

## “Nonsecretory” Multiple Myeloma

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A case of “nonsecretory” multiple myeloma with careful study of urine and serum immunoglobulins is presented. Marrow immunofluorescent studies failed to show production of identifiable immunoglobulins. Bone marrow examination may be the only method of diagnosis in such cases.

**M**ULTIPLE MYELOMA PROTEIN STUDIES were pivotal in unraveling the mysteries of the immunoglobulins by allowing study of large quantities of a single, immunoglobulin molecule or a fragment thereof. The absence of any detectable abnormal protein in either serum or urine has been rarely well documented in multiple myeloma.<sup>1-6</sup> In these cases, as well as in the one reported here, bone marrow aspiration provided the diagnosis.

### CASE REPORT

A 69-yr-old white woman became unable to walk due to severe back pain in July 1965. She had been well until the onset of back pain 2 mo earlier. Generalized bone tenderness was the only significant abnormality on physical examination. Bone x-rays showed widespread osteolytic lesions and osteoporosis. Aspirated bone marrow was heavily infiltrated by malignant-appearing plasma cells typical of multiple myeloma (Fig. 1). The following studies were either normal or negative: complete blood count, urinalysis, electrocardiogram, blood sugar, blood urea nitrogen, serum bilirubins, SGOT and SGPT, serum calcium, phosphorus, uric acid, alkaline phosphatase, sulfobromophthalein retention, lactic dehydrogenase, and x-rays of stomach, colon, and gall bladder.

Cyclophosphamide, testosterone enanthate, and melphelan were used without apparent benefit during the 9½ mo between diagnosis and death.

### RESULTS

#### *Protein Studies*

No abnormal serum protein was found on cellulose acetate electrophoresis, paper electrophoresis, agar gel electrophoresis, or Weime high-voltage agar electrophoresis. No evidence of an abnormal serum protein was found on immunoelectrophoresis using antisera specific for IgG, IgA, IgM, IgD, and kappa and lambda light chains. A rabbit was immunized with the patient's serum. Electrophoresis of the patient's serum using this antipatient serum showed a normal pattern. All of the precipitation lines could be removed by prior absorption of the rabbit antipatient serum with pooled normal human

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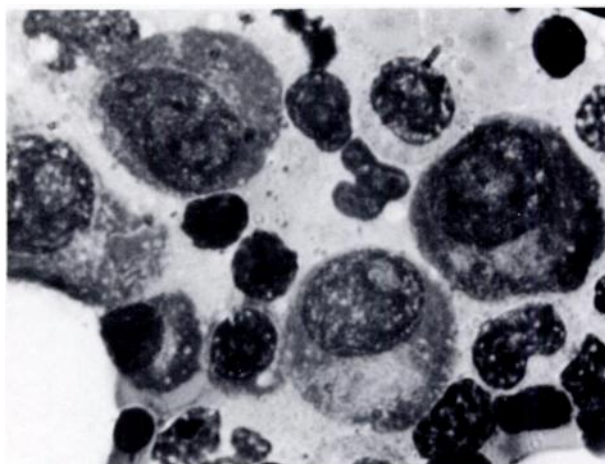
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*Received March 7, 1972; accepted March 17, 1972.*

*Supported in part by American Cancer Society (ET-13E) and Jane Coffin Childs Memorial Fund for Medical Research.*

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Fig. 1. Photomicrograph of bone marrow aspiration showing large, immature plasma cells (myeloma cells), most with a single, large nucleolus. Many cells are multinucleated. Cytoplasm was deep blue with an occasional indistinct, perinuclear halo.  $\times 1200$ .



sera. The only precipitation lines detectable in a concentration of the urine on immunoelectrophoresis using antihuman serum were due to albumin and another protein that moved just behind albumin. No immunoglobulins were detected using specific antisera. Immunoelectrophoresis of the urine concentrate using the rabbit antipatient serum showed only the above-mentioned two lines.

Immunofluorescent studies were performed on the patient's bone marrow smear with fluorescent, conjugated antisera with specificities of the type described above, except for anti-IgD. Positive results were not obtained with any antisera. Control myeloma marrows run simultaneously fluoresced with either antikappa or antilambda, or with either anti-IgG or anti-IgA.

Quantitative levels of IgG, IgA, and IgM were determined by radial immunodiffusion. Values in the patient's serum were: IgG, 760 mg/100 ml; IgM, 42 mg/100 ml; and IgA, 97 mg/100 ml. The normal values for adult serum by this method are: IgG,  $1200 \pm 300$  mg/100 ml; IgM,  $100 \pm 27$  mg/ml; and IgA,  $200 \pm 60$  mg/100 ml.

#### DISCUSSION

We have located 13 reported cases of multiple myeloma in which no abnormal protein could be detected in serum or urine after a more or less complete study using specific antisera.<sup>1-6</sup> Absence of specific, immunofluorescent, marrow cell staining was reported in one case.<sup>6</sup> The incidence of "non-secretory" multiple myeloma would appear to be 1%–2%.<sup>2,4</sup>

Since osteolytic, skeletal x-ray lesions may be lacking, bone marrow aspiration may be the only diagnostic test.<sup>1</sup> The following various explanations for the lack of detectable immunoglobulin abnormalities have been offered: (1) The cellular protein-synthesizing apparatus may not be working due to defective "molecular machinery" (DNA transcription, messenger or ribosomal RNA translation, etc.). (2) "Nonantigenic" immunoglobulin fragments are being produced and cannot be detected by current methods. (3) The malignant cell may be derived from a nonprotein-producing "stem," such as the reticulum cell.<sup>6</sup>

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