Tocilizumab in a patient with newly diagnosed rheumatoid arthritis secondary to checkpoint inhibitor therapy

Sirs,

The frequent use of immune checkpoint inhibitors (ICI) for a variety of malignancies has led to an increase of immune related adverse events (irAE). Rheumatologic manifestations secondary to ICI-therapy may present as unspecific arthralgias, myalgias and sicca symptoms, as well as rheumatoid arthritis, polymyalgia rheumatica, vasculitis, myopathy/myositis, spondyloarthritis, lupus nephritis and eosinophilic fasciitis (1). Steroid refractory irAE often require interdisciplinary management. There are no clear treatment strategies derived from controlled trials for rheumatic manifestations secondary to checkpoint inhibitor therapy. Interleukin 6 (IL-6) is a cytokine which plays an important role in systemic inflammation, mediating multiple proinflammatory processes. Inhibition of the IL-6 signalling pathway with the IL-6R inhibitor tocilizumab is used successfully in treating rheumatoid arthritis (RA) and giant cell arteritis (2). We report the case of a patient with seronegative arthritis secondary to checkpoint inhibitor therapy, in whom remission was achieved with tocilizumab.

A 57-year-old female with a history of non-pigmented melanoma was treated with pembrolizumab, a programmed death receptor ligand 1 (PD-L1) antibody (200 mg/Q3W, intravenous) from November 2017 to July 2018 (stopped due to disease progression and further therapy with dabrafenib/trametinib, a tyrosine kinase inhibitor). Four months after the first administration of pembrolizumab, she developed morning stiffness and polyarthritis with joint swelling (mainly knees and finger joints). Her evaluation by our rheumatology department revealed active arthritis involving both knees, wrists, proximal and distal interphalangeal joints of both hands and the right elbow. Ultrasound of the right knee showed effusion with fluid in the suprapatellar space. Magnetic resonance imaging confirmed synovitis of the right knee (Fig. 1). C-reactive protein and ESR were elevated with 119 mg/l (normal <8 mg/l) and 59 mm/h (normal <12mm/h), respectively, rheumatoid factor (IgM) and antibodies to cyclic citrullinated peptides (IgG) were not detected. Due to the presence of symmetric polyarthritis of small and large joints we established the diagnosis of RA secondary to ICI-therapy, according to the 2010 ACR classification criteria.

The patient was treated with prednisone orally starting with 100 mg/d and subsequent tapering. Two months later we initiated tocilizumab (8 mg/kg body weight, administered every four weeks, intravenous) due to significant functional impairment as a consequence of persisting synovitis despite recurrent intraarticular infiltrations with corticosteroids and limited therapeutic response to even high dose prednisone use (50 mg/d).

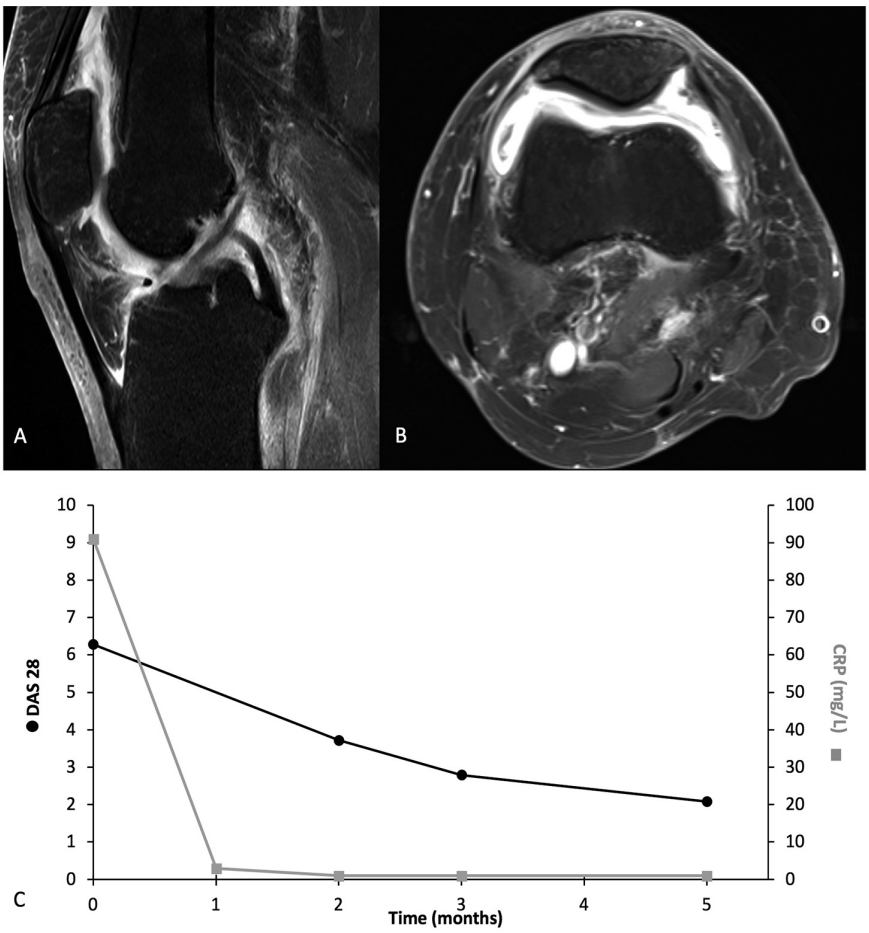

Fig. 1. Magnetic resonance (MR) images of the right knee prior to treatment with tocilizumab and DAS 28 course over time**.**

Sagittal (**A**) and transverse (**B**) T1-weighted MR images with fat-suppression after intravenous contrast agent administration illustrate severe synovitis. Images courtesy of Dietrich T. MD, Department of Radiology, Cantonal Hospital St. Gallen, Switzerland.

(**C**) Time course of DAS 28 Score (DAS 28 Score: <2.6 corresponds with being in remission according to the American Rheumatism Association (ARA) criteria) and CRP.

After 3 infusions (12 weeks) of tocilizumab, symptoms improved significantly, and prednisone was successfully tapered and stopped after 5 months. DAS 28 improved from 6.28 (10 tender joints, 8 swollen joint counts, patient global health assessment: 80/100, ESR: 39 mm/h) to 2.08 (1 tender joint, 1 swollen joint, patient global health assessment: 20/100, ESR: 0 mm/h) after 5 months of therapy with tocilizumab (Fig. 1). No tumour progression was noted at that point (clinically and by imaging). We currently continue tocilizumab as a remission maintenance therapy for RA.

The occurrence of arthritis secondary to ICI-therapy has been reported in up to 7% of patients (3). The majority of patients achieved disease control with systemic corticosteroids and classic synthetic disease-modifying anti-rheumatic drugs (DMARDs, methotrexate and hydroxychloroquine) despite continuation of ICI-therapy (4). In steroid refractory arthritis, synthetic DMARDs or biological DMARDs may be considered. Elevated levels of IL-6 have been detected in patients with cytokine release syndromes secondary to PD1 directed therapies or CAR T cells (5). A small Korean case series reports on the successful use of tocilizumab in patients with polyarthritis induced by immune checkpoint inhibitor therapy (6). Inhibition of IL-6 might therefore be considered as an attractive option for treatment of irAE secondary to PD-1 blockade. However, it is currently unclear whether dose de-escalation and eventually cessation of therapy might be possible in the future.

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