A Case of Selective IgM Deficiency: Isotype-specific Suppressor T Lymphocytes

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A case of selective IgM deficiency with giant leiomyoma of the stomach in a 66-year-old male is reported. Peripheral blood mononuclear cells from the patient synthesized only a small amount of IgM in the presence of pokeweed mitogen (PWM) in vitro. Co-culture of counterpart lymphocytes from the patient and a disease-free individual revealed that increased activity of IgM-specific suppressor T lymphocytes led to a IgM deficiency in this case.

Key Words: Isotype-specific suppressor factor, Cell-surface immunoglobulins, Immunodeficiency, Leiomyoma, Selective IgM deficiency

Among the humoral immunodeficiencies, selective IgM deficiency is a relatively rare disorder, and there have been few assessments of the functional analysis of the peripheral lymphocytes for IgM synthesis. We now report a case with selective IgM deficiency accompanied with giant leiomyoma of the stomach. Increased activity of IgM-specific suppressor T lymphocytes was demonstrated in this case.

CASE REPORT

A 66-year-old Japanese man was admitted to our hospital in February 1982, because of epigastric discomfort of two months duration. Diabetes mellitus and hypertension were diagnosed when he was 51 years old and had been well-controlled by diet alone. He had no history of recurrent infection and there were no family members with immunodeficiency diseases or who died young. Physical examination showed a mass (12 x 10 cm) with an irregular surface in the epigastrium. There was no lymph node palpable in the cervix and axilla. The urinalysis was normal and no occult blood was noted in the stoll. Hb was 16.4 g/dl, WBC 6900 x 10^9/l with 35% lymphocytes and the platelet 190 x 10^9/l. The total serum protein was 6.7 g/dl, with albumin 63% and γ-globulin 11.3%. BUN was 16 mg/dl, GOT 31 U/l, LDH 160 U/l, total bilirubin 1.0 mg/dl, cholesterol 210 mg/dl, FBS 110 mg/dl, α-FP 2.6 ng/ml and CEA 3.0 ng/ml. CRP was 1+. The serum immunoglobulins measured by a Laser Nephelometer revealed IgG 850, IgA 253 and IgM 8 mg/dl. PPD skin testing was 16 x 18 mm. Lymphocytes were quantitated by immunofluorescence using FITC-conjugated heavy chain specific antihuman IgG, IgA and IgM goat antisera. Peripheral blood mononuclear cells examined by this technique showed sufficient amount of B cells with surface IgM (71%). An upper G.I. series revealed pressured lesser curvature of the stomach by a large submucosal or extrinsic mass. Histological examination of the specimen obtained by peroral gastric biopsy revealed a leiomyoma. Further examinations were performed before operation, since the neoplasm was too huge to be definitely diagnosed as benign. However, no evidence of metastasis was obtained by chest
X-ray films, abdominal echogram, liver scintigram, Ga scintigram, bone scintigram, cealiac angiography and CT scan. Cealiac angiography revealed a large mass richly supplied with blood vessels, mainly from the left gastric artery. Subtotal gastrectomy was performed on March 3, 1982, and a large mass (20 × 15 × 15 cm) was completely resected. The specimen was a leiomyoma as diagnosed by preoperative biopsy. No specific fluorescence was demonstrated on and in the neoplastic cells by immunofluorescence staining with fluorescein-labeled antihuman IgG, IgA and IgM. Subsequently, the patient has been well during follow-up for five months after operation. The serum IgM was 17 mg/dl right after operation, and 18 mg/dl 23 weeks after operation.

Measurement of immunoglobulin synthesis by peripheral lymphocytes in vitro

Mononuclear cells were separated from heparinized venous blood of the patient or from a normal donor by density sedimentation of Ficoll-Conray. For the separation of T and B cells, the neuraminidase treated sheep erythrocytes rosette formation method was used. T or B lymphocytes (5 × 10^5 cells/ml) from the patient were co-cultured in duplicate with counterpart lymphocytes from a healthy donor in RPMI 1640 in the presence of 10% FCS and PWM, at 37 °C for 7 days in a humidified atmosphere of 5% CO2 and air. The rate of macrophages contained in B-lymphocyte fraction was uniform in every culture. Each class of immunoglobulins (Ig) secreted in the culture media were radioimmunoassayed using the solid phase method. In order to selectively inactivate suppressor function, T cell suspensions (5 × 10^5 cells/ml) in plastic tubes were irradiated with X-ray in a total dose of 2000 rads. As shown in Table 1, T and B cells from the healthy donor synthesized sufficient amounts of IgG, IgA and IgM (NB + NT) in this culture. Culture of T and B cells from the patient resulted in the synthesis of usual amounts of IgG and IgA, while only a small amount of IgM was synthesized (PB + PT). Co-culture studies with counterpart lymphocytes from the patient and the normal donor revealed that IgM synthesis was reduced in the combination of normal B cells and the patient’s T cells (NB + PT). Furthermore, normal amounts of IgM were synthesized when T lymphocytes from the patient were irradiated (NB + *PT and PB + *PT).

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PWM induced Ig synthesis by lymphocytes from a healthy donor and the patient. B or T cells were co-cultured with counterpart lymphocytes for 7 days in duplicates and Ig secreted in the culture media were measured by solid phase radioimmunoassay. All data are expressed in terms of nanogram per ml per 5 × 10^6 cells.

DISCUSSION

Selective IgM deficiency is a relatively rare disorder, the reportedly being less than 0.03% in a community health study. Both the lack of susceptibility to infection in earlier years and a negative family history may support the idea that the selective IgM deficiency in our patient was acquired. Despite the low serum IgM level, a sufficient number of B lymphocytes with surface IgM was demonstrated in the peripheral lymphocytes. The presence of surface IgM-bearing lymphocytes in patients with selective IgM deficiency have been reported. This finding suggests that terminal differentiation of immature IgM lymphocytes into IgM-secreting cells is impaired. A similar impairment in the pathway of sequential differentiation of lymphocytes was usually observed in patients with selective IgA deficiency. Furthermore, the role of suppressor cells have been advocated by the co-culture experiment with whole mononuclear cells both in selective IgA and IgM deficiency. In this case, the pathogenesis of selective IgM deficiency was attributed.
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to the reduced synthesis of IgM, and the study of functional assessment of subpopulation of lymphocytes disclosed the increased activity of IgM-specific suppressor T lymphocytes.

No definite explanation could be made as to why suppression of IgM synthesis is approximately 6 times greater in PB + PT than in NB + PT. One possible explanation is that the patient also has abnormal B cell function, however it does not seem to be essential because PB + NT produces normal amount of IgM. The other possible explanation is that the suppressive effect is greater in a syngeneic system than in allogeneic one.

The case is also unique in that giant leiomyoma of the stomach co-existed with a selective IgM deficiency. Decreased serum IgM has been reported in association with specific neoplasms, e.g., carcinoma of th stomach, malignant lymphoma\textsuperscript{10} and carcinoma of the ovary\textsuperscript{11}. Furthermore, suppressive activity on IgM production was reported in the cultured supernates of the lymphocytes from cancer patients\textsuperscript{12}, and the decrease of serum IgM was also observed when tumors were rapidly expanding\textsuperscript{13}. Taking into account the finding that the serum IgM level did not change after removal of the tumor in this case, it appears unlikely that IgM deficiency was induced directly by the development of leiomyoma. However, the possibility exists that the deficiency of IgM or the IgM-specific suppressor T lymphocytes worked in some way to facilitate the tumor growth\textsuperscript{12}.

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REFERENCES