A Case Report of the Immunodysplasia Syndrome and Heavy Chain Disease Associated with Subacute Bacterial Endocarditis

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KUROYANAGI, T., KURA, K., AKAMATSU, Y. and ARAO, T. *A Case Report of the Immunodysplasia Syndrome and Heavy Chain Disease Associated with Subacute Bacterial Endocarditis.* Tohoku J. exp. Med., 1979, 128 (4), 325-331 — A 36-year-old man was admitted to Saitama Medical School Hospital because of a remittent fever which had continued for approximately 6 months, hepatosplenomegaly and lymphadenopathy. He had direct Coombs' test positive autoimmune hemolytic anemia associated with subacute bacterial endocarditis (SBE). The lymphnode demonstrated focal diffuse proliferation of immunoblasts and arborizing vessels with a few small germinal centers, which resembled histological features of the immunoblastic lymphadenopathy. The immunochemical analysis revealed the presence of free IgG Fc fragments in serum. From the above results the patient was diagnosed as immunodysplasia syndrome (IDS) and heavy chain disease (HCD) associated with SBE. It was suggested that the chronic antigenic stimulation due to SBE might have some role in the mechanism of the development of the IDS and HCD in our patient. — subacute bacterial endocarditis; immunoblastic lymphadenopathy; immunodysplasia syndrome; heavy chain disease; chronic antigenic stimulation

There are some patients who have the antibiotics resistant and steroid sensitive fever, migrating arthralgia, Raynaud's phenomenon, accelerated blood sedimentation rate, hypergammaglobulinemia, etc. These patients are suspected clinically to have so-called collagen diseases without the definite classification and usually diagnosed as hypersensitivity syndrome. The patients demonstrate the presence of various autoantibodies, generalized lymphadenopathy and hepatosplenomegaly. The lymphadenopathy shows pathohistological findings similar to those of the angioimmunoblastic lymphadenopathy with dysproteinemia (ALID) (Frizzera et al. 1974; Puzanski et al. 1976) and the immunoblastic lymphadenopathy (IBL) (Lukes and Lindle 1975; Kreisler et al. 1977) or partial nodular type lesions with diffuse interfollicular proliferation of immunoblasts. We have proposed to call this syndrome the immunodysplasia syndrome (IDS) since 1967 (Kuroyanagi et al. 1967). The lymphadenopathy of IDS is not the malignant lymphoma but the dysplastic proliferation of B cells associated with a decrease of suppressor T cells (Kuroyanagi 1977).

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The heavy chain diseases (HCD) are characterized by the malignant proliferation of immunoglobulin producing cells and the concomitant synthesis of M proteins, which have the immunochemical characteristics of incomplete heavy chain. The abnormal cells are predominantly lymphocytes or plasma cells (Osserman and Takatsuki 1964; Franklin 1970; Tsuji 1970; Frangione and Franklin 1973).

Recently we have had a patient who had subacute bacterial endocarditis and later developed IDS associated with HCD.

CASE REPORT

The patient, a 36-year-old man, was admitted to the Saitama Medical School Hospital because of fever, headache and general fatigue in February 1976. He had been quite well until August 1975, when he experienced the general fatigue, recurrent headache, muscle pain, muscle weakness and remittent fever. In October 1975 he complained of night perspiration and the dull pain in the left lower abdominal quadrant and in the left supraclavicular region. He was referred to the Ogawa Red Cross Hospital and suspected to have a collagen disease. During the admission to the Ogawa Red Cross Hospital he experienced the biopsy of the left inguinal lymph node without any definite diagnosis. There were no signs of photosensitivity, morning stiffness, joint pain or skin rash during the course of the present illness.

The past and familial histories were unremarkable.

The physical examination at the time of admission revealed the temperature of 38.5°C, pulse rate 102/min and regular, the blood pressure of 114/50 mmHg, and small, shotty left and right inguinal lymphadenopathies. The limit of cardiac dullness was within normal limits with Levine III systolic murmur at the apex. The percussion and auscultation of the lung revealed no abnormalities. The liver was felt 4 cm below the right costal margin and the spleen was felt 1 cm below the left costal margin. The kidney was not palpated. There was no abnormality of the nervous system.

The laboratory data at the time of admission were as follows: The urinalysis disclosed a slight proteinuria and a microscopic hematuria without any casts. The hemoglobin level was 8.9 g/100 ml, hematocrit 25%, red blood cell counts $275 \times 10^4/\text{mm}^3$ with 5.8% reticulocytes, white blood cell counts $4800/\text{mm}^3$ with 3% band form neutrophils, 35% polymorphonuclear neutrophils, 1% eosinophils, 2% monocytes and 59% lymphocytes. The bleeding time was 2 min 30 sec and the coagulation time 9 min. TEG was within normal limits. The bone marrow picture was as follows: 1% myeloblasts, 1.8% promyelocytes, 4.8% myelocytes, 11.2% metamyelocyte, 20% bandform neutrophils, 3.8% polymorphonuclear neutrophils, 2.4% eosinophils, 0.4% basophils, 6% lymphocytes, 7.5% monocytes, 0.6% proerythroblasts, 47.6% erythroblasts and M/E ratio was 0.9.

The serum copper level was 146 $\mu\text{g}/100$ ml, serum iron 57 $\mu\text{g}/100$ ml and total iron binding capacity 285 $\mu\text{g}/100$ ml. Electrolytes were within normal limits. GOT was 73 U/ml, GPT 48 U/ml, LDH 224 U/ml, total bilirubin 0.8 mg/100 ml,

TTT 9.7, ZTT 25, ChE (4PH) 0.3, CPK 11 U/ml and aldolase 8.4 U/ml. The creatinine level was 0.8 mg/100 ml, uric acid 5.6 mg/100 ml, BUN 15 mg/100 ml and total cholesterol 120 mg/100 ml. The kidney function test was within normal limits. The blood sedimentation rate was 122 mm/hr. Total serum protein was 9.4 g/100 ml with 45.1% albumin, 4.3% α_1 -globulin, 3.7% α_2 -globulin, 5.4% β -globulin and 41.3% γ -globulin. The ASLO titer was 12 U/ml, CRP six positive, cold agglutinins $\times 128$, anti-toxoplasma antibodies $< \times 128$, serological test for syphilis negative, anti-thyroglobulin and anti-microsome antibodies negative, RA test three positive, direct Combs test positive, anti-platelet antibodies positive, CH₅₀ 28 U, β_1 C/ β_1 A globulin 55 mg/100 ml, β_1 E globulin 38 mg/100 ml.

Both the Mantoux reaction and the DNCB skin reaction were negative. Repeated arterial blood cultures were negative.

The PHA blastoid transformation of peripheral lymphocytes was 19.2%. The population of lymphocytes was as follows: E rosette forming cells 29.2% and EAC rosette forming cells 30%.

Although his repeated blood cultures were negative, he was suspected to have subacute bacterial endocarditis and the administration of daily 20 g of sulbenicillin and daily 40 mg of gentamycin was instituted.

Three weeks later his remittent fever declined to normal and remained afebril. However, the blood sedimentation rate remained to be elevated in spite of a marked improvement of CRP. Six weeks after the admission he suddenly developed the left facialis palsy and the right hemiparesis with the dysarthry. On April 27, 1976 he became suddenly unconscious due to the subarachnoidal bleeding and died.

At post mortem examination, the heart weighed 420 g and the endocarditis verrucosa was present. The liver weighed 2400 g and demonstrated a mild

Fig. 1. Histology of the inguinal lymphnode. H-E stained.

infiltration of plasma cells, lymphocytes and neutrophils in portal canals. The spleen weighed 750 g and had multiple abscesses. A moderate enlargement of Malpighian bodies with hypertrophy of germinal centers was present. Germinal centers demonstrated an increase of somewhat atypical mononuclear cells. The majority of lymphocytes around germinal centers were immunoblasts. There was a marked increase of plasma cells in the red pulp in association with the hyperplasia of sinusoid. Lymphnodes demonstrated the focal diffuse proliferation of arborizing small vessels, immunoblasts and plasma cells with a few small germinal centers (Fig. 1).

There was a mild pulmonary emphysema. The kidney showed cloudy swelling and congestion with a mild infiltration of plasma cells and lymphocytes in the interstitium. Hemorrhages measuring 0.5×0.6 cm were found in the left thalamus. There was a moderate subarachnoidal hemorrhage due to the rupture of a branch of the left cerebral artery.

Fig. 2. Immunoelectrophoretic pattern of serum. PS, patient's serum; AHWS, anti-human whole serum antibodies; NS, normal serum.

Fig. 3. Immunoelectrophoresis of patient's urinary proteins. PU, patient's urinary protein; NS, normal serum; AHWS, anti-human whole serum antibodies.

STUDIES ON IMMUNOGLOBULINS

The immunoelectrophoretic examination of serum revealed a marked increase of IgG and the formation of double precipitation lines of IgG (Fig. 2). The IgG level was 5480 mg/100 ml, IgA 267 mg/100ml, IgM 267 mg/100 ml, and IgG 0.8 mg/100 ml. K/L ratio of IgG was 1.09 (normal 1.16~1.34).

The immunoelectrophoretic examination of urinary protein revealed the presence of the double precipitation lines in the IgG area. The outer precipitation line reacted with anti- κ and anti- λ antibodies and the inner line reacted with anti-IgG but not with anti-IgA, anti- κ and anti- λ antibodies (Fig. 3).

Fig. 4. Sephadex G 200 gel filtration of patient's IgG fractionated by DEAE cellulose column-chromatography.

Fig. 5. Immunoelectrophoretic pattern of the peak II of Sephadex G 200 gel filtration of patient's IgG. Fc, Fc fragment of normal IgG; PS, peak II of gel filtration of patient's IgG; A-Fc, anti-Fc antibodies; A-Fab, anti-Fab antibodies; A-IgG, anti-IgG antibodies.

From the above results the presence of free Fc fragments in the patient's serum was suspected and the Sephadex G 200 gel filtration of IgG fractionated by DEAE cellulose column-chromatography was carried out. As shown in Fig. 4, there were two peaks. The first peak was IgG. The second peak reacted with anti-Fc antibodies but not with anti-Fab antibodies, as shown in Fig. 5.

COMMENT

It seems likely that the onset of the patient's present illness was August 1975 when he complained of fever, headache and general fatigue and since then the patient remained febrile for a long period without any definite diagnosis and the proper treatment. On the admission to the Saitama Medical School Hospital it was found that he had had subacute bacterial endocarditis. He died of cerebral vascular accidents, although he became afebrile by the treatment with sulbenicillin and gentamycin.

The patient had symptoms and signs of the IDS such as the hypergammaglobulinemia, positive RA test, direct Coombs' test positive autoimmune hemolytic anemia, hepatosplenomegaly and lymphadenopathy resembling AILD. The immunochemical examinations of serum revealed the coexistence of the free IgG Fc fragments and the residual IgG.

From these results the patient was considered to have IDS and HCD associated with SBE.

The AILD usually shows the diffuse type proliferation of lymphoid cells in lymphnodes. Lymphnodes of our patient demonstrated a focal diffuse type proliferation of immunoblasts and plasma cells with a few small germinal centers. However, it was reported that the nodular type proliferation might be found in the course of the AILD (Frizzera et al. 1975).

The proliferating lymphocytes in the IDS lymphnodes are predominantly B cells with a marked decrease of suppressor T cells (Kuroyanagi 1977). Lymphnode B cells of IDS are resistant to the regulation of suppressor T cells. It seems likely that the lymphadenopathy of IDS is the dysplasia of B cells and the decrease of suppressor T cells plays a role in the mechanism of autoimmune phenomenon in IDS.

The pathogenesis of IDS remains still to be clarified.

Previously we have pointed out that there are usually the chronic delayed sensitization due to chronic inflammations and the decreased cell-mediated immunity in patients with IDS. The chronic delayed sensitization due to SBE might play a role in the mechanism of the dysplasia of B cells and of the decrease of suppressor T cells in our patient, resulting in IDS.

It is generally accepted that HCD is a malignant neoplastic proliferation of immunoglobulin synthesizing cells. IDS is not a malignant neoplastic proliferation of the immunocyte system. Our patient had HCD associated with IDS without any malignant neoplastic proliferation of immunoglobulin synthesizing cells. Zawadzki et al. (1969) reported a case of rheumatoid arthritis terminating

in heavy chain disease. He suggested that HCD might be caused by chronic antigenic stimulations due to chronic inflammation. It seems likely that the HCD of our patient might be induced by the dysplasia of B cells which resulted from a chronic antigenic stimulation due to SBE.

References

- 1) Frangione, B. & Franklin, E.C. (1973) Heavy chain diseases: clinical features and molecular significance of the disordered immunoglobulin structure. *Seminar Hemat.*, **10**, 53-76.
 - 2) Franklin, E.C. (1970) Heavy chain diseases. *New Engl. J. Med.*, **282**, 1098-1099.
 - 3) Frizzera, G., Moran, E.M. & Rappaport, H. (1974) Angioimmunoblastic lymphadenopathy with dysproteinemia. *Lancet*, **1**, 1070-1073.
 - 4) Frizzera, G., Moran, E.M. & Rappaport, H. (1975) Angioimmunoblastic lymphadenopathy. Diagnosis and clinical course. *Amer. J. Med.*, **59**, 803-818.
 - 5) Kreisler, J.M., Moreno, E., Bootello, A., Bobza, A. & Martinez de Letona, J. (1977) Immunological findings in immunoblastic lymphadenopathy. A detailed study. *Clin. exp. Immunol.*, **27**, 497-501.
 - 6) Kuroyanagi, T., Kurashina, S. & Kimura, K. (1967) Immunodysplasia syndrome. *Jap. med. J.*, No. 2195, 3-10. (Japanese)
 - 7) Kuroyanagi, T. (1977) Autoimmune disease. *J. Saitama med. Sch.*, **4**, 349-363.
 - 8) Lukes, R.J. & Tindle, B.H. (1975) Immunoblastic lymphadenopathy. A hyper-immune entity resembling Hodgkin's disease. *New Engl. J. Med.*, **35**, 351-373.
 - 9) Osserman, E.F. & Takatsuki, K. (1964) Clinical and immunochemical studies of four cases of heavy (H) chain disease. *Amer. J. Med.*, **35**, 351-373.
 - 10) Pruzanski, W., Sutton, D.M.C. & Pantalony, D. (1976) Angioimmunoblastic lymphadenopathy: an immunochemical study. *Clin. Immunol. Immunopath.*, **6**, 62-76.
 - 11) Tsuji, T. (1970) Heavy-chain (Fc fragment) disease. Immunological reactions of the first case in Japan and the incorporation of ^{14}C -amino acids into the protein in vitro. *Acta haemat. jap.*, **33**, 89-97.
 - 12) Zawadzki, Z.A., Benedek, T.G., Fin, D. & Eaton, J.M. (1969) Rheumatoid arthritis terminating in heavy chain disease. *Ann. intern. Med.*, **70**, 335-347.
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