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Inflammatory polyarthritis induced by nivolumab treatment in a patient with malignant melanoma: A case report

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Abstract

Nivolumab is a monoclonal antibody that inhibits the programmed death ligand 1 from binding with PD-1 and restricts T-cell inactivation against cancer cells. After the introduction of nivolumab, in addition to its known side effects, its relationship with some rheumatic diseases has been reported, but it has not been clearly demonstrated. Here, we presented a case of inflammatory polyarthritis in a patient treated with nivolumab for malignant melanoma. This case resulted from the use of PD-1 blocker; It supports that we should be careful about rare side effects besides causing some adverse events due to autoimmune activation in patients.

Introduction

Monoclonal antibodies against PD-L1 expressed in tumor cells are used in the treatment of malignant melanoma and a number of malignancies.

Advances in immunotherapy are increasingly used to treat advanced malignancies, and this has significantly changed the treatment and prognosis of cancer [1]. Nivolumab, a PD-1 immune checkpoint inhibitor, is a monoclonal antibody approved for use by the Food and Drug Administration (FDA) [2].

The percentage of adverse events with nivolumab has been reported as 10-15%.After the introduction of nivolumab, in addition to its known side effects, its relationship with some rheumatic diseases has been reported, but it has not been clearly demonstrated [3]. We present a patient who received nivolumab treatment for malignant melanoma and developed inflammatory polyarthritis after treatment.

Case Report

Voluntary consent form was obtained from the patient.

A 66 year old female patient was diagnosed with metastatic malignant melanoma in the oncology outpatient clinic and nivolumab treatment was started. Three days after the first infusion, she applied to our rheumatology outpatient clinic with complaints of pain and swelling in her hands and knees. The patient, who was diagnosed with malignant melanoma, had no history of psoriasis in her medical and family history.

On physical examination, bilateral swelling and temperature increase were present in both metacarpophalangeal joints (MCPs), proximal interphalangeal joints (PIPs) and knee joints (Figure 1). The patient's activities were restricted according to the Katz daily living activity scale. Her complaints continued despite taking non-steroidal anti-inflammatory drugs before applying to our outpatient clinic.

In laboratory tests, kidney and liver functions were within the normal range.White blood cells 7800/µL (4.400-11.000), hemoglobin 12.2 g/dL (13.5-17.5), platelets 452.000/µL (150.000- 450.00), C-reactive protein 70 mg/L (0-5) and erythrocyte sedimentation rate 50 mm/h (0-20),uric acid level 4.9 mg/dl (3.5-7.2), antinuclear antibody, anti Sjögren's syndrome antibody A and B, Anti-double stranded DNA, anti-cyclic citrulline peptide an-

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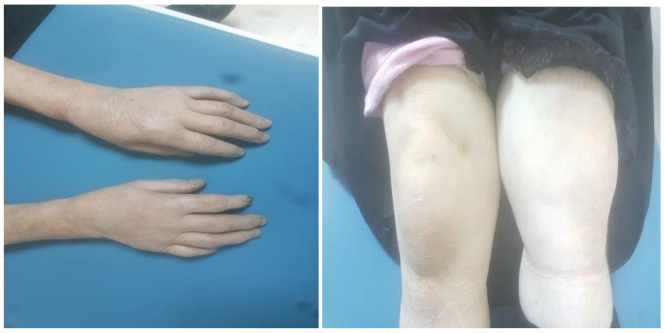

Figure 1. Photos of hand and knees : Symmetrical polyarthritis and swelling of both metacarpophalangeal joints (MCPs), proximal interphalangealjoints (PIPs) and knee joints.

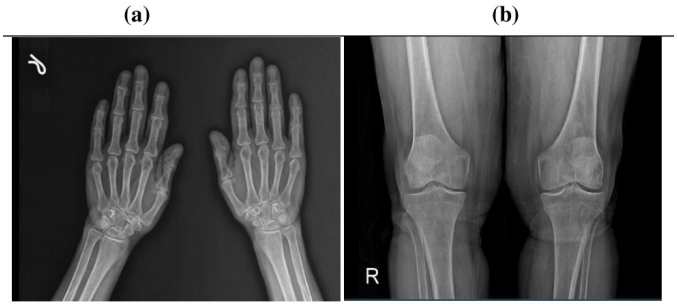

Figure 2. X-ray of the both hand joints and bilateral knee joints. (a) Soft tissue swelling in hand joints. (b) Soft tissue swelling in the knee joints.

tibody, rheumatoid factor, bacteriological and viral tests were negative. Urinalysis was normal. X-rays of both hand joints and bilateral knee joints showed soft tissue swelling. There is an increase in subchondral sclerosis medially in both knees (Figure 2, a,b).Prednisolone 15 mg/day treatment was started with the diagnosis of inflammatory polyarthritis.

After the rheumatological symptoms resolved, steroid treatment was rapidly reduced and the patient was treated with 5 mg prednisolone daily, after which clinical and laboratory response was obtained. No other disease-modifying antirheumatic drugs (DMARDs) could be initiated for the patient whose metastatic melanoma treatment was continued, because it was not approved by oncology. The patient, whose symptoms have improved significantly, continues to be followed up regularly in our clinic.

Discussion

Nivolumab is a monoclonal antibody that inhibits the programmed death ligand 1 from binding with PD-1 and restricts T-cell inactivation against cancer cells. As a result of their use, both inhibition of autoimmunity regulation and unrestricted T cells trigger immune-related adverse events. The frequency of immune-related adverse events depends on the drug used and the type of cancer [3,4]. Immune-related adverse events can develop at any time during treatment with immune checkpoint inhibitors, but most occur in the first 4-6 months of treatment [5].Monoclonal antibody related adverse event in our case occurred 3 days after the first nivolumab infusion. Skin findings and liver enzyme elevation can be observed at a rate of approximately 30%.Severe immune related adverse events such as life threatening colitis, pneumonitis or hepatitis are rare [6,7].The most common musculoskeletal immune related adverse events are arthralgia and myalgia, and they have been reported at rates of up to 40% in clinical studies [8,9].

Our case had multiple joint involvements, but the patient's absence of dry mouth and negative antibodies prevented us from the diagnosis of Sjögren's. Severe immune-mediated arthritis is rare and has been reported in the literature as case series.

Pseudogout was not considered because the patient's complaint started after nivolumab and there was no chondrocalcinosis in the knee radiography. Acute phase elevation, bilateral metacarpophalangeal, proximal interphalangeal and knee joint involvement have excluded us from the diagnosis of gonarthrosis.

Early recognition of rheumatologic immune-related adverse events and their management by rheumatologists play a crucial role in improving outcomes in patients receiving immune checkpoint inhibitors and maintaining immune checkpoint inhibitors for treatment of the underlying malignancy [9].

In the literature, musculoskeletal immune-related adverse events have a heterogeneous phenotypic presentation, mostly symmetrical polyarthritis associated with synovitis.

The clinical course ranges from large joint oligoarthritis, sometimes accompanied by reactive symptoms such as conjunctivitis and urethritis, to polyarthritis involving small joints [8].

Adverse effects such as inflammatory tissue damage have been reported as a result of immune checkpoint inhibitors triggering non-specific T hc activation [12].

In addition, immune checkpoint inhibitor related myositis and fasciitis were also reported among musculoskeletal immune-related adverse events in some published case series [10,11]. In our case, polyarthritis accompanied by large joint involvement was present and it was similar to the literature. Rheumatic autoantibodies such as Rheumatoid factor (RF) and cyclic citrullinated peptide antibody (Anti-CCP) are usually negative in drug-associated arthritis [10,11]. In our case, auto antibodies were found to be negative in line with the literature.

In our patient who received nivolumab treatment for malignant melanoma and developed early side effects, nivulomab treatment was not discontinued and was combined with low- dose glucocorticoids. The glucocorticoid dose was reduced to avoid potential adverse effects on cancer therapy and clinical symptoms improved dramatically with treatment. Side effects induced by nivolumab and improved by steroid therapy suggest that inflammatory polyarthritis symptoms can be treated without discontinuation of the inducer.

Clinicians should be aware of paraneoplastic syndrome in malignancies or rheumatological manifestations that can

be seen as side effects of immune checkpoint inhibitors.

Currently, immune checkpoint inhibitors are promising and are widely used among oncology patients. Therefore, clinicians' awareness of immune-related adverse events becomes more important in the treatment process. This case supports that we should be careful about rare side effects besides the fact that PD-1 blocker use causes some adverse events due to autoimmune activation in patients.

In addition, although there are many similar cases in the literature [4,7], the onset of inflammatory polyarthritis symptoms in the early period after immune checkpoint inhibitors treatment may make the case interesting.

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