Case report

Autoimmunity and immunodeficiency at the crossroad: autoimmune disorders as the presenting feature of selective IgM deficiency

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accepted 17 December 2018

Summary

selective immunoglobulin M deficiency (sIgMD) is an immunodeficiency with undefined pathogenesis and commonly presenting with recurrent infections.1 the european society for Immunodeficiencies registry defines sIgMD as a serum IgM level repeatedly below 2 sD of normal with normal levels of serum Iga, IgG and IgG subclasses, normal vaccination responses, absence of

t-cell defects and absence of causative external factors. rarely it can also be associated with autoimmune diseases.2–7 Here we describe a patient with primary sIgMD; who presented with multiple autoimmune diseases without a history of recurrent infections and we provide a short literature review on sIgMD and autoimmune diseases.

Background

Immunoglobulin (Ig) M is the first Ig produced by B lymphocytes during the immune response and most of the primary humoral immune responses are mediated by IgM.8 IgM is found in two types: membrane-bound (located on the surface of B cells) and secreted IgM. The normal concentration of IgM in the serum is approximatively 37–286 mg/ dL.8

Selective IgM deficiency (sIgMD) is an immuno- deficiency characterised by low serum IgM levels (<0.20 g/L in children and <0.30 g/L in adults or <2 SD below the age-adjusted mean), alongside normal number and function of B and T lympho- cytes, normal serum IgG and IgA levels (the IgE levels can be increased) and without other identifi- able immunodeficiency.1 8

The most common clinical manifestation of sIgMD is recurrent infections such as upper and lower respiratory tract infections (otitis media, chronic sinusitis, bronchitis, bronchiectasis and pneumonia), urinary tract infections and less frequently meningitis, sepsis, diarrhoea, cholan- gitis, hepatitis, chronic candidiasis, deep tissue and liver abscess.9–15 Patients can also be asymptomatic or present with allergies,9 autoimmune diseases and malignancies. Presentation with autoimmune diseases is more common in adults rather than chil- dren.9 sIgMD is considered a rare disease with an estimated prevalence of 0.03%.16–18 There have been fewer than 300 cases reported in the litera- ture and only a few cases describing patients with sIgMD diagnosed after the onset of autoimmune diseases.

Case Presentation

The patient was referred to our Rheumatology Department in 2011, at the age of 28 years. He presented with psoriasis and severe Raynaud's signs. He also had Hashimoto's disease and history of dysautonomia. The Raynaud's signs started when he was 14 years old. Over the years, he had devel- oped chilblains on both fingers and toes. He never had true digital ulceration or cutaneous vasculitis. During his first presentation, he also had a degree of synovitis of the hands, arthralgias of both wrists and PIP joints, puffy fingers and myalgias.

Investigations

Given his background of multiple autoimmune diseases, we suspected an underlying disorder and checked serum Ig levels (nephelometry). Surpris- ingly, before starting the therapy, his IgM serum levels were below the normal range (0.1 g/L) with normal serum IgG (7.5 g/L) and IgA (2.1 g/L). The

patient had never been treated with corticoste- roids or immunosuppressant drugs which could cause immunodeficiency and there was no family history of any immunodeficiency. The Ig serum levels were repeated after 6 months, before starting any immunosuppressive treatment, and they confirmed the presence of low serum IgM (0.1 g/L) with normal serum IgG (7.3 g/L) and IgA (2.2 g/L). IgG subclasses were also within the normal range (IgG1 4.7 g/L, IgG2 1.8 g/L, IgG3 0.4 g/L and IgG4 0.3 g/L). Immunodeficiency panel including B and T cells and HIV ruled out any other disorder in B or T cells. To confirm his sIgMD, we checked the antibody titre responses to the pneumococcal poly- saccharide and tetanus antigens and they showed adequate specific antibody response.

Blood tests revealed ANA positivity >1:1000 with a coarse speckled pattern and anti-U1RNP positivity. CCP and ANCA were negative. Organ surveillance (with echocardiogram and lung function tests) did not show any lung or heart involvement.

Treatment

The patient met Khan's criteria for mixed connective tissue disease (anti-U1RNP, Raynaud's Findings that shed new light on the possible pathogenesis of a disease or an adverse effect phenomenon, synovitis and puffy fingers) but not for systemic lupus erythematosus (SLE) or systemic sclerosis.19 He was initially treated with nifedipine, hydroxychloroquine 400 mg daily and iloprost infusions.

Outcome and follow up

Over 6 years, the patient has remained well and has never devel- oped any serious infection. The IgM levels have been constantly low and remained stable with hydroxychloroquine. No modifi- cation over the other Ig classes and IgG subclasses were observed over the 6 years. The immunodeficiency panel has been repeated and confirmed the absence of B-cell and T-cell disorder. His Raynaud's and musculoskeletal symptoms have been well controlled with the therapy initially prescribed.

Discussion

SIgMD is a rare primary immunodeficiency with various clin- ical manifestations. The diagnosis is based on isolated low or undetectable serum IgM levels in the absence of accompanying immunodeficiencies. In this report, we presented a case of sIgMD in a patient with uncommon clinical manifestations who was previously diagnosed with multiple autoimmune diseases. To our knowledge, this is the first case describing sIgMD diag- nosed after the onset of multiple autoimmune diseases and it highlights the relationship between autoimmune diseases and selective IgM deficiency. The underlying mechanism of sIgMD is still unknown. There is currently no evidence to support any specific genetic mutation nor a definitive inheritance pattern. Russell-Silver syndrome, chromosome abnormality in 22q11.2 and chromosomes 1 and 18 have been reported with sIgMD. However, these associations require further research before being confirmed.9 Despite normal or elevated serum IgG and IgA levels and normal counts of T and B lymphocytes, there is an increased susceptibility to infections in patients with sIgMD; which may be explained by an impairment in B-cell or T-cell func- tion.9 A significant increase in CD8 +Treg cells and CD2 +low B cells has been reported in some patients.20 Increased activity of IgM-specific suppressor T lymphocytes was demonstrated in a 66-year-old male patient with giant leiomyoma and sIgMD.21 In one of the patients diagnosed with SLE and sIgMD,3 it was found that the cell surface IgM expression was normal, thereby suggesting a possible defect in the secretion of IgM. A study on

immunoglobulins in patients with sIgMD also indicates an inhibitory effect of patients' IgG on IgM production.4

We searched the English Literature and we found sex cases of patients diagnosed with primary sIgMD and autoimmune diseases. Two of them had SLE2 3 with single cases of Hashimoto' s disease,4 glomerulonephritis,5 autoimmune hepatitis6 and adult-onset Still Disease.7 The mean age at diagnosis was 55 years. The male to female ratio is 2:3. In all cases, the patients were diagnosed after the onset of the autoimmune disease except the patient who was diagnosed with glomerulonephritis which was initially considered as postinfectious and was subsequently confirmed histologically as auto- immune glomerulonephritis.5 Only one of these five patients presented recurrent infections which is the most common clinical presentation of sIgMD.3

During the follow- up, the serum IgM levels of one patient increased after treatment thus, this case was reclassified as secondary sIgMD.4 There are no follow-up data of the four remaining patients.

The relationship between low serum IgM levels and increased susceptibility to autoimmune conditions is yet to be defined since high IgM levels can also be associated with autoimmune diseases. There are studies suggesting that the absence or decreased levels of IgM impact the removal of self-antigens and clearing of apop- totic cells.8 The demonstration of the effect of IgM on B-cell development and prevention from autoantibody formation may further clarify the role of IgM in autoimmunity.22 The triggering effect of recurrent infections was postulated as the cause of auto-immunity in a patient with autoimmune glomerulonephritis.5 Our case raises the hypothesis that low IgM may be permissive to increased infection and immunostimulation which may predis- pose to autoimmunity. This may be especially the case in the context of immune dysregulation secondary to the condition.

It is clear that the pathogenesis of sIgMD is still poorly under- stood and its clinical manifestations can vary. The treatment for sIgMD is not specific. The use of prophylactic antibiotics is not recommended. The other therapy option is intravenous Ig. In the case of secondary sIgMD, the treatment of the associated diseases can improve the immunodeficiency. However, there is no evidence to indicate suggesting a secondary sIgMD in our patient.

Contributors CC and SA: wrote the manuscript. Vo, CPD and KENC revised it and substantially contributed to the latest version.

Funding the authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

patient consent obtained.

provenance and peer review Not commissioned; externally peer reviewed.

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