Frequency of Calcium Binding by Monoclonal Immunoglobulins in Multiple Myeloma*

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ABSTRACT

Total and ionized calcium and other related parameters were measured in 34 patients with multiple myeloma. Hypercalcemia was not a major feature of the group of patients studied with only three patients exhibiting marked increases in total (Ca total) and ionized (Ca+++) calcium concentrations. The Ca+++/Ca total ratio was also maintained within relatively narrow limits. No major differences were found in the calcium fractions of patients with different types of multiple myeloma. Serum immunoreactive parathyroid hormone showed no consistent relationship with either the total or ionized calcium concentration. There were no correlations between increased total protein or reduced serum albumin concentrations and changes in total and ionized calcium fractions or Ca+++/Ca total ratios. These results imply that in this group of myeloma patients, there was no significant binding of calcium by the monoclonal immunoglobulins.

Introduction

A disturbance in calcium homeostasis is a recognized complication in patients with multiple myeloma and is usually seen as an increase in total serum calcium concentration. The clinical manifestations are protean and include nausea, vomiting, polyurea, polydypsia, stupor and, in severe cases, coma. Although the signs and symptoms are quite variable, the severity usually correlates with the degree of hypercalcemia. Some patients with hypercalcemia, however, do not manifest any of the usual clinical symptoms associated with that condition. In these patients, the free or unbound calcium concentrations are normal despite significant elevations in the total serum calcium concentration. This apparent discrepancy has been attributed, in rare cases, to calcium-binding by the paraprotein.1-6 In a prospective study, total and ionized calcium and other related parameters were measured in 34 patients with multiple myeloma in an attempt to determine the frequency of al-
terations in serum calcium concentration and to differentiate variations in calcium-binding by various monoclonal immunoglobulins.

**Materials and Methods**

**Patients**

Thirty-four patients with multiple myeloma were studied. The diagnosis in each case was confirmed by an increased number of plasma cells in the bone marrow, the presence of a monoclonal immunoglobulin or light chains in the serum and/or urine, and discrete lytic bone lesions. The patients were classified according to the type of monoclonal protein detected in their serum or urine by immunoelectrophoresis: Nine of the patients had IgG-kappa, eight had IgG-lambda, six had IgA-kappa, four had IgA-lambda, one had IgG-kappa and IgA-lambda, four had kappa light chains, and two had lambda light chains. Ten patients had varying degrees of renal dysfunction, as assessed by elevated serum creatinine and blood urea nitrogen concentrations.

**Analytical Procedures**

Total serum calcium concentration was measured by atomic absorption spectroscopy and the ionized fraction with an ion-specific electrode.* Total serum protein, albumin, sodium, chloride, CO₂ content, creatinine, and BUN were measured.† Parathyroid hormone was quantitated by radioimmunoassay of the C-terminal PTH fragment.‡

**Results and Discussion**

Total (Ca total) and ionized (Ca⁺⁺) calcium concentrations and Ca⁺⁺/Ca total ratios for each patient are presented in figure 1. Only three of the 34 patients studied (#10, 22, and 28) had marked increases in both total and ionized calcium concentrations; two other patients (#17 and 19) had mild increases in their total calcium concentrations which was apparently due to increases in the ionized fraction. In one patient (#5), there was an increase in the ionized fraction which was not associated with an increase in the total calcium concentration. None of the patients had an increased Ca total with a normal Ca⁺⁺ concentration. All of the other patients, except for patient (#6) who was hypocalcemic, had total and ionized calcium concentrations that were either within or very close to the reference range values. The Ca⁺⁺/Ca total ratio was maintained within relatively narrow limits except for the hypocalcemic patient (#6) who had an elevated ratio because of his low Ca total and normal Ca⁺⁺ concentrations. No major differences were found in the calcium fractions of patients with different types of multiple myeloma.

Serum immunoreactive parathyroid hormone (i-PTH) (figure 2) showed no consistent relationship with either the total or ionized calcium concentrations. The i-PTH value in the patients with elevated calcium concentrations were all within the reference range. In the patients whose i-PTH levels were unmeasurable (#8, 17, 20, 21, 23, and 34), the corresponding serum calcium concentrations were within or very close to the reference range. Within the population studied, abnormally high i-PTH concentrations were found only in association with renal failure.

Serum albumin and total protein concentrations for the patients studied are shown in figure 3. Hypoalbuminemia, as anticipated, was a common finding in this myeloma population. In most of the patients with a decreased serum albumin
concentration, the corresponding total protein values were either normal or significantly elevated, which was consistent with the presence of monoclonal immunoglobulins. None of the patients with marked protein disturbances had a decreased Ca++/Ca total ratio; all of the other patients had total protein and albumin concentrations that were either within or very close to the reference range.

Calcium binding by monoclonal immunoglobulins in patients with multiple myeloma is a rare cause of asymptomatic hypercalcemia and has been documented in the literature only a few times. In this prospective study of 34 patients, there were no correlations between increased total protein or reduced serum albumin concentrations and changes in total and ionized calcium fractions or Ca++/Ca total ratios. In the myeloma population studied here, there was a low incidence of hypercalcemia and there was no significant calcium binding by the paraproteins. In those patients in whom significant calcium binding has been documented, it has been shown to be a consequence of the intrinsic property of that particular monoclonal immunoglobulin. The rare occurrence of asymptomatic hypercalcemia in patients with
multiple myeloma would imply that only a small number of normal immunoglobulins bind calcium.

References


