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Case Report

Myelofibrosis and Pancytopenia Associated With Primary Hyperparathyroidism

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ABSTRACT

Objective: Primary hyperparathyroidism (PHPT) has varied clinical presentations. Hematologic abnormalities secondary to PHPT have been described before. However, pancytopenia as the initial presentation has rarely been reported. We report a patient with PHPT who presented for evaluation of pancytopenia.

Methods: Histopathology of the bone marrow at presentation is described. Bone biochemistry results and the hematologic profile before and after curative parathyroidectomy are presented.

Results: A 48-year-old woman presented with pancytopenia (hemoglobin, 6.3 g/dL; total leucocyte count, 3000 cells/mm^3; and platelet count, 60 000 cells/mm^3), and her bone marrow study showed marrow fibrosis. Biochemical evaluation revealed hypercalcemia (15.5 mg/dL), hypophosphatemia (2.2 mg/dL), and elevated total alkaline phosphatase (4132 U/L). Bone mineral density assessment by dual-energy X-ray absorptiometry scan revealed osteoporosis at all 3 sites, which was more severe in the distal one third of the forearm. Further investigations confirmed the diagnosis of PHPT (serum parathyroid hormone, 2082 pg/mL). Following curative parathyroidectomy, in addition to normalization of calcium, there was restoration of all 3 hematologic cell lines at 3 months.

Conclusion: Pancytopenia may be a rare manifestation of PHPT. Thus, it may be prudent to evaluate the calcium profile in patients with chronic refractory anemia and pancytopenia.

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Introduction

Primary hyperparathyroidism (PHPT) has varied clinical presentations, as described by Albright et al.[1] Although predominantly asymptomatic in Western populations, symptomatic cases still account for the majority in developing countries.[2] Hematologic abnormalities secondary to PHPT, though under-recognized, have been described previously.[3] Hunter et al and Albright et al first described the association between PHPT and anemia as early as the 1930s.[1,4] Data on PHPT affecting other blood cell lines and resulting in pancytopenia have rarely been reported.[3,5] We describe the case of a 48-year-old woman with PHPT and pancytopenia who presented for evaluation of refractory anemia and was subsequently diagnosed as PHPT, based on the results of biochemistry and imaging tests. Successful surgical treatment led to the resolution of pancytopenia.

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A 48-year-old woman presented to the hematologist for evaluation of chronic refractory anemia. She complained of easy

Abbreviations: PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

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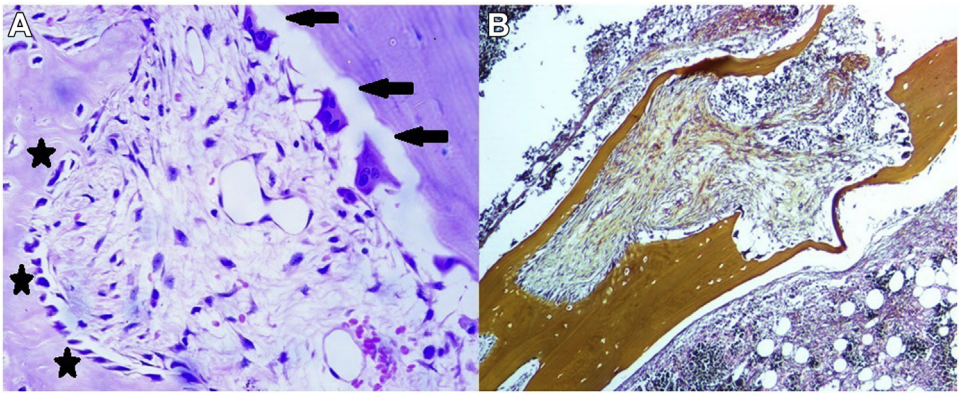

Fig. 1. Trephine biopsy of the bone marrow. *A*, Increased bone turnover characterized by osteoclastic resorption (arrows) and osteoblastic activity (stars). *B*, Intratrabecular osteoclastic tunneling resorption cones with peritrabecular fibrosis, which is the hallmark of hyperparathyroidism affecting the bone.

fatigability and generalized weakness for the last 4 years. She also complained of lower backache and ankle pain for the same duration. Despite being been on treatment of anemia with oral iron and vitamin B12 tablets for almost 2 years, she required a transfusion of 4 units of packed red blood cells. She had no history of blood loss, fracture, renal calculi, or recurrent abdominal pain. On evaluation by the hematologist, she was found to have pancytopenia (normocytic normochromic anemia, leucopenia, and thrombocytopenia). The reticulocyte production index was 1.75. She underwent a bone marrow biopsy, which showed bone marrow fibrosis (Fig. 1). During further evaluation, she was found to have hypercalcemia, hypophosphatemia, and elevated total alkaline phosphatase (Table 1). Hence, she was referred to the metabolic bone disease clinic. A biochemical evaluation confirmed the diagnosis of PHPT. Dual-energy X-ray absorptiometry showed low bone mass (Z-score [bone mineral density]: lumbar spine, −2.3 [0.728], total hip −2.4 [0.603], and distal one third of the radius −4.1 [0.410]). Ultrasound of the neck revealed a 4.4 × 4.5 × 1.8-cm isodense lesion with cystic spaces in the inferior part of the right lobe of the thyroid. Parathyroid scintigraphy revealed a right parathyroid adenoma (Fig. 2), which was concordant with the ultrasound findings.

Her serum calcium level was optimized preoperatively by saline hydration and intravenous zoledronic acid. She was given a transfusion of 1 unit of packed red blood cells prior to surgery. She underwent focused right inferior parathyroidectomy. Her serum calcium normalized postoperatively. On further follow-up at 3 months, she was asymptomatic, her hemoglobin had improved to 10.1 g/dL, and the other blood cell lines had also normalized (Table 2).

Discussion

We present a unique case of a 48-year-old woman with PHPT whose initial presentation was pancytopenia secondary to marrow fibrosis. Following curative parathyroidectomy, in addition to normalization of calcium, there was restoration of all 3 blood cell lines.

The most common presentation of symptomatic PHPT is skeletal manifestations, followed by renal calculi and proximal muscle weakness.[6] Though anemia has been documented as a peculiar manifestation, pancytopenia has rarely been reported as the presenting feature. Anemia in PHPT is typically normocytic normochromic and resembles anemia of chronic disease. The etiology of anemia in PHPT is multifactorial, including poor nutrition, associated renal failure, and bone marrow fibrosis.[7]

Bone marrow fibrosis as the cause of anemia in PHPT was described by Albright et al in 1934.[1] High intact parathyroid hormone (PTH) leading to downregulation of erythropoietin receptors by making the erythroid progenitors insensitive to erythropoietin was described as one of the mechanisms for anemia in PHPT by Sikole.[8] Also, in vitro studies have shown the inhibitory effect of high levels of intact PTH on erythropoiesis, leading to a decrease in colony-forming unit erythroids.[9] However, the improvement in bone marrow fibrosis post parathyroidectomy and the resultant improvement in anemia, as demonstrated by Bhadada et al,[7] may suggest bone marrow fibrosis as the most likely underlying mechanism in PHPT.

The marrow fibrosis in PHPT is likely to be related to the high PTH, which stimulates marrow fibroblasts, leading to bone marrow fibrosis. High PTH levels also promote the release of cytokines (interleukin 6 and tumor necrosis factor α) from the osteoclasts or resorbed bone, which may have an indirect role in marrow fibrosis. Marrow fibrosis leads to a decrease in hematopoietic elements that may result in pancytopenia. Increased cytokines also contribute to the reduced production and action of erythropoietin and thrombopoietin.[10,11]

Both anemia and marrow fibrosis have been shown to improve following curative parathyroidectomy,[7] and the effect was sustainable.[12] Very high levels of PTH, the duration of disease, high calcium levels, low vitamin D levels, high alkaline phosphatase levels, and radiological evidence of subperiosteal bone resorption have been described as predictors of marrow fibrosis in patients

Table 1
Preoperative Biochemical Parameters of the Patient

Parameter (unit)	Preoperative result	Reference range
Hemoglobin (g/dL)	6.3	12-15
Mean corpuscular volume (fL)	90	80-100
Mean corpuscular hemoglobin (pg)	30	26-34
Reticulocyte count (%)	3.6	0.5-2.5
Hematocrit (%)	25	38-46
Total leucocyte count (cells/mm^3)	3000	4000-12 000
Platelet count (cells/mm^3)	60 000	150 000-450 000
Corrected calcium (mg/dL)	15.5	8.3-10.4
Inorganic phosphate (mg/dL)	2.2	2.5-4.6
Creatinine (mg/dL)	0.86	0.4-1.4
Alkaline phosphatase (U/L)	4132	40-125
25-hydroxy vitamin D (ng/mL)	8	30-60
Parathyroid hormone (pg/mL)	2082	8-72
Ferritin (ng/mL)	135	20-290
Iron (μg/dL)	64	40-145
Total iron-binding capacity (μg/dL)	304	250-350
Vitamin B12 (pg/mL)	1226	200-950
Lactate dehydrogenase (U/L)	406	225-460
Serum bilirubin (mg/dL)	0.32	0.5-1
24-hour urine calcium (mg/day)	473	<200

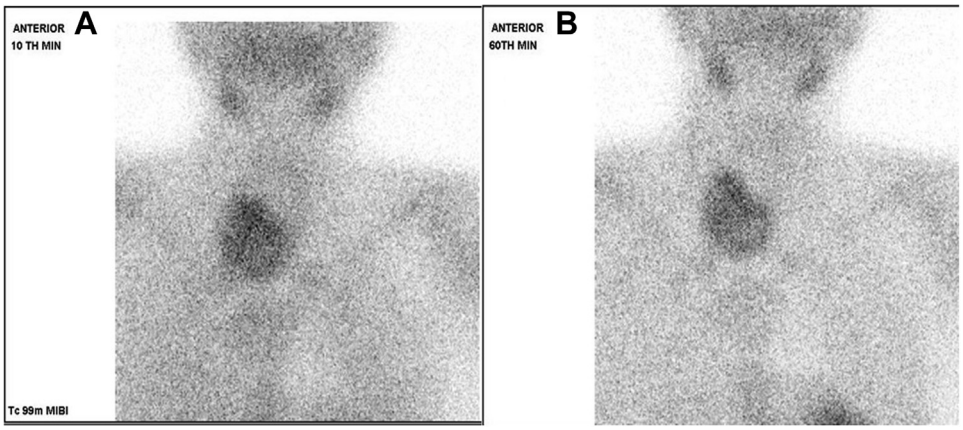

Fig. 2. PTH scintigraphy showing tracer accumulation in the lesion noted in the right lower pole of thyroid in the initial image at 10 minutes (*A*), which persists in the delayed image at 60 minutes (*B*). *PTH* = parathyroid hormone.

Table 2
Serial Follow-up Parameters of the Patient Showing Resolution of Pancytopenia

Parameter (unit)	Postoperative day 3	Postoperative 1 mo	Postoperative 2 mo	Postoperative 3 mo
Hemoglobin (g/dL)	8	8.3	8.3	10.1
Total leucocyte count (cells/mm^3)	…	3000	4000	4600
Platelet count (cells/mm^3)	…	72 000	172 000	150 000
Corrected calcium (mg/dL)	8.4	8.2	8.4	8.3
Alkaline phosphatase (U/L)	…	…	1065	812

with PHPT.[5,13] Our patient had a long duration of disease (symptoms present for 4-5 years) and high PTH (2082 pg/mL), low 25-hydroxy vitamin D (8 ng/mL), high corrected calcium (15.5 mg/dL), and high alkaline phosphatase (4132 U/L) levels, which would have predisposed her to myelofibrosis.

Conclusion

Pancytopenia may be a rare manifestation of PHPT. The significant improvement in the hematologic derangements after surgical cure of PHPT may suggest a causal association. It is important to look for these derangements in patients presenting with severe hyperparathyroidism. Moreover, evaluation of calcium levels is suggested in patients with chronic refractory anemia and pancytopenia.

Disclosure

The authors have no multiplicity of interest to disclose.

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