Evidence for Parathyroid Hormone-Related Peptide As a Cause of Hypercalcemia in Myeloma

To the Editor:

Parathyroid hormone-related peptide (PTHrP) produced from malignant tumor cells has been established as a biologic activity inducing bone resorption followed by hypercalcemia. Although increased serum immunoreactive PTHrP level was reported in three of six myeloma cases complicated with hypercalcemia,[1] the involvement of PTHrP as a cause of hypercalcemia in myeloma patients has not been established yet.

A 72-year-old Japanese woman was diagnosed as having IgAκ myeloma complicated with hypercalcemia in March 1992. Clinical and laboratory findings strongly suggested the involvement of PTHrP

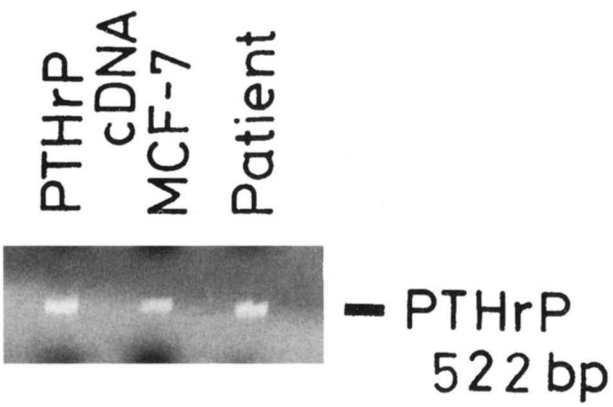

Fig 1. Expression of PTHrP mRNA.

as a cause of hypercalcemia, although PTHrP was not directly measured at this time. In July 1992, hypercalcemia recurred. The serum levels of albumin-adjusted calcium and inorganic phosphorus were 3.74 mmol/L and 1.13 mmol/L, respectively. The serum levels of the intact, mid-region, and C-region PTH were 11 ng/L (normal 15 to 50), 890 ng/L (normal 160 to 520), and <500 ng/L (normal <500), respectively. The serum $1,25(OH)_2$ vitamin D_3 was <5 ng/L (normal 20 to 76) and calcitonin was 19 ng/L (normal 27 to 46). Nephrogenous cyclic adenosine monophosphate (AMP) was 39 nmol/L GF (normal 8 to 28) and tubular reabsorption of phosphate was 39% (normal 85 to 95). The serum level of creatinine was 180 μmol/L. In addition, increased urinary excretion of C-terminal PTHrP was determined by radioimmunoassay, 4.17 μg/g creatinine (normal 0.3 to 1.1). Hypercalcemia was again controlled by chemotherapy combined with conventional treatment. During the 1-year clinical course until death by pneumonia in March 1993, such hypercalcemic episodes were repeated almost every 2 months.

The expression of PTHrP mRNA was analyzed by the method described previously.[2] After informed consent was obtained, nonadherent mononuclear bone marrow cells containing over 80% myeloma cells were prepared. Then, double-stranded cDNA synthesized from poly-A RNA obtained from the cells was used as a template for PCR. Oligonucleotide primers were designed based on the DNA sequence of human PTHrP. The sense and antisense primers for PTHrP were 5′-ATGCAGCGGAGACTGGTTCA-3′ and 5′-CGTCGCTGGAGCTCGATTCA-3′, respectively. MCF-7 cells established from human breast cancer and PTHrP cDNA kindly provided by Dr H. Katakami of Miyazaki Medical College[3] were used as positive controls. Both MCF-7 cells and bone marrow cells obtained from this patient expressed PTHrP mRNA (Fig 1).

This study has shown that PTHrP can be added to one of the humoral factors inducing bone destruction followed by hypercalcemia in myelomas. Whereas the production of PTHrP was reported in human myeloma cell lines,[3] this is the first patient whose bone marrow cells, probably myeloma cells, expressed PTHrP mRNA. Furthermore, the PTHrP produced had a biologic activity that was confirmed by the increased nephrogenous cyclic AMP and decreased tubular reabsorption of phosphate. Interestingly, such hypercalcemic episodes recurred in parallel with the increase in myeloma cells and disappeared in response to chemotherapy. These observations further support the idea that PTHrP produced in myeloma cells is the cause of hypercalcemia in this patient.

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