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Case Report

A case of primary immune deficiency presenting with nephrotic syndrome

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Abstract

Common variable immunodeficiency (CVID) is the most common form of severe antibody deficiency. The disorder is associated with a broad spectrum of clinical manifestations, including infections and chronic lung, gastrointestinal and autoimmune diseases. A 29-year-old female patient has had frequent sinopulmonary infections and gastroenteritis for the last 20 years and had been given broad-spectrum antibiotics for treatment. Immunoglobulin (Ig) levels were at undetectable levels. Renal biopsy was consistent with AA amyloidosis. She is now under follow-up with periodic intravenous Ig treatment without any infection during the last 10 months. CVID must be kept in mind in patients with recurrent sinopulmonary infections.

Keywords: amyloidosis; common variable immunodeficiency; nephrotic syndrome

Background

Common variable immunodeficiency (CVID) is the most common form of severe antibody deficiency affecting both children and adults. The characteristic immune defect in CVID is impaired B-cell differentiation with defective secretion of immunoglobulin (Ig). The disorder is associated with a broad spectrum of clinical manifestations, including infections, chronic lung disease, gastrointestinal (GI) disease and autoimmune disease [1,2].

Bacterial infections of the sinopulmonary tract, particularly sinusitis and pneumonia, are experienced by most patients with CVID. Here, we present a case of CVID presenting with diarrhoea and nephrotic syndrome.

Case

A 29-year-old female patient was admitted with complaints of cough, fever, diarrhoea and swelling all over her body. She has had frequent sinopulmonary infections and gastroenteritis attacks for the last 20 years.

Physical examination revealed massive oedema, fever of 39°C, crepitations on the lower lungs, increased bowel sounds and retarded development with weight of 40 kg and height of 145 cm.

Pathological: The laboratory results that were out of limits were leukocyte 11 400/μL, hemoglobin 10 g/dL, hematocrite 31%, platelets 568 000/μL, C-reactive protein (CRP) 399 mg/dL, total protein 3 g/dL, albumin 1 g/dL, proteinuria 9 g/day and many leukocytes and fatty acids on direct examination of the faeces. Ig levels were low: IgG <33.3 mg/dL ($N = 751–1560$), IgA <6.67 mg/dL ($N = 82–453$), IgM 7.08 mg/dL ($N = 46–304$). We detected 10 g/day fat upon examination of the stool. There was pneumonic infiltration on the inferior lobe of the right lung. Chest computed tomography furthermore revealed diffuse bronchiectasia. Ig levels were at undetectable levels. Serum amyloid A deposition was detected on biopsies (Figure 1) obtained during gastroduodenoscopy and colonoscopy. Renal biopsy performed to evaluate nephrotic syndrome was also consistent with AA amyloidosis (Figure 2). With the history of recurrent infections and low Ig levels, she was diagnosed as having CVID leading to secondary amyloidosis. After her hospitalization, her signs and symptoms cleared with antibiotic and antiproteinuric treatment and with antibiotherapy, intravenous Ig, antiproteinuric treatment including losartan and cilazapril; oedema and pleural effusion regressed with mild pretibial oedema remaining, CRP level declined to 18 mg/dL, proteinuria declined to 7 g/day and albumin level rised to 2.2 g/dL. After resolution of GI symptoms, she was started on colchicines therapy; she is under follow-up with intravenous Ig treatment without any infection during the last 10 months.

Discussion

CVID is estimated to affect as many as 1 in 25,000 individuals [1,2]. Age of onset is typically after puberty and before 30 years of age, with some evidence of a bimodal distribution demonstrating peaks between 1 and 5 years and between 18 and 25 years. CVID is a primary immune

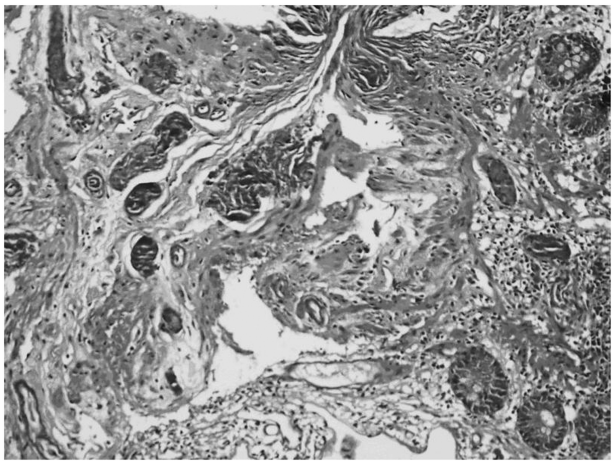

Fig. 1. Amyloid deposition in the vessel walls and submucosal connective tissue with Congo staining.

deficiency disorder characterized by markedly reduced serum levels of IgG and low IgA or IgM, with impaired antibody responses, despite the presence of B cells. However, CVID is associated with a high incidence of inflammatory, autoimmune and malignant conditions, features of more fundamental immune dysregulation [2].

Sinopulmonary infections, including pneumonia, bronchitis and sinusitis, as well as otitis and conjunctivitis, are observed in the majority of patients with CVID [2]. These infections may be acute, chronic or recurrent. Over three-quarters of patients have at least one episode of pneumonia prior to diagnosis [2].

Chronic lung disease is a common problem in patients with CVID and can lead to recurrent hospitalizations, significant morbidity and early death [2]. In a large clinical study of 248 patients, 27% had either bronchiectasis or restrictive or obstructive lung disease [2]. Another study of 224 patients found that 34% had chronic lung disease at the time of diagnosis, which increased to 46% during a mean follow-up of 11 years [3]. Our patient was hospitalized due to pneumonia for 20 times.

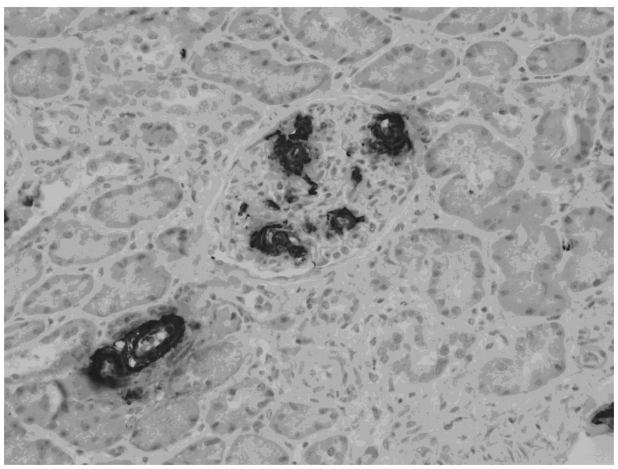

Fig. 2. Strong positivity for serum amyloid A antibody with immunohistochemical examination.

The risk factors for the development of chronic lung disease in patients with CVID have not been fully defined. One report of 18 CVID patients found that those with reduced total memory B cells (CD27+ B cells) and very low numbers of switched memory B cells (CD27+IgM−IgD−) were more likely to have chronic lung disease [4].

GI disease is identified in ~20% of CVID patients and may be the presenting disorder in some [2]. Specific disorders include inflammatory bowel disease, sprue-like illness with flat villi, nodular lymphoid hyperplasia, pernicious anaemia, chronic giardiasis, protein-losing enteropathy and nonspecific malabsorption. Diarrhoea is the most common symptom, with malabsorption and weight loss also reported [5]. One biopsy study of GI pathology in 20 CVID patients over a 26-year period found that over one-half of the patients lacked plasma cells throughout the intestinal tract, and 47% showed lymphoid aggregates [6]. We detected deposition of serum amyloid A besides nodular lymphoid hyperplasia in biopsies taken from the stomach, duodenum and colon. Amyloidosis was thought to be due to chronic inflammation and recurrent infections.

Routine laboratory studies are often normal in CVID, in the absence of an associated disorder. However, a reduction in globulin and/or total protein level may be seen. In addition, modest lymphopenia and a reduced CD4+ level may develop over time. In contrast, serum Ig levels are markedly abnormal. CVID patients have low serum IgG, accompanied by low IgA and/or low IgM [2]. Our case had Ig levels at undetectable levels and serious hypoalbuminaemia due to proteinuria and malabsorption.

The management of CVID involves sufficient gamma globulin replacement therapy and monitoring for and treatment of associated inflammatory disorders and malignancies [2]. Ig replacement therapy reduces the frequency of most types of infections as in our case, as well as slows the progression of chronic lung disease and offers some protection against autoimmune disorders. The usual initial dosing for intravenous Ig is 300–400 mg/kg, given every 3–4 weeks, with the goal of maintaining a trough IgG level in the middle of the normal range.

Isolated nephrotic syndrome cases responsive to steroid therapy have been reported in the literature associated with CVID [6]. But there is no case with nephrotic syndrome due to amyloidosis documented with renal biopsy. Another patient with nephrotic-range proteinuria (9 g/day) was reported to have amyloid deposition in gastric and duodenal biopsy, but renal biopsy was not performed [7]. Our case is the only one with renal amyloidosis documented with biopsy.

Even if intravenous Ig treatment may prevent infections and consequently amyloid deposition, insufficient treatment may lead to amyloidosis. Otherwise, with the increasing life expectancy of the patients and resultant increased number of infections, renal amyloidosis may be expected to increase in frequency. It is important to monitor patients' urine for proteinuria. Renal amyloidosis in our patient is also thought to be due to delayed diagnosis and gamma globulin treatment [8].

Patients with late diagnosis and insufficient treatment of infections are prone to develop amyloidosis and nephrotic syndrome which worsens the prognosis of the disease

which has already high morbidity and mortality rates. CVID must be kept in mind in patients with recurrent sinopulmonary infections in order to prevent co-morbidities.

Conflict of interest statement. None declared.

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