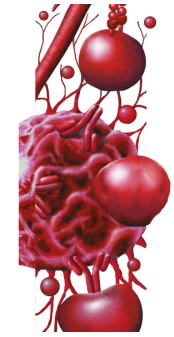
Case Report

Immunotherapy



Successful use of secukinumab in two melanoma patients with immune checkpoint inhibitor-induced inflammatory arthropathy

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Immune-related adverse events (irAEs) are a major concern when treating cancer patients with immune checkpoint inhibitor (ICI) therapy. Selecting the most appropriate management of irAEs remains an ongoing challenge because prolonged use of glucocorticoids come with their own side effects and may counteract the antineoplastic effects from immunotherapy. In this case report, we present two patients with metastatic melanoma who developed symptoms of inflammatory arthritis attributed to ICI therapy. We found that treatment with secukinumab, an anti-IL-17A inhibitor, effectively managed their symptoms and did not lead to tumor progression. Our study suggests that secukinumab can be a safe and effective treatment option for ICI-induced inflammatory arthropathy.

Plain language summary: Immune-related adverse events (irAEs) are unwanted side effects commonly seen in cancer patients treated with immunotherapy. A frequently underreported irAE is inflammation of the joints (ankles, knees, shoulders, etc.), which is known as inflammatory arthropathy. Inflammatory arthropathy is frequently treated with steroids, but there is concern that it may counteract the anticancer effect from immunotherapy. Alternative treatments are needed to better treat this irAE without compromising the benefit of immunotherapy. In this case report, we present two patients with stage 4 melanoma who developed immunotherapy-induced inflammatory arthropathy and were successfully treated with secukinumab. We found that treating the inflammatory arthropathy was safe, effective, and did not lead to cancer progression in either patient.

Tweetable abstract: Successful use of secukinumab in two cases of inflammatory arthropathy occurring in melanoma patients treated with immune checkpoint inhibitors.

First draft submitted: 5 October 2021; Accepted for publication: 24 February 2022; Published online: 13 April 2022

Keywords: IL-17 • IL-17A inhibitor • immune-related adverse events • inflammatory arthritis • melanoma • psoriasis • psoriatic arthritis • secukinumab

Over the past decade, immune checkpoint inhibitors (ICIs) have revolutionized the treatment of advanced melanoma and many other cancers. These agents act by blocking the negative costimulatory molecules on T cells, antigen presenting cells and tumor cells [1]. Despite its durable antitumor benefits, ICI use is associated with a wide spectrum of toxicities called immune-related adverse events (irAEs) [2]. These ICI-associated irAEs can affect multiple organs of the body including the skin, colon, liver, lung, endocrine glands and musculoskeletal system.

Rheumatologic irAEs have been described in case series and reports, but inflammatory arthropathy (IA) appears to be the most common type of rheumatologic event [3]. The prevalence of ICI-induced inflammatory arthropathy (ICI-IA) is between 3.0 and 7.5% of patients treated with ICI and can develop almost any time during therapy ranging from 2 weeks to more than a year after ICI initiation [4,5]. Management of ICI-IA is challenging because there are no well-established guidelines for evaluating and managing ICI-IA [3]. This may stem from a lack of consistent

Future Medicine

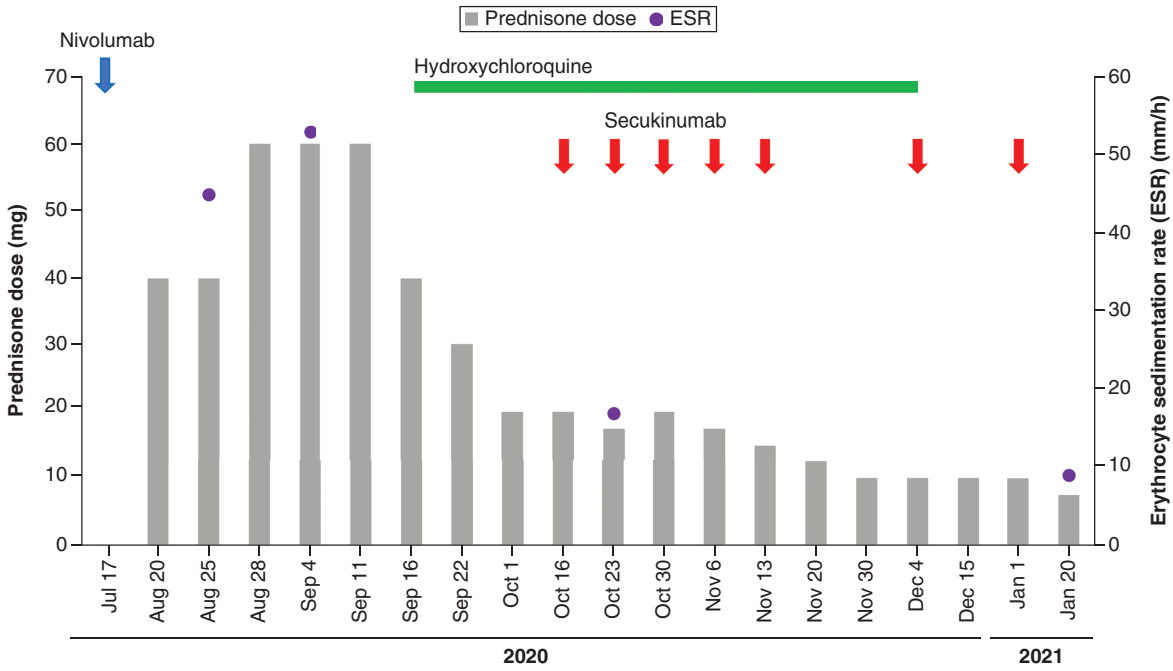

Figure 1. Course of treatment in Patient 1 with immune checkpoint inhibitor induced inflammatory arthropathy.

reporting of IA in clinical trials, the non-life-threatening nature of IA and lack of recognition of musculoskeletal symptoms by treating medical oncologists. Furthermore, ICI-IA is a heterogeneous entity with different subtypes based on clinical features [2], which can often be treated differently.

Current guidelines do not specify the preferred antirheumatic agents beyond glucocorticoid therapy in the management of ICI-IA [2]. Retrospective studies have shown that patients exposed to glucocorticoids preceding initiation, or early in treatment, of ICI led to worse survival outcomes [6,7]. Efforts are ongoing to identify effective agents to manage irAEs without steroid side effects or compromising the antitumor effects from immunotherapy.

Secukinumab (Cosentyx®) is an anti-IL-17A inhibitor that reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. It is currently US FDA approved for moderate-to-severe plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and nonradiographic axial spondylarthritis [8]. Its efficacy and favorable safety profile has been demonstrated in the real-world setting, consistent with that of phase III clinical trials [9,10]. Secukinumab has been investigated in clinical trials for rheumatoid arthritis (RA) and has shown to reduce disease activity in patients with active RA who had an inadequate response to prior TNF inhibitors [11].

In this case report, we describe two metastatic melanoma patients with acute symptoms of IA precipitated by ICI therapy that was effectively managed with secukinumab. Furthermore, we found that secukinumab was well tolerated and did not lead to melanoma tumor progression.

Case presentation

Patient 1

Patient 1 is a 59-year-old man with no preexisting autoimmune disease who was diagnosed with locoregionally advanced, unresectable, anorectal melanoma in October 2019. He received three of four planned doses of induction ipilimumab/nivolumab, which was complicated by immune-mediated hypothyroidism, insulin-dependent diabetes and colitis. After resolution of his toxicities with steroid therapy, he resumed treatment with nivolumab monotherapy in April 2020. After four cycles of nivolumab monotherapy in July 2020, he developed symptoms of dysuria with sterile pyuria, bilateral conjunctivitis and worsening nontraumatic right ankle arthralgia that later involved his contralateral ankle and bilateral knees, impacting his activities of daily living (ADL). He was referred to and seen by a rheumatologist at an academic center. On physical exam, he had joint effusions involving his bilateral ankles and left knee but no evidence of synovitis, dactylitis or enthesitis. Prednisone was initiated given concern for ICI-IA. See Figure 1 for timeline. Initial labs revealed elevated inflammatory markers: C-reactive protein (CRP;

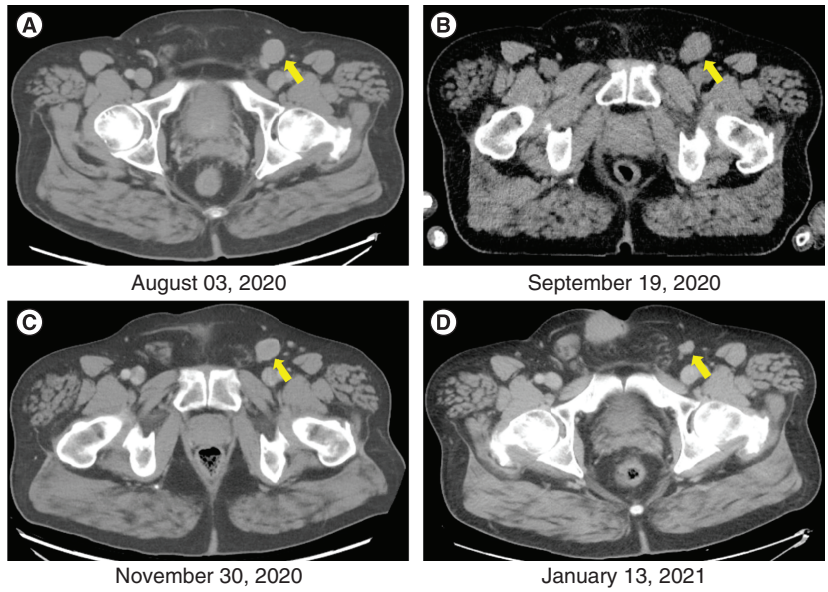

Figure 2. Computed tomography scan time lapse (A–D) of left inguinal lymphadenopathy (yellow arrow) from metastatic melanoma in Patient 1.

8.9 mg/dl) and erythrocyte sedimentation rate (ESR; 41 mm/h). Further workup included normal complement (C3 and C4) levels, normal uric acid level (4.8 mg/dl), negative antinuclear antibody (ANA), negative rheumatoid factor (RF), negative cyclic citrullinated peptide, negative HLA-B27 and negative urine gonorrhea/chlamydia nucleic acid amplification test.

Due to minimal improvement of his arthralgias with high-dose steroids, hydroxychloroquine was initiated in September 2020. During that time, restaging scans noted clear progression of his melanoma with new bilateral lung metastases and an enlarging left inguinal adenopathy. In an effort to decrease his steroid dose and permit candidacy for resuming immunotherapy or participation in a clinical trial, he was started on weekly loading doses of secukinumab 150 mg subcutaneous for four doses in October 2020. After initiation of secukinumab, he noted gradual improvement in his arthralgias while slowly tapering his steroids. Inflammatory markers gradually down-trended. Interestingly, serial computed tomography (CT) imaging showed notable decrease in size of his left inguinal adenopathy [Figure 2] and several lung metastases, despite remaining off antineoplastic therapy. As of December 2021, he remains on active surveillance for his melanoma and continues on monthly secukinumab with ongoing improvement in his arthropathy symptoms and no recurrence of conjunctivitis, colitis or sterile pyuria.

Patient 2

Patient 2 is a 75-year-old man with a history of biopsy-confirmed pulmonary sarcoidosis (on close observation) and a history of psoriasis that is treatment-naive to biologic therapies. His last psoriasis flare was in 2010, at which time his disease was effectively managed with high-potency topical corticosteroids. He has no prior history of inflammatory arthritis. In January 2018, he was started on pembrolizumab every 3 weeks for a diagnosis of metastatic melanoma. His treatment course was complicated by immune-mediated polymyalgia rheumatica (PMR) after presenting with bilateral shoulder pain and elevated CRP and ESR. He was referred to a rheumatologist at an academic referral center and was treated with a low-dose prednisone taper from April 2018 to October 2018 but continued on immunotherapy during that time. After taper completion and resolution of his PMR symptoms, he developed new morning stiffness and pain involving his axial and appendicular joints (hips and knees), recurrent psoriatic plaques on knees/elbows and dactylitis with multiple tender and swollen metacarpal and PIP joints affecting his ADL. Enthesitis and fingernail pitting was not present on exam. X-ray imaging showed no evidence of erosive changes or periostitis in the hands, wrists and feet and no evidence of sacroiliitis or sacroiliac joint ankylosis. His presentation was consistent with psoriatic arthritis based on the Classification of Psoriatic Arthritis (CASPAR) criteria [12]. To avoid resuming steroids while on immunotherapy, the patient was started on secukinumab 150 mg subcutaneous injections in November 2018. He completed 4 weekly doses which led to complete resolution of his psoriatic lesions

and dramatic improvement in his arthralgias. He received monthly secukinumab doses from December 2018 to April 2019 and discontinued dosing after symptoms of arthritis and psoriatic plaques had resolved. He continued on pembrolizumab until November 2019, receiving a total of 28 doses, with ongoing response. In December 2019, he had a cardiac arrest, attributed to bilateral pulmonary emboli, and died. His autopsy revealed no evidence of viable melanoma.

Discussion & conclusion

Up to 43% of patients experience arthralgia during ICI therapy [5], but the true incidence of ICI-IA may be underreported in the literature. To our knowledge, we are the first to highlight ICI-IA and report the success in management with secukinumab.

Secukinumab is the first anti-IL-17A agent approved in the United States, which has opened a new era of alternative cytokine targets for rheumatic disease management beyond anti-TNF-α inhibitors [8,13]. Studies have shown that TNF-α and IL-17 play important roles in the pathogenesis of inflammatory arthritis, skin diseases and other autoimmune conditions [14,15]. Interaction of IL-23 and IL-17 with different tissue-specific cells lead to activation of cytokine-mediated pathways resulting in severe inflammation causing bone erosion, synovio-entheseal complex abnormalities and other tissue modeling. In tissues, IL-17A exacerbates the chronicity and severity of the disease process. Secukinumab is a recombinant human immunoglobulin G1 monoclonal antibody that selectively binds to IL-17A and inhibits its interaction with the IL-17 receptor [8], thereby blocking the release of proinflammatory cytokines. Long-term outcomes of a secukinumab trial found that more than 80% of patients completed 5 years of treatment, indicative of its sustained clinical benefit [8,14].

Several agents, with variable success, may be used to manage ICI-IA that is refractory to nonsteroidal antiinflammatory drugs or glucocorticoids including: hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, TNF-α inhibitors and IL-6 inhibitors [2]. Among the available agents, secukinumab was preferentially chosen in our two patients given its approved indication for psoriatic arthritis (specifically for Patient 2) and its suspected lack of impact on their malignancy. This agent had dramatic improvement in their arthropathy symptoms with Patient 2 having complete resolution of his psoriasis. In both cases, treatment was well tolerated with no side effects. Glucocorticoids were either minimized or tapered off.

The increasing use of ICIs across multiple cancers has led to increasing prevalence of irAEs. Ongoing investigations are needed to identify glucocorticoid-sparing biologic agents to effectively manage these toxicities without increased risk of malignancy progression. There is lack of data on patients with preexisting or previous malignancies treated with antirheumatic biologic agents because clinical trials typically exclude such patients from participation [16]. In a combined analysis of two phase III studies, malignant or unspecified tumors were reported in 12 of 1638 patients (0.7%) treated with secukinumab at varying doses and two of 574 patients (0.3%) treated with placebo [17]. The exposure-adjusted malignancy rates were low and showed no clinically meaningful differences across treatment groups [16]. Case reports of immune-mediated psoriasis have shown that secukinumab can be safely co-administered with ICI therapy without complications or progression of active malignancy [18,19]. In trials, only 10% of patients discontinued secukinumab due to adverse events, with the most common side effects including nasopharyngitis, headache and diarrhea [14].

In our case presentations, neither patient had progression of metastatic melanoma while being treated with secukinumab. Patient 1 had ongoing tumor response even after being off ICI therapy for months, suggesting a possible antitumor effect of IL-17A inhibition. It is known that the tumor microenvironment in melanoma plays a critical role in both antitumor and protumor effects. Overexpression of IL-17 by Th17 cells has been associated with tumor angiogenesis and invasiveness in melanoma [20,21]. IL-17 can enhance melanoma growth through its direct effects on IL-17 receptors expressing cells such as melanoma cells, fibroblasts, endothelial cells and dendritic cells [20,22]. Furthermore, preclinical studies have demonstrated IL-17/IL-17RA inhibition can lead to suppressed tumor growth and metastasis in melanoma cell models [23].

IL-17 may play a critical role in immune suppression, particularly in the setting of malignancy. Recent studies suggest that elevated IL-17 levels may promote cancer growth and contribute to resistance to anti-PD-1 inhibition [24]. Blockade of IL-17/IL-17RA has been shown to enhance T-cell-mediated antitumor response by suppressing T regulatory cells, resulting in cytotoxic T lymphocyte activation [23]. Although larger case series and prospective trials are warranted, secukinumab could be further investigated as a novel anticancer agent alongside ICI therapy.

Executive summary

- We are the first to report cases of immune checkpoint inhibitor-induced inflammatory arthropathy and report the success in management with secukinumab, an anti-IL-17A inhibitor.
- Overexpression of IL-17 is implicated in tumor angiogenesis and invasiveness in melanoma.
- IL-17 levels may promote cancer growth and contribute to resistance to anti-PD-1 inhibition.
- In this case report, treatment with secukinumab was well tolerated and did not lead to melanoma tumor progression.
- Secukinumab should be further investigated for its possible antitumor effects.

Author contributions

VT Ma and E Schiopu were involved with the conceptualization, writing and revision of the original draft. CD Lao and LA Fecher were involved with the revision and editing of the original draft.

Financial & competing interests disclosure

VT Ma has received honoraria from Conquer Cancer. CD Lao serves as a consulting or advisory role for Bristol-Myers Squibb and Immunocore. LA Fecher serves as a consulting or advisory role for Elsevier/Via Oncology and Hoosier Cancer Research Network. CD Lao receives research funding from Bristol-Myers Squibb, Dynavax Technologies and Genentech. LA Fecher receives research funding from Array BioPharma, Bristol-Myers Squibb, Incyte, Kartos Therapeutics, Merck and Pfizer/EMD Serono. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The study protocol was approved by the University of Michigan institutional ethical guidelines and complies with the guidelines of the responsible governmental agency. Institutional review board approval was obtained (HUM00156014). Verbal and written consent was obtained from the non-deceased patient.

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