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On the missing link between inflammation and cancer

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Abstract

A various array of cutaneous granulomatous disorders have been found to be associated with internal malignancy. Among them, sarcoidosis, granuloma anulare (GA), psoriasis, pyoderma gangrenosum (PG), or other neutrophilic dermatoses such as the Sweet syndrome and subcorneal pustular dermatosis may precede the development of a neoplastic process by months or years. Pathogenic links of inflammation with cancer are discussed, including inflammation, intrinsic immune dysfunction, cytokines and interleukins, angiogenetic factors, and epigenetic changes.

Introduction

Various cutaneous granulomatous disorders have been found to be associated with internal malignancy. Granuloma anulare (GA), psoriasis, pyoderma gangrenosum (PG), or other neutrophilic dermatoses such as the Sweet syndrome and subcorneal pustular dermatosis may precede the development of a neoplastic process by months or years [**1**, **2**, **3**]. Our report in the current issue of Dermatology Online Journal, January 2011, Volume 17, Number 1, "**Cutaneous sarcoidosis and malignancy: An association between sarcoidosis with skin manifestations and systemic neoplasia**" details a comprehensive list of cases demonstrating the association of cutaneous sarcoidosis with cancer. As clinical identification of such cases linked etiologically to inflammation is likely to foster investigation of the pathogenesis of the process, we would like to present in the current review the data supporting an association of chronic inflammation with cancer. In fact, various cutaneous granulomatous processes have been found to be associated with the development of internal malignancies, in addition to the classical case of skin sarcoidosis. Psoriasis, granuloma anulare (GA), pyoderma gangrenosum (PG), or other neutrophilic dermatoses such as the Sweet syndrome and subcorneal pustular dermatosis may antedate the development of cancers by months or years [**1**, **2**, **3**].

Flawed by an intrinsic time-lead bias, development of internal cancers can and in fact should be recognized at the time of the initial clinical evaluation for patients presenting with inflammatory or granulomatous processes.

Herein is a review of the most important pathogenic links of inflammation with cancer.

Inflammation

The first suggestion of a link between inflammation and cancer dates to 1863, when Rudolph Virchoff postulated the existence of an interdependence between the presence of chronic inflammation, manifested as a lymphoreticular infiltrate, and the development of neoplasia. Approximately 1/6 to 1/4 of all cancers were estimated to be attributable to underlying infection/inflammation (such as colon, prostate, ovarian, pancreatic, cervical cancers) and the incidence of several types of cancer appears to decrease after the use of non-steroidal anti-inflammatory drugs

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Examples of non-infectious inflammatory conditions that increase the risk of neoplastic transformation are: airway inflammation by tobacco and airborne allergens, which produces lung cancer; large bowel inflammatory conditions (UC and Crohn), which create a risk of colorectal cancer that is directly proportional to the degree of inflammation present; and chronic prostatic inflammation, which may precede the development of prostate cancer. Anti-inflammatory medications, such as aspirin and COX-2 inhibitors, appear to have a protective effect on the development of cancers, such as colon cancer. Beneficial effects have been demonstrated for esophageal, breast, lung, and gastric cancers. In colon cancer, for example, up to a 50 percent decrease in disease-specific mortality was demonstrated with the use of non-steroid anti-inflammatory medications [**4**, **5**].

Cellular effectors and mediators of inflammation also participate in the intrinsic milieu of cancer cells. Certain neoplasias are associated with inflammation anteceding carcinogenesis. On the other hand, other tumors manifest oncogenesis, which produces a resultant inflammatory microenvironment, which further stimulates tumor development. Chronic tumor microenvironment inflammation is associated with significant tumor-promoting effects, such as angiogenesis, cellular migration, and immunosuppression [**6**]. Signaling through the toll-ligand-receptors (TLR) present on the cells belonging to the innate immunity classically results in inflammation-promoting effects through the production of chemokines and cytokines. Interestingly, TLRs are also expressed in transformed cells; the activation of these receptors may affect the progression of the tumor. Thus, along with stimulation through the classical ligand LPS (lypopolysaccharide), TLR4 signaling can also be triggered by endogenous ligands, such as DAMPs (damage-associated molecular patterns), leading to a non-infectious inflammatory process. An intrinsic pathway was designated connecting inflammatory reactions and tumor genesis, based on the fact that significant cellular pathways (RET, MYC, RAS) in tumors can trigger the expression of inflammatory molecules, which contribute to tumor progression [**7**].

The presence of a systemic inflammatory state in sarcoidosis, which extends beyond the local granulomatous response, is demonstrated by the fact that the erythrocyte sedimentation rate (ESR) in sarcoidosis patients reaches a median of 12 mm/h (range 1-77), compared to normal controls in which it is only an average of 4 mm/h (range 1-26) [**8**]. Another marker of systemic inflammation, IL-6, which is present in sarcoidosis [**9**], has additional immunosuppressive effects on DC differentiation [**8**].

Presence of an intrinsic immune dysfunction

In a majority of cases, sarcoidosis precedes malignancy, suggesting that an immune dysfunction secondary to sarcoidosis may facilitate tumorigenesis. Evidence is strongest for lymphoproliferative malignancies, myeloproliferative malignancies, and lung cancer; in an estimated 67-76 percent of cases these malignancies appear more than 12 months after the onset of sarcoidosis [**10**]. On the other hand, testicular and cervical cancers predominantly precede sarcoidosis, which may reflect the presence of different etiologies between these types of malignancies and others that demonstrate a reverse sequence between the onset of sarcoidosis and cancer.

Clinical anergy and other evidence of diminished cellular immunity are commonly found in sarcoidosis [**8**]. Mostly, global immune abnormalities (detected by the measurement of skin DTH reactions, T lymphocyte subsets, or immunoglobulin production) have been reported in sarcoidosis. However, recent evidence pointed out molecular defects that appear to relate to the observed clinical abnormalities, such as the presence of a 15-kb segment of the gene butyrophilin-like 2 (BTNL2), which represents a member of the immunoglobulin superfamily. BTNL2 is involved as a co-stimulatory molecule for T-cell activation and appears to be involved in the pathogenesis of sarcoidosis [**11**].

Granulomas, such as the ones present in chronic granulomatous disorders, occur when the cellular immunity system fails to clear antigenic stimuli. In sarcoidosis, a diminished function of the myeloid dendritic cells in the blood occurs during active disease, despite the presence of appropriate numbers of circulating pDCs and mDCs. This state may explain the anergy and the decreased DTH responses to recall antigens. Sarcoidosis, therefore, exhibits foci of chronic inflammation on a background of decreased systemic cellular immunity [**8**]. Altered DC maturation was also described in malignancies and infectious disorders, such as tuberculosis, breast cancer, myeloma, and other solid tumors [**8**]. A decrease in myeloid dendritic cell (mDC) function in the allogeneic mixed lymphocyte reaction (MLR) directly correlates with the magnitude of skin DTH reactions and was found to be present in spite of the presence of up-regulated co-stimulatory and maturation markers. This dysfunction, which was postulated to possibly contribute to susceptibility for chronic inflammation [**8**], may also be an important factor for decreased tumor immune surveillance. In addition, the circulating levels of DCs have been also found to be decreased in sarcoidosis [**12**].

Another class of immune cells, the myeloid-derived suppressor cells (MDSC) are found to be present in the blood, lymphatic nodes, and at tumor sites in the majority of patients and animal models with cancer. Whereas these cells exert inhibitory influences on the innate and adaptive immune loops, their induction by pro-inflammatory mediators

has generated the hypothesis that chronic inflammation promotes their accumulation, which inhibits immune surveillance and antitumor immunity [**5**].

Furthermore, patients with sarcoidosis were found to manifest a global T regulatory (T-reg) cell subset amplification, which is nevertheless insufficient to control the local granulomatous inflammatory process. The immune paradox of sarcoidosis, consisting of systemic anergy associated with the presence of intense local inflammation, can, therefore, be explained through the presence of disequilibrium between the effectors and regulatory T lymphocytes (T reg cells). These CD4+CD25++FoxP3+ cells have been found to be present at the periphery of granulomas, in BAL (bronchoalveolar lavage) fluid, and in peripheral blood during active disease. Although their influence is anti-proliferative, T regs do not completely inhibit the production of TNF-alpha [**13**] and are not able to suppress granuloma formation [**14**]. Recent evidence reveals a profound role of T-regs in the development, progression, and resistance to immunotherapy of cancer cells [**15**].

An interesting finding is that the presence of MHC class Ib molecule Human Leukocyte Antigen (HLA)-G appears to be important for the induction and maintenance of immunological tolerance. In addition, HLA-G expression may have a role in different cancers. Expression of HLA-G*010102/-G*0106 alleles were observed more often in sarcoidosis patients (39.4%) than in controls (26.4%), p = 0.025 [**16**], thus, providing an additional link between sarcoidosis and cancer.

Background effects on immunity are suggested also by the clinical evidence on the association of sarcoidosis with autoimmune phenomena, such as autoimmune thyroid disease (clinical autoimmune thyroid disease, Graves disease, autoimmune thyroiditis), Addison disease, or polyglandular autoimmune (PGA) syndrome type II, III [**17**]. It was extensively demonstrated that the presence of autoimmune disorders, or possibly the existence of an associated modified immunological background, is associated with development of lymphatic neoplasms. Such an association was reported for both for Hodgkin and non-Hodgkin lymphomas [**18**].

A down-regulation of T-cell receptor (TCR) ζ-chain resulting in impairment in T-cell function was demonstrated in the presence of chronic inflammatory conditions, such as cancer, infectious disease, and autoimmune disorders. This loss of expression of the TCR ζ-chain, along with an increased accumulation of regulatory CD11b+GR1+ myeloid suppressor cells (MSCs) inside an inflammatory background results in impaired T-cell proliferation and a defective generation of cytokines in response to antigenic exposure. This mechanism was shown to involve a bystander effect, where the T-cells, which do not participate directly in the elicitation of the immune response, are also involved. One mechanism through which MSCs prevent the activation of T cells is through depriving them of L-ornithine, a metabolite essential for T-cell proliferation and differentiation [**19**].

A possible link, between diminished cellular immunity and a background susceptibility to the formation of granulomas in sarcoidosis, is also suggested by the biphasic response of the granulomas to treatment with thalidomide; early treatment induces a proliferation of T-lymph, DC and multinucleated giant cells, with a later phase consisting of regression [**8**].

The setting of chronic inflammation against persistent unknown antigenic stimuli, increased mitotic activity, and an unbalanced proliferation of lymphocytes, increases the likelihood of mutation and malignant transformation, which then possibly leads to the development of malignancy. This is consistent with observations that patients with chronic active sarcoidosis are at highest risk of developing cancer. Impairment of cellular immunity and decreased resistance to oncogenic viruses has also been implicated.

Within the past decade, emerging research on the function and role of gamma-delta (γδ) T cells has shed important information. While γδ T cells represent a small subset of all peripheral blood lymphocytes (1-10%), they are known to play a critical role in the pathogenesis of tuberculosis and leprosy. Subsets of patients with sarcoidosis have been associated with significantly increased levels of γδ T-cell populations in the peripheral blood [**20**], tissue, and bronchoalveolar lavage (BAL) fluid [**21**]. Among patients with sarcoidosis, Shigehara et al reported that a high TCR γδ + expression was associated with significantly decreased levels of CD4+ T lymphocytes [**20**], impaired cellular immunity, and increased levels of serum angiotensin-converting enzyme (ACE). Circulating levels of gamma-delta T lymphocytes are lasting when associated with sarcoidosis [**22**]. Nakata et al reported consistent findings in their series, also noting an inverse correlation between levels of γδ T cells and CD4+ lymphocytes. Patients with high circulating levels of γδ T cells, compared to normal controls, had significantly lower absolute count ($P<0.002$) and proportion ($P<0.001$) of CD4+ lymphocytes, and weaker cellular immune responses [**23**, **24**]. Impaired T cell immunity may predispose to γδ T cell expansion, or the reverse can be true in which γδ T cell proliferation promotes immune dysfunction. Diverse cases corroborating this association are found in the literature, ranging from disseminated histoplasmosis to bone marrow transplantation [**25**].

These findings suggest that among patients with sarcoidosis, those in the subset with expanded γδ T cell populations may differ in their immunological response and disease activity. Gamma delta T cells in the peripheral blood were significantly higher in patients with clinically active sarcoidosis than in patients with inactive sarcoidosis or active tuberculosis or in normal subjects [**24**]. Thus, paralleling the fact that patients with active disease appear to be at the highest risk for the development of malignancy.

Differences in the presence of immune effectors in cutaneous sarcoidosis versus other disease locations, may explain the propensity of sarcoidosis skin involvement to be associated with malignancy. Gamma delta T cells have been scarcely seen in bronchoalveolar lavage and in biopsy specimens [**20**]. Similar results were obtained by Tazi et al, who found that the vast majority of T-lymphocytes present in lymph nodes from patients with sarcoidosis expressed alpha beta TCR, whereas only rare gamma delta T-lymphocytes were observed inside or at the periphery of the granulomas. However, cutaneous sarcoidosis appears to be associated with a more substantial presence of these immune cells. Using the pan-gamma-delta T-lymphocyte antibody anti-TCRγ1, only 0.3 gamma-delta T-cells cells/mm² (0.7% of CD3+ cells) were found in normal human skin dermis, compared to: 3.14 gamma-delta T-cells cells/mm² (0.36% of CD3+ cells) in sarcoidosis [**26**]. Comparatively, gamma-delta T lymphocytes are rarely seen in the lymph nodes (0.2/hpf) of patients with sarcoidosis [**27**]. The presence and persistence of gamma-delta TCR+ lymphocytes in the post-transplantation setting [**28**] is associated with an increased incidence of various cancers.

Another difference between cutaneous and non-cutaneous granulomatous involvement in sarcoidosis is in the presence of DCs. The cutaneous form is associated with a higher presence of these immune cells, which may explain their decreased presence and potential efficacy in the systemic circulation [**12**]. Similar findings were reported by Munro et al, who described that dendritic cells and Langerhans cells (NA1/34+ = OKT6+) with an interdigitating cell (RFD1+) phenotype were consistently associated with granulomas only in cutaneous sarcoidal lesions [**29**].

Role of soluble factors: cytokines and interleukins

Sarcoidosis represents a predominant Th1 type immune response mediated through an intricate network of chemokines, interleukins, lymphocytes, and macrophages [**30**].

Supernatants of PBMC cultures in sarcoidosis patients produce increased levels of MCP-1, IL-2 and IL-12p40/p70 [**8**]. MCP-1, a C-C subfamily chemokine, which produces inflammatory monocyte and macrophage recruitment (monocyte chemoattractant protein), is present in increased levels in patients with active stable sarcoidosis [**31**]. This cytokine was implicated in breast carcinogenesis. In patients with breast cancer, increased MCP-1 levels have been correlated with an advanced tumor stage and lymphatic involvement. MCP-1 gene dysregulation was postulated to represent a significant step for cervical intra-epithelial neoplasia formation, permitting the escape of HPV-positive cells from the control of the local immune response [**32**].

Macrophage migration inhibitory factor (MIF), a mediator associated with chronic inflammation, has been shown to be an important inducer of tumorigenesis, metastasis, and angiogenesis, through its critical role in cell cycle regulation [**33**]. One of the mainstay effects of this pro-inflammatory cytokine is in downregulating the tumor suppressor protein p53. In addition, cutaneous inflammation mediated by the mast cells present in cutaneous granulomas results in upregulation of CD30, a TNF receptor family member, with consequent induction of de novo synthesis of MIP-1alpha and MIP-1beta (macrophage inflammatory protein) [**34**]. MIP promotes angiogenesis, cell migration, and tumor growth in hepatic metastasis [**35**].

Bronchoalveolar lavage (BAL) macrophages in sarcoidosis release high levels of TNF-alpha [**36**]. In fact, a high serum level of TNF-alpha was seen in over 90 percent of patients with sarcoidosis 207.7 pg/ml [**37**]. Furthermore, a genetic predisposition for TNF-alpha production may play a causative role in sarcoidosis pathogenesis, as its clinical course was correlated with the patient's ability to spontaneously produce TNF-alpha in alveolar macrophages [**38**]. TNF, a significant mediator of inflammation, can function as an endogenous tumor promoter, which induces stromal growth and tissue remodeling, both required for tumor development and metastasis. TNF represents a transforming agent for carcinogen-treated fibroblasts, which may be induced by the generation of reactive oxygen species (ROS). It also stimulates cellular proliferation and the synthesis of proteases involved in cancer cells invasion.

Other aberrant soluble factors, which were found to be produced in sarcoidosis, are Th1-derived cytokine IFN-gamma, TNF-ligand and TNF-receptor super families, macrophage-derived cytokines (IL-1, IL-6, IL-8, IL-15, GM-CSF, MIP-1alpha, and macrophage-derived fibrogenic cytokines (TGF-beta, PDGF, IGF-1) [**5**, **39**]. The involvement of these cytokines in carcinogenesis and neoplastic dissemination has been shown in various cancer models. IL-1 production facilitates the development of metastases, as demonstrated by the resistance to experimental metastases development of mice deficient in IL-1β. The presence of IL-1 stimulates the development of melanoma

metastases development of mice deficient in IL-1β. The presence of IL-1 stimulates the development of melanoma,

gastric carcinoma, and leukemia [**40**, **41**]. IL-6, in addition to its roles in inflammation, functions as a growth factor for hematological malignancies [**40**]. Serum IL-8, which is present in higher concentrations in active than in inactive sarcoidosis (18.7 vs. 8.0 pg/mL), may exert a tumor promoting effect in sporadic colon cancer [**42**].

Angiogenesis

Angiogenesis, the formation of new blood vessels, is linked to both cancer and chronic inflammation. An event connecting inflammation and cancer is represented by an augmentation of adhesion molecule expression on the luminal surface of endothelium during inflammation. Such molecules are also produced by certain cancer cells and may induce formation of metastasis [**43**]. For example, nitric oxide (NO) is a free radical that is involved in the inflammatory process and carcinogenesis. NO, along with eNOS and iNOS, is able to influence angiogenesis, cancer cell cycle, apoptosis, invasion, and metastasis [**44**]. Serum from patients with sarcoidosis was demonstrated to significantly stimulate angiogenesis in comparison with serum from normal controls in a leukocyte-induced angiogenesis assay (17 vs. 13 new vessels) [**45**]. Furthermore, serum VEGF in patients with extra-thoracic sarcoidosis was found in higher concentrations than in patients with intra-thoracic sarcoidosis ($p < 0.05$), potentially signifying, another peculiarity of cutaneous sarcoidosis [**46**].

Epigenetic changes

DNA aberrant hyper-methylation at promoter CpG islands, commonly detected in chronic inflammation and precancerous lesions, has been demonstrated to represent a mechanism of inactivation of tumor suppressor genes [**47**]. Pro-tumorigenic effects are exerted also by oxidative stress, which induces increased DNA mutagenesis and damage, thereby promoting instability of the genome and cellular proliferation. Chronic inflammation is associated with an increased level of oxidative stress, suggesting a possible relationship between the two conditions. For example, the absence of glutathione peroxidase 1 (GPx1) is linked to the development of both colitis and colon cancer, which may be influenced by the fact that GPx-mediated regulation of cyclooxygenase functions may be connected to the early stages of inflammation-mediated carcinogenesis [**48**]. Intracellular ROS, such as peroxynitrites, are able to induce mutagenesis through DNA damage and resultant genetic instability when the extracellular aerobic degradation of damage associated molecular pattern molecules (DAMPs) is impaired [**49**]. Prolonged exposure to DAMPS induces angiogenesis and immunosuppression, mediated through myeloid-derived suppressor cells (MDSCs) and T-regs [**50**]. Production of matrix metaloproteinases (MMPs) is also induced by inflammation; these facilitate cellular invasion and distant metastasis [**5**, **50**].

Crossroads: the initiation pathway for cellular proliferation and survival

Another molecular link between cancer and chronic inflammation is produced by the transcription factor nuclear factor of κB (NF-κB), which is activated as part of the DNA damage and microbial pathogen recognition system. As such, NF-κB induces transcriptional activation of inflammatory and immune response genes, as well as activation of processes determining cell survival and proliferation, with distant implications in carcinogenesis and cancer progression [**51**]. Mononuclear cell expression of NF-κB was found to be double in both untreated and treated patients with sarcoidosis compared to the normal controls ($p < 0.001$) [**52**].

As shown in our article in the current issue of Dermatology Online Journal, January 2011, Volume 17, Number 1, "**Cutaneous sarcoidosis and malignancy: An association between sarcoidosis with skin manifestations and systemic neoplasia**" there might be an increased frequency of cutaneous sarcoidosis in patients displaying both cancer and sarcoidosis. The particular characteristics of DC and gamma-delta T-cells in cutaneous disease may contribute to a more inflammatory phenotype in skin sarcoidosis, which may be correlated through various mechanisms with the formation of diverse cancers. Despite the overall favorable prognosis in patients with sarcoidosis, physicians should be aware of the potential risk for malignancy in these patients and pursue appropriate measures to detect cancers, particularly when new lesions or adenopathy emerge that may signal occurrence or recurrence of malignancy.

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