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Primary Hyperparathyroidism and Monoclonal Gammopathy

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Coexistent primary hyperparathyroidism and monoclonal gammopathy, although rare, has been reported previously by a number of investigators. We report four patients with such an occurrence who were seen between 1976 and 1988. Another patient with primary hyperparathyroidism also had multiple myeloma and was in remission for 12 years. These patients represent approximately 1% of the 386 patients with primary hyperparathyroidism seen during the same 12-year period. Although several mechanisms have been proposed to explain this concurrence, we believe it is the result of a chance occurrence. A review of the literature, an estimate of the chance occurrence of coincidental monoclonal gammopathy, benign or malignant, in patients with primary hyperparathyroidism, and some practical implications of this interesting coexistence are presented. (Henry Ford Hosp Med J 1991;39:41-4)

Primary hyperparathyroidism (PHPT) and monoclonal gammopathy (MG) each can occur in association with a variety of other benign or malignant diseases (1-3). However, when these two conditions coexist, the resultant hypercalcemia and monoclonal protein spike can be misleading both from a diagnostic and management point of view. Although the presence of typical lytic bone lesions of multiple myeloma in a patient with hypercalcemia greatly facilitates the diagnostic evaluation, absence of such skeletal manifestations might complicate management decisions.

Between 1976 and 1988 we encountered four patients with PHPT and benign MG and one patient with PHPT and multiple myeloma. This report documents these five cases, reviews previously reported cases of coexistent PHPT and MG, discusses the possible reason for this concurrence, and proposes recommendations for management and adequate evaluation of such patients.

Case Reports

Case 1

A 62-year-old white man was found to have hypercalcemia during hospitalization for treatment of carpal tunnel syndrome. He denied any symptoms related to either hypercalcemia or PHPT. His only complaints included tingling and numbness related to carpal tunnel syndrome, instability of the left ankle and foot as a result of remote surgery, and pain in the right hip. He was taking no medications known to cause hypercalcemia with the exception of lithium carbonate which he had received for manic depression for 15 years.

Serum electrolytes and creatinine, liver and thyroid function tests, and complete blood count with differential count were normal. Serum protein electrophoresis, performed as part of the evaluation of hypercalcemia, revealed an IgM kappa monoclonal spike. Other immunoglobulins were within the normal range. Skeletal survey showed generalized decrease in bone density without the specific lesions of either PHPT or myeloma. Bone mineral content at the mid-radius was normal. Advanced arthritic changes were noted in the lower spine and right hip. Bone marrow examination was negative for myeloma. Other pertinent investigations related to PHPT are summarized in Table 1.

Discontinuation of lithium for one year, under close supervision, did not alter either serum calcium or indices of parathyroid function tests. Parathyroidectomy was advised but the patient reluctantly refused and agreed to regular follow-up. He subsequently underwent total right hip replacement and remains asymptomatic from hypercalcemia five years later. Serial bone mineral measurements did not show any decline and the MG remains unchanged.

Case 2

A 73-year-old black man with a four-year history of hypertension was incidentally found to have hypercalcemia. He acknowledged symptoms related to benign prostatic hypertrophy and atherosclerotic heart and aortic valvular disease but denied any symptoms related to hypercalcemia. Discontinuation of the thiazide diuretic that he was taking at the time hypercalcemia was discovered did not alter serum calcium significantly. Further evaluation showed a normal serum protein electrophoresis, but an IgG lambda monoclonal spike was present on immunoglobulin electrophoresis. Urinary light chains were undetectable. Skeletal survey and bone scan were normal. Bone marrow aspirate showed a slight increase in plasmacytes but was negative for myeloma. Serum electrolytes and creatinine and complete blood count

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Table 1
Parathyroid Function Studies

Measurement	Case 1	Case 2	Case 3	Case 4	Case 5
Serum:					
Calcium (mg/dL)	11.0	11.2	11.3	10.8	11.1
Phosphate (mg/dL)	2.7	2.6	2.5	2.9	2.1
Creatinine (mg/dL)	1.0	1.3	1.0	1.1	1.2
PTH (ng/mL)	138	1,600	490	97	86
Urine:					
NcAMP (nmol/dL GFR)	3.77	5.84	2.42	4.63	ND
TmP/GFR (mg/dL)	1.73	1.86	1.45	2.43	ND
Calcium (mg/24 hrs)	297	107	ND	267	529

All values were confirmed by repeat measurements.
PTH: < 150 ng/mL for cases 1-3, < 50 ng/mL for case 4, and < 40 ng/mL for case 5.
PTH = parathyroid hormone, NcAMP = nephrogenous cyclic adenosine monophosphate, GFR = glomerular filtration rate, TmP = renal phosphate threshold, ND = not done or not available at the time.

with differential count were normal. Results of parathyroid function studies are summarized in Table 1.

The patient refused surgery but agreed to be seen regularly. He was followed closely for three years during which a gradual increase in IgG component was noted (from 12.9 to 17.3 g/L [1,290 to 1,730 mg/dL], normal 7 to 16 g/L [700 to 1,600 mg/dL]). Small amounts of free lambda light chains were noted in the urine on two occasions, but subsequent evaluations failed to detect these proteins. The mild anemia which developed (hemoglobin 118 g/L [11.8 g/dL]) was attributed to intermittent blood loss secondary to diverticulosis.

The patient was lost to follow-up for two years, but when he returned the hypercalcemia and monoclonal protein spike were unchanged. He again refused parathyroidectomy and died suddenly of cardiac arrhythmia five years after the initial detection of hypercalcemia and benign MG. Repeat bone marrow examination could not be done and an autopsy was not permitted.

Case 3

A 69-year-old black man was found to have hypercalcemia during hospitalization for an automobile accident. Serum protein electrophoresis, performed as part of the evaluation for hypercalcemia, revealed an IgG lambda monoclonal spike. Quantitative serum immunoglobulins were normal and no free light chains were seen in the urine. He was asymptomatic from hypercalcemia but had moderate dementia which was initially thought to be related to his history of heavy alcohol abuse. Later, neurologic evaluation confirmed the presence of Alzheimer's disease.

Serum electrolytes and creatinine, liver function tests, and complete blood count with differential count were normal. The skeletal survey was normal as was the bone mineral content at the mid-radius. Other pertinent laboratory investigations related to PHPT are shown in Table 1. The patient was felt to be incapable of making a decision regarding parathyroidectomy, but his family remains undecided about surgical intervention in view of his lack of symptoms of hypercalcemia and the presence of significant dementia. He is currently being followed at six-month intervals and no change in serum calcium, creatinine, or immunoglobulin levels or bone density has been noted. His dementia has been stable over the past two years.

Case 4

A 79-year-old white woman was referred for evaluation of accidentally discovered hypercalcemia. Two years previously she was diagnosed to have polymyalgia rheumatica (PMR) and had been receiving corticosteroids. Serum calcium remained stable, unaffected by prednisone therapy. Immunoglobulin electrophoresis performed as part of the evaluation of PMR showed an IgG kappa monoclonal spike, along with elevated sedimentation rate and hypercalcemia. The skeletal survey was normal and bone marrow examination was not performed. Nine years previously she had been seen by one of us for evaluation of osteoporosis. Serum calcium, phosphate, creatinine, and parathyroid hormone levels and bone density were normal and there was no evidence of osteoporosis. In the ensuing seven years she had remained asymptomatic until she was found to have PMR.

At the time of the recent evaluation she was asymptomatic from hypercalcemia and the response of PMR to corticosteroid therapy was excellent. Results of the parathyroid function studies are summarized in Table 1. Parathyroidectomy was recommended, even though she is asymptomatic, because of her benign MG and the possible additional deleterious effects of corticosteroids on bone.

Case 5

A 54-year-old black man with hypertension was found to have hypercalcemia during an annual screening test. Mild anemia (hemoglobin 113 g/L [11.3 g/dL]) and proteinuria (1+) were also noted for the first time. He was asymptomatic from hypercalcemia. An intravenous pyelogram, performed as part of the evaluation of hypertension, revealed the presence of a kidney stone in the lower pole of the left kidney. Serum protein electrophoresis showed increased gamma globulins, and immunoglobulin electrophoresis revealed an IgG monoclonal spike with depression of other immunoglobulins. Skeletal survey and bone scan were normal, as was the radial bone mineral content. Bone marrow examination confirmed the diagnosis of multiple myeloma.

Although the parathyroid function studies were consistent with a diagnosis of PHPT (Table 1), neck exploration was deferred in order to initiate treatment for myeloma. Therapy with adriamycin, cyclophosphamide, melphalan, and prednisone was commenced. Over the next six months the myeloma responded well to therapy and was judged to be in remission. During the same six-month period serial measurements of serum calcium, phosphorus, creatinine, alkaline phosphatase, and immunoreactive parathyroid hormone levels remained unchanged, which is consistent with the equilibrium type of hypercalcemia of PHPT. Parathyroidectomy was recommended and a 7.52 g adenoma was removed at surgery. Serum calcium was normal for the next 12 years and multiple myeloma remained in remission with intermittent chemotherapy. However, hypercalcemia recurred in association with a pathologic fracture through a typical lytic lesion of myeloma in the right humerus. Unlike the previous episode of stable hypercalcemia, serum calcium now fluctuated widely between 2.99 and 3.99 mmol/L (12 and 16 mg/dL) and parathyroid hormone levels were suppressed. He died eight weeks later of pneumonia and sepsis. An autopsy was not permitted.

Comment

These five cases have in common PHPT and MG, one of whom also had multiple myeloma. Several other cases of such concurrence have been reported (Tables 2 and 3).

We have found 18 reported cases of PHPT and benign MG to which we add four cases (1,4-7). Three additional cases of PHPT were discovered during a retrospective analysis of patients with MG of unknown significance, but further details were not given (3). It is unclear whether these three patients were included

Table 2
Details of 22 Cases of PHPT and Benign MG

Case (Ref)	Age/Sex/ Race	Immunoglobulin	Preoperative Calcium	Surgical Findings	Follow-up Period*
1 (1)	Details could not be ascertained from the report.				
2 (1)	Details could not be ascertained from the report.				
3 (4)	51/F/W	IgG lambda	11.5	Adenoma	96
4 (5)	62/M/B	IgG kappa	13.5	Adenoma	12
5 (5)	74/F/B	IgG lambda	14.8	Hyperplasia	12
6 (5)	68/F/B	IgG lambda	14.6	Adenoma	5
7 (6)	64/F/-	IgA kappa	13.2	Adenoma	NFU
8 (6)	73/F/-	IgG lambda	11.6	NOP	NFU
9 (6)	71/F/-	IgA lambda	13.1	Adenoma	NFU
10 (7)	69/F/W	IgG lambda	14.6	Adenoma	119
11 (7)	73/F/W	IgG kappa	13.7	Adenoma	7
12 (7)	66/F/W	IgG lambda	10.9	Adenoma	78
13 (7)	55/M/W	IgA kappa	11.2	Adenoma	80
14 (7)	59/F/W	IgG kappa	11.7	Adenoma	61
15 (7)	72/F/W	IgM kappa	13.3	Adenoma	60
16 (7)	60/F/W	IgG kappa	11.1	Adenoma	19
17 (7)	69/M/W	IgA kappa	11.6	Adenoma	62
18 (7)	52/F/W	IgG kappa	12.2	Adenoma	60
19†	62/M/W	IgM kappa	11.0	NOP	40
20†	73/M/B	IgG lambda	12.2	NOP	60
21†	69/M/B	IgG lambda	11.3	NOP	36
22†	79/F/W	IgG kappa	10.8	NOP	12

*Follow-up period is in months from the time of diagnosis of PHPT.
†Current cases.
NFU = no follow-up data given, NOP = not operated.

Table 3
Details of 13 Cases of PHPT and Multiple Myeloma

Case (Ref)	Age/Sex/ Race	Immunoglobulin	Preoperative Calcium	Surgical Findings
1 (1)	ND	ND	ND	? Adenoma
2 (1)	ND	ND	ND	? Adenoma
3 (1)	ND	ND	ND	? Adenoma
4 (1)	ND	ND	ND	Hyperplasia
5 (2)	ND	ND	ND	Adenoma
6 (7)	76/F/-	IgG kappa	11.1	Adenoma
7 (8)	45/F/W	IgG lambda	17.1	Adenoma*
8 (9)	80/M/B	Kappa chains	13.1	Adenoma
9 (10)	70/F/-	Lambda chain	11.6	Adenoma†
10 (11)	47/F/-	IgA kappa	14.3	Adenoma
11 (12)	51/F/-	IgG lambda	11.9	Adenoma
12 (13)	74/F/W	IgG kappa	12.0	Adenoma
13‡	54/M/B	IgG lambda	11.2	Adenoma

*By noninvasive method.
†Autopsy findings.
‡Current case.
ND = no details given.

among the nine patients with PHPT and MG later reported from the same institution (7).

Concurrent PHPT and multiple myeloma has also been reported in 12 instances to which we add another case (1,2,7-13). Additional cases of coexistent PHPT and multiple myeloma have been referred to but no details were given (14). Hypercalcemia was an incidental finding in the majority of the patients in both groups (i.e., PHPT and benign MG, and PHPT and multiple myeloma).

All patients with PHPT and benign MG in whom information was provided were over 50 years old. This is consistent with the increasing prevalence of both diseases with advancing age (15, 16). The preponderance of women (13 of the 19 cases, Table 2) reflects the increased prevalence of PHPT in women, even though benign MG is more common among men. Parathyroid pathology was an adenoma in 15 of the 16 cases (Table 2); this is similar to the findings in an unselected group of patients with PHPT (17). None of the patients developed multiple myeloma, although follow-up was relatively short in a few cases (Table 2). Transient disappearance of monoclonal protein spike occurred in one patient, but it reappeared and remained stable over an eight-year follow-up (4,5).

Assessment of the age and sex distribution among patients with PHPT and multiple myeloma was difficult because of the lack of information in five of the 13 cases (Table 3). However, among those with sufficent information, females outnumbered males (six women versus two men). At surgery, an adenoma was found in nine of the 10 patients in whom parathyroid pathology was reported (Table 3). An additional patient probably had an adenoma as assessed by a noninvasive method (8). Hypercalcemia remained stable and did not respond to the usual chemotherapy for myeloma in six patients (including our patient) in whom it was studied (7,8,10,12,13). This is consistent with the concept of equilibrium hypercalcemia of PHPT (18). Osteolytic lesions of myeloma were present in three of the seven reported patients. A second episode of hypercalcemia, presumably nonparathyroid hormone mediated, has been documented in two cases (9,11). Our patient with PHPT and myeloma illustrates such an occurrence 12 years after the diagnosis of myeloma and parathyroidectomy, emphasizing the need for continued surveillance of these patients. Death ensued within two years of recurrence of hypercalcemia in all patients despite intensive chemotherapy.

The nature of the coexistence of PHPT and benign MG and of PHPT and multiple myeloma is unclear. Although several mechanisms have been proposed, none are satisfactory (4-6). Based on available information and our own experience, the estimated prevalence is 0.6% to 1.0% for benign MG in PHPT and 0.1% to 1.14% for myeloma in PHPT (1,7). Conversely, the prevalence is 1.2% for PHPT in benign MG and 0.1% for PHPT in myeloma (3,19). Furthermore, the prevalence rates in the general population for benign MG, multiple myeloma, and PHPT are approximately 1% to 3%, 0.1%, and 0.1% to 0.5%, respectively (14-16). Given these various estimates, the concurrence of PHPT with either benign MG or myeloma appears to be coincidental and conforms to the expected frequency. Our four patients with PHPT and benign MG and the patient with PHPT and myeloma were detected from among 386 cases of PHPT seen during the same 12-year period. An additional patient with myeloma and probable PHPT was encountered among our patients with PHPT, but full confirmation of PHPT was lacking. Thus the coexistence of benign MG or myeloma with PHPT in our population of patients with PHPT is in agreement with other estimates where a systematic evaluation of patients with hypercalcemia with serum protein electrophoresis is performed (1,7).

Apart from this interesting coexistence of PHPT with either benign MG or multiple myeloma, several important practical implications can be drawn from these cases. First, accidental discovery of hypercalcemia in an otherwise healthy individual is almost always due to PHPT and rarely to sarcoidosis or multiple myeloma. All of our patients were found to have hypercalcemia during routine biochemical screening and the MG was discovered on further evaluation of hypercalcemia. We do not routinely perform serum protein or immunoglobulin electrophoresis in patients with PHPT, and all five patients reported here were referred to us after the initial electrophoresis had already been performed. Second, in the absence of other indicators of disease such as anemia, serum protein abnormalities, azotemia, and bone pain, routine studies of serum protein or immunoglobulin electrophoresis do not appear to be justified in all patients with PHPT; the cost is high, the diagnostic yield is low, and the outcome is essentially unaffected. Third, presence of a monoclonal spike in a patient with stable hypercalcemia does not necessarily indicate myeloma nor a poor prognosis. Correction of PHPT-related hypercalcemia by parathyroidectomy, which was accomplished in our patient with myeloma, alters the classification of the myeloma tumor mass and offers a favorable prognosis. Furthermore, hypercalcemia is not a feature of benign MG. Fourth, elevated serum parathyroid hormone levels strongly indicate an underlying PHPT. There has not been a single negative neck exploration in any of the 30 patients with PHPT and benign MG or myeloma (Tables 2 and 3). A similar success rate has been reported in another group of patients with PHPT and presumed paraneoplastic hypercalcemia in whom nephrogenous cAMP was increased (2). Fifth, with the emergence of mild asymptomatic PHPT as the major proportion of patients with PHPT, a conservative nonsurgical approach is being adopted by an increasing number of clinicians (20-22). While this approach is fully justified, parathyroidectomy is probably indicated in asymptomatic patients with PHPT when it coexists with benign MG and multiple myeloma. Parathyroidectomy in such patients subserves three important functions: it eliminates the confusion regarding the pathogenesis of hypercalcemia, alters the prognosis of concurrent myeloma, and preserves the validity of hypercalcemia as a tumor marker in both benign MG and myeloma should hypercalcemia recur.

Finally, it is important to distinguish "association" from "concurrence"; the former implies a cause-and-effect relationship and the latter a simple chance occurrence. The probability of finding multiple diseases in hospital or clinic populations, compared to the general population, is increased because of selection factors that are at work in such patients (23). This phenomenon has resulted in many reports of "associations" with PHPT, when in fact these are purely random events and tend to aggregate in hospital or clinic populations. It is therefore hazardous to draw conclusions about an "association" between two diseases in such populations.

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