Double Spike in the Electropherogram of a Myeloma Serum, from Bence Jones Protein

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Serum from a 71-year-old man with multiple myeloma complicated with renal failure showed a monoclonal IgG lambda. A second spike appearing in the serum protein electropherogram, suggesting a biclonal gammopathy, was found to be due to lambda Bence Jones protein (29.9 g/liter). Lambda Bence Jones protein was also found in smaller concentration (3.8 g/liter) in the urine. Tetramers of Bence Jones protein were not demonstrable by gel filtration and ultracentrifugation, and renal failure was probably the main reason for this very high concentration of Bence Jones protein in the serum.

Additional Keyphrases: biclonal gammopathies • M-components • gel filtration

The prevalence of multiple M-components in serum protein electropherograms is low. Of 6141 recorded cases of myelomas, only 60 (1%) have been recognized as having more than one M-component (1). These particular cases are interesting because they raise the question of whether the cells producing the abnormal globulins belong to the same or different clones. Two paraproteins found in the same patient are generally considered to be produced by different clones, hence the name diclonal (or biclonal) gammopathies (2). However, similarities in the primary structures of two abnormal globulins found in the same patient have been shown, suggesting their common origin from the same precursor cells (3).

Discussed here is a patient with multiple myeloma whose serum protein electrophoresis showed two M-components, one of which was attributable to a very high concentration of Bence Jones protein—to our knowledge, the highest yet reported.

Case History

A 71-year-old man was admitted to the Buffalo General Hospital for increasing tiredness during the previous four months. Pertinent physical findings included a right inguinal hernia, frequent premature ventricular beats, exudate on the left fundus, and flame-shaped hemorrhages in the right fundus. Laboratory studies revealed a sedimentation rate of 159 mm/h, hemoglobin 64 g/liter, hematocrit 19%, platelets 104,000/μl, blood urea nitrogen 1.67 g/liter, CO₂ 15 mmol/liter, serum potassium 6.8 mmol/liter, calcium 3.8 mmol/liter, chloride 108 mmol/liter, sodium 137 mmol/liter, creatinine 75 mg/liter, phosphate 59 mg/liter, urate 94 mg/liter (later 195 mg/liter), cholesterol 1.14 g/liter, albumin 22 g/liter, and globulins 70 g/liter. The urine had a relative density of 1.016 and gave a 1+ reaction for protein.

A bone marrow aspirate showed 59% plasma cells, most of them appearing abnormal. Serum-protein electrophoresis showed two homogeneous bands in the beta and gamma region (Figure 1). The diagnosis of multiple myeloma complicated with renal failure was made and the patient was treated with cyclophosphamide, prednisone, allopurinol, and aluminum hydroxide gel (Amphogel). He underwent peritoneal dialysis. During the hospitalization he developed herpes zoster and septicemia with hemolytic streptococcus and died about five weeks after admission.

Methods of Further Study

Serum and concentrated urine were electrophoresed in agarose gel as previously described (4). Several antisera to each immunoglobulin and to kappa and lambda light chains were obtained from Behring Diagnostics (Sommerville, N.J. 08876), Hyland (Costa Mesa, Calif. 92626), Cappel (Dowingtown, Pa. 19335), and Melloy...
Laboratories (Springfield, Va. 22151). Antisera to free kappa and lambda light chains were obtained from Behring Diagnostics and did not show any reaction in double diffusion with normal human serum. All antisera, tested for specificity, were found to be monospecific. Immunoelectrophoresis of serum and concentrated urine was performed as previously described (4). Serum concentrations of immunoglobulins G, A, and M (IgG, IgA and IgM) and of C3 and C4 components of complement were determined by radial immunodiffusion (5) with commercial plates (Melloy Laboratories). Gel filtration was performed in columns containing Sephadex G-200 and G-100 equilibrated with 0.15 mol/liter sodium chloride. Sedimentation constants were determined in a Spinco Model E ultracentrifuge at 60,000 rpm at 20 °C at 256,000 × g.

Smears of bone marrow from this patient and from other patients without multiple myeloma were dried, fixed in acetone for 10 min, rinsed with phosphate-buffered saline solution, pH 7.2, and incubated with appropriate dilutions of fluorescein isothiocyanatelabeled antisera to IgG, IgA, IgM, kappa, and lambda (Cappel and Melloy Laboratories) for direct fluorescence.

Results

Serum protein electrophoresis showed two M-components, one in the beta region (corresponding to a concentration of 29.9 g/liter) and one corresponding to 39.1 g/liter in the gamma region (Figure 1). Urinary protein electrophoresis also showed a homogeneous band in the beta region, representing 3.8 g/liter of the total urinary proteins of 4.24 g/liter (860 ml/24 h). Immunoelectrophoresis identified the beta region bands from the serum and urine as lambda Bence Jones protein and the gamma region band from the serum as IgG lambda (Figure 2). We measured serum IgG, IgA, and IgM and found 50 g/liter, 120, and 210 mg/liter, respectively; the concentration of C3 was 1.10 g/liter and of C4 200 mg/liter. Gel filtration analysis showed that the free lambda light chains were eluted in the 4S peak, suggesting that they are dimers. The ultracentrifugation gave a sedimentation constant of just less than 4, which does not indicate the presence of tetracentramers of lambda Bence Jones protein. Immunofluorescence of bone marrow showed an approximately equal number of cells stained with anti-IgG and anti-kappa sera.

Discussion

The case reported here had a serum protein electrophoregram suggesting a biclonal gammopathy. However, immunoelectrophoresis revealed that one of the electrophoretic spikes was due to Bence Jones protein, presumably secreted by the same abnormal cells that were secreting the homogeneous IgG. In very rare instances, Bence Jones protein and the monoclonal immunoglobulin are of different types; these cases representing truly biclonal gammopathies (6). Bence Jones proteins are homogeneous free light chains of immunoglobulins. The concentration of Bence Jones protein in the serum depends on their rates of synthesis, excretion, and catabolism (7). In persons with normal kidneys, about 90% of the glomerular-filtered light chains are reabsorbed and catabolized by the renal tubules. In renal insufficiency the light chains are retained in the serum, where their biological half life is greatly increased. Surprisingly, in cases of light chains disease, characterized by the absence of abnormal immunoglobulins, Bence Jones proteins are not usually seen as spikes on serum protein electrophoresis.

Lambda-type Bence Jones proteins were more frequently found than kappa type in cases of myeloma with Bence Jones proteinemia. In contrast to kappa light chains, which form noncovalently bound dimers, lambda light chains form covalently linked dimers. In patients with multiple myeloma the renal clearance of proteins is inversely related to their molecular size (8).
Grey and Kohler (9) and Caggiano et al. (10) each described a case of tetramers of lambda Bence Jones protein appearing as a monoclonal spike on serum protein electrophoresis. However, their cases did not show Bence Jones protein in the urine. In our case ultracentrifugation and gel filtration failed to show the presence of Bence Jones protein tetramers. To our knowledge, the serum concentration of Bence Jones protein in this patient is the highest reported. The high concentration was largely accounted for by the great impairment of kidney function (the patient's creatinine clearance was less than 2 ml/min).

Cases of multiple myeloma with Bence Jones protein appearing as an abnormal spike in serum protein electrophoresis should be distinguished from cases of truly biclonal gammopathy, where two distinct abnormal immunoglobulins are found. Cases of the former have an ominous prognosis. Chronic dialysis in cases of myeloma with Bence Jones proteinemia could be beneficial (11).

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References