Prevalence of Monoclonal Gammopathy in Patients With Primary Hyperparathyroidism

A Prospective Study

Bertrand Arnulf, MD; Djaouida Bengoufa, MD; Emile Sarfati, MD; Marie-Elisabeth Toubert, MD; Véronique Meignin, MD; Jean-Claude Brouet, MD, PhD; Jean-Paul Fermand, MD

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 Waldenstrom 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 described 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]).
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 radioimmunooassay). 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 control group, comprised of patients without features of PHPT selected at random among patients older than 40 years in the same surgical department, and the thyroid group, 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 χ² analysis or the Fisher exact test. P<.05 was considered statistically significant.

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=.0067 (10% vs 2%) and P=.04 (10% vs 3%), respectively.

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. 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. In a recent large US study, 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. In contrast, the prevalence of MIg in persons younger than 50 years is low (approximately 0.2%).

The present study reports a prevalence of monoclonal gammopathies of 10% in a series of consecutive pa-
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.23 All patients but 1 with Mlg 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 Mlg 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 Mlg in this group (2%) was probably slightly high, but many patients, including the 2 with Mlg, had a nonhematological solid tumor, a condition that might be associated with an increased frequency of monoclonal gammopathies.23 The prevalence of Mlg 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 Mlg in 6 (2%) of 350 patients, and Mundis and Kyle8 found a prevalence of Mlg 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 Mlg detection by combining agarose gel electrophoresis with immunofixation. These methodological differences likely explain the higher prevalence of Mlg in our series. Indeed, because of its low level, the Mlg 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 Mlg 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 Mlg 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,7 we found no binding of immunoglobulin, including on adenoma sections derived from patients with Mlg (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 hypercalcemia. 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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Corresponding author and reprints: Jean-Paul Fermand, MD, Service d’Immuno-Hématologie, Hôpital Saint-Louis, 1, avenue Claude Vellefaux, 75475 Paris, Cedex 10, France (e-mail: jfermand@yahoo.fr).

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