



## Macro-PTH, a rare cause of unexplained elevated serum PTH levels

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Dear Editor,

We report a patient with elevated serum parathyroid hormone (PTH) and normal total and ionized calcium finally shown caused to an immunoassay interference due to macro-PTH.

A 59-year-old Italian man was referred to our outpatient clinic in June 2022 for evaluation of repeatedly high PTH levels (155 ng/L, normal range 8–79) incidentally discovered 12 years earlier. Serum calcium, phosphate, and renal function were normal and 25-hydroxyvitamin D (25OHD) 12 ng/mL. Cholecalciferol 2000 UI daily was started, but subsequent blood tests confirmed elevated PTH measured by 2nd generation assay (median 253 ng/L, normal range 15–65) and normal serum calcium. Parathyroid imaging (ultrasound and 99mTc-sestamibi scintigraphy) was negative. A diagnosis of normocalcemic primary hyperparathyroidism was made. At our evaluation, the patient was in good health. Biochemical tests confirmed an elevated serum PTH measured by 3rd generation assay [205 ng/L (8–40)]. Total and ionized serum calcium [9 mg/dL (normal range 8.4–10.2) and 1.25 mmol/L (normal range 1.13–0.32), respectively], phosphate [2.5 mg/dL (2.5–4.5)] magnesium [2 mg/dL (1.7–2.5)], creatinine and estimated glomerular filtration rate (eGFR), 25OHD (30.9 ng/mL), bone-specific alkaline phosphatase and C-terminal telopeptide type 1 were normal. Twenty-four-hour urinary calcium excretion was normal (180 mg). Other causes of secondary hyperparathyroidism were excluded [1]. Dual-X-Ray Absorptiometry showed normal bone mineral density of the lumbar spine (T-score 1.6),

total hip (T-score 0.1), femoral neck (T-score -0.4), and 1/3 distal radius (T-score -0.6). Neck ultrasound did not show enlarged parathyroid glands. Abdomen ultrasound was normal. The past medical history was notable for hypertension, hypercholesterolemia, and prostatic hypertrophy.

Apart from advanced chronic renal failure and severe long-standing vitamin D deficiency, the increase of serum PTH in all other causes of secondary hyperparathyroidism as well as in normocalcemic hyperparathyroidism is usually moderate. Thus, the finding in our patient of normal total, albumin adjusted, and ionized serum calcium associated with moderate-marked increase of PTH prompted us to search for an assay interference. To this purpose a third-generation two-step "sandwich" immunoassay (LIAISON<sup>®</sup> 1–84 PTH Assay, implemented on the LIAISON-XL<sup>®</sup> instrument) was used. Serum dilutions showed linearity and heterophilic antibody interference was excluded. To investigate the presence of macro-PTH, namely aggregates between PTH and an unknown component, a serum sample was treated with an equal volume of 25% polyethylene glycol 6000 in distilled water. After centrifugation to remove macromolecules, the PTH concentration in the supernatant was 22 ng/L (considering the dilution factor 1:2), compared with 259 ng/L in the untreated serum. On dilution (1:10 and 1:50) of the PEG treated sample, the diluted PTH concentration showed an appropriate response to dilution. PEG treatment of control serum sample from a patient with chronic kidney disease showed a modest reduction of PTH levels from 444 ng/L to 346 ng/L.

There are only a few reports of serum PTH elevation due to immunoassay interferences [2, 3] and only one case of macro-PTH [4]. In our case, both 2nd and 3rd generation assays detected elevated PTH levels, approximately four and five times above the upper reference limit, respectively. The 2nd generation assay recognizes intact PTH (1–84) as well as large amino-truncated PTH fragments, of which the most abundant is PTH (7–84). The 3rd generation assay is more specific for PTH (1–84), but it also detects a post-translational modified form of PTH (1–84) known as nontruncated amino-terminal PTH. Conversely, markedly higher PTH

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levels measured by 2nd generation assay (approximately 20 times the upper reference limit) were reported by Prodan et al. in a 56-year-old Caucasian woman [4].

Macro-hormones are high molecular weight conjugates of hormones often with immunoglobulins which may cause artefactually elevated biochemical tests results. Macro-prolactin is the most frequently detected macro-hormone (prevalence 9–42%) [5], whereas macro-TSH is rare (prevalence ranging from 0.6 to 1.6% [6]. The etiology behind the development of macro-PTH as well as TSH is unknown. It can be hypothesized that macro-PTH could be a large antigen–antibody complex consisting of PTH and anti-PTH autoantibodies. This mechanism is true for macroprolactin although it may also be due to a heterogeneous complex of covalently and noncovalently bound PRL with increased glycosylation [7]. The question of whether macro-PTH may be associated with autoimmune diseases remains to be elucidated. Of interest, our patient was affected by psoriatic arthritis, an autoimmune disease, and no other autoimmune disorders. The case reported by Prodan et al. was affected by hypothyroidism, however no further details were reported [4].

In conclusion, we report a case of increased serum PTH levels due to macro-PTH. Once other causes of secondary hyperparathyroidism are excluded, search for macro-PTH should be performed in patients with normal total (albumin adjusted) and ionized serum calcium associated with PTH levels greater than 4–5 times the upper reference limit.

## Declarations

**Conflict of interest** The authors declare that they have no competing interests.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the insti-

tutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** The patient gave his informed consent for publication.

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