

# Primary hyperparathyroidism associated to thrombocytopenia: an issue to consider?

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## Summary

**Primary hyperparathyroidism (PHPT) is probably the most common endocrine disorder of the parathyroid glands, causing hypercalcemia. It is diagnosed often in persons with elevated serum calcium levels. However, hematological manifestations, such as thrombocytopenia are less known. In this case we describe the possible association of PHPT with reversible thrombocytopenia after parathyroidectomy. This hematological abnormality can be included in the spectrum of possible causes, including seemingly non-specific symptoms, in the decision tree towards surgical assessment.**

*KEY WORDS:* primary hyperparathyroidism; parathyroidectomy; thrombocytopenia.

## Introduction

Primary hyperparathyroidism (PHPT), is probably the most common cause of hypercalcemia and should be considered in persons with increased serum calcium levels (1, 2). PHPT results from excessive secretion of parathyroid hormone from one or more parathyroid glands as a result of loss of feedback regulation by extracellular calcium levels. Its prevalence is estimated at about 21.6 cases per 100,000 person-years, and its incidence peaks in older patients in the seventh decade (2, 3). A higher prevalence is observed in women than in men by a

ratio of 3:1 (4). Nowadays the clinical profile of PHPT has significantly changed from a symptomatic disease, characterized by hypercalcemic symptoms, nephrolithiasis, overt bone disease, and neuromuscular symptoms to one with easily overlooked or nonspecific symptoms (including fatigue, apathy, depression, impaired mental clarity and vague aches and pain) (1). Until now, hematological manifestations, such as thrombocytopenia are less known manifestations of PHPT. In this case we describe the possible association of PHPT and reversible thrombocytopenia.

## Clinical case

In March 2004, a 21-year-old young male presented with hypercalcemia to his primary-care physician. He was referred to internal medicine for further investigations. In 2006, he presented at our department of General Internal Medicine. Repeated laboratory investigations confirmed a persistent hypercalcemia with a normal serum phosphate level and an intact parathyroid hormone (iPTH) level. Before the diagnosis of PHPT, iPTH was elevated for one year. Furthermore, a slightly elevated 25-hydroxy vitamin D level was observed (Table 1, Figure 1). He had no specific symptoms towards PHPT (including absence of polyuria, polydipsia, dehydration, obstipation, anorexia, nausea, myopathy, renal stones, duodenal ulcer, pancreatitis, depression, bone pain, bone fracture and in worse cases: multiple adenoma, carcinoma or hyperplasia). He was taking no medication and had no family history of hypercalcemia, MEN- syndrome or renal calculi. His history was negative for gallstone disease, pancreatitis, bone pain, fractures, fever, or drug intake in the recent past. Ultrasonography of the kidney showed no abnormalities, neither did CT (computed tomography) thorax - and abdomen. DXA (Dual X-ray absorptiometry)- scan revealed progressive bone loss. Based on these findings, the diagnosis of asymptomatic PHPT was established. The patient refused surgical management and opted for a watchful waiting approach with clinical and biochemical follow-up every two years. During follow up visits, the patient remained asymptomatic, with elevated calcium and iPTH levels, as shown in Table 1 without hematological abnormalities. In July 2015, clinical and biochemical parameters deteriorated (Table 1, Figure 1). The patient indicated a 3- month history of general malaise, diffuse myalgia, muscle weakness and obstipation. Laboratory results revealed elevated calcium: 3.1 mmol/L (normal range: 2.2-2.6 mmol/L), elevated iPTH: 125 ng/L (normal range: 10-65 ng/mL), and an isolated thrombocytopenia:  $89 \times 10^6/L$  (normal range:  $150-400 \times 10^6/L$ ). The thrombocytopenia was never observed during earlier routine follow-up visits. On examination, he had no purpuric/ecchymotic skin lesions or bony tenderness. The platelet morphology was normal. To exclude other frequent causes of thrombocytopenia, additional tests were performed. Viral markers of HIV, hepatitis B surface antigen, and hepatitis C virus RNA were negative. The patient has had no recent viral infections and was negative

for autoimmune serology testing. Immune thrombocytopenic purpura and drug induced thrombocytopenia were also excluded. No apparent cause for isolated thrombocytopenia was found. No bone marrow aspiration or biopsy was performed or deemed necessary before surgery. Based on the marked elevation of biochemical parameters and appearance of clinical symptoms, parathyroidectomy was planned. <sup>99m</sup>Tc sestamibi imaging and ultrasonography of the neck were performed. A left inferior parathyroid adenoma was identified by ultrasonography of the neck and confirmed by <sup>99m</sup>Tc-petechnetate/sestamibi subtraction scintigraphy combined with SPECT/CT (Figure 2). During surgery, an enlarged parathyroid gland with measuring 1.5 cm by 0.7 cm by 0.5 cm was removed. After removal of the enlarged parathyroid gland iPTH levels fell by 70%. Histology confirmed that the removed gland was a benign adenoma. On the third postoperative day, normalization of iPTH (20 ng/L), calcium level (2.31 mmol/L) and a rising phosphate level (1.16 mmol/L; normal range: 0.78-1.42 mmol/L) were observed. Nevertheless the patient suffered from clinical features of hypocalcemia including perioral and acral paresthesia. The hypocalcemia related symptoms disappeared after 5 days and serum iPTH and calcium concentrations normalized. No postoperative calcium carbonate supplementation or vitamin D (calcitriol) treatment were required. During follow-up visits, the platelet count gradually increased and reached normal values by 6 months after parathyroidectomy (Table 1, Figure 1). A continued follow-up at 4 and 9 months after surgery confirmed the drop of iPTH.

### Discussion

In general, PHPT has a broad variable clinical and biochemical expression, including kidney stones, headache, fatigue, depression, loss of appetite, etc. Bhadada et al. (2012) suggested an association of hematologic manifestations, including both anemia and thrombocytopenia in symptomatic PHPT patients (5). Anemia has already been described as a complication of PHPT in 5-30% of PHPT individuals (6). A possible cause of anemia might be bone marrow fibrosis likely to be related to elevated levels of iPTH, having a stimulatory effect on bone marrow fibroblasts (7, 8). Thrombocytopenia as a manifestation of PHPT is rarely reported (8). The exact underlying mechanism still remains unknown. PHPT can cause thrombocytopenia by replacement of the marrow cavity, leading to a decrease in hematopoietic elements. Furthermore high iPTH levels promote the release of cytokines from osteoclasts, which influence the pathogenesis of marrow fibrosis and bone loss. Improvement of hematological parameters after parathyroidectomy is suggestive for marrow fibrosis due to PHPT (5, 9, 10). Nowadays, only asymptomatic patients who fulfill criteria underlined by the *Third International Workshop on Asymptomatic PHPT* indications are considered for surgery. These indications include: 1) age under 50, 2) serum calcium levels 0.25 mmol/L above the normal upper limit, 3) creatinine clearance < 60 mL/min/1,73 m<sup>2</sup>, 4) DXA t-score < -2.5 at any site, and/or 5) previous fractures (11). While a good attempt was made by the councilors present at the *Third International Workshop on Asymptomatic PHPT* these guidelines remain a matter of controversy. Our patient was an obvious candidate for surgery: the subject had the definitive biochemical hallmarks of PHPT, was young and had, besides an isolated thrombocytopenia, no specific complaints which might have led to the diagnosis of PHPT. Approximately 25% of PHPT patients with asymptomatic

Table 1 - Sequential key biochemical parameters.

Test (SI units)	March 2004	January 2006	February 2007	September 2009	February 2011	March 2012	February 2013	March 2014	July 2015	August 2015 (3 days after surgery)	September 2015 (6 weeks after surgery)	December 2015	April 2016 (9 months after surgery)	Normal range
Serum calcium (mmol/L)	3,05	3	2,85	2,75	2,98	2,98	2,98	2,85	3,1	2,31	2,32	2,38	2,39	2,15 - 2,5
(mg/dL)	12,2	12	11,4	11	11,9	11,9	11,9	11,4	12,4	9,24	9,28	9,6	9,6	
Serum iPTH (ng/L)	ND	58	71	77	76	75	87	110	125	20	58	ND	58	15 - 65
Serum phosphate (mmol/L)	ND	0,94	0,87	0,77	1,07	1,03	1,26	1,01	0,68	1,16	1,12	1,28	1,34	0,78 - 1,42
Serum alkaline phosphatase (U/L)	ND	87	73	45	78	67	49	56	78	79	60	37	41	40 - 129
Serum creatinine (mg/dL)	0,73	0,77	0,7	0,75	0,78	0,82	0,75	0,84	1,1	0,99	1	0,9	0,9	0,67 - 1,17
Serum 25-hydroxy vitamin D (nmol/L)	ND	28,3	30,4	28	24	18,8	20	20,2	23,6	36,2	29,6	ND	32	> 30
Urine 24h calcium (mmol/24 u)	ND	10,5	13,6	21,9	ND	ND	ND	ND	18,4	ND	ND	ND	ND	2,5 - 7,5
Hemoglobin (g/L)	16,3	15,9	15,2	13	13,1	13,2	13,6	12,6	14,1	12,9	12,8	13,1	13,2	13,2 - 17,3
Platelet count (x10 <sup>9</sup> /L)	168	169	152	132	134	121	139	137	89	95	86	126	152	150 - 450

Abbreviations: ND, not done

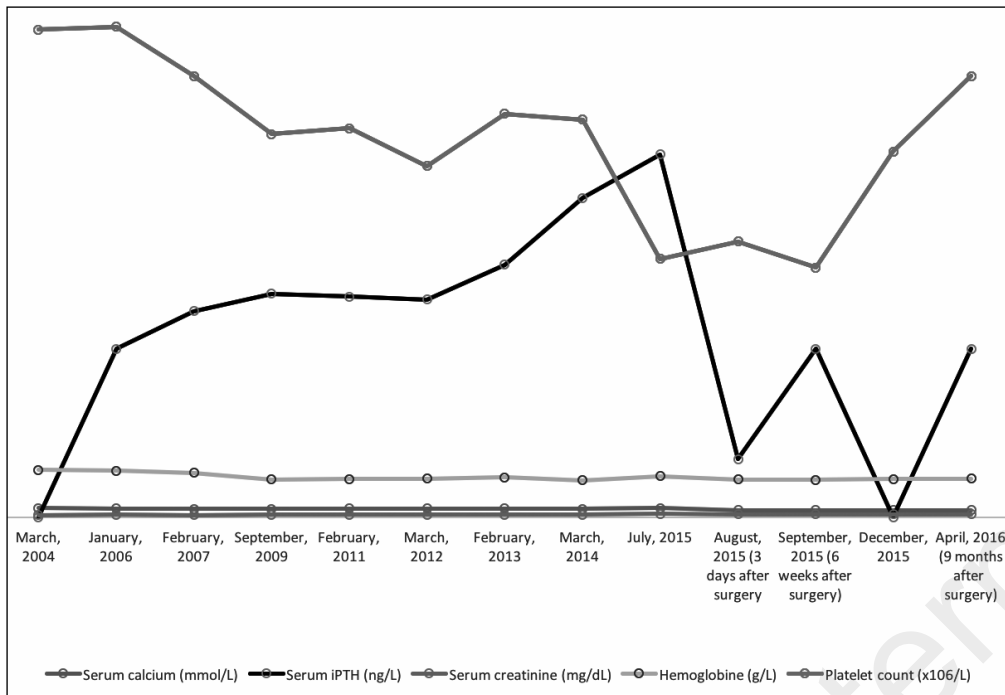


Figure 1 - Graph of biochemical parameters.

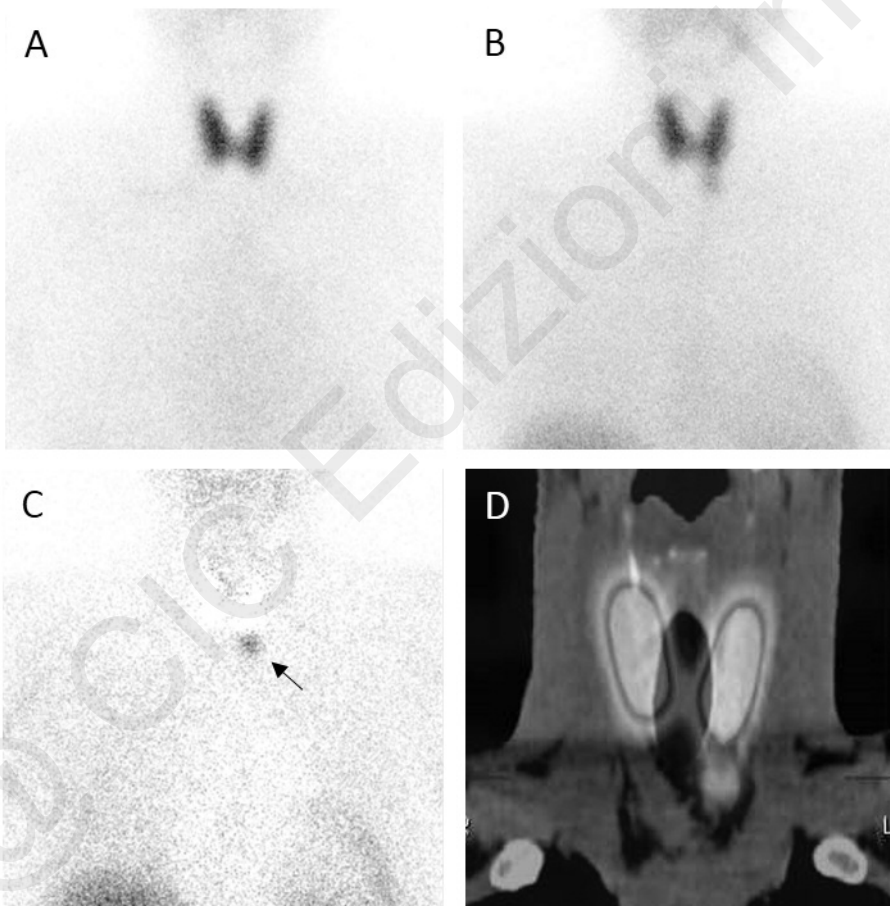


Figure 2 - Scintigraphic imaging of the left inferior parathyroid adenoma. A: planar 99mTc-petechnetate image; B: planar 99mTc-sestamibi subtraction scintigraphy; C: subtraction scan (B - A); D: coronal SPECT/CT-image.

PHPT will demonstrate disease progression in the form of progressive silent bone loss, increased risk of fractures and renal impairment secondary to nephrolithiasis or nephrocalcinosis (12). Progression was observed through development of non-

specific symptoms in our patient, after a 11-year period (e.g. rheumatologic symptoms, joint aches, muscle weakness), with markedly disturbed hematological and biochemical parameters. Successful surgical removal of all pathologic parathyroid

tissue is the only definitive therapy leading to normalization of hematologic and biochemical markers and disappearance of nonspecific symptoms, as observed in our patient (1, 2). In conclusion, this case highlights, together with those of Bhadada et al. (5, 8) the possible association of PHPT with thrombocytopenia. This hematological abnormality could be considered in the spectrum of factors next to seemingly nonspecific symptoms, in the decision tree towards surgical management, in otherwise asymptomatic patients.

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### Conflict of interest

The Authors have no conflict of interests related to this publication.

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