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CASE REPORT

Nivolumab-induced new-onset seronegative rheumatoid arthritis in a patient with advanced metastatic melanoma: A case report and literature review

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ABSTRACT

Immune-related adverse events have been reported in patients treated with anti-programmed death-1 receptor drugs such as nivolumab. We present a case of a new-onset seronegative rheumatoid arthritis in a patient with metastatic melanoma treated with nivolumab.

Key words: Immune-related adverse event, immunotherapy, inflammatory arthropathy, nivolumab, rheumatoid arthritis

INTRODUCTION

The immune system's natural capacity to detect and destroy abnormal cells may prevent the development of many cancers. However, cancer cells have immune escape mechanisms to avoid host response.[1] Immunotherapy restores the physiological antitumor response by modifying host response.[2] Nivolumab (Opdivo manufactured by Bristol-Myers Squibb), a human IgG4 monoclonal antibody with high affinity for the programmed death-1 (PD-1) receptor, is the first PD-1 immune checkpoint inhibitor approved by the US Food and Drug Administration (FDA). This drug is the first-line treatment of metastatic melanoma. In addition to melanoma, nivolumab is also used as the second-line treatment for other malignancies such as renal cell carcinoma, squamous cell lung cancer, other advanced nonsmall cell lung cancers (NSCLCs) and lymphoma.[3] Nivolumab inhibits the interaction between PD-1 and programmed death-ligand-1 (PD-L1)[1,2,4,5] thus inhibiting the cancer immune escape pathway[1,2,4,5] and allowing the immune system to recognize and fight cancer cells.

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CASE REPORT

A 65-year-old Caucasian female with Stage IV melanoma (BRAF-positive) was referred to our Rheumatology Clinic at the University of Kansas Medical Center for arthritis evaluation after the initiation of nivolumab treatment. She was initially treated with vemurafenib and ipilimumab. Following progression of the disease with metastatic lesions to multiple organs despite the initial treatments, intravenous nivolumab was given between May 2013 and December 2014 with marked improvement. During treatment with nivolumab, she developed symmetrical polyarthritis with synovitis and swelling of both Metacarpophalangeal Joints (MCPs) and (PIPs) Proximal Interphalangeal Joints bilaterally. No synovitis was appreciated outside of the hands. She reported significant limitations in the daily activities. For example, she complained of morning

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stiffness that lasted for an hour, but she reported that this discomfort progressively improved through the day. Before the referral, she was on both low-dose prednisone and hydroxychloroquine. Both medications were not effective in controlling her arthritis even after 4 weeks of therapy. As a result, she had abruptly stopped these medications. She was not able to recall the initial doses of these medications during our visit. Methotrexate and leflunomide were attempted, and she did not tolerate them either. Laboratory evaluation revealed negative rheumatoid factor (<14 IU/mL) and negative anti-CCP IgG (<17 units/mL). Both C-reactive protein (0.71 mg/L) and SED rate erythrocyte sedimentation rate (9 mm/h) were low. Uric acid was low (3.6 mg/dl). Hand radiographs revealed arthrosis in MCP with subchondral lucencies and sclerosis, joint space narrowing, and right first MCP erosions. Hydroxychloroquine was initiated again at 300 mg daily with good symptom control. The patient also had osteoarthritis and underwent right total hip arthroplasty during the time that she was receiving nivolumab. Given a history of metastatic melanoma, no other disease-modifying antirheumatic drugs (DMARDs) were started. As of April 2017, the patient's symptoms have remained stable and stayed under control. Her symptom has improved remarkably. She still continues to follow-up regularly at our clinic.

DISCUSSION

The PD-1/PD-L1 checkpoint plays an important role as a negative regulator of T-cells, maintaining self-tolerance in the peripheral tissues.[2,4,6] This mechanism also prevents the development of autoimmune reactions[2,7] and controls local inflammation.[4] The PD-1 on T-cells[1,2,4] and PD-L1 on tumor cell interaction decreases the release of T-cell cytokines and evades host immunity in the microenvironment (cancer immune escape phenomena).[1,4] Tumors such as melanoma, breast cancer, urothelial, gastrointestinal, lung, and ovarian cancer express PD-L1 which binds to PD-1 and inhibit the immune system response.

Nivolumab enhances the ability of the immune system to recognize tumors which can lead to loss of self-tolerance and adverse immune effects.[1,5] Immune-related adverse events (IRAEs) can develop at any time, but the majority of those side effects happen in the first 4–6 months of treatment.[1,8] In one study, 17% of metastatic melanoma patients treated with nivolumab had IRAEs.[1] Rash, colitis, pneumonitis, endocrinopathies, nephritis, and hepatitis are the main IRAEs in patients treated with nivolumab as data from the European Medicines Agency and FDA have shown.[8] Other IRAEs associated with anti-PD-1 therapy include dermatitis, autoimmune hemolytic anemia,[9] vitiligo, and thyroiditis. Severe IRAEs such as colitis with intestinal perforation, anaphylactic shock, insulin-dependent diabetes, immune thrombocytopenia, Guillain-Barré syndrome, myocarditis, and acute adrenal insufficiency may occur[1,5] but are rare.

Our patient did not have personal or family history of autoimmune diseases to suggest a predisposition to such IRAEs. Furthermore, the patient developed atypical arthritis associated with erosions. It is unclear if the duration of exposure to such medications contributes to the severity of arthritis. Despite convincing evidence that checkpoint blockade drugs are associated with immune side effects, the role of nivolumab in inflammatory joint disease is unclear. One study relates arthralgia after the use of nivolumab but does not describe inflammatory joint involvement.[1] Recurrent rheumatoid arthritis (RA) in a patient with advanced NSCLC with the previous clinical and laboratory remission was reported 15 days after the first nivolumab infusion.[10] It is known that defects in PD-1/PD-L1 pathway contribute to synovial inflammation in RA patients.[6,11] The studies suggest that the patients with RA have a soluble form of PD-1 (sPD-1) within the synovial fluid that binds competitively to PD-L1. This phenomena creates autoinflammation because the sPD-1 interaction with PD-1 is not able to create immunosuppression as PD-1/PD-L1 pathway does.[6] It is unclear if nivolumab and other anti-PD-1 therapies create similar effects that lead to the above-mentioned IRAEs. The cause of T-cell reactivity is unclear either, and it is certainly different from one patient to the other. Furthermore, different mechanisms have been suggested to cause type 1 diabetes and myocarditis in patient received anti-PD-1.[12]

The use of corticosteroids and discontinuation of the culprit drug are the mainstay treatment of immune-related side effects of PD-1 inhibitors.[1,2,4,7,8] IV steroids should be used in severe IRAEs such as colitis and pneumonitis.[2,8] Skin immune side effects (rash, erythema, urticaria, vitiligo, and toxic epidermal necrolysis) were mostly treated with local and oral steroids.[8] Immunosuppressive agents as tumor necrosis factor (TNF)-inhibitors[2,3] or mycophenolate[2,8] could be considered if corticosteroids are not effective in treating IRAEs. In patients with RA and previously treated or untreated skin cancers (melanoma and nonmelanoma), the American College of Rheumatology recommends the use of DMARDs over TNF-inhibitors due to lower risk of recurrence of skin cancers.[13]

All in all, our patient had features which were consistent RA. Such traits were supported by the presentation of her arthritis and imaging studies. To be more specific, we also reached to the conclusion of seronegative RA by the absence of both rheumatoid factors and anti-CCP IgG serological markers and the exclusion of other joint diseases.

CONCLUSION

This case teaches the significance of immunotherapy and its side effects in the treatment of active cancer. Our case demonstrates that patients can be at risk of acquiring seronegative RA as a deleterious side effect. We stress the need of further studies to better understand the association between the toxicity of immunotherapy and the mechanisms of autoimmune inflammatory arthropathy like RA. In conclusion, we hope that this case helps increase the awareness of immune-based reactions to cancer immunotherapy among physicians and patients. Such discussions can facilitate the prevention of debilitating side-effects and can also translate better patient care in the setting of cancer treatment.

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Conflicts of interest

There are no conflicts of interest.

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