JOURNAL OF CURRENT RESEARCH IN MEDICINE
ISSN 2709-7323
MAR. 2021 VOL. 2, NO. 1

Immunotherapy of Inflammatory Arthritis: A Case Series

April Kelleher
University of Virginia Department of Physical Medicine and Rehabilitation, USA

ABSTRACT

The clinical manifestations and treatment of inflammatory arthritis patients were studied in this case. In immunotherapy, we studied 6 patients with malignant melanoma. All patients presented with pain and swelling of the affected joints. The patients were given a course of oral steroids and symptoms of joint pain and swelling improved. Rheumatic drugs were not initiated because of concerns about the risk of immunosuppression and malignant tumor reactivation. In general, there is a lack of literature and treatment options for immunotherapy in inflammatory arthritis, and more research in this area is needed.

KEYWORDS

Melanoma; Immunotherapy; Arthralgia; Inflammatory arthritis; Intra-Articular injection; Corticosteroid.

1. Introduction

As immunotherapies have expanded for oncologic use, incidence of immunotherapy-associated inflammatory arthritis (IA) in cancer patients has also increased. At our institution, this is particularly true for patients being treated for malignant melanoma. In addition, there is limited literature to guide treatment. Immune checkpoint inhibitors (ICIs) are used to combat tumors by activating T-cells. For instance, ipilimumab, pembrolizumab, and nivolumab are approved by the FDA for treatment of metastatic melanoma. Ipilimumab targets CTLA-4, while pembrolizumab and nivolumab target PD-1. However, increased immune activation can also result in immune-related adverse events (IRAEs), including rash, colitis, pneumonitis, hepatitis, and arthritis.1,2 In this case series, we explore the results of various treatment modalities pertaining to IRAEs, particularly arthralgias.

2. Case Series

Case 1

A 63-year-old female with a history of malignant melanoma, previously treated with dabrafenib/trametinib and currently with pembrolizumab presented with right knee pain. Her symptoms began in-between infusion treatments. Exam was pertinent for a moderate joint effusion, and tenderness over medial and lateral joint lines with an antalgic gait. X-ray of the right knee showed a moderate joint effusion and moderate tricompartmental degenerative changes. Acetaminophen provided mild symptomatic relief but significant

improvement in pain was noted post right knee intra-articular CSI. Adequate pain relief lasted for 4 months, at which point conservative management with diclofenac gel, ice, and acetaminophen was initiated.

Case 2

A 61-year-old male with a history of malignant melanoma, previously treated with ipilimumab/nivolumab, and currently with nivolumab as a single agent, presented with a six-week history of bilateral knee pain. His pain worsened 1 week after nivolumab infusion, with some improvement prior to the following treatment. Exam was pertinent for bilateral knee effusions and medial and lateral joint line tenderness bilaterally. Bilateral knee x-rays noted mild degenerative changes in the patellofemoral compartment on the left, mild degenerative changes on the right, and moderate to large effusions plus or minus synovitis bilaterally. Initial conservative management included diclofenac gel, ice, and compression stockings which provided mild symptomatic relief. Subsequently, bilateral intra-articular knee CSI were performed which provided significant pain relief.

Case 3

An 84-year-old male with a history of malignant melanoma being treated with pembrolizumab presented with right knee pain. On presentation, he complained of swelling and knee pain. He had an intra-articular corticosteroid injection prior to presentation with some improvement. Additionally, he had completed a 2-week course of oral dexamethasone for brain metastases. Exam was pertinent for mild effusion, and joint line tenderness. X-ray of his right knee demonstrated moderate tricompartmental changes, most severe in the patellofemoral compartment and a mild joint effusion. His treatment consisted of gait training with PT, diclofenac gel/ ice/acetaminophen, and a R knee intra-articular CSI which yielded improvement in his pain level. Patient was deceased prior to subsequent follow-up.

Case 4

A 77-year-old female with a history of malignant melanoma, previously treated with pembrolizumab/dabrafenib/trametinib, and currently binimetinib/encorafenib, presented with bilateral knee pain and swelling. She was on a prednisone taper on presentation. Patient complained of pain with ambulation. On exam, bilateral effusions and joint line tenderness were noted. Bilateral knee CT showed tricompartmental degenerative changes in both knees. Her pain levels increased while prednisone was tapered, so the dosage was up-titrated. In addition, bilateral knee CSI were performed with significant improvement in pain level overall.

Case 5

A 61-year-old female with a history of malignant melanoma, previously on ipilimumab/nivolumab, and currently on pembrolizumab/prednisone presented with right knee pain and swelling. On presentation, she had elevated temperature, and was on a steroid taper. Physical exam was notable for large effusion with mild erythema and warmth, joint line tenderness, and restriction in flexion and extension. She was initially sent to the ED for evaluation for septic arthritis, which was later ruled out. Right knee MRI showed diffuse high-grade chondral loss and fissuring without focal defect. She received two rounds of R knee CSI as well as up-titration of oral prednisone which resulted in improvement in pain level.

Case 6

A 59-year-old male with a history of malignant melanoma on ipilimumab/nivolumab presented with left knee swelling. He had mild chronic knee pain prior to starting ipilimumab/ nivolumab. Exam was notable for

effusion and medial and lateral joint line tenderness. Left knee x-ray noted advanced tricompartmental osteoarthritis with chondro-calcification in the lateral joint space as well as a suprapatellar effusion. L knee CSI was performed and near complete resolution of his pain was noted one week later.

3. Results

The following table organizes each case with respect to each patient's immune checkpoint inhibitor(s) induced inflammatory arthropathy. The treatment modalities implemented for each case are then listed as well as the symptomatic outcomes of the treatment plans.

4. Discussion

The above six cases were studied. All patients presented with knee pain and/or effusion, after initiation of immunotherapy. All patients had improvement in symptoms with oral or intra-articular steroids. There is currently no standard of treatment for this side effect of immunotherapy. Rheumatologic agents have been suggested, however were not started in the above cases due to concern for immunosuppression and risk of reactivation of malignancy.

A 2017 systematic review of literature on musculoskeletal and rheumatic IRAEs reported that arthralgia and myalgias were common complaints in clinical trials, but the prevalence of inflammatory arthritis and rheumatic IRAEs was not well described in clinical trials.3 Cappelli et al. (2017) reported 9 patients from 2012-2016 with new IA in the setting of ipilimumab and/or nivolumab treatment for solid tumors, 4 of whom had synovitis on imaging and 4 with inflammatory synovial fluid.4 Belkhir et al. (2017) reported rheumatoid arthritis development in 6 patients at a median of one month after receiving ICI therapy for cancer (all positive for anti-CCP antibodies and four positive for RF), none with preexisting rheumatic or autoimmune disease.5 Prompt diagnosis of IA is crucial to preventing long-term disability and joint deformity or erosion. Clues to diagnosis include morning stiffness lasting more than 30-60 minutes and joint swelling/warmth/erythema. Naidoo et al. (2017) proposed an algorithm for the diagnosis and management of ICI-related IA. It provides guidance for the clinical assessment of joint pain, swelling, and inflammatory symptoms, as well as suggested laboratory tests and imaging. Depending on the clinical grade of the IA, treatment may involve NSAIDs, intra-articular steroids, prednisone, and/or immunosuppressive agents (such as methotrexate or TNF-inhibitors).6 Grading is based on the Common Terminology for Adverse Events (CTCAE), with grade 3+ considered to be severe.

IA has been reported to persist over a year after ICIs are colitis, which tends to be self-limiting after treatment with corticosteroids or TNF-inhibitor infliximab.1 A retrospective study at Memorial Sloan Kettering Cancer Center reported that the mean time to resolution of joint symptoms after the last dose of ICI therapy was 9.6 +/- 6.1 months for 6 of 10 patients, with all 10 patients receiving systemic corticosteroids, 3 requiring DMARDs, and 1 requiring infliximab. However, 4 patients continued to be treated for arthritis at the time of last rheumatology follow-up.7

In addition, it is important to consider that patients may have preexisting or undiagnosed autoimmune disease that may be exacerbated or unmasked by ICIs. Johnson et al. (2016) reported 30 patients with preexisting autoimmune disease who were treated with ipilimumab for metastatic melanoma; 27% had exacerbations of their autoimmune disease, 33% had conventional IRAEs, and 20% had partial or complete response to ipilimumab.8 They concluded that ICI therapy can be carefully considered in patients with preexisting autoimmunity, although there is substantial risk of flare and Given the growing use of ICIs to treat malignancies, it is essential to consider the potential adverse effects, including inflammatory arthritis and exacerbation or unmasking of underlying autoimmune disease. Here we presented 6 cases of patients presenting with inflammatory arthritis while on ICI therapy for metastatic melanoma. We observed pre-

existing structural joint damage for all patients who underwent imaging. This observation suggests that the existence of preexisting joint disease may help to inform risk profiles for adverse effects related to immunotherapies.

5. Conclusion

Inflammatory arthritis is an adverse reaction which can be seen in patients who are on immunotherapy. There is limited published literature on this topic and there is no definitive standard of treatment for this disease process. This case series offers potential treatment modalities that yielded promising results for the six patients included in the study. Overall, further research is needed to establish best practice treatment protocols, which would ideally be informed by randomized controlled trials of the various therapy options currently in use.

References

Cappelli LC, Naidoo J, Bingham CO, Shah AA. Inflammatory arthritis due to immune checkpoint inhibitors: challenges in diagnosis and treatment. Immunotherapy. 2017;9(1):5-8. doi:10.2217/imt-2016-0117.

Cappelli LC, Shah AA, Bingham CO. Immune-Related Adverse Effects of Cancer Immunotherapy-Implications for Rheumatology. Rheumatic Disease Clinics of North America. 2017;43(1):65-78. doi:10.1016/j.rdc.2016.09.007.

Cappelli LC, Gutierrez AK, Bingham CO, Shah A. Rheumatic and Musculoskeletal Immune-Related Adverse Events Due to Immune Checkpoint Inhibitors: A Systematic Review of the Literature. Arthritis Care Res (Hoboken). 2017;69(11):1751-1763. doi:10.1002/acr.23177.

Cappelli LC, Gutierrez AK, Baer AN, et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. Annals of the Rheumatic Diseases. 2017;76(1):4350. doi:10.1136/annrheumdis-2016-209595.

Belkhir R, Burel SL, Dunogeant L, et al. Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. Annals of the Rheumatic Diseases. 2017;76(10):1747-1750. doi:10.1136/annrheumdis-2017-211216.

Naidoo J, Cappelli LC, Forde PM, et al. Inflammatory Arthritis: A Newly Recognized Adverse Event of Immune Checkpoint Blockade. The Oncologist. 2017;22(6):627630. doi:10.1634/theoncologist.2016-0390.

Smith MH, Bass AR. Arthritis After Cancer Immunotherapy: Symptom Duration and Treatment Response. Arthritis Care & Research. November 2017. doi:10.1002/ acr.23467.

Johnson DB, Sullivan RJ, Ott PA, et al. Ipilimumab Therapy in Patients with Advanced Melanoma and Preexisting Autoimmune Disorders. JAMA Oncology. 2016;2(2):234. doi:10.1001/jamaoncol.2015.4368.

Copyrights