Improvement of the autoimmune phenomenon after treatment of primary hyperparathyroidism: Possible role of dynamics of parathyroid hormone-1-receptor in B-lymphocytes

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Abstract

We report a case of 65-year-old male patient with primary hyperparathyroidism (PHPT) who was admitted to the hospital for autoimmune manifestations (including autoimmune hepatitis and autoantibody development) and exhibited subsequent clinical and paraclinical improvement after parathyroidectomy. By flow cytometry, the expression of PTH receptor 1 (PTHR1) on B lymphocytes of peripheral blood was documented to be higher than that in healthy controls. After parathyroidectomy, autoimmune manifestations improved, while PTH1R expression on B-lymphocytes increased. The possible role of the dynamics of B-lymphocyte PTHR1 in the development of this autoimmune phenomenon is discussed.

1. Introduction

Parathyroid hormone (PTH) is a peptide secreted by the parathyroid glands that maintains calcium homeostasis through effects on the bone and kidney and indirectly on the intestine through vitamin D absorption [1,2]. Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by hypercalcemia and elevated levels of PTH [3]. PHPT results from excessive secretion of PTH from one or more parathyroid glands. This excess secretion is caused by a solitary parathyroid adenoma in 80% of cases, whereas four-gland hyperplasia accounts for 10–15%, multiple adenomas account for 5%, and parathyroid carcinoma accounts for <1% [3].

Previous evidence has shown a clinical association between PHPT and the development of autoimmune diseases in some cases; those patients recover completely from the autoimmune condition after parathyroidectomy [4,5]. We have previously determined the expression of PTH receptor (PTHR1) on B-lymphocytes from patients with systemic lupus erythematosus (SLE) and primary Sjögren syndrome (pSS), as well as healthy controls [6]. Interestingly, the expression of PTH1R was significantly higher in B-lymphocytes from patients with SLE and pSS than in those from healthy controls, suggesting that PTH may activate B cells in patients with autoimmune diseases [6].

Here, we report a patient with PHPT and autoimmune manifestations who exhibited subsequent clinical and paraclinical improvement after parathyroidectomy. His immunological profile, including autoantibodies and PTHR1 expression before and after parathyroidectomy, is presented. The possible pathogenic role of B-lymphocyte PTHR1 expression is discussed.

2. Case report

A 65-year-old male patient with a previous history of high blood pressure treated by losartan was admitted due to several months of asthenia and malaise. A thorough evaluation ruled out renal or cardiac disturbances. However, clinical laboratory results revealed hypercalcemia with increased PTH and normal vitamin D levels (Table 1, T0). The parathyroid scintigraphy indicated the presence of a parathyroid adenoma in the left paratracheal region.

Laboratory tests revealed an increase in liver enzymes (AST: 121 UI/L and ALT: 160 UI/L). Nonetheless, the patient was negative for hepatitis A, B, and C. Other clinical laboratory results showed high IgG levels and positive anti-smooth muscle antibodies (ASMA) and antinuclear
antibodies (ANAs) (Table 1, T0). A diagnosis of probable autoimmune hepatitis was made. The expression of PTHR1 in total peripheral B-lymphocytes and their subsets was evaluated using flow cytometry (Table 1). A higher expression of PTHR1 compared with healthy controls was found in previous research (18.5% in the current patient vs. 5% in controls) [6] (Table 1, T0).

Parathyroidectomy was conducted, and two months after surgery, vitamin D was deficient (20 ng/mL), while PTH decreased (although it did not reach normal levels) (Table 1, T1). This led us to consider a vitamin D was deficient (20 ng/mL), while PTH decreased (although it did not reach normal levels) (Table 1, T1). This led us to consider a hypothesis that vitamin D deficiency was related to autoimmune phenomena [6].

In conclusion, this paper presents a clinical demonstrative case of PHPT and secondary autoimmunity. A possible role of PTHR1 dynamics in the development of autoimmune phenomena is also demonstrated.

### Table 1

| Variable | Time   | Calcium (mg/dL) | PTH (pg/mL) | ANAs 1:320 | ANAs 1:160 |
|----------|--------|-----------------|-------------|------------|------------|
|          | T0     | 12.4            | 652         | 3.20       | 1.60       |
|          | T1     | 9.5             | 84.0        | 1.60       | 1.80       |
|          | T2     | 9.4             | 62          | 1.80       | 1.80       |
|          | T3     | 9.5             | 30          | 1.80       | 1.80       |

* B-cell subsets based on membrane IgD and CD38 expression: Bm1, naïve cells; Bm2 and Bm2′, germinal center founder cells; Bm3, 4, and Bm5, memory cells. B cell: B lymphocyte; T0: Prior to parathyroidectomy; T1: 2 months after surgery; T2: 5 months after surgery; T3: 10 months after surgery. NV: Normal values stabilized in healthy controls in our previous study (Ref 6).

### 3. Discussion

PHPT is associated with diverse rheumatological manifestations, including osteitis, pseudogout, muscular weakness, osteoporosis (in addition to that caused by gammopathies) [9] and autoimmune phenomena [4]. After the removal of the parathyroid adenoma, the musculoskeletal manifestations of patients and, in some cases, the clinical consequences related to gammapathy and autoimmunity improve [5,10,11], which suggests a causal relationship. A possible explanation for this phenomenon is the effect of PTH on stromal cells (i.e., osteoblasts), inducing the release of interleukin-6 (IL-6), which in turn stimulates B lymphocytes for the activation and differentiation of plasmocytes and the subsequent production of antibodies [12,13]. Additionally, IL-6 is produced and secreted by human parathyroids [14].

Another consideration is that the activation of B lymphocytes mediated by PTHR1 occurs through the phospholipase C pathway, which cleaves phosphatidylinositol (4,5)-bisphosphate into diacylglycerol and inositol (1,4,5)-trisphosphate (IP3). IP3 activates Ca2+ channels in the endoplasmic reticulum (ER) membrane, releasing stored Ca2+ into the cytosol [16]. This same molecular pathway is present in stromal interaction molecule 1 (STIM1), which detects ER Ca2+ depletion and activates Ca2+ channels in the plasma membrane, allowing a sustained influx that increases intracytoplasmic Ca2+ levels, leading to the activation of multiple transcription factors in B cells related to their immune function [16].

Preclinical studies in patients with SLE and pSS showed higher expression of PTHR1 on B-cell membranes [6]. The same alterations were observed in the current patient.

In conclusion, this paper presents a clinical demonstrative case of PHPT and secondary autoimmunity. A possible role of PTHR1 dynamics in the development of autoimmune phenomena is also demonstrated.

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### Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Gabriel J. Tobon reports financial support was provided by Colombia Ministry of Science Technology and Innovation.

### Data availability

The authors do not have permission to share data.

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