis (20%) but one must stay vigilant. On the other hand, the existence of atypical signs of sarcoidosis such as: an onset after the age of 50, mediastinal lymphadenopathies which aren't classically affected during sarcoidosis (right latero-tracheal, inter-broncho-tracheal), unilateral or compressive lymphadenopathies, or a rapid increase in

their size, unusual visceral sites (digestive tube, peritoneum …), a splenic affection without hypodense lesions, the presence of necrotic or excavated lesions, elevated inflammatory markers and corticosteroid resistance, constitute alarming signs. The appearance of a new affection after two years of diagnosing a sarcoidosis is rare and one must reconsider the diagnosis of a neoplastic disease[8,18]

Histologically, there are some diagnostic difficulties, since the sarcoid reaction may appear within a primary tumor or a lymph node draining the site affected by cancer, or even in a distant lymph node [2].This sarcoid reaction is morphologically identical to the non-caseous granulomas seen in systemic sarcoidosis, found in 4.4% of all carcinomas hence the importance of immunohistochemistry [19,20], in our study none of the granulomas were invaded by cancer cells. This information is in favor of a reactional granuloma, contrary to granulomas associated with lymphomas where it's difficult to differentiate between the two entities based only on the histological characteristics of the granuloma [14,21]

When a granuloma appears during the progression of cancer especially with the use of chemotherapy and/or anti-cancerous immunotherapy or long after the end of a treatment period, many diagnostic hypotheses maybe considered, most notably, tuberculosis, histoplasmosis, a primary or secondary immune deficiency, an inflammatory enteropathy, a generalized annular granuloma, a progressing or a recurrent tumor, a granulomatous reaction to anti-cancerous treatment or an authentic systemic sarcoidosis [22].

About ten observations of systemic granulomatosis developing after chemotherapy were reported in the literature, the main drugs responsible were: 5-fluorouracil, epirubicin, cyclophosphamide, docetaxel, doxorubicin, vincristine,leucovorin andoxaliplatin, within four to 72 months of treatment [23]. In our series, four cases (40%) of systemic granulomatosis were observed after the discovery of cancer and some were treated with neoadjuvant chemotherapy and others with adjuvant chemotherapy using cyclophosphamide, doxorubicin, paclitaxel, anthracycline, carboplatin within 14 to 24 months. Among the pathological mechanisms proposed for the explanation of post chemotherapy sarcoidosis: an immunological reconstitution after stopping

chemotherapy, treatment side effect, an excessive immunological response to antigens or factors produced by the tumor.

Many observations in the literature described localized or generalized granulomatous reactions secondary to immune checkpoint inhibitors (anti-PD1 antibodies (programmed cell death protein1, nivolumab, pembrolizumab, etc.), anti PD-L1 antibodies (ligand) (atezolizumab, durvalumab, avelumab, etc.) anti-CTLA1 antibodies (cytotoxic T-lymphocyte-associated protein 4, ipilimumab, etc.) or kinase inhibitors (BRAF or MEK) (e.g., vemurafenib) [24]

Radiologically, to distinguish between granulomatous and neoplastic lesions, it could be beneficial to use diffusion-weighted magnetic resonance imaging for bone lesions (diffusion hypersignal and a low apparent diffusion coefficient in the course of sarcoidosis) [12], the use of 3'deoxy-3'fluorothymidine (a more specific marker to detect a tumor) instead of 18-FDG as a tracer to PET-Scan [25].

## Conclusion

This work underlines the different associations between solid tumors and granulomatosis even though they're rare. These associations take many forms. Firstly, sarcoidosis observations were reported during cancer follow-ups, suggesting a late immune system reaction although a surveillance bias could not be excluded. A simultaneous diagnosis of systemic granulomatosis and cancer may prove to be a challenge due to thepseudo-tumor presentation of sarcoidosis: the doctor must always suspect a neoplastic disease when there are signs in favor of cancer or an atypical presentation of sarcoidosis.

The sarcoid reaction may be beneficial in certain cases (as a sort of cantonment or a barrier to the progression of cancer) or sometimes deleterious, due to a delay of diagnosis.

Table 1 : global results

| | Before (n=1) | Concomitant(n=5) | After (n=4) |
|---|---|---|---|
| **Median age (years)** | 47 | 62 (42-86) | 54 (50-63) |
| **Biopsy site** | | | |
| **_ Mediastinal LAN** | 1 | 1 | 0 |
| **_ Abdominal LAN** | 0 | 2 | 2 |
| **_ Cervical LAN** | 1 | 2 | 0 |
| **_ Inguinal LAN** | 0 | 1 | 0 |
| **_ Skin** | 0 | 2 | 1 |
| **_ Liver** | 0 | 0 | 2 |
| **_ Bronchus** | 0 | 0 | 1 |
| **_ Cavum** | 0 | 0 | 1 |
| **_ Bone marrow** | 0 | 0 | 1 |
| **Histological granuloma** | | | |
| **_ Giant cells** | 0 | 3 | 1 |
| **_ Necrosis** | 0 | 0 | 0 |
| **Clinical signs** | | | |
| **_ Fatigue** | 0 | 2 | 2 |
| **_ Fever** | 0 | 0 | 1 |
| **_ ILD** | 0 | 3 | 1 |
| **_ Sicca** | 1 | 0 | 1 |
| **_ Articular signs** | 1 | 1 | 1 |
| **_ Erythema nodosum** | 0 | 1 | 1 |
| **_ Uveitis** | 0 | 0 | 2 |
| **Blood investigations** | | | |
| **_ Elevated ACE** | 1 | 1 | 1 |
| **_Abnormal calcium and phosphorus levels** | 0 | 0 | 0 |
| **_ Elevated inflammatory markers** | 0 | 3 | 0 |
| **Granuloma treatment** | 0 | 2 | 3 |
| **Cancer** | | | |
| **_ Breast Invasive ductal carcinoma** | 0 | 1 | 3 |
| **_ Breast squamous cell carcinoma** | 0 | 1 | 0 |
| **_ Uterine sarcoma** | 1 | 0 | 0 |
| **_ Thyroid papillary carcinoma** | 0 | 1 | 0 |
| **_ Colorectal adenocarcinoma** | 0 | 1 | 0 |
| **_ Esophageal squamous cell carcinoma** | 0 | 1 | 0 |
| **Cancer stage** | | | |
| **_ Local** | 1 | 3 | 3 |
| **_ Regional metastasis** | 0 | 2 | 1 |
| **_ Distant metastasis** | 0 | 1 | 0 |
| **Cancer treatment** | | | |
| **_ Surgery** | 1 | 5 | 4 |
| **_ Neoadjuvant chemotherapy** | 0 | 3 | 0 |
| **_ Adjuvant chemotherapy** | 0 | 3 | 4 |
| **_ Radiotherapy** | 0 | 4 | 3 |
| **_ Hormone therapy** | 0 | 1 | 1 |

Table 2 : principal characteristics of the 10 obsevations collected

| | Granuloma | | | | | Solid tumor | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Age** | **Date** | **Site** | **Accompanying signs** | **Blood exams** | **Date** | **Type** | **treatment** | **evolution** |
| 1 | 47 | 2012 | Cervical mediastinum | Sicca Arthralgia | ACE = 98 U/l | 2013 | Uterine sarcoma grade I well differentiated | Hysterectomy | Good |
| 2 | 51 | 2019 | Skin | -Linear violaceous lesions<br>- Erythema nodosum<br>-ILD*<br>- Fatigue | -CRP = 19 mg/l<br>hypergammaglobulinemia<br><br>ACE = 112 U/l | 2019 | Breast invasive ductal carcinoma with bonne metastasis | -Chemo neoadjuvant<br>- Chemo adjuvant-<br>hormone therapy | |
| **3** | 73 | 2014 | Cervical Abdominal | -LAD* cervicaland abdominal<br>-ILD | | 2014 | Papillary thyroid carcinoma | -thyroidectomy<br>- lymph node dissection<br>- Iode 131 | |
| **4** | 42 | 2020 | Inguinal | - Large inguinal LAD | | 2020 | Breast squamous cell carcinoma | - mastectomy<br>-Chemo adjuvant<br>-radiotherapy | |
| **5** | 56 | 2019 | Skin mediastinum | - lupus pernio<br>- linear violacious lesions<br>- ILD<br>- Fatigue | CRP = 30 mg/l<br>SPEP : hypergammaglobulinemia | 2019 | Esophageal squamous cellcarcinoma T3N2M0 | - Chemo neoadjuvant<br>-Radio external<br>-oesophagectomy | Death |
| **6** | 86 | 2014 | Axillary Cervical | - LAD axillary Cervical | | 2014 | Colorectal adenocarcinoma stage II T3N0M0 | -CTH neoadjuvant<br>-Surgery with lymph node dissection<br>-Chemo adjuvant-<br>radiotherapy | |
| **7** | 50 | 2012 | - liver | - erythema nodosum<br>- sicca<br>- anterior uveitis<br>- recurrent arthritis | CRP= 43 mg/l<br>Moderate hypergammaglobulinemia | 2008 | Epithelial ovarian tumor | - hysterectomy<br>- Chemo : carboplatin | Good |
| **8** | 63 | 2017 | - skin<br>- bone marrow | -violaceous lesions : arms<br>-Fatigue<br>-PET scan : Nodular spleen/ abdominal LAD / bonne marrow hypermetabolism | | 2015 | Breast ductal invasive carcinoma T2N0M0 | -tumerectomy<br>- Chemoadjuvant Cyclophosphamide + doxorubicin<br>- Radiotherapy | Good |
| **9** | 53 | 2015 | - bronchus<br>- cavum | - nasal obstruction<br>-arthralgia<br>- ILD* | ACE= 100U/l | 2014 | Breast invasive ductal carcinoma T2N0M0 | -tumerectomy+ lymph node dissection<br>- Chemoadjuvant Cyclophosphamide + doxorubicin then paclitaxel<br>- Radiotherapy | Good |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **10** | 52 | 2013 | - Liver -LAD abdominal | - Liver nodule -LAD abdominal -Fatigue | 2010 | Breast invasive ductal carcinoma N4N1M | - surgery - Chemo adjuvant anthracycline+ paclitaxel - hormone therapy | Good |

* ILD: Interstitial Lung Disease.

* LAD: Lymphadenopathy.

*ACE : Angiotensin Convection Enzyme

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