EDITORIAL

IMMUNOPATHOGENESIS OF SARCOIDOSIS AND RISK OF MALIGNANCY: A LOST TRUTH?

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The hypothesis of a relationship between sarcoidosis and malignancy was firstly formulated in 1972 by Brincker. He documented an association of sarcoid reactions or sarcoidosis with 19 lymphomas and associated malignancies. Based on various epidemiological studies, for more than 20 years sarcoidosis has been considered as a condition at increased risk for cancer, particularly lymphoproliferative disorders. The existence of a sarcoidosis-lymphoma syndrome was therefore proposed, highlighting, as a potential mechanism, the uncontrolled lymphocyte proliferation and mitotic activity. A reduced ability to eliminate an antigen and chronic inflammation have been suggested as triggering events. Leading to a reduced tumor immune surveillance, a diminished myeloid dendritic cells (mDC) function, despite up-regulated co-stimulatory and maturation markers, was also raised as potential mechanism. However, some subsequent studies have questioned the presence of a close association between the two entities and have explained those previously published as the result of selection bias and misclassification. Recently, a Swedish population-based cohort study documented a significant overall excess incidence of cancer among sarcoidosis patients, especially those with multiple hospitalizations or admission in older age, emphasizing again a potential neoplastic risk. Therefore, currently, whether these patients have an increased risk of developing malignant lesions is still debated. Larger and unbiased studies are needed before drawing definite conclusions.

For more than 20 years an increased risk of developing neoplastic lesions was acknowledged in patients with sarcoidosis. Later, some studies questioned the presence of a close association between the two entities. Sarcoidosis is a multisystem granulomatous disease which most often affects the lungs but can also manifest with cardiomyopathy, arrhythmias, neurological symptoms, vision disturbances, hypercalcemia, and renal failure. An appropriate diagnostic approach includes the exclusion of other diseases such as lymphoma and tuberculosis and the documentation of non-caseating granulomas by biopsy of accessible sites.

Sarcoidosis mainly affects female patients, with two peaks of incidence, between 25-40 and between 45-65 years, respectively. Northern Europe is the area with the highest incidence (5-40 cases per 100,000 inhabitants). African Americans have a worse prognosis, with higher mortality and a tendency to multi-organ involvement and chronicity

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of the disease (1, 2).

Recent advances in the etiopathogenesis

The etiology of sarcoidosis is still largely unknown; protein catalase-peroxidase of *Mycobacterium tuberculosis* (mKatG) has been suspected to be involved: IgG antibodies to recombinant mKatG were detected in the sera of 12 of 25 (48%) sarcoidosis patients by Song et al. (3). The ACCESS study identified various exogenous agents modestly associated with sarcoidosis risk, such as agricultural employment (OR 1.46), insecticides at work (OR 1.52) and work environments with mold/mildew exposures (OR 1.61). This study was not able to identify a single predominant cause of sarcoidosis. The increased frequency and severity of the disease in the black patients and the evidence of a higher familial relative risk in white cases compared with African-American, suggested a predominant role of genetic and host factors (4). A single-nucleotide polymorphism (rs2076530 G→A in white population) of the gene butyrophilin-like 2 (BTNL2), a member of the immunoglobulin superfamily, was found to be an independent risk factor for sarcoidosis, probably by influencing T-lymphocyte activation and regulation. The role of major Histocompatibility Complex Region haplotypes such as HLA-DRB1*03, HLA-DRB1*11, HLA-DRB1*12, HLA-DRB1*14, and HLA-DRB1*15 in disease development has also been postulated (5). Recently, Fischer et al. identified chromosome 11q13.1 (rs479777) as a locus influencing the susceptibility to sarcoidosis in Europeans, confirming the importance of a genetic predisposition in these patients (6).

While the etiology of sarcoidosis is still largely unknown, its pathogenesis is likely to involve mechanisms that, if perpetuated, may lead to the development of cancerous lesions. According to recent data, after the exposure to yet unknown exogenous or endogenous antigenic proteins, antigen presenting cells (APCs), more likely peripheral immature dendritic cells (iDCs), take and process them into peptide fragments. After becoming mature and migrating to the lymph node, DCs present the fragments, loaded onto the peptide-binding groove of MHC class II molecules, to T-cell receptors (TCR) of naive CD4+ T (Th0) lymphocytes, in the context of co-stimulatory molecules (B7 to CD28, CD40 to CD40L). Then, DCs produce Th1-polarizing inflammatory mediators such as TNF, interleukin (IL)-12 and -18 and promote the T cell expansion. Subsequently, T cells migrate back to the end organ and release a disease-specific profile of inflammatory cytokines and chemokine (7, 8). Despite quite a large body of evidence for an important role for DCs in the immunopathogenesis of sarcoidosis, alveolar macrophages have long been considered as the major causative APCs (7). In a later phase, the latter may present the antigens to Th1 cells, and both produce chemo- and cytokines (e.g. IL-1, IL-2, IL-6, TNF-α, IFN -γ) which may further promote recruitment, migration, local proliferation and organization of cells, particularly T lymphocytes and monocytes/macrophages (Mo), leading to the granuloma formation (8). Fig. 1 shows the formation of granulomas in patients with sarcoidosis, following exposure to an antigen.

Dysregulation of the T-cell system and the immune paradox of sarcoidosis

Numerous studies have shown an oligoclonal expansion of T cells at sites of the disease: an AV2S3(Va2.3)+ T-cell proliferation was found in the bronchoalveolar lavage fluid of HLA-DR17+ (now designated DRB1*0301) Scandinavian patients; moreover, specific Vbeta+ (e.g. Vbeta2, Vbeta6) or other Valpha+ T-cell subsets were more expressed in lungs, skin or blood of subjects with sarcoidosis than controls (8, 9). Whether an oligoclonal proliferation may favour cancer development in these patients is unknown; the impairment of T-cell immunity or the consequences of the therapy may contribute to increasing the risk of malignancy in predisposed subjects (10). Sarcoidosis, a condition of chronic and systemic inflammation, is characterized by the presence of granulomas in affected tissues (signs of extensive local inflammation with cytokine secretion). Furthermore, an anergic state (poor response to antigens *in vitro* and *in vivo*) can occur. These events, also known as the "immune paradox" of sarcoidosis, remain unexplained and have been attributed to a diminished myeloid dendritic cell (mDC) function and to a disequilibrium between effector and T-regulatory (T-reg) cells, resulting in a diminished cellular immunity (11, 12). Myeloid DCs are descendants of blood myeloid hematopoietic

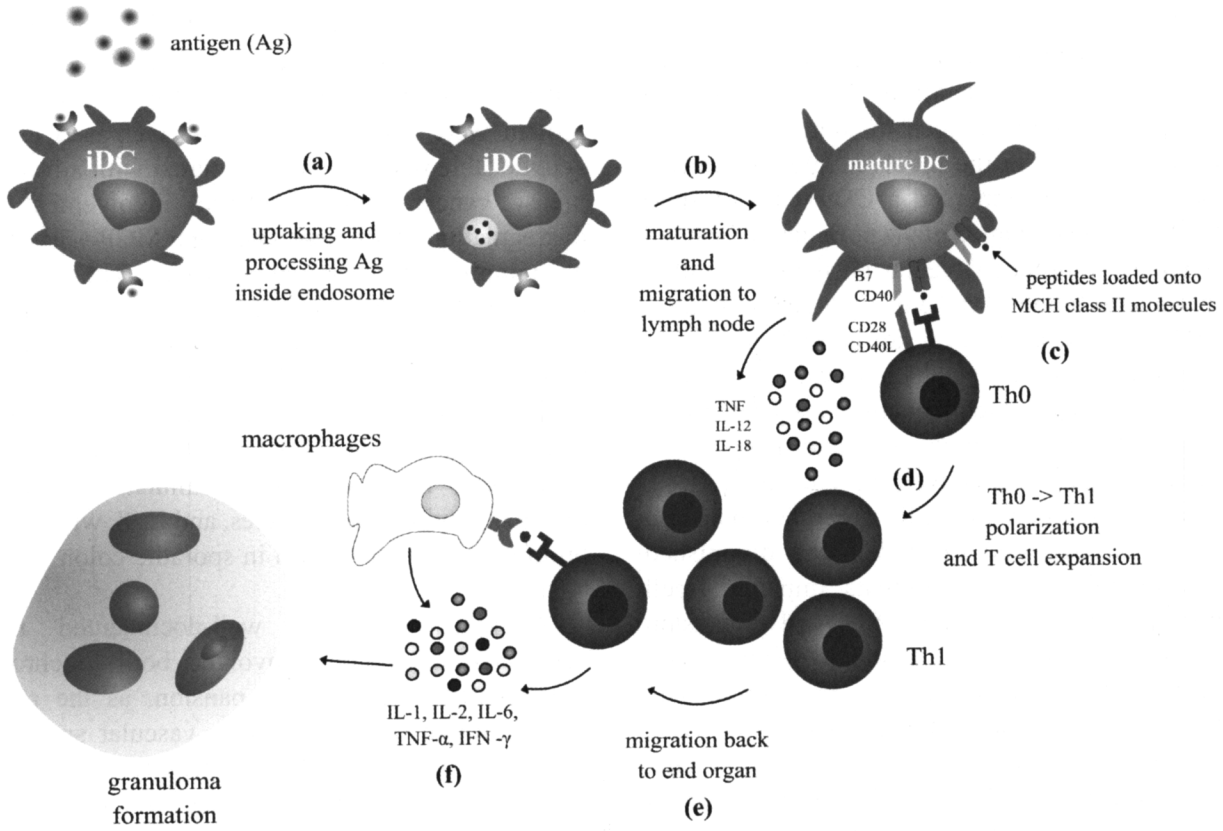

Fig. 1. *Pathogenesis of sarcoidosis, the granulomas formation. Modified from: Grutters et al. Eur Respir Mon 2009;. Zaba et al. Am J Respir Cell Mol Biol 2010. Immature dendritic cells (iDCs), take antigens and process them into peptide fragments inside the endosome (**a**). After maturation and migration to the lymph node (**b**), DCs present the fragments to naive CD4+ T (Th0) lymphocytes, through Ag-mediated interaction between MHC class II molecules with T-cell receptors, in the presence of co-stimulatory molecules (B7 to CD28, CD40 to CD40L) (**c**). Th0->Th1 polarization and expansion process is cytokine dependent (TNF-alfa, Il-12, IL-18) (**d**). Th1 migrate back to end organ (**e**) and produce, together with macrophages, chemo- and cytokines necessary for the formation of granulomas (**f**).*

precursor cells and recognize antigenic stimuli, such as bacteria, by binding their Toll-like receptors (TLR) 2 and 4 to bacterial cell wall components. *Mycobacterium tuberculosis*, suggested as causative agent for sarcoidosis, contains ligands for both receptors (7). Mathew et al. found that mDCs from sarcoidosis subjects had, *ex vivo*, a significantly decreased ability to stimulate T cells, compared to mDCs from healthy controls, despite normal cell count and up-regulated co-stimulatory and maturation markers, resulting, *in vivo*, in a reduced skin delayed-type hypersensitivity (DTH) to recall antigens in affected individuals. Nevertheless, the function of T cells in patients with sarcoidosis remained relatively preserved (12). In sarcoidosis, mDCs dysfunction may contribute to reduce the ability to eliminate antigenic stimuli, favoring the typical chronic inflammatory state, and may contribute to reducing the tumor immune surveillance. An altered maturation of mDC has indeed been found in various tumors (e.g. hepatocellular carcinoma and breast cancer) (13). Regulatory cells are a subpopulation of T cells capable of inhibiting different immunopathologic phenomena by controlling the proliferation of $CD4^+$ and $CD8^+$ T lymphocytes *in vivo*. They can be distinguished into two groups: the first, composed by Tr1 and Th3 cells, which act by releasing inhibitory cytokines such as IL-10 (Tr1) and TGF-beta (Th3),

and the second, consisting of naturally occurring, or innate, regulatory T cells (Treg cells), which act through a mechanism of contact inhibition with the target cells (11). In sarcoidosis, Treg cells are not sufficient in the control of local inflammation, despite their amplification in the involved sites. Miyara et al. have indeed documented a CD4+CD25(bright) FoxP3+ cell accumulation at the periphery of sarcoid granulomas, in bronchoalveolar lavage fluid, and in the peripheral blood of patients with active disease. Nevertheless, these cells do not completely inhibit TNF-alpha production (11). Increased levels of γδ T-cell populations, which have been associated with reduction of CD4+ T lymphocytes and rising values of serum angiotensin-converting enzyme (ACE), and down-regulation of TCR, are other potential mechanisms suggested to explain the diminished cellular immunity in these patients. Impaired T-cell immunity may promote the γδ T cell expansion and vice-versa. A reduced T and/or dendritic cell capacity to eliminate the antigenic stimuli may lead to the formation of granulomas and increase the risk of malignancy. Thus, a chronic inflammatory state, caused by the reduced ability to eliminate an unknown antigen, and a condition of compromised tumor immune surveillance, may result in an uncontrolled cellular proliferation and mitotic activity, which may increase the risk of mutations and neoplastic expansion. This is in agreement with the evidence of a greater risk of malignancy in patients with chronic active sarcoidosis (13). Fig. 2 shows the proposed mechanisms associated with an increased risk of cancer in patients with sarcoidosis.

Role of cytokines and angiogenesis

High levels of soluble factors such as cytokines and interleukins have been detected in sarcoidosis, most likely as the result of a Th1 type immune response. It is also well known that they have been implicated in tumor development. Above all, Tumor necrosis factor (TNF)-alpha is the most significant inflammatory mediator in sarcoidosis and is highly released by activated alveolar macrophages. It can promote angiogenesis, cellular proliferation, stromal growth and tissue remodeling, all required for tumor development and metastasis (13). As above-mentioned, DCs may play a key role in the pathogenesis of sarcoidosis, and their recruitment depends on blood levels of Monocyte chemoattractant protein (MCP)-1, a protein which usually also recalls memory T cells at the site of inflammation and tissue injury. The levels of the protein were indeed found to be increased in the active stable disease, and associated with advanced breast cancer and lymphatic involvement. A dysregulation of the gene encoding MCP-1 has also been implicated in cervical neoplasias. The potential degree of connection between inflammation and risk of developing cancer in these patients is also shown by the wide production of other cytokines such as IL-1, which may promote the formation of melanoma, leukemia, gastric carcinoma and the development of metastases, IL-6, which may stimulate the growth of hematological malignancies, and IL-8, which may promote the tumor growth in sporadic colon cancer (13).

Angiogenesis is a well-documented neo-vascularization process involved both in chronic inflammation and tumor expansion, as the result of the growth of capillaries by vascular sprouting from pre-existing vessels. It is required for various physiological processes such as wound healing, regeneration of organ and tissues and embryonic development, and is regulated by the combined action of pro-angiogenic proteins, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), angiopoietins and several chemokines, and antiangiogenic factors, above all angiostatin, endostatin and thrombospondin-1. Due to the loss of an adequate balance among these factors, tumors, also called as "wounds that never heal", result in an independent and uncontrolled production of proangiogenic proteins (14). Sarcoidosis, as well as cancerous lesions, is in effect a constant source of growth factors, cyto- and chemokines and, therefore, a continuous stimulus for angiogenesis. Indeed, in comparison with sera from healthy donors, sera from patients with sarcoidosis display significantly enhanced angiogenic activity of peripheral human mononuclear cells (MNC) ($P<0.001$). This appeared most pronounced in stage II of the disease ($P<0.05$) (15). Nitric oxide (NO), a free radical able to promote angiogenesis and involved both in carcinogenesis (cancer cell cycle,

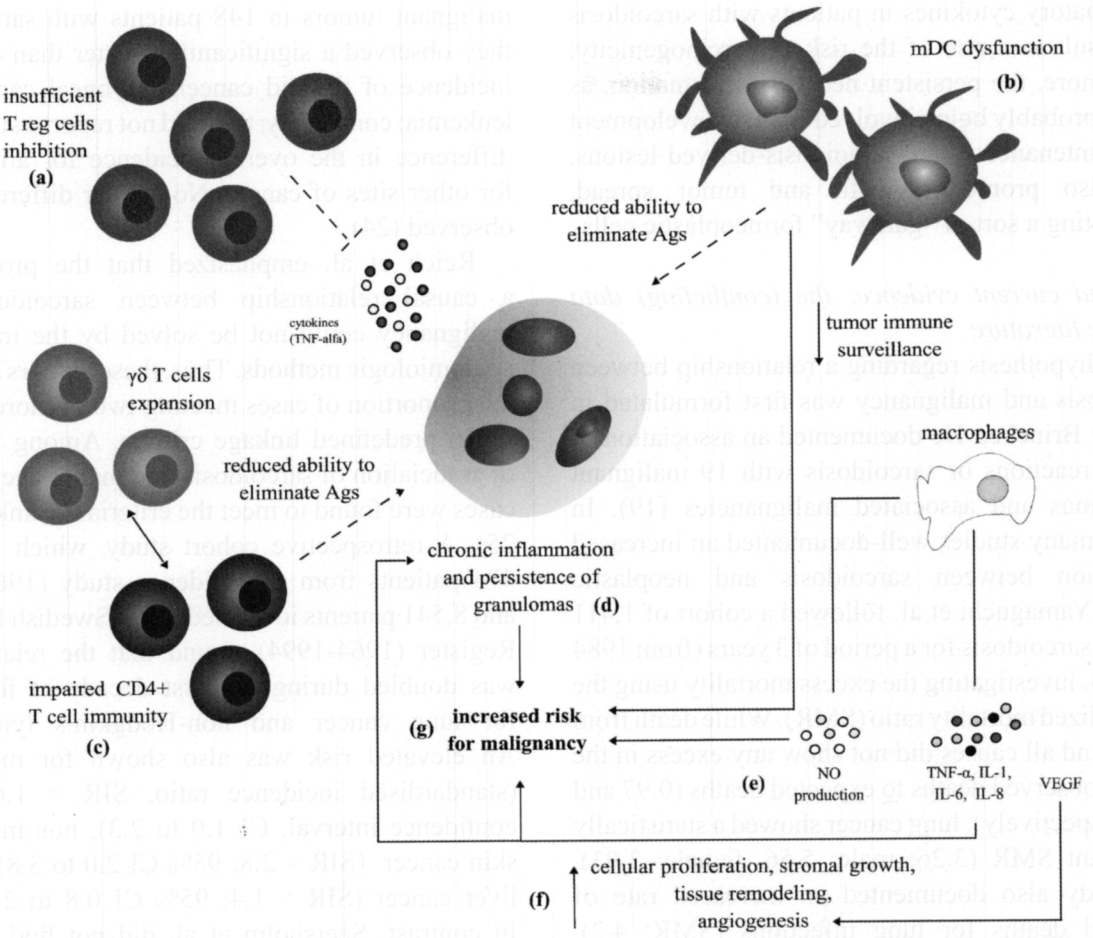

Fig. 2. *Proposed mechanisms at the basis of an increased risk for malignancy in patients with sarcoidosis. An insufficient ability of T regulatory cells to control the local inflammation (**a**), a dysfunction of myeloid Dentritic Cells (mDC) (**b**), and an impaired CD4+ T cell immunity (**c**) may lead to a decreased tumor immune surveillance (mDC dysfunction), a reduced ability to eliminate antigens, a state of chronic inflammation and formation and persistence of granulomas (**d**). An uncontrolled production of cytokines, nitric oxide by macrophages and Vascular endothelial growth factor (VEGF) (**e**) may promote angiogenesis, cellular proliferation, stromal growth and tissue remodeling (**f**), determining an increased risk for malignancy (**g**). Ags: antigens; mDCs: myeloid Dentritic Cells, VEGF: Vascular endothelial growth factor; NO: nitric oxide*

invasion, and metastasis) and inflammatory process (13), was found to be significantly elevated in subjects with sarcoidosis, due to the stimulation of inducible nitric oxide synthase (iNOS) by activated alveolar macrophages (16).

Angiogenesis, other than promoting the tumor growth, is also important in spreading metastases and feeding them. VEGF, the main regulator of angiogenesis which acts by binding to endothelium receptors, increasing vascular permeability and stimulating the diffusion of metastasis, also has an important role in the development of granulomas. Levels of serum VEGF were significantly higher ($p<0.05$) in patients with extrathoracic than those with thoracic involvement, with tendency to increase with the number of organs involved. In addition to inflammatory diseases, VEGF was also found to be elevated in neoplastic processes (17). Recently, Pabst et al. showed that VEGF and its receptors are involved at the onset of sarcoidosis, and may influence the entire course of the disease (18). Based on these data, the continuous production of

inflammatory cytokines in patients with sarcoidosis may result in a rise of the risk of carcinogenicity; furthermore, the persistent neo-vessel formation, as well as probably being involved both in development and maintenance of the sarcoidosis-derived lesions, may also promote growth and tumor spread, constituting a sort of "gateway" for neoplastic cells.

Past and current evidence: the (conflicting) data from the literature

The hypothesis regarding a relationship between sarcoidosis and malignancy was first formulated in 1972 by Brincker. He documented an association of sarcoid reactions or sarcoidosis with 19 malignant lymphomas and associated malignancies (19). In the 90s many studies well-documented an increased association between sarcoidosis and neoplastic lesions. Yamaguchi et al. followed a cohort of 1,411 cases of sarcoidosis for a period of 3 years (from 1984 to 1987), investigating the excess mortality using the standardized mortality ratio (SMR). While death from cancer and all causes did not show any excess in the ratio of observed deaths to expected deaths (0.97 and 0.98, respectively), lung cancer showed a statistically significant SMR (3.26; male: 5.56, female: 3.03). The study also documented an increased rate of observed deaths for lung infections (SMR: 4.2), leukaemia and uterine cancer (SMR: 5.88 and 8.70, respectively) (20). Sarcoidosis almost invariably preceded malignancies such as lymphoproliferative disorders: the reported association was so strong that the existence of a sarcoidosis-lymphoma syndrome was suggested; the chronic active type of sarcoidosis would be involved much more than the subacute self-healing type (21-23). This close relationship supports the hypothesis of an uncontrolled lymphocyte proliferation and mitotic activity at the basis of the increased risk for cancer in these patients (13). In an evaluation of cases by Brincker, regarding the association between sarcoidosis and malignancy, reported from 1911 to 1990, lymphoproliferative malignancies, myeloproliferative malignancies and lung cancer appeared more than 12 months after the onset of sarcoidosis in 67-76% (median 3 years), whereas cancer of testes and uterine presented before sarcoidosis in the majority of the cases (79 and 100%, respectively, median 28 months) (23). Kataoka et al. evaluated the occurrence and type of malignant tumors in 148 patients with sarcoidosis: they observed a significantly greater than expected incidence of thyroid cancer, laryngeal cancer, and leukemia; conversely, they did not report a significant difference in the overall incidence for all sites or for other sites of cancer. No gender difference was observed (24).

Reich et al. emphasized that the problem of a causal relationship between sarcoidosis and malignancy could not be solved by the traditional epidemiologic methods. Thus, these authors analysed the proportion of cases meeting two or more of their seven predefined linkage criteria. Among 12 cases of association of sarcoidosis and malignancy, only 7 cases were found to meet the criteria for linkage (23, 25). A retrospective cohort study, which included 474 patients from an incidence study (1966-1980) and 8,541 patients identified in the Swedish Inpatient Register (1964-1994), found that the relative risk was doubled during the first decade of follow-up for lung cancer and non-Hodgkin's lymphoma. An elevated risk was also shown for melanoma (standardised incidence ratio, SIR = 1.6; 95%; confidence interval, CI 1.0 to 2.3), non-melanoma skin cancer (SIR = 2.8; 95% CI 2.0 to 3.8) and for liver cancer (SIR = 1.4; 95% CI 0.8 to 2.2) (26). In contrast, Seersholm et al. did not find a major incidence of lymphoproliferative disorders: in their cohort study, which comprised 254 patients followed for a median of 25 years, no lymphomas occurred and only one case of leukaemia was demonstrated. Lung cancer was demonstrated in 5 patients, as compared to the expected 2.5 (SIR=2.0; 95% CI 0.7 to 4.7). However, these data did not support the theory of a sarcoidosis-lymphoma syndrome, since the finding of twice the number of lung cancers as expected was not significant, and the authors hypothesized that the higher incidence could be attributable to a higher incidence of lung cancer in Copenhagen, probably due to smoke. They explained the sarcoidosis-cancer association, reported by previously published data, as the result of selection bias and misclassification (27). Furthermore, a long-term follow-up study of 555 Danish patients, with a diagnosis of sarcoidosis carried out in two areas during the periods of 1960-1971 and 1970-1981 and observed for 9-30 years, did not show an increased occurrence of lung cancer or malignant lymphoma (observed *versus* expected

Table I. *A comparison of the available studies assessing the relationship between sarcoidosis and risk of malignancy.*

	Study design	Patients Nr *	Population	Mean years to onset	Statistical analysis	Risk of malignancy	
						Increased	Not increased
Brincker 1986 (22)	Case series	17	Denmark	7,9	n/a	• lymphoma	
Brincker 1989 (21)	Review	131	n/a	n/a	n/a	• lymphoma	
Yamaguchi et al. 1991 (20)	Epidemiologic cohort study	n/a of 1411	Japan	n/a	SMR	• lung cancer • leukemia • uterine cancer	• death from all causes • death from cancers
Kataoka et al. 1992 (24)	Epidemiologic cohort study	9 of 148	Japan	11.7	P value < 0.05	• leukemia • thyroid cancer • laryngeal cancer	
Seersholm et al. 1997 (27)	Epidemiologic cohort study	36 of 254	Denmark	n/a	SIR	• leukaemia (1 case) • lung cancer • pharyngeal cancers • skin cancer	• lymphoma
Rømer et al. 1998 (28)	Epidemiologic cohort study	48 of 555	Denmark	14	SMR		• lung cancer • lymphoma
Askling et al. 1999 (26)	Retrospective cohort study	703 of 9015	Sweden	First decade for lung cancer and non-Hodgkin's lymphoma	SIR P value < 0.001	• lung cancer • non-Hodgkin's lymphoma • melanoma • non-melanoma skin cancer • liver cancer	
Boffetta et al. 2009 (29)	Epidemiologic cohort study	241 of 5768	United States	10	RR	• rectal, colon cancer • kidney cancer	• lung cancer
Ji et al. 2009 (30)	Retrospective cohort study	1045 of 10037	Sweden	First year after hospitalization	SIR	• 40% overall excess cancer risk • squamous cell skin cancer • non-Hodgkin's	
						lymphoma • leukemia.	
Shu et al. 2011 (31)	Population-based cohort study	1167 patients with sarcoidosis and cancer compared with 1,023,725 cancer patients without sarcoidosis	Sweden	2,5	Cox regression model	• breast cancer • prostate cancer • lung cancer • colon cancer • non-Hodgkin's lymphoma	

SMR: standardized mortality ratio; SIR: standardized incidence ratio; RR: relative risk
** Patient Nr: Patients with diagnosis of malignancy out of those with diagnosis of sarcoidosis*

-O/E- ratios 0.23, 95% CI 0.00-1.25 and 1.25, 95% CI 0.02-6.95, respectively). The O/E ratio was 1.16 in males and 1.28 in females (28). In a large cohort study, which compared the incidence of cancer among 5,768 patients with sarcoidosis (2013 white and 3,755 black male patients) admitted to Veterans hospitals in the United States during the period 1969-1996, with that of 3,454,707 non-sarcoidosis patients (2,792,503 white and 662,204 black) there was not any additional increase in the overall cancer risk, despite an increased relative risk of specific cancer such as rectal, colon or kidney cancer (the last two were observed only in white patients). The incidence of lung cancer was unexpectedly reduced (29). The recent Swedish population-based cohort study, which included a total of 10,037 patients hospitalized for sarcoidosis during the years 1964-2004, identified from the sarcoidosis research database of the Swedish Hospital Discharge Registry, has instead documented, in the first year after hospitalization, a 40% overall excess incidence of cancer among 1,045 sarcoidosis patients. A higher risk was noted for the patients with multiple hospitalizations or admission in older age. The most commonly observed malignancies were skin and kidney cancer, non-thyroid endocrine tumors, non-Hodgkin's lymphoma and leukaemia (30). Later, the authors showed that sarcoidosis, besides increasing the risk of cancer, may worsen the prognosis, particularly in the patients under 65 years (31). Table I summarizes the available studies assessing the relationship between sarcoidosis and risk of malignancy.

CONCLUSIONS

The conflicting results among the available studies may be attributed to several factors: first, the rarity of the disease and the increased incidence in certain geographical areas (Northern Europe), led researchers to perform most studies only in certain populations (e.g. Sweden, Denmark); second, the presence of some risk factors in these areas (e.g. smoking) may have influenced the increased risk of cancer; third, a misclassification may occur as sarcoidosis can mimic cancer and vice-versa (27, 32). The recent Swedish cohort study, which documented a significant overall excess incidence of cancer among sarcoidosis patients, especially those with multiple hospitalizations or admission in older age, raised again the hypothesis of a possible risk of malignancy in patients with sarcoidosis. The clinical relevance of these data is manifold: first, some patients may constitute a category at increased risk of developing cancer and, thus, have a worse prognosis; this may result in the need to intensify the therapy in order to obtain a rapid remission and reduction of risk of malignancy. In this regard, dendritic cells, given their putative role in the disease and its chronicity, could be, in the future, a hypothetical therapeutic target. In view of the common mechanism, anti-VEGF drugs (e.g. bevacizumab) could work with a synergistic mechanism in these patients; Bevacizumab has been approved by the Food and Drug Administration (FDA) for the treatment of metastatic colon, lung and kidney cancer. The indication for breast carcinoma has been recently revoked by FDA, due to an unbalanced risk-benefit ratio. Results on patients with sarcoidosis are limited and mainly described for ocular localizations of the disease. Adalimumab, an anti-TNF-alpha drug, has been successfully administered to patients with active sarcoidosis, documenting a reduction of the tracer uptake at 18-Fluorodeoxyglucose positron emission tomography (18-FDG PET), but may result in an increased risk for malignancy, particularly non-melanoma skin cancer. Cases of paradoxical sarcoidosis after the administration of the drug have also been reported (33). On the basis of the available data, whether patients with the Besnier-Boeck-Shauman's disease have an increased hazard of developing malignant lesions is still debated. Larger and unbiased studies are needed before drawing definite conclusions.

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