Review

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Hypocalcemia in cancer treatment

Kanser hastalarında hipokalsemi

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Abstract

The primary objective of this review is to provide a concise summary and critical appraisal of the current literature on the differential diagnosis and management of hypocalcemia. Calcium plays a crucial role in muscle function and neurotransmitter release. However, hypocalcemia, defined as serum calcium levels below 8 mg/dL (2.12 mmol/L), can affect various organs and systems and lead to a range of clinical symptoms. This condition can range from being completely asymptomatic to life-threatening situations.

Disorders responsible for hypocalcemia can be divided into two groups: those influenced by parathyroid hormone (PTH) and those not affected. In non-surgical and PTH-mediated forms, more comprehensive investigation is necessary to identify the underlying cause and determine appropriate treatment.

In cases of acute hypocalcemia, intravenous calcium infusion is required to rapidly increase calcium levels and correct symptoms. On the other hand, treatment of chronic hypocalcemia generally involves oral calcium and/or vitamin D supplementation.

In conclusion, this review specifically emphasizes iatrogenic (treatment-related) hypocalcemia while assessing the causes, dimensions, and management of hypocalcemia in cancer patients. Physicians' familiarity with these conditions is crucial in treatment management.

Keywords: Hypocalcemia, hypomagnesemia, cancer treatment, chemotherapy, cisplatin.

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Öz

Bu derlemenin temel amacı, hipokalseminin ayırıcı tanısı ve yönetimi ile ilgili mevcut literatürün kısa bir özetini ve eleştirel bir değerlendirmesini sunmaktır. Kalsiyum, kas fonksiyonu ve nörotransmitter salınımında önemli bir rol oynar. Bununla birlikte, 8 mg/dL'nin (2,12 mmol/L) altındaki serum kalsiyum seviyeleri olarak tanımlanan hipokalsemi, çeşitli organ ve sistemleri etkileyebilir ve çeşitli klinik belirtilere yol açabilir. Bu tablo tamamen asemptomatik olabileceği gibi hayatı tehdit eden durumlara da yol açabilir.

Hipokalsemiden sorumlu bozukluklar iki gruba ayrılabilir: paratiroid hormonundan (PTH) etkilenenler ve etkilenmeyenler. Cerrahi nedenlerden kaynaklanmayan ve PTH aracılı olmayan formlarda, altta yatan nedeni tanımlamak ve uygun tedaviyi belirlemek için daha kapsamlı bir araştırma gereklidir.

Akut hipokalsemi vakalarında, intravenöz kalsiyum infüzyonu kalsiyum seviyelerini hızla artırmak ve semptomları düzeltmek gereklidir. Öte yandan, kronik hipokalsemi tedavisinde oral kalsiyum ve/veya D vitamini takviyesi genellikle yeterlidir.

Sonuç olarak, bu derleme kanser hastalarında hipokalseminin nedenlerini, boyutlarını ve yönetimini değerlendirirken tedavi ilişkili (iatrojenik) hipokalsemiye özellikle vurgu yapmaktadır. Hekimlerin bu durumları iyi tanıması tedavi yönetiminde önemlidir.

Anahtar kelimeler: Hipokalsemi, hipomagnezemi, kanser tedavisi, kemoterapi, sisplatin.

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Introduction

Calcium is an essential molecule for muscle contraction and neurotransmitter release [1]. Hypercalcemia in cancer patients is considered a poor prognostic marker but there’s no prognostic statement for hypocalcemia in this population [2].

Hypocalcemia is defined as a serum level of calcium under 8 mg/dl or 2.12 mmol/L. Measurement of ionized calcium is preferred as serum calcium levels are easily affected by serum protein levels [3].

While calcium metabolism proceeds in a balance between intestinal absorption and

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renal excretion in a process in which vitamin D and parathormone play an active role, finding the cause of hypocalcemia in our patients will relieve the patient from complaints and findings. Patients may be asymptomatic, or have nonspecific complaints such as fatigue, irritability, tetany, anxiety, or depression; and even bronchospasm and cardiac arrhythmias as a result of prolonged QT that may result in death [3]. Muscular irritability may be presented with cramps, numbness, and paresthesias. Clinical hypocalcemia can affect almost all organ systems and can have fatal consequences. We are therefore lucky if we have time to investigate the etiology of hypocalcemia. In acute hypocalcemia, the first thing to do is to alleviate or, if possible, even eliminate the symptoms with intravenous calcium replacement. In chronic hypocalcemia treatment, oral calcium and vitamin D replacement are often sufficient [4].

The most common clinical etiology for hypocalcemia is vitamin D insufficiency which may be prevalent as high as 50% [5]. Surgical causes follow, often as a result of loss of the parathyroid gland after thyroidectomy. Hypocalcemia can be seen in up to 38% of patients following thyroid surgery [6].

Surgical causes can be easily recognizable both from the patient's history and the observation of the incision scar during physical examination. However, hypocalcemia due to medical causes should be meticulously investigated. In this context, the patient's medication use should be questioned well. Bisphosphonates, cisplatin, antiepileptics, aminoglycosides, and proton pump inhibitors well-known agents to cause hypocalcemia in cancer patients [7].

We frequently see hypocalcemia in cancer patients after bone-sparing therapies [8]. For this reason, we administer calcium and vitamin D replacement after treatment with RANKL inhibitors or bisphosphonates and even without evident hypocalcemia [9]. Monitoring serum vitamin D levels in these patients taking vitamin D supplements is questioned [10]. However, calcium levels need to be monitored periodically. A high vitamin D level before treatment is considered protective against hypocalcemia [11]. Treatment-related hypocalcemia rates for denosumab and bisphosphonates are similar, although hypocalcemia is not expected with replaced patients [12]. Chronic kidney disease, malabsorption syndromes, or hypoparathyroidism may predispose to hypocalcemia in this group of patients [13]. During continued denosumab treatment, there is a risk of experiencing hypocalcemia for each administered dose [13]. However, once hypocalcemia occurs, denosumab should not be continued until the calcium level is normalized [14].

In immunotherapy, one of the new oncologic treatment approaches, TLS may occur after CAR-T cell-associated target cell damage [15]. Furthermore, PD1 inhibitors may rarely cause acute kidney injury and hypocalcemia, but the mechanism is unclear [16, 17].

Conditions such as massive hydration, intensive diuretic use, and massive blood transfusions may be among the iatrogenic causes. In a study that reviewed TLSs, the rate of solid cancers was found to be 38%, which is not insignificant.

Cases of asymptomatic hypocalcemia have also been reported after hyperthermic intraperitoneal chemotherapy (HIPEC), which is a modern treatment modality used in peritoneal involvement of gastrointestinal and gynecological malignancies [18, 19].

Hypocalcemia may appear as a component of tumor lysis syndrome (TLS) which is characterized by at least two of the following abnormalities; hyperuricemia, hyperpotassemia, hyperphosphatemia, and hypocalcemia [20]. Hyperphosphatemia can cause secondary hypocalcemia and calcium can precipitate as phosphate crystals in organs such as the kidney [21]. TLS may occur following a biopsy, radiotherapy, or chemotherapy, or it may develop spontaneously [22]. TLS is more common in hematologic malignancies, but patients with solid malignancies may be prone to TLS in such situations as extrinsic compression of the genitourinary tract leading to renal dysfunction, high tumor burden, large tumors, high sensitivity to chemotherapy, and patient-related factors such as dehydration, hypotension, nephrotoxic agent intake, and obstructive uropathy [23, 24].

Another important point that concerns us as medical oncologists is hypocalcemia, which is seen after chemotherapy and is confusing in etiology because it is a rare condition. Here, magnesium level should be questioned as an underlying factor. Hypomagnesemia leads to parathormone resistance and causes hypocalcemia. This occurs in the setting of severe hypomagnesemia, in which the serum magnesium level drops to 0.8 mg/dL or under. Calcium level does not normalize without magnesium replacement. The most common chemotherapy drug causing this is cisplatin [25]. In a study by Komurcuoglu et al. [26] among 35 patients receiving cisplatin-based chemotherapy, hypomagnesemia was observed in half of the patients, while hypocalcemia was described in only one patient. Hypomagnesemia is observed in approximately 10% of patients who received cisplatin and may persist even months to years after treatment [27].

Hypomagnesemia can also be seen with EGFR inhibitors cetuximab and panitumumab [28].

Tyrosine kinase inhibitors (TKIs), which are better tolerated than chemotherapy, have many effects on almost all endocrine glands as well as on bone metabolism. They decrease osteoclastogenesis and bone turnover, which eventually results in hyperparathyroidism. Hypocalcemia has been reported as a side effect of treatment with lenvatinib and vandetanib [29, 30].

Recognizing hypocalcemia, which we rarely see in the management of cancer patients, should be promptly treated especially when any symptoms such as muscle cramps, numbness or tingling in the fingers or around the mouth, or seizures are present. It requires a multidisciplinary approach and a complex process, which can be life-saving beyond eliminating complaints that reduce the quality of life such as weakness and fatigue.

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References

1. Pepe J, Colangelo L, Biamonte F, et al. Diagnosis and management of hypocalcemia. Endocrine 2020;69:485-495. https://doi.org/10.1007/s12020-020-02324-2
2. Guise TA, Wysolmerski JJ. Cancer-associated hypercalcemia. NEJM 2022;386:1443-1451. https://doi.org/10.1056/NEJMcp2113128
3. Kelly A, Levine MA. Hypocalcemia in the critically ill patient. J Intensive Care Med 2013;28:166-177. https://doi.org/10.1177/0885066611411543
4. Bove Fenderson E, Mannstadt M. Hypocalcemic disorders. Best Prac Res Clin Endocrinol Metab 2018;32:639-656. https://doi.org/10.1016/j.beem.2018.05.006
5. Cooper MS, Gittoes NJ. Diagnosis and management of hypocalcaemia. BMJ 2008;336:1298-1302. https://doi.org/10.1136/bmj.39582.589433.BE
6. Lechner M, Moghul G, Chandrasekharan D, et al. Preoperative and postoperative optimisation of patients undergoing thyroid surgery: a multicentre quality improvement project at Barts Health NHS Trust. BMJ Open Qual 2023;12:e001190. https://doi.org/10.1136/bmjoq-2020-001190
7. Liamis G, Milionis HJ, Elisaf M. A review of drug-induced hypocalcemia. J Bone Miner Metab 2009;27:635-642. https://doi.org/10.1007/s00774-009-0119-x
8. Alıcı S, Çekici S. Malign hastalıklarda bisfosfonatların rolü. Van Med J 2002;9:66-72.
9. Pittman K, Antill YC, Goldrick A, Goh J, de Boer RH. Denosumab: prevention and management of hypocalcemia, osteonecrosis of the jaw and atypical fractures. Asia Pac J Clin Oncol 2017;13:266-276. https://doi.org/10.1111/ajco.12517
10. Cummings SR, Rosen C. VITAL findings-a decisive verdict on vitamin D supplementation. NEJM 2022;387:368-370. https://doi.org/10.1056/NEJMe2205993
11. Crotti C, Watts NB, De Santis M, et al. Acute phase reactions after zoledronic acid infusion: protective role of 25-hydroxyvitamin D and previous oral bisphosphonate therapy. Endocr Pract 2018;24:405-410. https://doi.org/10.4158/EP161638.OR
12. Huang SY, Yoon, SS, Shimizu K, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, randomized controlled phase 3 study-Asian subgroup analysis. Adv Ther 2020;37:3404-3416. https://doi.org/10.1007/s12325-020-01395-x
13. Tsvetov G, Amitai O, Shochat T, Shimon I, Akirov A, Diker Cohen T. Denosumab-induced hypocalcemia in patients with osteoporosis: can you know who will get low? Osteoporos Int 2020;31:655-665. https://doi.org/10.1007/s00198-019-05261-7
14. Soytaş RB, Avci S, Yavuzer H, Ozkok S, Doventas A, Erdincler DS. 65 yaş üstü osteoporoz hastalarında denosumab ve zoledronik asitin yan etkilerinin karşılaştırılması. GTD 2021;31:135-139. https://doi.org/10.15321/GenelTipDer.2021.300

15. Joseph A, Lafarge A, Azoulay E, Zafrani L. Acute kidney injury in cancer immunotherapy recipients. Cells 2002;11:3991. https://doi.org/10.3390/cells1124399
16. Manohar S, Kompotiatis P, Thongprayoon C, Cheungpasitporn W, Herrman J, Herrmann SM. Programmed cell death protein 1 inhibitor treatment is associated with acute kidney injury and hypocalcemia: meta-analysis. Nephrol Dial Transplant 2019;34:108-117. https://doi.org/10.1093/ndt/gfy105
17. Uppal NN, Workeneh BT, Rondon Berrios H, Jhaveri KD. Electrolyte and acid-base disorders associated with cancer immunotherapy. Clinic Am Soc Nephrol 2022;17:922-933. https://doi.org/10.2215/CJN.14671121
18. Tharmalingam S, Reddy S, Sharda P, Koch CA. Severe hypocalcemia and transient hypoparathyroidism after hyperthermic intraperitoneal chemotherapy. Horm Metab Res 2020;52:689-690. https://doi.org/10.1055/a-1220-6971
19. Hu J, Wang Z, Wang X, Xie S. Side-effects of hyperthermic intraperitoneal chemotherapy in patients with gastrointestinal cancers. PeerJ 2023;11:e15277. https://doi.org/10.7717/peerj.15277
20. Cohen PR, Prieto VG, Kurzrock R. Tumor lysis syndrome: introduction of a cutaneous variant and a new classification system. Cureus 2021;13:e13816. https://doi.org/10.7759/cureus.13816
21. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. NEJM 2011;364:1844-1854. https://doi.org/10.1016/B978-0-12-415948-8.00004-0
22. Hüzmeli, C. Assessment of tumor lysis syndrome cases. CMJ 2019;41:28-33. http://dx.doi.org/10.7197/223.vi.460369
23. Calvo Villas JM. Tumour lysis syndrome. Med Clin (Barc) 2019;152:397-404. https://doi.org/10.1016/j.medcli.2018.10.029
24. Vodopivec DM, Rubio JE, Fornoni A, Lenz O. An unusual presentation of tumor lysis syndrome in a patient with advanced gastric adenocarcinoma: case report and literature review. Case Rep Med 2012;2012:468452. https://doi.org/10.1155/2012/468452
25. Eren E, Ata A, Arıcan A. Kanser tedavisinde kullanılan ilaçlar ve nefrotoksisite. DEÜ Tıp Fakültesi Dergisi 2012;26:229-235.
26. Kömürcüoğlu B, Büyükşirin M, İşgüder H, Kalenci D, Özden E. Cisplatin uygulanan akciğer Ca'lı hastalarda serum magnezyum ve kalsiyum düzeylerinin monitorizasyonu gerekli midir? İzmir Göğüs Hastanesi Dergisi 2004;18:101-106.
27. Nicholas J, Vogelzang NJ, Torkelson JL, Kennedy BJ. Hypomagnesemia, renal dysfunction, and Raynould's Phenomenon in patients with cisplatin, vinblastine, and bleomycin. Cancer 1985;56:2765-2770. https://doi.org/10.1002/1097-0142(19851215)56:12<2765::aid-cncr2820561208>3.0.co;2-2
28. Izzedine H, Perazella MA. Adverse kidney effects of epidermal growth factor receptor inhibitors. Nephrol Dial Transplant 2017;32:1089-1097. https://doi.org/10.1093/ndt/gfw467
29. De Leo S, Trevisan M, Colombo C, Moneta C, Giancola N, Fugazzola L. Hypocalcemia during lenvatinib treatment for advanced thyroid cancer: clinical features and management in a real-life setting. Thyroid 2023;33:74-81. https://doi.org/10.1089/thy.2022.0439
30. Hu MI, Elisei R, Dedecjus M, et al. Safety and efficacy of two starting doses of vandetanib in advanced medullary thyroid cancer. Endocr Relat Cancer 2019;26:241-250. https://doi.org/10.1530/ERC-18-0258

Authors' contributions to the article

S.A. have constructed the main idea of the paper. She developed the theory, pooled the information and arranged/edited the text. Written by S.A., and reviewed, corrected and approved by O.U.U. In addition, all authors discussed the entire paper and approved the final version.