Acta haemat. 75: 1–5 (1986)

0001–5792/86/0751–0001 $ 2.75/0

Evan's Syndrome, Chronic Active Hepatitis and Focal Glomerulonephritis in IgA Deficiency

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Key Words. Chronic active hepatitis · Evan's syndrome · Focal glomerulonephritis · IgA deficiency · Secretory IgA ·

Abstract. A 10-year-old female with a complete selective IgA deficiency and recurrent autoimmune disease (chronic active hepatitis, focal glomerulonephritis, hemolytic anemia and thrombopenic purpura) is presented. Both serum IgA and saliva secretory IgA were below the detection limit. The small bowel biopsy using a peroxidase-antiperoxidase technique showed absence of plasma cells secreting IgA. Circulating antibodies against mitochondria, microsomal thyroid antigen were detected as well as rheumatoid factor. Circulating immune complexes were present. A positive Coombs' test and a slightly positive reaction for cryoagglutinines were demonstrated. No alterations in cellular immunity were observed. Clinical and analytical improvement with prednisone and azathioprine was obtained.

Introduction

Selective IgA deficiency (S-IgAD) is a very frequent form of immunodeficiency occurring in 1:400 to 1:700 healthy individuals [1, 2] and 1:200 in patients with recurrent pulmonary infections [3]. Although often asymptomatic it can predispose to a number of clinical disorders. Rheumatic disease [4], pulmonary and gastrointestinal infections [5, 6], asthma [7] and malignancy [8] can occur frequently. Sometimes it is associated with Niemmann-Pick [9] or ataxia telangiectasia [6]. Autoimmune diseases and increased incidence of autoantibodies may also be present [10–12]. The origin of S-IgAD is unknown but immune complexes (IC) have been implicated both in its pathogenesis and in its clinical course [13]. In this report we describe a S-IgAD in a 10-year old female who presented with autoimmune phenomena (chronic active hepatitis, focal glomerulonephritis, and Evan's syndrome), circulating IC, autoantibodies and rheumatoid factor.

Material and Methods

Serum IgG, IgA and IgM were determined by nephelometric immunoassay using an ICS Beckman Immunochemistry analyzer with a detection limit of IgA of 0.0002 g/l. Serum IgE was measured by conventional enzyme immunoanalysis and serum IgD by radial immunodiffusion. Unstimulated whole saliva was collected from the patient to quantify secretory IgA by the same nephelometric procedure. Circulating anti-IgA antibodies were determined by double diffusion on 1% agarose containing 3.5% polyethylene glycol 6000, different dilutions of patient serum were placed against purified IgA [14]. Peripheral blood mononuclear cells were isolated on Ficoll-Hypaque gradient (Pharmacia Fine Chemicals) as previously described [15]. T and B lymphocytes were estimated from the number of E and EAC rosette-forming cells, respectively, as described [16, 17]. The lymphocyte transformation test was performed as reported [18]. The mitogen employed was phytohemagglutinin (PHA-P, Difco).

T-cell subtypes were distinguished microscopically by indirect immunofluorescence using the monoclonal antibodies OKT4 and OKT8 (Ortho Pharmaceuticals). Cells that reacted with OKT4 are referred to as helper T cells. Cells reacting with OKT8 are referred to as suppressor T cells.

Circulating immune complexes were assayed by the anticomplementary activity of the patient serum [19].

Samples from kidney, bone, liver and small bowel were obtained through percutaneous biopsy. Immunoperoxidase technique (PAP) of small bowel specimens was performed according to *Sternberg* et al. [20]. Different dilutions of rabbit antihuman globulin against kappa and lambda chains were used.

Case History

A 10-year-old female in good health up to the age of 4 was admitted to a hospital in 1978 with asthenia, anorexia, jaundice, diarrhea and hematuria. Liver and renal biopsies showed chronic active hepatitis and focal glomerulonephritis. The clinical signs improved after 2–3 months of prednisone therapy. At 5 she presented recurrent respiratory tract infections with a good response to antibiotics. At age 9 she presented epistaxis and thrombocytopenic purpura (platelet count: 20×10^9/l). No platelet response was observed with prednisone treatment.

Seven months afterwards she referred bilateral knee pain. Two months later she was admitted to our hospital with a severe degree of jaundice. On physical examination the girl showed yellow coloration of the skin and scleral icterus. Enlargement of the spleen and liver was evident.

Disseminated purpura was presented. The following laboratory abnormalities were found: Hb 7.5 g/dl, reticulocyte count 189×10^9/l, haptoglobin 0.05 g/l, platelet count 5×10^9/l, platelet half-life 6 h with a high captation in the spleen. LDH, bilirubin, GOT and GPT were increased. The complement fraction 4 was very low. A positive Coombs' test showed anti-C_3 and anti-IgG. The direct antiglobulin test using an eluate obtained from the patient's red cells was positive. Drug-induced hemolytic anemia was excluded and there was no history of previous transfusions. No thrombocyte antibodies were demonstrable in serum. Increased number of megakaryocytes in the bone marrow was observed. Serum IgM and IgE concentrations were normal, but serum IgG was increased and IgA was always below the detection limit of the analysis. Secretory IgA was below the detection limit as well. Immune complexes were detected in serum by anticomplementary activity at 1×64 dilution. Circulating antibodies against mitochondria and microsomal thyroid antigen were detected. On the other hand rheumatoid factor and cryoagglutinins were positive. Anti-DNA antibodies and tests to detect disseminated lupus erythematosus were also negative. Serological antibodies indicative of toxoplasmosis, mononucleosis and cytomegalovirus were absent. The Ham-Crosby test, inuline test and sucrose test were all negative. Cellular immunity was normal. The HLA tissue type was A_1, A_{30+31}, B_8, B_{w6}. Treatment was started with prednisone 2 mg/kg/day and azathioprine 2.5 mg/kg/day with clinical improvement and normalization of the Hb (13.1 g/dl) and platelet count (300×10^9/l) as shown in figure 1, as well as liver function tests, haptoglobin and Coombs' test. Prednisone treatment was gradually reduced and the patient continued receiving azathioprine. The clinical picture and the analytical examination were normalized 6 months later except for the serum IgA concentration.

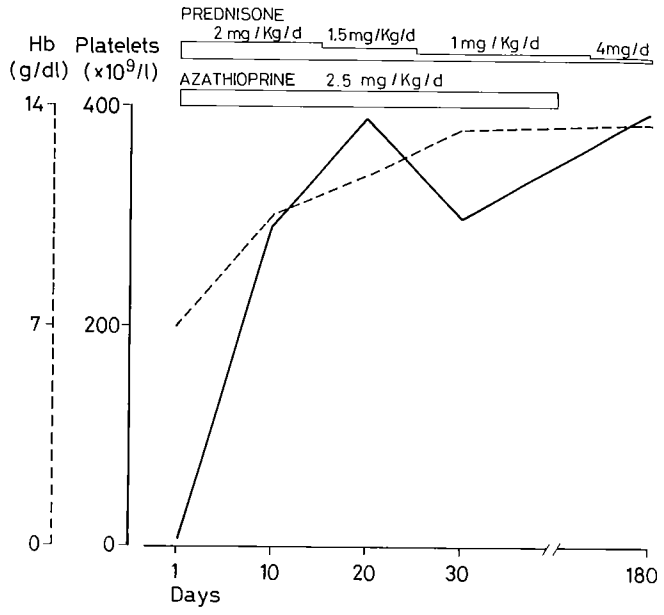

Fig. 1. Time course of hemoglobin and platelets in response to treatment.

Table I. Levels of serum and whole saliva immunoglobulins in a patient with selective IgA deficiency

Type		Technique	Concentration	Normal values
Serum	IgG	nephelometric	30 g/l	8–18 g/l
	IgA	nephelometric	< 0.0002 g/l	0.9–4.5 g/l
	IgM	nephelometric	1.4 g/l	0.6–2.5 g/l
	IgD	radial immunodiffusion	0.1 g/l	0.003–0.4 g/l
	IgE	enzyme-linked immunosorbent assay (ELISA)	100 IU/ml	10–120 IU/ml
Whole saliva	IgA	nephelometric	< 0.0002 g/l	0.02–0.06 g/l

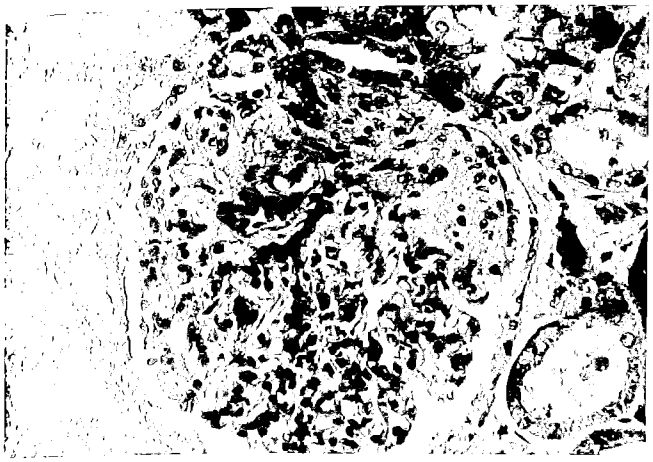

Fig. 2. Glomerulus with segmentary proliferation of mesangian and endothelial cells. Masson's trichrome. × 480.

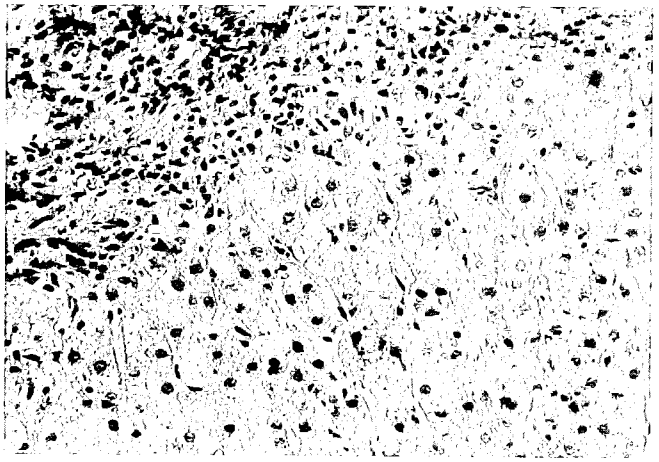

Fig. 3. Piecemeal necrosis of lymphocytes in the periportal space. HE. × 240.

Results

Serum and whole saliva immunoglobulin concentrations are shown in table I. No circulating anti-IgA antibodies were detected in serum.

The percentage of E-rosette forming cells was 64 (normal 53–72%) and the percentage of EAC-rosette forming cells 27 (normal 17–28%). The percentage of T helper (OKT4) was 44 (normal 39.2 ± 6.2) and the percentage of T suppressors (OKT8) 21 (normal 22.5 ± 6.6). The OKT4/OKT8 ratio was 2.09 (normal 1.83 ± 0.45). The transformation response to phytohemagglutinin was 55% (normal 50%). Circulating immune complexes 1:64 were demonstrable.

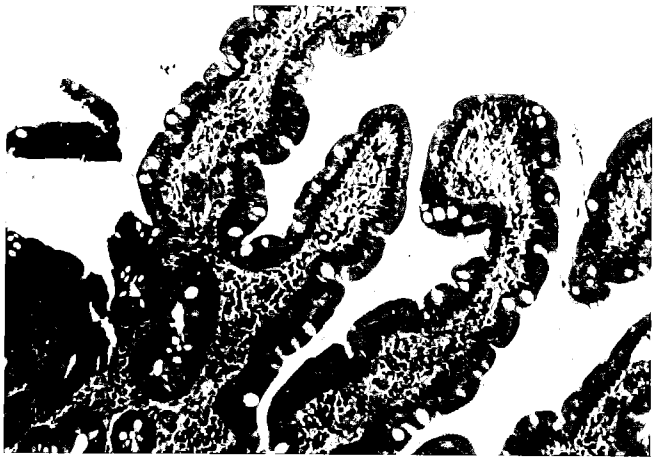

Fig. 4. Normal villi in the jejunal mucosa. Plasmacytoid cells in the lamina propria are quantitatively normal. HE. × 120.

Histological Findings

Renal biopsy revealed a focal proliferative glomerulonephritis with increased mesangial and endothelial cellularity. In some instances a mild increase in epithelial cells was present. No tubulointerstitial changes were observed. Focal glomerulonephritis was the definitive diagnosis (fig. 2).

Liver biopsy showed portal fibrosis and expansion of portal areas which were infiltrated by lymphocytes. A variable degree of bridging necrosis was observed. A diagnosis of chronic active hepatitis was made (fig. 3).

No histological abnormalities were demonstrated after small bowel biopsy (fig. 4). Plasma cells secreting IgA were absent with the PAP technique.

Discussion

In this report we show a selective IgA deficiency associated with Evan's syndrome, chronic active hepatitis and focal glomerulonephritis.

The association between selective IgA deficiency and autoimmune disease, especially systemic lupus erythematosus and rheumatoid arthritis, has been reported previously [21]. IgA deficiency with isolated autoimmune hemolytic anemia, idiopathic thrombopenic purpura and chronic active hepatitis have been described [5, 13, 21]. Combined autoimmune hemolytic anemia and thrombocytopenic purpura has also been reported [11, 22]. We believe that the association of selective IgA deficiency with autoimmune hemolytic anemia, idiopathic thrombopenic purpura, chronic active hepatitis and focal glomerulonephritis found in our patient is the first report published in the literature.

The nature of hemolytic anemia is autoimmune with positive Coombs' test for C_3 and IgG. The origin of the thrombocytopenia seems to be autoimmune as suggested by the positive response to corticosteroids and immunosuppressor therapy, although no antibodies against platelets were detected. Chronic active hepatitis and focal glomerulonephritis may be related to autoimmune phenomena since a good response to therapy was obtained.

The association between IgA deficiency and autoimmune disease has not yet been established. It has been suggested that secretory immunoglobulins block viruses, bacteria and antigens. IgA deficiency would facilitate the entrance of these antigens and thus the development of autoimmune phenomena [23]. However, correlation between IC and the severity of IgA deficiency is not always present [13]. Moreover, no anti-IgA antibodies can be demonstrated in serum, as in our patient [21, 22].

Our results demonstrate a normal cellular immune response as in the case of *Hansen* et al. [11]. However, a disturbed cellular immune response has been reported in some patients with S-IgAD [24, 25].

The prevalence of HLA A_1 and B_8 found in our patient has been described in S-IgAD associated with autoimmune disease [26, 27].

This is, to our knowledge, the first description of a selective IgA deficiency associated with chronic active hepatitis, focal glomerulonephritis and Evan's syndrome.

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Received: September 16, 1985
Accepted: December 10, 1985

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