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A Case of Common Variable Immunodeficiency

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= **Abstract** =Common variable immunodeficiency is a heterogeneous group of disorders characterized by hypogammaglobulinemia, impaired antibody response and recurrent bacterial infections. Although it is represented by an acquired defect of humoral immunity, cellular defect is occasionally found. Though variable, it usually manifests in the second or third decade of life.

This report deals with a case of common variable immunodeficiency in a 6-year-old boy who presented with recurrent infections since 3 7/12 years of age, associated with aortic aneurysm and involvement of the liver, testis and polyserosa, which were believed to be autoimmune in nature.

Key words: ***Common variable immunodeficiency, Aortic aneurysm, Autoimmunity***

INTRODUCTION

Agammaglobulinemia or hypogammaglobulinemia falls into three pathological categories: primary congenital agammaglobulinemia which is a sex-linked recessive trait and usually becomes manifest late in the first year of life; primary acquired or common variable agammaglobulinemia which has no clear-cut genetic basis; and secondary agammaglobulinemia which is a symptom found in certain neoplastic diseases such as Hodgkin's disease and other malignant lymphoma, multiple myeloma and chronic lymphatic leukemia.

Common variable immunodeficiency (CVI) is one of the primary immunodeficiency diseases, that encompasses a heterogeneous group of disorders characterized by low levels of serum immunoglobulins, normal or low proportions of circulating B lymphocytes. Though humoral immunity is primarily affected, abnormalities of cellular immunity have also been demonstrated occasionally (Kopp *et al.* 1968; Douglas *et al.* 1970). The principal defects have been thought as occurring at various steps in the maturation pathway of B cells into antibody secreting cells, which may be intrinsic to B cells itself or influenced by T cells (Geha *et al.* 1974; Waldmann *et al.* 1974; Ciccimarra *et al.* 1976; Cunningham-Rundles *et al.* 1982).

Clinically the disease is manifested by recurrent bacterial infections which begin sometime after infancy, usually in the second or third decade. Another characteristic of this disorder is its frequent association with autoimmune disorders and manifestations involving the reticuloendothelial system. These include rheumatoid arthritis (Good *et al.* 1957), dermatomyositis (Venters and Good 1963), scleroderma (Van Gelder 1957), hepatomegaly (Van Gelder 1957; Painter and Korst 1959), splenomegaly (Firkin and Blackburn 1958; Painter and Korst 1959) and hepatosplenomegaly (Citron 1957) with anemia, leukopenia, thrombocytopenia and other signs of hypersplenism.

The 6 7/12- year-old boy described here is of interest because of its rather early age of onset, involvement of the aorta, liver and testis, and polyserositis in his disease process. In Korea, only one case has been reported in a young lady (Lee *et al.* 1985) and following report is the first case diagnosed in the first decade of life.

CASE REPORT

A 6 7/12-year-old boy was admitted to the Seoul

National University Children's Hospital on Sept. 26, 1985, because of abdominal distension and fever. He was born as a second baby with normal term delivery. In Sept., 1982, at 3 7/12 years of age, he was admitted to a hospital because of fever and cough and received antituberculous medications under the impression of pulmonary tuberculosis. He was admitted again to that hospital in Jul., 1983, due to pneumonia. In Feb., 1984, he was readmitted to the hospital due to cervical lymphadenitis, when immunoglobulin quantitation revealed IgG, 320 mg/dl; IgA, 5 mg/dl; and undetectable IgM. Thereafter gamma globulin had been administered every three weeks. In Feb., 1985, jaundice and abdominal distension developed which waxed and waned thereafter. In Jul., 1985, he was admitted to the hospital because of more deepened jaundice and painless enlargement of both testes. Microscopic examination of the liver specimen obtained by needle biopsy showed general preservation of lobular architecture with prominent portal tract. The hepatic cell cords were preserved in most portions, however, there was a pronounced Kupffer cell proliferation in the sinusoids. The hepatocytes often showed microvacuolar changes and occasional ballooning. In a few foci, there was focal necrosis with collections of mononuclear cells. The portal tracts were infiltrated with a significant number of lymphocytes, plasma cells and mononuclears. However, the limiting plates were preserved in most portions except for one focus, where suspicious susceptible disruption was identified. No acidophilic bodies or active neutrophilic infiltrates were present (Fig. 1). Abdominal aortic aneurysm was found incidentally on computed tomogram (Fig. 2). On Sept. 26, 1985, he was referred to the Seoul National University Children's Hospital for further evaluation. His parents and elder brother aged 9 were all healthy, and history of early death in his close relatives was not found.

Physical examination on admission showed a chronically ill looking, markedly emaciated boy with clear consciousness. The blood pressure was 90/60 mmHg, the pulse rate 140/min, the respiratory rate 38/min and the body temperature 38.6°C. The conjunctivae were mildly anemic and the sclerae were icteric. The tonsillar tissue was hardly visible.

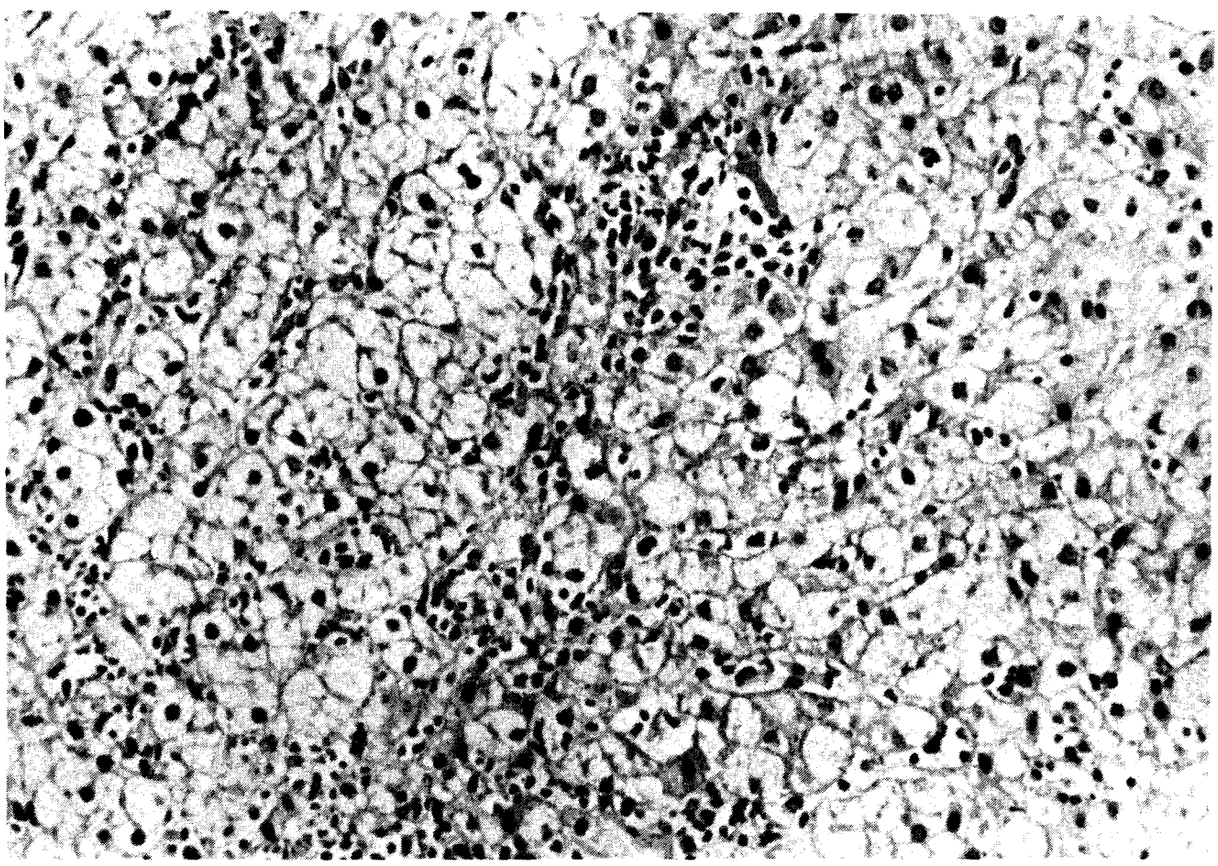

Fig. 1. Photomicrograph of the liver biopsy showing intralobular spillage of mononuclear inflammatory cells. H & E. X250.

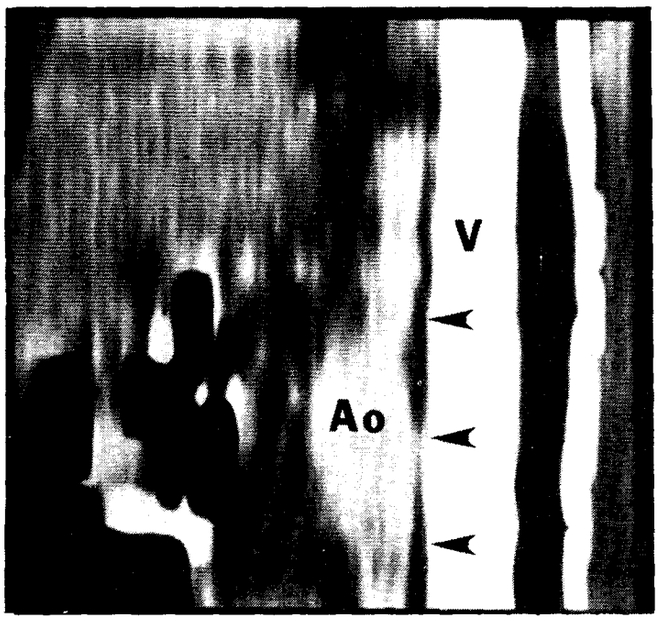

Fig. 2a. Sagittal reconstruction of the aorta (Ao) showing fusiform dilatation. The aneurysm begins at the level just below the origin of renal arteries and extends downward. The extent of aneurysm is indicated by arrowheads. V = vertebral column.

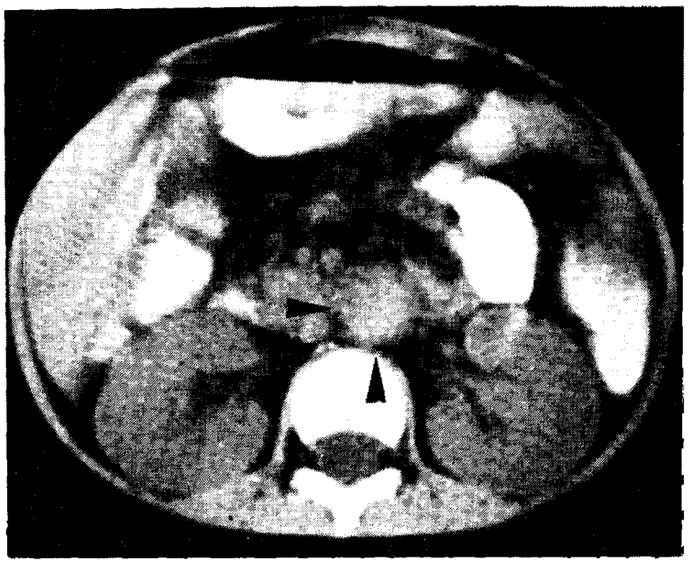

Fig. 2b. Computed tomogram taken at the L_2 level. Dilated aorta is indicated by arrowheads.

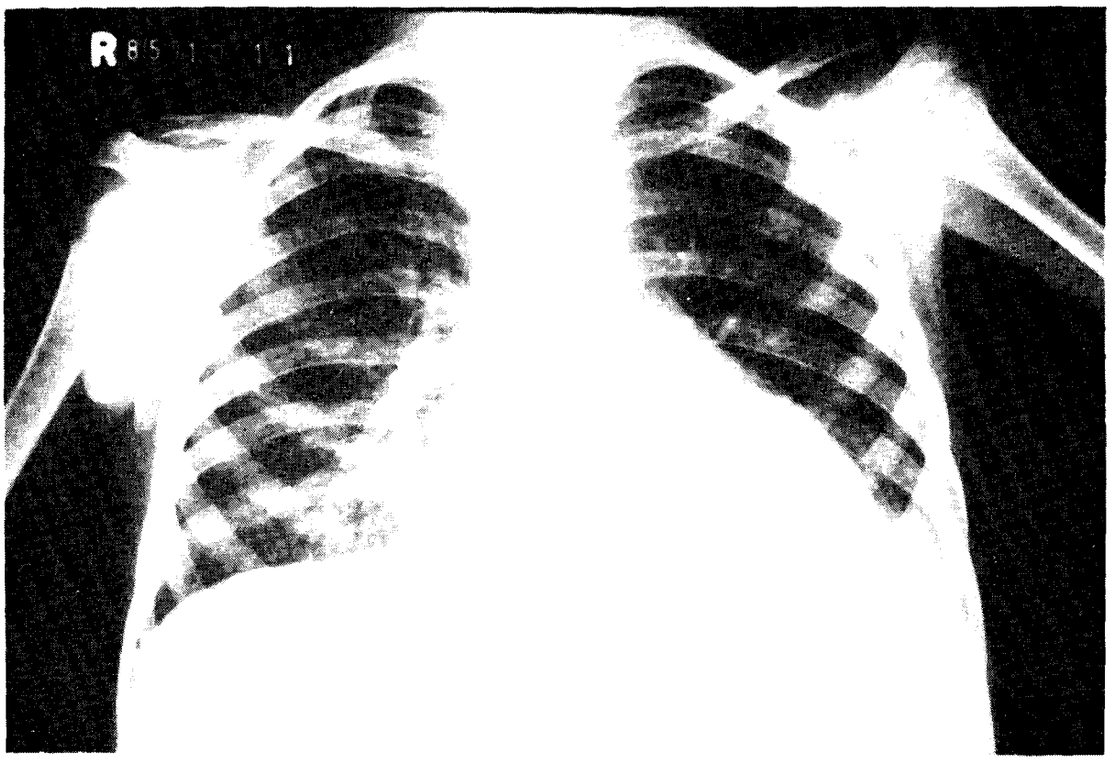

Fig. 3. Chest P-A showing pneumonic infiltrations of the both lower lung fields and pleural effusion of the left lung.

Table 1. Immunologic tests

	Patient		Normal values at 6-8 years
B cell			
Ig G (mg/dl)	320*	375**	667-1,179
Ig M (mg/dl)	0*	12.5**	40-90
Ig A (mg/dl)	5*	15**	79-169
SmIg (%)	0		10-20
T cell			
Lymphocyte count (/mm^3)	429		1,500-4,500
Delayed skin test	negative		
Response to PHA stimulation	not impaired		
E rosettes (%)	73		55-75
T_3 (%)	84		58-78
T_4 (%)	0		33-49
T_8 (%)	34		17-35
Phagocytosis			
Neutrophil count (/mm^3)	3,276		3,000-7,000
NBT (%)	13		0-12
Complement			
C_3 (mg/dl)	139		45-105
C_4 (mg/dl)	88		15-45
CH_{50} (u/ml)	57		18-35

*; Before gamma globulin therapy
**; One month after the last gamma globulin injection
SmIg; Surface Ig-bearing cells
PHA; Phytohemagglutinin
NBT; Nitroblue tetrazolium test

Multiple, finger-tip sized submandibular lymph nodes were palpable. Moist rales were heard over the left lower lung field. The abdomen was markedly distended with ascites, and the liver and spleen were palpable 8 cm and 3.5 cm below the respective costal margins. Both testes were enlarged, firm and slightly tender. There was marked muscle wasting of the extremities.

Laboratory findings were as follows: the hemoglobin was 9.5 gm/dl, the WBC count 3,900/mm^3 with band forms, 2%; neutrophils, 84%; lymphocytes, 11%; monocytes, 3%; and the platelet count 50,000/mm^3. The red cells were normochromic, normocytic, and the both direct and indirect Coombs tests were negative. The reticulocyte count was 1.0%, but 4.8%, 2 months later. Serum protein was 5.0 gm/dl, albumin 3.3 gm/dl, SGOT 37 IU/1, SGPT 40 IU/1 and alkaline phosphatase 1,600 IU/1 Total and direct bilirubin were 3.2 mg/dl and 1.9 mg/dl, but one day before death, 14.8 mg/dl and 12.8 mg/dl, respectively. BUN, creatinine, serum α-fetoprotein and ceruloplasmin were all within the normal range. HBsAg, VDRL, rheumatoid factor, antinuclear antibody and LE cell were all negative. Stool examination was negative for parasites. Blood, urine and stool cultures for bacteriae were negative. Liver scan showed hepatosplenomegaly with decreased liver uptake, increased spleen uptake, but without space-occupying lesion. On sinus roentgenogram, haziness of both maxillary sinuses suggested sinusitis. The chest X-ray disclosed cardiomegaly and pneumonic infiltrations of the both lungs with effusion (Fig. 3). Tuberculin skin test and sputum smear for tubercle bacilli were negative. Echocardiogram revealed moderate pericardial effusion. Cytologic and microbiologic studies of pleural, pericardial and ascitic fluid for bacteriae, tubercle bacilli and fungi

were all negative. These fluids were all exudate with predominance of lymphocytes. Submandibular lymph node biopsy was tried, but the specimen proved to be salivary gland. Testicular biopsy specimen revealed interstitial inflammation. Pleural biopsy specimen showed mesothelial hyperplasia. Bone marrow examination revealed normocellular marrow with moderate erythroid hyperplasia. The proportion of plasma cells was about 1%.

Immunologic studies were as follows (Table 1): serum immunoglobulins determined one month after the last gamma globulin injection showed panhypogammaglobulinemia, and peripheral B lymphocytes were not found. The total lymphocyte count in the peripheral blood was 429/mm^3, but the percentage of E-rosetting cells was adequate. Analysis of T cell subsets by OK T series monoclonal antibodies showed absence of T_4 lymphocytes. Though the skin tests for delayed hypersensitivity to tetanus, diphtheria, streptococcus, tuberculin, candida, trichophyton and proteus antigens were negative, *in vitro* lymphocyte response to phytohemagglutinin stimulation was not impaired. There was no evidence of deficiency in phagocytic and complement system. Anti HTLV-III antibody was negative.

During hospitalization, gamma globulin was given every four weeks and intensive antibiotic therapy with cephalosporin, aminoglycoside and bactrim was done, but the patient's clinical condition got worse. Continuous fever ranging from 37.5°C to 39°C persisted, jaundice deepened progressively and pneumonic lesions were more extended. One day before death, he became comatose after development of sudden convulsion. He expired on the 89th hospital day. Autopsy was refused by his parents.

DISCUSSION

The first reports of CVI appeared two years after the Bruton's description of congenital agammaglobulinemia in 1952 (Bruton 1952; Prasad and Koza 1954; Zinneman *et al.* 1954). CVI presents clinically like X-linked agammaglobulinemia, but several features are helpful in differentiation. In the congenital form, the age of onset is usually late in the first year of life, diarrhea and malabsorption are rare and the development of tonsils and other lymphoid tissue is poor. In the CVI, the age of onset is variable, gastrointestinal symptoms and autoimmune disorders are common and tonsillar hyperplasia and nodular lymphoid hyperplasia of the small intestine are often present.

CVI may be sporadic or familial, and a number of mechanisms have been postulated to explain the defect. They include markedly depressed or absent B cells as in our case (Geha *et al.* 1974), intrinsic defect of B cells (Geha *et al.* 1974; Waldmann *et al.* 1974), block of immunoglobulin secretion associated with failure of heavy-chain glycosylation (Ciccimarra *et al.* 1976), serum inhibitory factor (Geha *et al.* 1974), increased suppressor T cell activity (Waldmann *et al.* 1974) and decreased helper T cell activity (Reinherz *et al.* 1981).

The age of onset in CVI is variable but it begins sometime after infancy, usually in the second or third decade. Male and female are equally affected. The presenting feature in most patients is recurrent sinopulmonary infections and many of these patients develop bronchiectasis (Ochs and Wedgwood 1980). Also the incidence of otitis media, meningitis and septicemia is increased. Lymphoid tissue and tonsils are usually lacking, although several of these patients may have hepatosplenomegaly and lymphadenopathy (Ochs and Wedgwood 1980). Patients with CVI have a high incidence of gastrointestinal abnormalities such as diarrhea, lactose intolerance, malabsorption and protein-losing enteropathy (Hermans *et al.* 1976). In some patients villous atrophy and nodular lymphoid hyperplasia of the intestine can be seen. *Giardia lamblia* is commonly found in these patients. Thus metronidazole therapy can be quite effective in relieving gastrointestinal symptoms. A high percentage of patients with CVI have associated hematologic disorders (Waldmann *et al.* 1980). Autoimmune hemolytic anemia, perniicious anemia (Twomey *et al.* 1970) and hypersplenism with anemia, leukopenia and thrombocytopenia occur occasionally. In our case, pancytopenia and bone marrow findings are supposed to be caused by hypersplenism. Autoimmune disorders such as rheumatoid arthritis, dermatomyositis, scleroderma, systemic lupus erythematosus and idiopathic thrombocytopenic purpura are frequently found in patients with CVI (Good *et al.* 1957; Fudenberg *et al.* 1962; Wolf 1962). In our case presented, involvement of the liver, testis, aorta and polyserosa is very interesting. Similar pattern hasn't been reported in the literature. One may assume that this may be due to long-standing systemic viral infection, but we can hardly imagine viral infection with such manifestations. Another possibility is a manifestation of autoimmune disease process which is commonly seen in CVI.

Though autoantibodies were not demonstrated, this can be possible in a hypogammaglobulinemic patient (Good and Yunis 1974). The incidence of malignancy of lymphoreticular and epithelial origin, and thymoma is increased in patients with CVI (Gafni *et al.* 1960; Kersey *et al.* 1973; Hermans *et al.* 1976).

Serum immunoglobulin levels are usually higher in CVI than in congenital agammaglobulinemia, but serum IgG rarely exceeds 250 to 300 mg/dl (Ochs and Wedgwood 1980). IgM and IgA levels are undetectable in most patients but may be near normal in others. Peripheral B cells are normal in most patients, but about one fourth the patients lack B cells. Biopsy of lymphoid tissue usually demonstrates a striking absence of lymphoid cells in the B cell dependent areas and a lack of plasma cells. Though cellular immunity is usually not impaired, cellular defect such as decreased delayed hypersensitivity has been reported (Kopp *et al.* 1968). In our case, total lymphocyte count was reduced which may be partly explained by hypersplenism and the skin test for delayed hypersensitivity was negative, which suggest defect in cellular immunity. Nevertheless the response to phytohemagglutinin stimulation was not impaired.

Therapy with gamma globulin (0.6 ml/kg/month) and broad-spectrum antibiotics is the mainstay in the treatment of CVI. Plasma therapy can be helpful in patients who continue to have severe infections or diarrhea on gamma globulin therapy (Buckley 1972). As noted above, metronidazole may be of help in patients with gastrointestinal symptoms. The use of steroid or other immunosuppressive agents in CVI associated with autoimmune disorders is not recommended (Ochs and Wedgwood 1980).

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= 국문초록 =

Common Variable Immunodeficiency (CVI) 1례

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CVI는 저감마글로불린혈증, 항체형성 장애, 반복적인 세균감염으로 특징지어진다. 이 질환은 원발성 면역결핍증후군의 한 종류로서, 대개 10대나 20대에서 발병하며, 일반적으로 체액성 면역의 장애가 오지만 때로 세포성 면역의 장애 및 자가면역질환이 동반된다.

저자들은 6세된 남아에서 3년 7개월부터 발현한 CVI에 복부 대동맥류와 자가면역질환이 동반된 것으로 추정되는 증례를 경험하였고, 소아과 연령층에서는 국내 최초의 증례로 생각되어 이를 보고하는 바이다.