Biclonal IgA and IgM Gammopathy in Lymphocytic Lymphoma

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We report the case of a 76-year-old white man with a diffuse, well-differentiated lymphocytic lymphoma at the base of his tongue. Although serum electrophoresis, immunoelectrophoresis, and immunofixation showed he had a biclonal IgA kappa and IgM kappa gammopathy, biopsy of the tumor showed a positive immunoperoxidase reaction only for IgM kappa. The biclonal pattern persisted after chemotherapy, despite shrinkage of the tumor mass. The association of IgA and IgM appears to be the least frequent combination of separate biclonal immunoglobulins, the clinical course of such patients being more often that of lymphoma or macroglobulinemia than of myeloma. However, the symptomatology can be highly variable, as our case uniquely demonstrates.

Additional Keyphrases: electrophoresis · immunoelectrophoresis · immunofixation · polyclonal gammopathy · immunoglobulins

In patients with biclonal gammopathies, the association of IgA and IgM appears to be the least frequent combination of all previously reported combinations of separate immunoglobulins. Although the clinical features of biclonal gammopathy are more often those of macroglobulinemia or lymphoma than of myeloma, they can be highly variable and confusing (1). Early laboratory diagnosis can be of great importance in the treatment and prognosis of this disease (2).

We report the occurrence of IgA and IgM paraproteins in a patient with lymphocytic lymphoma, whose only clinical manifestation was a painless pharyngeal mass.

Case History

R. D., a white, 76-year-old jeweller, first consulted his physician in October 1981, complaining of a lump at the back of his tongue. Results of the initial biopsy were non-conclusive, but he continued to complain of sore throats and increasing dysphagia. The diagnosis was delayed when three scheduled repeat biopsies were cancelled because of a prolonged bleeding time, the patient's refusal, and the inability to pass an endotracheal tube because of the mass. When refusing a biopsy, the patient proceeded to treat himself by going on a strict diet, including prolonged fasting. A successful biopsy, finally obtained in February 1983, showed a well-differentiated lymphocytic infiltrate consistent with a diffuse, well-differentiated lymphocytic lymphoma.

The patient's past medical history included a chronic duodenal ulcer, an adenomatous colonic polyp, old rheumatoid arthritis, and iron-deficiency anemia. Physical examination revealed no peripheral lymphadenopathy. Direct laryngoscopy showed a smooth 3–4 cm swelling of the epiglottic region involving part of the base of the tongue without signs of inflammation. The prostate was enlarged and the remainder of the physical examination was unremarkable.

Laboratory data obtained shortly after the biopsy (March 1983) indicated anemia: hemoglobin 104 g/L, hematocrit 31.6%, erythrocyte count 3.59 × 10¹²/L, and mean cell volume 88 fl. The leukocyte count was 6.0 × 10⁹/L with a lymphocytosis of 71%, including a few atypical forms, 25% polymorphonuclear leukocytes, 3% monocytes, and 1% eosinophils. Activated partial thromboplastin time was prolonged at 38 s. Stool was repeatedly negative for occult blood. Urinalysis was remarkable for trace protein, large amount of ketones, and five to 10 hyaline casts. The ketonuria was probably related to the patient's strict diet and fasting.

Abnormal findings in serum included above-normal urea nitrogen (260 mg/L; normal range 90–250) and low iron concentration (350 μg/L; normal 420–1350). Total protein was 71 g/L, albumin 43.7 g/L. Electrophoresis of serum on cellulose acetate revealed a double-peak gamma-globulin fraction on two occasions (Figure 1). Immunoglobulin quantification by nephelometry revealed a biclonal paraproteinemia with dysproteinemia: IgG 4.1 g/L (normal 6.4–13.5); IgA 7.7 g/L (normal 0.7–3.1); IgM 20.6 g/L (normal 0.8–5.0). Immunoelectrophoresis showed that both IgA and IgM were apparently of the kappa light-chain type (Figure 2).

Electrophoresis of urinary protein revealed a monoclonal spike in the gamma region that consisted of kappa light chains, as shown by immunoelectrophoresis. Histochemical stains with immunoperoxidase on sections of the original biopsy showed the tissue to be strongly positive for IgM and kappa light chains and negative for IgG, IgA, and lambda light chains. Repeating the electrophoresis in April 1984 after chemotherapy showed that the double peak in the gamma region had persisted, with IgG 3.4 g/L, IgA 4.3 g/L, and IgM 12.4 g/L. Repeat immunoelectrophoresis showed persistent biclonal IgA and IgM kappa. Immunofixation again confirmed the identity of the two paraproteins as IgA and IgM kappa (Figure 3).

We did not perform T and B lymphocyte immunofixation studies, nor did we ultracentrifuge for Ig subunits. Radiolog-

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Fig. 1. Densitometric trace of cellulose acetate electrophoresis of patient's serum
ical studies, which included a computerized tomography scan of the neck, showed a large mass involving the base of the tongue and the epiglottis, extending into the left pharyngeal wall, with evidence of bilateral lymph node enlargement. Bone scan revealed no significant abnormality. Examination of the upper gastrointestinal tract demonstrated chronic duodenal ulcers, and the small bowel had small rounded defects in the proximal jejunum, possibly representing lymphoid hyperplasia. Results of liver and spleen scans were normal. Bone-marrow biopsy and aspirate showed no infiltrate or lymphocytic aggregates.

The patient was treated with four cycles of cyclophosphamide, vincristine, and prednisone, to which he responded well: the tumor mass shrank and his ability to swallow improved markedly. He had no constitutional symptoms, such as fever, night sweats, or weight loss, and displayed no particular manifestations of multiple myeloma or macroglobulinemia, such as bone pain or hyperviscosity syndrome. A prostatic adenocarcinoma was diagnosed in March 1984.

Discussion

Although they are increasingly recognized, biclonal gammopathies remain an unusual finding. In a review of 1906 paraproteinemias, Ritchie and Case (3) found only 104 (5.4%) to be biclonal. Of these, three were IgA and IgM. Kyle et al. (I) reviewed 57 patients with biclonal gammopathy, of which three were IgA and IgM, and indicated that this was an unusual combination, ranking well behind combinations of immunoglobulins G and M, G and A, or G and G in frequency. These authors (I) divided their biclonal gammo-

Fig. 2. Serum protein immunoelectrophoretograms
C, control; P, patient

Fig. 3. Immunofixation of serum protein
Note the presence of two monoclonal bands, in the IgA and IgM lane, both kappa type

pathies into three clinical categories: myeloma or plasmacytoma (16%), lymphoproliferative disorders (19%), and biclonal gammopathy of undetermined significance (65%). Our patient falls into the lymphoproliferative category, which includes well-differentiated and poorly differentiated lymphocytic lymphoma, macroglobulinemia, and chronic lymphocytic leukemia, accounting for two of the three cases of combined IgA and IgM of Kyle et al. An earlier case of IgA and M biclonal paraproteinemia in lymphocytic lymphoma was described by Tormey et al. (4). Prauzner et al. (5) reported four cases of "macroglobulinemia-myeloma" with variable clinical symptomatology; one of these was IgA and IgM biclonal gammopathy and was diagnosed as "lymphosarcoma" by lymph node biopsy.

The histochemical detection of strong IgM kappa by immunoperoxidase only on the lymphoma biopsy is evidence for at least IgM kappa production at that time in that site. The absence of IgA kappa response to immunoperoxidase at the time when this class of immunoglobulin was noted in the serum raises the possibility that the clonal IgA kappa component was being produced in a different part of the pharyngeal tumor, or even in some more-distant site at that time. Rheumatoid arthritis can be a source of monoclonal immunoglobulins, but this was unlikely with this patient, whose arthritis was inactive. The possible role of the co-existing prostatic carcinoma remains uncertain. One of the patients of Kyle et al. with biclonal gammopathy had a prostatic carcinoma (I), but this appears to be an incidental association, because this tumor is not unusual in men of this age. Although production of monoclonal immunoglobulins has been associated with many different types of tumors, it
has not been specifically associated with prostatic carcinoma.

Malignant cells producing biclonal immunoglobulins may originate from a common stem cell. The finding of identical heavy- and light-chain domains in the biclonal pairs (1), specific chromosomal determinants, and the presence of more than one class of immunoglobulin in lymphocytes (4) suggest a monoclonal origin of these paraproteins. Moreover, this appears to support the "genetic switch" hypothesis, whereby one cell line can switch from producing IgM to IgG, or from IgM to IgA class, with identical antigenic binding specificity.

We acknowledge the technical assistance of Thekma Oshiro and Linda Powers.

References


