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Primary Acquired Hypogammaglobulinemia Associated With Behçet Disease ——An Observation For 12 Years

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An observation for 12 years of a patient with primary acquired hypogammaglobulinemia was reported. The patient is a 27-year-old female, with an onset of fever and splenomegaly at the age of 6, followed by occasional symptoms of Behçet disease. Cellular immunity became defective in the course of her disease. A hereditary basis is suggested by the presence of hypergammaglobulinemia in her family. It is noteworthy that symptoms of Behçet disease in the case appeared with on evidence of B-cell deficiency.

Key words
Primary immunodeficiency,
Family history,
Behçet disease,
Hypogammaglobulinemia,
B cell deficiency.

INTRODUCTION

There has been various reports of immunoglobulin deficiency syndrome since 1952, when Bruton(1) reported a 8-year-old boy found to have no appreciable gammaglobulin in his serum, who had been suffered from recurrent respiratory infections. There have also been found different types of immune deficiency syndrome, including adult type of primary acquired hypogammaglobulinemia(2-8). We present a 27-year-old female found to have hypogammaglobulinemia, especially very low IgM, and recurrent infections associated with Behçet syndrome after 12 years of observations.

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CASE PRESENTATION

H.K. age of 27, a Korean female, was first seen by us at the age of 16, because of recurrent infections. Her family history revealed nothing particular by taking history. Her past history of present illness started at the age of 6, when she visited a doctor because of rise of fever with chills. During the following years, the frequent episodes of fever, occured usually after exercise which subsided within about several hours without medication. At the age of 7, she was found to have splenomegaly. The frequency of fever was recorded twice a week. She was noted as having several spots of erythema in the lower legs at the every summer time after the age of 7. Erythema were slightly pain-

ful, tender, and of coin-size, probably the initial manifestation of Bechçet disease in her clinical course.

For 10 years from the onset, from the age of 6 to 16, she had visited different medical services including 3 times of hospitalizations at Okayama (age 9), Fukuoka (age 10), and Hiroshima (age 12). None of these occasions could not help establishing the diagnosis or being on effective treatments.

At the age of 16, she visited our clinic for the check up of her disease. Physical examination on admission revealed her body length 142 cm, body weight 34.5 kg, showing that she was poorly nourished. Hepatomegaly 1.5 cm and splenomegaly 8 cm below the costal margin were noted. Arachinodactylia and erythema nodosum on the legs were noted. Pubic hair was absent, although gynecological examination revealed normal. Laboratory examinations were as follows: Ocular vision of VR 1.5 and VL 1.5. Total bilirubin 0.4 with direct bilirubin 0.1 mg/dℓ, TTT 0.1, CCLF (−), BSP 3.9%, cholesterol 183 mg/dℓ, uric acid 5.0 mg/dℓ, GOT 23u, GPT 13u, LDH 560u, alkaline phosphatase 13.8u, acid phosphatase 2.5. Of an urinalysis, pH 6.5, protein sugar negative, urobilinogen normal. Feces occult blood (−), parasite ova (−). ^{131}I uptake, ACTH stimulation test and urinary gonadotropin were all normal. As to peripheral blood view, WBC 2,000 with a differential of stab 25%, segments 10%, monocytes 6% and lymphocyte 59%, RBC 390 × 10^4, Hb 74%, reticulocytes 22‰, platelets 11.2 × 10^4, red cell fragility test normal. Serum iron 42 γ/dℓ, UIBC 208 γ/dℓ, fibrinogen 241 mg/dℓ. A myelogram revealed 26.2% of erythropoiesis, 57.2% of granulopoiesis, 2.2% of reticulum cell, 1.6% of monocytes, and 12.8% of lymphocytes. Only two plasma cells were found out of 5,000 of nucleated marrow cells, suggesting the B-cell deficiency. Repeated blood cultures were negative. An axillary lymphnode biopsy revealed no evidence of development of germinal centers. There were scanty lymphocytes and absence of plasma cells in the biopsied node. Systemic X-ray survey was negative.

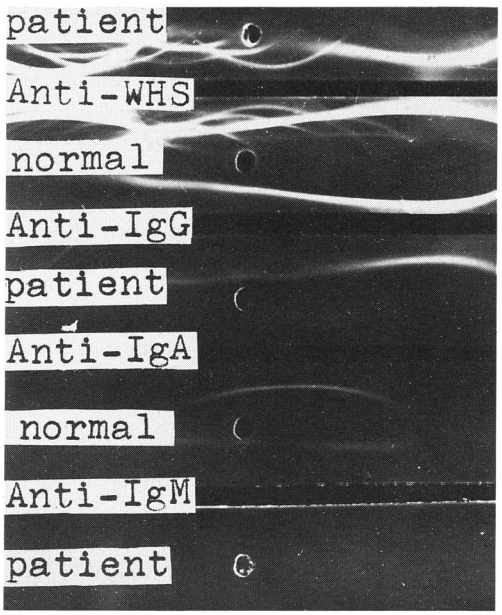

Figure 1. Immunoelectrophoresis of the patient serum along with a normal control serm.
Precipitation lines with the patient serum were reduced in density, expressing hypogammaglobulinemia.

Immunological findings were as follows; CRP (−), ASLO (−), RA (−), cold hemoagglutinin (−), Paul-Bunnel (−), STS (−), Widal (−), Weil-Felix OX-K, OX-19 and OX-2 (−), Coombs (−), Polio type Ⅰ, Ⅱ, and Ⅲ (−), Coxsachie (−), Echo (−), Influenza A and

Table 1: Agglutinin titer before and after antigenic stimulation. A subcutoneous injection of 0.4 ml, followed by 0.1 ml injection of Typhoid paratyphoid vacine one week week later.

		Prior to vaccination	Day after Vaccination			
			3	11	20	30
TA	O	(-)	(-)	(-)	(-)	(-)
TA	OH	(-)	40	40	80	20
PA	O	(-)	(-)	(-)	(-)	(-)
PA	OH	(-)	(-)	(-)	(-)	(-)
PB	O	(-)	20	(-)	(-)	(-)
PB	OH	(-)	(-)	(-)	(-)	(-)
Vi		(-)	(-)	(-)	(-)	(-)

B (−), Mumps (−), Adenovirus (−), Encephalitis Japonica (−), Isohemagglutinin anti A (×2) and anti B (×8), PPD skin test x 2,000 (−), DNCB sensitization to the skin was positive.

Agglutination titer before and after antigenic stimmulation was shown in Table 1. There was no antigenic responses seen in this patients. Familial analysis of serum protein was shown in Table 2. There were 2 persons, one sister and one brother, who were found to have hypergammaglobulinemia. IgA, IgG or IgM were not deficient among the family members. Rheumatoid factors and other autoantibodies were not found in the family at this time of analysis.

The analysis of patient serum protein revealed 380 mg/dℓ of γ-globulin by cellulose acetate electrophoresis, and IgA 70 mg/dℓ, IgG 300 mg/dℓ and IgM 10 mg/dℓ were measured by immunodiffusion. As shown in Fig. 1, the precipitations of patient IgM was very faint, along with the evidence of decreased IgA and IgG by demonstration of the shortness or faintness of precipitation lines of the patient serum compared to those of normal serum. Thus the diagnosis of adult primary hypogammaglobulinemia was established.

As to clinical course, high fever and abnormal X-ray shadow of left lower lung field due to bronchopneumonia with streptococcus was complicated after hospitalization. Kanamycin 1.0 gm a day, Tetracyclin 1.5 gm a day, and γ-globulin intramuscular injections 2 ml a day for 10 days followed by 3 ml a day for another 10 days of γ-globulin improved her clinical conditions within the month. The level of serum γ-

Table 2: Serum protein analysis of family. Numbers are expressed by gm/dℓ.

	Age	Tp	Alb	Glo	α_1	α_2	β	γ
Patient	(18)	6.1	3.9	2.2	0.3	0.7	0.8	0.4
Father	(54)	7.0	4.1	2.9	0.3	0.6	0.6	1.4
Mother	(54)	6.9	4.0	2.9	0.4	0.6	0.9	1.0
Sister	(29)	8.0	4.2	3.8	0.2	0.7	0.9	2.0
Sister	(24)	6.6	3.3	3.3	0.2	0.7	0.9	1.5
Brother	(15)	6.6	2.5	4.1	0.4	0.8	1.0	1.9

globulin increased from 378.2 to 604.5 mg/dℓ during repeated injections, and then decreased to 409.2 mg/dℓ in concentration in a month. The exacerbation and the following improvement along with bacterial pneumonia within 2 months disclosed the changes as follows: WBC (2,000 → 9,800 → 2,000/cmm), Spleen size (8 → 10 → 5 cm), γ-globulin levels (378.2 → 604.5 → 409.2 mg/dℓ), ESR (4 → 22 → 3 mm/hour) and fever (37.2 → 39.2 → 36.8°C).

There were episodes of fever associated with aphtha in the oral mucous membrane and painful erythema nodosum in the lower legs. Even after 10 ml of γ-globulin injections intravenously every two weeks she had attacks of fever, oral aphtha, genital ulcer and chorioiditis peripherica, and thus a diagnosis of Behçet disease was made. Institutions of prednisolone 15 mg a day and 3ml γ-globulin injection a day for 7 days were given. Fever, and then ulcer and aphtha disappeared in 2 weeks and erythema disappeared in 4 weeks.

From age of 17 to 27, she had 5 times episodes of bronchopneumonia (age of 18, 20, 21, and 24 twice) with less sevireity of clinical symptoms and smaller size of spleen (2 to 4 cm) compared to the large splenomegaly at the age of 16. Antibiotics were effective on these episodes. Besides pneumonia, there have been episodes of exacerbations of Behçet's disease, i. e. the eye symptoms, skin rash in the legs and genital ulcer with febrile conditions once or twice every year. Betamethasone 3 or 4 mg a day for 4 days with tapering dose was effective on the attacks of Behçet's disease. Levels of serum γ-globulin have ranged from 100 to 400 mg/dℓ. Peripheral leucocyte counts ranged from 3,300 to 5,000/cmm. She has been checked by our outpatient clinic once a month. She has been treated only when she had any abnormal symptoms.

Immunological analysis at the age of 27 were as follows. As for the subpopulation of a peripheral lymphocyte counts (1,107/cmm) out of a total white cell counts of 2,700/cmm, T cells were

43.2% i.e. 472/cmm compared to 73.1% i.e. 1,718/cmm of T cell counts from a normal healthy control calculated by T rosette-formations with sheep red blood cells at 37°C, whereas B cells were 26.2% i.e. 290/cmm comparded to 26.2% i.e. 290/cmm of B cell counts from a normal control calculated by detecting the receptors for the third complement on the B cells at 37°C. As for the skin tests, there were negative results for PPD (5T.U., 0.1 ml), Candida (1:10,000 diluted, 0.05 ml), SK-SD (5u, 0.1 ml) as well as control PBS (phosphate buffered saline), except for a positive result for mumps (0.1 ml). Examinations of HL-A antigens on the peripheral lymphocytes disclosed AW 26 on the locus A, B 12 plus BW 15 on the locus B, and CW 2 on the locus C.

Serum immunoglobulins were all measurably reduced in concentration, estimating IgA 60 mg/dℓ, IgG 320 mg/dℓ, IgM 10 mg/dℓ, IgD lower than 0.3 mg/dℓ and IgE 34 u/ml.

Regarding the follow-up of the family, her mother died of liver cirrhosis with hepatoma 7 years after the analysis of the serum as shown in Table 1. One sister, aged 35, is currently under hospitalization with a diagnosis of liver cirrhosis on the basis of histology of a biopsied material. Hepatitis A antigen and alpha-feto-protein were negative. Rheumatoid factor was positive. Serum protein analysis revealed 4.2 gm% in concentration (Albumin 2.5 and globulin 1.7 gm, with α_1-0.1, α_2-0.2, β-0.4 and gamma-globulin 1.0 gm%). There was no evidence of immunoglobulin deficiency of any class in this sister.

In 1986, the patient is working without any major problems after an additional course of 12 years. Unfortunately, she has been unable to visit a clinic for further check-up until now.

DISCUSSION

The classification of immune deficiency syndrome includes various types of diseases(2-8). One of the types is adult type primary acquired form, where major clinical symptoms act on in the late stage of childhood, but not in the neonatal stage, without any anticedant causative disorders detected. The present case can be classified as of primary acquired form of immunoglobulin deficiency syndrome. Age at the onset of this type of syndrome reported in the literature had a wide range from 1 to 70 years.

Familial hypergammaglobulinemia, as seen in brotherhood in the present case, were reported(10,11). There is a report(12) with acquired hypo-γ-globulinemia seen in 2 sisters and a report(13) with father, one son and 2 daughters. Thus, there must be the genetic background unrelated to the sex in the consideration of the pathogenesis of acquired hypo-γ-globulinemia. The levels of immunoglobulins reported previously in this categories showed a range from 0 to 600 mg/ml, which are somewhat higher than the congenital agammaglobulinemia. Three classes of immunoglobulins, IgA, IgG and IgM, are usually low or deficient. Our case showed 380 mg/100 ml associated with unbalancedly low IgM along with the decreased concentrations of IgG and IgA.

Clinical manifestations of this categories include chronic recurrent respiratory infections, sprue like symp-

toms, splenomegaly, the frequent associations of connective tissue diseases such as rheumatoid arthritis(5,14,15), dermatomyositis(16), PSS, Lupus erythematosus, autoimmune hemolytic anemia(17), etc., the association of thymoma, or the absence of germinal center and the absence of plasma cells in the lymph nodes. Genetic deficiency in the mesenchymal tissues, both the connective tissues and the reticuloendothelial system, as Good(2) speculated, is assumed to be possibly present in the present case as well as in the reported cases above mentioned.

To the best of our knowledge, however, there has been no report of the association of Behçet disease. Behçet disease is considered as a disorder of mesenchymal origin, and of connective tissues i.e. eye, oral membrane, genital organ, skin, joint, gastrointestinal, nervous and vascular systems. Background immunologic abberations present in this case such as hypogammaglobulinemia and impaired responses to antigenic stimuli can be closely related to the pathogenesis of Behçet disease at the age of 7.

Fudenberg(18) suggested that adult onset agammaglobulinemia are genetically determined and cellular immunity, although often normal in the course of the disease, eventually becomes defective as measured by skin tests. This may be relevant to this case, since a good response to DNCB sensitization at the age of 15, but some evidences of T-cell defects at the age of 27.

Recent developments in immunology have opened new area of T-cell subsets, functions and their significances. Abnormalities of T-cell subsets, in Behçet disease(19-21).

It is noteworthy that symptoms of Behçet disease in this case appeared with B-cell deficiency possibly without T-cell defects. This case may also provide an information in cosideration of the pathogenesis of Behçet disease.

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