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【 CASE REPORT 】

Tenosynovitis Induced by an Immune Checkpoint Inhibitor: A Case Report and Literature Review

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Abstract:
A 51-year-old man underwent second-line treatment for non-small-cell lung cancer (NSCLC) with the immune checkpoint inhibitor (ICI) pembrolizumab. On day 2 after two cycles of pembrolizumab, he presented with edema limited to the left third, fourth, and fifth fingers. Based on symptoms, laboratory results, and contrast-enhanced magnetic resonance imaging (MRI) findings, we diagnosed him with tenosynovitis. We prescribed oral prednisolone (0.5 mg/kg/day), and pembrolizumab was continued. Prednisolone immediately relieved the symptoms, and the tumor was still shrinking on day 21 after eight cycles of pembrolizumab. ICI-induced tenosynovitis was managed while continuing ICI usage, suggesting that 0.5 mg/kg/day prednisone might be effective for tenosynovitis without ICI cessation.

Key words: tenosynovitis, pembrolizumab, prednisolone

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Introduction

Immune checkpoint inhibitors (ICIs) are antibodies that target the primary immune surveillance escape mechanisms, i.e. the immune checkpoints. Immune checkpoints are involved in maintaining the homeostasis of immune responses and in the establishment of peripheral immune tolerance to self-antigens. Therefore, the failure of this tolerance causes autoimmune diseases (1).

Related adverse events (AEs) are called immune-related AEs (irAEs). Although it is thought that T cells are mainly involved in irAEs, B cells that produce antibodies and granulocytes that produce inflammatory cytokines are also thought to be involved (1-4). IrAEs commonly occur in the skin, gastrointestinal tract, liver, and endocrine system (5). However, irAEs can also occur in other areas, such as the kidneys, nerves, muscles, and lungs. The rate of arthralgia reported in clinical trials of ICIs has ranged from 1% to 43% (6). As tenosynovitis is only seen in a few case reports, its optimum management has yet to be established.

We herein report a patient who developed tenosynovitis induced by pembrolizumab and experienced a good response to systemic corticosteroid treatment while continuing pembrolizumab.

Case Report

In November 2017, a 51-year-old man was diagnosed with stage IIIB non-small cell lung cancer (NSCLC) lacking epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and c-ros oncogene-1 (*ROS-1*) gene mutations. The expression of programmed cell death ligand-1 (PD-L1) was 20%. There was neither a medical history nor a family history of lung cancer or collagen-related diseases. The patient's vital signs were normal, and the Eastern Cooperative Oncology Group performance status (ECOG PS) score was 0.

Initially, the patient was treated with 4 cycles of cisplatin (60 mg/m^2) on day 1 and TS-1 (120 mg/body) on days 1-21

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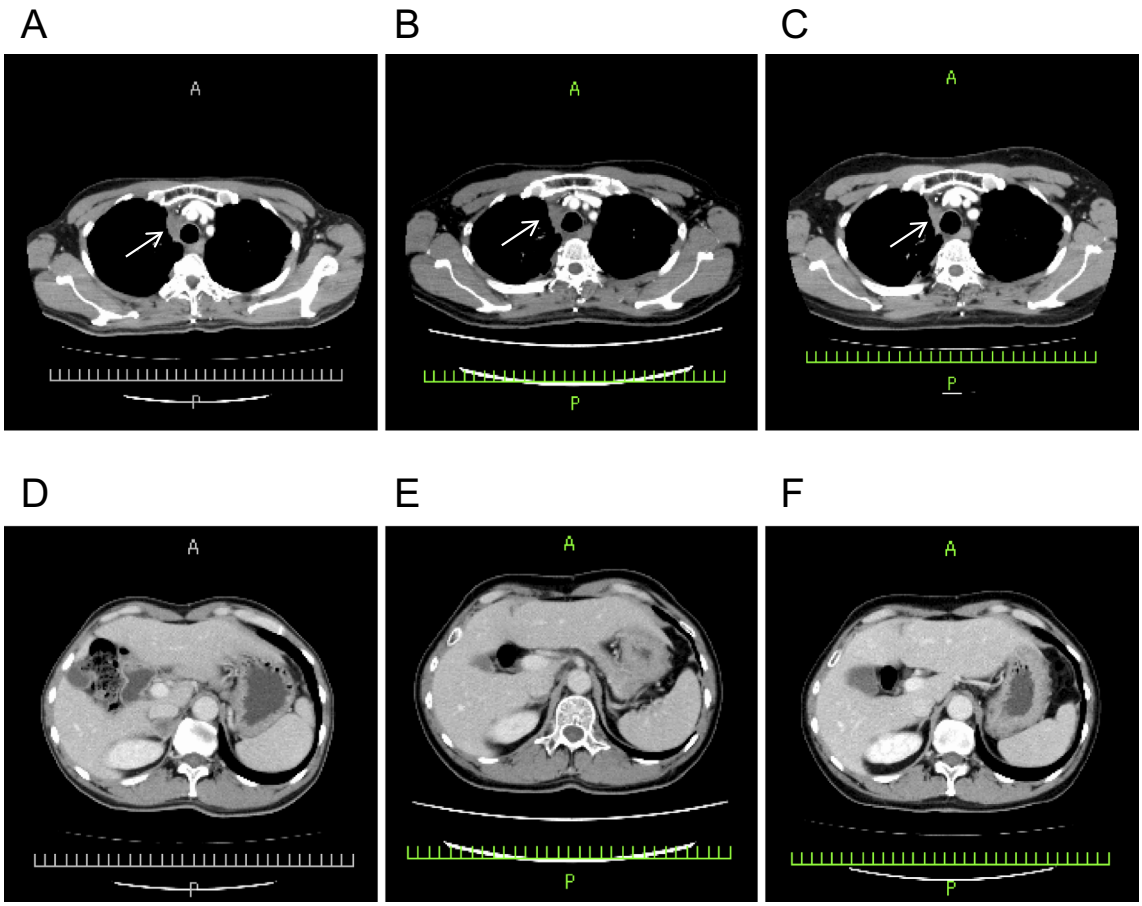

Figure 1. Computed tomography (CT) revealed the shrinkage of the primary lesion (arrow) and the right adrenal gland metastasis before pembrolizumab (A and D), after four cycles of pembrolizumab (B and E), and after eight cycles of pembrolizumab (C and F).

concurrently with radiotherapy (60 Gy/30 fr). After four cycles of cisplatin and TS-1 chemotherapy, computed tomography (CT) revealed disease progression involving the right adrenal gland, although the primary tumor in the right upper lobe had shrunk (Fig. 1A and D). Therefore, second-line treatment with pembrolizumab [200 mg every 3 weeks (q3w)] was introduced in May 2018.

On day 2, after two cycles of pembrolizumab, the patient presented with edema with a Common Terminology Criteria for Adverse Events (CTCAE) grade of 1, which was limited to the left third, fourth, and fifth fingers and led to a poor function. Pembrolizumab was continued, and the edema was carefully observed. The patient gradually developed edema with pain in the interphalangeal joints and left wrist joint. On day 24, after three cycles of pembrolizumab, a venous echo-Doppler assessment showed no thrombi between the left subclavian vein and the left dorsal hand vein. Laboratory tests revealed negative results for rheumatoid factor, anti-cyclic citrullinated peptide (CCP) antibodies, anti-ribonucleoprotein (RNP) antibodies, anti-Smith (Sm) antibodies, anti-Sjögren's syndrome-related antigen-A (SS-A) antibodies, anti-dsDNA antibodies, anti-ssDNA antibodies, proteinase 3 (PR3)-anti-neutrophil cytoplasmic antibody (ANCA), and myeloperoxidase (MPO)-ANCA. However, the results for anti-nuclear antibodies were positive (80), and the C-reactive protein (CRP) level (0.33 mg/dL) and erythrocyte sedimentation rate (21 mm/h) were slightly elevated (Table 1).

On day 15, after four cycles of pembrolizumab, contrast-enhanced magnetic resonance imaging (MRI) revealed that the left third, fourth, and fifth fingers and right first finger had become enlarged. Regarding the proximal and distal interphalangeal joints, there was low signal intensity on T1-weighted imaging (T1WI) and high signal intensity on T2-weighted imaging (T2WI), short-tau inversion-recovery (STIR) imaging, and gradient echo (GE) imaging (Fig. 2). There was no erosion or joint space narrowing. In contrast, the CT scan on day 21, after four cycles of pembrolizumab, showed that the right upper lobe tumor and the right adrenal gland metastasis had shrunk [partial response based on Response Evaluation Criteria in Solid Tumor (RECIST) guidelines v1.1] (Fig. 1B and E). On day 1, after five cycles of pembrolizumab, the patient had pain and stiffness in the left third, fourth, and fifth fingers and the left wrist when initiating movement. In addition, he had pain in his right thumb, bilateral knees, and ankles.

Biological tests ruled out infectious agents, venous thrombosis, and rheumatoid arthritis. Based on the clinical, serologic, and imaging results, we diagnosed him with tenosynovitis. On day 1, after 5 cycles of pembrolizumab, we pre-

Table 1. Summary of Laboratory Data.

Hematology		Creatinine (mg/dL)	0.74
White blood cell (/μL)	11,300	Glucose (mg/dL)	113
Neutropil (%)	78	Sodium (mmol/L)	143
Eosinophil (%)	1	Potassium (mmol/L)	3.9
Basophil (%)	1	Chloride (mmol/L)	105
Monocyte (%)	6	Corrected calcium (mmol/L)	9.5
Lymphocyte (%)	14	Serological examination	
Red blood cell (/μL)	352×10^4	C-reactive protein (mg/dL)	3.16
Hemoglobin (g/dL)	12	erythrocyte sedimentation rate (mm/h)	21
Hematocrit (%)	35.6	Antinuclear antibody	80
Platelet (/μL)	214×10^3	Rheumatoid factor (IU/mL)	<5
Biochemistry		anti-cyclic citrullinated peptide antibodies (U/mL)	0.6
Aspartate transaminase (U/L)	22	anti-ribonucleoprotein antibodies (U/mL)	3.6
Alanine transaminase (U/L)	18	anti-Smith antibodies (U/mL)	0.8
γ-glutamyl transpeptidase (U/L)	82	anti-Sjögren's syndrome-related antigen-A antibodies (U/mL)	0.3
Alkaline phosphatase (U/L)	470	anti-dsDNA antibodies (U/mL)	3.4
Lactate dehydrogenase isozyme (IU/L)	160	anti-ssDNA antibodies (U/mL)	7.8
Total bilirubin (mg/dL)	0.5	proteinase 3-anti-neutrophil cytoplasmic antibody (U/mL)	<0.1
Blood urea nitrogen (mg/dL)	14	myeloperoxidase-anti-neutrophil cytoplasmic antibody (U/mL)	<0.1

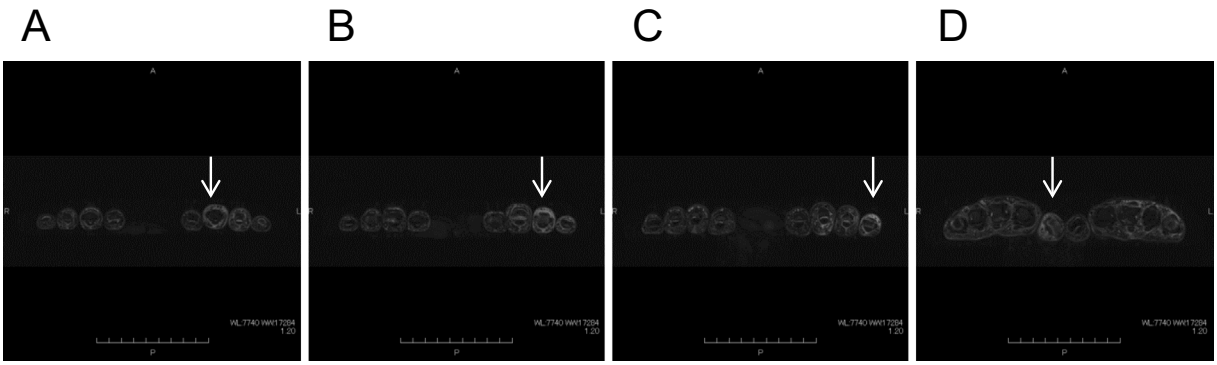

Figure 2. Short-tau inversion-recovery (STIR) magnetic resonance imaging (MRI) showed high-intensity signals for the tenosynovium of the left third (A, arrow), fourth (B, arrow), and fifth fingers (C, arrow) and the right first finger (D, arrow).

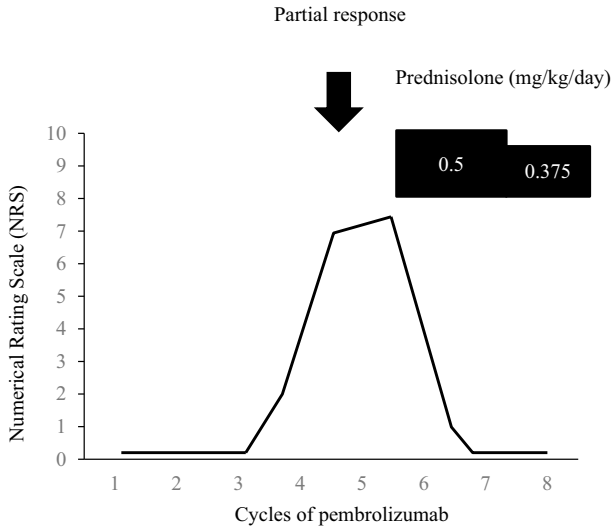

Figure 3. The clinical course of the patient.

scribed oral prednisolone (0.5 mg/kg/day, amounting to 20 mg/day), while pembrolizumab was continued. After prednisolone administration, the symptoms were relieved within 2 weeks (Fig. 3). At 5 weeks after starting prednisolone, the prednisolone dose was tapered (0.375 mg/kg/day) because the patient developed significant facial swelling known as "moon face". On day 21, after eight cycles of pembrolizumab, the tumor was continuing to shrink, and the partial response was continuing.

Discussion

To our knowledge, this is a first case of tenosynovitis shown to be controlled with systemic corticosteroid treatment administered with continuous ICI use.

External stimuli over-activate innate immune cells, including neutrophils, macrophages, and γδT cells, and induce the production of pro-inflammatory cytokines, leading to tenosynovitis (7) and the systemic overexpression of interleukin

Table 2. Summary of Characteristics of the Patients with Tenosynovitis after Immune Checkpoint Inhibitor for Cancer.

Case	Reference	Sex	Age, years	Cancer type	ICI	Duration from ICI to tenosynovitis, months	Site	Treatment	Tenosynovitis outcome	Continuation or recommence of ICI	Duration of ICI after tenosynovitis, months
1	(11)	Male	60	Melanoma	PD-1	19	Wrist and forearm	Pamidronate 90 mg, salazopyrin 2 g/d and opioid	Improved	Yes	20
2	(11)	Female	68	Melanoma	PD-1	12	Wrist, forearm, and knee	Naproxen 500 mg bid, hydroxychloroquine 200 mg/d, paracetamol 1g q6h and opioid	Not resolved to grade 1 or less	No	0
3	(6)	Female	46	Melanoma	PD-1 and CTLA-4	13	Wrists	Infliximab and etanercept	Improved	Not available	Not available
4	(13)	Male	57	NSCLC	PD-1 and CTLA-4	11	Wrists	Prednisone 10 mg/d and tendon sheath injection	Not resolved until stopping ICI	Yes	9
5	(13)	Female	74	Melanoma	PD-1	4	Wrist and shoulder	Prednisone 10 mg/d and intraarticular steroid injection	Not resolved until stopping ICI	Yes	10
6	(14)	Female	56	NSCLC	PD-1	5	MCPs and wrists	Opioids	Improved within 6 months	Not available	Not available
7	(14)	Male	61	NSCLC	PD-1	1	Fingers	NSAIDs	Improved within 6 months	Not available	Not available
9	Present case	Male	51	NSCLC	PD-1	1	Fingers	Prednisone 20 mg/d	Improved within 2 weeks	Yes	3

ICI: immune checkpoint inhibitor, PD-1: programmed cell death 1, CTLA-4: cytotoxic T-lymphocyte-associated protein 4, NSCLC: non-small cell lung cancer, MCP: metacarpophalangeal, NSAIDs: non-steroidal anti-inflammatory drugs, PD-L1: programmed cell death 1 ligand

(IL)-23 in B10. RIII mice shows severe paw swelling (8). SKG mice that have a gain-of-function mutation in T cell receptor protein ZAP 70 spontaneously develop tail vertebral disease as well as autoimmune inflammatory arthritis with high titers of autoimmune antibodies (9, 10). This mouse model suggests the crucial role of the IL-17-IL23 axis in the pathogenesis of tenosynovitis. This immune pathway in the pathogenesis of tenosynovitis might be affected by ICI treatment.

A few case reports of tenosynovitis caused by ICIs have been reported (11-14). Although corticosteroid injection is generally used as the primary treatment modality in patients with tenosynovitis (15), as summarized in Table 2, oral corticosteroid is also effective for the improvement of tenosynovitis. In the current case, 20 mg/day prednisone improved the symptoms faster than other drugs, such as sul-

fasalazine (Salazopyrin), non-steroidal anti-inflammatory drugs (NSAIDs), and opioids.

Arbour et al. reported that, in 2 independent cohorts of NSCLC patients, baseline corticosteroid treatment (involving ≥10 mg/day prednisone equivalent), most commonly for dyspnea (33%), fatigue (21%), or brain metastases (19%), was associated with a significantly decreased progression-free survival and overall survival (16). In addition, a multivariate analysis of the pooled population confirmed that baseline corticosteroid treatment was significantly associated with a decreased progression-free survival (hazard ratio, 1.3; p=0.03) and overall survival (hazard ratio, 1.7; p< 0.001) (16). They also reported that six patients who experienced a partial response to ICI therapy in combination with corticosteroid had nothing in common other than a PS of 1. In general, corticosteroid tends to be prescribed to patients who have a PS ≥2 and a poor prognosis, but the confounding factors of that multivariate analysis (smoking history, PS, brain metastasis) were not clearly indicated. In addition, the results of the univariate analysis are also not shown. As such, a PS ≥2 might be a fundamental prognostic indicator, while there may also be other factors influencing the results.

Whether or not corticosteroid at the beginning of ICI administration directly affects the outcome of ICI treatment remains controversial. Indeed, corticosteroids are also used for the management of irAEs, and corticosteroid use in this context has not been associated with a decreased efficacy of ICIs in either melanoma (17, 18) or NSCLC (19). In addition, previous studies have shown that resuming ICIs did not affect the survival after irAE-related cessation, especially in cases with a partial response (20, 21). These findings suggest that, if irAEs occur, there is no need for responders to continue ICI use; however, continuing ICIs is still a viable treatment option in cases with stable disease.

Conclusion

In this case report, we described for the first time the successful management of ICI-induced tenosynovitis while continuing ICI use, suggesting that 0.5 mg/kg/day systemic prednisone might be effective for treating tenosynovitis without requiring ICI cessation.

The authors state that they have no Conflict of Interest (COI).

References

1. Haanen JB, Thienen H, Blank CU. Toxicity patterns with immunomodulating antibodies and their combinations. Semin Oncol **42**: 423-428, 2015.
2. Good-Jacobson KL, Szumilas CG, Chen L, Sharpe AH, Tomayko MM, Shlomchik MJ. PD-1 regulates germinal center B cell survival and the formation and affinity of long-lived plasma cells. Nat Immunol **11**: 535-542, 2010.
3. Zitvogel L, Kroemer G. Targeting PD-1/PD-L1 interactions for cancer immunotherapy. Oncoimmunology **1**: 1223-1225, 2012.
4. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med **6**: 230ra245, 2014.
5. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med **378**: 158-168, 2018.
6. Cappelli LC, Gutierrez AK, Bingham CO, Shah AA. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. Arthritis Care Res (Hoboken) **69**: 1751-1763, 2017.
7. McGonagle D, Tan AL, Watad A, Helliwell P. Pathophysiology, assessment and treatment of psoriatic dactylitis. Nat Rev Rheumatol **15**: 113-122, 2019.
8. Sherlock JP, Joyce-Shaikh B, Turner SP, et al. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4-CD8- entheseal resident T cells. Nat Med **18**: 1069-1076, 2012.
9. Sakaguchi N, Takahashi T, Hata H, et al. Altered thymic T-cell selection due to a mutation of the ZAP-70 gene causes autoimmune arthritis in mice. Nature **426**: 454-460, 2003.
10. Vieira-Sousa E, van Duivenvoorde LM, Fonseca JE, Lories RJ, Baeten DL. Review: animal models as a tool to dissect pivotal pathways driving spondyloarthritis. Arthritis Rheumatol **67**: 2813-2827, 2015.
11. Chan MM, Kefford RF, Carlino M, Clements A, Manolios N. Arthritis and tenosynovitis associated with the anti-PD1 antibody pembrolizumab in metastatic melanoma. J Immunother **38**: 37-39, 2015.
12. Cappelli LC, Gutierrez AK, Baer AN, et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. Ann Rheum Dis **76**: 43-50, 2017.
13. Smith MH, Bass AR. Arthritis after cancer immunotherapy: symptom duration and treatment response. Arthritis Care Res (Hoboken) **71**: 362-366, 2019.
14. Inamo J, Kaneko Y, Takeuchi T. Inflammatory tenosynovitis and enthesitis induced by immune checkpoint inhibitor treatment. Clin Rheumatol **37**: 1107-1110, 2018.
15. Blood TD, Morrell NT, Weiss AP. Tenosynovitis of the hand and wrist: a critical analysis review. JBJS Rev 4, 2016.
16. Arbour KC, Mezquita L, Long N, et al. Impact of baseline steroids on efficacy of programmed cell death-1 and programmed death-ligand 1 blockade in patients with non-small-cell lung cancer. J Clin Oncol **36**: 2872-2878, 2018.
17. Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment gailure in patients with melanoma treated with ipilimumab at memorial sloan kettering cancer center. J Clin Oncol **33**: 3193-3198, 2015.
18. Weber JS, Larkin JMG, Schadendorf D, et al. Management of gastrointestinal (GI) toxicity associated with nivolumab (NIVO) plus ipilimumab (IPI) or IPI alone in phase II and III trials in advanced melanoma (MEL). J Clin Oncol **35**: 9523, 2017.
19. Santini FC, Rizvi H, Wilkins O, et al. Safety of retreatment with immunotherapy after immune-related toxicity in patients with lung cancers treated with anti-PD(L)-1 therapy. J Clin Oncol **35**: 9012, 2017.
20. Tachihara M, Negoro S, Inoue T, et al. Efficacy of anti-PD-1/PD-L1 antibodies after discontinuation due to adverse events in non-small cell lung cancer patients (HANSHIN 0316). BMC Cancer **18**: 946, 2018.
21. Santini FC, Rizvi H, Plodkowski AJ, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. Cancer Immunol Res **6**: 1093-1099, 2018.