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Granulomatosis and Cancer

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1. Introduction

Sarcoidosis is a granulomatous disease of unknown cause that can virtually affect any organ system. The commonly affected organ areas are thoracic lymph nodes and lungs (90 %). The granulomas appears to be due to an aberant immune response to a persistent antigen in a susceptible host; the antigen, however, is yet to be identified(Shigemitsu, 2008). The diagnosis typically rests on the demonstration of characteristic granulomas in biopsy specimens of one or more organs and exclusion of other causes of chronic granulomatous inflammation(Boffetta et al., 2009; Pavic et al., 2008b). Sarcoidosis affects more frequently young adults. Genetic studies have shown that some major histocompatibility complex alleles and tumor necrosis factor (TNF) polymorphisms are associated with an increased risk of sarcoidosis. The disease is usually characterized by an increased macrophage and CD4 T-cell activation, whereas sarcoidosis patients also show suppressed response to antigen challenges. The coexistent of hyper- and hypoactivity indicates a state of anergy in the immune system(Ji et al., 2009). Relationships betwen granulomatosis and cancers have been suspected for a long time(Askling et al., 1999; Brincker and Wilbek, 1974; Pavic and Rousset, 2008; Romer et al., 1998). Nevertheless, few evidence has been reported until recently. Aside from granulomatosis due to infectious disease (eg: opportunist infections), granulomas can be observed in cancer patients, mainly in two situations. Patients may rarely present with typical sarcoidosis occuring before, during or after the diagnosis of cancer. Secondly granulomas may be found as a sarcoid reaction in the vicinity of the tumour itself ore more frequently in regional lymph nodes(Pavic et al., 2008a). Sarcoidosis has although been reported to occur with some chemotherapeutic agents or immunotherapy such as interferon. The presence of granulomas within the tumor tissue or in regional ganglions is a frequent situation and corresponds to a defense reaction against the tumor-associated antigen (sarcoid like reaction)(Kennedy et al., 2008; Steinfort and Irving, 2009). The precise mechanism of the sarcoid-cancer syndrome is not yet clear, though there are several descriptions in the literature as to the temporal relationship of granulomas developing in cancer and vice versa. The etiology of sarcoidosis and sarcoid reactions in malignancy remains uncertain but some speculations have been made(Trikudanathan et al.): 1/ induction of robust effector T cell response to a tumor antigen or other products of cancer cells either spontaneously or with treatment that result in T helper 1 response along with secretion of TH1 cytokines; 2/ increased vulnerability to a potential infective agent due to immune system imbalance that occurs with cancer; 3/ radiation therapy and antineoplastic agents might enhance granulomatous reactions in tumors; 4/granulomatous reaction could

play an important role in the host's defences against metastatic extension. So granulomatous reaction has been associated for some cancers with a better prognosis(O'Connell et al., 1975)

2. Cancer - sarcoidosis syndrome

The literature remained very controversial during many years on the association between sarcoidosis and cancer(Battesti et al., 1977; Brincker, 1989; Brincker and Wilbek, 1974). The association of these two pathologies was first considered as fortuitous(Reich et al., 1995; Romer, et al., 1998; Seersholm et al., 1997). The swedish study of Askling et al. published in 1999 concerns a very large cohort and brings a first objective element of answer to this question(Askling, et al., 1999). This study reported on a retrospective cohort's study analyzing two registers of patients presenting with sarcoidosis (474 and 8541 patients) followed respectively from 1966 till 1980 and from 1964 till 1994. The risk of developping a cancer within these patients's group was studied by crossing the results of the cancer's registers and of the death's registers. The authors investigated the risk of developping a cancer in the sites commonly affected by sarcoidosis. The relative risk of cancer was increased equally in both registers of sarcoidosis (RR: 1,3; CI 95 %: 1,2-1,4). The risk of lung cancer and non-Hodgkin's lymphoma was doubled in the first decade following the diagnosis of sarcoidosis. The relative risk was also increased for the other cancers: melanomas (RR: 1,6; CI 95 %: 1-2,3), other skin cancers (RR: 2,8; CI 95 %: 2-3,8) and unsignificantly for the hepatocarcinomas (RR: 1,4; CI 95 % 0,8-2,2). Le Jeune et al. studied in an English population, the incidence of cancer in patients affected by sarcoidosis (1153 cases) and found a relative risk of 1,65 (CI 95 %: 1,22-2,24)(Le Jeune et al., 2007). Adjusted according to the age, the sex and smoking, the risk was significantly increased for the skin cancers (RR: 1, 86; CI 95 %: 1,11-3,11) and for the lymphomas (RR: 7,04; CI 95 %: 1,54-32,1). Ji et al studied retrospectively 10037 patients having been hospitalized in Germany for a sarcoidosis between 1964 and 2004 and found 1045 cases of cancers occuring in this patients(Ji, et al., 2009). A 40% overall excess incidence of cancer was noted among sarcoidosis patients. Notified cancers were the skin cancers (apart from the melanomas), the renal cancers, the extra-thyroid endocrine tumors, the non-Hodgkin's lymphomas and the leukemias. The increased incidence was confined mainly to the first year after hospitalization. However, for specific cancers, such as squamous cell carcinoma of the skin and non-hodgkin's lymphoma and leukemia, the increases were still significant for patients diagnosed later than 1 year after hospitalization, especially for those with multiple hospitalizations. A late age at hospitalization was associated with a high risk, which calls for clinical attention. All these studies have notified that the association of cancer and sarcoidosis was not fortuitous with an increased incidence (about 40 %) of skin cancers, lymphomas and probably of renal cancers, cancers of the lungs, endocrine tumors and leukemias. Some authors proposed the term of "cancer - sarcoidosis syndrome" to appoint this association(Shigemitsu, 2008). The independant course of the two pathologies are unconsistent to consider sarcoidosis as a paraneoplastic syndrome.

3. Sarcoidosis - lymphoma syndrome

This term was first used by Brincker to describe the association of systemic sarcoidosis and malignant lymphoma(Brincker, 1989). Several cases of lymphomas following various forms of systemic sarcoidosis have been published since then. The increased prevalence of granulomatous disease during the malignant hemopathies is now well established,

especially for Hodgkin's disease (14 %) but also for non hodgkin lymphomas (4 in 7 %) (Brincker, 1986a; Brunner et al., 2005). Malignant lymphoproliferative disorders, including B cell lymphomas, Hodgkin's lymphomas, chronic myeloid leukaemias and chronic lymphoid leukaelias, are more often seen among patients affected by sarcoidosis, with an incidence almost 5,5-fold higher than in general population(Apalla et al., ; Brincker, 1986b). Development of lymphoma in an individual with a personal history of sarcoidosis, even though rare, is not considered fortuitous. In the vast majority of reported cases, systemic sarcoidosis precedes the diagnosis of lymphoma by many years. The sarcoidosis – lymphoma syndrome is characterized by a later age of onset of the sarcoidosis (about 41 years, approximately 10 years more than the age of the classical sarcoidosis). Taking into account that the symptoms of sarcoidosis may resemble, or even mask, the symptoms of internal malignancy, physician awareness is considered crucial. Conversely, when a patient presents with a granulomatosis occuring at the end of a malignant hemopathy's treatment, this granulomatosis must be suspected to be linked to an infectious complication (opportunist infection, tuberculosis or other mycobacterias, pneumocystosis, fungal infections). The HHV-8 virus has been incriminated in the genesis of lymphoid pathologies and for some authors of the sarcoidosis, but this remains very controversial. The granulomatous pathology occuring in patients affected by a hodgkin's lymphoma motivated a plentiful literature(Sacks et al., 1978). Approximately 10 % of the patients presenting with a diagnosis of Hodgkin's lymphoma would develop granulomas affecting mainly the spleen and the liver. Some granulomatous vasculitis involving central nervous system have also been reported. Some more unusual sites have also been reported: lymph nodes, bone marrow, testicles, lungs. The granulomatous disease occurs generally concomitantly to the Hodgkin's lymphoma. Nevertheless it also can precede or arise conversely numerous years later. Patients with a history of sarcoidosis develop more often a Hodgkin's lymphoma than the general population with a relative risk of 14,1 (CI 95 %: 5,4-36,8)(Landgren et al., 2006). The antineoplastic treatments (chemotherapy and/or radiotherapy) are sometimes suspected to be causative when the granulomatosis arises with a long delay after the diagnosis of Hodgkin's lymphoma. The organ areas affected by the granulomatous reaction can also contain a neoplastic infiltration which is generally very difficult to determine. Hodgkin's patients presenting with a granulomatous disease have usually a favourable course. Granulomatous disease seems to be a favorable prognosis factor in term of survival and relapse(O'Connell, et al., 1975; Sacks, et al., 1978).

4. Melanomas and other skin cancers

In the swedish study of Askling et al., the relative risk was increased for melanomas (RR: 1,6; CI 95 %: 1-2,3) and other skin cancers (RR: 2,8; CI 95 %: 2-3,8)(Askling, et al., 1999). In a recent work, Sève et al examined the relation between sarcoidosis and melanoma. They identified 7 cases in their population of 1,199 melanoma inpatients(Seve et al., 2009). Including these cases, 20 cases of sarcoidosis have been described in melanoma patients in the literature. Fifteen patients had their sarcoidosis diagnosed after melanoma. In 7 cases, sarcoidosis was related to immunotherapy. Sarcoidosis presented mainly as pulmonary disease without severe organ involvement, with a benign evolution. In this referral center study showed a prevalence of sarcoidosis of 0.58% among melanoma inpatients. By excluding two cases related to immunotherapy, the prevalence was 0.42%, what is close to the prevalence of sarcoidosis found in the general population. This study does not support a

strong relationship between malignant melanoma and sarcoidosis. However, clinicians should be aware of the possibility that sarcoidosis may initially manifest or be reactivated in melanoma patients, especially during or after treatment with immunotherapy. Because sarcoidosis is a diagnostic pitfall, biopsies must always be performed before starting an antineoplastic treatment. Although Asking et al. found an increased incidence of other skin cancers presenting with sarcoidosis, very few cases are reported in the literature about this concern(McLoone et al., 2005; Setoyama et al., 1998).

5. Hepatocarcinomas

Sarcoidosis-associated hepatocellular carcinoma (HCC) is rare with only few cases reports(Askling, et al., 1999; Chalasani et al., 2005; Ogata et al., ; Wong et al., 1999). Such a rare association of sarcoidosis with HCC may reflect the presence of relatively weak inflammation or weak hepatocytic regeneration in sarcoid liver disease(Ogata, et al.). Despite a favorable-looking suggesting host immunity against the tumor, its significance on prognosis is unclear.

6. Renal cancers

Only a few publications that mention the presence of granulomatous reaction in renal cell cancer have been published until yet(Bottone et al., 1993; Campbell and Douglas-Jones, 1993; Kovacs et al., 2004; Lucci et al., 2002; Marinides et al., 1994; Moder et al., 1990). In some cases the granulomatous reaction is not related to the cancer but it is a primary process of the kidney, like xanthogranulomatous pyelonephritis, and we must note that cancer and true sarcoidosis may coexist(Kovacs, et al., 2004). According to the few publications that mention cancer associated sarcoid-like reaction, such lesions do not influence the prognosis.
Interferon and interleukin 2 have been usual therapies for the kidney cancers during years. As sarcoidosis induced by interferon or high dose interleukin 2 therapies have been reported in the literature, the role of this agents must be kept in mind(Logan and Bensadoun, 2005; Massaguer et al., 2004; Pietropaoli et al., 1999).

7. Germ cell tumors

I the relevant literature, several case reports and small case series have described a total of 67 patients with "sarcoidosis" or "sarcoidosis-like reaction" and testicular germ-cell tumors (GCT) so far (Dick et al., ; Paparel et al., 2007). The phenomenon is clinically relevant, because the finding of granulomatous lesions in patients with cancer may lead to difficulties of interpretation resulting in appropriate treatment of both the granulomatous disease and the malignancy. Some data in the literature have raised the question of an increased incidence of sarcoidosis in GCT. It is suggested that the incidence of sarcoidosis could be increased following testicular cancer with an estimated incidence of 1.1% (Pandha et al., 1995; Rayson et al., 1998). Analysis of data from 1 center suggested that the incidence of testicular cancer in patients with sarcoidosis was 100 times the expected rate(Rayson, et al., 1998). Sarcoidosis is associated with different types of testicular cancer, with seminoma being the most common. In 80% of the cases with concomitant sarcoidosis, the sarcoidosis regresses simultaneously. The coexistence of sarcoidosis and testicular cancer doesn't change the overall prognosis(Paparel, et al., 2007). Epidemiological studies of sarcoidosis

and malignancy have potential confounding factors; both maximal incidences of testicular cancer and sarcoidosis occur at the same age. It is known that sarcoidosis is often a latent disease and is more easily discovered when the clinical survey is tight as in patients treated and followed for cancer. Thus, a great attention has to be paid to the group used to compare the incidence of sarcoidosis. The coexistence of sarcoidosis and testicular cancer presents potential pitfalls for oncologists during initial staging and follow-up of patients. Clinicians who deal with testis cancer should always consider one of the "great imitator" granulomatosis in the differential diagnosis of patients with GCT. An usual distribution of metastatic spread or coincident findings such as the rash of erythema nodosum demands further investigation. Conventional cross-sectional imaging and functional imaging with FDG PET can be unreliable, and histological assessment remains the only reliable way of confirming the diagnosis(Dick, et al.).

8. Lung cancers

Several cases of the occurence of sarcoidosis and lung cancer have been reported (Kobayashi et al., ; Yamasawa et al., 2000). In most of these cases, sarcoidosis was present for some years preceding the development of lung cancer, but in some cases both diseases were detected simultaneously. It is sometimes difficult to determine whether non-caseinting epithelioid cell granulomas coexisting with lung cancer represent sarcoid reaction or true systemic sarcoidosis. Epidemiologically, the causal relationship between the two diseases is controversial. Some reports supported the theory of an association between the 2 diseases(Brincker and Wilbek, 1974; Yamaguchi et al., 1991) but some reports did not(Romer, 1982; Seersholm, et al., 1997). Either causality or coincidence, lung cancer, a condition that can be observed in patients with sarcoidosis, should be considered in the differential diagnosis when suspicious findings of it are discovered(Kobayashi, et al.).

Tumor-related sarcoid reactions may be found in lymph nodes draining an area containing malignant tumor, in the tumor itself, or even in non regional tissues(Segawa et al., 1996). The association of sarcoidal reaction and cancer makes the cancer patient with lymphadenopathy a diagnostic dilemma: malignant involvement of the lymph nodes is common, but benign diagnoses are possible and must be considered(Hunt et al., 2009). Sarcoidal reactions in the setting of lung cancer (NSCLC) have been identified in two Japenese studies of lung cancer, with an incidence rates of 1,2% and 1,3% (Kamiyoshihara et al., 1998; Tomimaru et al., 2007). Steinford et al found in a recent Australian work an overall incidence of sarcoidal reactions occuring in regional lymph nodes of NSCLC patients of 4,3%(Steinfort and Irving, 2009). The findings were confined to patients with Stage I disease, with in an incidence in this group of 7,7%. In 1975, Laurberg reported an incidence of 3,2% among 734 Danish patients with lung malignancy, noting that sarcoidal reactions were seen only in patients with Stage I disease(Laurberg, 1975). Other authors have also noted a significantly increased incidence in Stage I disease, though very rare occurrence in Stages II and III disease has been reported(Kamiyoshihara, et al., 1998; Tomimaru, et al., 2007). Most of the authors have noted no association with histological sub-type. Laureberg noted a preponderance of squamous cell tumours and postulated that the slower growth and higher tendency to necrosis of this tumour type may result in a more vigorous and longer-lasting stimulation of the regional lymph nodes(Laurberg, 1975). A significant proportion of the sarcoidal reactions in regional lymph nodes of lung cancers are radiologically and metabolically occult. It appears that metastatic involvement by NSCLC is not seen in lymph

nodes exhibiting sarcoidal granulomatous reactions. The sarcoidal reaction do not influence the prognosis, and may be a local reaction or resistance to cancer cells(Kamiyoshihara, et al., 1998). Sarcoidosis must be considered in the differential diagnosis of patients with a history of malignancy who develop lymphadenopathy. It is imperative to obtain a tissue diagnosis before instituting therapy for presumed cancer recurrence(Hunt, et al., 2009).

9. Breast cancers

Lower et al reviewed the medical records of 629 women with sarcoidosis followed in the Interstitial Lung Disease Clinic at the University of Cincinnati for findings associated with breast disease(Lower et al., 2001). In addition, three women with breast cancer who had granulomas in proximity to their tumors were also examined. Abnormal breast examinations or mammograms were reported in 15 patients with sarcoidosis (2% of women with sarcoidosis). Breast biopsy revealed granulomas consistent with sarcoidosis in six. One of them developed breast cancer five years later. Breast cancer was identified in twelve further patients, therefore a total of thirteen patients with breast cancer were identified. Ten were diagnosed with breast cancer plus sarcoidosis: sarcoidosis preceded breast cancer in three, followed breast cancer in five, the two diseases appeared simultaneously in two. Three additional women with breast cancer were also evaluated and classified as patients with sarcoid-like reaction. Review of the mammographic and physical findings could not distinguish between sarcoidosis in the breast and breast cancer. The autors concluded that sarcoidosis patients develop breast cancer at the expected frequency. The breast cancer diagnosis may precede or follow that of sarcoidosis. There is no relationship between stage of sarcoidosis or treatment and the development of cancer. Because physical examination and mammography findings are unable to distinguish between sarcoidosis and malignancy, biopsy of all suspicious lesions in sarcoidosis is recommended.

10. Digestif tract cancers

The incidence of a sarcoid reaction in surgical specimens, derived from 319 Japenese gastric cancer patients, was first reported to be 5% (Takeuchi et al., 1982). To clarify the occurence of sarcoid-like reaction in the spleen of the gastric carcinoma patients, 100 consecutive specimens from gastrosplenectomy were examined(Kojima et al., 1997). Sarcoid-like reaction was observed in the lymph nodes of 13 cases (13%) and the spleen of five cases (5%). None of them showed any symptoms or signs indicative of systemic sarcoidosis. It seems that the cases with sarcoid-like reaction in the spleen ocurred more frequently in an advanced stage of the gastric cancer than those without this phenomenon. Epithelioid cell granulomas (EPGs) appeared to arise in the periarteriolar lymphoid sheaths of the spleen histologically, but were never found in red pulp or germinal centers. None of the 13 cases contained EPGs in the primary tumor. This study indicates that sarcoid-like reaction in the spleen is possibly not a rare phenomenon in the gastric cancer and more frequently seen in the advanced stage of the gastric cancer. Sarcoid-like reactions of the regional lymph nodes are more frequently seen in the patients with EPGs in the spleen than in those without. The incidence of sarcoid-like reactions in the spleen seems to be closely related to those in pancreaticosplenic nodes and/or nodes of the hilus of the spleen. Granulomatous gastritis is a rarely observed pathological diagnosis. This condition often mimics gastric adenocarcinoma clinically, resulting in gastric resection. However, granulomatous gastritis has long been viewed as a benign process not observed in association with adenocarcinoma of the stomach. Newton et

al. described a patient with granulomatous gastritis occurring in close proximity to an area of superficially invading gastric adenocarcinoma. The findings in this patient did not support a diagnosis of Crohn's disease, tuberculosis, sarcoidosis, syphilis, histoplasmosis, berylliosis, or foreign-body reaction. This unique case suggests a possible association between isolated granulomatous gastritis and metaplastic mucosal changes(Newton et al., 1998). Sarcoid reactions in colorectal is considered to be quite rare. There has been some case reports in the Japenese literature on colorectal cancers with sarcoid reactions in the dissected lymph nodes or continous to the tumor(Nozoe et al., 1999). In these cases, the most outstanding common clinicopathologic feature was the lack of metastatic carcinoma in the dissected lymph nodes despite the large size of the tumors.

11. Possible role of antineoplastic treatments in the pathogenesis of granulomatosis

Immunotherapy such as interferon (IFN) and interleukine-2 (IL-2) has been reported to induce systemic sarcoidosis probably by reproducing some physiological mechanisms involved in sarcoidosis(Logan and Bensadoun, 2005; Massaguer, et al., 2004; Pietropaoli, et al., 1999; Raanani and Ben-Bassat, 2002). Although no specific etiology has been implicated in the pathogenesis of the sarcoidosis, inflammatory mediators such as IL-2 and IFN are probably involved(Raanani and Ben-Bassat, 2002). IFN is released spontaneously from lung T lymphocytes and alveolar macrophages of patients with sarcoidosis. Moreover, quiescent macrophages of these patients are activated by exposure to IFN. Therefore, IFN given in pharmacological doses could cause macrophage activation especially in patients with a certain predisposition and thus might induce the clinical development of sarcoidosis. IFN γ appears to play a major role as a mediator responsible for macrophage activation. IFN g is released from lung T-lymphocytes and alveolar macrophages when these cells are obtained from normal subjects ans are exogenously stimulated(Robinson et al., 1985). It has been demonstrated that the same cells from patients with sarcoidosis release this cytokine spontaneously. Quiescent macrophages from patients with inactive sarcoidosis are activated by exposure to IFN γ. There is little published evidence implicating any of the other IFNs in the pathogenesis of sarcoidosis. IL-2, a T helper 1 (Th1) also plays an important role in the pathogenesis of the granulomatous inflammation in sarcoidosis(Logan and Bensadoun, 2005; Ziegenhagen and Muller-Quernheim, 2003). It has been postulated that a Th1 predominant pattern may be more important in promoting granulomatous inflammation while a Th2 predominant pattern may be more involved in the development of fibrosis. There is usually a chronological link between the occurrence of the granulomatosis and the beginning of the immunotherapy. The association can so rapidly be suspected. The occurrence of granulomatosis attributed to the classic antineoplastic chemotherapies is exceptionally reported in the literature.

To date, alpha interferon appears to be the most common agent that causes sarcoidosis in patients treated for malignancies, although many other agents such as cisplatin have also been reported(Shigemitsu, 2008).

12. Diagnostic strategy

Clinicians in charged with tumoral pathology would be interested in a non-invasive test allowing him to avoid a systematic a biopsy to distinguish cancer and benign pathology. Nevertheless clinicians have to keep in mind that neoplastic tissue and sarcoidosis can coexist.

Differenciation between malignant and benign pulmonary nodules is a common probleme encountered by radiologists which has provided the impetus to explore alternative imaging techniques(Chang et al., 2006). Accurates diagnosis can reduce unnecessary thoracotomies in patients with benign diseases. Metabolic imaging with 2-(18F)-fluoro-2-deoxy-D-glucose positron emission tomography (PET) is being used more and more to differentiate benign from malignant focal lesions and it has been shown to be more efficious than conventional chest CT. However, fluorodeoxyglucose (FDG) is not a cancer-specific agent, and false positive findings in benign diseases have been reported in active inflammation or infection, causing false-positive results. Active granulomatous conditions with agregation of inflammatory cells in sarcoidosis results in accumulation of FDG and it has been suggested that the intensity of FDG uptake may reflect disease activity(Brudin et al., 1994). A retrospective study was conducted by Chowdhury et al. to evaluate the prevalence of sarcoid-like reaction to malignancy detected using integrated 18 FDG PET/CT in patients undergoing staging or restaging of solid-organ malignancy(Chowdhury et al., 2009). Sarcoid-like reaction was initially suspected in 23 of the 2048 (1.1%) FDG PET/CT examinations, with the diagnosis confirmed histologically or by clinico-radiological follow-up in 13 of the 23 cases (57%). Sarcoid-like reaction was more commonly seen in patients undergoing FDG PET/CT for restaging of suspected recurrence rather than for primary tumour staging (77% versus 23%; p=0.05). The mean maximum standardized uptake value (SUV(max)) of confirmed hilar and mediastinal sarcoid-like reaction was 7.3 (range 3.1-13.6). Symmetric hilar uptake was demonstrated in 11 of the 13 (85%) and all 13 had additional mediastinal nodal uptake. Pulmonary uptake was seen in seven of the 13 cases (54%). Extra-thoracic involvement was present in eight of the 13 (61.5%), including nodal, splenic, and hepatic lesions. Sarcoid-like reaction was suspected in 1.1% of cancer patients at FDG PET/CT examination, with confirmation of the diagnosis in 0.6%. With the increasing use of FDG PET/CT in cancer patients, it is important to be aware of the prevalence of this uncommon, but important, disease entity and to consider this diagnosis in appropriate cases in order to avoid a false-positive interpretation of metastatic disease. Some authors have suggested that early metabolic response to systemic corticosteroid treatment may be used as a tool in the establishment of final diagnosis when sarcoidosis is suspected in a cancer patient and could be capable of differentiating cancer from sarcoidosis in the case of coexisting diseases(Aide et al., 2009). New radiopharmaceutical probes are under development and will improve the performance of PET(Bonardel et al., 2011).

Hence clinicians must be aware that a florid sarcoid-like reaction can camouflage tumor recurance and hence, should preferably perform multiple sections of the tissues or perform multiple biopsies at different sites in addition to continually following these patients for tumor recurrence(Trikudanathan, et al.). This is particularly true for Hodgkin's lymphomas and non-Hodgkin's lymphomas. So when a patient presents with an atypical sarcoidosis (age of beginning > 50 years, change of the general health status, no involvement of the lung or of the mediastinum, personal history of cancer), physicians must take the diagnosis of sarcoidosis very cautiously. The pathologist will have to look the whole block of inclusion with a particular attention. He also will have to look for cytokeratin expressions and to search a clonality. In this context, a corticotherapy must be avoided not to erase later the possibility of bringing to light lymphoma's cells.

13. Conclusion

Thanks to recent epidemiological studies the links between sarcoidoses and cancer are finally demonstrated. Nevertheless the over-risk of cancer after sarcoidosis remains modest.

The clinician has to remain particularly watchful when he is in front of an atypical sarcoidosis. In this situation he has first to suspect a possible lymphoma or an infectious pathology. This approach can avoid to delay an adapted specific treatment.

- **Infections:** • Fungal: Histoplasma, Coccidioides, Blastomyces, Sporotrichum, *Pneumocystis jirovecii*, Cryptococcosis • Mycobacterial: *Mycobacterium tuberculosis*, Atypical mycobacterial infections (*Mycobacterium avium complex, Mycobacterium gordonae, Mycobacterium kansasii*) • Bacterial : Brucella, Chlamydia, Tularemia • Spirochaeta : Treponema (Pallidum, *Pertenue carateum*) • Parasites: Leshmaniasis, Toxoplasmosis • Virus (Cytomegalovirus, Immune Reconstitution Inflammatory Syndrome during HIV)
- **Occupational and environmental exposures:** • Hypersensitivity pneumonitis: Farmer's lung, Bird fancier's, Other (> 50 types) • Chemical/drugs: Silica, Calcium carbonate or oxalate, Metals (Chronic beryllium disease, titanium, zirconium, aluminium), Glass fibers, Hydrocarbons, Methotrexate, BCG therapy, Interferon…)
- **Immunologic:** • Sarcoidosis, Wegener granulomatosis, Crohn disease, Rheumatoid arthritis
- **Immunodeficiency :** • Common Variable Immune Deficiency…
- **Malignancy:** • Radiation and chemotherapy • Neoplasia (carcinoma, seminoma, sarcoma, lymphoma) • Sarcoid-like reaction

Table 1. Main diseases (affecting preferentially the lungs) associated with granulomas on histologic examination

- Granulomatous reaction in loco-regional adenopathy
- Unfortuitous association between cancer and sarcoidosis but without paraneoplastic characteristics
- Opportunist infection
- Antineoplastic therapy

Table 2. Main contexts of granulomatosis during cancers

Features	Local sarcoid reaction	Multisystem sarcoidosis
Organ(s) involved	Single	Multiorgan
Age	Any	Middle age
Associated disease	Malignancy	None
Pathogenesis	May be local immune response	Unknown
Chest radiograph	Normal	Abnormal
Delayed hypersensitivity	Normal	Usually depressed
Elevated serum ACE	Rare	Common
Kveim-Siltzbach test	Negative	Positive
BAL lymphocytosis	Absent	Present
Slit lamp examination	Normal	Abnormal in 15-20%
Hypercalcemia	Absent	Common
Gallium body scan	Localized uptake	Multisystem uptake

ACE, angiotensin-converting enzyme ; BAL, bronchoalveolar lavage. Reproduced from Shigemitsu, 2008.

Table 3. Difference between a local sarcoid reaction and systemic sarcoidosis

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