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A Case of Primary Hyperparathyroidism Accompanying Multiple Myeloma

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Abstract. We report a case of 77-year-old woman who presented with lumbago and hypercalcemia. Multiple myeloma (MM) was first diagnosed by serum protein electrophoresis and bone marrow aspiration, but intact parathyroid hormone (intactPTH) was also found to be high in the presence of persistent hypercalcemia with anorexia and nausea. After lowering serum calcium with bisphosphonate administration, parathyroidectomy was performed. Upon histologic examination, the tumor was determined to be parathyroidal chief-cell hyperplasia and the patient was treated with melphalan and prednisolone. The relationship between MM and primary hyperparathyroidism (I°HPT) remains unknown. Although the co-existence of MM and I°HPT was reported in 12 reports from various parts of the world, there was only 1 report in Japan. The present case is an example of successful treatment for a complicated disorder, and suggests that patients suffering from bone pain or hypercalcemia need to be examined both endocrinologically and hematologically.

Key words: Multiple myeloma (MM), Primary hyperparathyroidism (I°HPT), Parathyroidal chief-cell hyperplasia, Hypercalcemia, Bisphosphonate, Interleukin-6, Melphalan, Prednisolone

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MULTIPLE myeloma (MM) and primary hyperparathyroidism (I°HPT) are occasionally observed in the elderly and each can provoke hypercalcemia, but the concurrent presentation of these two disorders in the same patient is rare. Although these two conditions commonly cause hypercalcemia and result in osteoporotic changes, their mechanisms are complicated. This case report not only defines the rarity of this condition, but also introduces a successful therapeutic course which has seldom been described in detail.

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Case Report

The patient was a 77-year-old Japanese woman who presented with a 3-year history of lumbago and back pain. She had been evaluated previously and found on radiographic examination to have severe osteoporosis, which had been treated with calcitonin injection (20 units weekly), but since the investigation revealed an increase serum total protein with a monoclonal peak in conjunction with an increase in serum parathyroid hormone, she was admitted to our hospital for further evaluation. In addition to the bone pain, she complained of nausea, anorexia, and a 10-day history of constipation. She was recently diagnosed as having a duodenal ulcer.

Physical examination revealed a diminutive

frame (height, 135 cm; body weight, 26 kg), facial pallor, dorsal kyphosis and tenderness over the dorsal and lumbar spine. On laboratory examination, she was anemic and leukopenic (hemoglobin: 7.6 g/dl, white blood cells: 2,300/mm^3, platelets: 186,000/mm^3). Serum calcium (12.5 mg/dl) was high, with a low serum phosphate concentration (2.0 mg/dl). The other electrolytes were normal. Liver and renal functions were normal. The serum alkaline phosphatase (ALP) concentration (246 IU/l) was high, predominantly consisting of bone ALP (81%). The serum protein level was normal (7.7 g/dl), but serum protein electrophoresis demonstrated an M-protein spike (M-protein: 1.9 g/dl), with high serum IgG (3,060 mg/dl) but suppressed IgM and IgA levels (26.2 mg/dl and 37.7 mg/dl, respectively). Serum immunoglobulin electrophoresis demonstrated a monoclonal gammopathy of lambda-light chain. Bence-Jones proteinuria was not identified. Arterial blood gas analysis revealed slight metabolic acidosis (pH: 7.35, base excess: −3.7 mmol/l). A bone marrow aspirate revealed 25% plasmacytes with immature forms and the monoclonality was proven by immunohistochemical staining of the immunoglobulin lambda-chain. After the diagnosis of multiple myeloma (IgG-lambda type), the patient underwent various endocrinological tests (Table 1). Serum parathyroid hormone (PTH) was found to be high. PTH-related peptide (PTHrP) was undetectable in her serum. Nephrogenous cAMP and bone resorptive markers were increased, and % tubular resorption of phosphate was decreased. Thyroid, adrenal and pituitary functions were normal. Soluble cytokines including interleukin (IL)-1α, IL-1β, IL-6 and tumor necrosis factors (TNF)-α and β were undetectable in her serum. Ultrasonography and magnetic resonance imaging (MRI) of the cervical area disclosed an enlarged left inferior parathyroid gland (Fig. 1), which was comfirmed by ^{201}Tl-^{99m}Tc scinitigraphy. She was diagnosed as having primary hyperparathyroidism accompanying multiple myeloma. Abdominal computed tomography and cranial MRI revealed no abnormality. Roentgenograms of the skull, iliac bones and lumbar vertebrae revealed severe diffuse osteoporotic changes in the absence of "punched out" lesions. The bone mineral density of the lumbar region was severely diminished at 0.379 g/cm^2. After the patient's hypercalcemia was treated with sodium pamidronate (total 45 mg/month) and calcitonin (20 units weekly), the serum calcium level subsequently decreased to 8.7 mg/dl, and parathyroidectomy of the left inferior parathyroid gland was performed. Histological examination revealed parathyroid hyperplasia predominantly consisting of chief-cells (Fig. 2). Although all electrolytes normalized post-operatively, the serum IgG and M-protein concentrations had increased to 4,300 mg/dl and 2.9 g/dl, respectively, and the bone pain also continued. The patient received follow up treatment with melphalan 4 mg/day and

Table 1. Endocrinologic data on admission

intactPTH	233 pg/mL	(14–66)
hs-PTH	3690 pg/mL	(230–560)
C-PTH	2.0 ng/mL	(<0.7)
PTHrP	N.D.	
Calcitonin	24 pg/mL	(27–48)
Osteocalcin	23.6 pg/mL	(3.5–13.7)
1,25(OH)$_2$-VD	39.9 pg/mL	(27.5–68.7)
P-cAMP	20 pmol/mL	(15–37)
U-cAMP	1.8 μmol/day	(4.4-14.5)
N-cAMP	11.1 nmol/dlGRF	(0.8–2.8)
%TRP	76.3%	(82–95)
U-Hyp	113 μmol/day	(115–460)
U-pyridinoline	75 μmol/molCr	(13–36)
U-deoxypyridinoline	10 μmol/molCr	(<7)

PTH, parathyroid hormone; C-, carboxy-terminal; hs-, high sensitive; PTHrP, parathyroid hormone related peptide; VD, vitamin D; N-cAMP, nephrogenous cAMP; %TRP, % tubular resorption of phosphate; Hyp, hydroxyproline; N.D., not detectable.

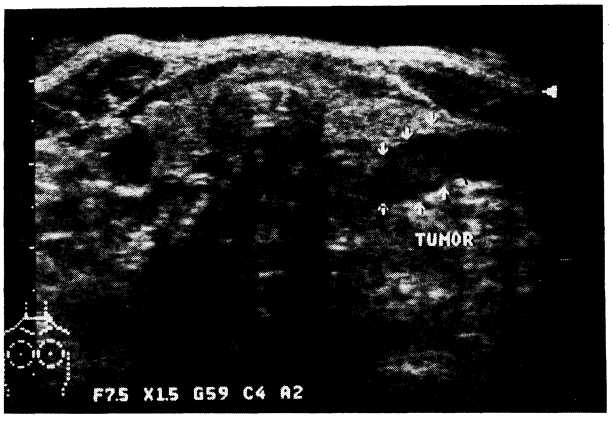

Fig. 1. Ultrasonography of the cervical region. Ultrasonography demonstrating a swollen left parathyroidal gland with diffuse low echogenicity.

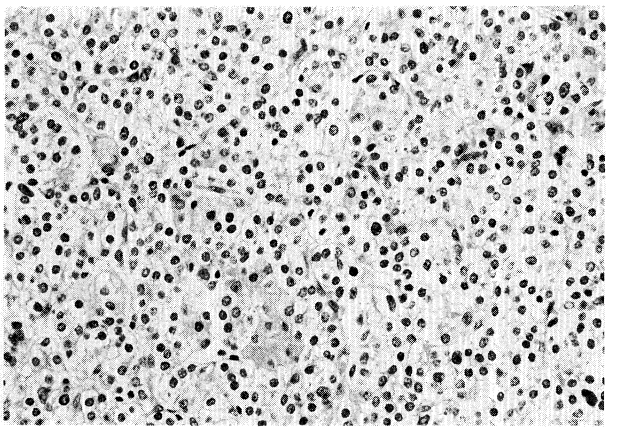

Fig. 2. The microscopic findings in surgically removed parathyroid gland. The resected left parathyroid gland measured 2.5 cm × 1 cm × 2 cm. Microscopic examination revealed parathyroidal chief-cell hyperplasia, which consists of predominant chief-cells with scattered oxiphil-cells (HE stain, × 338).

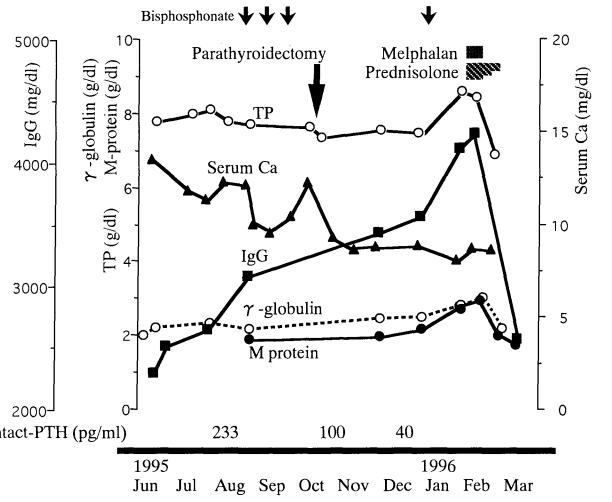

Fig. 3. The clinical course. On admission, as the serum calcium concentration increased (12.5 mg/dl), bisphosphonate (total 45 mg) was administered, being followed by parathyroidectomy. Although postoperative serum intactPTH decreased gradually, the serum IgG (maximum, 4,300 mg/dl) and M-protein concentrations (maximum, 2.9 g/dl) had been increasing and systemic bone pain was greater than in the preoperative state. For the severe bone pain, re-administration of bisphosphonate was not effective. Chemotherapy with melphalan (4 mg/day × 4 days) and prednisolone (40 mg/day × 4 days) were performed 3 months after the parathyroidectomy. About 3 weeks after the initial chemotherapy, serum IgG and M-protein levels were noticeably decreased and there was less bone pain.

prednisolone 40 mg/day for 4 days three months after the parathyroidectomy. Serum immunoglobulin and M-protein concentrations decreased and bone pain was remarkably improved 3 weeks after the chemotherapy (Fig. 3). We are following this patient up both immunologically and endocrinologically.

Discussion

The concurrent diagnosis of hyperparathyroidism and multiple myeloma (MM) should be entertained in patients presenting with hypercalcemia. Either diagnosis does not exclude the other, and inadequate intervention may result in partially increased morbidity or mortality. Although the association of MM with I°HPT has been reported previously in 12 case reports (adenoma: 10 cases, hyperplasia: 1 case) [1–12], only one case of this combination has been reported in Japan [12]. The mechanisms leading to the onset of I°HPT and MM in this patient are unclear. Previous reports have suggested this finding to be incidental [1–10]. Hypercalcemia with malignancy (MAH) has been classified into two groups; humoral hypercalcemia of malignancy (HHM) secondary to parathyroid hormone related peptide (PTHrP) or PTH, and local osteolytic hypercalcemia (LOH) such as MM. In this case, hypercalcemia was a result of PTH alone, which resolved completely after parathyroidectomy (Fig. 3).

The pathogenesis of MM and I°HPT in bone was complicated. In MM, the proliferation of myeloma cells is suggested to be stimulated by IL-6 in autocrine/paracrine mechanism [13], and in the case of I°HPT, PTH not only directly causes bone resorption by osteoclasts affected by stimulated osteoblasts, but also indirectly stimulates IL-6 production in osteoblasts [14]. IL-6 induces increased conversion of the osteoclast-precurcer to osteoclast, and consequently allows myeloma cells to mature and proliferate [15]. These findings suggest that the mechanism of bone resorption between MM and I°HPT is complicated but partly similar as regards some cytokines, but in this patient concentrations of serum soluble IL-1α, β and IL-6 and TNF-α, β were below the limits of

detection, so that these cytokines may be involved at least via an autocrine/paracrine mechanism. Although the role of cytokines attributable to bone remodeling has not been completely clarified, myeloma cells were suspected to be stimulated by both cytokines and PTH. We expected that the activity of MM would gradually diminish postparathyroidectomy because PTH-excess itself contributes to the progression and development of MM. Nevertheless, in this case, since bone pain and the serum M-protein level continued to be increasing postoperatively, we were forced to choose the initial chemotherapy with melphalan 4 mg/day and prednisolone 40 mg/day for 4 days three months after the parathyroidectomy. The description on the inhibition of immunoglobulin production by PTH [16] may explain a part of this postoperative worsening of MM. Consequently, this treatment was able to decrease the patient's bone pain and M-protein level successfully (Fig. 3).

A summary of the reported combined case of MM and I°HPT is shown in Table 2. In previous reports, 9 of 12 cases were treated for MM before parathyroidectomy. In all these 9 case, MM was firstly diagnosed by immunoglobulin abnormality, and subsequent endocrinological examinations revealed hyper-parathyroidism because of persistent hypercalcemia after the chemotherapy. This complication tends to occur predominantly in the elderly. Because chemotherapy, radiation of bone marrow and parathyroidectomy are all invasive for the elderly, the method of treatment must be chosen very carefully. In the chemotherapy in these cases, MP therapy (a combination of melphalan and prednisolone) which was relatively invasiveless even for the elderly was mainly performed. On the other hand, toward I°HPT, parathyroidectomy is the best treatment, but No. 10 case is reported as a successful parathyroid aspiration course. In our case, because the patient was already diagnosed as a combined case, we firstly chose parathyroidectomy after normalization of the serum calcium concentration with bisphosphonate. And sequential low dose MP-therapy was effective for the M-proteinemia and bone pain. The same therapy was reported in case No. 2 and 12, which initially underwent parathyroidectomy followed by both irradiation to plasmacytoma and chemotherapy or chemotherapy alone, respectively, but the treatment for this No. 2 or 12 case was not successful because of cardiac troubles or severe anemia, respectively.

Another interesting features in the present case was histological findings of parathyroid tumor. The resected tumor was histologically solitary chief-cell hyperplasia consisting of predominant chief-cells accompanying scattered oxiphil-cells, which was much fewer than adenoma. Although the pathological diagnosis as parathyroid hyperplasia in this case was based on the remaining lobular structures and the lack of the rim of normal

Table 2. Reported cases in the literature

No.	Author (year)	Sex/Age	Monoclonality	Calcium (mg/dl)	Histology of parathyroid	Therapy	Outcome
1.	Jackson RM (1979)	F/45	IgG-lambda	16.8	adenoma	Ch (MP)	N.D.
2.	Chisholm RC (1981)	M/80	kappa	13.1	adenoma (chief cell)	PTX+RT+Ch (MP, CPA, VCR, BCNU)	death
3.	Mundis RJ (1982)	F/76	IgG-kappa	11.0	adenoma (chief cell)	Ch (MP)+PTX	improved
4.	Francis RM (1982)	F/70	lambda	11.6	adenoma	Ch (MP)	death
5.	Stone MJ (1982)	F/47	IgA-kappa	13.7	adenoma (chief cell)	Ch (MP)+RT+PTX	death
6.	Hoelzer DR (1984)	F/51	IgA-lambda	11.4	adenoma (chief cell)	PTX+?	N.D.
7.	Sarfati E (1985)	F/62	IgA-kappa	16.4	adenoma	Ch (ADM, VCR, PSL)+PTX	improved
8.	Schneider W (1989)	F/74	IgG-kappa	12.0	adenoma (oxiphil cell)	Ch (MP)+PTX	improved
9.	Rao DS (1991)	M/54	IgG-lambda	11.2	adenoma	Ch (ADM, CPA, MP)+PTX	death
10.	Rosen C (1992)	M/81	IgG-kappa	13.4	N.D.	Ch (MP)+RT+*aspiration	improved
11.	Toussirot E (1994)	M/82	kappa	15.2	hyperplasia	Ch (MP)+PTX	death
12.	Goto S (1995)	F/73	kappa	13.2	adenoma	PTX+Ch (M)	death

Ch, chemotherapy; MP, melphalan-prednisolone therapy; PTX, parathyroidectomy; RT, irradiation; ADM, adriamycin; VCR, vincristine; BCNU, carmustine; PSL, prednisolone; N.D., not detailed; *, parathyroidal aspiration following saline injection.

parathyroid, the differential diagnosis between adenoma and hyperplasia of parathyoid has been controversial. The definite parathyroidal diagnosis in this case may require the pathological findings on the other three parathyroid glands, which were found no enlargement by the manipulation during the operation. As shown in Table 2, almost all histology of the parathyroid in these complicated cases was parathyroid adenoma. Although this case was investigated for complication with multiple endocrine neoplasia (MEN), endocrinological and morphological proof was not obtained.

Our case report suggested that patients with hypercalcemia and lumbago should be subjected to both endocrine and immune evaluations. Although the relationship between I°HPT and MM has been unknown, some common cytokines may be involved in these disorders, taking into consideration the existence of such things as POEMS (polyneuropathy, organomegaly, endocrinopathy, M-proteins and skin changes) syndrome. In future, accumulation of these complicated cases would partly clarify the pathogenesis.

References

1. Sarfati E, de Ferron P, Dubost C, Assens P, Veyssier P, Detour B (1985) Myeloma multiple associe a une hyperparathyroidie primitive par adenome. *Ann Med Inteme* 136: 684.
2. Rao DS, Antonelli R, Kane KR, Kuhn JE, Hetnal C (1991) Primary hyperparathyroidism and monoclonal gammopathy. *Henry Ford Hosp Med* 39: 41–44.
3. Rosen C, Segal H, Hartz E, Mroz F, Carlton E (1992) Primary hyperparathyroidism in an elderly patient with multiple myeloma. *JAGS* 40: 703–705.
4. Mundis RJ, Kyle RA (1982) Primary hyperparathyroidism and monoclonal gammopathy of undermined significance. *Am J Clin Pathol* 77: 619–621.
5. Jackson RM, Orland MJ (1979) Parathyroid adenoma in a patient with multiple myeloma. *South Med J* 72: 1336–1337.
6. Chisholm RC, Weaver YJ, Chung EB, Townsend JL (1981) Parathyroid adenoma and light chain myeloma. *J Nath Med Assoc* 73: 875–880.
7. Francis RM, Bynoe AG, Gray C (1982) Hypercalcemia due to the coexistence of parathyroid adenoma and myelomatosis. *J Clin Pathol* 35: 732–736.
8. Stone MJ, Lieberman ZH, Chakmadjian ZH, Matthews JL (1982) Coexistent multiple myeloma and primary hyperparathyroidism. *JAMA* 247: 823–824.
9. Hoezler DR, Silverberg AB (1984) Primary hyperparathyroidism complicated by multiple myeloma. *Arch Intern Med* 144: 2069–2071.
10. Schneider W, Thomas M (1989) Hypercalcemia in coexistent parathyroid adenoma and multiple myeloma. *Dtsch Med Wochenschr* 114: 1199–1202.
11. Toussirot E, Bille F, Henry JF, Acquaviva PC (1994) Coexisting kappa light chain multiple myeloma and primary hyperparathyroidism. *Scand J Rheumatol* 23: 49–50.
12. Goto S, Yoshioka M, Nagai K, Abe A, Murakawa E, Yamazaki N, Koyama T, Sekiya M (1995) Primary hyperparathyroidism associated with multiple myeloma. *Internal Medicine* 34: 988–991.
13. Klein B, Zhang XG, Lu ZY, Bataille R (1995) IL-6 in human multiple myeloma. *Blood* 85: 863.
14. Greenfield EM, Shaw SM, Gornik SA, Banks MA (1995) Adenyl cyclase and interleukin-6 are downstream effectors of parathyroid hormone resulting in stimulation of bone resoroption. *J Clin Invest* 96: 1238–1244.
15. Kishimoto T (1989) The biology of interleukin-6. *Blood* 74: 1–10.
16. Gaciong Z, Alexiewicz JM, Linker-Israeli M, Shulman IA, Pitts TO, Massry SG (1991) Inhibition of immunoglobulin production by parathyroid hormone. Implications in chronic renal failure. *Kidney Int* 40: 96–106.