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/m²) on day 1 and TS-1 (120 mg/body) on days 1-21

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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, antiribonucleoprotein (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-

![Figure 1](image-url)

**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).
**Table 1. Summary of Laboratory Data.**

| Test                        | Units   | Value  |
|-----------------------------|---------|--------|
| Hematocrit (%)              |         | 35.6   |
| Red blood cell (× 10^6/L)   |         | 352    |
| Hemoglobin (g/dL)           |         | 12     |
| Platelet (× 10^3/L)         |         | 214    |
| Eosinophil (%)              |         | 1      |
| Neutrophil (%)              |         | 78     |
| Lymphocyte (%)              |         | 14     |
| Hemoglobin (g/dL)           |         | 12     |
| C-reactive protein (mg/dL)  |         | 3.16   |
| Aspartate transaminase (U/L)|         | 22     |
| Glutamate dehydrogenase isozyme (IU/L) | 160 |
| Alkaline phosphatase (U/L)  |         | 470    |
| Lactate dehydrogenase isozyme (IU/L) | 160 |
| Partial response            |         | 3.16   |

**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...
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 corticosteroids are also effective for the improvement of tenosynovitis. In the current case, 20 mg/day prednisone improved the symptoms faster than other drugs, such as sulfa-drugs and non-steroidal anti-inflammatory drugs (NSAIDs). This immune pathway in the pathogenesis of tenosynovitis might be affected by ICI treatment.

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 1 g q6h and opioid | Not resolved to grade 1 or less | No                               | 0                                        |
| 3    | (6)       | Female | 46        | Melanoma    | PD-1 and CTLA-4 | 13                                         | Wrist                 | Infliximab and etanercept | Improved             | Not available                     | Not available                          |
| 4    | (13)      | Male  | 57         | NSCLC       | PD-1 and CTLA-4 | 11                                         | Wrist                 | Prednisone 10 mg/d and intraarticular steroid 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   | 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.
Treatment options in cases with stable disease.

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 patients 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).

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