Pulmonary and cutaneous sarcoidosis in a patient with selective immunoglobulin M deficiency

Sarcidosis pulmonar y cutánea en un paciente con déficit selectivo de inmunoglobulina M

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ABSTRACT

Selective immunoglobulin M deficiency (SIgMD) is a rare primary immunodeficiency characterized by decreased serum levels of immunoglobulin M. The pathogenesis of SIgMD is unclear, as well as its association with various immunopathological disorders. We describe a case of sarcoidosis associated with SIgMD. To our knowledge, such association has not been reported previously.

Keywords: Sarcoidosis; Selective immunoglobulin M deficiency

INTRODUCTION

Sarcoidosis is a multisystemic granulomatous disease whose etiology remains unknown. It usually develops before the age of 50 years, with the incidence peaking at 20 to 39 years. Diagnosis implies compatible clinical and radiological findings, histologic evidence of non-caseating granulomas in one or more organs and exclusion of all other causes of granulomas[1].

Primary selective immunoglobulin M deficiency (SIgMD), previously known as type V dysgammaglobulinemia, is a rare disorder defined as serum immunoglobulin M (IgM) levels two standard deviations below the mean for healthy controls and normal IgG and IgA levels[2,3,4]. Its pathogenesis is unclear and there are few published case reports[3]. Patients with SIgMD may be asymptomatic or present with infections, allergic or autoimmune diseases and malignancies[5,6].

To the best of our knowledge, this is the first case report of sarcoidosis associated with SIgMD.

CASE REPORT

A 45-year-old man with a history of renal lithiasis was admitted to the emergency department for presenting exertional dyspnea, chills and night sweats in the last month. One week before admission, he presented to another hospital for worsening dyspnea, orthopnea, and fever. Based on the clinical features, a presumptive diagnosis of respiratory infection was made and empirical treatment with levofloxacin was started. He had no history of recent travel, immunosuppressive therapy, weight loss, or exposure to persons with similar symptoms or known pulmonary tuberculosis. There was no family history of any immunodeficiency.

On examination, the temperature was 38.5ºC, the pulse 89 beats per minute, the blood pressure 142/75 mm Hg, peripheral oxygen saturation 99% (FiO2 21%), and there were no abnormalities in pulmonary auscultation. Arterial blood gas analysis revealed hypoxemia (PaO2 76 mm Hg). On laboratory testing, total white cell count was 7.84x10^9/L and C reactive protein level was 3.49 mg/dL. Chest radiography revealed bilateral hilar adenopathy and small infiltrates in the left upper lobe. Empirical antimicrobial therapy with ceftriaxone was initiated and admission for etiological investigation and inpatient care was proposed.

Computed tomography (CT) of the chest showed bilateral mediastinal and hilar adenopathies, some with central necrosis, and pulmonary parenchyma with discrete bilateral infiltrates and nodular opacities. Blood tests revealed negative antinuclear and antineutrophil cytoplasmic antibodies, angiotensin converting enzyme level of 49.2 U/L (normal range 8-55U/L), and IgM serum level of 26 mg/dl (normal range 40-230 mg/dL) with normal serum IgG (991 mg/dL) and IgA (358 mg/dL). Immunophenotypic lymphocyte analysis was unremarkable. Blood cultures and serologies for human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, and syphilis were negative.

Bronchofibroscopy was performed and cytological, bacteriological, mycological, and mycobacteriological direct and cultural examination of the bronchial aspirate was negative. Histopathologic examination of specimens obtained by transbronchial biopsy was inconclusive, as well as that of the samples obtained by endobronchial ultrasound-guided fine-needle aspiration of intrathoracic lymph nodes.

On physical examination on the tenth day of hospitalization, multiple tender, erythematous subcutaneous nodules were observed in the patient's legs, compatible with erythema nodosum.

Biopsy of intrathoracic lymph nodes by means of mediastinoscopy revealed non-necrotizing granulomatous lymphadenopathy. Thus, the patient was diagnosed with SIgMD complicated by sarcoidosis.

Pulmonary function tests, including spirometry, lung volumes and diffusing capacity for carbon monoxide were unremarkable, as well as transthoracic echocardiography.

The patient did not require oral glucocorticoid therapy because he had spontaneous remission of symptoms. After a one-year follow-up, he maintained clinical remission of sarcoidosis and had no infectious complications. However, IgM serum levels remained low and no modifications over the other Ig classes were observed.

DISCUSSION

The presence of mediastinal and hilar adenopathies with central necrosis on CT made the differential diagnosis challenging, requiring multiple hypotheses, from the non-rare pulmonary tuberculosis to the rare necrotizing sarcoid granulomatosis. The case became even more interesting by the finding of SIgMD.

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Although SIgMD was first described more than 5 decades ago[2,7], only in 2017 was incorporated in the International Union of Immunological Societies classification of primary immunodeficiency diseases[5,8].

SIgMD is associated with various immunopathological disorders. However, the pathogenic mechanisms involved are unclear and it is difficult to elucidate how strong these associations are[3]. IgM plays an important role in immune tolerance[5] and there are studies suggesting that the deficiency of serum IgM may impact the clearance of self-antigens and induce secondary autoimmune disease[6]. Mice genetically generated to be deficient in secreted IgM showed a tendency towards spontaneous development of autoantibodies and autoimmune diseases[2,5]. However, high IgM levels can also be associated with autoimmune diseases, which make it more difficult to clarify the relationship between low serum IgM levels and increased susceptibility to autoimmune conditions[2,3]. It might be a compensatory mechanism for inhibiting inflammation[2].

Further research on the effect of IgM on B-cell development and prevention from autoantibody formation is needed in order to elucidate the precise mechanism of IgM-mediated regulation of tolerance and so, the role of IgM in autoimmunity[6].

Although patients who present with recurrent infections and specific antibody deficiency responses may benefit from current immunoglobulin treatment, given to the possible immunomodulatory and antimicrobial effects of IgM, highly enriched IgM preparations could reveal to be a more desirable option, either for these patients or for those with autoimmune diseases[2,7]. In cases of secondary SIgMD, treatment for associated diseases may lead to an improvement in immunodeficiency. However, when it is primary, even if remission of autoimmune disease occurs, as in the case we present, the IgM deficit persists.

Patients with decreased serum IgM levels should undergo regular immunological evaluation for any recovery (to exclude secondary causes) or for progression to common variable immunodeficiency[2,3].

CONCLUSION

Patients with recurrent infections, atopic or autoimmune diseases should be investigated for IgM deficiency. On the other hand, since SIgMD can be complicated by sarcoidosis, this disease should be considered in the differential diagnosis of patients with SIgMD who present with cough, dyspnea, fatigue, fever and/or weight loss.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this work.

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ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

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