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Immune checkpoint inhibitor-associated arthritis in advanced pulmonary adenocarcinoma: A case report

Yang Y *et al.* Severe ICIs-associated arthritis

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Abstract

BACKGROUND

With the wide application of immune checkpoint inhibitors (ICIs) in cancer treatment, immune-related adverse events occur frequently, involving almost all organs and systems. The incidence of ICI-associated arthritis (IA) is unknown. In most cases, IA is not serious and non-lethal. Higher checkpoint inhibitor arthritis disease activity may be associated with cancer progression. Here, we report a severe case of IA with high arthritis disease activity in advanced pulmonary adenocarcinoma, causing permanent withdrawal of pembrolizumab but remained in complete remission (CR) 20 mo after the development of IA.

CASE SUMMARY

An 81-year-old smoking male was admitted to our hospital because of left chest pain for 9 mo. He was finally diagnosed with advanced pulmonary adenocarcinoma, with programmed cell death 1 Ligand 1 expression of 70%. The patient responded to pembrolizumab treatment and achieved CR, but IA occurred after the 5th cycle of pembrolizumab administration. Although non-steroidal anti-inflammatory drugs and disease-modifying anti-rheumatic drugs were prescribed, arthralgia and joint swelling occurred. The symptoms of arthritis were further aggravated when immunotherapy was given again after short-term withdrawal. Clinical Disease Activity Index (CDAI) score, a traditional measure of arthritis activity was 43. Intravenous methylprednisolone was prescribed at 20 mg/d and then tapered over the subsequent 4 wk. The symptoms

of arthritis steadily improved and completely resolved 4 mo after withdrawal of pembrolizumab. A recent follow-up in June 2022 revealed satisfactory clinical recovery of arthritis and the patient remained in CR.

CONCLUSION

Our aim is to highlight that early recognition of IA and appropriate treatment are critical to improving the outcome of both ICI-arthritis and lung cancer.

Key Words: Immune checkpoint inhibitors; Immune checkpoint inhibitor-associated arthritis; Pembrolizumab; Clinical Disease Activity Index

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Core Tip: We report a severe case of immune checkpoint inhibitor-associated arthritis (IA) in advanced pulmonary adenocarcinoma. A recent study suggested that higher checkpoint inhibitor arthritis disease activity may be associated with cancer progression. In our case, Clinical Disease Activity Index (CDAI) score increased as high as 43, but cancer disease remained in complete remission 20 mo after the development of IA. Whether CDAI can be a predictor of disease progression needs to be confirmed in future studies.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have resulted in a marked change in the therapeutic modality of non-small cell lung cancer (NSCLC). However, due to the widespread application of ICIs, immune-related adverse events (irAEs) involving all organs and systems may occur due to immunological enhancement. ICI-associated arthritis (IA) is rarely reported as case reports or in randomized controlled clinical studies. The reason for this may be that the symptoms such as joint pain are usually not

serious and are non-fatal. Therefore, it does not attract enough attention from patients and clinicians, and the diagnosis is easily missed. In addition, some patients have osteoarthritis, which is easily confused with immune-related arthritis symptoms by patients themselves. With the wide application of immunotherapy in the field of cancer, we have reason to believe that many more cases of IA will be reported. In most cases, IA is mild or moderate and non-fatal. However, it can affect the life quality of patients, reduce their confidence in disease treatment, interrupt the treatment plan, and finally affect the treatment effect or survival. Prompt recognition and appropriate treatment are critical to improving the outcome of IA, which can be realized if physicians are familiar with the clinical manifestations and therapeutic measures. However, in clinical practice, sometimes the diagnosis of IA is difficult or delayed.

² Herein, we report a case of IA in a patient with advanced lung adenocarcinoma treated with pembrolizumab. The patient achieved complete remission (CR), but had to permanently discontinue pembrolizumab after 10 treatment cycles due to severe IA. A recent study found that ⁶ Clinical Disease Activity Index (CDAI) may be a predictor of disease progression^[1]. Our patient had a high CDAI score of 43, but remained in CR 20 mo after the development of IA. Thus, whether the CDAI can be used a predictor of disease progression requires confirmation in future studies.

CASE PRESENTATION

Chief complaints

An 81-year-old smoking male, complained of bilateral wrist, knee and ankle pain (grade 1) with mild edema (grade 1) after the 5th cycle of pembrolizumab administration for lung cancer.

History of present illness

⁴ The patient was admitted to the Second Affiliated Hospital, Zhejiang University School of Medicine on May 31, 2020 due to left chest pain for 9 mo. Diffuse thickening of the left pleura and interlobar pleura was found on a chest computed tomography (CT) scan

(Figure 1A). CT-guided lung puncture was performed and pathology revealed adenocarcinoma of the lung, with ⁵ programmed cell death 1 Ligand 1 (PD-L1) expression of 70%. He was finally diagnosed with NSCLC (stage IV, adenocarcinoma) at our hospital. Lung cancer related genes including *EGFR*, *ALK* and *ROS1* were negative. The patient was treated with first-line pembrolizumab monotherapy at a standard dosage of 2 mg/kg every 3 wk. From June 2020 to August 2020, the patient received 3 cycles of pembrolizumab. His left chest pain was relieved and chest CT scanning revealed ⁸ stable disease (Figure 1B). The patient complained of mild weakness, which was grade 1 according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0). Another 2 cycles of pembrolizumab were administered. Left chest pain disappeared and he achieved CR (Figure 1C).

History of past illness

The patient had a history of lumbar 2 vertebral compression fractures and recovered well after surgical treatment.

Personal and family history

The patient had smoked for more than 50 years, 20 cigarettes/d, and stopped smoking following the diagnosis of lung cancer. He had a history of penicillin anaphylaxis. The patient had no previous rheumatoid arthritis or rheumatic immune system diseases.

Physical examination

Bilateral wrist, knee and ankle showed slightly depressed edema with pain. Functional limitation was reported and symptoms did not abate after mobilization.

Laboratory examinations

⁷ Anti-cyclic citrullinated peptide antibody, rheumatoid factor, antinuclear antibody, anti-neutrophil cytoplasmic antibodies, hepatic ¹ and renal function analysis were

performed and were found to be normal. ¹ C-reactive protein level was 18.5 mg/L, and the erythrocyte sedimentation rate was 44 mm/h. The CDAI score was 43.

Imaging examinations

X-ray of the hands was normal (Figure 2).

FINAL DIAGNOSIS

IA and advanced lung adenocarcinoma.

TREATMENT

¹² Non-steroidal anti-inflammatory drugs (NSAIDs) were administered and treatment with pembrolizumab was continued. However, the manifestations of arthritis persisted defined as arthralgia (grade 1) and swollen joints (grade 2). After consultation with a Rheumatic immunologist, diuretics and disease modifying anti-rheumatic drugs (DMARDs) were prescribed. Pembrolizumab was discontinued temporarily. When IA returned to grade 1, pembrolizumab therapy was continued. After the 10th cycle of pembrolizumab administration, pain in the fingers, wrists and ankles increased (grade 3). The life quality of the patient was seriously affected due to joint swelling and pain. In addition, the patient felt anxious and fearful of lung cancer progression. Intravenous methylprednisolone at 20 mg/d was prescribed and then tapered over the subsequent 4 wk.

OUTCOME AND FOLLOW-UP

The symptoms of arthritis steadily improved after steroids treatment and completely resolved 4 mo after withdrawal of immunotherapy. A recent follow-up in June 2022 revealed satisfactory clinical recovery of arthritis and lung cancer was still in CR as shown by CT scanning.

DISCUSSION

ICIs have been confirmed to be an effective treatment modality and are widely used for the treatment of NSCLC. With increasing use of ICIs, a large spectrum of immune side effects, described as irAEs have emerged. Dermatologic, gastrointestinal, pulmonary, cardiac, endocrine, skin, and rheumatologic systems, and almost all organs of the body can be affected^[2,3]. Unlike irAEs in other systems, rheumatic irAEs are mainly reported in case reports, and are usually ignored in the clinic both by patients and physicians^[4]. Arthralgia/arthritis and myalgia/myositis are the most frequently reported rheumatic irAEs^[5]. A single-center prospective cohort study reported the incidence of IA to be 3.8%^[6].

The most frequent clinical manifestations of IA are similar to rheumatoid arthritis^[7,8]. As in our case, IA is characterized by small-joint involvement of the metacarpophalangeal joint, proximal interphalangeal joint, the wrist, knee and feet^[4]. ¹¹ Rheumatoid factor and anti-citrullinated peptide antibody levels are usually normal^[9]. Another relatively rare phenotype closely resembles spinal arthritis, which is characterized by large joint involvement, such as inflammatory back pain, adhesion point inflammation, and phalangitis^[10-12]. Unlike spinal arthritis, human leukocyte antigen-B27 was negative in most of these patients^[13].

The time to arthritis occurrence after administration of ICIs varies, ranging from 2 mo to 24 mo, and symptoms may persist for more than one year^[14-18], regardless of whether the ICI is discontinued^[1]. The persistence of IA demonstrated in our study lasted 9 mo (6 mo after pembrolizumab discontinuation), which was consistent with other reported cases^[19,20].

The treatment principles ¹ recommended by the National Comprehensive Cancer Network, European Society for Medical Oncology, and Chinese Society of Clinical Oncology guidelines are basically the same. Therapeutic drugs mainly include NSAIDs, glucocorticoids, and DMARDs. For patients above the G2 Level, most require systemic corticosteroids in addition to DMARDs. A large single-institution retrospective study found that 37% of patients with musculoskeletal irAEs needed either higher prednisone doses or low-dose maintenance therapy. Several patients even received steroids for

more than 1 year^[21]. If symptoms do not improve after initial treatment, consultation with rheumatology experts is necessary for disease control. Some patients even require more than one type of immunosuppressive therapy.

IA patients rarely require hospitalization and most cases are defined as grade 1 or 2. However, some patients reported significant impairment both in function and emotion, even when characterized as low grade^[1,21]. Thus, in addition to the CTCAE grade, the CDAI, a traditional measure of arthritis activity is recommended to assess IA^[1]. It is interesting that increased CDAI may be related to cancer progression^[1]. However, in our case, the CDAI increased during the treatment of IA, but the patient remained in CR (Figure 3). Whether the CDAI can be used as a predictor of disease progression requires confirmation in future studies.

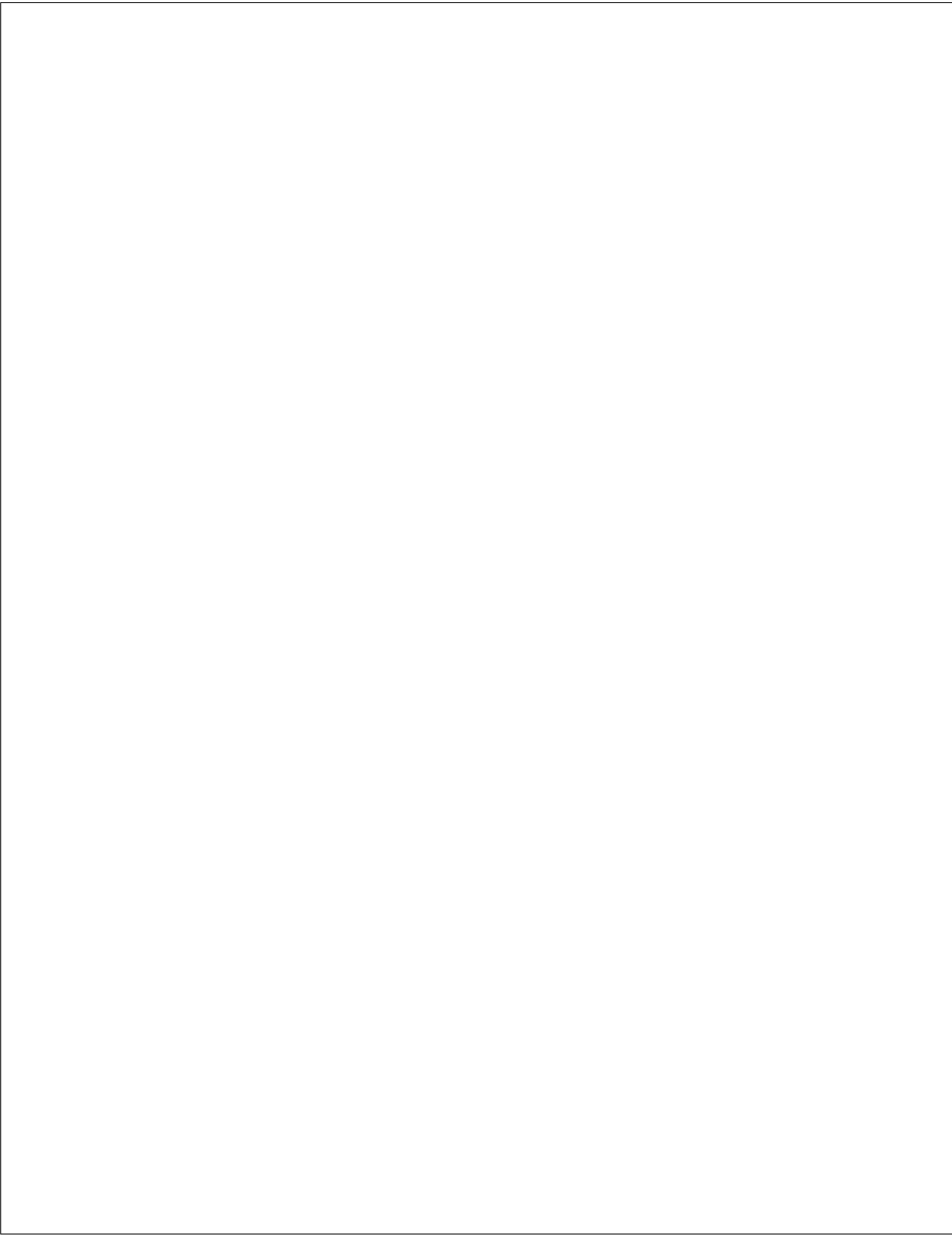
CONCLUSION

Immunotherapy has opened a new chapter ² in the treatment of advanced NSCLC. However, with the wide application of ICIs, more and more irAEs have been reported. Rheumatic arthritis/myalgia has rarely been reported in previous clinical trials. However, the actual incidence in the real world may be much higher than the data shown in current clinical studies. During the course of immunotherapy, clinicians should pay attention to symptoms of arthritis, distinguish IA from traditional rheumatic diseases and provide appropriate treatment. In addition to the CTCAE grade, the CDAI is recommended to assess IA. A recent study found that the CDAI may be a predictor of cancer disease progression, which, needs to be confirmed in future studies. Early recognition of IA and appropriate treatment are critical to improving the outcome of both IA and lung cancer.

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We thank the patient for providing consent for the publication of this case.

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