Severe Hypocalcemia Due to Cisplatin Toxicity: A Case Report and Review of Literature

Cisplatin Toksisitesine Bağlı Ciddi Hipokalsemi: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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ABSTRACT Hypocalcemia is defined as total calcium (Ca) lower than 8.5 mg/dl or ionised Ca <4.7 mg/dl. It can be associated with certain drugs used in daily clinical practice. Here we report a case of severe symptomatic hypocalcemia who was treated with cisplatin and radiotherapy for cervix cancer. A 56 year old female patient admitted to emergency room with tetany. In the physical examination Chvostek and Trousseau signs were positive. In the detailed history, we learned that she had cervix cancer for 5 years and received her last cisplatin based chemotherapy 3 days ago. Severe hypocalcemia, hypomagnesemia, hyperphosphatemia were detected along with high PTH and low serum vitamin D levels. We have given intravenous calcium gluconate infusion together with magnessium until the symptoms were relieved. Hypocalcemia is usually caused by hypoparathyroidism, resistance to PTH or vitamin D. Cisplatin is an agent which has several side effects such as nephrotoxicity and leads to hypocalcemia.

Key Words: Hypocalcemia; cisplatin; vitamin D deficiency

ÖZET Hipokalsemi total kalsiyumun serumda 8.5 mg/dl'nin altında olması veya iyonize kalsiyumun 4,7 mg/dl altında olması olarak tanımlanır. Günlük hayatta sık kullanılan medikal ajanlar hipokalsemiye sebep olabilir. Bu yazıda serviks kanseri nedeni ile cisplatin ve radyoterapi almakta olan bir hastada ilaca bağlı gelişmiş ciddi hipokalsemi olgusu sunulmuştur. 56 yaşında kadın hasta acil servise tetani şikayetiyle başvurdu. Hastanın öyküsünde 5 yıl önce serviks kanseri tanısı aldığı, bu nedenle 3 gün önce cisplatin eş zamanlı radyoterapi başlandığı öğrenildi. Fizik muayenesinde Chvostek ve Trousseau bulguları mevcuttu. Laboratuvar bulgularında hipokalsemi, hiperfosfatemi ve hipomagnezemi saptandı. PTH düzeyi yüksek, D vitamin düzeyi düşük idi. Semptomatik olan hastaya acil intravenöz kalsiyum glukonat ve magnezyum replasmanı yapıldı. Hipokalsemi PTH sentezi, sekresyonu veya fonksiyonlarındaki defektlerden kaynaklanabileceği gibi, D vitamini eksikliği yada işlev bozukluğundan da kaynaklanabilir. Bunun dışında ilaçlar da geçici hafif hipokalsemiye yol açabilirler. Cisplatin bu ilaçlardan biridir, renal toksisite ile hipomagnezemiye ve dolayısı ile hipokalsemiye sebep olur.

Anahtar Kelimeler: Hipokalsemi; sisplatin; D vitamini eksikliği

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Hypocalcemia is defined as total calcium (Ca) lower than 8.5 mg/dl or ionised Ca lower than 4.7 mg/dl. Major factors determining the serum Ca levels are; parathyroid hormone (PTH), vitamin D and serum phosphate (PO4).[1] Most common causes of hypocalcemia are disorders related with PTH or vitamin D. It can also be associated with certain drugs that are used in daily clinical practice such as antiepileptics, biphosphonates and proton pump inhibitors. Drug-related hypocalcemia is usually

mild and asymptomatic. Hypocalcemia may also occur in cancer patients receiving chemotherapy. Cisplatin is one of those agents which can lead to hypocalcemia via several mechanisms. Here we report a case of severe symptomatic hypocalcemia in a patient being treated with cisplatin and radiotherapy for cervix cancer.

CASE REPORT

A 56 year- old-female patient admitted to emergency room with the complaints of perioral numbness paresthesia and tetany on her fingertips started one month before the admission. In the physical examination Chvostek and Trousseau signs were positive together with increased patellar reflex. Her electrocardiogram revealed prolonged QT interval. When we questioned the patient and recorded the detailed clinical history, we detected that she had cervix cancer for 5 years, was operated twice and after her last operation, 3 months ago, cisplatin based chemotherapy was started concomittant with radiotherapy. She received last cisplatin dose 3 days before admitting to the emergency room. In addition to that, she had coronary artery disease, metabolic syndrome and rheumatoid arthritis as comorbid conditions. In the laboratory investigation serum Ca level was 5.4 mg/dl (normal range: 8,6-10,2 mg/dl), corrected Ca (according to serum albumin level) was 5,8 mg/dl, ionised Ca was 2.7 mg/dl. Renal and liver function tests were normal, creatinine clearance calculated by Cocroft-Gault formula was 80 ml/min whereas in blood gas test, there was mild metabolic alkalosis. Complete blood count was abnormal and compatible with pancytopenia. All laboratory parameters were shown on Table 1. We have given intravenous calcium gluconate infusion together with magnesium until the symptoms were relieved and after then we started perioral supplementation. We have monitored Ca and Mg levels on daily basis and they have increased gradually and returned to normal in three consecutive days. Her QT intervals also returned to normal on the electrocardiogram. More laboratory tests were performed in order to reveal the etiology of hypocalcemia. Her serum PTH level was 125 pg/ml, above the normal range (15-60 pg/ml).

TABLE 1: Initial labaratory test results of the patient.

Lab Tests	Result	Normal Range
Calcium	5,4 mg/dl	8,6-10,2
Phosphate	5,3 mg/dl	2,5-4,5
Magnesium	0,6mg/dl	1,6-2,6
Sodium	133 mmol/l	135-145
Potassium	3,4mmol/l	3,5-5,1
Creatine	0,6mg/dl	0,5-1,2
Albumin	3,4g/dl	3,5-5,2
ALT	18 U/l	0-33
CK	118 U/l	26-192
PTH	125 pg/ml	15-60
Vitamin D	12 µg/l	10-80
Hemoglobin	8 gr/dl	12-16
WBC	8,9 K/uL	4000-10000
Platelet	80000 K/uL	150-400000

Serum 25 (OH) Vit D was 12 µg/L that was low (<30 µg/L). Since the PTH was high we have eliminated hypoparathyroidism as a cause of hypocalcemia. Vit D deficiency was not compatible with hyperphosphatemia. We have decided that cisplatin was responsible from the whole clinical picture.

DISCUSSION

Acute severe hypocalcemia is a highly dangerous ionic disturbance, because it can enhance neuronal excitability and causes tetany, seizures, laryngospazm and arrhythmia. In order to make differential diagnosis, we need to know serum PTH level. If the serum PTH level is low in case of hypocalcemia, we should consider destructed parathyroid glands (surgical, autoimmune, infiltrative diseases, infection, etc), abnormal parathyroid development and altered regulation of PTH due to genetic defects.[2] However when serum PTH level is high or normal, possible causative disorders can be PTH resistance (pseudohypoparathyroidism), vitamin D deficiency or resistance, extravascular deposition, tumor lysis, osteoblastic metastasis, acute pancreatitis, severe illness or sepsis, malabsorbtion, hypomagnesemia and drugs. Medical agents such as citrate, foscarnet, fluoride, biphosphanates, loop diuretics, anticonvulsants, gluco-

corticoids and estrogen are all reported to cause hypocalcemia.[3-7]

Cisplatin is a commonly used anti neoplastic agent. Some of the well documented adverse reactions of this drug include nausea, vomiting, renal toxicity, ototoxicity, peripheral neuropathy, hypersensitivity reactions and electrolyte disturbances. In a classic case, serum-adjusted calcium levels are expected to show only minimal reduction and it is caused by excessive urinary loss due to proximal tubular damage and decreased renal uptake during high-dose cisplatin treatment.[8]

Cisplatin also induces hypomagnesemia through its renal toxicity possibly by a direct injury to mechanisms of magnesium reabsorption in the ascending limb of the loop of Henle and the distal tubule.[9-12] Hypomagnesemia contributes to hypocalcemia by reducing end organ responsiveness to PTH, decreasing release of Ca from bone or causing relative hypoparathyroidism.[9] Correction of serum magnesium level usually should improves the hypocalcemia. In the previous reports of cisplatin associated hypomagnesemia and hypocalcemia, measurement of serum PTH levels revealed mostly low values. However Allgrove et al have reported that amino terminals of PTH were elevated in case of mild or moderate hypomagnesemia.[11] In our case serum PTH was high supporting the aforementioned report and we suggested that accompanying vitamin D deficiency further increased PTH level and caused secondary hyperparathyroidism.

Our case is important because cisplatin caused severe symptomatic hypocalcemia requiring urgent intravenous replacement. Hypocalcaemia may be associated with tetany, depression, carpopedal spasm, neuromuscular excitability, cardiac arrythmias with prolonged Q-T interval and sudden death which makes it an important but usually overlooked emergency of oncology. In the light of this data, we can say that patients receiving cisplatin or other drugs which are known to cause hypocalcemia, should be monitored closely, given appropriate vitamin D supplementation and informed about the possible side effect of the drug and advised to admit emergency room in case of symptoms or signs.

REFERENCES

1. Riccardi D, Brown EM. Physiology and pathophysiology of the calcium-sensing receptor in the kidney. Am J Physiol Renal Physiol 2010;298(3):F485-99.
2. Öztürk F, Cantürk Z. [Autoimmune hypoparathyroidism]. Turkiye Klinikleri J Endocrin-Special Topics 2010;3(2):14-7.
3. Smallridge RC, Wray HL, Schaaf M. Hypocalcemia with osteoblastic metastases in patient with prostate carcinoma. A cause of secondary hyperparathyroidism. Am J Med 1981;71(1):184-8.
4. Dettelbach MA, Deftos LJ, Stewart AF. Intraperitoneal free fatty acids induce severe hypocalcemia in rats: a model for the hypocalcemia of pancreatitis. J Bone Miner Res 1990;5(12):1249-55.
5. Zivin JR, Gooley T, Zager RA, Ryan MJ. Hypocalcemia: a pervasive metabolic abnormality in the critically ill. Am J Kidney Dis 2001;37(4):689-98.
6. Rutledge R, Sheldon GF, Collins ML. Massive transfusion. Crit Care Clin 1986;2(4):791-805.
7. Conte PF, Latreille J, Mauriac L, Calabresi F, Santos R, Campos D, et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. J Clin Oncol 1996;14(9):2552-9.
8. Hoffmann K, Marten A, Lindel K, Fritz S, Jager D, Buchler MW, et al. Major combined electrolyte deficiency during therapy with low-dose cisplatin, 5-fluorouracil and interferon alpha: report on several cases and review of the literature [ISRCTN62866759]. BMC Cancer 2006;6:128. doi:10.1186/1471-2407-6-128
9. Estep H, Shaw WA, Watlington C, Hobe R, Holland W, Tucker SG. Hypocalcemia due to hypomagnesemia and reversible parathyroid hormone unresponsiveness. J Clin Endocrinol Metab 1969;29(6):842-8.
10. Rude RK, Oldham SB, Singer FR. Functional hypoparathyroidism and parathyroid hormone end-organ resistance in human magnesium deficiency. Clin Endocrinol (Oxf) 1976;5(3): 209-24.
11. Allgrove J, Adami S, Fraher L, Reuben A, O'Riordan JL. Hypomagnesaemia: studies of parathyroid hormone secretion and function. Clin Endocrinol (Oxf) 1984;21(4):435-49.
12. Lajer H, Daugaard G. Cisplatin and hypomagnesemia. Cancer Treat Rev 1999;25(1): 47-58.