Open Access https://www.jparathyroid.com

Journal of Parathyroid Disease

Journal of Parathyroid Disease 2026,14, e13323

DOI:10.34172/jpd.13323

Review

Calcitriol, PTHrP and beyond; pathophysiological pathways of hypercalcemia as an immune-related adverse event of checkpoint inhibitors

Maryam Aghabozorgi[1], Shahin Asgari[2], Seyyed Hamidreza Motafakeran[1], Ahmadreza Maghsoudi[1*]

Abstract

Hypercalcemia is a rare yet potentially life-threatening immune-related adverse event (irAE) of immune checkpoint inhibitors (ICIs). While disease progression is the primary differential, distinct immune-mediated pathways necessitate specific clinical recognition. This review explores mechanisms involving calcitriol, parathyroid hormone-related protein (PTHrP), and inflammatory cascades. Classically, humoral hypercalcemia of malignancy involves tumor-secreted PTHrP. However, ICI-induced cases often exhibit suppressed parathyroid hormone with variable PTHrP, suggesting immune dysregulation rather than pure tumor burden. A significant pathway involves excessive calcitriol production, mirroring granulomatous diseases. Here, ICI-activated macrophages express 1-alpha-hydroxylase, converting vitamin D to its active form, thereby increasing intestinal calcium absorption and bone resorption. Additionally, PTHrP elevation may arise from immune-mediated tissue inflammation or sarcoid-like reactions triggered by T-cell activation rather than direct tumor secretion. Beyond these canonical pathways, cytokine release syndromes involving interleukin-6 and tumor necrosis factor-alpha can directly stimulate osteoclastogenesis by the RANKL pathway, accelerating bone breakdown. Direct immune infiltration into parathyroid glands or bone marrow might also disrupt calcium homeostasis. Distinguishing these mechanisms is critical, as management diverges from malignancy-associated hypercalcemia. Though, hydration and bisphosphonates are standard; however, corticosteroids are particularly effective for calcitriol-mediated or inflammatory mechanisms. Recognizing specific drivers prevents unnecessary treatments and ensures timely intervention. As ICI administration expands across oncology, clinicians must maintain high suspicion for these rare endocrine irAEs. Therefore, larger studies should define biomarkers to predict susceptibility and clarify molecular interactions. Eventually, elucidating these complex pathways ensures patient safety, preserving the therapeutic benefits of immunotherapy while effectively diminishing severe metabolic complications through optimal and targeted management strategies.

Keywords: Immune checkpoint inhibitors, Parathyroid hormone-related protein, Hypercalcemia, Immune-related adverse events, Vitamin D, Parathyroid hormone, Granulomatous disease, Primary hyperparathyroidism

Please cite this paper as: Aghabozorgi M, Asgari Sh, Motafakeran SH, Maghsoudi A. Calcitriol, PTHrP and beyond; pathophysiological pathways of hypercalcemia as an immune-related adverse event of checkpoint inhibitors. J Parathyr Dis. 2026;14:e13323. doi:10.34172/jpd.13323.

Introduction

The background of oncological treatment has undergone a paradigm shift in the last decade, primarily driven by the advent of immune checkpoint inhibitors (ICIs). These agents, which include monoclonal antibodies targeting cytotoxic T-lymphocyte-associated protein 4, programmed cell death protein 1, and its ligand, have revolutionized the management of various malignancies, including melanoma, non-small cell lung cancer, and renal cell carcinoma (1). By blocking the inhibitory pathways that tumors exploit to evade immune surveillance, these drugs unleash the host's T-cells to recognize and destroy cancer cells. However, this potentiation of the immune system is a double-edged sword, frequently resulting in immune-related adverse events (irAEs) (2). Though dermatological, gastrointestinal, and endocrine toxicities such as thyroiditis and hypophysitis are well-documented and relatively common, metabolic disturbances remain a less frequent but clinically significant category of toxicity. Among these, hypercalcemia presents a unique diagnostic and therapeutic challenge, since it requires the clinician to distinguish between disease progression, paraneoplastic syndromes, and a direct immune-mediated adverse effect of the therapy itself (3). Hypercalcemia in the context of cancer is traditionally associated with the malignancy rather than the treatment. Humoral hypercalcemia of malignancy, driven by the secretion of parathyroid hormone-related protein (PTHrP) by tumor cells, or osteolytic hypercalcemia resulting from bone metastases, are common occurrences in advanced

Received: 7 Apr. 2026, **Revised:** 23 May 2026, **Accepted:** 2 Jun. 2026, **ePublished:** 10 Jun. 2026

[1]Internal Medicine Department, Isfahan University of Medical Sciences, Isfahan, Iran. [2]Internal Medicine Department, Shahrekord University of Medical Sciences, Shahrekord, Iran.

***Corresponding author:** Ahmadreza Maghsoudi, Email: ahmaghsoudi@med.mui.ac.ir, dr.maghsoudi.md.2018@gmail.com

Implication for health policy/practice/research/medical education

Checkpoint inhibitors revolutionize oncology; however, they provoke immune-related adverse events (irAEs). Hypercalcemia represents a rare, serious irAE frequently confused with malignant disease progression. Unlike humoral hypercalcemia of malignancy driven primarily by tumor-derived parathyroid hormone-related protein (PTHrP), the immune checkpoint inhibitor-associated hypercalcemia arises from immune dysregulation. Activated T-cells and macrophages may form sarcoid-like granulomas, upregulating 1-alpha-hydroxylase, thereby converting vitamin D to active calcitriol, enhancing intestinal calcium absorption significantly. Conversely, inflammatory cytokines can stimulate non-malignant tissues to secrete PTHrP or directly activate osteoclasts by RANKL signaling. Differentiating these immune-mediated mechanisms from bone metastasis is crucial for clinical management. Treatment typically requires corticosteroids to suppress immune activation, rather than solely relying on bisphosphonates or denosumab. Recognizing distinct etiologies prevents premature checkpoint inhibitors discontinuation and ensures appropriate therapy. Future investigations must define prevalence, risk factors, and biomarkers to optimize management strategies for patients experiencing checkpoint inhibitors-induced hypercalcemia amidst complex oncological care settings.

cancer (4). Consequently, when a patient receiving ICIs presents with elevated serum calcium, the immediate clinical assumption is often disease progression or a paraneoplastic phenomenon (5). However, recent studies and pharmacovigilance data have identified a distinct entity of ICI-associated hypercalcemia. This condition is considered a rare irAE, yet its incidence is likely underreported due to the complexity of differentiating it from malignancy-associated hypercalcemia (6). Identification of this condition is critical because the management strategies differ fundamentally. Treating malignancy-associated hypercalcemia focuses on inhibiting bone resorption and treating the cancer, whereas immune-mediated hypercalcemia often requires immunosuppression to halt the aberrant immune activation driving the calcium elevation (4). This review sought to discuss on the pathophysiological pathways of hypercalcemia as an irAE of checkpoint inhibitors.

Search strategy

For this review, we performed a literature search across multiple databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase. The search strategy employed a variety of relevant keywords, such as "immune checkpoint inhibitors," "parathyroid hormone-related protein," "hypercalcemia," "immune-related adverse events," "vitamin D," "parathyroid hormone," "granulomatous disease," and "primary hyperparathyroidism."

Mechanisms of ICI-associated hypercalcemia

The pathophysiology of ICI-associated hypercalcemia is multifactorial and distinct from the mechanisms typically seen in humoral hypercalcemia of malignancy. The prevailing hypothesis centers on the development of a sarcoid-like reaction or granulomatous disease induced by the disinhibition of the immune system (7). When checkpoint pathways are blocked, T-cell activation is strengthened, which can lead to the recruitment and activation of macrophages in various tissues, including the lymph nodes, lungs, and liver. In a sarcoid-like reaction, these activated macrophages form non-caseating granulomas (8). Remarkably, macrophages within these granulomas express the enzyme 1-alpha-hydroxylase, which converts 25-hydroxyvitamin D into the biologically active 1,25-dihydroxyvitamin D (9). Unlike the renal production of active vitamin D, which is tightly regulated by parathyroid hormone and serum calcium levels, the extrarenal production within granulomas is unregulated. This condition leads to excessive intestinal absorption of calcium and increased bone resorption, resulting in hypercalcemia. This mechanism mirrors the pathophysiology seen in sarcoidosis, suggesting that the ICIs are essentially inducing a systemic inflammatory state that mimics granulomatous disease (10,11). In addition to the granulomatous hypothesis, cytokine release plays a significant role in the development of this adverse event. The activation of T-cells and the subsequent immune cascade result in the release of various pro-inflammatory cytokines, such as interleukin-6, tumor necrosis factor-alpha, and interferon-gamma. These cytokines can directly stimulate osteoclast activity, leading to increased bone resorption and the release of calcium into the bloodstream (12). Furthermore, there is evidence to suggest that ICIs may unmask underlying primary hyperparathyroidism or exacerbate subclinical conditions (13). In some reported cases, patients have been found to have concurrent primary hyperparathyroidism that was previously compensated but became decompensated following the immune stimulation provided by the therapy. This complexity necessitates a thorough endocrine workup, as the presence of an elevated parathyroid hormone level would point toward primary hyperparathyroidism rather than a direct immune-mediated effect or malignancy, both of which typically suppress parathyroid hormone secretion (14). The interplay between these mechanisms highlights the systemic nature of irAEs and underscores the need for a high index of suspicion when metabolic abnormalities arise during immunotherapy. Diagnosing ICI-associated hypercalcemia requires a meticulous exclusion of other causes, primarily malignancy progression (15). The diagnostic workup begins with the confirmation of hypercalcemia through repeated measurements of serum calcium, preferably corrected for albumin or measured as ionized calcium to ensure accuracy (16). Once hypercalcemia is confirmed, the measurement of intact parathyroid hormone is the decisive first step in the differential diagnosis. In the vast majority of cancer-associated hypercalcemia cases, whether due to bone metastasis or PTHrP secretion, the parathyroid hormone level will be suppressed due to the negative feedback loop

exerted by high calcium levels (17). Similarly, in immune-mediated hypercalcemia driven by granulomatous vitamin D production, parathyroid hormone is typically suppressed. Therefore, a suppressed parathyroid hormone does not distinguish between malignancy and drug toxicity. The differentiation relies heavily on the measurement of PTHrP and vitamin D metabolites (18). If PTHrP is elevated, humoral hypercalcemia of malignancy is the likely culprit (19,20). Conversely, if PTHrP is undetectable and 1,25-dihydroxyvitamin D levels are elevated, this strongly supports a diagnosis of granulomatous disease induced by the ICI (21,22).

Diagnostic studies

Imaging studies play a complementary role in the diagnostic algorithm. Computed tomography scans of the chest, abdomen, and pelvis are standard for staging cancer, but in the context of suspected immune-mediated hypercalcemia, radiologists should specifically look for new or enlarging lymphadenopathy that might suggest a sarcoid-like reaction rather than metastatic disease (23). Sarcoid-like lymphadenopathy often presents with bilateral hilar lymphadenopathy or mediastinal involvement that can mimic metastatic spread but lacks the aggressive features of tumor progression (24). In some cases, a biopsy of the lymph nodes may be necessary to confirm the presence of non-caseating granulomas and rule out malignant infiltration. This distinction is vital because misdiagnosing a sarcoid-like reaction as cancer progression could lead to the unnecessary discontinuation of an effective cancer therapy (25). Furthermore, bone scans or positron emission tomography scans can help identify osteolytic lesions. The absence of new bone metastasis in a patient with rising calcium levels strengthens the argument for an immune-mediated etiology (26). The diagnostic process is therefore a synthesis of biochemical markers, imaging findings, and clinical timing relative to the administration of the drug. The timing of the onset of hypercalcemia provides another clue to its etiology. Immune-related adverse events can occur at any time during treatment, but they often present within the first few months of initiating therapy (27). However, cases of ICI-associated hypercalcemia have been reported both early in the treatment course and after prolonged exposure, sometimes even after the discontinuation of the drug. This variability contrasts with malignancy-associated hypercalcemia, which typically correlates with increasing tumor burden over time (7). Clinicians should also assess the patient for other signs of immune-related toxicity, such as rash, colitis, or pneumonitis, as hypercalcemia rarely occurs in isolation when it is immune-mediated. The presence of concurrent irAEs increases the likelihood that the hypercalcemia is also immune-driven (28). Additionally, the severity of the hypercalcemia can vary from asymptomatic biochemical abnormalities to life-threatening levels requiring emergency intervention (29). Symptoms of hypercalcemia, often remembered by the mnemonic bones, stones, groans, and moans, include fatigue, nausea, vomiting, constipation, polyuria, and confusion (30,31). In severe cases, cardiac arrhythmias can occur. Recognizing these symptoms promptly is essential to prevent morbidity and mortality, particularly in a population that is already compromised by advanced malignancy (32).

Management of ICI-associated hypercalcemia

Management of ICI-associated hypercalcemia follows a two-separate approach, consisted of acute correction of the calcium levels and specific treatment of the underlying immune dysregulation (33). The immediate priority is to lower the serum calcium to a safe range to prevent end-organ damage. This approach begins with aggressive intravenous hydration using isotonic saline to restore intravascular volume and promote renal calcium excretion (34). Loop diuretics may be added once volume status is restored to further enhance calciuresis, although they are no longer considered first-line monotherapy (35). For moderate to severe hypercalcemia, antiresorptive agents such as intravenous bisphosphonates or the RANK-ligand inhibitor denosumab are indicated. These agents inhibit osteoclast-mediated bone resorption and are effective in lowering calcium levels regardless of the underlying cause (36). However, these measures address the symptom, and do not treat the root cause in immune-mediated cases (36). Therefore, the administration of corticosteroids is the cornerstone of specific therapy for ICI-associated hypercalcemia (7). Corticosteroids, such as prednisone or methylprednisolone, act by reducing the granulomatous inflammation and inhibiting the 1-alpha-hydroxylase activity within the macrophages, thereby reducing the production of active vitamin D (37,38). The decision to administer corticosteroids in a cancer patient receiving immunotherapy is often with concern regarding the potential attenuation of the antitumor immune response. There is a longstanding debate in oncology about whether immunosuppression negates the efficacy of ICIs (39). However, current guidelines from major oncological societies suggest that for grade 3 or 4 irAEs, high-dose corticosteroids are necessary and should not be withheld due to fears of reducing cancer treatment efficacy (40). In the specific context of hypercalcemia, the rapid resolution of the metabolic disturbance is critical for patient survival and quality of life. Most case reports indicated that hypercalcemia responds rapidly to corticosteroid therapy, often within days, allowing for the normalization of calcium levels. Once the calcium is controlled, the steroids can be tapered slowly over several weeks to prevent rebound hypercalcemia (41). If the hypercalcemia is refractory to corticosteroids, additional immunosuppressive agents such as infliximab or mycophenolate mofetil may be considered, although data on their use specifically for this indication is limited (42). The goal is to administer

the minimum effective dose of immunosuppression required to manage the toxicity while preserving as much antitumor immunity as possible (43). A critical component of management is the decision regarding the continuation of the ICI. This decision is guided by the severity of the hypercalcemia and the response to treatment. For mild, asymptomatic hypercalcemia, it may be permissible to continue the immunotherapy with close monitoring and supportive care (28). However, for moderate to severe cases, the general recommendation is to withhold the ICI until the toxicity resolves to grade 1 or baseline. In cases of life-threatening hypercalcemia or those that are recurrent despite optimal management, permanent discontinuation of the drug may be necessary. This decision should be made in a multidisciplinary setting involving medical oncologists, endocrinologists, and sometimes intensivists (28). The potential benefit of continuing the cancer therapy must be weighed against the risk of recurrent or worsening toxicity. In many instances, once the hypercalcemia is managed with steroids and the drug is temporarily held, patients can successfully resume immunotherapy without recurrence of the metabolic disturbance (28,44). However, rechallenge should be approached with caution, and patients should be educated on the symptoms of hypercalcemia to ensure early detection if it recurs. Accordingly, long-term monitoring is essential for patients who have experienced ICI-associated hypercalcemia (7). Even after the acute episode has resolved and the drug has been resumed or discontinued, there is a risk of late-onset endocrine dysfunction. Regular monitoring of serum calcium, renal function, and vitamin D metabolites should be incorporated into the follow-up schedule (45). Patients should also be advised to maintain adequate hydration and to avoid excessive intake of calcium or vitamin D supplements, which could exacerbate the tendency toward hypercalcemia (45). Bone health is another consideration, particularly if the patient has received bisphosphonates or denosumab, as these agents carry risks such as osteonecrosis of the jaw and atypical femoral fractures (46). Furthermore, the use of corticosteroids introduces its own set of long-term risks, including hyperglycemia, osteoporosis, and increased susceptibility to infection (47). Therefore, the management plan must be holistic, addressing not only the calcium levels but also the sequelae of the treatment required to correct them. Prophylactic measures, such as calcium and vitamin D supplementation to protect bone density during steroid use, should be balanced carefully against the risk of worsening hypercalcemia, often requiring a tailored approach where calcium supplementation is withheld while active hypercalcemia is present but reintroduced once levels normalize (36).

Conclusion

Checkpoint inhibitors revolutionize oncology but provoke irAEs, including hypercalcemia. While malignancy-associated hypercalcemia typically arises from bone metastasis or PTHrP secretion, ICI-induced hypercalcemia involves distinct immunological pathways. A primary mechanism addresses granulomatous diseases, where activated macrophages excessively convert vitamin D to calcitriol, enhancing intestinal calcium absorption. Alternatively, immune activation may stimulate tumor or stromal cells to secrete PTHrP, mimicking humoral hypercalcemia of malignancy but driven by inflammatory cytokines. Beyond calcitriol and PTHrP, other pathways like direct osteoclast activation. Pro-inflammatory cytokines upregulate RANKL expression, accelerating bone resorption independently of parathyroid hormone. Distinguishing ICI-induced hypercalcemia from tumor progression is necessary, since management differs significantly. Though hydration and bisphosphonates address calcium levels, corticosteroids are often required to suppress the underlying immune dysregulation, particularly in calcitriol-mediated cases.

Authors' contribution

Conceptualization: Ahmadreza Maghsoudi.
Data curation: Seyyed Hamidreza Motafakeran.
Formal analysis: Ahmadreza Maghsoudi.
Investigation: Seyyed Hamidreza Motafakeran.
Methodology: Maryam Aghabozorgi.
Project administration: Ahmadreza Maghsoudi.
Resources: Shahin Asgari.
Supervision: Shahin Asgari.
Validation: Shahin Asgari.
Visualization: Seyyed Hamidreza Motafakeran.
Writing–original draft: Maryam Aghabozorgi.
Writing–review and editing: Ahmadreza Maghsoudi.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

References

1. Chen H, Yang H, Guo L, Sun Q. The Role of Immune Checkpoint Inhibitors in Cancer Therapy: Mechanism and Therapeutic Advances. MedComm (2020). 2025;6:e70412. doi: 10.1002/mco2.70412.
2. Almawash S. Revolutionary Cancer Therapy for Personalization and Improved Efficacy: Strategies to Overcome Resistance to Immune Checkpoint Inhibitor Therapy. Cancers (Basel). 2025;17:880. doi: 10.3390/cancers17050880.
3. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine Toxicity of Cancer Immunotherapy Targeting Immune Checkpoints. Endocr Rev. 2019;40:17-65. doi:

10.1210/er.2018-00006.
4. Bartkiewicz P, Kunachowicz D, Filipski M, Stebel A, Ligoda J, Rembiałkowska N. Hypercalcemia in cancer: causes, effects, and treatment strategies. Cells. 2024;13:1051. doi: 10.3390/cells13121051.
5. Plessers S, Mebis J, De Moor N, Wessels T, Luyten D, Requilé A. Hypercalcemia as an Immune-Related Adverse Event in a Patient Receiving Nivolumab and Ipilimumab for Metastatic Melanoma: A Case Report. Case Rep Oncol Med. 2025; 2025:8600200. doi: 10.1155/crom/8600200.
6. Albarrán-Artahona V, Laguna JC, Gorría T, Torres-Jiménez J, Pascal M, Mezquita L. Immune-Related Uncommon Adverse Events in Patients with Cancer Treated with Immunotherapy. Diagnostics (Basel). 2022;12:2091. doi: 10.3390/diagnostics12092091.
7. Izzedine H, Chazal T, Wanchoo R, Jhaveri KD. Immune checkpoint inhibitor-associated hypercalcaemia. Nephrol Dial Transplant. 2022;37:1598-608. doi: 10.1093/ndt/gfaa326.
8. Melin A, Routier É, Roy S, Pradere P, Le Pavec J, Pierre T, et al. Sarcoid-like Granulomatosis Associated with Immune Checkpoint Inhibitors in Melanoma. Cancers (Basel). 2022;14:2937. doi: 10.3390/cancers14122937.
9. Fletcher J, Bishop EL, Harrison SR, Swift A, Cooper SC, Dimeloe SK, et al. Autoimmune disease and interconnections with vitamin D. Endocr Connect. 2022;11:e210554. doi: 10.1530/ec-21-0554.
10. Sharma OP. Hypercalcemia in granulomatous disorders: a clinical review. Curr Opin Pulm Med. 2000;6:442-7. doi: 10.1097/00063198-200009000-00010.
11. Theilade S, Yahyavi SK, Jensen MB, Eldrup E. Exacerbated hypercalcemia, nephrolithiasis, and renal impairment after vitamin D supplementation in granulomatous disease: a case report. J Med Case Rep. 2025;19:187. doi: 10.1186/s13256-025-05078-5.
12. Megha KB, Joseph X, Akhil V, Mohanan PV. Cascade of immune mechanism and consequences of inflammatory disorders. Phytomedicine. 2021;91:153712. doi: 10.1016/j.phymed.2021.153712.
13. Tan MH, Iyengar R, Mizokami-Stout K, Yentz S, MacEachern MP, Shen LY, et al. Spectrum of immune checkpoint inhibitors-induced endocrinopathies in cancer patients: a scoping review of case reports. Clin Diabetes Endocrinol. 2019;5:1. doi: 10.1186/s40842-018-0073-4.
14. Uludag M, Unlu MT, Kostek M, Caliskan O, Aygun N, Isgor A. Persistent and Recurrent Primary Hyperparathyroidism: Etiological Factors and Pre-Operative Evaluation. Sisli Etfal Hastan Tip Bul. 2023;57:1-17. doi: 10.14744/semb.2023.39260.
15. Weinmann SC, Pisetsky DS. Mechanisms of immune-related adverse events during the treatment of cancer with immune checkpoint inhibitors. Rheumatology (Oxford). 2019;58:vii59-vii67. doi: 10.1093/rheumatology/kez308.
16. Khoury N, Carmichael KA. Evaluation and therapy of hypercalcemia. Mo Med. 2011;108:99-103.
17. Kim DW, Miller A, Li A, Hardy N, Silver KD. Hypercalcemia of Malignancy: Simultaneous Elevation in Parathyroid Hormone-Related Peptide and 1,25 Dihydroxyvitamin D in Sarcoma. AACE Clin Case Rep. 2021;7:169-73. doi: 10.1016/j.aace.2020.11.037.
18. Tebben PJ, Singh RJ, Kumar R. Vitamin D-Mediated Hypercalcemia: Mechanisms, Diagnosis, and Treatment. Endocr Rev. 2016;37:521-47. doi: 10.1210/er.2016-1070.
19. Takeda K, Kimura R, Nishigaki N, Sato S, Okamoto A, Watanabe K, et al. Humoral Hypercalcemia of Malignancy with a Parathyroid Hormone-Related Peptide-Secreting Intrahepatic Cholangiocarcinoma Accompanied by a Gastric Cancer. Case Rep Endocrinol. 2017;2017:7012520. doi: 10.1155/2017/7012520.
20. Pitts S, Mahipal A, Bajor D, Mohamed A. Hypercalcemia of malignancy caused by parathyroid hormone-related peptide-secreting pancreatic neuroendocrine tumors (PTHrP-PNETs): Case Report. Front Oncol. 2023;13:1197288. doi: 10.3389/fonc.2023.1197288.
21. Charkviani M, Herrmann SM. Immune Checkpoint Inhibitor-Associated Sarcoidosis Reaction in the Kidney: Case Report. Kidney Med. 2023;5:100626. doi: 10.1016/j.xkme.2023.100626.
22. Zouras S, Surya A, Abusahmin H, Hassan M, Humphreys E, Nagaraja P, et al. GRANULOMATOUS DISEASE OF UNUSUAL SITES CAUSING HYPERCALCEMIA: TWO CASE REPORTS. AACE Clin Case Rep. 2019;5:e44-e9. doi: 10.4158/accr-2018-0313.
23. Mecoli CA, Chee B, Chen M, Wang X, Albayda J, Paik JJ, et al. Diagnostic Yield of Computed Tomography for Cancer Detection in a Tertiary Referral Population of Idiopathic Inflammatory Myositis Patients. Arthritis Care Res (Hoboken). 2023;75:2142-50. doi: 10.1002/acr.25114.
24. Canedo F, Duarte I, Rodrigues J, Carvalhinho MI, Borba A. Sarcoidosis Mimicking Metastatic Disease: Multisystem Involvement With Osseous Manifestations. Cureus. 2025;17:e98390. doi: 10.7759/cureus.98390.
25. Narula N, Iannuzzi M. Sarcoidosis: Pitfalls and Challenging Mimickers. Front Med (Lausanne). 2020;7:594275. doi: 10.3389/fmed.2020.594275.
26. Lipton A, Uzzo R, Amato RJ, Ellis GK, Hakimian B, Roodman GD, et al. The science and practice of bone health in oncology: managing bone loss and metastasis in patients with solid tumors. J Natl Compr Canc Netw. 2009;7 Suppl 7:S1-29; quiz S30. doi: 10.6004/jnccn.2009.0080.
27. Minisola S, Pepe J, Piemonte S, Cipriani C. The diagnosis and management of hypercalcaemia. BMJ. 2015;350:h2723. doi: 10.1136/bmj.h2723.
28. Puzanov I, Diab A, Abdallah K, Bingham CO, 3rd, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5:95. doi: 10.1186/s40425-017-0300-z.
29. Ben Dori S, Kabaha N, Abu Husseine A, Rabina E, Barzilay Yoseph L, Rotman-Pikielny P, et al. Beyond Malignancy: Clinical Insights from Three Cases of Severe Hypercalcemia. J Clin Med. 2026;15:2412. doi: 10.3390/jcm15062412.
30. Saleem M, Iftikhar H. Stones, Bones, Groans, and Psychic Moans: Primary Hyperparathyroidism Presenting as Surgical Emergency. Cureus. 2019;11:e4989. doi: 10.7759/cureus.4989.
31. Omotosho YB, Zahra F. Resistant Hypercalcemia. Treasure Island (FL): StatPearls Publishing LLC.; 2026.
32. Keramida K, Kariki O, Angelopoulou E, Kalafatis I, Lafaras C, Letsas KP, et al. Arrhythmias, conduction disorders and sudden cardiac death in cancer patients and survivors: expert opinion of the working groups on cardio-oncology and on electrophysiology of the hellenic cardiac society. Cardiooncology. 2025;11:71. doi: 10.1186/s40959-025-00363-0.
33. Stelmachowska-Banaś M, Czajka-Oraniec I. Management of endocrine immune-related adverse events of immune checkpoint inhibitors: an updated review. Endocr Connect. 2020;9:R207-r28. doi: 10.1530/ec-20-0342.
34. Walsh J, Gittoes N, Selby P. Society for Endocrinology Endocrine Emergency Guidance: Emergency management of acute hypercalcaemia in adult patients. Endocr Connect.

2016;5:G9-g11. doi: 10.1530/ec-16-0055.
35. Hu MI, Glezerman IG, Leboulleux S, Insogna K, Gucalp R, Misiorowski W, et al. Denosumab for treatment of hypercalcemia of malignancy. J Clin Endocrinol Metab. 2014;99:3144-52. doi: 10.1210/jc.2014-1001.
36. LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2022;33:2049-102. doi: 10.1007/s00198-021-05900-y.
37. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol. 2011;335:2-13. doi: 10.1016/j.mce.2010.04.005.
38. Gerke AK. Treatment of Sarcoidosis: A Multidisciplinary Approach. Front Immunol. 2020;11:545413. doi: 10.3389/fimmu.2020.545413.
39. Byron Y, Yegorova-Lee S, Tio M. Do corticosteroids affect immunotherapy efficacy in malignancy? - A systematic review. Cancer Med. 2024;13:e70254. doi: 10.1002/cam4.70254.
40. Huang JJ, YousefiAsl M, Singh N, Grivas P, Bhatia S. Steroid-sparing strategies for managing immune-related adverse events. J Immunother Cancer. 2026;14:e013776. doi: 10.1136/jitc-2025-013776.
41. Carroll R, Matfin G. Endocrine and metabolic emergencies: hypercalcaemia. Ther Adv Endocrinol Metab. 2010;1:225-34. doi: 10.1177/2042018810390260.
42. Eklund A, du Bois RM. Approaches to the treatment of some of the troublesome manifestations of sarcoidosis. J Intern Med. 2014;275:335-49. doi: 10.1111/joim.12198.
43. Diehl R, Ferrara F, Müller C, Dreyer AY, McLeod DD, Fricke S, et al. Immunosuppression for in vivo research: state-of-the-art protocols and experimental approaches. Cell Mol Immunol. 2017;14:146-79. doi: 10.1038/cmi.2016.39.
44. Sternlicht H, Glezerman IG. Hypercalcemia of malignancy and new treatment options. Ther Clin Risk Manag. 2015;11:1779-88. doi: 10.2147/tcrm.S83681.
45. Bishop CW, Ashfaq A, Choe J, Strugnell SA, Johnson LL, Norris KC, et al. Extended-Release Calcifediol Normalized 1,25-Dihydroxyvitamin D and Prevented Progression of Secondary Hyperparathyroidism in Hemodialysis Patients in a Pilot Randomized Clinical Trial. Am J Nephrol. 2026;57:109-19. doi: 10.1159/000546615.
46. Everts-Graber J, Lehmann D, Burkard JP, Schaller B, Gahl B, Häuselmann H, et al. Risk of Osteonecrosis of the Jaw Under Denosumab Compared to Bisphosphonates in Patients With Osteoporosis. J Bone Miner Res. 2022;37:340-8. doi: 10.1002/jbmr.4472.
47. Youssef J, Novosad SA, Winthrop KL. Infection Risk and Safety of Corticosteroid Use. Rheum Dis Clin North Am. 2016;42:157-76, ix-x. doi: 10.1016/j.rdc.2015.08.004.