RHEUMATOLOGY ADVANCES IN PRACTICE

Rheumatology Advances in Practice 2018;0:1–2
doi: 10.1093/rap/rky001

Clinical Vignette

Successful use of adalimumab in immune checkpoint inhibitor-associated inflammatory arthritis

Immune checkpoints are pathways that regulate the immune response in order to maintain self-tolerance and prevent autoimmunity. Examples of such pathways are those regulated by cytotoxic T lymphocyte antigen 4 (CTLA4) and programmed death 1 (PD1). CTLA4 is a molecule expressed by activated T cells and counteracts the T-cell co-stimulatory receptor CD28, thereby inhibiting T-cell activation. PD1 is expressed on T cells and inhibits kinases that are involved in T-cell activation in the presence of its ligands PD-L1 and PD-L2. Tumour cells can use these inhibitory mechanisms to evade T-cell-mediated elimination. Checkpoint blockade by monoclonal antibodies enhances the cell-mediated response against tumour cells, and immunotherapy has proved a successful treatment option for a range of cancers. However, these therapies are associated with a wide spectrum of side effects, known as immune-related adverse events (IRAEs), thought to arise from general immunological enhancement. Limited data are available to guide the treatment of IRAEs. We present a case of inflammatory arthritis following treatment with immune checkpoint inhibitors (ICIs) ipilimumab (anti-CTLA4) and pembrolizumab (anti-PD1) in a patient with malignant melanoma.

A 52-year-old female underwent excision of left leg stage 2A malignant melanoma in 2009. She re-presented in 2013 with recurrence in the inguinal lymph nodes, which were resected (V600E BRAF mutation positive). She entered the active arm of a placebo-controlled trial of adjuvant B-Raf protein/mitogen-activated protein kinase (BRAF/MEK) inhibitor therapy with dabrafenib and trametinib for 1 year, completed in 2015. In August 2015, imaging revealed metastatic spread to the liver.

Four doses of ipilimumab were given during September–November 2015, but because of disease progression she switched to pembrolizumab in December 2015. While on ipilimumab, she reported intermittent arthralgia, which responded to NSAIDs. After the second dose of pembrolizumab, she developed a polyarthritis [Common Terminology Criteria for Adverse Events (CTCEA) grade 2] requiring treatment with prednisolone 60 mg daily. Symptoms persisted while tapering the prednisolone. She continued on prednisolone 10 mg daily, with prophylactic increases to 20 mg on days 3 and 4 after each infusion of pembrolizumab.

In July 2016, imaging demonstrated enlargement of porta hepatis lymph nodes. She was switched back to combination therapy with dabrafenib and trametinib. Two weeks later, she developed a polyarthritis affecting the hands, wrists, knees and ankles. Prednisolone was increased to 60 mg daily with no effect, and she was referred to rheumatology. Examination revealed synovitis of multiple PIP joints and MTP joints, knee effusions and tenosynovitis of the wrists. No erosions were seen on hand and foot radiographs. CRP was elevated (128 mg/l). RF, ANA, ANCA, anti-CCP, thyroid function, hepatitis serology, HIV serology and QuantiFERON were normal or negative. MTX 15 mg weekly was initiated, but after 8 weeks the arthritis persisted, with 23 tender joints, 16 swollen joints, CRP 82 mg/l (DAS28-CRP 7.36). Wrist injection was performed, MTX increased to 25 mg weekly and prednisolone increased to 30 mg daily, leading to some improvement (DAS28-CRP 5.78). In January 2017, the arthritis became more active (DAS28-CRP 6.54) despite MTX 25 mg weekly and prednisolone 10 mg. She commenced adalimumab 40 mg every fortnight in February 2017 and switched to s.c. MTX. She was able to discontinue prednisolone in April 2017. The patient reported an excellent response to adalimumab, with no tender or swollen joints in June and July 2017. In August 2017, small knee effusions were noted (CTCEA grade 1), and MTX was reintroduced. In September 2017, 8 months after starting adalimumab, DAS28-CRP was 4.39 and restaging CT demonstrated overall stable disease, but imaging in November 2017 demonstrated enlarging porta hepatis lymph nodes, and the patient chose to stop adalimumab.

BRAF inhibitors are recognized to cause arthralgia, which is usually manageable with NSAIDs and temporary suspension of the drug. To our knowledge, there are no reports of a persistent inflammatory arthritis associated with BRAF/MEK inhibition, although arthritis responding to glucocorticoids has been reported [1]. In this patient, an immunotherapy-related arthritis was probably triggered by checkpoint inhibitor therapy (ipilimumab and pembrolizumab). The arthritis persisted despite high-dose glucocorticoids and MTX. Adalimumab was effective and allowed discontinuation of glucocorticoids.

Various IRAEs have been reported with the use of ICIs, including pruritus, diarrhoea, colitis, pneumonitis, endocrinopathies and hepatitis [2–4]. Rheumatological adverse events are less well described but include inflammatory arthritis, tenosynovitis, DM, GCA, PM and sicca symptoms [5, 6]. There are reports of ICI-related arthritis persisting for >12 months after cessation of the offending medication [7]. The most extensive case series of patients with inflammatory arthritis describes the successful use of infliximab in one patient, adalimumab in three patients and etanercept in one patient [6]. Use of tocilizumab is also described [8]. Infliximab is recommended for the treatment of severe colitis [6]; however, treatment recommendations for inflammatory arthritis are lacking.

As cancer immunotherapy advances, rheumatologists will need to become familiar with IRAEs and with the data

that might help to guide treatment. These patients should be managed in close collaboration with oncologists.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors declare no conflict of interest.

Anuoluwapo R. Oke[1], Matthew Wheater[2], Ioannis Karydis[2] and Dinny Wallis[1]

[1]Rheumatology Department and [2]Oncology Department, University Hospital Southampton, Tremona Road, Southampton SO16 6YD, UK

Correspondence to: Dinny Wallis, Rheumatology Department, University Hospital Southampton Tremona Road, Southampton SO16 6YD, UK. E-mail: dinny.wallis@uhs.nhs.uk

References

1 Babacan T, Türkbeyler IH, Balakan O et al. A case of vemurafenib-induced polyarhritis in a patient with melanoma: how to manage it? *Int J Rheum Dis* 2017;20:398–401.

2 Larkin J, Chiarion-Sileni V, Gonzalez R et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015;2015:23–34.

3 Robert C, Schachter J, Long GV et al. Pembrolizumab versus ipilimumab in advanced melanoma. *New Engl J Med* 2015;372:2521–32.

4 Suarez-Almazor ME, Kim ST, Abdel-Wahab N, Diab A. Review: immune-related adverse events with use of checkpoint inhibitors for immunotherapy of cancer. *Arthritis Rheumatol* 2017;69:687–99.

5 Chan MM, Kefford RF, Carlino M, Clements A, Manolios N. Arthritis and tenosynovitis associated with the anti-PD1 antibody pembrolizumab in metastatic melanoma. *J Immunother* 2015;38:37–9.

6 Cappelli LC, Gutierrez AK, Baer AN et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. *Ann Rheum Dis* 2017;76:43–50.

7 Cappelli LC, Naidoo J, Bingham CO 3rd, Shah AA. Inflammatory arthritis due to immune checkpoint inhibitors: challenges in diagnosis and treatment. *Immunotherapy* 2017;9:5–8.

8 Kim ST, Tayar J, Suarez-Almazor M et al. Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: a case series. *Ann Rheum Dis* 2017;76:2061–4.