*JCEM Case Reports*, 2024, **2**, luae068
https://doi.org/10.1210/jcemcr/luae068
Advance access publication 5 June 2024
**Case Report**

# Random Occurrence or Real Association? Primary Hyperparathyroidism in a Young Man With Sickle Cell Disease

**Raul Lopez Fanas,[1] Rateb Fouad,[1] and Kristin A. Swedish[1]**

[1]Wakefield Division, Montefiore Medical Center, Bronx, NY, 10466, USA

**Correspondence:** Raul Lopez Fanas, MD, Wakefield Division, Montefiore Medical Center, 600 E. 233rd St, Bronx, NY, 10466 USA.
Email: rlopezfana@montefiore.org.

## Abstract

A 32-year-old man with sickle cell disease (SCD) was admitted to the hospital for sickle cell crisis, during which laboratory workup revealed primary hyperparathyroidism. His treatment regimen included hydration, calcitonin, and calcimimetics. A parathyroid nuclear scan revealed anomalous parathyroid tissue. The precise relationship between primary hyperparathyroidism (PHPT) and SCD remains incompletely understood but may involve factors such as vitamin D deficiency, elevated erythropoietin levels, and the influence of growth factors on the development of parathyroid adenomas. Furthermore, the concurrent occurrence of both PHPT and SCD at an earlier age may potentiate adverse long-term outcomes. Effective management of PHPT in SCD entails addressing hypercalcemia and treating the underlying cause of hyperparathyroidism. While a potential association between PHPT and SCD exists, further research is essential to better elucidate their interaction, prevalence, clinical presentations, and outcomes.

**Key Words:** primary hyperparathyroidism, hypercalcemia, sickle cell disease

## Introduction

Primary hyperparathyroidism (PHPT) is an endocrinological disorder characterized by excessive secretion of PTH, resulting in hypercalcemia (1). PHPT predominantly affects women aged 60 to 70 years (2). The primary cause of PHPT is often attributed to parathyroid adenomas, which may manifest sporadically or be linked to familial syndromes such as multiple endocrine neoplasia. In this report, we describe a case of PHPT in a young man with sickle cell disease (SCD).

## Case Presentation

A 32-year-old man with SCD (HbS 91%) presented to the emergency department with abdominal pain, nausea, and vomiting. The patient reported no prior episodes of kidney stones, fractures, exposure to radiation, family history of cancer, or multiple endocrine neoplasia syndrome.

## Diagnostic Assessment

Initial assessment revealed severe anemia and elevated liver function tests, prompting admission to the general medical ward for sickle cell crisis. During hospitalization, elevated corrected calcium levels were observed (Fig. 1). Further testing revealed elevated PTH (Table 1). No evidence of granulomatous disease was observed on chest X-ray. Abdominal magnetic resonance imaging did not detect kidney stones. Ultrasound examination revealed normal thyroid and parathyroid glands without any discernible nodules.

## Treatment

Pain medications and intravenous (IV) fluids were initiated upon admission to treat the sickle cell crisis in addition to hypercalcemia. However, due to persistent hypercalcemia refractory to IV fluids, he received calcitonin 4 units/kg every 12 hours for 48 hours, cinacalcet 30 mg daily, and vitamin D3 1000 units daily on the sixth day of hospitalization. Despite this treatment regimen and aggressive magnesium repletion, hypercalcemia persisted, requiring escalation of cinacalcet dosage to 30 mg every 8 hours.

## Outcome and Follow-up

Finally, the patient's calcium level stabilized, and he was discharged with vitamin D 1000 IU daily, cinacalcet 30 mg every 8 hours, and magnesium oxide 400 mg every 8 hours to maintain calcium at a normal level.

In the outpatient setting, a parathyroid nuclear scan revealed subtle uptake, indicating potential abnormal parathyroid tissue in the bilateral lower poles (Fig. 2). Currently, the patient is considered a candidate for surgical intervention. However, due to multiple sickle cell crisis episodes, he has been unable to attend follow-up appointments.

## Discussion

Only a few studies have documented the incidence of PHPT among individuals with SCD. A study evaluating clinical and biological characteristics of PHPT in 18 patients with

**Received:** 15 January 2024. **Editorial Decision:** 3 April 2024. **Corrected and Typeset:** 5 June 2024

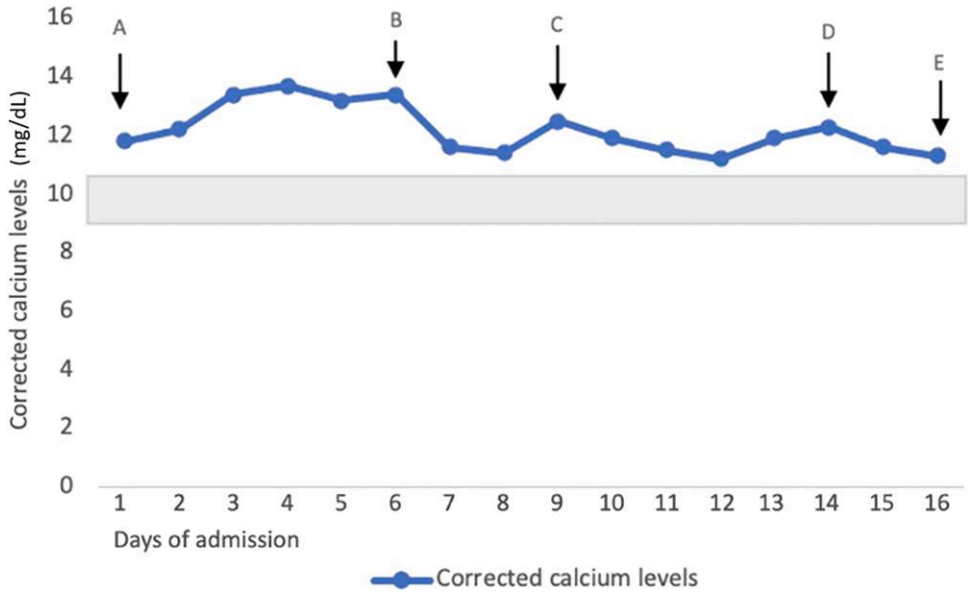


**Figure 1.** Corrected calcium trend during admission. The x-axis indicates the admission days, while the y-axis indicates the corrected calcium levels. The gray zone exhibits normocalcemia range. (A) indicates day of admission and initiation of intravenous fluids; (B) represents day of calcitonin administration, as well as initiation of vitamin D and cinacalcet 30 mg daily; (C) exhibits day of increase of cinacalcet to 30 mg every 12 hours; (D) indicates day of increase of cinacalcet to 30 mg every 8 hours; (E) represents day of discharge.

**Table 1. Basic and complementary workup**

| Laboratory test | Result | Normal range |
|---|---|---|
| Blood studies | | |
| Calcium | **11.1 mg/dL (2.77 mmol/L)** | 8.5-10.5 mg/dL (2.12-2.62 mmol/L) |
| Albumin | **3.1 g/dL (31 g/L)** | 3.5-5 g/dL (30-50 g/L) |
| Phosphorus | 2.7 mg/dL (0.87 mmol/L) | 2.5-4.5 mg/dL (0.81-1.45 mmol/L) |
| Magnesium | **1.4 mEq/L (0.58 mmol/L)** | 1.5-2.4 mEq/L (0.75-1.2 mmol/L) |
| Creatinine | 0.75 µmol/L (66.32 µmol/L) | <1.2 µmol/L (</= 106 µmol/L) |
| Intact PTH | **204.8 pg/mL (21.7179 pmol/L)** | 20.0-80.0 pg/mL (2.1- 8.5 pmol/L) |
| 25-OH vitamin D | **<10 ng/mL (<25 nmol/L)** | 30.0-60.0 ng/mL (25-137 nmol/L) |
| 1,25-OH vitamin D | **12 pg/mL (29.95 pmol/L)** | 18-72 pg/mL (58-156 pmol/L) |
| TSH | 3.0 µIU/mL (3.0 mIU/L) | 0.30-4.20 µIU/mL (0.5-4.70 mIU/L) |
| Urine studies | | |
| 24-hour urinary calcium | **311 mg (7.78 mmol/day)** | <300 mg/day (<7.5 mmol/day) |
| 24-hour urine creatinine | 1399.5 g (12.4 mmol/day) | 0.8-2.4 g/day (7.1-21.2 mmol/day) |
| Urine volume | 4500 mL | 800-2000mL |

Abnormal values are shown in bold text. Values in parenthesis are International System of Units.

Unable to obtain PTH related protein since the patient was icteric.

SCD found that most affected patients were female (64%), with a median age of 41 years. The majority of patients were from Sub-Saharan Africa (82%) and homozygous for SCD (79%). At the time of diagnosis, 57% had no symptoms, 11% had kidney stones, and 7% had gastric ulcers. Hypercalcemia was generally mild, with a median total serum calcium level of 10.5 mg/dL (2.62 mmol/L). Most patients had elevated PTH levels, though 8 (44%) had hypercalcemia with normal PTH levels. Oral calcimimetics were given to 14 non-surgical patients, but half of the participants ultimately required parathyroidectomy (3).

Conversely, conflicting data exists regarding the potential association between PHPT and SCD, with uncertainties regarding whether they are genuinely linked or merely coincide as random events. A retrospective study conducted in France from 2011 to 2020 aimed to discern the differences between individuals with SCD with and without PHPT. This study compared 177 patients with SCD (12 patients with hypercalcemia and PHPT, 165 patients with hypercalcemia without PHPT) with 72 patients without SCD (64 patients with PHPT and hypercalcemia, 8 patients with familial hypocalciuric hypercalcemia). In contrast to patients with PHPT without SCD, the study revealed that patients with concurrent SCD and PHPT had lower serum calcium levels, decreased concentrations of PTH, and diminished fasting fractional excretion of calcium. These findings suggest that individuals with PHPT and SCD may possess a metabolic profile similar to familial hypocalciuric hypercalcemia. The study's authors proposed the following mechanism suggesting that chronic hemolytic molecules could augment calcium excretion via the nephron and diminish the function of the calcium-sensing receptor in the kidney (4). However, this hypothesis does not align with the biochemical analysis and 24-hour urine calcium findings in our patient, which indicated an overactive parathyroid gland as the cause of his hypercalcemia.

Although not fully understood, several pathophysiological mechanisms have been suggested to explain the association between PHPT and SCD (Fig. 3). Individuals with SCD often experience chronic vitamin D deficiency, with prevalence

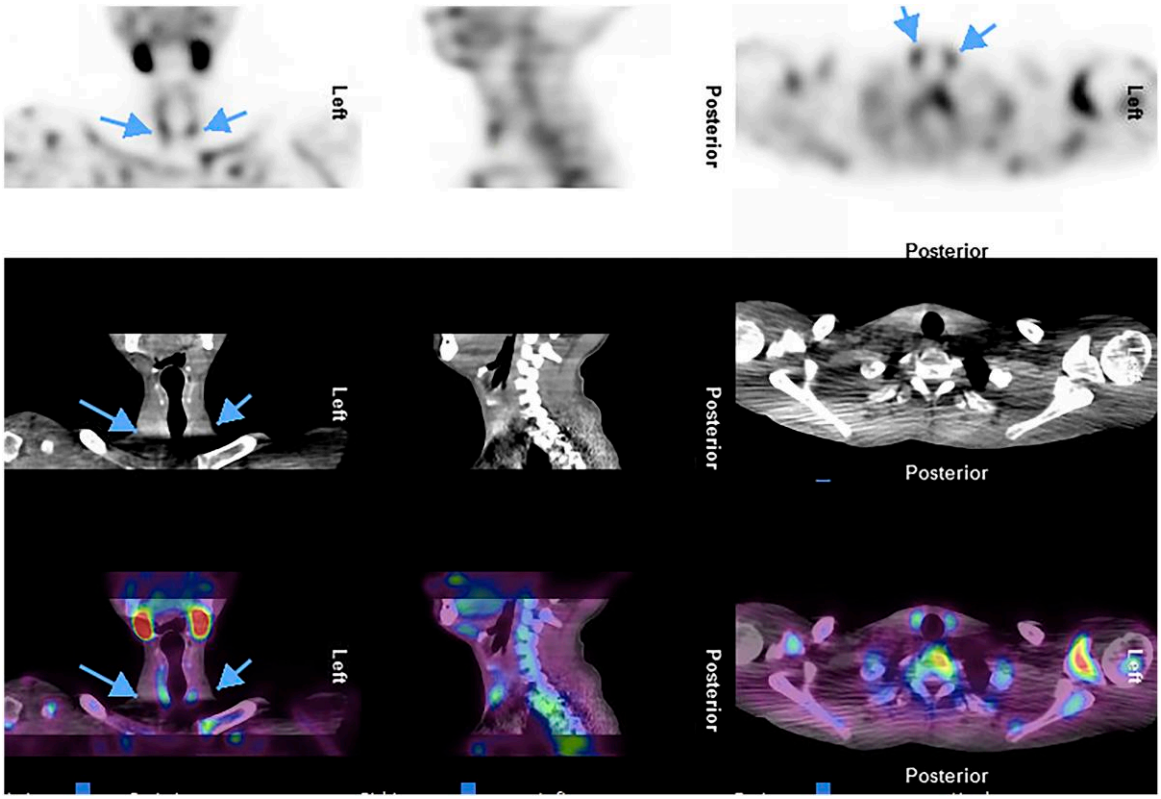


**Figure 2.** The nuclear medicine parathyroid scan using single photon emission tomography/computed tomography indicated a slight elevation in uptake, suggesting potential abnormal parathyroid tissue in the lower poles of both sides, as indicated by arrows. This heightened uptake became more evident 60 minutes after the administration of the radioisotope.

exceeding 56%. This occurrence is believed to stem from reduced oral intake in patients with SCD, in addition to limited cutaneous synthesis of vitamin D, impaired absorption of fat-soluble vitamins in the intestinal mucosa, heightened nutritional requirements due to continuous red blood cell turnover, and decreased levels of vitamin D binding protein induced by inflammation (5). While vitamin D deficiency typically results in hypocalcemia and secondary hyperparathyroidism (6), studies indicate that persistent vitamin D depletion could prompt the enlargement of the parathyroid gland, leading to the onset of primary hyperparathyroidism (3, 7).

Another proposed mechanism links PHPT with increased erythropoietin (EPO) levels in patients with chronic hemolytic anemia, such as SCD. It is postulated that persistently elevated EPO could activate EPO receptors within the parathyroid gland, promoting adenomatous growth (3). Immunohistochemical studies have demonstrated the presence of EPO receptors in parathyroid cells, indicating a potential role in parathyroid hyperplasia and adenomas (8). A small-scale study involving 20 patients undergoing orthopedic surgery showed that the induction of hypoxia led to significantly elevated levels of both PTH and EPO ($P < .001$). Furthermore, a positive correlation was observed between PTH and EPO levels ($P < .05$) (9).

The third proposed mechanism explains that individuals with SCD exhibit heightened concentrations of growth factors, specifically vascular endothelial growth factor and fibroblast growth factor as reported in studies (10-12). These biomolecules are thought to potentially stimulate the proliferation of parathyroid cells and induce endothelial cell activity (13, 14). Nevertheless, additional research is essential to gain a more comprehensive understanding of the specific role of growth factors in the context of SCD.

Having both SCD and PHPT can be life-threatening for patients, and our patient's early diagnosis of PHPT suggests potentially worse long-term outcomes compared to typical presentations (15). Several studies suggest that individuals with PHPT may contribute to sickle cell crisis through the Gardos effect (Fig. 4), which involves calcium-activated potassium channels in red blood cells (6). Elevated levels of intracellular calcium, triggered by PTH, activate these channels, leading to dehydration and exacerbating vaso-occlusive crises in SCD (3). Additionally, hypercalcemia in PHPT further promotes dehydration, increasing the likelihood of sickling and sickle cell crisis. Hence, while pain is commonly associated with vaso-occlusive crises in SCD, not all pain that SCD patients experience may be directly attributable to crises (16). A case series of 2 patients with both PHPT and SCD demonstrated improvement in pain crises following parathyroidectomy (17).

The skeletal system is affected in both PHPT and SCD. Increased PTH levels in PHPT can result in metabolic bone disease, affecting bone structure, reducing bone density, and increasing risk of fracture (18). Studies indicate that low bone mineral densities are widespread among young adult SCD patients, suggesting that PHPT could further exacerbate skeletal issues in a subgroup of adult SCD patients (3).

Likewise, the kidneys are frequently impacted in patients with both SCD and PHPT. Hypercalcemia due to PHPT is typically linked to dehydration and reduced renal function (19). Similarly, renal function deteriorates more rapidly in individuals with SCD compared to those without the disease, contributing

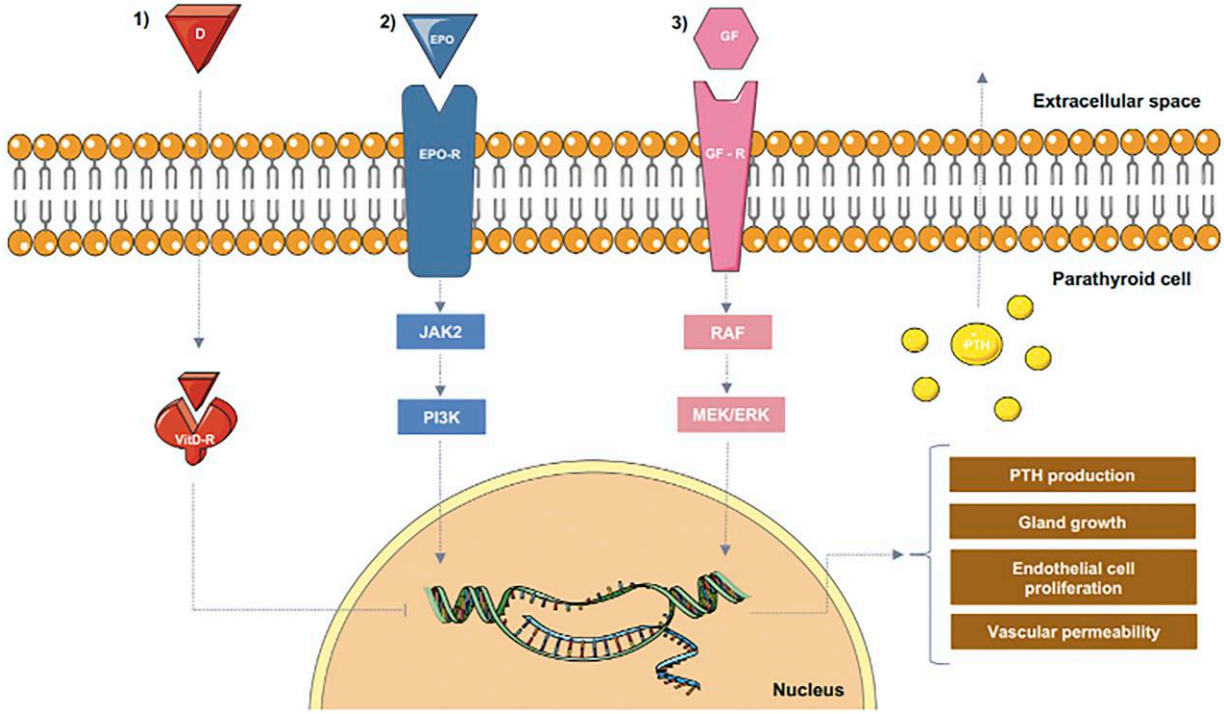


**Figure 3.** Proposed mechanisms leading to primary hyperparathyroidism in sickle cell disease (1). Chronic vitamin D depletion promotes PTH production (2); EPO stimulates its receptor (EPO-R) facilitating parathyroid gland growth; (3) GFs stimulate their receptors (GF-R) favoring endothelial proliferation and parathyroid cell growth. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

Abbreviations: EPO, erythropoietin; EPO-R, erythropoietin receptor; GF, growth factor; GF-R, growth factor receptor.

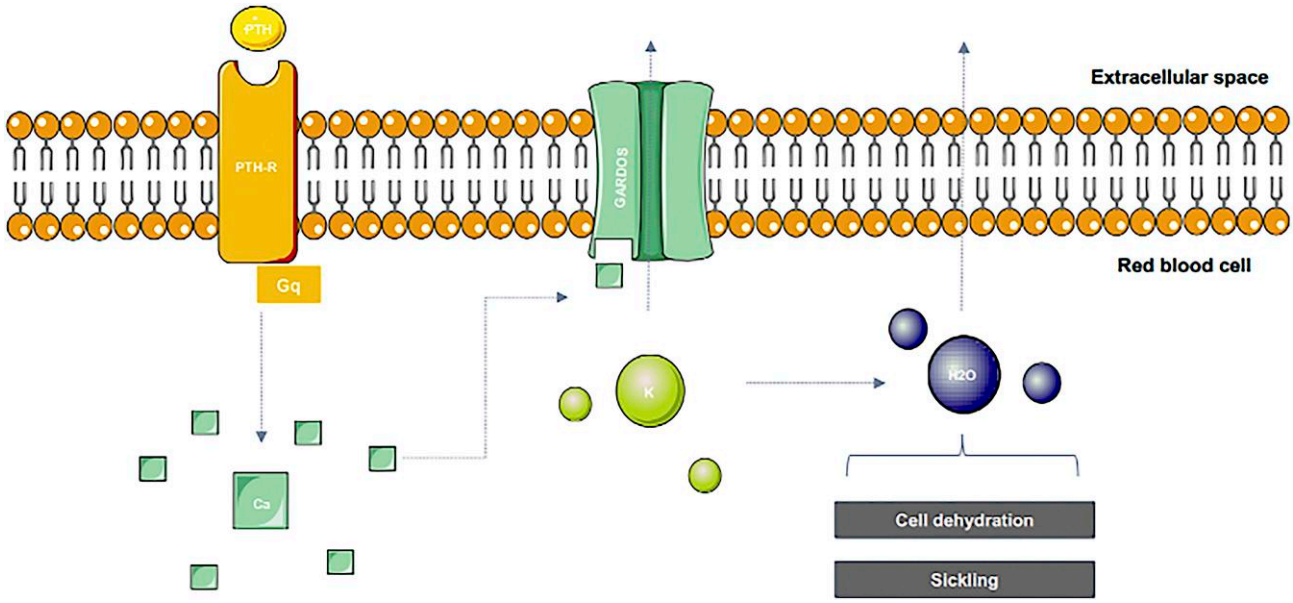


**Figure 4.** Gardos effect, in which elevated PTH levels increases calcium concentration in the red blood cell, favoring cell dehydration and sickling. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

to higher morbidity and mortality (20). However, the specific effects of both diseases occurring concurrently on renal function have not been thoroughly investigated.

Therefore, prompt identification and management of PHPT and hypercalcemia are crucial in patients with SCD. We propose that in individuals with SCD exhibiting hypercalcemia, screening for elevated PTH levels should be conducted. If PTH levels are elevated, further evaluation with neck ultrasound and/or parathyroid nuclear scan is recommended. Additionally, given the increased likelihood of low bone mineral density in this patient population, performing a bone density test is imperative.

The primary treatment approach for individuals diagnosed with PHPT involves surgical resection. Clinical guidelines have delineated specific criteria for determining the necessity of parathyroidectomy, which includes not only the calcium levels but also a comprehensive assessment of skeletal and renal health in these patients. The indications for parathyroidectomy include age below 50 years; evidence of renal involvement (defined as nephrolithiasis or nephrocalcinosis, creatinine clearance < 60 mL/min (<1 mL/s), or hypercalciuria > 10 mmol/day (>400 mg/d) associated with an increased risk of renal stone formation; skeletal involvement (such as osteoporosis as demonstrated by bone mineral density testing or a history of fragility fractures); and serum calcium concentration exceeding 1.0 mg/dL (0.25 mmol/L) above the upper limit of normal. Currently, our patient meets the criteria for surgical resection. However, due to recurrent sickle cell crises, he has been unable to attend follow-up appointments. In cases where surgery is not feasible, clinicians can opt to pursue ongoing medical management (3).

There are several medical interventions available to manage hypercalcemia. These may involve avoiding triggering factors and administering IV fluids at a high rate with or without loop diuretics; medications such as calcitonin, bisphosphonates, denosumab, steroids, or calcimimetics; and dialysis. The treatment choice should be individualized, considering the specific indications and contraindications for each therapeutic approach (21, 22).

In summary, PHPT is a frequent cause of hypercalcemia, and there is some evidence linking it to SCD. However, the precise pathophysiological mechanisms underlying the association between PHPT and SCD remain incompletely understood. Further research is needed to better understand the relationship between these conditions and to further awareness of prevalence, clinical presentation, and outcomes.

## Learning Points

- PHPT is a disorder marked by an overproduction of PTH, resulting in elevated calcium levels. This condition is commonly observed in elderly women and is frequently associated with parathyroid adenoma. Research and case reports have indicated an association between PHPT and SCD.
- While the precise relationship between PHPT and SCD remains unclear, potential contributing factors may include low levels of vitamin D, increased EPO levels, and the influence of growth factors on the development of parathyroid adenoma. Additionally, PHPT has been observed to exacerbate sickle cell crises.
- Fluids, calcitonin, vitamin D, bisphosphonates, calcimimetics, and addressing the root cause are among the interventions required to manage hypercalcemia.

## Acknowledgments

The authors acknowledge the contribution of Dr. Santiago Beltran, who assisted in caring for this patient, and Dr. Ana Valdivia, for her support in analyzing and interpreting the patient's medical imaging.

## Contributors

All authors made individual contributions to authorship. All authors were involved in the diagnosis and management of the patient and manuscript submission. R.L.F. was responsible for the initial drafting of the manuscript with R.F. and K.A.S. responsible for editing. All authors reviewed and approved the final draft.

## Funding

No public or commercial funding.

## Disclosures

None of the authors have any conflicts to disclose.

## Informed Patient Consent for Publication

Signed informed consent was obtained directly from patient.

## Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## References

1. Walker MD, Silverberg SJ. Primary hyperparathyroidism. *Nat Rev Endocrinol*. 2018;14:115-125.
2. Clarke BL. Epidemiology of primary hyperparathyroidism. *J Clin Densitom*. 2013;16(1):8-13.
3. Denoix E, Bomahou C, Clavier L, *et al*. Primary hyperparathyroidism in sickle cell disease: an unknown complication of the disease in adulthood. *J Clin Med*. 2020;9(2):308.
4. Khan EA, Cheddani L, Saint-Jacques C, *et al*. Primary hyperparathyroidism in homozygous sickle cell patients: a hemolysis-mediated hypocalciuric hypercalcemia phenotype? *J Clin Med*. 2021;10(21):5179.
5. Nolan VG, Nottage KA, Cole EW, Hankins JS, Gurney JG. Prevalence of vitamin D deficiency in sickle cell disease: a systematic review. *PLoS One*. 2015;10(3):e0119908.
6. Lakkakula BVKS, Neral A. Parathyroid hormone abnormities in sickle cell anemia patients. *J Parathyroid Dis*. 2019;7(1):1-4.
7. Silverberg SJ. Vitamin D deficiency and primary hyperparathyroidism. *J Bone Miner Res*. 2007;22(Suppl 2):V100-V104.
8. Öztürk M, Üstek D, Akbaş F, *et al*. The presence of erythropoietin receptor in parathyroid cells. *J Endocrinol Invest*. 2007;30:RC35-RC37.
9. Gönüllü E, Özkan S, Adanaş C, Özbay MF, Kılıç E, Atmaca M. Effects of endogen erythropoietin on parathormone secretion. *Forbes J Med*. 2021;2(3):171-174.
10. Antwi-Boasiako C, Frimpong E, Gyan B, *et al*. Elevated proangiogenic markers are associated with vascular complications within Ghanaian sickle cell disease patients. *Med Sci (Basel)*. 2018;6(3):53.
11. Duits AJ, Schnog JB. Vascular growth factors in patients with sickle cell disease. *Blood*. 2005;106(11):3787.
12. Qari MH, Dier U, Mousa SA. Biomarkers of inflammation, growth factor, and coagulation activation in patients with sickle cell disease. *Clin Appl Thromb Hemost*. 2012;18(2):195-200.
13. Carter WB, Uy K, Ward MD, Hoying JB. Parathyroid-induced angiogenesis is VEGF-dependent. *Surgery*. 2000;128(3):458-464.
14. Lambert D, Eaton CL, Harrison BJ. Fibroblast growth factors and their receptors in parathyroid disease. *World J Surg*. 1998;22(6):520-525.
15. Jridi M, Mekni S, Meriem A, *et al*. Sickle cell disease and hyperparathyroidism: case report. *Endocrine Abstracts*. 2022;81:EP178.
16. Krishnamoorthy P, Alyaarubi S, Abish S, Gale M, Albuquerque P, Jabado N. Primary hyperparathyroidism mimicking vaso-occlusive crises in sickle cell disease. *Pediatrics*. 2006;118(2):e537-e539.
17. Muthu J, Ali M. Amelioration of sickle cell pain after parathyroidectomy in two patients with concurrent hyperparathyroidism: an interesting finding. *Case Rep Med*. 2016;2016:3263951.

18. Bennet J, Suliburk JW, Moron FE. Osseous manifestations of primary hyperparathyroidism: imaging findings. *Int J Endocrinol*. 2020;2020:3146535.
19. Bhat NA, Mustafa F, Sheikh RY, *et al*. Incidence, etiology, and course of hypercalcemia-induced AKI in a tertiary care center from northern India. *Egypt J Intern Med*. 2021;33:36.
20. Ataga KI, Saraf SL, Derebail VK. The nephropathy of sickle cell trait and sickle cell disease. *Nat Rev Nephrol*. 2022;18(6):361-377.
21. Donovan Walker M, Shane E. Hypercalcemia. A review. *JAMA*. 2022;328(16):1624-1636.
22. Carroll MF, Schade DS. A practical approach to hypercalcemia. *Am Fam Physician*. 2003;67(9):1959-1966.