Double Light-Chain Disease: A Case Report

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A patient with massive proteinuria was discovered to have double light-chain disease. Immunological studies demonstrated monoclonal light chains of both the lambda and kappa type in urine. The light chains were separate and distinct and were not found to be a part of any of the whole molecule immunoglobulins such as IgG, IgM, IgA, IgD, or IgE. Uniqueness of the proteins was confirmed by column chromatography. Clinical studies showed that the patient had multiple myeloma.

Multiple myeloma, a plasma cell neoplasm, usually results in the proliferation of a single line of plasma cells producing a specific monoclonal immunoglobulin, often referred to as an M or myeloma protein. A review of 869 cases of this disease (1) indicated that some of these patients also excrete significant amounts of monoclonal light chains in their urine. In 1966, Williams et al. (2) first used the term “light chain disease” to describe a form of myeloma in which the only detectable immunoglobulin abnormality consisted of excess production of monoclonal kappa or lambda type light chains. The serum of these patients showed only hypogamma-globulinemia by ordinary electrophoresis; because of their comparatively low relative molecular mass, light chains are excreted in the urine and are present in serum only in very small amounts in the absence of severe renal failure (3-5).

Plasma cell neoplasms secreting only kappa or lambda light chains are found in about one-fourth of patients with myeloma (2, 6) and are generally reported to be more aggressive than myelomas secreting whole immunoglobulin molecules (7). The median survival from time of diagnosis is significantly greater in patients with kappa light chain than those with lambda light chains (8). In all published cases of light chain disease, the monoclonal light chain has been either of the kappa or lambda type.

This communication reports the case of a patient with monoclonal light chains of both types in urine.

Materials and Methods

Agar Noble was obtained from Difco Laboratories, Detroit, MI. 48232. Specific antisera to human proteins were obtained from Behring Diagnostics, Somerville, NJ 08876; from Hyland Division of Travenol Labs Inc., Costa Mesa, CA 92626; and from Meloy Laboratories, Springfield, VA 22151. Bio-Gel A 0.5-m, 100-200 mesh, an agarose gel specifically prepared for gel filtration, and “DEAE Bio-gel A,” 100-200 mesh, a basic anion-exchanger composed of diethylaminoethyl ether groups in a beaded agarose gel matrix, were obtained from Bio-Rad Laboratories, Richmond, CA 94804.

For electrophoretic separation of proteins in urine and serum we used cellulose acetate strips or agarose gel plates and barbital buffer (0.1 mol/L, pH 8.6); for immunoelectrophoresis we used agar gel (1 g/L of the barbital buffer) coated on glass microscope slides.

Urinary proteins were chromatographically separated as follows: DEAE Bio-gel A was equilibrated in tris(hydroxymethyl)aminomethane-HCl buffer (2 mmol/L, pH 8.0) and packed into a glass column, 2.5 cm i.d., to a height of 30 cm. The urine sample, containing 250 to 300 mg of total protein, was dialyzed overnight against 100 volumes of the same buffer and then was passed through the column. The retained proteins were eluted in 4-mL fractions by a linear gradient of increasing concentrations of NaCl (0 to 15 mmol/L in 500 mL of the 2 mmol/L buffer). The protein content of the fractions was followed from their absorbance at 280 nm. The light chain concentration in each fraction was determined by radial immunodiffusion according to the Fahey-McKelvey technique (9). Goat antiserum to (and specific for) either human kappa or lambda light chains was incorporated in the agar gel, and purified kappa and lambda light chains of known concentration (supplied by Mr. Edward Czarnetsky, Meloy Laboratories) were used as standards.

The relative molecular mass of the urinary light chains was estimated by gel chromatography on the Bio-Gel A-5.5m. As eluent we used tris(hydroxymethyl)aminomethane-HCl buffer, 1 mmol/L, pH 8.0, containing sodium chloride, 150 mmol/L.

Case History

An 80-year-old white man was seen by a hematologist for evaluation of an anemia, first detected three months earlier, which had not responded to treatment with iron and vitamins. A bone-marrow aspirate done at this time showed 45% plasma cells, with many abnormal cells. The patient was admitted to the hospital with a working diagnosis of multiple myeloma. A bone survey showed no evidence of metastatic disease or myeloma. Results of pertinent laboratory studies on admission were: hemoglobin 90 g/L, hematocrit 28%, platelets 144 000/uL, serum urea nitrogen 170 mg/L, total protein 68 g/L, and albumin 51 g/L—all essentially normal. Electrophoresis of the patient’s serum on cellulose acetate showed marked hypogamma-globulinemia with no evidence of any distinct homogeneous band. Only a trace of albumin could be detected in the patient’s urine as measured by Dipstix (Ames Co., Elkhart, IN 46514) test, but the trichloroacetic acid precipitation procedure indicated urinary excretion of 18 g of total protein per 24 h. The behavior of the urinary protein

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on heating was typical of Bence Jones protein. A single homogeneous band, large and discrete, was observed on cellulose acetate electrophoresis of a 10-fold concentrated sample of urine (Figure 1). The band was close to the point of application in the gamma-globulin region. Immunoelectrophoretic and column-chromatographic studies on the abnormal protein are described in detail under Results.

The patient was discharged to the care of a hematologist with a diagnosis of multiple myeloma. He was treated with a regimen of blood transfusion and chemotherapy for about nine months. About three months after the initial hospital admission, a small but distinct homogeneous band was observed in the patient's serum by electrophoresis, both on cellulose acetate and agarose gel. The location of this band, which persisted and in fact increased in concentration during the illness, was identical with that of the band found in urine samples (Figure 1).

Nine months after the initial visit to the hematologist, the patient was re-admitted to the hospital for diagnosis and treatment of developing jaundice. A bone survey at that time again failed to reveal evidence of myeloma. Laboratory data obtained at the time of this admission included: hemoglobin 71 g/L; hematocrit 21%; platelets 170,000/uL; direct and total bilirubin 23 and 32 mg/L, respectively; alkaline phosphatase 88 U/L (reference limits, 13-45 U/L); albumin 41 g/L and globulin 16 g/L. Alanine aminotransferase (EC 2.6.1.2) activity in the serum ranged from 170 to 330 U/L during the hospitalization (normal limits, 10-45 U/L) and aspartate aminotransferase (EC 2.6.1.1) activity from 115 to 295 U/L (normal limits, 15-35 U/L). Serum urea nitrogen and creatinine concentrations at the time of this admission reached values of 250 and 24 mg/L, respectively. High amounts of urinary protein persisted, ranging from 16 to 21 g per 24 h. A monoclonal band was always present on cellulose acetate electrophoresis, but moderate amounts of albumin were also detected, both on the electrophoretic patterns and by the Dipstix procedure. The patient was discharged about two weeks after this admission.

One month later he was re-admitted to the hospital. His chief complaint now was severe weakness and backache. A roentgenogram of the lumbar spine revealed demineralization of the osseous structures, an observation compatible with a clinical diagnosis of myeloma. He was treated with radiation therapy for his back pain. While in the hospital he developed pneumonia, which responded to treatment. Results of laboratory studies were essentially similar to those for his previous admission, except that serum urea nitrogen and creatinine reached concentrations of 410 and 42 mg/L, respectively, and there was always a mild but persistent total hyperbilirubinemia of about 17 mg/L.

The patient was discharged to an extended-care facility where, despite therapy, he continued to deteriorate. He died about 15 months after the anemia was first detected. No autopsy was performed.

Results

Immunoelectrophoresis of Patient's Serum and Urine

Serum and concentrated urine specimens obtained at the time of the first admission were subjected to agar-gel immunoelectrophoresis. We used antisera against human IgG, IgA, IgM, IgD, IgE, and kappa and lambda light chains prepared in goats, obtained commercially from Meloy Labs. No monoclonal paraproteins were seen in serum at this time (Figure 2), but in concentrated urine monoclonal kappa and lambda light chains were detected (Figure 3). This was confirmed by using the corresponding antisera from other commercial sources (Behring and Hyland). Similar immunoelectrophoretic evaluations of urine samples at each subsequent admission indicated essentially no change in the excretion of monoclonal light chains, but the serum samples now revealed the presence of a small but distinct monoclonal lambda light chain (Figure 3).

Column Chromatography of the Patient's Urine

The chromatographic separation of urinary proteins on DEAE Bio-Gel A as described in Methods led to a partial separation of the kappa and lambda light chains (Figure 4). A urine sample obtained at the time of the initial admission was chromatographed; it contained negligible quantities of albumin. Fractions 19 through 25 (indicated by the black bar
in Figure 4) were pooled, concentrated about 10-fold, and rechromatographed on DEAE Bio-Gel A under identical conditions. This effected a complete separation of kappa chains from the lambda chain contamination of the first separation, as assessed by the Ouchterlony double-diffusion technique.

We estimated the relative molecular mass of the urinary light chains by column chromatography on Bio-Gel A-0.5m, which indicated that both the kappa and lambda light chains were present in the urine as dimers. Five comparison proteins with relative molecular masses ranging around that of the light chains were used in this study.

Discussion

The simultaneous presence of more than one monoclonal component in a single serum specimen is relatively infrequent, occurring in about 1% of patients with demonstrable paraproteinemia. In a rather extensive statistical study of paraproteinemias (10) only 60 of the 6141 recorded cases had more than one M component. In most of these cases of multiple paraproteins, heavy chains of different classes were associated with light chains of the same type. The simultaneous presence of light chains of both kappa and lambda type associated with the same heavy chain was even more rare, being detected in only 10 cases. It is therefore not surprising that despite an exhaustive search of the literature we could not find a single case of light chain disease reported in which monoclonal light chains of both lambda and kappa types were present simultaneously in either urine or serum.

The usual explanation for double paraproteinemias is that two clones of malignant cells develop simultaneously, each responsible for production of a specific paraprotein. This has been confirmed by immunofluorescence studies, which frequently show that each of the immunoglobulins was synthesized in different cells (11-14), although in some cases (15, 16) both M proteins were found to be produced in the same cells. We were interested in determining if the monoclonal kappa and lambda light chains in our patient were synthesized by the same or different cells. Initial immunofluorescence studies of bone-marrow smears, similar to those described by Bouvet et al. (16), indicated that the different light chain types were not being produced by the same cells. Unfortunately, the patient died before these studies could be confirmed and extended.

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References