Primary hyperparathyroidism and multiple myeloma complicated by Fanconi syndrome: A fortuitous association?

Hyperparathyroidie primitive et myélome multiple compliqués d’un syndrome de Fanconi : une association fortuite ?

Hypercalcemia is both frequent and threatening in acute medicine. The large differential diagnosis requires a thorough work-up, considering parathormone (PTH) dependant versus non-PTH dependant causes [1]. Multiple myeloma (MM) and primary hyperparathyroidism (PHPT) are among the most common causes of hypercalcemia but concomitant diagnosis of the two pathologic processes in one patient has rarely been reported in the literature. We discuss a case of a patient presenting with this rare phenomenon, also complicated by Fanconi syndrome.

Case report
An 88-year-old patient with a history of arterial hypertension, ischemic stroke, type 2 diabetes mellitus and lung cancer in remission for 16 years after surgery only, was hospitalized in the acute geriatric unit for delirium begun 48 hours earlier. His family reported a marked decline of his general condition within the past month, with asthenia, anorexia and an associated weight loss of five kilograms. On clinical exam, the patient was afebrile; vital signs were within normal limits. He presented significant psychomotor slowing as well as diffuse microangiopathy described by periventricular caps and rims, diffuses white-matter hyperintensities of non-specific microvascular origin, without abnormal diffusion’s intensity. Lumbar puncture found no abnormalities. These results pointed to a link between the neurological disorders and the state of hypercalcemia. Calcium levels declined under intravenous bisphosphonates treatment, in parallel the patient’s mental status improved significantly.

The work up for hypercalcemia revealed hypergammaglobulinemia of 23 g/L with a monoclonal peak of IgG kappa. Bone marrow puncture revealed a plasma cell infiltration of 27%. Radiographic survey showed lytic lesions compatible with bone myeloma (figure 1), located at the atlas, skull, and long bones of all four extremities. These results allowed for a diagnosis of MM stage III, according to Durie and Salmon classification.

The patient was also diagnosed with Fanconi syndrome without associated renal failure, hypokalemia (3.2 mmol/L, normal range: 3.5-5), severe and persistent hypophosphatemia (0.18 mmol/L) after calcium normalisation and associated hyperphosphaturia to 7.20 mmol/d, glycosuria to 43.89 mmol/day (after glyceremia normalisation) and generalized hyperaminociduria to aminoacidogramme urine. Serum bicarbonate level was low (17 mmol/L, normal range: 22-26), with mild acidosis (pH: 7.36 in arterial blood gas).

Urinary electrophoresis showed an increase of β2-microglobuline (1531 μg/L, normal range: inferior to 350), a large excess of immunoglobulin free light chain kappa (140,000 μg/L) as well as an increased kappa/lambda ratio (over 90%). Elevated PTH with associated hypercalcemia confirmed a diagnosis of PHPT. Parathyroid ultrasound and scintigraphy was scheduled. Unfortunately, the patient’s clinical course was acutely complicated by septic shock related to Enterobacter aerogenes bacteraemia leading to his death, before hemato-logic therapy or further diagnostic measures could be realised.

Discussion
The diagnosis of parathyroid autonomy is based on elevated PTH associated with hypercalcemia, even if low level of 25-OH vitamin D may have partly contributed to HPT. If hypercalcemia were solely due to MM, one would expect low or undetectable PTH [1]. If mild asymptomatic hypophosphatemia is usual in PHPT, severe phosphatemia deficiency with supplementation failure must lead to explore concomitant non-PTH dependant diseases, like Fanconi syndrome.

Like hypercalcemia, two potential causes of hypophosphatemia might also be identified. In some cases, hypophosphatemia associated with primary hyperparathyroidism is usually of moderate severity; increased urinary phosphate excretion is
balanced by the mobilization of phosphate from bone and enhanced intestinal absorption [2]. In other cases, impaired reabsorption of phosphate by proximal tubules is a manifestation of Fanconi syndrome. This syndrome’s causes are now well known (inheritance, heavy metals, monoclonal gammopathy and metabolic disorders, antiretroviral medications, e.g. tenofovir, cidofovir, adefovir dipivoxil, and aristocholic acid) [3]. Phophaturia is elevated in both. We report the first case of coexisting PHPT and MM associated with Fanconi Syndrome. A recent review [4] identified a total of 29 case reports describing the association of PHPT and MM, including the first case described by Drezner and Lebovitz in 1978 [5]. The mechanism of this association remains unclear. Given that the diagnosis of PHPT often precedes the diagnosis of MM it has been hypothesized that the high rate of PTH induces MM [6]. An epidemiologic study [7] found that patients with PHPT had a significantly increased risk of hematopoietic malignancies (standardized incidence ratio: 1.88), especially for MM (four out of 13 patients). Another one [8] found a higher prevalence of monoclonal gammapathies in patients with PHPT (10%) compared with benign thyroid diseases (3%, \( P = 0.04 \)) or other diseases (2%, \( P = 0.005 \)). Moreover, an original in vivo study [9] found that PTH induces interleukin 6 (IL-6) released by osteoclasts. IL-6 has been shown to inhibit apoptosis of plasmocytes and to thereby generate MM [10]. However, in our patient the IL-6 plasma levels were not increased. Only a few of the case reports mentioned above included IL-6 levels and they all failed to find any increase; one of the main explanation is that IL-6 may acts by a paracrine or autocrine way, leading to a normal range in plasma. The control of the PTH level is crucial to avoid further bone destruction and worsening hypercalcemia. Current treatment of choice for patients with moderate and severe hyperparathyroidism is parathyroidectomy [11]. It is also discussed whether surgical treatment of hyperparathyroidism could reduce [12] or not [13] the monoclonal gammapathy; but all authors report lower calcemia. For patients at high surgical risk, the use of cinacalcet and biphosphonates seems to be efficient in at least one reported case [14], associated with the hematological treatment. Cinacalcet [11,15] activates the calcium-sensing receptor on the parathyroid gland, and thereby inhibits PTH secretion. Furthermore, biphosphonates increase bone mass in patients with PHPT by promoting apoptosis of osteoclasts involved in degrading minerals on the surface of bone [11,16].

Future research and additional case reports may help to clarify pathogenesis and improve treatment strategies.

**Conclusion**

Even though a relationship between PHPT and MM has not been proven and it is difficult to determine the extent to which each disease contributes to the level of hypercalcemia, the systematic work up of hypercalcemia is required in clinical practice, taking into consideration a possible double diagnosis [6,14,17].

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**References**


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