

Case Report

An Unusual Cause of Hypercalcemia in Polycythemia Vera: Parathyroid Adenoma

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In this paper we describe a patient with polycythemia vera (PV), who presented with hypercalcemia due to a parathyroid adenoma. In November 1999, the patient was admitted to our hospital with meteorism and constipation. Her physical examination revealed plethora and hepatosplenomegaly. Laboratory data revealed hyperparathyroidism in addition to PV: Rbc $8 \times 10^6/\text{mm}^3$, Hct 63.7%, serum calcium 13.4 mg/dl, serum phosphorus 1.2 mg/dl, albumin 4.25 mg/dl, and alkaline phosphatase activity 433 U/l. Intact Parathyroid Hormone level (iPTH) was 376 pg/ml (n.v.12-72 pg/ml). Twenty-four hour urinary calcium excretion was higher than normal (900 mg). A parathyroid adenoma was detected with Tc-99m sesta-MIBI scanning under the left lobe of the thyroid gland and an ultrasonographic examination of the neck also supported the diagnosis. The patient was recommended for surgery. The histopathological examination confirmed the diagnosis. Postoperatively, iPTH dropped to 53.4 pg/ml at the 15 th minute and to 33.5 pg/ml at the first hour. The calcium level was 7.5 mg/dl one hour after the operation. Five days later, Hct was 40.8%. This case represents a rare association between PV and primary hyperparathyroidism, and may provide evidence for a causal link between PTH and polycythemia vera in our patient. In conclusion, this case indicates that the differential diagnosis of hypercalcemia and polycythemia vera should also include the possibility of a parathyroid tumor in addition to malignancy.

Key words: hyperparathyroidism, intact PTH, scintigraphy and myeloid hyperplasia

Hypercalcemia in myeloproliferative disorders such as polycythemia vera is usually thought to be related to malignancy. The co-incidence of polycythemia vera and renal cell carcinoma is well known [1]. In addition, other carcinomas, such as hepatocellular carcinoma [2], pheochromocytomas [3], and ovarian carcinomas [4], may co-occur with polycythemia vera, but an association between hyperparathyroidism and

polycythemia vera has rarely been reported.

This paper describes a patient with polycythemia vera presenting with hypercalcemia due to a parathyroid adenoma.

Case Report

A 58-year-old woman was diagnosed with polycythemia vera in January 1995 according to the criteria of the Polycythemia Vera Study Group [5]. There were no endocrinological or hematological disorders in her familial history. On her physical examination a hepatomegaly of 2

cm, and a splenomegaly of 5 cm was detected. Her blood counts were Red Blood Cell (Rbc) $7.4 \times 10^6/\text{mm}^3$, Hematocrit (Hct) 58%, White blood cell (Wbc) $12.800/\text{mm}^3$ (7% band neutrophil, 83% neutrophil, 8% lymphocyte, 2% monocyte), platelet $170.000/\text{mm}^3$, erythrocyte mass: 49.4 ml/kg (normal value: 20–30 ml/kg), arterial oxygen saturation 96%, serum calcium 9.2 mg/dl (n.v. 8.5–11.9 mg/dl), serum phosphorus 1.8 mg/dl (n.v. 1.6–6.8 mg/dl), albumin 4.45 g/dl, alkaline phosphatase activity 250 U/l (n.v. 98–279 U/l), and intact Parathyroid Hormone level (iPTH) 58 pg/ml (n.v. 12–72 pg/ml). The disease was controlled by phlebotomies (500 ml/day with 30 days interval) until November 1998, when she developed progressive splenomegaly and thrombocytopenia (platelet: $75.000/\text{mm}^3$). The bone marrow biopsy showed grade II reticular fiber increment, focal megaloblastic changes, and erythroid and myeloid hyperplasia. Laboratory data also included normal serum calcium (8.8 mg/dl) and phosphorus (1.8 mg/dl) in this period.

In November 1999, the patient was again admitted to our hospital, with meteorism and constipation. Her physical examination revealed plethora, hepatomegaly (2 cm), splenomegaly (14 cm), and crepitations in the left lower lung field on chest auscultation. She showed no signs of osmotic dehydration in her physical examination. Laboratory data included: Rbc $8 \times 10^6/\text{mm}^3$, Hct 63.7%, a leukocyte count of $7.900/\text{mm}^3$, platelet $81.000/\text{mm}^3$, serum calcium 13.4 mg/dl, serum phosphorus 1.2 mg/dl, albumin 4.25 g/dl, and alkaline phosphatase activity 433 U/l. iPTH level was 376 pg/ml (n.v. 12–72 pg/ml, DPC, LA, USA). Twenty-four hour urinary calcium excretion was higher than normal (900 mg) (n.v. 100–250 mg). Serum bilirubin levels were both normal [total bilirubin 0.8 mg/dl (n.v.), indirect bilirubin 0.4 mg/dl (n.v.)]. On her telecardiography, cardio-thoracic index was 0.5 and the left atrium was dilated. On ECG, the QT interval was shortened (0.3 sec) (N: 0.35–0.44 sec) and there was a bi-phasic P wave indicating a left atrial hypertrophy. Nephrocalcinosis was absent on the renal sonogram.

She was phlebotomized (500 ml/day for a total of 1.5 l) and treated for hypercalcemia with saline diuresis, methylprednisolone (80 mg/day, iv) and calcitonin (200 $\mu\text{g}/\text{day}$, sc). The calcium level was insufficiently controlled and the patient was developing confusion. In response, a single dose of pamidronate disodium (15 mg, iv) was given on the third day of admission. The confu-

sion disappeared on the first day and the calcium value returned to 10.3 mg/dl on the third day after pamidronate. The saline diuresis and glucocorticoid treatments were stopped.

A parathyroid adenoma was detected with Tc-99m sesta-MIBI scanning under the left lobe of the thyroid gland (Fig. 1). An ultrasonographic examination of the neck supported the diagnosis. Total body bone scanning with Tc-99m sesta-MIBI showed the parathyroid adenoma along with increased bone marrow activity, which is seen in myeloproliferative disorders.

The patient was diagnosed to with hyperparathyroidism due to parathyroid adenoma and underwent surgery in December 1999. Intraoperative exploration of the neck and mediastinum revealed a nodular lesion in the left lobe at the location noted on parathyroid ultrasonography and scintigraphy. The histopathological examination of this nodule showed a parathyroid adenoma. Postoperatively, PTH dropped to 53.4 pg/dl at the 15 th min and to 33.5 pg/ml at first hour. Calcium level was 7.5 mg/dl 1 h after the operation, and 5 days later Rbc count was $5.5 \times 10^6/\text{mm}^3$, Hb 12.5 g/dl, Hct 40.8%, Wbc count $9.1 \times 10^6/\text{mm}^3$ and platelet $110 \times 10^3/\text{mm}^3$, although only 150 ml blood was lost postoperatively through the drain. As shown in Fig. 2, a dramatic decrease in Hct (from 63.7% to 40.8%) and in calcium levels (from 13.4 mg/dl to 7.5 mg/dl) was observed after calcium-lowering treatment and parathyroid surgery, and no additional phlebotomy was needed for 4 months. There was no increase in bilirubin levels (Total bilirubin 0.9 mg/dl, indirect bilirubin 0.5 mg/dl). The developing hungry bone syndrome was

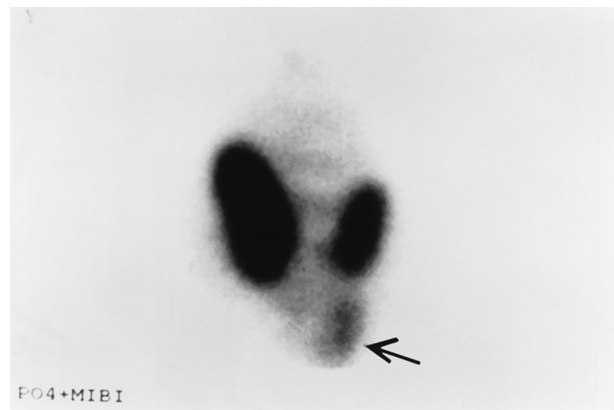


Fig. 1 Tc-99m sesta-MIBI scintigraphy of the neck shows a parathyroid adenoma under the left lobe of the thyroid gland.

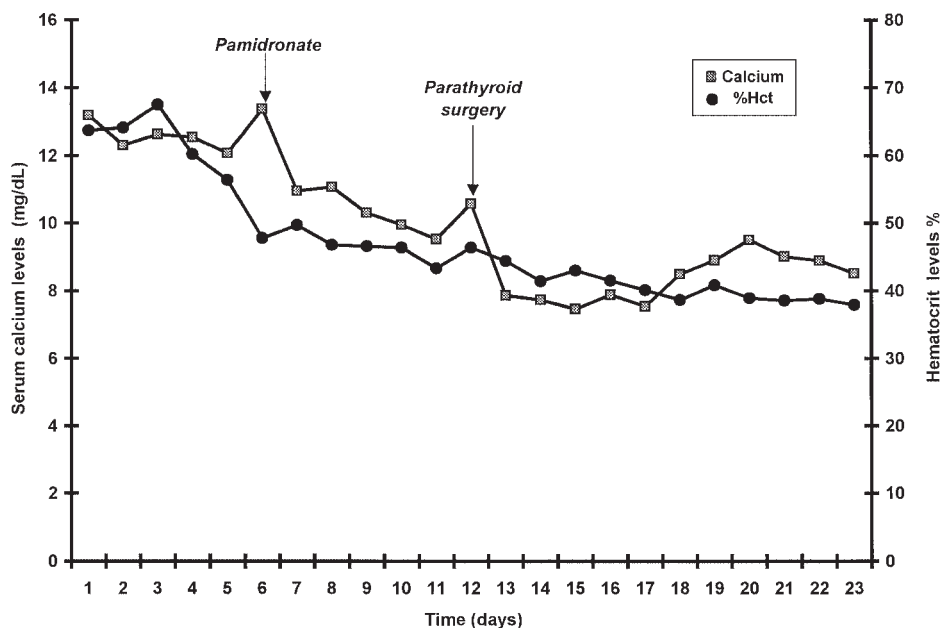


Fig. 2 Effects of medical therapy and parathyroid surgery on patient's calcium and hematocrit levels.

treated with oral calcium replacement (2,940 mg calcium lactate gluconate + 300 mg calcium carbonate) and 1-25 dihydroxycholecalciferol (0.5 μ g/day).

The patient was discharged 10 days after the operation without any complications. She received phlebotomies (500 ml/day at a 60 day interval) for the following 2 years without any subsequent problems.

Discussion

This case represents a rare association between polycythemia vera and parathyroid adenoma. An association between these 2 entities was first described by Berlin in 1949 [6]. Since then, 4 additional patients with hyperparathyroidism and polycythemia vera have been reported [7-10]. In these later cases, remission of the hypercalcemia and polycythemia vera was observed after resection of a parathyroid adenoma. In the present case, the need for phlebotomy was also increased during the hypercalcemic period. Recently, Pizzolitto *et al.* reported in a cohort study that a strong and statistically significant direct association was found between parathyroid adenoma and PV [11]. Our case report is another example of this rare association.

A bimodal effect of PTH on erythropoiesis has been

reported in the literature [12]. Levi *et al.* and Zevin *et al.* showed that a low level of PTH increases heme synthesis [13, 14]. On the other hand, Meytes *et al.* showed that high levels of PTH cause a pronounced decrease of heme synthesis [15]. This inhibition was however, only found with a high level of PTH typical of advanced uremia. Another tie between parathyroid tumors and hematopoiesis was suggested by Marx *et al.* in 1989 [16]. The authors reported that an increase in the intranuclear ionized calcium concentration might lead to the transcription of a region of chromosome 11, which is associated with the oncogenes in hematological disorders. Yelamarty *et al.* [17] also reported that in the presence of ionized hypercalcemia such as that seen in parathyroid cancer, the production of a growth factor that causes hematopoietic stem cell proliferation may be produced or stimulated.

This case report may provide evidence of a causal link between PTH or hypercalcemia and polycythemia vera in our patient. Although phlebotomies and surgery may lead to some degrees of blood loss, iron deficiency alone fails to account for the maintenance of low Hct levels after resection of parathyroid adenoma in this patient. On the other hand, this immediate reduction of Hct may be due to hepatosplenomegaly, although we did not detect any

increase in serum bilirubin levels during the pre- or postoperative period. After applied therapies for acute hypercalcemia such as *iv* infusion of methylprednisolone and pamidronate, the presentation of polycythemia vera improved but we could not determine whether calcium or parathormone had influenced its course. However, this improvement suggests that the calcium-PTH axis is important for the activation of erythropoiesis, and also demonstrates an association of polycythemia vera and parathyroid adenoma.

In conclusion, the cause-effect relationship between PTH and myeloproliferative disorders is not yet completely understood. This case emphasizes that *in vivo* and *in vitro* studies are necessary to investigate the effect of calcium-PTH axis on bone marrow and erythropoiesis.

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