Ticlopidine Treatment in Idiopathic Plasmacytic Lymphadenopathy with Polyclonal Hyperimmunoglobulinemia Accompanied by Nephrotic Syndrome

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A 36-year-old woman was admitted for idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL) associated with nephrotic syndrome. She was expected to lapse into renal failure because renal biopsy showed focal glomerulosclerosis. VEMP chemotherapy and bolus methyl prednisolone were not effective against excessive urine protein of over 10 g/day. We thus began administration of ticlopidine (6 mg/kg/day), prednisolone (0.4 mg/kg/day) and cyclophosphamide (1 mg/kg/day). After 3 months of this regimen, the urine protein level decreased to less than 0.5 g/day, and renal function was maintained for more than 3 years. It is suggested that ticlopidine is effective for nephropathy complications associated with IPL.

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Introduction

Gaba et al. reported a patient afflicted with systemic multicentric Castleman's lymphoma in 1978 (1). This notion was expanded by Mori et al. (2), who proposed the concept of idiopathic plasmacytic lymphadenopathy with polyclonal hyperimmunoglobulinemia (IPL) based on the clinical and pathologic findings.

A few cases of IPL accompanied by nephropathy have been reported, but no effective therapy has been established (3-5). The pathogenesis of IPL has been suggested to be disordered production of interleukin-6 (IL-6) (6) and the induction of nephropathy by IL-6 involving the activation of platelets (7). Therefore we attempted treatment of a patient with IPL who had the complication of nephrotic syndrome, using ticlopidine, cyclophosphamide and prednisolone.

Case Report

A 36-year-old Japanese woman was admitted because of fever, severe edema, and generalized lymphadenopathy. Her father died of lung cancer and her mother suffered from rheumatoid arthritis. She had been healthy until after a lapse of remittent fever exceeding 38°C in March 1987. Antibiotics given in another hospital were not effective against the fever. After two weeks, edema of the face and lower and upper limbs and an increase of abdominal circumference appeared. Swelling of cervical and axillary lymph nodes was noted. She developed dyspnea, and was transferred to Aichi Medical College Hospital in June 1987.

On physical examination, the cervical, supraclavicular, axillary and inguinal lymph nodes were enlarged, 1 to 2 cm in diameter, firm, mobile and not tender. The spleen was palpable 3 cm below the costal margin. The liver was firm and palpable 4 cm below the costal margin. The heart rate was 72 beats/min. The blood pressure was 120/72 mmHg. Moderate pitting edema at the ankles was present. An x-ray film of the chest disclosed moderate bilateral pleural effusion. The neurologic findings were within normal limits.

Results of initial laboratory findings were as follows: red cell count, 2,700,000/μl; hematocrit, 22.0%; leucocyte count, 5,900/μl with normal differential; platelet count, 339,000/μl; erythrocyte sedimentation rate (ESR),
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140 mm/h; C-reactive protein (CRP), 10.7 mg/dl; serum fibrinogen, 601 mg/dl; total hemolytic complement (CH50), 38 U/ml; cholesterol, 102 mg/dl. The urinalysis revealed a large amount of protein, and 24 hour urinary protein excretion was 11.0 g. The sediment contained a large number of erythrocytes and hyaline casts. Albumin was 1.9 g/dl, and globulin 4.8 g/dl. Immunoelectrophoretic analysis revealed polyclonal elevations of immunoglobulin. IgG was 4,120 mg/dl, IgA 397 mg/dl, IgM 683 mg/dl and IgE 2,000 U/ml, respectively. Creatinine was 0.67 mg/dl, and creatinine clearance (CCr) was 94 ml/min. No cryoglobulin, monoclonal immunoglobulin or Bence Jones protein were found in the serum or urine. No antinuclear factor was detected either. Human T-lymphotropic virus 1 (HTLV-1) antibodies and HIV-1 antibodies were negative. EBV antibodies were positive (EB. VCA IgG 320x, EB. EBNA 40x).

The bone marrow aspirate was normal except for a moderate increase of mature plasma cells (11.6%). The ratio of suppressor T cells both with CD8 and with CD11b (8) in peripheral lymphocytes was analyzed by flow cytometry. The percentage of suppressor T cells was 22.2%, which was 4 times greater than the normal control (5.6 ± 3.7%).

Histologic figures of the biopsy specimen of an axillary lymph node showed many lymph follicles with hyperplastic secondary follicles and lymphoid cells containing numerous well-differentiated plasma cells and very few immunoblasts. The proliferation of small vessels with thickened hyaline walls and plump endothelium was prominent in the interfollicular spaces that radially penetrated the secondary follicles, occasionally creating a hyalinus appearance (Figs. 1, 2).

Examination of a biopsy specimen of the right kidney showed 20 glomeruli with mild mesangial expansion and sclerosis in one-fourth of the glomeruli. One complete global obsolescence glomerulus was observed. Four glomeruli with sclerosing, segmental lesions were present without hyalinosis, which were characterized by irregular patencies of capillary loops, loosened mesangial anchoring and adhesions between tuft and capsule. There was neither hypercellularity nor infiltration of plasma cells in the affected segments. These findings were in accord with a report of focal glomerulosclerosis at an early stage (9) (Figs. 3, 4).
Clinical course (Fig. 5)

High fever did not respond to various kinds of antibiotics. The patient was then treated with 2 courses of VEMP chemotherapy (vincristine, cyclophosphamide, mercaptopurine, and prednisolone) (10). The alleviation of fever was achieved subsequently. However, lymphadenopathy indicated only a slight decrease of swelling, and the reduction of urine protein was transient. Four courses of bolus methyl prednisolone (mPSL) pulse therapy at a dose of 1,000 mg were given for 3 consecutive days. Only a transient decrease in the urine protein resulted. Therefore, administration of ticlopidine (6 mg/kg/day), prednisolone (0.4 mg/kg/day) and cyclophosphamide (1 mg/kg/day) were started. Three months after the start of administration, the urine protein levels were under 0.5 g/day and microscopic hematuria disappeared. The administration of ticlopidine (6 mg/kg/day), prednisolone (0.2 mg/kg/day) and cyclophosphamide (1 mg/kg/day) has been maintained.

As of May 1991, the patient showed slight anemia (Hb 10.0 g/dl), hyperimmunoglobulinemia (IgG 3,620 mg/dl) and a persistently high serum CRP level (13.1 mg/dl). However, she had no fever. Serum albumin (3.8 g/dl), the renal function (CCr: 84 ml/min) and urinalysis remained normal, and there was no evidence of growing lymphadenopathy or hepatosplenomegaly.

Discussion

This report documents a case of IPL accompanied by nephrotic syndrome. The pathogenesis of IPL is unknown, but recently similarities in the clinical and pathological aspects of IPL and IL-6 transgenic mice (11) and the possibility of abnormal IL-6 production have been reported as the factors in the development of IPL (6). IL-6 can induce polyclonal hyperimmunoglobulinemia by its ability to stimulate B lymphocytes (12). IL-6 also possesses the ability to stimulate liver cells to produce acute phase reactants such as fibrinogen and CRP (13).

In the present case, serum fibrinogen and CRP levels were high, and polyclonal hyperimmunoglobulinemia was noted. Furthermore, an increase in the suppressor T cell fraction was observed on analysis of lymphocyte subsets. We speculated that these suppressor T cells were induced by normal immune reactions against the disordered immunoglobulin production and/or some cytokines such as interferon-γ (14), because the induction of these suppressor T cells is also observed in multiple myeloma patients with characteristic hyperimmunoglobulinemia and synthesis of some cytokines (15).

Horii et al reported that abnormal conditions of the immune system cause an excessive release of IL-6 and induction of nephropathy (7). To date, eight cases of
Castleman’s lymphoma or IPL with pathological and histological examinations of the nephropathy have been reported (16). Five of these cases were associated with nephrotic syndrome. The causes of nephropathy were attributed to renal amyloidosis in two cases, and direct infiltration of plasma cells to the kidney in two other cases. Minimal-change nephropathy, membranous nephropathy, interstitial nephritis and glomerulosclerosis have been reported in other cases (16).

In the present case, the renal function was thought to be deteriorating and the therapeutic problem appeared similar to the reported cases due to the evidence of focal glomerulosclerosis (16-18). However, the combination therapy of ticlopidine with small doses of prednisolone and cyclophosphamide was effective against nephrotic syndrome, and renal function has been kept stable for more than 3 years. Activated platelets contribute to clinicopathologic expression in renal diseases (19), and the inhibitory effect of ticlopidine on platelet aggregation has been known to be effective against nephrotic syndrome (20). The present case demonstrated that the administration of ticlopidine is also effective and it should be considered for a therapy against IPL complicated with nephropathy.

References