Reumatol Clin. 2009;5(1):31-33

Reumatología Clínica

www.reumatologiaclinica.org

Case Report

Sarcoidosis-Lymphoma Syndrome

Elisabet García Casares, [a,*] Lourdes Mateo Soria, [a] Emma García Melchor, [a] Sonia Mínguez Blasco, [a] Ferran Vall-Llobera Calmet, [b] Gerónima Cañellas Oliver, [a] and Susana Holgado Pérez [a]

[a] *Sección de Reumatología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain*
[b] *Servicio de Hematología, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain*

ARTICLE INFO

Article history:
Received October 3, 2007
Accepted January 3, 2008

Keywords:
Granuloma
Sarcoidosis
Lymphoma

ABSTRACT

Sarcoidosis may occur in association with lymphoma (sarcoidosis-lymphoma syndrome), it is an uncommon but well-known association. Some clinical features can be similar and clinicians have the challenge to differentiate between these 2 diseases or prove their co-existence. Clinical and laboratory data are not characteristic in any of them, and an anatomopathological study of lymphadenopathy is necessary to establish the diagnosis. The sarcoidosis-lymphoma syndrome could occur as a result of a disturbance in the host immune system in sarcoidosis and in some patients with solid tumors or hematologic malignancies who have received chemotherapy. We present a case report of a patient with sarcoidosis-lymphoma syndrome.

Síndrome sarcoidosis-linfoma

Palabras clave:
Adenopatía
Granuloma
Sarcoidosis

RESUMEN

La combinación de sarcoidosis y linfoma (síndrome sarcoidosis-linfoma) es poco frecuente pero bien conocida. Algunas manifestaciones pueden ser comunes y es un reto para el clínico establecer el diagnóstico diferencial entre ambas entidades o de su verdadera coexistencia. En estos casos ni la presentación clínica ni los parámetros de laboratorio son específicos, por lo que es esencial el estudio anatomopatológico de una adenopatía para llegar al diagnóstico definitivo. El síndrome sarcoidosis-linfoma podría aparecer como consecuencia de algunas alteraciones inmunitarias que acontecen en la sarcoidosis y en algunos pacientes con una neoplasia sólida o hemática que reciben quimioterapia. Se presenta un caso de síndrome sarcoidosis-linfoma y se analizan los aspectos clave en el diagnóstico de esta forma clínica.

Introduction

Granulomas can appear in different types of diseases: infections, sarcoidosis, strange-body reactions, Crohn´s disease, lymphoma, metastasis, or drug reactions, among others. Sarcoidosis is a systemic granulomatous disease of unknown etiology and constitutes an exclusion diagnosis. This entity occasionally accompanies a lymphoma, an association known as a sarcoidosis-lymphoma syndrome. Cases have been published in which sarcoidosis precedes lymphoma and vice-versa, albeit they can infrequently appear simultaneously.

Clinical Observation

We present the case of a 68-year-old woman who had a history of hypertension and chronic atrial fibrillation, heart failure, simple chronic bronchitis, and ferropenic anemia. At 58 she was diagnosed with a ductal carcinoma of the right breast and underwent surgery, chemotherapy, radiotherapy, and hormone therapy. After that the patient has been cancer-free. In June 2006, a control computerized tomography (CT) detected multiple axillary, pelvic, retroperitoneal, precarinal, pretracheal, and hyliar adenopathies (Figure 1A). Two pulmonary nodules of less than 1 cm in diameter were detected in the right middle lobe. A bronchoscopy with transbronchial aspiration of one of the paratracheal lymph nodes was performed, and the anatomopathological study was compatible with reactive lymphadenitis with numerous granulomas. The analysis of the bronchoalveolar lavage

* Corresponding author.
E-mail address: 37710egc@comb.es (E. García Casares).

1699-258X/$ - see front matter

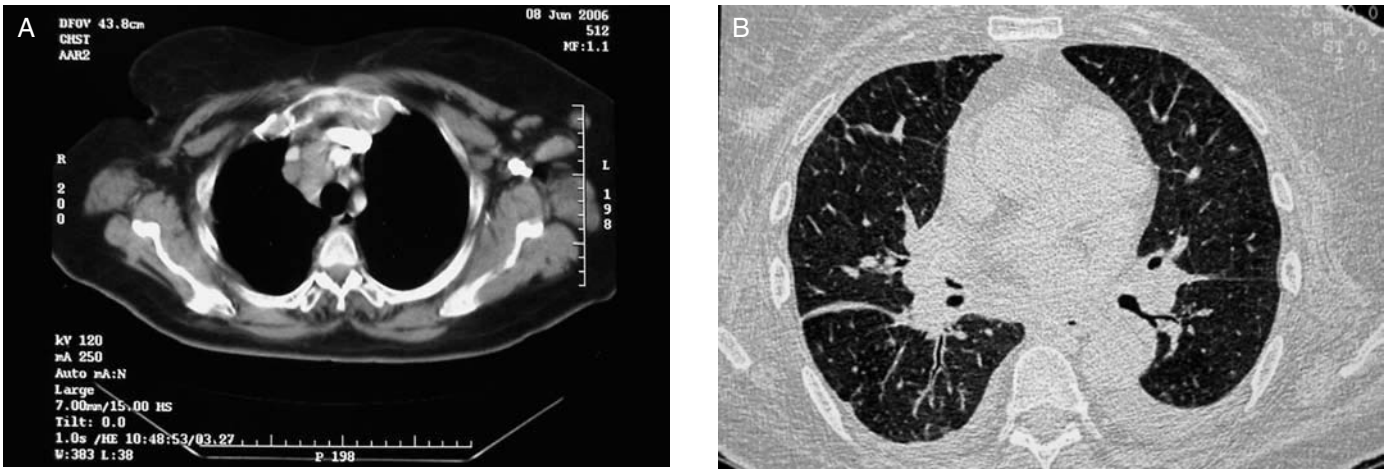


Figure 1. A, computerized lung tomography. Multiple peritracheal adenopathies. B, computerized high-resolution thoracic tomography. Interstitial lung affection and bilateral pleural effusion.

did not detect malignant cells and cultures for bacteria and mycobacteria were negative. In December 2006 the patient came to the rheumatology consult due to generalized joint pain, toxic syndrome, pruriginous skin lesions on the extremities, and bilateral laterocervical and inguinal adenopathies. A cervical CT once again detected multiple cervical, intraparotid, and mediastinal adenopathies of a non-specific aspect. To the physical examination, the patient had no fever, presented bilateral palpable, painful, and fixed laterocervical adenopathiesas well as axillary and inguinal adenopathies, and the left groin area presented a large adenopathy of tumoral aspect. On the dorsal side of the hands and the feet the patient had erythematous-purple infiltrated lesions (Figure 2), and on both thighs there were evident purple and hard lesions compatible with panniculitis. Lung rales were heard upon chest examination, with no other signs of heart failure. No enlarged organs were found. She had left knee pain and diffuse inflammation of both hand without arthritis. A skin biopsy of the feet lesions was compatible with a reaction to an insect bite.

Laboratory testing showed: ESR, 12 mm/h; CRP, 5.23 mg/L (<3); leukocytes, 4300 (normal); Hb, 10.3 g/dL; platelets, renal, and liver function tests, as well as proteins and tumor markers were normal; calcium, 8.6 mg/dL; lactatedehydrogenase, 558 U/L (240-480); creatinkinase, 28 U/L (30-220); angiotensin-converting enzyme, 67 U/L (8-55); microglobulin β_2, 3.6 mg/L (0.7-3.4); ANA, 1/160 speckled; the rest of autoimmunity tests were normal; thyroid and parathyroid hormones were normal; hepatitis, HIV, syphilis, and brucella serology was negative. A tuberculin test was negative. A chest x-ray showed a bilateral pleural effusion and after studying it, an hematic exudate was documented, with the presence of reactive mesothelial cells, with predominance of CD4 T lymphocytes and a negative culture. A gamma scan with ^{67}Ga detected pathological laterocervical, paratracheal, axillary, inguinal, and crural deposits. Based on the presence of adenopathies, joint pain, panniculitis, non-caseating granulomas, elevated angiotensin-converting enzyme, and compatible gallium gammagram, the diagnosis of probable sarcoidosis was established, initiating treatment with prednisone at a dose of 1 mg/kg/day. A high resolution CT scan after 1 week with steroid-based treatment showed interstitial lung disease and bilateral pleural effusion, with disappearance of the lung nodules and a reduction in the size of the adenopathies (Figure 1B). Finally, a fine needle aspiration was performed on the left inguinal adenopathic conglomerate, leading to the diagnosis of non-Hodgkin lymphoma. The node was excised. The anatomopathological study, as well as the positive immunohistochemistry techniques (CD23, CD20, bcl2, bcl6, MUM1, and Ki67), was compatible with diffuse lymphoma of large type B cells.

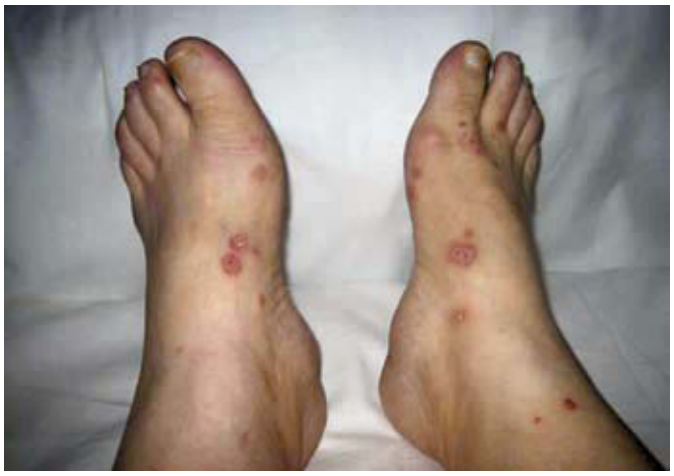
Discussion

The sarcoidosis-lymphoma syndrome was described for the first time in 1986 by Brincker, in a group of 46 cases in which a relationship was seen between sarcoidosis and the development of a lymphoproliferative disease.[1] A lymphoma can develop years after the diagnosis of sarcoidosis, but can also precede it or can be exacerbated by the immunosuppresive effect of chemotherapy.[2-4] On the other hand, cases have been described in which sarcoidosis coexists with lymphoma and are present as a paraneoplastic syndrome. It is also possible to detect non-caseating granulomas in oncological patients who do not fill the criteria of systemic sarcoidosis (sarcoid-like reaction). Sarcoid-like granulomas can appear in association with Hodgkin's (96.4%) or non-Hodgkin's lymphoma (3.6%),[5] and can be so extensive as to mask the diagnosis of a malignant process. These non-caseating granulomas can be detected in a concomitant manner to malignant lymphoproliferative disease, even when the clinical manifestations do not appear until months after. It is estimated that the mean interval of appearance between sarcoidosis and lymphoma is 24 months,[6] although some cases have been known to appear after decades have passed. Middle aged persons who have chronic active sarcoidosis have an incidence which is 5 times that of lymphoproliferative diseases,[6] and in half of the cases they are low-grade lymphomas localized to the lungs. The frequency of solid tumors is also elevated, especially on the cervix, liver, lung, skin, testicles, and uterus.

In sarcoidosis, an alteration of the immune system in the form of a cell reaction versus tumor antigens[7] leads to an increase in T-helper cells in the granulomatous tissues and a secondary reduction of these circulating cells; this determines a reduction in the reaction versus tumoral antigens and in the resistance to oncogenic viruses.[8] In addition there is hyperactivity of B cells which leads to an increase in the mitotic activity of lymphocytes, increasing the risk of mutation and malignant transformation.[9,10] Both in sarcoidosis and lymphoma, the role of the Epstein-Barr virus is controversial as a cause of the genetic transformation and induction of the disease.[11]

Hypercalcemia and the increase in angiotensin converting enzyme are also associated to sarcoidosis, but cases have been described of patients with isolated lymphoma.[12]

Sarcoidosis is diagnosed based on clinical and histological criteria, after ruling out the existence of lymphoproliferative disease through the anatomopathological study of the adenopathy,[13] defining the morphologic characteristics with the use of immunophenotyping techniques with immunoperoxidase such as CD20, CD3, bcl2, CD5, among others.[6]



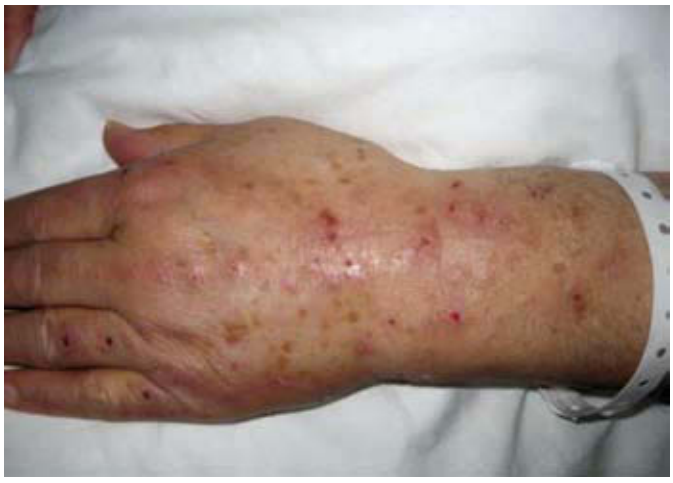


Figure 2. Skin lesions compatible with insect bites on the extremities.

The skin reaction, which is similar to that of an insect bite or eosynophillic dermatosis, is an entity described in association to myeloproliferative syndromes and consists in the appearance or erythematous-purple lesions in exposed areas, characterized by an inflammatory infiltrate of the dermis with abundant eosynophils. They are characteristically associated to chronic lymphocytic leukemia and other hematologic neoplasias, once other causes have been excluded.[14]

Conclusions

Sarcoidosis and some lymphomas share not only clinical manifestations, but also laboratory and even histological findings. Faced with multiple adenopathies, we must rule out a subclinical lymphoproliferative process through the anatomopathological study and immunohistochemistry techniques, including the presence of an evidence-based diagnosis of sarcoidosis.

References

1. Brincker H. The sarcoidosis-lymphoma síndrome. Br J Cancer. 1986;54:467-73.
2. Simsek S, van Leuven F, Bronsveld W, Ooms GH, Groeneveld ABJ, Graaff CS. Unusual association of Hodgkin's disease and sarcoidosis. Neth J Med. 2002;60:438-40.
3. Cohen PR, Krzrock R. Sarcoidosis and malignancy. Clin Dermatol. 2007;25:326-33.
4. Kornacher M, Kraemer A, Leo E, Ho AD. Ocurrence of sarcoidosis subsequent to chemotherapy for non-Hodgkin's lymphoma: report of two cases. Ann Hematol. 2002;81:103-5.
5. Kim H, Dorfman RF. Morphological studies of 84 untreated patients subjected to laparotomy for the staging of non-Hodgkin's lymphomas. Cancer. 1974;33: 657-74.
6. Dunphy CH, Panella MJ, Grosso LE. Low-grade B-cell lymphoma and concomitant extensive sarcoidlike granulomas. Arch Pathol Lab Med. 2000;124:152-6.
7. Reich JM, Mullooly JP, Johnson RE. Linkage analysis of malignancy-associated sarcoidosis. Chest. 1995;105:605-13.
8. Daniele RP, Dauber JH, Rossman MD. Immunologic abnormalities in sarcoidosis. Ann Int Med. 1980;92:406.
9. Louie S, Schwartz RS. Immunodeficiency and the pathogenesis of lymphoma and leukemia. Semin Hematol. 1978;15:117.
10. Karakantza M, Matutes E, McLennan K, O'Connor NTJ, Srivastava PC, Catovsky D. Association between sarcoidosis and lymphoma revisited. J Clin Pathol. 1996;49:208-12.
11. Linnenberg HS, Medici TC, Rhyner K. The "sarcoidosis-lymphoma syndrome" — A lymphocyte dysregulation? Pneumologie. 1992;46:229-35.
12. de Remee RA, Banks PM. Non-Hodgkin's lymphoma associated with hypercalcemia and increased activity of serum angiotensin-converting enzyme. Mayo Clin Proc. 1986;61:714-8.
13. Suvajdzic N, Milenkovic B, Perunicic M, Stojsic J, Jankovic S. Two cases of sarcoidosis-lymphoma syndrome. Med Oncol. 2007;24:469-71.
14. Mangas C, Bielsa I, Mate JL, Fernández-Figueras MT, Ribera M, Ferrándiz C. Dermatosis eosinofílica asociada a leucemia linfática crónica: estudio clínico, microscópico e inmunoshistoquímico de 5 casos. Actas Dermosifiliogr. 2004;95: 165-70.