Hypercalcemia due to sun exposure in a patient with multiple myeloma and elevated parathyroid hormone-related protein

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Abstract
A patient with multiple myeloma who developed hypercalcemia during three different stages of his disease, with a different hypercalcemic agent elevated in his serum on each occasion, is described. The initial episode of hypercalcemia was associated with high serum interleukin-6 (IL-6). After treatment for myeloma normocalcemia was achieved. Subsequently, a relapse of hypercalcemia occurred, this time characterized by frankly elevated plasma parathyroid hormone-related protein (PTHrP) but normal IL-6. Monotherapy with pamidronate infusions resulted in remission of the hypercalcemia and a significant fall in PTHrP levels. A third spell of hypercalcemia characterized by an acute rise in serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D to abnormally high levels occurred during the summer season after prolonged and intense exposure to the sun.

Introduction
Multiple myeloma (MM) is a malignancy often causing hypercalcemia. We describe a patient with MM who developed hypercalcemia during three different stages of his disease, each episode characterized by the elevation of a distinct hypercalcemic agent detected in his serum, namely interleukin-6 (IL-6), parathyroid hormone-related protein (PTHrP) and 1.25-dihydroxyvitamin D (1,25-(OH)2D). The high serum 1,25-(OH)2D levels which caused a spell of hypercalcemia in this patient were detected during the summer after intense and prolonged exposure of the patient to the sun.

Hormone assays
Plasma human PTHrP was measured using a two-site IRMA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The sensitivity of this assay was 0.1 pmol/l and the intra- and interassay coefficients of variation (CV) at concentrations of 0.5, 2.4 and 4.3 pmol/l were 6.6%, 4.5%, 2.5% and 10.6%, 7.6%, 4.3% respectively. Parathyroid hormone (PTH(1–84)) was measured by a two-site IRMA (Nichols Institute Diagnostics) with a sensitivity of 0.2 pmol/l and intra- and interassay CV at the 3.5 pmol/l level of 3.2% and 4.6%, and at the 29.4 pmol/l level of 2.8% and 4%. Serum 25-hydroxyvitamin D (25OHD) was measured in alcohol serum extract by a competitive binding assay (Nichols Institute Diagnostics) with a sensitivity of 2.2 ng/ml; intra- and interassay CV at 19.0 ng/ml were 10% and 14%, and at 76.0 ng/ml were 8% and 13%. Serum 1,25-(OH)2D was measured in immunoextracted serum by RIA (Nichols Institute Diagnostics) with a sensitivity of 2.1 pg/ml and intra-assay CV of 8% and 5%, and interassay CV of 16.8% and 10.8% at the 13.0 pg/ml and 40.0 pg/ml levels respectively. Serum IL-6 was determined by a sandwich enzyme immunoassay (R&D Systems Inc., Abingdon, Oxon, UK) with a sensitivity of 0.1 pg/ml, an intra-assay CV of 5.9% and an interassay CV of 16.5% at a concentration of 3.0 pg/ml. Serum osteocalcin (OC) was measured by a two-site IRMA (Nichols Institute Diagnostics), and urinary cross-linked N-telopeptides of type I collagen (NTx) were measured using an enzyme-linked immunoabsorbent assay (Osteomark; Ostex International, Inc., Seattle, WA, USA). Calcium, phosphorus, creatinine and alkaline phosphatase (ALP) were measured by autoanalyzer using standard laboratory methods. Serum calcium was corrected for serum albumin. Informed consent was obtained from the patient for the determination of the various parameters. The Scientific Committee of the Hospital approved this report.
Case report

A 42-year-old man with MM was referred to these hospitals for the management of MM complicated by relapsing hypercalcemia. About a year before his presentation to these hospitals the patient experienced fatigue and diffuse bone pain. There was no lymphadenopathy or enlarged spleen. A serum calcium of 11.5 mg/dl was found and the diagnosis of MM was made based on the following findings: the bone marrow contained 20% monoclonal (G lambda) plasma cells, an M-protein (IgG lambda) was present in the serum while the other immunoglobulins were decreased, and light chains (lambda) were present in the urine. The T-score of the bone mineral density in the lumbar spine (L2-L4) was -2.2. An X-ray and CAT survey of the skeleton did not reveal any osteolytic lesions. Serum PTH was undetectable, plasma PTHrP was 0.8 pmol/l (normal value < 0.64), and serum IL-6 was 64.0 pg/ml (normal value < 10.1). Treatment with VAD chemotherapy (vincristine, doxorubicin, dexamethasone) was initially administered for 6 months together with infusions of pamidronate sodium (30 mg once every month). On this regimen serum calcium was maintained at 11.0–11.2 mg/dl. Subsequently, the patient received a preparative treatment for bone marrow transplantation. During this therapy serum calcium was about 10.0 mg/dl. One month after the bone marrow transplantation he was in good general condition but serum calcium rose to 12.1 mg/dl and he was referred to these hospitals (time zero in Fig. 1). At this time (months 0–5.8) plasma PTHrP was found to be elevated at 3.0 pmol/l, serum IL-6 was 7.4 pg/ml, serum 25-OHD was 38.0 ng/ml (normal range 10.0–74.0), and serum 1,25-(OH)2D was 26.0 pg/ml (normal range 18.0–62.0). PTH was suppressed to 0.2 pmol/l (normal range 1.1–6.8) and urinary NTx was elevated to 78.7 nmol/l Bone Collagen Equivalents/mmol/l creatinine (Cr) (normal range 5.0–65.0). The urinary excretion of calcium was 350.0 mg/24 h, and the fractional excretion of calcium was 5.8% and of phosphorus was 25.8% in a double voided fasting morning urine specimen. Treatment with pamidronate was resumed, 90 mg infused every 15 days. The longitudinal changes in serum calcium and some parameters of bone and mineral metabolism are shown in Fig. 1. On monotherapy with pamidronate sodium (90 mg every 2 weeks) serum calcium declined to normal levels and a gradual fall in the level of PTHrP was also observed (months 5.8–11.5 in Fig. 1). Subsequently (at month 12.7), a relapse of hypercalcemia occurred despite the mildly elevated and relatively stable level of PTHrP to about 1.3 pmol/l and normal IL-6 (3.2 pg/ml).

During this new episode of hypercalcemia serum 1,25-(OH)2D was found to be high at 120.0 pg/ml and 25OHD was above the upper limit of normal or was frankly elevated up to 86.0 ng/ml. This spell of hypercalcemia which was associated with very high calcitriol levels occurred during the summer (the 5.8–15.5 month interval in Fig. 1 corresponds to the period of time between June 1st – August 31st). The patient admitted to intense and frequent sunbathing during his summer vacation in Cyprus (latitude 34.7°), without any use of vitamins or change in his dietary habits. It is estimated that he was exposed to the sun for about one hour daily during the entire month of June and less frequently until the last week of July when he was advised to avoid exposure to the sun. On September 17 (month 16.1) treatment with methylprednisolone (24 mg/day) was started while the infusions of pamidronate were continued as before: during the next 3.5 months on this treatment the hypercalcemia subsided, and serum 25OHD fell to normal, serum 1,25-(OH)2D fell to low normal and plasma PTHrP to normal levels, while plasma PTH rose to the low normal range. From month 19.5 the patient developed massive proteinuria. Treatment with interferon alpha was administered for 6 weeks followed by chemotherapy with a modified VAD protocol. From month 28.5 thalidomide was administered for 2.5 months and then treatment with dexamethasone was resumed. Only the treatments with pamidronate and glucocorticoids are shown in Fig. 1. From month 26 the patient developed renal failure with serum creatinine rising progressively over the next 10 months up to 5.6 mg/dl. He also developed amyloidosis causing a massive enlargement of his tongue. The patient died 6 months later.

Discussion

The most common mechanism of the hypercalcemia in MM is considered to be the secretion by the myeloma cells of various cytokines known to stimulate osteoclastic bone resorption (1, 2). Recently, the secretion of PTHrP by the MM cells has been identified in a large proportion of hypercalcemic patients with this malignancy (3, 4). These hypercalcemic agents apparently act in a paracrine manner stimulating the osteoclasts surrounding the myeloma cells. However, elevated circulating concentrations of these hypercalcemic factors can apparently induce humoral malignancy-associated

Figure 1 Longitudinal changes of some parameters of bone and mineral metabolism. The horizontal bars in the upper left panel denote duration of treatments and the shaded areas denote normal ranges. The seasonal rise of 1,25-(OH)2D and 25OHD which coincided with a spell of hypercalcemia during the summer (the 12.5–15.5-month interval corresponds to June 1st-August 31st) are illustrated.
hypercalcemia (MAH) in MM by stimulating the osteoclasts over the entire skeleton. Our patient suffered from three episodes of hypercalcemia during the course of his disease, each apparently caused by different circulating hypercalcemic factors. The disease presented with hypercalcemia caused by very high IL-6. Therapy for MM induced normocalcemia with a fall of IL-6 to normal levels. Subsequently, a relapse of hypercalcemia was characterized by frankly elevated plasma PTHrP and normal IL-6 and calcitriol. Monotherapy with pamidronate infusions resulted in normocalcemia despite the persistently mildly elevated PTHrP. Then, after exposure to the sun during the summer, a third episode of hypercalcemia occurred characterized by an acute rise of previously low normal calcitriol to levels two times above the upper limit of normal and a similar rise in 25OHD to levels just above the upper limit of normal, while PTHrP remained mildly elevated and IL-6 was normal. This spell of hypercalcemia responded to moderate doses of methylprednisolone which was added to the pamidronate infusions. The fall in serum calcium after methylprednisolone therapy was associated with a fall in both 25OHD and 1,25-(OH)2D as well as PTHrP to within the normal range. We consider that the latter episode of hypercalcemia was caused by a seasonal rise in serum 25OHD due to intense exposure to the sun and the consequent unregulated overproduction of 1,25-(OH)2D by the myeloma cells, since the circulating factors which were apparently causing hypercalcemia previously in this patient were either normal (IL-6) or mildly elevated and stable (PTHrP) on this occasion. Seasonal hypercalcemia during the summer ascribed to a similar mechanism has been described in patients with sarcoidosis (5). The unregulated production of 1,25-(OH)2D in MM is probably extremely rare and some investigators consider that it is very unlikely to appear in this malignancy (6). Thus, serum levels of 1,25-(OH)2D in hypercalcemic patients with MM are commonly considered to be suppressed and in an investigation (6) were found to be less than 42 pg/ml. Calcitriol is the major humoral mediator of hypercalcemia in lymphomas (7), but we are not aware of any published report of seasonal exacerbation of hypercalcemia in patients with these malignancies or with myeloma. In our patient, the increased availability of substrate (25OHD) during the summer may not be the sole factor which caused the unregulated production of calcitriol. Recently, the production and secretion of PTHrP by the MM cells in vitro and in vivo have been reported to occur very often (3, 4, 8). Simultaneous production of both IL-6 and PTHrP by a myeloma cell line has also been reported (9). The MAH caused by PTHrP is generally characterized by low normal to frankly low levels of circulating calcitriol whereas patients with primary hyperparathyroidism and a similar degree of hypercalcemia have elevated levels of 1,25-(OH)2D (10). The mechanism of the suppression of calcitriol in MAH may be complex (11). It is possible, therefore, that myeloma cells possess 25OHD-1-hydroxylase but the activity of the enzyme is usually suppressed by the PTHrP-induced hypercalcemia, resulting in the low normal circulating levels of calcitriol commonly found in patients with MM.

We think that in our patient the following sequence of events may have happened: during the hypercalcemic phase caused by PTHrP, the production of calcitriol remained suppressed. The chemotherapy before and the prolonged monotherapy with high doses of pamidronate after the bone marrow transplantation apparently resulted in normalization of IL-6 and in a substantial fall in PTHrP (time interval 0–11 months in Fig. 1) with resultant normocalcemia. Recent studies provide evidence that bisphosphonates can directly decrease cell proliferation and induce apoptosis in human myeloma cells in vitro (12), and can decrease the disease activity in humans causing a fall in the production of IL-6 (13). The fall in serum calcium to normal values together with the decline in PTHrP production in our patient (at about month 11.5 in Fig. 1) probably permitted increased expression of 25OHD-1-hydroxylase in the myeloma cells; these changes coincided with the intense exposure of the patient to the sun during the summer, with the consequent increase in the availability of substrate (25OHD) for the unregulated overproduction of calcitriol which apparently caused the seasonal hypercalcemia.

Although the coexistence of MM with sarcoidosis cannot be excluded in our patient it seems unlikely because of the low normal levels of calcitriol during the several months preceding its acute seasonal elevation. In sarcoidosis, 1,25-(OH)2D is abnormally regulated and remains elevated throughout the year with a further moderate increase in the summer season (5).

At the beginning of our regular follow-up of the patient (time zero) the hypercalcemia was characterized by high plasma PTHrP and urine NTx while serum OC was normal. This uncoupling between increased bone resorption and decreased bone formation is characteristic of the MAH (14). During treatment of our patient with pamidronate (0–8 months interval) plasma PTHrP, urine NTx and serum calcium declined harmoniously while serum OC increased to levels above the normal range. This probably represents a rebound increase in serum OC, due to the elimination by the treatment of the humoral uncoupling factor postulated by Delmas et al. (14) to be responsible for the stimulation of bone resorption and suppression of bone formation in MAH. This factor might be PTHrP; however, there is no evidence that either the N-terminal (15) or the C-terminal (16) fragments of the PTHrP molecule can affect the release of OC by the osteoblasts. The acute rise in serum calcitriol may have caused the concordant rise in serum ALP (17) and of OC (18) observed during the interval between
months 13 and 16. The case presented here indicates that patients with malignancies or granulomatous diseases in which the major mediator of hypercalcemia is calcitriol should be monitored for the possibility of seasonal exacerbation of hypercalcemia during the summer. Multiple myeloma should be included in these diseases.

References


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