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Case Report

Late-onset bone granulomatous reaction of hand from immune checkpoint-inhibitors detected on FDG-PET/CT ☆,☆☆

Miki Nishimori[a,*], *Kouki Togami*[a], *Noriko Nitta*[a], *Kana Miyatake*[a], *Hitomi Iwasa*[a], *Kosuke Nakaji*[a], *Kenta Ogi*[a], *Takayasu Izumi*[a], *Tomohiro Matsumoto*[a], *Rika Yoshimatsu*[a], *Tomoaki Yamanishi*[a], *Kazufumi Takamatsu*[b], *Shudai Muramatsu*[c], *Mayuko Yamamoto*[d], *Takuji Yamagami*[a]

[a] *Department of Diagnostic and Interventional Radiology, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi, 783-8505, Japan*
[b] *Department of Respiratory medicine and Allergology, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi, 783-8505, Japan*
[c] *Department of Orthopedic Surgery, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi, 783-8505, Japan*
[d] *Department of Dermatology, Kochi Medical School, Kohasu, Oko-cho, Nankoku, Kochi, 783-8505, Japan*

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ABSTRACT

Immune checkpoint inhibitors (ICIs) enhance antitumor immunity by inhibiting intrinsic immune-suppressive pathways. Although immune-related adverse events (irAEs) typically arise in the early phase of ICI therapy, delayed manifestations have been reported, even months to years following treatment discontinuation. We report a case of a late-onset bone granulomatous reaction in the hand of a male patient in his seventies with a history of ICI therapy, identified on FDG-PET/CT, 4 years after discontinuation of ICI therapy. This case indicates the importance of recognizing the possibility of delayed irAEs, even in patients who have undergone long-term discontinuation of immunotherapy.

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* Corresponding author.
E-mail address: miki-nishimori@kochi-u.ac.jp (M. Nishimori).

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Introduction

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy; however, they frequently cause immune-related adverse events (irAEs). These immune-related adverse events (irAE) exhibit a broad spectrum of organs impacted and degrees of severity. Dermatologic, endocrine, neurologic, gastrointestinal, respiratory, and musculoskeletal toxicities may manifest individually or in combination [1]. The majority are self-limiting or resolved with immunosuppressants such as corticosteroids. The onset of irAEs ranged from 2.2 to 14.8 weeks [2]. However, the possibility of delayed autoimmunity appearing months or years following discontinuation of immunotherapy is frequently mentioned in recent literature [3]. Similar to regular irAE, involvement included endocrine, neurologic, GI, pulmonary, cardiac, rheumatologic, and dermatologic delayed irAE [3]; however, bone granulomatous lesions are uncommon.

Case presentation

A 75-year-old man was initially diagnosed with right lower lobe lung cancer (c-Stage IIIA) during a preoperative examination for an inguinal hernia repair. He underwent surgery followed by adjuvant chemotherapy for the lung cancer. The patient had no history of smoking. His surgical history included septoplasty and inguinal hernia repair, while his past medical history included colorectal polyps and atrial fibrillation. He had no prior history of malignancy. However, there was a family history of malignancy. At the initial diagnosis, elevated tumor markers, including IL-2R, CYFRA, NSE, and CEA, were noted (Table 1). Two months after surgery, he experienced local and mediastinal lymph node recurrence, which was treated with radiation therapy. Subsequently, chemotherapy (TS-1) was administered, but due to persistently elevated tumor markers, the treatment was switched to PD-L1 blockade with pembrolizumab. The patient later developed drug-induced interstitial pneumonia, a known immune-related adverse event (irAE), following 3 cycles of treatment. Pembrolizumab was discontinued; no other immunochemotherapy was administered according to his wishes. His condition was stable after discontinuation of pembrolizumab. However, he experienced suspicion of irAEs such as hypothyroidism (2 months after discontinuation of pembrolizumab), cutaneous granulomatous lesions (10 months after discontinuation), and granulation tissue of the left clavicle (28 months after discontinuation). Forty-six months after the discontinuation, he underwent FDG-PET/CT for surveillance of lung cancer, during which no elevation in tumor markers was observed. FDG-PET/CT showed an FDG-positive bone lesion corresponding to SUVmax = 5.4 on the right hand (Fig. 1). Computed tomography showed a lytic lesion (Fig. 2). Because right lung recurrence was also evident (Fig. 1), bone metastasis from lung cancer was first considered. However, the patient had other irAEs related to pembrolizumab, and the distribution pattern was atypical for metastasis of lung cancer. A biopsy was recommended. A needle biopsy indicated a bone granulomatous lesion with necrosis. Malignancy was not evident, and the lesion was negative for a typical infection. Therefore, the diagnosis of a bone granulomatous reaction from pembrolizumab was suspected. Subsequently, the progression of lung cancer worsened, and the patient subsequently died to progressive lung cancer approximately 1 year later (Fig. 3).

Table 1 – Blood test.

Parameter	Value	Reference range
TP	7.8	6.6-8.1 g/dL
GLU	114	73–109 mg/dL
ALP	225	106–322 U/L
Total cholesterol	191	142–248 mg/dL
γGT	84	13–64 U/L
Total bilirubin	1.1	0.4–1.5 mg/dL
ChE	206	240–486 U/L
ALB	3.7	4.1–5.1 g/dL
ALT	24	10–42 U/L
AST	22	13–30 U/L
LD	182	124–222 U/L
CK	109	M: 59–248 U/L
CRE	0.79	0.65–1.07 mg/dL
UN	13	8–20 mg/dL
UA	7.3	3.7–7.8 mg/dL
CRP	1.3	$\leq$0.14 mg/dL
RBC	534	435–555 $\times$ $10^4/\mu$L
PLT	21	15.8–34.8 $\times$ $10^4/\mu$L
WBC	10.4	3.3–8.6 $\times$ $10^3/\mu$L
sIL-2R	655	127–582 U/mL
Pro GRP	70.3	$\leqq$80.0 pg/mL
CYFRA	7.6	$<$3.5 ng/mL
NSE	18.4	$\leq$16.3 ng/mL
SLX	34.2	$\leq$38 U/mL
CEA	7.9	$<$5.0 ng/mL
SCC	1.4	$\leq$1.5 ng/mL
eGFR	73.6	$\geq$60 mL/min/1.73m^2

TP, total Protein; GLU, glucose; ALP, alkaline phosphatase; γGT, γ-glutamyl transpeptidase; ChE, cholinesterase; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LD, lactate dehydrogenase; CK, creatine kinase; CRE, CREATININE; UN, urea nitrogen; UA, uric acid; CRP, C-reactive protein; RBC, red blood cells; PLT, platelet; WBC, white blood cells; sIL-2R, soluble interleukin-2 receptor; Pro GRP, gastrin-releasing peptide; CYFRA, cytokeratin 19 fragment; NSE, neuron-specific enolase; SLX, sialyl Lewis-x antigen; CEA, carcinoembryonic antigen; SCC, squamous cell carcinoma antigen; eGFR, estimated glemerular filtration rate.

Discussion

The ICI aims to boost antitumor immunity by inhibiting intrinsic immune-depressing regulators. The inhibiting of immune-down regulators, responsible for a breakdown in immune homeostasis with an overly activated immune system, leads to irAEs [4]. irAEs may affect any organ system, such as the skin, gut, thyroid, lungs, liver, and joints [5]. Moreover, checkpoint inhibitor-induced bone granulomatous reactions were reported [6,7]. In those cases, the vertebra and hip bone were affected, and there were associations with cutaneous lesions and lymphadenopathy of the lung. Most irAEs occur in the first

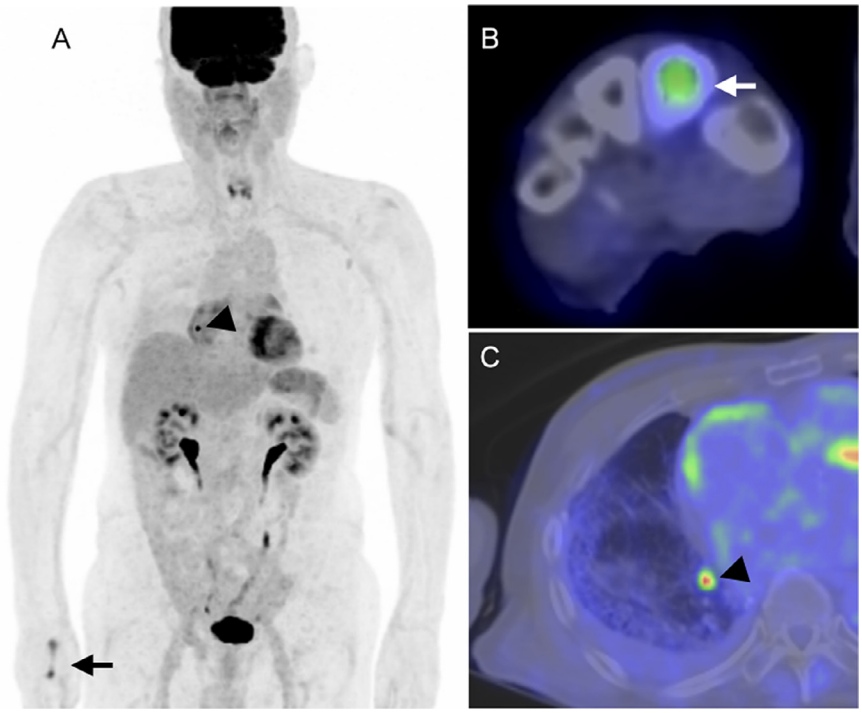

Fig. 1 – FDG-PET/CT findings. (A) Maximum intensity projection images and (B and C) transverse fusion PET/CT scans. PET/CT demonstrated an FDG-avid bone lesion with a corresponding SUVmax of 5.4 in the right hand (A and B, arrow). Additionally, right lung recurrence was identified (A and C, arrowhead).

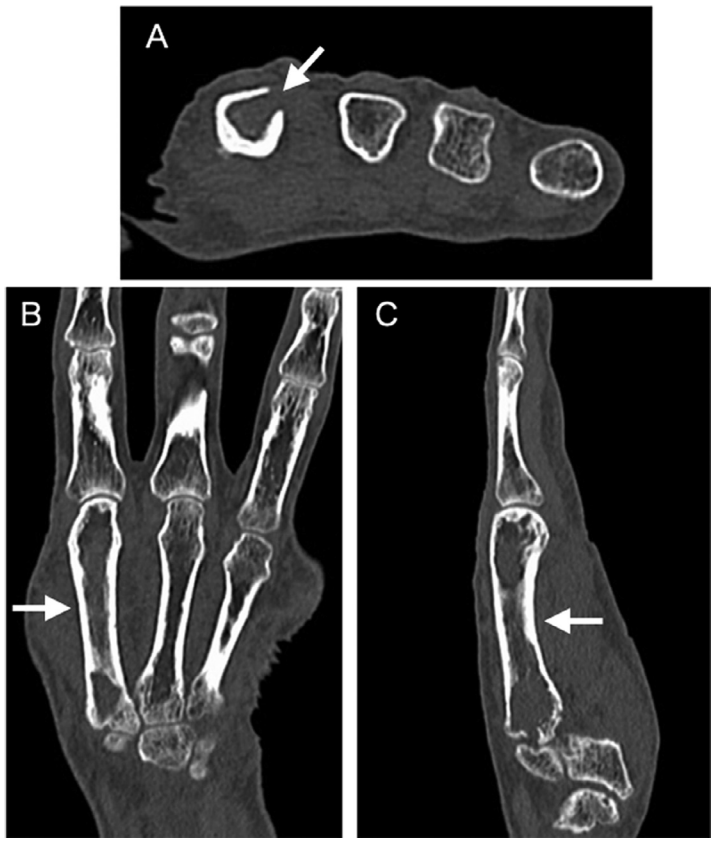

Fig. 2 – Plain CT findings of the second metacarpal bone of the right hand. (A) Axial view, (B) Coronal view, (C) Sagittal view. A lytic lesion was identified in the metacarpal bone, accompanied by cortical disruption (arrow).

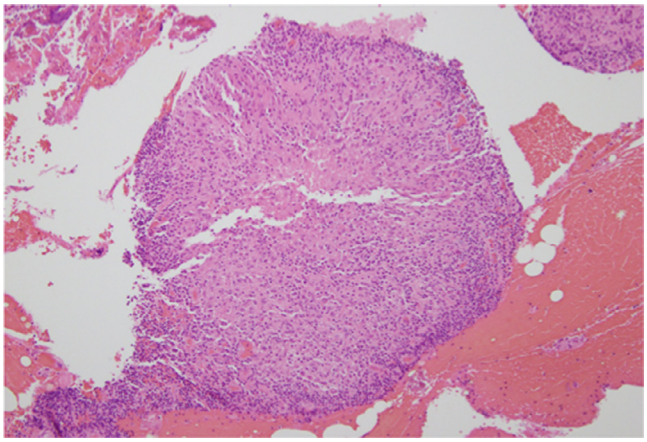

Fig. 3 – Hematoxylin and eosin-stained section of the biopsy specimen from the right metacarpal bone lesion revealed a granuloma with central necrosis. No evidence of malignancy observed. (Obj x10).

4 months of ICI treatment [8]; however, the risk of delayed autoimmunity occurring months or years after discontinuation of immunotherapy was reported [3,9,10]. There is sound mechanistic plausibility to support these reports. In a previous study, despite that the serum half-life of anti-PD-1 was 12 to 20 days, pharmacodynamics indicated a sustained mean occupancy of >70% of PD-1 molecules in circulating T cells ≥2 months following infusion, regardless of dose [11]. Our case indicated that an irAE manifested by a bone granulomatous lesion may occur even 4 years after ICI treatment. Bone granulomatous reactions can importantly mimic metastatic bone lesions on imaging modalities, e.g., CT, MRI, and FDG-PET/CT. A false diagnosis of progression of a malignancy may result. Most irAEs have been mild and managed successfully with supportive care, differing from metastatic lesions, thus making a correct diagnosis extremely important. Therefore, a bone FDG-avid lesion in patients with a history of immune checkpoint inhibitors, even after long-term discontinuation of an anti-PD1, may raise the suspicion of a bone granulomatous reaction. Especially when the patient has had other granulomatous lesions, such as cutaneous lesions and lung lymphadenopathy, or when the site of suspected bone metastasis is atypical, a biopsy should be considered to establish the correct diagnosis.

Conclusion

We reported a case of a late-onset bone granulomatous reaction as a delayed irAE. Although irAEs are commonly known to occur in the early stages of immune checkpoint inhibitor (ICI) treatment, this case indicates the importance of recognizing the possibility of delayed irAEs even in patients with a long interval since the occurrence of previous irAEs.

Ethics committee approval

This is a case report involving 1 patient; thus, institutional ethics committee approval was not required.

Patient consent

Informed consent was obtained from the patient described in this manuscript.

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