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Case Report

New forms of resistance to the action of human parathyroid hormone analogues

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Abstract

Introduction: we report the emergence of resistance to the action of teriparatide in a patient with postsurgical hypoparathyroidism under replacement therapy with this molecule, who initially showed an optimal response.

Case report: description of a case report in which a patient with postsurgical hypoparathyroidism treated with teriparatide showed progressive decrease in its effectiveness, and resistance to the biosimilar teriparatide with which the patient was treated was tested. The Ellsworth-Howard test was used to evaluate teriparatide resistance.

Discussion: the patient showed a response to the Ellsworth-Howard test consistent with resistance to teriparatide. A comparison was made with a patient with chronic hypoparathyroidism who underwent the same test with the same molecule, obtaining an appropriate functional response. The occurrence of primary failure to teriparatide replacement therapy in the context of chronic hypoparathyroidism is presented. Autoimmune etiology due to the development of blocking autoantibodies is the most likely hypothesis.

Keywords:
Teriparatide.
Postsurgical chronic hypoparathyroidism.
Resistance.

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CASE REPORT

We present the case of a 28-year-old male with a history of total thyroidectomy for stage II papillary thyroid carcinoma at the age of 17 years. Following surgery, he developed difficult-to-control hypoparathyroidism, for which he was initiated on replacement therapy with teriparatide 20 mcg subcutaneously every 12 hours in February 2022, resulting in normalization of phosphocalcic metabolism that remained stable for 18 months from the start of treatment (1). Since August 2021, he again presented analytical alterations compatible with hypoparathyroidism, with partial corrections occasionally requiring re-association of calcitriol and calcium carbonate or adjustment of the teriparatide dose to 0.8 mcg/kg/day in 3 doses (20-20-20 mcg subcutaneously) following the protocol described by K.K. Winer, in which the teriparatide dose to achieve normocalcemia without the need for calcitriol or calcium salts ranged from 0.47 + 0.33 mcg/kg/day (2). Analytical evolutions and therapeutic changes are presented in figure 1. Given the doses achieved under replacement therapy with teriparatide (equal to the maximum doses presented in the known case series to date), we considered the possibility of primary treatment failure once therapeutic adherence was ruled out, given the resistance pattern to it.

DISCUSSION

We know that PTH is an 84-amino acid peptide hormone produced in the parathyroid glands. Its amino terminal end 1-34 constitutes the active fraction. Its membrane receptor PTH-PTHrp is coupled to a stimulatory G protein of adenylate cyclase that generates cAMP as a second messenger. At the renal level, it inhibits the expression of Na-P 2A and 2C cotransporters, inducing a phosphaturic response. Both responses (phosphaturic and increased urinary cAMP excretion) have been the basis of PTH functionality studies. In the 1970s, Broadus (3) further delineated the renal

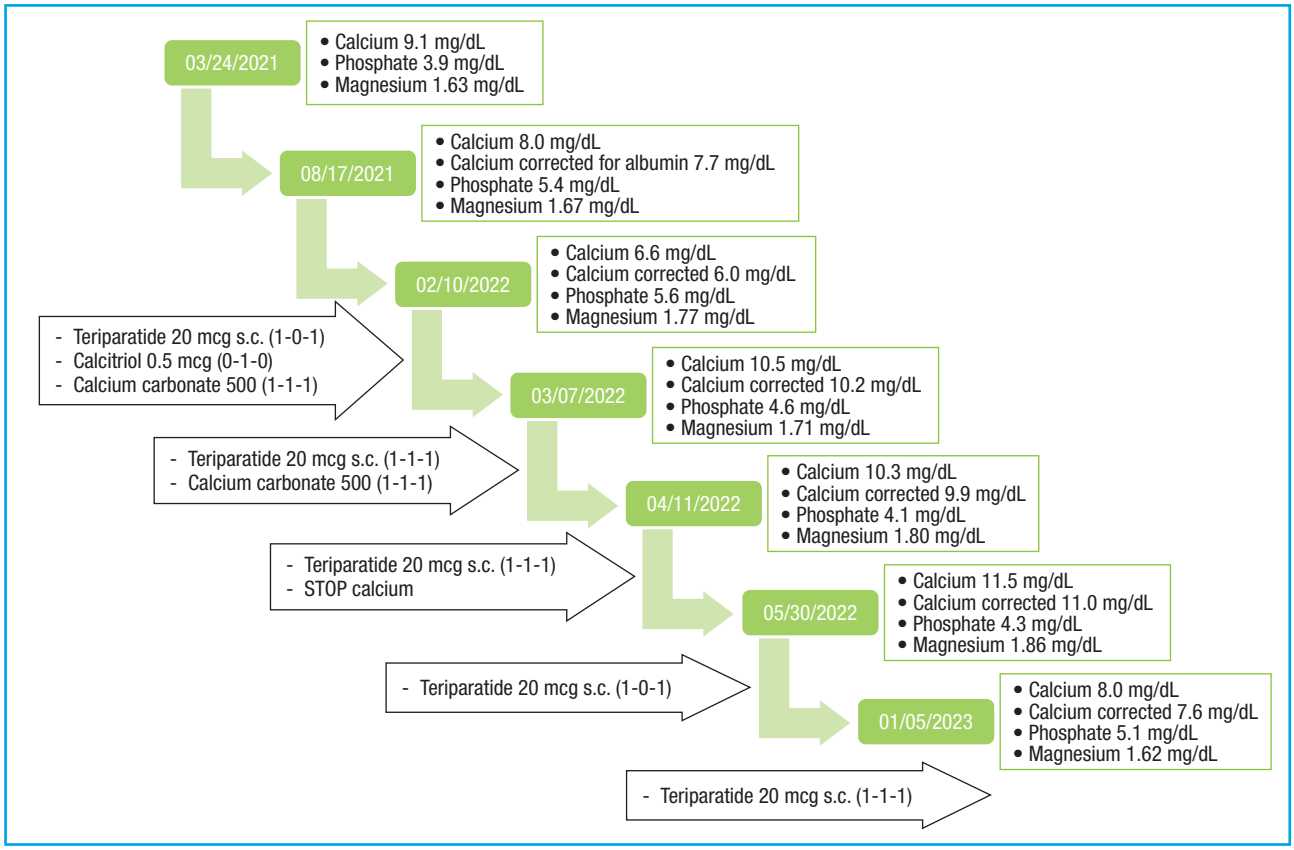

Figure 1. Evolution of phosphocalcic metabolism since August 2021.

response to PTH by determining nephrogenic cAMP (NcAMP) by eliminating factors that could interfere with the interpretation of urinary cAMP excretion (other hormonal hyperfunctions or pharmacological responses mediated by cAMP). The genesis of NcAMP is almost entirely secondary to the renal action of PTH, with a component due to vasopressin practically negligible at physiological levels. These findings led to the standardization of the Ellsworth-Howard test (4) for determining the organic response to PTH. Subsequently, its standardization with teriparatide instead of using purified PTH extract appeared (5). An increase in phosphaturic response of at least 200 % and in nephrogenic cAMP response of at least 1000 % (6) is considered normal; this response is more striking in patients with hypoparathyroidism. Conversely, a lower response is described in states of PTH resistance (pseudohypoparathyroidism).

An Ellsworth-Howard (E-H) test was performed on the case patient (patient 1) administering 20 mcg of teriparatide intravenously by slow infusion over 15 minutes; simultaneously, the same test was performed on a control patient (patient 2) similarly affected by postsurgical hypoparathyroidism and osteoporosis, who was prescribed daily teriparatide 20 mcg for treatment. Both tests followed the same protocol, and the same biomolecule was administered (teriparatide Movymia [STADA Laboratories]). The phosphocalcic metabolism responses of both patients are summarized in the following table (Table I).

Analyzing the response to PTH 1-34 stimulus of patient 1, we observed a blocked phosphaturic response, as well as a suboptimal increase in nephrogenic cAMP. Patient 2, however, presented an optimal phosphaturic response, as well as a significant increase in nephrogenic cAMP genesis (Fig. 2).

In the case of patient 1, suffering from chronic hypoparathyroidism, with an initial optimal response to teriparatide, the decrease in treatment effectiveness and the response to the Ellsworth-Howard test is compatible with primary failure to teriparatide replacement therapy with a pattern of resistance to its action. This conclusion is supported by the adequate response of a control patient (patient 2) with the same underlying condition (chronic hypoparathyroidism under replacement therapy with PTH 1-34) to the E-H test with a teriparatide dose from the same batch and pen as the case reported, ruling out the possibility of adulterated or inactive drug.

In the clinical development of teriparatide Movymia, the presence of anti-teriparatide antibodies was described in 2 out of 126 individuals included in the Forsteo teriparatide group, none of them blocking, and no development of autoantibodies was described in the group assigned to teriparatide Movymia (7). It should be noted that the clinical development studies of teriparatide Movymia were conducted in patients with osteoporosis without hypoparathyroidism, so we cannot extrapolate the results of autoimmunity to our patient.

Table I. Responses to phosphocalcic metabolism

	Patient	0´	15´	30´	60´	120´	360´	Levels of normality
Glomerular filtration	1	> 90	> 90	> 90	> 90	> 90	> 90	> 60 mL/min/1.73 m^2
	2	72	75	75	82	85	78	
PTH	1	< 10						15-65 pg/mL
	2	11.4						
Calcium adjusted to albumin	1	6.9	7.2	7.2	8.08	7.8	6.9	8.4-10.2 md/dL
	2	8.5	8.5	8.54	8.6	8.9	9.2	
Magnesium	1	1.62	1.66	1.65	1.59	1.7	1.53	1.6-2.6 mg/dL
	2	1.81	2.04	1.85	1.82	1.84	1.91	
Phosphate	1	4.6	4.4	4.6	4.8	4.7	4.7	2.5-4.5 mg/dL
	2	4.8	4.4	4.4	4.4	4.5	4.7	
25(OH)-D (25-hydroxyvitamin D)	1	13.5						20-40 mg/mL
	2	20.9						
1.25(OH)-2D (1.25-dihydroxyvitamin D)	1	44						20-54 mg/mL
	2	22						
Fosfaturia	1	329	295	292	269	211	No calc	40-136 mg/dL
	2	772	882	1885	1518	2952	909	
NcAMP	1	0.71	4.76	4.73	1.32	< 0.3	< 0.3	0.30-3.80 nmol/dL FG
	2	> 0.3	119.62	29.75	2.16	> 0.3	< 0.3	

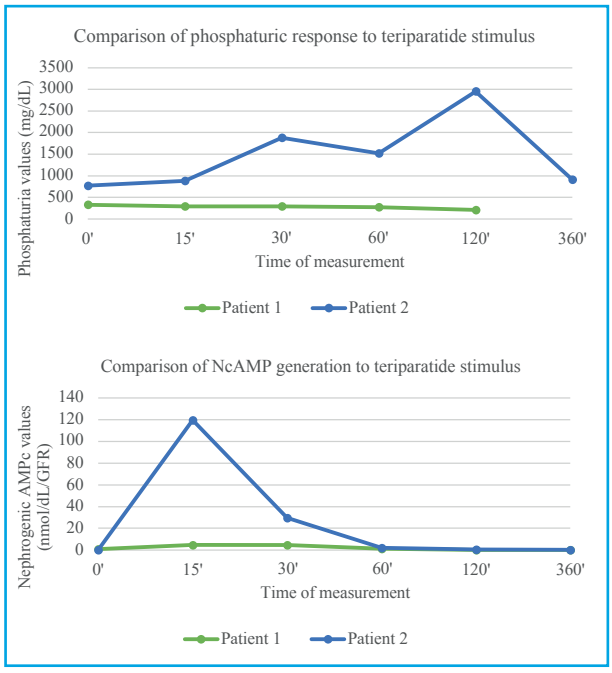

Figure 2. Comparison of Ellsworth-Howard Test results.

To clarify the nature of the blocking substance, attempts were made to request a kit for the determination of anti-teriparatide antibodies (not commercially available) or serial determinations of PTH 1-34 in diluted solutions or precipitation in polyethylene glycol to eliminate the interference of blocking antibodies. However, current third-generation commercial assays for PTH determination have a double binding to fragments 1-38 and 38-84, so these tests could not be performed. Nevertheless, the development of autoantibodies is the main hypothesis for the genesis of the blockade to the action of teriparatide, following the models of primary failure to respond to treatments with other molecules such as biological drugs.

In conclusion, we present our first case of primary failure to teriparatide replacement therapy in a male with long-standing postsurgical chronic hypoparathyroidism, with a response compatible with resistance likely induced by blocking autoantibodies against teriparatide. It would be of interest to study the loss of effectiveness of replacement therapy in patients with these characteristics in the long term and clarify its origin, considering the determination of anti-teriparatide antibodies in case of loss of activity.

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