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Sarcoid-like Granulomatosis: Systemic Reactions to Different Noxae

Granulomatosis símil sarcoidosis: reacciones sistémicas ante diferentes noxas

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ABSTRACT

Sarcoidosis is a chronic inflammatory condition of unknown origin, characterized by the presence of non-caseating granulomas in the affected organ. There is no single cause for this condition. Granulomatosis similar to sarcoidosis can be caused by infections, anti-tumor treatments and use of electronic cigarettes. The possibility of its appearance in these scenarios should be considered.

Key words: Sarcoidosis; E-Cigarrette; Noxae

RESUMEN

La Sarcoidosis es una afección inflamatoria crónica de origen desconocido, caracterizada por la presencia de granulomas no caseosos en el órgano comprometido. No existe una única causa para este padecimiento. La Granulomatosis símil Sarcoidosis se puede originar ante infecciones, tratamientos antitumorales y uso del cigarrillo electrónico. Considerar la posibilidad de su aparición ante estos escenarios

Palabras clave: Sarcoidosis; Cigarrillo electrónico; Noxas

Sarcoidosis is a chronic inflammatory condition of unknown origin, characterized by the presence of non-caseating granulomas in the affected organ. It was first described in 1869 by E. Besnier (1831-1909). It was later characterized by A. Bittorf (1876-1940) as a multi-organ syndrome, and in the mid-20th century, L. Siltzbach (1906-1980) wrote a 750-page text on this mysterious entity.[1]

In recent decades, it has been unquestionably accepted that there is no single cause for this condition. Possibly, any antigen (Ag) in a susceptible individual can trigger the characteristic granulomatous inflammation. Additionally, individual genetics and exposure to drugs or noxae in the workplace are considered risk factors.[2-6]

Immunotherapy has transformed the therapeutic response in patients with tumors, as it is more effective and has lower toxicity than previous treatments. The immune system can attack and destroy malignant tumors through various types of immunomodulators, such as targeted antibodies (AB), immune checkpoint inhibitors (ICI), cell-based immunotherapies, vaccines, and oncolytic viruses. Nevertheless, it must be acknowledged

that immunotherapy can be associated with significant adverse events. These side effects interact with the immune system by harmonizing the immunotherapy with other agents, reactivating diseases such as tuberculosis (TB), posing challenges in certain patient populations with solid organ transplants or those suffering from autoimmune diseases, and leading to the development of "sarcoid-like granulomatosis" (SLG). [2-3]

Non-caseating granulomatous inflammation is considered a type IV immune reaction.[2-3] It is formed by CD4 T lymphocytes aberrantly activated by foreign antigens. Following this interaction, they differentiate into T helper (Th1) lymphocytes and secrete interleukin-2 (IL-2) and interferon-gamma (IFN-γ), as well as chemoattractants such as tumor necrosis factor-alpha (TNF-α) from macrophages.[2-4] This process leads to the formation of "clusters" or groupings of epithelioid histiocytes and macrophages, surrounded by multinucleated giant cells and lymphocytes (non-caseating granulomas). Additionally, T helper 17 lymphocytes (Th17) have been implicated in the pathogenesis of sarcoidosis.[2-4]

The term SLG refers to granulomatous inflammation occurring in the context of cancer or an autoimmune disease. It can be mistaken for metastases or autoimmune disease activity due to the uptake on positron emission tomography (PET) and lymph node involvement. However, it is generally asymptomatic and is an incidental finding during follow-up. From a histopathological perspective, it is indistinguishable from sarcoidosis.

Some authors have even coined the acronym DISR (drug-induced sarcoid-like reactions).[9] DISR can affect one or multiple organs, such as the skin, lungs, lymph nodes, spleen, etc. Its onset may not coincide with drug administration and can even occur months after drug discontinuation.

Given the available literature, the vast range of therapeutic possibilities, and the variability of individual responses to specific antigens, an exhaustive bibliographic review exceeds the scope of this article. Therefore, it has been divided into sections to facilitate better knowledge, analysis, and understanding.

SLG AND COVID 19

COVID-19 is a disease caused by the SARS-CoV-2 virus. In general, affected patients develop mild to moderate forms of the illness, except in cases where they have significant comorbidities or in the case of older adults. This virus has been linked to immune system dysregulation, which leads to inappropriate responses, exacerbating inflammation and causing multiorgan dysfunction. As a newly emerged condition, ongoing research continues to explore its clinical manifestations, its progression, and therapeutic approaches to take into consideration in order to achieve better outcomes and control this threat to humans.[10]

COVID-19 can present two types of SLG phenomena: a) Inherent to the virus b) Linked to vaccination. Both are very rare, but some case reports have been published for consideration.

Behbahani et al described a case of COVID-19 pneumonia that developed multiple skin lesions, with a biopsy revealing SLG. In another report, a COVID-19 patient developed SLG with nodular lesions and hilar lymphadenopathy, while another case documented the appearance of a SLG pulmonary nodule in a kidney transplant recipient. In all the cases, the patients had severe comorbidities.[11-13]

The COVID-19 vaccine is not exempt from complications, although they are rare. [14-22] Ghazal et al have described nodules, lupus pernio-like lesions, petechiae, purpura, exanthems, and dengue-like fever (considering that dengue is a viral disease).[14] Numakura et al reported the case of a patient with multi-organ SLG involving ocular, pulmonary, and hilar locations, as well as elevated ACE (angiotensin-converting enzyme) levels, after receiving the first dose of BNT162b2 (Pfizer/BioNTech).[15] Cazzato et al described a patient who developed perioral SLG after receiving the second dose of BNT162b2. Another publication reported a case of SLG appearing three months after vaccination.[16] Rademacher et al published two cases of SLG mimicking Löfgren's syndrome following a second vaccine dose, occurring between 3 and 28 days post-vaccination, respectively.[18] Reports of patients with unilateral axillary lymphadenopathy after COVID-19 vaccination have increased, with a significant proportion detected in FDG-PET/CT scans (fluorodeoxyglucose positron emission tomography and computed tomography imaging).[19-20] McIntosh et al reported that intensive COVID-19 vaccination has shown transient FDG uptake in axillary, supraclavicular, and ipsilateral cervical lymph nodes post-immunization, which may lead to misinterpretation in cancer patients undergoing FDG-PET/CT scans.[21] They

suggest performing the study at least two weeks post-vaccination in patients whose cancer evaluation could be affected.[21] Ideally, the scan should be done 4 to 6 weeks after immunization due to the immunogenicity of mRNA vaccines and the potentially prolonged resolution time.[21] Finally, it is recommended to administer the vaccine in the arm opposite to a unilateral cancer to avoid FDG uptake on the tumor-affected side.[21]

A thorough anamnesis including the type and timing of COVID-19 vaccination is essential to avoid misinterpretation of imaging findings. The presence of SLG in FDG-avid lymph nodes highlights the need to distinguish between vaccine-related reactions and newly diagnosed concomitant diseases, especially when other hypermetabolic lymph node regions are present.[22]

SLG AND NEOPLASMS

SLG is presumed to be an immune response mediated by T cells and macrophages against malignant tumor markers, leading to granuloma formation in lymph nodes.[23] These reactions can have infectious or non-infectious causes. When associated with malignant tumors, they are classified as SLG, excluding infectious processes. SLG refers primarily to Hodgkin's lymphoma but can also be observed in non-small cell lung cancer (NSCLC).[23] SLG-related lymphadenopathy is often difficult to differentiate from malignant adenopathy, even in high-resolution imaging. The differential diagnosis includes lymphoma, tuberculosis, and sarcoidosis, with the lymph node biopsy being the most definitive diagnostic tool.[24]

There is limited understanding of the natural course of SLG and its impact on the prognosis of malignancies. A higher risk is suggested in patients with a history of cancer. While some research indicates increased cancer risk in patients with sarcoidosis, several findings remain inconsistent. Bonifazi et al conducted a meta-analysis of 16 studies, including 25,000 patients, to better define and assess the association between sarcoidosis and cancer.[25] The study demonstrated a significantly increased risk of hematologic, upper digestive tract, skin, liver, and colorectal cancer.[25] The authors' findings suggest a moderately significant association between tumors and sarcoidosis.[25] Although the coexistence of neoplasms and SLG is uncommon, various publications have reported cases of different tumors in the body triggering a subsequent sarcoid reaction.[26-33] In a retrospective, multicenter, and observational study, Murthi et al investigated 133 patients who met the study criteria to evaluate the incidence and clinical characteristics of cancer patients with biopsies showing SLG.[34] The most frequently associated tumors were skin cancer (22.5%), breast cancer (20.3%), and lymph node malignancies (12.8%).[34] Among these patients, 18% developed SLG within a year of their cancer diagnosis, 40.6% between 1 and 5 years, and 36.8% afterward.[34] The authors concluded that SLG is a rare pathological finding in cancer patients, with a significant association between the presence of granulomas, increased survival rates, and reduced metastases.[34] A similar observation was made by Pastré et al, who compared 38 patients with biopsy-confirmed SLG to a control group with systemic sarcoidosis.[35] Their study revealed thoracic involvement in all cases, typically asymptomatic, with less lesion progression and a significantly more favorable prognosis. These findings could suggest potential discrepancies in the physiopathology that have yet to be fully explained.[35]

However, in a smaller cohort study on cancer-related SLG, Huh et al did not find evidence of systemic sarcoidosis. Most lesions were either reduced or remained unchanged, and the development of SLG was not associated with overall survival or disease-free survival in patients with NSCLC. [36]

SLG AND ELECTRONIC CIGARETTE

The widespread use of electronic cigarettes (or vaping) is not exempt from risks, as it can cause damage to the lung parenchyma.[37] This condition includes a broad spectrum of manifestations, ranging from "ground-glass opacities" visible in radiological studies to acute respiratory distress syndrome in adults (ARDS), which may require hospitalization in an Intensive Care Unit. This has led to publications by the American Thoracic Society and reviews by Werner, Marrocco, et al which documented 2,258 hospitalized cases and 60 deaths related to vaping by January 2020.[37-39]

The occurrence of SLG in patients using vaping devices is rare. In 1999, Dicpinigaitis et al reported a case involving a habitual crack user who developed progressive dyspnea. A comprehensive examination revealed bilateral interstitial lung opacities, hilar lymphadenopathy, diffuse pulmonary uptake of Ga-67, and a markedly elevated level of angio-

tensin-converting enzyme (ACE). The lung biopsy revealed an interstitial and perivascular infiltrate of histiocytes containing refringent material, possibly inhaled along with the drug. The enlarged and reactive paratracheal lymph nodes also contained similar refringent material. The non-necrotizing granulomas characteristic of sarcoidosis were not present in the lung tissue. The authors noted that the chronic inhalation of "crack" had not been previously associated with this combination of clinical findings typical of sarcoidosis.[40] In the available literature, the only documented case was reported by Soybel et al, describing a patient who experienced remission and recurrence of SLG upon stopping and resuming vaping, respectively.[41] Morris et al have linked systemic sarcoidosis exacerbations to possible exposure to triggering agents, though without necessarily leading to the development of the disease itself.[42]

SLG AND DRUGS

Due to the incidence of drug-induced SLG, it is generally classified into four categories: highly active antiretroviral therapy (HAART), interferons, immune checkpoint inhibitors (ICI), and TNF-α antagonists.[43-44] However, other monoclonal antibody (MAB) drugs can also induce SLG, such as BRAF/MEK inhibitors and others.[44] A review by the World Health Organization (WHO) identified 55 drugs considered potential inducers of SLG, with 45.4% of them not previously described.[44] Typically, it improves or resolves after discontinuation of the suspected drug.[43] Similar to sarcoidosis, drug-induced SLG does not always require treatment: it can be asymptomatic, without affecting quality of life or causing organ dysfunction. When treatment is necessary, it follows certain regimens similar to those used for sarcoidosis. However, the suspected drug should only be discontinued if it is beneficial to do so. For example, in melanoma treatment, BRAF/MEK inhibitors should be continued even if the patient develops SLG, with the addition of anti-granulomatous therapy.[43]

The following section will analyze each of the main pharmacological groups implicated in the development of drug-induced SLG.

DRUG-INDUCED SLG DUE TO ANTIRETROVIRALS

HAART is used to treat the human immunodeficiency virus (HIV), which depletes the CD4 T lymphocyte population.[45] The decrease in CD4 T lymphocytes in HIV patients can lead to remission in those with preexisting sarcoidosis.[46] Conversely, in HIV-positive patients treated with HAART, CD4 levels increase to values above 150–200 cells/μL, potentially leading to a SLG indistinguishable from sarcoidosis as part of an immune reconstitution syndrome.[43,46] HAART can also worsen a preexisting sarcoidosis.[46- 48] Several drugs administered in HAART are associated with SLG, indicating that this is not the effect of one specific drug.[43] Although this is not always the case, it can appear between 9–20 months after starting HAART.[43,47] Lebrun et al reported a national cohort study of 18,431 HIV patients, and found a high incidence of sarcoidosis (141/100,000).[49] 11% of those cases were diagnosed before HIV infection, and 84% after the diagnosis, during proper virological control. The interval between HIV and sarcoidosis diagnosis was 11.6 (7.5) years.[49] This suggests that while some cases may be drug-related, others may not be connected to immune reconstitution due to early treatment initiation and could represent true sarcoidosis.

DRUG-INDUCED SLG DUE TO INTERFERONS

Interferon is a cytokine composed of three primary subtypes: Type 1 Interferon (α and β) binds to the Interferon α receptor, while Type 2 Interferon binds to its unique receptor.[50-51] Both classes stimulate antitumor and antiviral mechanisms in the host by enhancing p53 activity.[50-51] Due to its ability to boost the immune response, interferon is used to treat viral infections such as hepatitis B and C, papillomatosis, and different types of cancer including lymphomas, leukemias, melanomas, and Kaposi's sarcoma.[50-51] Interferon γ, produced by T lymphocytes in response to an antigenic stimulus, acts solely as an immunomodulator.[50- 51]

The adverse effects associated with these agents are varied and numerous. The most common adverse reactions include leukopenia and/or thrombocytopenia, insomnia, alopecia, dermatological rashes, flu-like syndrome, depression, nephropathies, and thyroid function imbalance. [52-53]

It is likely that treatment with interferon produces the onset of SLG. In 1993, Blum et al published the first report of SLG caused by this cytokine. [54] Since then, cases of SLG with cutaneous and/or pulmonary involvement have been reported, including rare instances such as

localization in the lacrimal region during antiviral treatment for Hepatitis C.[55-56]

In the reviewed literature, reported cases of SLG associated with interferon have been linked to antiviral therapies for hepatitis C.[54-59]

DRUG-INDUCED SLG DUE TO MONOCLONAL ANTIBODIES

To review this topic, monoclonal antibodies (MABs) are categorized into three groups, primarily used to treat neoplastic diseases –such as immune checkpoint inhibitors (ICI) PD-1, BRAF and MEK inhibitors– and rheumatological conditions (TNF-α inhibitors).[43-44]

a. Immune checkpoint inhibitors (ICIs)

ICIs are innovative agents that block inhibitory receptors of the immune system, including programmed cell death protein 1 (PD-1) and its ligand (PD-L1), as well as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).[60] The proposed mechanism of action suggests that MABs block PD-1 and CTLA-4 receptors located on T lymphocyte membranes, enhancing T-cell responses against tumor cells. The use of ICIs decreases PD-1 expression while increasing T-cell proliferation and IFN-γ release, leading to the formation of granulomas.[60]

They are indicated in some cases of advanced solid tumors, such as melanoma and NSCLC (as second-line treatment if EGFR, ALK, or ROS-1 mutations are absent), as well as hematologic malignancies like Hodgkin lymphoma.[61-64] Phase II and III trials are investigating their efficacy in other types of cancer (esophageal, hepatocellular carcinoma, and breast cancer).[62-64] Compared to traditional chemotherapy, immunotherapy has revolutionized cancer treatment due to its improved safety profile and efficacy. Adverse events have been observed with the combination of ipilimumab and nivolumab, as well as with other ICIs such as pembrolizumab, sintilimab, avelumab, atezolizumab, and durvalumab.[65-75] According to Gkiozos et al, SLG associated with ICI therapy appeared within a median of 14 days.[62] As the role of ICI therapy in advanced tumors rapidly evolves, immunological adverse events are being reported and published with increasing frequency. A comprehensive review by Gosangi et al describes all potential immune-related effects of ICIs.[63] Nishino et al described SLG as a distinct phenomenon rather than an adverse event, occurring in 5-7% of patients, with specific clinical, radiological, and histological features. Patients receiving ICIs developed SLG with bilateral hilar lymphadenitis or pulmonary nodules, with a histology revealing non-necrotizing granulomas and no evidence of tumor cells. Without the need for specific treatment, the use of ICIs led to the spontaneous resolution of these findings. Recognizing SLG as an adverse event in ICI therapy will help refine and improve such findings.[64]

b. BRAF and MEK inhibitors

Cases of SLG have also been reported in melanoma patients with mutations in the BRAF proto-oncogene (present in 50% of cases) who, in recent years, have been treated with BRAF and mitogen-activated protein/extracellular signal-regulated kinase (MEK) inhibitors.[76-78] Literature reports describe dermatological, ocular, lymph node, and pulmonary lesions, with less common involvement of the kidneys, heart, and central nervous system (CNS).[76-78] The *BRAF* inhibitors include **vemurafenib**, **dabrafenib, encorafenib, and trametinib.**[76-79]

The suggested mechanism of action is that the BRAF gene encodes a protein involved in the mitogen-activated protein kinase (MAPK) pathway, playing a crucial role in regulating cell growth and survival. [76] Activating mutations in the BRAF gene leads to continuous activation of the MAPK cascade (which includes MEK), triggering uncontrolled cell proliferation and tumor mutation. Patients treated with BRAF inhibitors exhibit increased serum levels of TNF-α and IFN-γ, which may promote the formation of granulomas.[76] Also leukopenia has been observed, which could be due to CD4+ T-lymphocyte recruitment in melanoma-affected organs as an immune response to tumor antigens stimulated by BRAF inhibitors. [76] Furthermore, BRAF and MEK inhibitors have been associated with immunomodulatory effects in the tumor microenvironment, increasing melanoma antigen expression, boosting CD8+ T lymphocytes, reducing immunosuppressive cytokines (IL-6 and IL-8), and enhancing cytotoxic T-cell activity.[76]

It is essential to differentiate drug-induced SLG from melanoma-related SLG. Before the introduction of targeted therapy, the prevalence of SLG in 1,199 melanoma patients was 0.42%. Beutler and Cohen identified only 17 cases of SLG in

melanoma patients. [77] Melanoma-associated SLG is typically adjacent to the primary tumor, within its lymphatic drainage, or in nearby metastatic sites. Non-regional involvement is rare. Immunohistochemistry aids in proper diagnosis, as melanoma-related granulomas contain B lymphocytes but lack histiocytes. [76] On average, SLG lesions develop nine months after initiating treatment (range: 1–21 months). If lesions occur, treatment should not be discontinued.[76]

c. Tumor necrosis factor-alpha (TNF-α) inhibitors

Among the three TNF-α inhibitor drugs, etanercept is a soluble receptor antagonist, while adalimumab and infliximab are monoclonal antibodies (MABs).[80] All three drugs have been reported to trigger SLG reactions.[80] By 2005, Wallis et al had documented 37 cases: 22 with etanercept (59.5%), 10 with infliximab (27.0%), and 5 with adalimumab (13.5%)[80-83] This suggests that the receptor antagonist would carry a higher risk of inducing SLG, compared to monoclonal antibodies.[80] The proposed mechanism of action is based on the fact that TNF-α is produced by inflammatory cells such as macrophages, thus, blocking its production would logically help prevent an inflammatory response.[80] This explains its use in rheumatoid and psoriatic arthritis. However, SLG reactions have been reported after the initiation of anti-TNF-αtherapy, showing improvement upon discontinuation. A potential mechanism is that anti-TNF-αtherapies modulate the response to CD4+ Th1 cytokines, which are crucial in the pathogenesis of sarcoidosis.[80] CD4+ T cells interact with antigen-presenting cells to initiate and sustain granuloma formation, differentiating into Th1 cells that synthesize IFN-γ and IL-2.[80] Overproduction of IFN-γ could promote granuloma formation in acute stages (etanercept).[80, 84] In chronic inflammatory state, TNF-α, IL-12, and IL-18 cytokines are synthesized, playing a fundamental role in Th1 cell function within granulomas. Blocking TNF-α synthesis, therefore, has therapeutic reasoning in sarcoidosis.[80, 84] Infliximab increases CD4 and CD8 cell lysis while reducing IFN-γ expression.[80] Also, a difference between these drugs is that etanercept preserves the function of the p75-TNF-α receptor protein, maintaining some TNF-α activity, whereas infliximab completely inhibits both the p75 and p55 TNF-α receptors.[80, 84] Adalimumab has also been reported to cause SLG lesions in patients with psoriatic arthritis and even pulmonary sarcoidosis, as a paradoxical effect, including cases affecting the CNS.[85-86]

d. Other monoclonal antibodies

Other MABs have been reported to induce SLG reactions, particularly in the skin and kidneys with rituximab in two patients with lymphoma.[87-88] Rituximab binds to CD20+ lymphocytes, preventing pre-lymphocyte transformation into plasmablasts, leading to complete depletion within three weeks post-infusion. Peripheral B-cell repopulation occurs four to six months later, even exceeding the levels reported at the beginning of the treatment.[87-88]

Cases of patients have been published with SLG reactions with daclizumab, an anti-CD25 agent used in multiple sclerosis and lesions affecting the lungs and skin.[89] An anti-IL-6 agent (tocilizumab) has been reported in a patient with giant cell arteritis who developed pulmonary and hepatic reactions.[90] In conclusion, an anti-IL-12/23 agent, ustekinumab, has been reported to produce SLG reactions with mediastinal lymphadenopathy and lung involvement in a psoriatic arthritis patient.[91]

In summary

1. Sarcoidosis is a multi-organ syndrome triggered by several etiologies, many of them still unknown.

2. SLG can arise due to infections, antitumor treatments, and e-cigarette use.

3. The possibility of its appearance in these scenarios should be considered.

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