

Prevalence of Monoclonal Gammopathy in Patients With Primary Hyperparathyroidism

A Prospective Study

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Background: The association between primary hyperparathyroidism (PHPT) and monoclonal gammopathy has been reported, but whether it is fortuitous remains unsettled. We conducted a prospective study to determine the prevalence of monoclonal gammopathies in patients with surgically proved PHPT.

Methods: In 101 consecutive patients with PHPT, serum immunoglobulins were systematically studied using agarose gel electrophoresis and immunofixation before and, when appropriate, after parathyroid surgery. The PHPT population was compared with a control series of patients with other diseases requiring surgery and with a group of patients with benign disease of the thyroid gland matched for age and sex to the PHPT population.

Results: Monoclonal immunoglobulin was detected in 10 (10%) of 101 patients with PHPT (including 2 with multiple myeloma) compared with 2 (2%) of 127 patients who underwent other surgery ($P=.005$) and 3 (3%) of 101 patients with benign thyroid diseases ($P=.04$).

Conclusions: The prevalence of monoclonal gammopathies is high in patients with PHPT. At minimum, sensitive serum protein electrophoresis should be performed routinely in all patients with PHPT. Conversely, in patients with monoclonal gammopathy who have hypercalcemia but no other symptoms of progressive disease, clinicians must seek PHPT.

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MONOCLONAL gammopathy may be detected in the absence of any overt lymphoid disorder, defining the so-called monoclonal gammopathies of undetermined significance, or in association with B-cell malignancies, mostly multiple myeloma and Waldenström macroglobulinemia. The prevalence of monoclonal gammopathies, which is about 1% in the general adult population, increases with age and with some pathological conditions, particularly in patients with hepatitis C virus infection, in whom it may exceed 10%.¹

Primary hyperparathyroidism (PHPT) is also a relatively frequent disease. The introduction of automated serum calcium measurements in the 1970s greatly modified the prevalence and the clinical spectrum of this condition. Primary hyperparathyroidism affects approximately 1 in 10000 persons, most of whom have an asymptomatic and uncomplicated disease identified because of the fortuitous discovery of a mild increase in the serum calcium level.

The association of monoclonal gammopathies with PHPT is mentioned in current medical textbooks.² It was first de-

scribed in 1964 in a patient with monoclonal gammopathies of undetermined significance in whom the monoclonal immunoglobulin (MIg) disappeared after surgical resection of a parathyroid adenoma, suggesting a possible link between the 2 conditions.³ However, no similar postoperative outcome was observed in any of the additional cases that were published. Therefore, the association between the 2 disorders is still controversial.⁴⁻¹¹ This prompted us to prospectively evaluate the prevalence of monoclonal gammopathies in patients with surgically proved PHPT.

RESULTS

Serum samples from 101 patients (72 women and 29 men) with PHPT were studied. There were 3 black patients, and the remainder were white. The median patient age was 58 years (range, 30-92 years), and 14 were older than 70 years. Two patients had a familial or personal history that might suggest multiple endocrine neoplasia type I.¹² The preoperative highest serum calcium level varied between 10.44 and 14.00 mg/dL (2.61 and 3.50 mmol/L) (median, 12.00 mg/dL [3.00 mmol/L]).

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PATIENTS AND METHODS

PATIENTS

Between June 1, 1997, and June 1, 1998, all consecutive patients referred to the Department of Surgery, Hôpital Saint-Louis, Paris, for treatment of PHPT were included in the study. Patients who underwent surgery because of hyperparathyroidism secondary to renal insufficiency were not included. All studied patients had hypercalcemia (reference range, 8.80-10.40 mg/dL [2.20-2.60 mmol/L]) with an inappropriately elevated serum parathyroid hormone level (>60 pg/mL [6.3 ng/L] by intact hormone radioimmunoassay). Surgical exploration of the 4 parathyroid glands, with standard histopathological analysis of removed tissue, was performed in all patients. After the surgical procedure, follow-up letters requesting information and a serum sample were sent to all patients with MIg and their physicians.

The prevalence of MIg in the PHPT population was compared with that in 2 control groups: the surgical group included patients without features of PHPT selected at random among patients older than 40 years in the same surgical department, and the thyroid group was selected among patients who were diagnosed in the nuclear medicine department of the hospital as having a thyroid tumor. This was either a toxic adenoma or a cold nodule with no cytological criteria for malignancy. In the thyroid group, patients were matched 1 to 1 for sex and age with patients with PHPT. In both control groups, patients with known hematological disorders, previous chemotherapy, or chronic liver diseases were excluded. All patients gave informed consent.

STUDY OF IMMUNOGLOBULINS

Serum specimens were obtained from all patients in the PHPT group before the surgical procedure and from all patients in each control group and were studied using electrophoresis of proteins on agarose gel (Paragon SPE; Beckman Coulter Inc, Fullerton, Calif) and using immunofixation to detect the MIg component (Paragon IFE; Beckman Coulter Inc).

STATISTICAL ANALYSIS

The prevalence of monoclonal gammopathies in patients with PHPT was compared with the prevalence of MIg in the surgical and thyroid groups using χ^2 analysis or the Fisher exact test. $P < .05$ was considered statistically significant.

Parathyroid hormone levels were between 60 and 1030 pg/mL (6.3 and 108.5 ng/L) (median, 200 pg/mL [21.1 ng/L]). Histological analysis of removed parathyroid tissues showed a solitary adenoma, multiple adenomas, and a diffuse proliferation of chief cells suggestive of hyperplasia in 96 (96%), 3 (3%), and 2 (2%) patients, respectively.

Serum MIg was detected in 10 (10%) of 101 patients. The main characteristics of these patients are given

in the **Table**. None of these patients had evidence of liver disease, chronic viral infection, or any other nonhematological conditions. Serologic test results for hepatitis B and C and human immunodeficiency virus infection were negative in all cases. Complete blood cell counts were always normal. The monoclonal protein produced a detectable narrow band on electrophoretic screening in 7 patients, whereas the MIg was detected by immunofixation only in 3. The serum level of polyclonal immunoglobulins was within reference limits in all patients but 2. In these 2 patients, stage I indolent multiple myeloma was diagnosed because bone marrow smears showed abnormal plasma cells, whereas bone radiographs did not disclose any lytic lesions. The 8 remaining patients had monoclonal gammopathies of undetermined significance, according to Southwest Oncology Group criteria.¹³ A control serum immunoglobulin study was performed within 3 months or more after the surgical procedure in 5 patients and showed the persistence of the MIg in all.

The surgical control group comprised 127 patients (66 women and 61 men), with a median age of 60 years (range, 40-78 years). Sixty patients (47%) had a solid tumor. Two patients (2%) had serum MIg, which was detectable on electrophoretic screening in only 1. In both patients, the isotype of the monoclonal components was IgG κ . Associated pathological conditions were thyroid carcinoma in 1 patient and a myxoid muscular tumor in the other.

The age- and sex-matched thyroid control group comprised 101 patients (median age, 56 years; range, 32-89 years), of whom three-quarters had a toxic nodule, either unique or within a multinodular goiter. All others had cytologically benign cold thyroid nodules. In this group, 3 women aged approximately 60 years with toxic multinodular goiters had an MIg (2 IgG λ and 1 IgA λ) that was detected only by immunofixation.

The prevalence of monoclonal gammopathies in patients with PHPT and in control patients was significantly different; comparing the PHPT group with the surgical group and thyroid group, $P \leq .005$ (10% vs 2%) and $P \leq .04$ (10% vs 3%), respectively.

COMMENT

The prevalence of monoclonal gammopathies in the population of healthy or hospitalized adult patients has been estimated to be approximately 1% by several large analyses of electrophoretic data performed in Sweden, Italy, the United States, and France.¹⁴⁻¹⁶ This prevalence increases with patient age and varies according to sex and race, being higher in men than women and in black patients than white patients.¹⁷ In a recent large US study¹⁸ using agarose gel electrophoresis and immunofixation, the frequency of a monoclonal protein in healthy individuals older than 70 years was 6.1% (3.8% in white subjects and 8.4% in black subjects). Frequency can reach nearly 15% in persons older than 90 years.¹⁹ In contrast, the prevalence of MIg in persons younger than 50 years is low (approximately 0.2%).²⁰

The present study reports a prevalence of monoclonal gammopathies of 10% in a series of consecutive pa-

Clinical, Laboratory, and Histological Features of Patients With Monoclonal Immunoglobulin and Primary Hyperparathyroidism

Patient No./ Sex/Age, y	Monoclonal Immunoglobulin (Ig)	Calcium Level, mg/dL*	Phosphorus Level, mg/dL†	Parathyroid Hormone Level, pg/mL‡	Histological Findings
1/F/32	IgG κ	11.20	1.8	120	Adenoma
2/F/63	IgA λ	11.84	2.5	198	Adenoma
3/F/75	IgG κ	11.20	2.8	154	Adenoma
4/F/51	IgA κ	11.28	2.3	118	Adenoma
5/F/83	IgMκ	12.32	2.5	179	Adenoma
6/F/77	IgG κ	11.84	2.5	198	Adenoma
7/F/64	IgA λ	10.88	1.9	95	Adenoma
8/F/84	IgMκ	12.00	2.5	105	Adenoma
9/F/68	IgG κ	10.80	...	85	Hyperplasia
10/F/90	IgG κ	11.76	2.8	190	Adenoma

*To convert calcium from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.25.

†To convert phosphorus from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.323.

‡To convert parathyroid hormone from picograms per milliliter to nanograms per liter, multiply picograms per milliliter by 0.1053.

tients with PHPT. This high prevalence is all the more striking because most of these patients were white and two thirds were female. In addition, their median age was younger than 60 years, as expected for patients with PHPT.^{21,22} All patients but 1 with MIg were women. One patient was very young (32 years old), whereas 4 (of the 14 patients of the series) were older than 70 years.

The prevalence of MIg in patients with PHPT was significantly higher than that of a control population randomly selected among patients who underwent surgery for various reasons. Compared with a healthy population, the frequency of MIg in this group (2%) was probably slightly high, but many patients, including the 2 with MIg, had a nonhematological solid tumor, a condition that might be associated with an increased frequency of monoclonal gammopathies.²³ The prevalence of MIg in the PHPT population was also significantly higher than that in the thyroid control group, which was more suitable than that in the surgical control group because this group was matched for age and sex and selected among patients with another cervical disorder, namely, a thyroid tumor. In addition, patients in the thyroid group had benign tumor, in most cases toxic adenoma.

Two previous studies,^{6,8} conducted in the 1970s, addressed the issue of the frequency of monoclonal gammopathies in patients with PHPT. Johansson and Wermer⁶ reported MIg in 6 (2%) of 350 patients, and Mundis and Kyle⁸ found a prevalence of MIg of 1% in a series of 911 patients older than 50 years with surgically proved parathyroid adenoma. Both studies were retrospective; the first study did not include systematic laboratory tests for immunoglobulins, whereas the second was based on eventual reexamination (if the γ - or β -globulin levels were above the reference limits) of previously performed electrophoretic cellulose acetate strips. Serum immunoelectrophoresis was performed only when the electrophoretic data showed a pattern suggesting monoclonal gammopathy.

The present study was prospective and used a more sensitive approach for serum MIg detection by combining agarose gel electrophoresis with immunofixation. These methodological differences likely explain the higher prevalence of MIg in our series. Indeed, because of its low level, the MIg would have been missed in at least 3

of our patients if only standard electrophoresis had been used. Urine proteins were not systematically studied, which could have led to detection of additional monoclonal gammopathies characterized by the presence of immunoglobulin monoclonal light chains only, as in 4 patients reported in the literature.²⁴

This study has several limitations. First, the sample size should have been larger to definitely rule out a chance association between monoclonal gammopathies and PHPT. In addition, the prevalence of PHPT in patients with monoclonal gammopathies of undetermined significance or myeloma was not determined. Of note, PHPT may not be rare because 10 patients referred to the Department of Immuno-Hematology, Hôpital Saint-Louis, during the past 3 years for MIg and hypercalcemia in fact had PHPT (B.A. and J.-P.F., unpublished data, 2000). Another possible limitation of this study is that patients referred for surgery may not be representative of the entire spectrum of patients with PHPT. However, the present PHPT population was similar to the large series of PHPT reported in the literature,^{21,22} particularly with regard to age and serum calcium level. Indeed, in our area, and as recently proposed,²⁵ parathyroidectomy is usually considered in most patients with PHPT, whether they are symptomatic or not.

The relationship between monoclonal gammopathy and PHPT remains speculative. Soluble factors secreted by one type of tumor cell (or their environment) may trigger the growth of the other tumor population. For instance, the MIg may act as a growth factor for the parathyroid cells, as does the IgG so-called thyroid-stimulating immunoglobulin on thyroid cells in Basedow disease.²⁶ To test this hypothesis, we performed immunofluorescence studies on parathyroid tissue sections, but, like Dexter et al,⁵ we found no binding of immunoglobulin, including on adenoma sections derived from patients with MIg (data not shown). Alternatively, parathyroid hormone stimulates stromal-osteoblastic cells to secrete interleukin 6,²⁷ and patients with PHPT have high circulating levels of interleukin 6.²⁸ Because this cytokine plays a key role in the development of plasma cell dyscrasias,²⁹ high parathyroid hormone levels may facilitate the emergence and growth of a plasma cell clone.

The latter possibility may argue in favor of systematic parathyroid surgery in all patients with PHPT and monoclonal gammopathy in an attempt to limit the risk of development of overt myeloma. However, because clearing of MIg seems to be rare after parathyroidectomy, the discovery of MIg in a patient with PHPT cannot be presently considered as a strong argument for surgery. In any case, the prevalence of the association of monoclonal gammopathy and PHPT may justify the systematic study of serum immunoglobulins in patients with PHPT. Such study may lead to the discovery of multiple myeloma, as in 2 patients of our series. Finally, our experience indicates that in patients with MIg who have an elevated serum calcium level but no other symptoms of a progressive disease, PHPT must be sought.

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REFERENCES

1. Andreone P, Zignego AL, Cursaro C, et al. Prevalence of monoclonal gammopathies in patients with hepatitis C virus infection. *Ann Intern Med.* 1998;129:294-298.
2. Foerster J. Plasma cell dyscrasias: general considerations. In: Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN, eds. *Wintrube's Clinical Hematology.* 9th ed. Philadelphia, Pa: Lea & Febiger; 1993:2202-2218.
3. Clubb JS, Posen S, Neale FC. Disappearance of a serum paraprotein after parathyroidectomy. *Arch Intern Med.* 1964;114:616-620.
4. Schnur MJ, Appel GB, Bilezikian JP. Primary hyperparathyroidism and benign monoclonal gammopathy. *Arch Intern Med.* 1977;137:1201-1203.
5. Dexter RN, Mullinax F, Estep HL, Williams RC. Monoclonal IgG gammopathy and hyperparathyroidism. *Ann Intern Med.* 1972;77:759-764.
6. Johansson H, Wermer I. Dysproteinemia, malignancy and hyperparathyroidism. *Ann Intern Med.* 1975;83:121-122.
7. Stone MJ, Lieberman ZH, Chakmakjian ZH, Matthews JL. Coexistent multiple myeloma and primary hyperparathyroidism. *JAMA.* 1982;247:823-824.
8. Mundis RJ, Kyle RA. Primary hyperparathyroidism and monoclonal gammopathy of undetermined significance. *Am J Clin Pathol.* 1982;77:619-621.
9. Rosen C, Segal H, Hartz F, Mroz F, Carlton E. Primary hyperparathyroidism in an elderly patient with multiple myeloma. *J Am Geriatr Soc.* 1992;40:703-705.
10. Toussrot E, Bille F, Henry JF, Acquaviva PC. Coexisting kappa light chain multiple myeloma and primary hyperparathyroidism. *Scand J Rheumatol.* 1994;23:49-50.
11. Goto S, Yoshioka M, Nagal K, et al. Primary hyperparathyroidism associated with multiple myeloma. *Ann Intern Med.* 1995;34:988-991.
12. Thompson NW. Multiple endocrine neoplasia type I: surgical therapy. *Cancer Treat Res.* 1997;89:407-419.
13. Salmon SE, Cassady JR. Plasma cell neoplasms. In: De Vita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology.* 3rd ed. Philadelphia, Pa: JB Lippincott; 1989:1884-1887.
14. Axelsson U, Bachmann R, Hällén J. Frequency of pathological proteins (M-components) in 6995 sera from an adult population. *Acta Med Scand.* 1966;179:235-247.
15. Malacrida V, De Francesco D, Banfi G, Porta FA, Riches PG. Laboratory investigation of monoclonal gammopathy during 10 years of screening in a general hospital. *J Clin Pathol.* 1987;40:793-797.
16. Saeun JP, Vicariot M, Deroff P, Morin JF. Monoclonal gammopathies in the adult population of Finistere, France. *J Clin Pathol.* 1982;35:63-68.
17. Singh J, Dudley AW Jr, Kulig KA. Increased incidence of monoclonal gammopathy of undetermined significance in blacks and its age-related differences with whites on the basis of a study of 397 men and one woman in a hospital setting. *J Lab Clin Med.* 1990;116:785-789.
18. Cohen HJ, Crawford J, Rao MK, Pieper CF, Currie MS. Racial differences in the prevalence of monoclonal gammopathy in a community-based sample of the elderly. *Am J Med.* 1998;104:439-444.
19. Connault L, Preud'homme JL, Gombert J, Aperce JM, Aucouturier P. Serum monoclonal immunoglobulins in healthy aged people: a study of incidence and isotype using a sensitive immunoblotting method. *Aging Immunol Infect Dis.* 1991;3:37-42.
20. Kyle RA. Monoclonal gammopathy of undetermined significance. *Blood Rev.* 1994;8:135-141.
21. Zahrani AA, Levine MA. Primary hyperparathyroidism. *Lancet.* 1997;349:1233-1238.
22. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med.* 1999;341:1249-1255.
23. Cen HP, Carroll JA. Monoclonal gammopathy in carcinoma of the colon. *Am J Clin Pathol.* 1980;73:607-610.
24. Kyle RA, Greipp PR. "Idiopathic" Bence Jones proteinuria: long-term follow-up in seven patients. *N Engl J Med.* 1982;306:564-567.
25. Toft AD. Surgery for primary hyperparathyroidism: sooner rather than later. *Lancet.* 2000;355:1748-1749.
26. Weetman AP, Yateman ME, Ealey PA, et al. Thyroid-stimulating antibody activity between different immunoglobulin G subclasses. *J Clin Invest.* 1990;86:723-727.
27. Greenfield EM, Hotowitz MC, Lavish SA. Stimulation by parathyroid hormone of interleukin-6 and leukemia inhibitory factor expression in osteoblasts is an immediate-early gene response induced by cAMP signal transduction. *J Biol Chem.* 1996;271:10984-10989.
28. Roodman GD. Interleukin-6: an osteotropic factor? *J Bone Miner Res.* 1992;7:475-478.
29. Treon SP, Anderson KC. Interleukin-6 in multiple myeloma and related plasma cell dyscrasias. *Curr Opin Hematol.* 1998;5:42-48.