

IgG2 and IgG4 subclass deficiency and Evan's syndrome in an adult patient

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We describe an adult patient with acquired IgG2 and IgG4 subclass deficiency, an impaired antibody response to polysaccharide antigens, recurrent autoimmune disorders, and a polyclonal lymphoproliferation.

CASE RECORD

This white male patient was well until the age of 17 years, when he underwent splenectomy after a traumatic rupture of the spleen that showed histologic features of a viral infection. He began to suffer from recurrent bronchopulmonary infections as a result of *Hemophilus influenza* type b (Hib) at the age of 23 years. IgG subclass deficiency of IgG2 and IgG4 and extremely low antibody titers against pooled polysaccharides and pneumococci type 4 and 9 were found (Tables I through III). With the exception of the mother who showed isolated IgG4 deficiency, all the family members had normal serum levels of IgG subclasses. A broad search for other bacterial or for viral infectious agents including Epstein-Barr virus (EBV) and human immunodeficiency virus was negative. After a short period of agranulocytosis, acute transient autoimmune hemolysis and chronic idiopathic thrombocytopenic purpura developed. Lowest hemoglobin level was 9.5 gm/dl, and platelets levels over time were within the range of 4 to $20 \times 10^9/L$. Autoantibodies against platelet glycoprotein Ib/IX were three times above normal. Tests for serum autoantibodies (ANA, ssDNA, dsDNA, ENA) were negative, as well as tests for cold-agglutinins and rheumatoid factor. CT scans revealed large accessory spleens with a histologic pattern similar to the initial specimen examined 10 years earlier. The patient was placed on intravenous immunoglobulin supplementation therapy (IVIG; 28 gm every 4 weeks), which prevented further infections. However, treatment of Evans syndrome with corticosteroids, plasmapheresis, and one cycle of high-dose IVIG (31 gm for 5 consecutive days) was ineffective.

Eighteen months after the onset of Evan's syndrome polylmphadenopathy developed in the patient. Histologic examination of an axillary lymph node revealed follicle-like structure and a regular distribution of T and B cells but no

TABLE I. IgG values in patient's serum (gm/L)

	IgG	IgG1	IgG2	IgG3	IgG4
Normal	(8.5)	(5.1)	(2.5)	(0.55)	(0.35)
Day					
10	6.84	4.41	<0.1	2.43	<0.02
210	7.25	4.5	<0.1	2.73	<0.02
286	5.99	4.2	<0.1	1.79	<0.02

evidence of malignant lymphoma. Immunogenotyping of DNA from spleen and lymph nodes showed germ line antigen receptor genes, and no EBV genomic sequences were found by Southern blot analysis.

Interleukin-6 (IL-6) bioactivity in plasma was measured on several occasions along the course of the patient's disease. Before immunoglobulin supplementation was started, IL-6 levels were intermittently high (up to 80 ng/ml at the time of acute bacterial infection), but they remained below the detection limit of the B9 hybridoma assay during the period of IVIG.

The patient has now been monitored over a period of more than 4 years, receiving monthly IVIG. He is feeling well and he has not been suffering from infections anymore. He has resumed full professional activity as an accountant. However, ITP and compensated hemolysis are still present.

DISCUSSION

This patient was admitted with an acquired humoral immune disorder chiefly characterized by IgG2 and IgG4 subclass deficiency and impaired immune response to polysaccharide antigens as well as Evan's syndrome and general polyclonal lymphoproliferation. Typically, recurrent bronchopulmonary infections were present with detection of Hib in the sputum.¹

This type of acquired immune disorder has very rarely been recognized in adults, and its etiology is unknown. We found no evidence for a genetic defect. The late onset of the disease and the histologic findings in spleen and lymph nodes much more suggested a viral etiology, in particular EBV. However, serologic and molecular genetic analyses failed to provide any evidence for chronic EBV infection. Immunogenotyping of DNA from spleen and lymph nodes showed

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TABLE II. Haemophilus influenzae specific immunoglobulins ($\mu\text{g/ml}$)

	IgM	IgG	IgG1	IgG2
Mean	0.93	1.75	0.10	0.95
SD	0.40 - 2.1	0.51 - 12.5	<0.02 - 0.81	<0.02 - 9.50
Day				
38	0.605	3.3	<0.02	<0.19
83	<0.081	0.5	<0.02	<0.19
210	<0.081	1.2	<0.02	<0.19

TABLE III. Antibody titers against pooled polysaccharides (PS; U/ml)

	Type 4 PS	Type 9 PS	Pooled PS
Normal	>100	>100	>100
Day			
38	Not det	10	3
966*	18	9	2

First admission to our hospital, Day 1. Value marked with * obtained under IVIG.

germ line antigen receptor genes, a strong argument against a monoclonal lymphoid neoplasm.

Immunodeficiencies are frequently associated with formation of autoantibodies. This patient had autoimmune hemolysis and chronic ITP, as well as intermittent agranulocytosis. Production of autoantibodies may be triggered by cytokines such as IL-6,² and in vivo this mechanism seems to be important in cases of cardiac myxoma.³ On the other hand, a recent study has shown that immunoglobulins can suppress IL-6 production by monocytes.⁴ Thus it may be interesting to note that IL-6 serum levels were high before immunoglobulin therapy but remained low during IVIG treatment.

In summary, this patient presents a most unusual acquired adult onset immune disorder of unknown cause, characterized by IgG2 and IgG4 deficiency and an impaired antibody response to polysaccharide antigens with recurrent infections, Evan's syndrome, and polyclonal lymphoproliferation.

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