HYPERCALCEMIC CRISIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

H.T. Kiper Yılmaz^{1,*}, P. Tosun Taşar², A. Carlioglu³

Regional Training and Research Hospital, ¹Department of Internal Medicine, ²Department of Geriatric Diseases, ³Department of Endocrinology, Erzurum, Turkey

Abstract

Severe hypercalcemia is often caused by primary hyperparathyroidism (PHP), which is not commonly seen in patients with systemic lupus erythematosus (SLE). In this case report a 77 years old woman with a history of SLE develops mild hypercalcemia secondary to unrecognized PHP that leads to a hypercalcemic crisis with a prolonged recovery. Therefore, early diagnostic evaluation of persistent hypercalcemia in patients with SLE is important for detection and appropriate treatment of PHP to avoid a hypercalcemic crisis and associated prolonged morbidity.

Key words: Primary hyperparathyroidism, hypercalcemic crisis, SLE, systemic lupus erythematosus.

INTRODUCTION

Hypercalcemic crisis (HCC) is a rare complication of acute or chronic hypercalcemia resulting from dysregulation of calcium homeostasis. Unrecognized primary hyperparathyroidism (PHP) is a major cause of HCC. Hypercalcemia can be seen in systemic lupus erythematosus (SLE) but rarely due to PHP (1). In this case report, we describe a 77-year-old woman with a history of SLE who developed HCC secondary to undiagnosed PHP and experienced a prolonged recovery of acute management of severe hypercalcemia.

CASE REPORT

A 77-year-old female patient was admitted to our hospital because of generalized weakness and blurred consciousness. She had known osteoporosis and a 6-month history of inflammatory polyarthritis involving the interphalangeal joints in particular. Her family history was unremarkable. On physical examination, her temperature was 36°C, blood pressure was 100/70 mmHg, heart rate was 72 beats /min,

respiration was normal, and a skin rash was observed. The mucocutaneous lesions included a butterfly-like exanthema on her nose and cheeks, and her lips were edematous and inflamed with angular cheilitis. Neck lymphadenopathy and tracheal deviation were not evident. Heart and lung sounds were normal, but hepatosplenomegaly was noted.

Results of the initial laboratory examination (Table 1) were as follows: white blood cell count: 2.8 (10³/μL) (3.7-10), hemoglobin: 8.2 (g/dL) (12.9-18.1), hematocrit: 30.7% (36-53), platelet count: 221 (10³/μL) (150-450), calcium: 15.7 (mg/dL) (8.4-10.6), phosphorus: 1 (mg/dL) (2.3-4.7), blood urea nitrogen (BUN): 12.6 (mg/dL) (8.2-25.7), serum creatinine: 0.4 (mg/dL) (0.7-1.25), sodium: 136 mmol/L (136-145), antinuclear antibody (ANA): ++, complement component C4: 0.03 (0.1-0.4), and parathyroid hormone (PTH): 1046.5 (pg/mL). Potassium and magnesium levels were within normal range. The patient was diagnosed with SLE based on her 6-month history of inflammatory polyarthritis and malar rash, ANA++ and low C4 level. Peripheral blood smear revealed normal morphology of the lymphocytes, lymphocyte count was 15, and toxic granulation was noted. Reticulocyte count was 1.8%. There was no M spike on protein electrophoresis. Abdominal ultrasound showed hepatosplenomegaly and splenic vein dilation. Cranial radiography showed a salt-and-pepper appearance; radiographs of both femur and hands showed generalized osteopenia. Bone mineral density (BMD) was measured in the lumbar spine and femoral neck. The BMD T-scores of the lumbar spine (L1-L4) and the femoral neck were -5.7 and -4.3, respectively. Parathyroid ultrasound showed a 27x20 mm heterogeneous, hypoechoic, solid nodule in the lower right lobe suggestive of parathyroid adenoma. On parathyroid scintigraphy, both early and Technetium-99m-methoxyisobutylisonitrile (late MIBI) accumulation was observed in the lower

*Correspondence to: Havva Tuğba Kiper Yılmaz MD, Regional Training and Research Hospital, Department of Internal Medicine, Erzurum, Turkey, E-mail: drtugbakiper@gmail.com

Table 1. Laboratory data

	Ca (mg/dL)	PTH (pg/mL)	HB (g/dL)	WBC (10 ³ /U)	Ne (10 ³ /U)	PLT (10 ³ /U)
1 week	15.7	1046.5	8.2	3089	1028	191.000
5 weeks	3.6	872.8	7.7	2900	600	190.000

right lobe of the thyroid, which also raised suspicion of parathyroid adenoma. She was diagnosed with HCC due to PHP in SLE. She received aggressive intravenous fluid infusion with furosemide and bisphosphonate for HCC. She received dexamethasone 5 mg, plaquanil 200 mg, and azathioprine for SLE. Her symptoms of bone pain regressed with analgesics and bisphosphonate. Cinacalcet was added, but her hypercalcemia showed no response to treatment. After 2 days, her serum calcium level raised to 13.6 (mg/dL) (8.4-10.6). She experienced loss of consciousness and was indicated for emergent surgery. Her ASA score was high. Parathyroidectomy could not be performed because her family did not provide consent, and the patient subsequently died.

DISCUSSION

Hypercalcemia is a common electrolyte abnormality. More than 90% of cases of hypercalcemia are due to PHP, malignancy, or a lymphoproliferative disease (2, 3). Rare causes of hypercalcemia include granulomatous diseases or conditions associated with increased bone turnover, vitamin D intoxication, or calcium overload (4). Hypercalcemia is caused by local bone destruction and/or by humoral factors, including PTHrP (parathyroid-related protein) (80% of cases of cancer-related hypercalcemia), interleukin 1, and 1,25(OH)²-vitamin D₃. iPTH (intact parathyroid hormone) is typically decreased in tumoral hypercalcemia (1, 3).

SLE is a chronic, multisystemic, and episodic autoimmune disease with a wide spectrum of autoantibodies (5). SLE is often seen in young women of child-bearing age, and the age at diagnosis is often 15-35 years. Elderly-onset lupus has been defined in various studies as onset of lupus after the age of 50-65 years (6). The frequency of late-onset SLE among published series ranges from 4 to 25% (7). Our case was diagnosed at age 77, which is rare. In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) network determined that a diagnosis of SLE is based on the presence of at least 4 (at least 1 clinical and 1 laboratory criterion) of the 17 criteria or biopsy-proven lupus nephritis with positive ANA or anti-DNA (8) SLE was diagnosed in our patient due to the

presence of malar rash, ANA positivity, low C4 level, and a 6-month history of inflammatory polyarthritis.

There are several cases in the literature in which hypercalcemia was the presenting feature of SLE. In all of those cases, hypercalcemia was detected when SLE was not in remission. The etiology of hypercalcemia in SLE is not clear. In some cases it has been attributed to production of parathyroid-related protein (PTHrP) and in some cases the stimulation of PTH-like autoantibodies has been implicated (9). It is hypothesized that the PTH autoantibodies might develop secondary to polyclonal activation of B lymphocytes (10). Moreover, proinflammatory cytokines (e.g. tumor necrosis factor alpha, transforming growth factor beta, interleukins 1, 2 and 6, prostaglandins E₂, and granulocyte-macrophage colony stimulating factors) are elevated during active SLE phases and may directly increase bone turnover, leading to hypercalcemia (11, 12). However, the observation that hypercalcemia does not occur in all patients with active SLE suggests that unknown individual factors contribute to the development of hypercalcaemia (4).

PHP has an incidence of approximately 25 cases per 100,000 persons in the general population (13). It is typically considered a disease of adulthood and is a common cause of hypercalcemia occurring either when PTH release is independent of calcium levels or the set point for calcium-induced suppression of PTH secretion is elevated. Approximately 80% to 85% of patients with PHP have benign parathyroid adenomas (14). It is typically treated by surgical removal. In our case, the patient died before parathyroidectomy could be performed. A preferred initial approach for treatment of moderate to severe hypercalcemia is aggressive intravenous hydration (3000 mL/m²/day) with calcitonin therapy for the first 48 hours, and then if hypercalcemia persists, treatment with one dose of a bisphosphonate is added. Loop diuretics like furosemide are frequently used to treat acute hypercalcemia. Calcitonin is generally effective for the first 48 hours because of the potential development of tachyphylaxis resulting from downregulation of the calcitonin receptor (15-17). We gave the bisphosphonate and cinacalcet. The patient died while the operation was in preparation.

Resistance to treatment of hypercalcemia due to PHP is low. Our aim in this report was to present a case of

SLE and severe refractory hypercalcemia. Mechanisms contributing to the etiology of hypercalcemia in SLE complicate medical care response. Physicians treating patients with PHP associated with SLE should act more cautiously and promptly.

Indeed, the diagnosis of lupus may not be established previous to the occurrence of hypercalcemia. Therefore, clinical and immunological clues may suggest the diagnosis of SLE in a patient with hypercalcemia of obscure origin. Because hypercalcemia seems to be related to lupus activity, response to immunosuppressive therapy is usually good. This case demonstrates that lupus should be considered when cases of HCC are encountered.

Conflict of interest

The authors declare that they have no conflict of interest.

References

- Ahmad S, Kuraganti G, Steenkamp D. Hypercalcemic crisis: a clinical review. *Am J Med.* 2015;128(3):239-245.
- Deftos LJ. Clinical Essentials of Calcium and Skeletal Disorders. Caddo, OK, USA: Professional Communications, 1998.
- Potts JT, Diseases of the parathyroid gland and other hyper- and hypocalcemia disorders. In Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL eds. *Harrison's Principles of Internal Medicine*, 15th edn. McGraw Hill: New York. 2001:2205–2226.
- Del Porto F, Proietta M, Koverech A, Trappolini M, Aliberti G. Hypercalcaemia in systemic lupus erythematosus. *Lupus.* 2011;20(7):758-762.
- Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: a critical review. *J Autoimmun.* 2014;48-49:10-13.
- Boddaert J, Huong DL, Amoura Z, Wechsler B, Godeau P, Piette JC. Late-onset systemic lupus erythematosus: a personal series of 47 patients and pooled analysis of 714 cases in the literature. *Medicine (Baltimore).* 2004;83(6):348-359.
- Gomez J, Suarez A, Lopez P, Mozo L, Diaz JB, Gutierrez C. Systemic lupus erythematosus in Asturias, Spain: clinical and serologic features. *Medicine (Baltimore).* 2006;85(3):157-168.
- Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, Bruce IN, Isenberg D, Wallace DJ, Nived O, Sturfelt G, Ramsey-Goldman R, Bae SC, Hanly JG, Sánchez-Guerrero J, Clarke A, Aranow C, Manzi S, Urowitz M, Gladman D, Kalunian K, Costner M, Werth VP, Zoma A, Bernatsky S, Ruiz-Irastorza G, Khamashta MA, Jacobsen S, Buyon JP, Maddison P, Dooley MA, van Vollenhoven RF, Ginzler E, Stoll T, Peschken C, Jorizzo JL, Callen JP, Lim SS, Fessler BJ, Inanc M, Kamen DL, Rahman A, Steinsson K, Franks AG Jr, Sigler L, Hameed S, Fang H, Pham N, Brey R, Weisman MH, McGwin G Jr, Magder LS. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum.* 2012;64(8):2677-2686.
- Lumachi F, Brunello A, Roma A, Basso U. Medical treatment of malignancy-associated hypercalcemia. *Curr Med Chem.* 2008;15(4):415-421.
- Crispín JC, Liossis SN, Kis-Toth K, Lieberman LA, Kyttaris VC, Juang YT, Tsokos GC. Pathogenesis of human systemic lupus erythematosus: recent advances. *Trends Mol Med.* 2010;16(2):47-57.
- Galrao LD, Lima IV, Santos L, Santiago MB. Primary hyperparathyroidism in a patient with systemic lupus erythematosus. *Arq Bras Endocrinol Metabol.* 2004;48(4):555-558.
- Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature.* 2003;423(6937):337-342.
- Suliburk JW, Perrier ND. Primary hyperparathyroidism. *Oncologist.* 2007;12(6):644-653.
- Silverberg SJ, Bilezikian JP. Asymptomatic primary hyperparathyroidism: a medical perspective. *Surg Clin North Am.* 2004;84(3):787-801.
- Hosking DJ, Cowley A, Bucknall CA. Rehydration in the treatment of severe hypercalcaemia. *Q J Med.* 1981;50(200):473-481.
- Shane E, Berenson JR. Treatment of hypercalcemia. In: Basow DS (ed.) *UpToDate.* 19.2 ed, Waltham, MA: UpToDate, 2011.
- Lee S, Mannstadt M, Guo J, Kim SM, Yi HS, Khatri A, Dean T, Okazaki M, Gardella TJ, Jüppner H. A Homozygous [Cys25] PTH(1-84) Mutation That Impairs PTH/PTHrP Receptor Activation Defines a Novel Form of Hypoparathyroidism. *J Bone Miner Res.* 2015;30(10):1803-1813.