Recurrence Eosinophilic Pneumonia in a Patient with Isolated Immunoglobulin M Deficiency and Celiac Disease

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Isolated immunoglobulin (Ig) M deficiency is an uncommon dysagammaglobulinemia. Although reported to be associated with recurrent infections, celiac disease, allergy and autoimmune diseases such as celiac disease, its clinical significance is unknown since it appears also in asymptomatic individuals [1].

We report a patient presenting with chronic eosinophilic pneumonia (CEP) followed by an episode of severe pericarditis with isolated IgM deficiency and celiac disease, explore the possible association between these disorders, and review the current literature.

PATIENT DESCRIPTION

A 52 year old male presented to our emergency room after 2 weeks of fever, cough and shortness of breath. Antibiotic treatment and inhalations failed to relieve his symptoms. During the preceding 2 years he experienced four similar events; all were diagnosed as pneumonia and were treated with antibiotics. His medical history included hyperlipidemia, a former head injury, and celiac disease that had been diagnosed 7 years prior to admission and was treated with a gluten-free diet followed by an adequate clinical improvement.

On admission, his temperature was 36.1°C, heart rate 106 beats/minute, blood pressure 100/71 mmHg and respiratory rate 24/minutes with oxygen saturation of 90% at room air. Examination revealed bilateral pulmonary crackles. A chest X-ray showed bilateral patchy infiltrates.

Chest computed tomography (CT) demonstrated mediastinal lymphadenopathy, bilateral small pleural effusions, peripheral consolidations and ground-glass opacities (Figure 1A). Complete blood count (CBC) was notable only for severe eosinophilia (3.8 x 10⁶/L) and mild thrombocytosis. Blood smear confirmed eosinophilia with numerous band cells and no evidence of malignancy. C-reactive protein was 7.9 mg/dl (normal range 0–0.5 mg/dl); liver transaminases, creatinine, urea and thyroid hormones were all within normal limits.

Serum autoimmune serology tests were within normal range. Serum immunoglobulins showed elevated IgE (647 mg/dl, normal < 100) and severe IgM deficiency (< 32 mg/dl, normal 65–280). Infectious etiology was also ruled out by negative cultures and serology tests.

A fiberoptic bronchoscopy was performed (Figure 1B). Bronchoalveolar lavage demonstrated 28 x 10⁶ cells/ml with 91% eosinophils. Biopsies from the lesions revealed severe chronic inflammation abundant with eosinophils. A diagnosis of CEP was made and treatment with prednisone 60 mg/day was initiated, resulting in rapid amelioration of symptoms and normalization of eosinophilia on the CBC.

In the following year, prednisone treatment was gradually tapered off. At a follow-up visit almost a year after discharge, treatment with prednisone was discontinued. The patient remained asymptomatic with normal physical examination and normal laboratory tests.

Figure 1. [A] Chest CT scan demonstrating bilateral small pleural effusions, consolidations and ground-glass opacities.

[B] Macroscopic view during bronchoscopy revealing numerous small white mucosal lesions (arrows)

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A few weeks later the patient was admitted again with fever and pleuritic and epigastric pain. Physical examination revealed decreased breath sounds over the left lung. White blood cell count and eosinophil counts were 6.5 and 0.3 x 10^-9/L, respectively. CT of the chest revealed bilateral pleural effusion, left lung atelectasis and moderate pericardial effusion. Electrocardiography demonstrated normal sinus rhythm, and cardiac magnetic resonance imaging (MRI) demonstrated thickening of the pericardium and pericardial fluid. Echocardiography displayed moderate circumferential pericardial effusion with regions of increased echogenicity consistent with fibrinous changes, without hemodynamic significance. Focal regions of significantly increased thickness and echogenicity of the pericardium, encasing the apex, posterior and lateral to the left atrium were seen, as well as a mass (2 cm diameter) in the vicinity of the left atrium. He was diagnosed with probable eosinophilic pericarditis and was treated with prednisone 60 mg/day, resulting in rapid and complete clinical and radiological resolution.

Prednisone was again gradually reduced over a period of 5 months. During the next 22 months he suffered two relapses of CEP, with eosinophilia rising up to 2.3 x 10^-9/L that was treated successfully, resulting in complete resolution. Since the patient suffered from rhinitis and pan-sinusitis, a skin prick test was performed revealing a hypersensitivity to *Parietaria diffusa* and olive pollen.

At his last follow-up, almost 4 years after the first admission, he was asymptomatic while on low dose prednisone (5 mg/day) with only mild eosinophilia (0.66 x 10^-9/L). Cardiac MRI, echocardiography and ergonometric test were all within normal ranges.

**COMMENT**

Isolated IgM deficiency is defined by the absence or deficiency of IgM with normal levels of other Ig and normal T cell levels. These patients may present with recurrent infections of *Staphylococcus aureus*, encapsulated pathogens and other microorganisms [1].

The prevalence of isolated IgM deficiency is difficult to estimate because most of the patients are asymptomatic and immunoglobulin levels are not routinely measured. It varies in different studies and was reported to be 0.03–1.68% in a community-based survey and 0.1–3.8% in hospitalized patients [1].

Autoimmune diseases among IgM-deficient patients were reported in long-term follow-up studies with an estimated rate of 8% [1]. Among other autoimmune diseases, celiac disease was also associated with isolated IgM deficiency. The prevalence of IgM deficiency is estimated to be 5% in patients with celiac as compared to 0.26% in the general population [2].

A previously reported 18 year old patient with seronegative celiac disease and isolated IgM deficiency further demonstrates this association. Treatment with a gluten-free diet for a year restored his IgM levels after healing of his duodenal mucosa, suggesting that isolated IgM deficiency in celiac patients may not be a primary condition [2].

Autoimmunity in IgM-deficient patients may result from the emergence of IgG autoantibodies. Although the exact mechanism is unknown, one possibility is that IgM-autoantigen complex may cross-link FcμR and B cell receptor on autoreactive B cells and trigger their anergy. In mice models FcμR-deficient mice had reduced specific antibody responses and, as a result, reduced foreign antigen responses and increased autoantibodies [1].

An autoimmune tendency in IgM-deficient patients can also be explained by the lack of IgM autoantibodies to oxidant-associated antigens, which can oppose inflammatory and apoptotic effects of IgG autoantibodies. They enhance phagocytosis of apoptotic cells and suppress key signaling pathways responsible for control of inflammatory responses to Toll-like receptor agonists and disease-associated IgG autoantibodies [3]. Our patient had allergic rhinitis, pan-sinusitis and recurrent episodes of CEP together with eosinophilia. IgM deficiency was previously described in patients with allergic diseases. Rates of allergic rhinitis and asthma in adults were reported to be 25% and in another series were as high as 47% and 36%, respectively [1]. The mechanism for this association is unknown.

Previous studies suggested an association between celiac disease and other eosinophilic disorders, although it was linked merely to eosinophilic gastroenteropathies [4]. For example, the prevalence of eosinophilic esophagitis in patients with celiac was about tenfold that of the general population. Eosinophilic esophagitis in celiac patients was also found to be responsive to gluten-free diet, suggesting a possible common pathogenic pathway [5].

This single report cannot establish a definite association between isolated IgM deficiency, celiac disease and CEP, but it may aid in illuminating the complex relationship of the immune system with these manifestations. Further studies are needed to properly evaluate the need to screen for one disorder in the presence of the other.

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