Letter to the Editor

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Spurious parathyroid hormone (PTH) elevation caused by macro-PTH

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To the Editor,

A 42-year-old woman known for chronic autoimmune hepatitis was referred to the endocrinologist for a persistent parathyroid hormone (PTH) elevation. A blood test revealed a PTH value of 389 ng/L with the second generation PTH assay on the Cobas Elecsys e602 platform (Roche Diagnostics, Mannheim, Baden-Wurttemberg, Germany), together with a 25-hydroxy-vitamin D level of 24 ng/L. This PTH result was multiple times the manufacturer's upper reference limit (reference interval 15–65 ng/L). In contrast, the patient had normal calcium and phosphate levels (calcium 2.33 mmol/L; reference interval 2.15–2.50 mmol/L; phosphate 0.97 mmol/L; reference interval 0.81–1.45), and normal renal function (eGFR≥60 mL/min/1.73 m^2), as well as no history of prior fracture, bone pain, pancreatitis, or urinary lithiasis. These findings raised suspicion of a spurious elevation of PTH. Nonetheless, the patient was first supplemented with oral vitamin D and calcium to rule out secondary hyperparathyroidism due to vitamin D deficiency. Upon reevaluation one month later, despite achieving vitamin D levels above 30 ng/mL and maintaining normal calcium and phosphate levels, her PTH value, measured on the same platform, remained elevated (501 ng/L). The differential diagnosis at this point includes normocalcemic primary hyperparathyroidism, either as an early and subclinical stage of primary hyperparathyroidism, or as a consequence of a partial resistance to PTH. However, given the magnitude of PTH elevation, an analytical interference was deemed more likely, prompting laboratory investigations.

As a first investigative step, we compared this doubtful result obtained with a second generation PTH assay on Roche Cobas with the values obtained with two other second generation PTH assays, Liaison XL (DiaSorin, Saluggia, Vercelli, Italy) and Vitros (Ortho Clinical Diagnostics, San Diego, CA, USA), and with the third generation PTH assay on Roche Cobas. PTH values remained elevated across all platforms, although variations in immunoreactivity were observed (see Table 1). We then treated some serum with heterophilic blocking tube (Scantibodies Laboratory, Inc., Santee, CA, USA) and VeraPrep (Veravas, Inc., Austin, USA), which did not reveal any interference. Serial dilution testing showed no significant deviation from linearity. Finally, a much lower PTH value of 22 ng/mL was obtained following polyethylene glycol precipitation, resulting in a corresponding recovery rate (percentage of initial value) as low as 4 %. To allow interpretation, samples from 32 subjects with PTH values within the normal range were treated with polyethylene glycol. Their median recovery rate for second generation PTH assay on Roche Cobas was 78.5 % (95 % CI [69.0–86.0 %]). The lowest value was 45.7 %. These results strongly suggested the presence of an analytical interference affecting PTH measurement in the patient's sample, which could be removed by precipitating macromolecules. The sample was then submitted to size exclusion chromatography and all obtained fractions were tested with second and third generation PTH assays on Roche Cobas Elecsys. This analysis confirmed the presence of a macro-PTH.

Spurious PTH elevation is uncommon. Most of the time, it is the result of an interference with heterophile or human anti-animal antibodies [1]. In one series, out of 63 suspicious PTH elevation, 25 (40 %) were caused by heterophile or human anti-animal antibodies, and 21 (33 %) were caused by rheumatoid factor [2]. In our case, a number of factors

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