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Lymphomatoid Granulomatosis as a Debut of Common Variable Immunodeficiency: A Case Report and Review of Literature

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Abstract

Lymphomatoid granulomatosis, currently called as extranodal angiocentric and angiodestructive immunoproliferative disorder, is a rare entity of unclear etiology. It involves most frequently lungs, central nervous system and skin. The clinical course is variable, but mortality is high. Today, it represents a diagnostic challenge because it can emulate autoimmunity, infection, and malignancy processes. Optimal therapy scheme is still unknown. We report the case of a 20 year-old man presenting with fever, weight loss, sweating, multiple bilateral lung nodules on the chest X-ray and cutaneous involvement.

Keywords

Lymphomatoid Granulomatosis, Common Variable Immunodeficiency, Epstein-Barr Virus

1. Introduction

Lymphomatoid granulomatosis **(**LG) is a B cell proliferation of uncertain malignant potential. This entity likely represents a lymphoproliferative disorder in the family of Epstein-Barr virus (EBV)-associated B cell lymphomas although its absence does not exclude the diagnosis. Laboratory tests are often nonspecific but in most cases show increases in IgG and IgM. LG can be seen in patients with an underlying immunodeficiency, whether

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drug-induced or primary and secondary immunodeficiencies. The clinical course is variable and it is related with the histologic grade of the lesions. Common variable immunodeficiency (CVID) is the most prevalent form of severe antibody deficiency. CVID patients may remain asymptomatic, suffer repeated infections or develop autoimmune and/or neoplastic diseases like LG.

2. Case Report

A 20 year-old man without relevant medical history was referred from his reference hospital where he was admitted with the diagnosis of right lower extremity cellulitis. He referred an involuntary weight loss, about 10 kg for the last two months. Despite the resolution of the cutaneous infection, mild fever persisted with the appearance of fever peaks. On arrival at our hospital, his temperature was 39˚C, his blood pressure, heart and respiratory rates were 90/70 mmHg, 130 b.p.m and 32 b.p.m. Physical examination showed pallor, profuse sweating, bilateral crepitant rales and hepato-splenomegaly without adenopathies. Analytical results were Hb 11 g/dL, ferritin 1535 ng/mL, 4700 leukocytes, LDH 413, plasma albumin 2.6, total protein 3.7, PCR 7.5 mg/dL, and ESR 8 mm/h. Arterial blood gas (FiO_2 1.0) showed pH 7.45, pCO_2 33.8 mmHg, pO_2 47.5 mmHg, HCO_3 24.3 mmol/L, and BE −0.3. Empirical treatments (wide spectrum antibiotherapy, hemodynamic and respiratory support) were started.

CT-scan revealed multiple bilateral lung nodules (**Figure 1(a)**) and a striking hepato-splenomegaly. The retroperitoneal area was occupied by multiple adenopathic conglomerates. An echocardiogram was normal. Serological tests (hepatotropic virus, toxoplasma, *L. pneumophila*, *M. pneumoniae*, *Bartonella*, *Borrelia*, *C. Burnetti*, and galactomannan test) were negative. Blood and sputum cultures were sterile. The tuberculin skin test, ANA, ANCA, and rheumatoid factor were negative. Blood determinations of immunoglobulins were IgG 65 (NR 734 - 1486 mg/dL), IgA 25 (NR 49 - 401) and IgM < 20 (NR 40 - 230 mg/dL), so a diagnosis consistent with common variable immunodeficiency (CVID) was set and replacement with intravenous immunoglobulin was initiated (IVIg).

The patient developed progressive respiratory distress without fever remission. A fibrobronchoscopy with transbronchial biopsies was done. Two subcutaneous nodules on the anterior abdominal wall, which were not present on admission, appeared and they were biopsied. The histopathological study and the immunohistochemical analysis of the conglomerate showed large groups of phenotype B lymphocytes (CD 20+) with a high proliferative index (Ki67), and a pattern of angiocentric affectation with large areas of vascular destruction consistent with Lymphomatoid Granulomatosis (LG), Grade 3 (**Figure 1(b)**). Studies of the skin biopsy were similar. Immunostain for Epstein-Barr virus was negative. The transbronchial biopsy showed a lymphoid infiltrate with acute vascular microthrombosis. The histopathological and microbiologic studies of bone marrow were normal. The patient was treated with CHOP-R (cyclophosphamide, adriamycin, vincristine, and prednisone) chemotherapy but developed severe neutropenia complicated by sepsis and died.

3. Discussion

LG is a rare entity of unclear etiology with a high mortality rate [1]. The incidence is higher among young male adults especially when states of immunosuppression coexist [2] [3]. The main differential diagnoses are granulomatous polyangiitis, lymphoreticular lung proliferations, Langerhans cell histiocytosis and primary pulmonary nodular lymphoreticular hyperplasia. Histologic grade is directly related to treatment response. Grade 3 is considered the worst prognosis.

CVID is a primary immunodeficiency characterized by an impaired differentiation of B cells with disrupted immunoglobulin production. The incidence of lymphoid tumors is higher in CVID patients compared with the general population. Most of these are well-differentiated NHL B cell extranodal diseases [4]. Nowadays, CVID is considered a heterogeneous group of disorders with a primary antibody deficiency as element of binding. In this sense, there are described five different clinical phenotypes: only infections, autoimmune phenomena, polyclonal lymphocytic infiltration, enteropathy, and lymphoid malignancies. In our case, the diagnosed CVID was the probably causative factor of LG, a very exceptional situation. In our literature review we only found one published case of an adult patient who developed a LG in context of a CVID previously diagnosed [5].

The aim of our work is to call attention on two apparently unrelated conditions with a fatal outcome in a young patient with no prior pathological history. LG should be included in the differential diagnosis of multi-

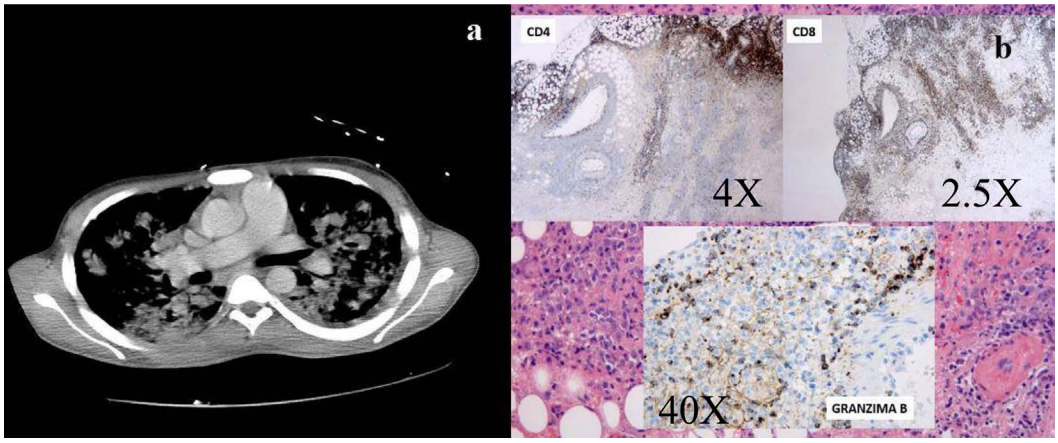

Figure 1. Panel (a) Chest-CT Scan: multiple bilateral lung nodules; Panel (b) Lymph Node Biopsy (hematoxylin and eosin stain): large phenotype B lymphomatous cells with a pattern of angiocentric affectation with large necrosis areas. In the sample predominate numerous lymphocytes CD4 phenotype in mild tumoral areas (immunohistochemistry using antibodies anti-CD4) and phenotype CD8 and granzyme B positive in frank neoplastic areas (immunohistochemistry using antibodies anti-CD8 and anti-granzyme B, respectively).

nodular pattern on chest-X ray and cutaneous lesions. The optimal therapy is still unknown, so further studies are needed to clarify its origin and to improve the prognosis. Internists, pneumologists, hematologists and dermatologists must recognize this condition in order to initiate the appropriate treatment as soon as possible.

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