Laboratory Diagnosis of Bence Jones Proteinuria in a Patient with Plasma Cell Leukemia

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Kappa Bence Jones proteinuria was found by immunoelectrophoretic techniques in a patient with plasma cell leukemia, who presented with no M-proteins either in serum or urine. However, a significant decrease in normal immunoglobulins was observed. On microscopic examination of kidney sections obtained at autopsy, protein casts were seen in the distal tubules. Bence Jones protein was not detected by the conventional heat test.

The application of immunoelectrophoresis to diagnosis connected with myelomatous hyperglobulinemia has been greatly increased since the introduction of the technique by Grabar and Williams (1) in 1953. In the cases of light and heavy chain diseases and of the recently described IgD and IgE myelomatosis (2-4), the diagnosis could also be ascertained by immunoelectrophoresis. This communication reports a case of plasma cell leukemia in which kappa light chain was detected in the urine by immunoelectrophoresis. The following is a summary of the case.

Case History

The patient, T.B., a 52-year-old Caucasian male, was referred to the Royal Columbian Hospital for investigation of obstruction in the urinary system 36 h after admission to the Riverview Hospital, Essondale, B.C. He had a history of chronic schizophrenia and apparently had not been doing very well for the preceding few weeks. Physical examination revealed nothing unusual except that the patient was confused and irritated. Laboratory investigation showed: hemoglobin, 85 g/liter; prothrombin time (Quick) 53%; blood urea nitrogen, 840 mg/liter; serum creatinine, 65 mg/liter; serum potassium, 6.5 mmol/liter; 1+ protein in the urine (150-300 mg/liter). Results of electrophoresis were unremarkable: 36, 2, 7, 10, and 9 g/liter of albumin, α1-, α2-, β-, and γ-globulins, respectively. We saw no evidence of monoclonal gammopathy on electrophoresis of a 50-fold concentrated urine specimen with total protein, after concentration, of 14 g/liter. However, radial immunodiffusion of the serum (Behring Tri-partigen plates) showed hypoglobulinemia with 3480, 340, and 220 mg/liter, respectively, for IgG, IgA, and IgM. Urine was negative for Bence Jones protein by the conventional heat test but was subsequently shown by immunoelectrophoresis (Hyland Agar-gel IEP system) to contain κ light chains (Figure 1). No IgD was detectable in the serum and the IgE concentration was shown to be 400 units/ml (against WHO research standard 60A/341; normal values up to 800 units/ml). Both tests

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Fig. 1. Immunoelectrophoresis of concentrated urine (top) and of serum (bottom) showing the presence of kappa light chains

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were performed on Behring LC ("low concentration") Partigen immunodiffusion plates. The serum was shown to have an abnormally high concentration of free kappa chains by immunoelectrophoresis (Figure 1). After suprapubic cystoscopy and peritoneal dialysis were performed, the patient was found to be bleeding from the operation site. Platelet count was 65,000/mm³. Plasma cells and myeloma cells were found in peripheral blood and bone marrow, respectively. Eight days after admission, he died of uremia caused by myelomatous kidneys.

At autopsy, gross examination showed disseminated disease involving the liver, spleen, and kidneys. Microscopic sections also showed lung involvement. Obstruction was found at the bulbous part of the urethra. Many protein casts, some of which were engulmed by foreign-body giant cells, were seen in the distal tubules. No amyloid was identified.

Discussion
This is a case of plasma cell leukemia in which the electrophoretic pattern for both serum and urine was normal. Proto et al. (5) described one acute case with a normal serum electrophoretogram. Plasma cell leukemia is the leukemic form of myelomatosis in which Bence Jones proteinuria is usually present. Because Bence Jones protein is being eliminated in the urine, a myelomatous kidney is often found at autopsy of patients with plasma cell leukemia (6). As illustrated in this particular case, the distal tubules are blocked by casts containing Bence Jones proteins, with giant cell formation. The low normal immunoglobulin titers of the serum examined could be attributed to decreased production. In more severe cases, however, the production of normal immunoglobulins is so inhibited that no normal immunoglobulins can be detected in the serum and this is known as "immune paresis" or "immune paralysis". Lamisz et al. (7) reported that in 10 of their 14 cases of light chain disease, marked hypogammaglobulinemia was present. According to Snapper and Kahn (8) the combination of hypogammaglobulinemia and Bence Jones proteinuria occurs in only about 20–30% of the myelomatous patients.

It is well known that the conventional heat test yields false negative results in about one-third of patients who are excreting light chains (14). This failure is probably due to the low sensitivity of the test. According to Putnam et al. (9), the heat test is positive only at concentrations exceeding about 300 mg/liter. This patient’s total urinary protein concentration was 280 mg/liter and therefore could not have been positive by heat test even if it were all Bence Jones protein.

The amount of light chains excreted in the urine was relatively low because of impaired clearance, which in turn was caused by precipitated protein plugging the tubules. This conclusion is supported by the high values for serum urea nitrogen and creatinine as well as by the histologic findings. Moreover, accumulation of abnormal proteins within the tubular epithelial cells and decreased renal blood flow probably play a significant role in the renal impairment. The marked increase in serum light chains in myelomatous patients has been reported previously by Lindstrom et al. (10). They have observed a marked increase (1.5 g/liter) in lambda light chains in the serum of a myelomatous patient who was excreting only 195 mg of light chains in the 24-h urine. The big deficit in immunoglobulins obtained by electrophoresis and by radial immunodiffusion was due to the fact that the kappa chains found in the serum travelled with the speed of gamma globulins on the electrophoretogram (11). But the amounts of the light chains were not shown by the immunoglobulin plates used.

In view of reports of high incidence in IgD (2) and IgE myelomas (3, 4) among patients with Bence Jones proteinuria, we looked for these two classes of immunoglobulins in the serum of this patient, but with negative results, thus eliminating the possibility of an IgD or an IgE myeloma in this patient. It has long been recognized that amyloidosis can be present in association with paraproteins, but no amyloid was identified on autopsy.

Recent statistics have indicated that the prognosis of light chain disease is poor, notwithstanding appropriate modern treatment (12). The light chain myelomas grow faster, have more complications, and lead to an early demise. Most fatalities are due to uremia caused by the intense Bence Jones proteinuria that commonly accompanies this form of myelomatosis. It is generally believed that the urinary excretion of lambda Bence Jones protein is prognostically more serious than is excretion of the kappa chains. In this particular case, the patient was dead shortly after the diagnosis was made, and the cause of death, as in most cases of light chain disease, was known to be uremia.

We conclude that it is important to appreciate the value of immunoelectrophoretic techniques in the diagnosis of myelomatosis in which electrophoretic patterns fail to show any anomalous proteins. In the case described here, the presence of light chain disease was not recognized until the kappa Bence Jones proteinuria was shown by immunoelectrophoresis. Therefore, it is essential to perform an immunoelectrophoresis on concentrated urine not only on all cases in which a sharp peak is found on serum protein electrophoretogram but also in any case in which myeloma or a related disorder is suspected. Booth et al. (13) state that "the possibility of multiple myeloma should be considered in all older patients with either acute or chronic renal failure."

Alternatively, a more sensitive test than the heat test may be used to screen for Bence Jones protein. As long ago as 1906, Bradshaw (15) proposed a number of chemical tests which could supplant the heat test. Hobbs (16), in 1966, reported that layering urine on concentrated HCl, according to Bradshaw,
detected 13 of 15 cases of Bence Jones proteinuria, and that it is about 30-fold as sensitive as the heat test. Any screening test must be confirmed by immunoelectrophoresis of concentrated urine.

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References


