Immunoglobulin Class Switch From IgG to IgA in a Patient With Smoldering Multiple Myeloma

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Serum of a 67-year-old male patient with smoldering multiple myeloma was shown to contain two monoclonal immunoglobulins, IgG and IgA. For the initial seven months, monoclonal IgG was predominantly elevated. During the next one year and eight months, however, serum concentration of the monoclonal IgA increased, with a concomitant decrease of IgG. N-terminal amino acid sequences of heavy and light chains separated from monoclonal IgG and IgA were analyzed. Both light chains were λ-type and showed identical amino acid sequences of variable regions. The heavy chains also had the same N-terminal amino acid sequence between IgG and IgA. These results strongly suggest that two monoclonal proteins, IgG and IgA, in this patient were produced by B lymphocytes within a clone and that class switch from IgG to IgA in immunoglobulin production during B cell differentiation has taken place in the clinical course of this case.

CASE REPORT

A 67-year-old male was noticed to have a bronchiectasia complicated with a monoclonal hypergammmaglobulinemia in May 1975 at a local hospital. A single peak of serum monoclonal immunoglobulin was demonstrated on theγ-region of cellulose-acetate electrophoresis and IgG was over 3,000 mg/dL. In May 1977, IgG was 3,700 mg/dL and IgA was 1,900 mg/dL. The patient gradually developed dullness of the head and pain in distal parts of extremities and was admitted to the Niigata Shimin Hospital on Oct 7, 1977. Physical examination revealed the enlargement of several inguinal lymph nodes and rales in the lung fields. No hepatosplenomegaly was observed. The hemoglobin level was 8.5 g/dL, white blood cell counts 5,800/μL, and platelet counts 277 x 10⁵/μL. Bone marrow aspiration revealed that plasma cells increased to 6.2% of nucleated cells. The total serum protein was 13.0 g/dL, and two separate peaks of monoclonal components were demonstrated first on theβ-region of cellulose-acetate electrophoresis. Serum IgG was 11,480 mg/dL, IgA 3,600 mg/dL, and IgM 92 mg/dL. Immunoelectrophoresis showed that two monoclonal components were IgG-λ and IgA-λ. Pyroglobulin was present in the serum.

Renal dysfunction was noticed, but there were no abnormal findings on a generalized bone survey. Histologic examination of the inguinal lymph node biopsy specimen showed diffuse infiltration of lymphocytes and plasma cells. The disease was diagnosed as multiple myeloma and treated with low doses of cyclophosphamide at first, because of hyperviscosity syndrome. However, leukocytopenia due to cyclophosphamide administration had developed, and then only plasmapheresis was performed. There was no sign of deterioration of multiple myeloma during the patient’s course. He died of sepsis on Sept 19, 1979. On his admission, monoclonal IgG was remarkably greater than monoclonal IgA, but the reverse of two immunoglobulin values occurred in February 1978, and IgA increased gradually with concomitant decrease of IgG. IgG was 1,240 mg/dL and IgA was 10,080 mg/dL in April 1979 (Fig 1).

MATERIALS AND METHODS

Two monoclonal components in this patient, IgG and IgA, were isolated from the plasma of their predominant phase by a combination of ammonium sulfate precipitation (33% saturation), diethyl aminoethyl (DEAE)-cellulose (sodium phosphate buffer, pH 8.0), and DEAE-Sephadex (Tris-HCl buffer, pH 8.0) chromatography. The purity of isolated proteins was checked by polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate and double immunodiffusion with specific antisera.

Purified IgG (or IgA) (150 mg) was completely reduced and alkylated by the method of Wadall and Konigsberg. The H- and
L-chains were separated by gel filtration on Sephadex G-200 (2.5 x 95.0 cm) in 5 mol/L guanidine-HCl/1 mol/L acetic acid.

The N-terminal amino acid residue was determined by Edman's method. Before the sequence analysis, H-chain peptides from IgG and IgA were digested with pyroglutamate aminopeptidase (from calf liver; Boehringer Manheim, Mannheim, FRG) by the method of Podell and Abraham. Automated Edman degradation was carried out in a JEOL JAS-47K sequence analyzer (0.5 mol/L Quadrol program; JEOL, Tokyo). Phenylthiohydantoin derivatives were identified by thin-layer chromatography and the back hydrolysis method.

RESULTS

Amino-terminal sequence analysis. Both L-chains obtained from IgG and IgA, designated \( \lambda_\gamma \) and \( \lambda_\alpha \)-chains, respectively, had only tyrosine as the N-terminal residue. Because no amino acid was detected by the Edman degradation of both H-chains obtained from IgG and IgA, designated \( \gamma \)- and \( \alpha \)-chains, respectively, these peptides were treated with pyroglutamate aminopeptidase to remove the N-terminal pyrrolidone carboxylic acid. Table 1 shows the results of the N-terminal amino acid sequence analyses. The N-terminal sequence of \( \gamma \)-chain was identical with that of \( \alpha \)-chain. The sequences of \( \lambda_\gamma \) and \( \lambda_\alpha \)-chains were also identical.

When these N-terminal sequences were compared with other known sequences of the V-regions of H- and \( \lambda \)-chains, the V-regions of H- and \( \lambda \)-chains in this patient were found to belong to \( V_H \) III and \( V_\lambda \) III subgroups, respectively (the subgrouping is based on a classification by Kabat and Wu).
IgM to IgG and IgA during clonal expansion of antigen-stimulated B cells.

The concept of intraclonal class switch was perfectly compatible to an allelic deletion model for mouse VH-CH gene recombination. Recently, the entire region of mouse CH gene family was cloned by Shimizu et al. The organization of which was shown as C γ 2-C γ 3-C γ 1-C γ 5-C γ 4-C γ 6-C γ 7-C γ 9-C γ 8-C γ 10. As to the human study, CH genes were identified on chromosome 14q32 in the order of μ, δ, γ, γ, ψ, α1, ψ, γ, γ, ψ, and α2. These results indicate that during differentiation of a single B lymphocyte, a given VH gene is first expressed in combination with the CH gene and then expressed with a different CH gene in the order described earlier.

The patient described here was observed to have monoclonal protein of IgG more than two years before admission to the hospital and then showed remarkable double monoclonal immunoglobulins on admission. They were identified as IgGk and IgGλ by immunoelectrophoresis. IgG was extremely more predominant than IgA in October 1977. However, the IgG value declined progressively during his clinical course. In contrast, IgA value kept increasing through his terminal stage, with crossing IgG in February 1978. The amino acid sequence analysis of variable regions in H- and L-chains from the patient's monoclonal IgG and IgA has been performed. The N-terminal amino acid sequence of γ-chain of IgG predominant phase was identical with that of α-chain of IgA predominant phase. In addition, the N-terminal sequences of λc and λa-chains were also identical. These results suggest that the variable regions of H-chains and the L-chains of IgG and IgA, respectively, are identical, which gives us a strong evidence that IgG and IgA were derived from a common clonal immunoglobulin-producing cell lineage. These results, together with the clinical finding that IgA in the patient plasma increased with a concomitant decrease of IgG, give enough evidence to conclude that neoplastic B lymphocytes within a clone in this case have undergone a class switch in CH gene expression from γ to α with cell differentiation in vivo. This is a novel case of myeloma in which an immunoglobulin class switch from IgG to IgA was observed during the clinical course.

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