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 polyarthralgia 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 <12 mm/h), respectively, rheumatoid factor (RF) and 59 mm/h (normal <8 mg/l) and 59 mm/h (normal <20 mm/h) were negative. Antinuclear antibodies were negative. Leptin and ESR were elevated with 119 mg/l (normal <5 mg/l) and 39 mm/h (normal <20 mm/h). C-reactive protein and ESR were elevated with 119 mg/l (normal <5 mg/l) and 39 mm/h (normal <20 mm/h). Rheumatoid factor and anti-CCP antibodies were negative. No tumour progression was noted at that time.

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 limited therapeutic response to even high dose prednisone use (50 mg/d).

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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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.

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References


