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CASE REPORT

Pembrolizumab-Induced Seronegative Arthritis and Fasciitis in a Patient with Lung Adenocarcinoma

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ARTICLE HISTORY

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Abstract: ***Background*:** Immune checkpoint inhibitors (CPIs) are new promising anti-cancer drugs that block negative costimulation of T-cells leading to an enhanced anti-tumor immune response. Pembrolizumab, an a monoclonal antibody, targeting the programmed cell death protein 1 (PD-1) pathway. CPIs have been associated with a number of immune-related adverse events (AEs), including musculoskeletal and rheumatic disease.

***Objective*:** To present a case with lung adenocarcinoma treated with pembrolizumab, which developed inflammatory arthritis and fasciitis.

***Case Report*:** A 73-year-old male patient was referred to the rheumatology outpatient clinic with complaints of pain in the pretibial area, pain and swelling in both ankles joints and the right first metacarpophalangeal (MCP) joint. Three months ago he had diagnosed with lung adenocarcinoma and pembrolizumab was started. Locomotor system complaints were started after receiving two infusions of pembrolizumab. Physical examination revealed both ankle arthritis, mild edema in the pretibial region, tenderness in the muscles and arthritis in the right first MCP joint. Laboratory examinations showed mild acute phase reactants elevation. Lower extremity MRI showed diffuse edema in both gastrocnemius muscle and fascia, compatible with fasciitis. Pembrolizumab-related fasciitis and seronegative arthritis were diagnosed. Low dose corticosteroid was started and a significant regression was observed in the patient's complaints.

***Conclusion*:** Inflammatory myositis with fasciitis and inflammatory arthritis in lower extremities appears to be a new adverse effect of pembrolizumab therapy.

Keywords: Immune checkpoint inhibitor, pembrolizumab, lung adenocarcinoma, rheumatic feature, fasciitis, arthritis.

1. INTRODUCTION

Immune Checkpoint Inhibitors (CPIs) are revolutionized drugs for cancer immunotherapy in the past years. The mechanism of action of CPIs is enhancing the self-immune response against tumour cells *via* inactivation of T-cells [1]. CPIs have significantly improved survival outcomes in metastatic melanoma, selected lymphomas and advanced Non-Small Cell Lung Cancer (NSCLC) [2]. Two PD-1, nivol-umab and pembrolizumab are two programmed cell death protein (PD-1) targeted monoclonal antibodies which have been approved in advanced melanoma management and in NSCLC [3]. CPIs may inbalancd the immune system resulting in some side effects, called immune-related adverse events (irAEs). Rheumatic diseases due to CPIs are also reported in the literature [4]. The spectrum of rheumaticmanifestations is quite wide; the most common are arthralgia/arthritis, myalgia/myositis, myalgia/myositis, polymyalgia rheumatica, lupus, Rheumatoid Arthritis (RA), Sjögren's syndrome (Table **1**). At the same time, these drugs can also cause an exacerbation of the known rheumatologic disease. Rheumatolog-

Table 1. CPIs-related rheumatic diseases.

S. No.	Rheumatic Diseases
1.	Arthralgia/ polyarthritis
2.	Systemic lupus erythematosus
3.	Polymyalgia rheumatica/giant cell arteritis
4.	Sicca syndrome/Sjögren's syndrome
5.	Vasculitis
6.	Rheumatoid arthritis
7.	Myalgia/ myositis
8.	Eosinophilic fasciitis
9.	Remitting seronegative symmetrical synovitis with pitting edema
10.	Psoriatic arthritis
11.	Scleroderma
12.	Sarcoidosis

Abbreviations: CPIs- checkpoint inhibitors.

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ic findings due to these drugs should be well known by rheumatologists [5].

Herein, the report of a patient is presented with lung adenocarcinoma treated with pembrolizumab, which developed inflammatory arthritis and fasciitis.

2. CASE PRESENTATION

A 73-year-old male patient was referred to the Rheumatology outpatient clinic with complaints of pain in the pretibial area, pain and swelling in both ankles joints and the right first Metacarpophalangeal (MCP) joint. In her past history, 3 months ago he had applied to physician because of dry cough, malaise and weight loss, and solid mass in the lung were detected on radiologic investigations (thorax CT and PET-CT, Figs. **1** and **2**). Endobronchial Ultranosonography (EBUS) biopsy was performed, and lung adenocarcinoma with nodal metastases was diagnosed on histopathological investigation. Pembrolizumab was started on the patient who applied medical oncology specialist. The patient had good response to pembrolizumab treatment regarding lung adenocarcinoma. Unfortunately, he was referred to the rheumatology clinic with the locomotor system complaints which started after receiving two infusions of pembrolizumab. Physical examination revealed both ankle arthritis, mild edema in the pretibial region, tenderness in the muscles and arthritis in the right first MCP joint. Laboratory examinations showed mild acute phase reactants elevation; Erythrocyte Sedimentation Rate (ESR): 37mm/h(normal 0-20mm/h) C-Reactive Protein (CRP): 13mg/dl(normal 0-5mg/dl). Complete blood count, liver and kidney function tests, routine urinalysis, muscle enzymes were found to be in normal ranges. In serological tests; Rheumatoid Factor (RF), Anti-Nuclear Antibody (ANA), anti-cyclic citrullinated peptide antibody (anti-CCP), Anti-Neutrophil Cytoplasmic Antibody (ANCA), anti-dsDNA were found to be negative. Lower extremity cruris MRI was taken; diffuse edema in both gastrocnemius muscle and fascia, and abnormal facial signal intensity and enhancement were reported; these findings were compatible with fasciitis (Fig. **3**). Degenerative changes were detected in the hands and sacroiliac joint graphy. A primary rheumatic disease was not considered to explain the patient's complaints. Pembrolizumab-related fasciitis and seronegative arthritis were evaluated. Low dose corticosteroid (prednisolone 16mg / day) was started. In the clinical follow-up, a significant regression was observed in the patient's complaints. The general condition of the patient is good, and the follow-up of the rheumatology and oncology outpatient clinic continues.

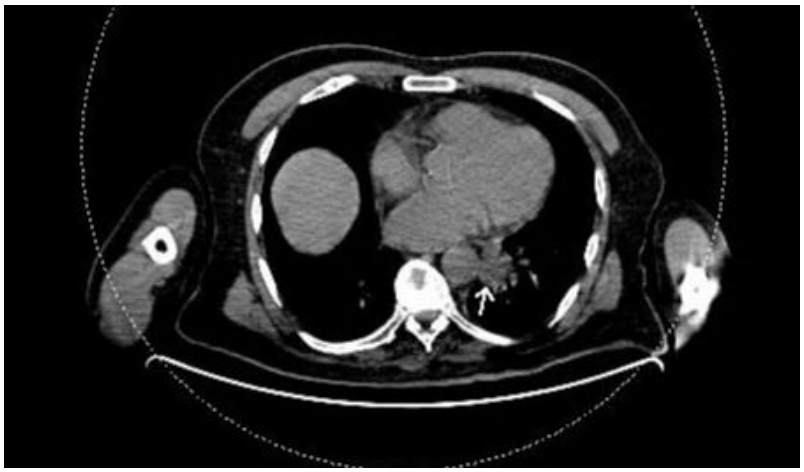

Fig. (1). Torax CT showed solid lung mass.

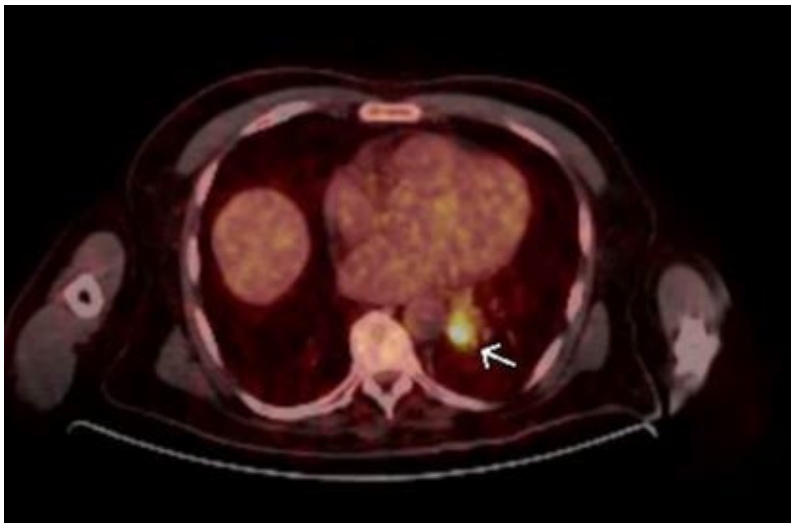

Fig. (2). PET-CT scan of the chest revealing high 18F-fluorodeoxyglucose uptake in a patient with lung adenocarcinoma.

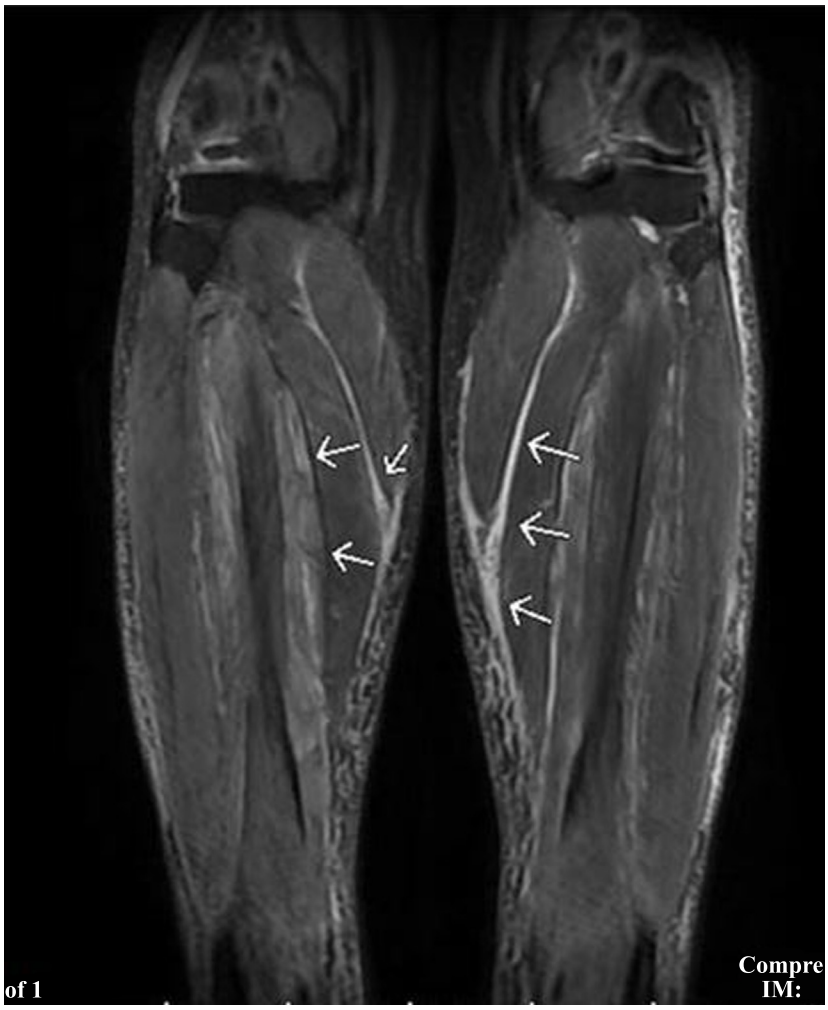

Fig. (3). MRI of both cruris showed oedema of fascia and muscle and abnormal fascial signal intensity and enhancement.

3. DISCUSSION

Herein, the pembrolizumab-related seronegative arthritis and fasciitis in a male patient with lung adenocarcinoma. After treatment with low dose corticosteroid, the patient's complaints were regressed without the need of pembrolizumab discontinuation. There are some anecdotal case reports in the literature about the development of facsiitis/myositis and inflammatory arthritis after CPIs immunotherapy. Sheik *et al*. reported a woman treated with ipilimumab for metastatic melanoma who developed cutaneous findings of dermatomyositis along with proximal muscle weakness and elevated muscle enzymes [6]. The CPIs were stopped and patients were treated with high dose corticosteroids. Khoja *et al*. reported a 51-year-old woman with melanoma who developed eosinophilic fasciitis and cerebral vasculitis due to anti-PD-1 agents [7]. The patient was treated with pulse intravenous corticosteroids and the symptoms were regressed. Bourgeois-Vionnet *et al*. reported nivolumab-induced myositis in a patient with lung adenocarcinoma [8]. The patient improved after nivolumab discontinuation and immunomodulating treatment. Gandiga *et al*. reported pembrolizumab-associated inflammatory myopathy in a patient with malign melanoma [9]. The patient's complaints improved with pulse methylprednisolone and IVIG. Pembrolizumab treatment was discontinued and oral glucocorticoids and monthly IVIG were maintained but unfortunately, she passed away 2 months later due to progressive melanoma. Narváez *et al*. reported two patients who presented with symptomatic inflammatory myositis with fasciitis in lower extremities who received anti-PD1 drug [10]. In both cases, the immunotherapy was discontinued due to cancer progression, with marked improvement of symptoms after the withdrawal of the treatment. As in our case, the patient's symptoms have been started after the fırst infusion of the anti-PD1 drug. Inflammatory arthritis has been described in some case reports [11]. Naidoo *et al*. reported three major types of CPIs -related inflammatory arthritis [1] polyarticular arthritis involving small and large joints similar to rheumatoid arthritis, [2] reactive arthritis-like syndrome with urethritis, conjunctivitis and oligoarthritis, and [3] large joint predominant seronegative arthritis [12]. Lidar *et al*. investigated the frequency and characteristics of rheumatic diseases in patients treated with CPIs in a large tertiary cancer center in Israel [13]. Rheumatic featured were reported in 14 of 400 patients (3.5%) who had received CPIs. The most common rheumatic manifestation was inflammatory arthritis (85%) for which a clear predisposing factor, such as a personal or family history of psoriasis, a prior episode of uveitis

or ACPA positivity was reported. Pulmonary sarcoidosis and eosinophilic fasciitis were diagnosed in two additional patients. Benfaremo *et al*. reviewing reports of musculoskeletal and rheumatic features were induced by CPIs [14]. Arthralgia and myalgia were the most commonly reported AEs, whereas the prevalence of arthritis, myositis and vasculitis is less common. Other rarely described AEs are sicca syndrome, polymyalgia rheumatica, systemic lupus erythematosus and sarcoidosis. Liew *et al*. investigated the development of rheumatic adverse events following PD-1 inhibitor therapy for cancer at a single center [15]. Rheumatic features were diagnosed in 19 (7.8%) patients, while 12 (5.1%) patients had de novo diagnosis without a pre-existing rheumatic disease and 7 patient had exacerbations of existing disease. Rheumatic manifestations were more common in patients with a good oncological response to therapy. Shafqat *et al*. retrospectively evaluated 157 cancer patients treated with anti-PD-1/PD-L1 therapy, and assess the effect of AEs and corticosteroids on Progression-Free Survival (PFS) [16]. They found that irAEs are associated with improved PFS in those patients which do not appear to be altered by the use of systemic corticosteroids. Characteristics of patients and data on the treatment of CPIs-related rheumatic manifestation are limited in the literature. Liepe *et al*. reported the characteristics and treatment approaches of patients developed rheumatic features after CPIs therapies [17]. Arthritis was described in 14 patients (predominantly male) of whom 7 showed monarthritis, 5 had oligoarthritis and 2 had polyarthritis. Nine patients were treated with systemic and eight patients with intra-articular glucocorticoids. Six patients were given methotrexate resulting in long-term remission. Patients with synovitis were more likely to have good tumour response. The rheumatologic findings associated with CPIs should be treated with a rheumatologist [18]. In general, the musculoskeletal side effects are transient and may regress after stopping CPIs. NSAIDs should be used for the treatment of arthralgia and myalgia. In the presence of inflammatory arthritis, low or medium doses of corticosteroids should be preferred. In addition, high dose corticosteroids should be given in the presence of severe life-threatening organ involvement (lupus nephritis, pneumonitis, refractory polyarthritis, CNS involvement, *etc*. [19]. Immunosuppressive drugs (HQ, MTX, anti-TNF-alpha, anti-IL-6) should be preferred when treatment is unresponsive or as steroid-sparing agents [20].

CONCLUSION

In conclusion, the concomitant development of the inflammatory myositis with fasciitis in lower extremities appears to be a new adverse effect of pembrolizumab therapy. More studies are needed to determine how to control and manage these complications.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

A written informed consent was obtained from the patient for this study.

STANDARD FOR REPORTING

The CARE guidelines and methodologies were followed in this study.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this study are available within the case report.

FUNDING

None.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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Declared none.

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