Case Report

Immune-related osteoblastic bone alterations mimicking bone metastasis in a small-cell lung cancer patient treated with durvalumab: a case report

Dan Pu, Hong-E Zhang, Lu Li

Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Contributions: (I) Conception and design: D Pu; (II) Administrative support: L Li; (III) Provision of study materials or patients: L Li; (IV) Collection and assembly of data: HE Zhang; (V) Data analysis and interpretation: D Pu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Lu Li, MD. Lung Cancer Center, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Chengdu 610041, China. Email: windflower1991@vip.163.com.

Background: Chemotherapy combined with immunotherapy is currently the standard first-line treatment for advanced small-cell lung cancer (SCLC). Immunotherapy can induce specific adverse events, called immune-related adverse events (irAEs). IrAEs of bones have rarely been reported. However, identifying bone irAEs could be important in avoiding misdiagnosis and ensuring appropriate patient management. This is the first report describing the diagnosis of irAEs of osteoblastic bone changes mimicking bone metastasis in a SCLC patient treated with durvalumab.

Case Description: In this report, we describe a unique and challenging case in which a 54-year-old female patient with SCLC treated with durvalumab, an immunotherapy drug, exhibited osteoblastic bone changes that appeared similar to bone metastasis on imaging but were actually a side effect of immunotherapy. Before treatment, imaging revealed no bone metastasis. In the third month after treatment with durvalumab, computed tomography (CT) revealed multiple bone alterations, predominantly osteoblastic lesions with minor osteolytic changes. Various imaging tests suggested bone metastasis, but she had no symptoms related to bone disease. Notably, the lesions in the chest had achieved a partial response. Based on a comprehensive analysis of the CT-guided pathological biopsy results, the patient's symptoms, and the biological characteristics of SCLC, we determined that these bone changes were irAEs occurring in the skeletal system. The patient was followed up for 10 months, during which time the bone lesions remained stable.

Conclusions: IrAEs of bones are rare, and their manifestations vary. Sometimes, the imaging manifestations of bone irAEs are difficult to distinguish from bone metastasis. If patients show variable treatment responses between different lesions, careful evaluation (including a pathological biopsy) is necessary.

Keywords: Durvalumab; small-cell lung cancer (SCLC); immune-related adverse events (irAEs); bone; case report

Submitted Jun 07, 2024. Accepted for publication Aug 02, 2024. Published online Aug 17, 2024.
doi: 10.21037/tlcr-24-461
View this article at: https://dx.doi.org/10.21037/tlcr-24-461

Introduction

In recent years, immune checkpoint inhibitors (ICIs), a type of tumor immunotherapy drug, have become a novel treatment method for advanced cancers and have significantly improved the long-term survival of cancer patients (1). ICIs commonly target programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte antigen-4 (CTLA-4), thereby reactivating the function of effector T cells and specifically killing tumor cells (1). However, overactivated immune cells can also

attack normal tissues and organs, leading to autoimmune damage known as immune-related adverse events (irAEs) (2). Common irAEs include endocrine disorders, skin rash, colitis, hepatitis, and pneumonitis (2,3).

With the increase in the use of ICIs, some rare side effects are gradually being discovered in clinical practice. Previous research has reported that the side effects of ICIs on musculoskeletal tissue commonly include arthralgia, myalgia, myositis, arthritis, and rhabdomyolysis (4,5), while novel adverse events include fracture, jaw necrosis, osteitis, and myelitis (4,6,7). In this article, we report the first detailed case of a small-cell lung cancer (SCLC) patient who developed widespread bone lesions mimicking tumor bone metastasis after receiving the PD-L1 inhibitor durvalumab. We presented this article in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-461/rc).

Case presentation

In May 2023, a 54-year-old female patient was diagnosed with SCLC of the left upper lobe with left hilar, mediastinal, left supraclavicular lymph node metastasis and pericardial effusion (stage IVa) (*Figure 1*). She was a food quality inspector without any exposure to asbestos, radon and other carcinogens, such as arsenic, chromium and nickel. She had no history of smoking or passive smoking, no history of autoimmune diseases, and no family history of lung cancer or genetic diseases. The patient's main symptoms were chest tightness and shortness of breath on exertion. She began treatment with etoposide (120 mg, days 1–4. Considering her PS score was 1–2, we gave etoposide slowly) and carboplatin (420 mg, day 1) combined with durvalumab (1,500 mg, day 1) every 3 weeks starting on May 12, 2023. After two cycles of treatment, the symptoms of chest tightness and shortness of breath were significantly relieved. A computed tomography (CT) scan on July 3, 2023, revealed a marked reduction in the primary lesion in the left upper lobe and in the lymph nodes of the left hilar, mediastinum, and cervical region. However, the CT scan revealed multiple uneven increases in bone density in the chest and abdomen, which did not exist before (*Figure 1*).

To further identify the newly discovered abnormal bone lesions, the patient underwent a single-photon emission computed tomography (SPECT)/CT bone scan and enhanced magnetic resonance imaging (MRI) of the vertebrae. The SPECT/CT bone scan indicated many abnormal spotted, scattered and asymmetric distributed radioactive concentrations in multiple cervical, thoracic, lumbar, and sacral vertebrae, and the pelvis, ribs, and long bones of the limbs, suggesting extensive bone metastasis. Enhanced MRI of the vertebrae revealed abnormal signals in the vertebrae, with scattered patchy, nodular lesions featured hypointense on T1 and T2-weighted images, and uneven enhancement, indicating osteoblastic bone metastasis. The CT and MRI scans were evaluated by two radiologists and identified multiple bone alterations were predominantly osteoblastic lesions with minor osteolytic changes. However, the patient showed a good response in terms of the chest lesions, and had no symptoms of bone metastasis, such as pain or activity limitations. Therefore, we decided to further test the bone lesions to clarify whether the current treatment had a differential efficacy in the chest and bone.

The patient subsequently underwent bone marrow aspiration (iliac anterior superior spine). The ratio of hematopoietic tissue to adipose tissue was approximately 3–4:1. The myeloid to erythroid ratio was about 4–6:1. There was a slight increase in the number of immature granulocytes. There were 4–6 megakaryocytes per high power field (HPF). No significant morphological abnormalities were observed in the three hematopoietic lineages. Additionally, a few lymphocytes and plasma cells were observed scattered in small focal clusters. There were no tumor cells observed. The increase in the number of granulocytes was related to the use of granulocyte colony-stimulating factor after chemotherapy. Bone biopsy guided by a CT scan (iliac bone where there was an osteoblastic

Highlight box

Key findings

- We report a rare case of immune-related osteoblastic changes of the bones following immunotherapy in a small-cell lung cancer patient and discuss the differential diagnosis of bone metastasis.

What is known and what is new?

- Immunotherapy can induce immune-related adverse events (irAEs) of the musculoskeletal system.
- The irAEs of osteoblastic bone changes induced by immunotherapy had not previously been reported.

What is the implication, and what should change now?

- In imaging, bone irAEs need to be distinguished from bone metastasis.
- Careful evaluation is necessary if patients show variable treatment responses between different lesions.

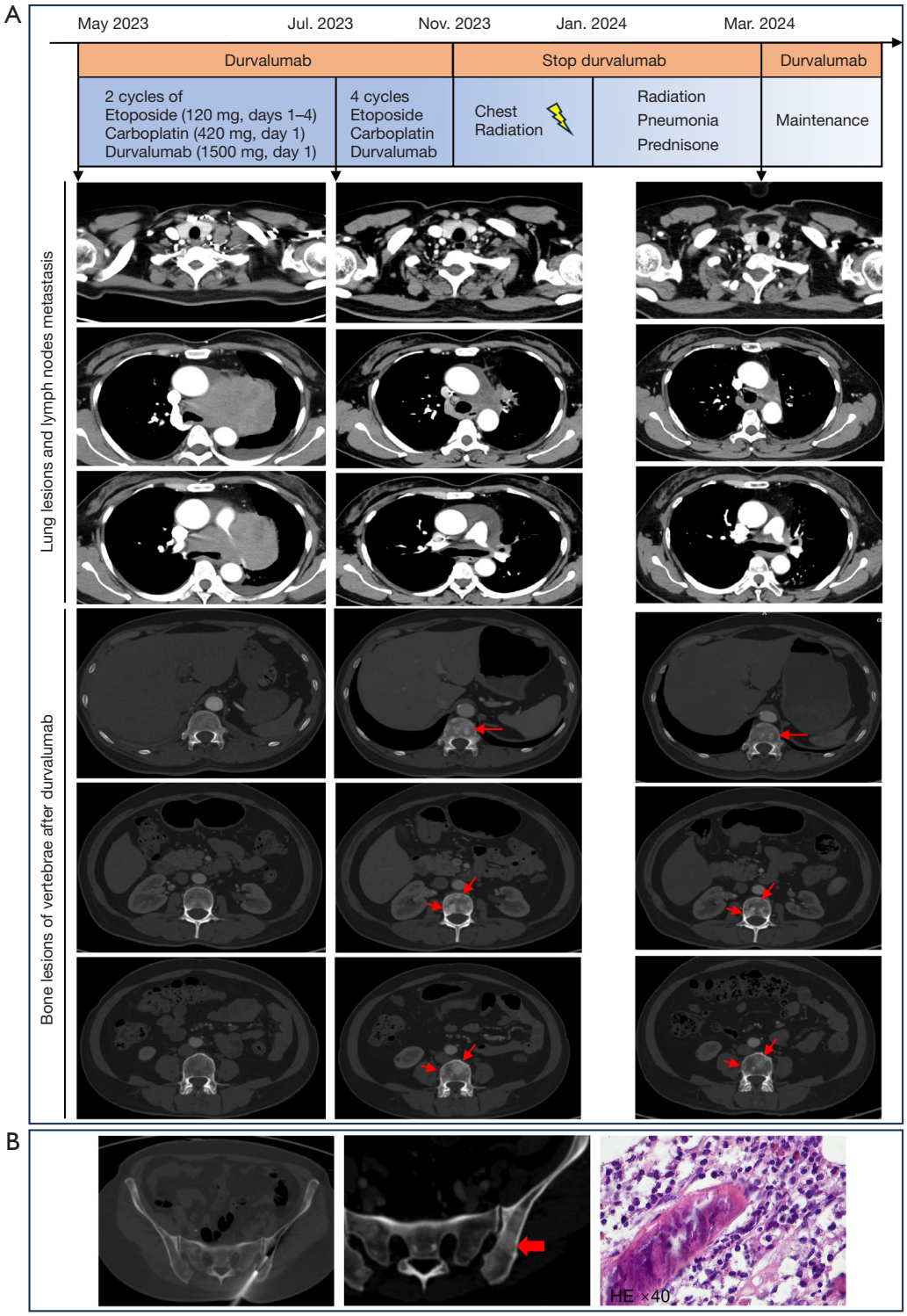

Figure 1 The timeline of the diagnosis and treatment of the patient. (A) The therapeutic management timeline and corresponding imaging. After 2 cycles of durvalumab treatment, the CT scan revealed multiple uneven increases in bone density in vertebrae (red arrow). Suspending durvalumab for 4 months and taking prednisone for 1 month, CT showed that the bone lesions were improving (red arrow). (B) The CT-guided biopsy was conducted in iliac bone, where there was an osteoblastic lesion (red arrow). Bone trabeculae were regularly arranged and normal bone marrow components were visible around them. No abnormal hematopoietic or tumor cells were observed. CT, computed tomography.

lesion) showed that bone trabeculae were regularly arranged and normal bone marrow components were visible around them. No abnormal hematopoietic or tumor cells were observed. Since the purpose of this bone biopsy was to determine the presence of tumor bone metastasis, the biopsy tissue was not decalcified, hence osteoclasts and osteoblasts were not clearly visible. Further tests, including serum protein electrophoresis, immunofixation electrophoresis, immunoglobulin light chain quantification, 24-hour urine light chain detection, the parathyroid hormone (PTH) test, the 25-hydroxyvitamin D test, the rheumatoid factor (RF) test, alkaline phosphatase (ALP, 160 IU/L, normal range 30–120 IU/L), bone-specific ALP (12.48 μg/L, normal rang ≤14.30 μg/L), interferon-γ release assays, the Xpert tuberculosis test and the purified protein derivative (PPD) skin test, suggested that the patient did not have multiple myeloma, hyperparathyroidism, rheumatoid arthritis, Paget's disease of bone (PDB) or tuberculosis.

Excluding bone metastasis and other diseases that might cause similar manifestations of bone abnormalities, we hypothesized that the bone lesions were potentially related to the ICIs. As similar irAEs have not been reported previously, the grade of this irAE has no standard. Based on experience, the patient's symptoms and image manifestations, we classified it as grade 1, and determined that the patient did not have to stop ICI therapy and receive steroid treatment. After six cycles of chemotherapy combined with durvalumab, a comprehensive evaluation revealed that tumor lesions were partial released, pericardial effusion disappeared and bone lesions remained stable. From November 2023 to February 2024, the patient underwent chest radical radiation and suffered from mild radiation pneumonitis. Durvalumab was suspended for 4 months and prednisone was administered for 1 month (prednisone 30 mg/day for 2 weeks, then 15 mg/day for 1 week, 5 mg/day for 1 week). An evaluation in March 2024 showed a clinical complete response and mild post-radiation changes in the lung. CT showed that the bone lesions were improving, which indicated that the bone lesions were related to the ICIs (*Figure 1*). Durvalumab (1,500 mg, every 4 weeks) was subsequently maintained.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. We made sure that this case report was sufficiently anonymized and patient identifiers were all removed.

Patient perspective

"I am grateful to the medical team at the Lung Cancer Center of West China Hospital for their help. Previously, I thought I had extensive bone metastases, which was a great shock to me and my family. Fortunately, my medical team did not give up. They keenly identified the issue and ultimately concluded that my past treatment regimen was effective. From initially having difficulty moving and breathing, I have now fully returned to a normal life. Going forward, I only need monthly immunotherapy and regular check-ups."

Discussion

In recent years, with the widespread use of immunotherapy, the Food Drug Administration (FDA) Adverse Event Reporting System (FAERS) database has reported a few cases of ICIs affecting the skeletal system, which have mainly included fractures, jaw necrosis, and osteitis (8). However, as cancers themselves also metastasize to bones, bone irAEs should also be distinguished from bone metastasis and other drug adverse events (e.g., adverse events related to bisphosphonates and denosumab).

In this case, the patient had no initial bone metastasis. After two cycles of chemotherapy combined with durvalumab, the primary lung lesion and metastatic lymph nodes shrunk significantly, and the patient's clinical symptoms were relieved. However, various imaging tests, including CT, MRI, and SPECT/CT bone scans, suggested widespread bone metastasis, presenting mainly osteoblastic changes. In lung cancer, 64%, 33%, and 3% bone metastasis was osteolytic, osteoblastic, and mixed, respectively (9). Literature reported osteoblastic bone metastases were more common in small cell lung cancer (10). This situation required consideration of the bone metastasis progression due to tumor heterogeneity and other bone-related diseases, such as multiple myeloma, hyperparathyroidism, rheumatoid arthritis, bone tuberculosis and PDB.

Multiple myeloma mainly manifests as hypercalcemia, renal impairment, anemia and secondary amyloidosis, and can be diagnosed through bone marrow biopsy. Hyperparathyroidism presents with elevated PTH levels, hypercalcemia, hypophosphatemia, hypercalciuria, and hyperphosphaturia. The symptoms of rheumatoid arthritis are nonspecific in the early stage, manifesting

as swelling or pain in small joints, with imaging showing osteoporosis or bone erosion and laboratory tests showing RF positivity. Tuberculosis patients usually have fever, night sweats, fatigue, and weight loss, and can test positive for interferon-γ release assays, Xpert tuberculosis tests, and PPD skin tests. PDB could also manifest osteolytic and osteoblastic changes. But several features of PDB in CT scan, like bone enlargement and deformity, "cotton wool" appearance, were not found in this patient and ALP was only slightly elevated. In addition, PDB is a chronic disease and frequently occurs in Europeans. The incidence of PDB in Asian is much lower (11). Combined with epidemiology, imaging findings, and blood tests, PDB was not considered to be diagnosed in this patient.

Bone metastasis commonly occurs in the spine, pelvis, and long bones, presenting as pain, mobility issues and pathological fractures at metastatic sites. This patient experienced no symptoms of the skeletal system. Although ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET)/CT can detect irAEs, its usage in distinguishing osteoblastic irAE and osteoblastic bone metastasis should be carefully evaluated, as tumors and inflammation can both increase glycolysis with increased FDG uptake (12). The ^{18}F-FDG uptake is frequently mild to moderately increased in irAEs compared with metastasis, but the manifestation of osteoblastic irAE has not been reported (13). So, as bone marrow and bone biopsy revealed no cancer cells and further tests excluded other possible causes of bone abnormalities, we confirmed that the patient's bone lesions were irAEs. As long-term follow-up monitoring showed stable bone lesions without further deterioration, durvalumab was continued.

Currently, the incidence of bone irAEs is unclear, partly because of the lack of awareness and underreporting of these irAEs. A few studies have reported that ICIs can increase bone resorption, which can trigger bone adverse events, such as fracture, in cancer patients (6,14,15). However, given the high incidence of bone metastasis in cancers, determining whether these fractures are caused by metastasis or ICIs requires careful evaluation.

Bone is a dynamic tissue that is remodeled throughout life in response to the demands of metabolism (16). Bone remodeling is a process that includes bone resorption and formation and is conducted by osteoclasts and osteoblasts, respectively (16). However, controversy remains as to how ICIs affect the bone remodeling process. Pantano *et al.* reported that the levels of type I collagen C-terminal telopeptide (CTX-I) increased, and N-terminal propeptide (PINP) decreased in plasma after 3 months of ICI treatment, indicating increased osteoclast activity (17). Basic research study showed that PD-L1 knockout mice exhibited osteoporosis, reduced trabecular bone volume, deteriorated microstructure, and increased osteoclastogenesis (18). Osteoclastogenesis was thought to be motivated by activated T cells. In the setting of ICIs, activated T-cells secrete cytokines, including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and RANK-L, favoring osteoclast formation and maturation (7). Another study showed a sharp and transient decrease in CTX levels and a delayed increase in PINP after 4 months of therapy. Further, their bioengineered three-dimensional bone model demonstrated impaired osteoclast maturation and increased osteoblasts differentiation upon exposure to ICIs (19). According to a laboratory study, the binding of PD-L1 to PD-1 in osteoclast precursors leads to JNK activation, and the release of the C-C motif chemokine ligand 2 (CCL2) that promotes osteoclast differentiation. Anti-PD-1 immunotherapy can produce the long-term suppression of osteoclastogenesis (20).

Both osteoclasts and osteoclast precursors can be influenced by ICIs. We hypothesized that ICIs act on different types of cells, leading to different manifestations. When ICIs mainly affect osteoclast precursors, they reduce the differentiation of osteoclast precursors into osteoclasts, which manifests as osteoblastic changes (21). Conversely, when ICIs mainly affect cells related to osteoclasts, they promote osteoclasts formation, resulting in osteolytic changes (7,18). In this case, the patient exhibited prominent osteoblastic bone features alongside minor osteolytic bone alterations, which were difficult to distinguish from bone metastasis (22). We performed a pathological biopsy guided by a CT scan. However, bias still existed among the sampling sites. Therefore, we made the diagnosis considering both the pathology and the patient's clinical features and prognosis.

The mechanisms and clinical manifestations of irAEs are complex and diverse. Sometimes, irAEs should be distinguished from pseudo-progression and hyper-progression (23), especially when patients exhibit variable treatment efficacy. The early and accurate identification of irAEs and progression can prevent the premature discontinuation of immunotherapy, ensuring that patients

benefit from the treatment.

Conclusions

This is the first report to describe irAEs of bones mimicking bone metastasis in a SCLC patient treated with durvalumab. These imaging manifestations were difficult to distinguish from bone metastasis. If patients show variable treatment responses, careful evaluation (including pathological biopsy) is necessary.

Acknowledgments

Funding: This work was supported by the Chengdu Municipal Health Commission (No. 2023061), Guangdong Association of Clinical Trials (GACT)/Chinese Thoracic Oncology Group (CTONG) (No. CTONG-YC20220103).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-461/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-461/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-461/coif). The authors have no competing interests to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Remon J, Aldea M, Besse B, et al. Small cell lung cancer: a slightly less orphan disease after immunotherapy. Ann Oncol 2021;32:698-709.
2. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med 2018;378:158-68.
3. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. CA Cancer J Clin 2020;70:86-104.
4. Cappelli LC, Gutierrez AK, Bingham CO 3rd, et al. Rheumatic and Musculoskeletal Immune-Related Adverse Events Due to Immune Checkpoint Inhibitors: A Systematic Review of the Literature. Arthritis Care Res (Hoboken) 2017;69:1751-63.
5. Melia A, Fockens E, Sfumato P, et al. Musculoskeletal immune-related adverse events in 927 patients treated with immune checkpoint inhibitors for solid cancer. Joint Bone Spine 2023;90:105457.
6. Filippini DM, Gatti M, Di Martino V, et al. Bone fracture as a novel immune-related adverse event with immune checkpoint inhibitors: Case series and large-scale pharmacovigilance analysis. Int J Cancer 2021;149:675-83.
7. Moseley KF, Naidoo J, Bingham CO, et al. Immune-related adverse events with immune checkpoint inhibitors affecting the skeleton: a seminal case series. J Immunother Cancer 2018;6:104.
8. Liu H, Li Y, Li J, et al. Musculoskeletal adverse events induced by immune checkpoint inhibitors: a large-scale pharmacovigilance study. Front Pharmacol 2023;14:1199031.
9. Reddington JA, Mendez GA, Ching A, et al. Imaging characteristic analysis of metastatic spine lesions from breast, prostate, lung, and renal cell carcinomas for surgical planning: Osteolytic versus osteoblastic. Surg Neurol Int 2016;7:S361-5.
10. Knapp BJ, Devarakonda S, Govindan R. Bone metastases in non-small cell lung cancer: a narrative review. J Thorac Dis 2022;14:1696-712.
11. Appelman-Dijkstra NM, Papapoulos SE. Paget's disease of bone. Best Pract Res Clin Endocrinol Metab 2018;32:657-68.

12. Gandy N, Arshad MA, Wallitt KL, et al. Immunotherapy-related adverse effects on (18)F-FDG PET/CT imaging. Br J Radiol 2020;93:20190832.
13. Cherk MH, Nadebaum DP, Barber TW, et al. (18) F-FDG PET/CT features of immune-related adverse events and pitfalls following immunotherapy. J Med Imaging Radiat Oncol 2022;66:483-94.
14. Ye C, Lee K, Leslie WD, et al. Fracture rate increases after immune checkpoint inhibitor treatment: a potential new immune related adverse event. Osteoporos Int 2023;34:735-40.
15. Kang JK, Lee EH, Lee JN, et al. Pathologic fractures of the humerus during adjuvant pembrolizumab in patients with renal cell carcinoma after radical nephrectomy: A case report. Int J Surg Case Rep 2024;115:109290.
16. Salhotra A, Shah HN, Levi B, et al. Mechanisms of bone development and repair. Nat Rev Mol Cell Biol 2020;21:696-711.
17. Pantano F, Tramontana F, Iuliani M, et al. Changes in bone turnover markers in patients without bone metastases receiving immune checkpoint inhibitors: An exploratory analysis. J Bone Oncol 2022;37:100459.
18. Greisen SR, Kragstrup TW, Thomsen JS, et al. The Programmed Death-1 Pathway Counter-Regulates Inflammation-Induced Osteoclast Activity in Clinical and Experimental Settings. Front Immunol 2022;13:773946.
19. Gassner T, Chittilappilly C, Pirich T, et al. Favorable impact of PD1/PD-L1 antagonists on bone remodeling: an exploratory prospective clinical study and ex vivo validation. J Immunother Cancer 2024;12:e008669.
20. Wang K, Gu Y, Liao Y, et al. PD-1 blockade inhibits osteoclast formation and murine bone cancer pain. J Clin Invest 2020;130:3603-20.
21. Brom VC, Strauss AC, Sieberath A, et al. Agonistic and antagonistic targeting of immune checkpoint molecules differentially regulate osteoclastogenesis. Front Immunol 2023;14:988365.
22. Esposito M, Guise T, Kang Y. The Biology of Bone Metastasis. Cold Spring Harb Perspect Med 2018;8:a031252.
23. Jia W, Gao Q, Han A, et al. The potential mechanism, recognition and clinical significance of tumor pseudoprogression after immunotherapy. Cancer Biol Med 2019;16:655-70.

Cite this article as: Pu D, Zhang HE, Li L. Immune-related osteoblastic bone alterations mimicking bone metastasis in a small-cell lung cancer patient treated with durvalumab: a case report. Transl Lung Cancer Res 2024;13(8):2043-2049. doi: 10.21037/tlcr-24-461