

A CASE REPORT OF A PATIENT WITH RHEUMATOID ARTHRITIS INDUCED BY CHECKPOINT INHIBITOR TREATMENT

V. Boyadzhieva¹, Y. Popova², Y. Milusheva², Zh. Doncheva-Dilova³, S. Emin¹, N. Stoilov¹

¹University Hospital "St. Ivan Rilski", Rheumatology Department, Medical University – Sofia

²Medical Oncology and Radiotherapy Clinic, University Hospital "Tsaritsa Joanna – ISUL" – Sofia

³University Hospital "St. Ivan Rilski", Department of Occupational Diseases, Medical University – Sofia

Abstract. Malignant melanoma accounts for only 1% of all skin neoplasms, but is characterized by the most aggressive clinical course and the lowest 5-year survival rate. Even after radical resection of patients in the non-metastatic stage, there is an increased risk of local recurrence and distant metastasis. Advances in molecular biology have aided the development of innovative targeted- and immunotherapies that have greatly improved patient prognosis. Among them is the suppression of the immune response through the expression of the transmembrane protein PD-L1 on the surface of neoplastic cells. Nivolumab is a humanized monoclonal antibody (the so-called immune "check point" inhibitors), first-line treatment in patients with metastatic malignant melanoma and also used as an adjuvant treatment in patients at high risk of relapse, which is associated with PD-1 and therefore supports the inhibited T-cell immune response. This, in turn, leads to the risk of various autoimmune life-threatening adverse reactions. In clinical studies, immune-related adverse events of various degrees and severity have been described with the use of anti-PD-1 antibodies: immune-mediated colitis, pneumonitis, nephritis, hepatitis, dermatitis, arthritis, myositis, vasculitis, polymyalgia rheumatica, eosinophilic fasciitis and scleroderma. In rheumatology practice, the most frequently described cases of arthritis occur after a different period of time from the start of nivolumab therapy. The specific mechanisms of the onset of immune-mediated arthritis in anti-PD-1 antibody therapy are not fully understood, but an overlapping pathogenesis with the onset of rheumatoid arthritis is suggested – PD-1 expression in the synovial fluid is a proven regulator of the T-cell immune response and is a possible future target for immunomodulatory therapy of rheumatoid arthritis (RA). We present a clinical case of a 52-year-old patient who developed RA following nivolumab treatment. After temporary discontinuation of nivolumab, methotrexate therapy was started and the patient showed a good clinical response after 3 months and reached minimal disease activity.

Key words: rheumatoid arthritis, malignant melanoma, PD-1 inhibitor, nivolumab

INTRODUCTION

Malignant melanoma accounts for only 1% of all skin neoplasms, but is characterized by the most aggressive clinical course and the lowest 5-year survival rate [1]. Even after radical resection of the tumor in patients in the non-metastatic stage, there is an increased risk of local recurrence and distant metastases [2]. Advances in molecular biology have led to the discovery of key mechanisms supporting tumor cell growth, division, migration, and the ability to evade apoptosis [3]. This, in turn, has facilitated the development of innovative targeted- and immunotherapies that have significantly improved patient prognosis. One of these mechanisms is the suppression of the immune response through the expression of the transmembrane protein PD-L1 on the surface of neoplastic cells. When PD-L1 binds to the key inhibitory receptor on the surface of T-lymphocytes – PD-1, the result is immune tolerance and survival of the tumor cell [4]. Disruption of the

relationship between PD-L1 and PD-1 is the basis of drug therapy with checkpoint inhibitors (the so-called immune "check point" inhibitors) [4]. Nivolumab is a humanized monoclonal antibody that binds to PD-1, preventing binding to PD-L1 and therefore inhibition of the T-cell immune response [5]. Nivolumab therapy has been effective in terms of overall survival in patients with malignant melanoma and is now used both as a first-line treatment in metastatic patients and as an adjuvant treatment in patients at high risk of recurrence [6]. Due to the fact that the body uses the interaction mechanism between PD-L1 and PD-1 to suppress autoimmunity, blocking it carries the risk of developing various autoimmune reactions, which can sometimes be life-threatening and require long-term immunosuppressive therapy or interruption of checkpoint inhibitors treatment [7]. Clinical studies have described immune-related adverse reactions of various degrees and severity when using anti-PD-1 antibodies – immune-mediated

colitis, pneumonitis, nephritis, hepatitis, dermatitis, etc. [7]. Rheumatic immune-mediated complications such as arthritis, myositis, vasculitis, polymyalgia rheumatica, eosinophilic fasciitis and scleroderma have also been reported with Nivolumab treatment, with the most commonly described cases of arthritis occurring after a different period of time from the start of therapy [8]. A flare-phenomenon in previously diagnosed rheumatoid arthritis is reported in 71% of patients and requires mandatory treatment and monitoring by experienced rheumatologist in order to avoid severe damage and interruption of oncological therapy [9]. The specific mechanisms of the onset of immune-mediated arthritis in anti-PD-1 antibody therapy are not fully understood, but an overlapping pathogenesis with the onset of rheumatoid arthritis is suggested – PD-1 expression in the synovial fluid is a proven regulator of the T-cell immune response and is a possible future target for immunomodulatory therapy of rheumatoid arthritis [10].

CLINICAL CASE DESCRIPTION

We present a clinical case of a 52-year-old Caucasian man with a 6-month history of complaints of pain and swelling in knee and ankle joints, and morning stiffness for more than 4 hours. At the first

appearance of symptoms in the summer of 2023, the patient was consulted by a rheumatologist and underwent outpatient treatment with a corticosteroid – Methylprednisolone 4 mg 2 x 1 tablet daily for 10 days. After the therapy, there was a temporary improvement, and the patient did not undergo further consultation and examinations. The patient has co-morbidities of arterial hypertension and had a myocardial infarction and stent placed 16-17 years ago.

In 2017 the patient underwent surgery to remove malignant melanoma in the right lower quadrant of the abdominal area, and in 2022, a lymphatic dissection was performed due to established metastases. After a consultation with an oncologist, treatment with Nivolumab was initiated for the patient in June 2023. While on treatment with Nivolumab, the patient developed arthritis in the knee and ankle joints a few days after the infusions. The patient was admitted in the Rheumatology Clinic at the “St. Ivan Rilski” Hospital. Physical examination revealed arthritis in the knee and ankle joints. Laboratory test results showed increased values of C-reactive protein (CRP – 97.80) and erythrocyte sedimentation rate (ESR – 72 mm/h), anemia (HBG – 112 g/L, HTC – 0.342 L/L, MCV – 79.8 fL, MCH – 26.1 pg) and thrombocytosis ($386 \times 10^9/L$), positive values for anti-MCV, RF IgM. The rest of the results are presented in Table 1.

Table 1. Laboratory test results

Parameter	Result	Units	Reference range
FBC and DBC (20 NOV 2023)			
ALAT	13.60	U/L	0-41.00
ASAT	13.10	U/L	0-40.00
Chol	3.55	mmol/L	0-5.20
Crea	69	$\mu\text{mol/l}$	0-104.00
CRP	97.80		
GGT	61	U/L	0-60.00
Blood sugar	5.74	mmol/L	3.50-6.70
Triglycerides	0.60	mmol/L	0-2.00
UA(S)	328	$\mu\text{mol/l}$	142.00-420.00
Urea	6.7		
WBC	$10.50 \times 10^9/L$		3.50-10.50
RBC	$4.29 \times 10^{12}/L$		3.70-5.90
HGB	112	g/L	120.00-180.00
HTC	0.342	L/L	0.36-0.53
MCV	79.8	fL	80.00-96.00
MCH	26.1	pg	27.00 3.00
MCHC	327	g/L	300.00-360.00
PLT	$386 \times 10^9/L$		130.00-360.00
LYM%	8.9%		20.00-48.00
MONO%	8.5 %		1.00-11.00
EO%	0.8%		0-6.50
BASO%	0.3%		0-2.00

NEUT%	80.9%		40.00-70.00
LYM#	0.93 x10 ⁹ /L		1.00-4.00
MONO#	0.89 x10 ⁹ /L		0-0.80
EO#	0.08 x10 ⁹ /L		0-0.50
BASO#	0.03 x10 ⁹ /L		0-0.14
NEUT#	8.48 x10 ⁹ /L		2-7.00
MPV	10.2	fL	6.10-12.50
Erythrocyte Sedimentation Rate	72	mm/h	
Sg	0.81		0.40 - 0.64
Ly	0.14		0.20 - 0.48
Urine sediment	Result	Units	Reference range
Casts – hyaline	0.7		
Crystals URIC	0		
Crystals CaPhos	0		
Erythrocytes	0.7		
Leucocytes	9.8		
Epithelial cells	3.7		
Casts	0		
Crystals	0		
Bacteria	0.4		
Urine chemical examination			
pH	6.0		
Specific Gravity	1.015		
Protein	Opalescent		
Glucose	Negative (-)		
Ketones	Negative (-)		
Urobilinogen	Increased		
Bilirubin	Negative (-)		
Blood	Negative (-)		
Nitrites	Negative (-)		
Leucocytes	Positive (+)		
Immunology			
Anti-CCP (IgG+IgA)	20.70		< 20
Rheumatoid Factor (RF)	< 30	IU/ml	< 30
Anti-MCV	94		< 20
Rheumatoid Factor IgM	54		< 20
Synovial fluid examination			
Synovial fluid erythrocytes	4400		
Synovial fluid leucocytes	450		
Synovial fluid cytology			
Neu	0.76		
SIN: Eo	0		
SIN: Mononuclears	0.03		
SIN: Macrophages	0		
SIN: Ly	0.21		
SIN: Activated lymphocytes	0		
SIN: mesothelial cells	0		
SIN: other cells	0		

Note: Due to the small amount of synovial fluid, UA cannot be examined

X-ray of the knee joints revealed a cystic effusion with a denser periphery in the distal diaphysis of the left femur and osteophytes of the tibial eminences bilaterally. (Fig.) The ultrasound examination of the right knee joint shows intraarticular effusion, pronounced synovial proliferation, without Power-Doppler (PD) signal, reduction of the hyaline cartilage; degenerative changes in the lateral and medial meniscus (fig. .)

An arthrocentesis of the right knee joint was performed, 20 ml of synovial fluid was evacuated; corticosteroid and lidocaine were administered intraarticular with good effect. After discussion, a diagnosis of rheumatoid arthritis was made, probably related to the PD-1 inhibitor treatment (Nivolumab). Treatment with Methotrexate 15 mg/week and folic acid 2 x 1 tablet/day, Medrol 4 mg – 2 tablets/morning with a subsequent dose reduction to 2 mg/day, was started. Six months after the treatment, the patient has no arthritis in the joints and there is going to be a multidisciplinary discussion about resumption of treatment with Nivolumab.

DISCUSSION AND CONCLUSIONS

The presented case exemplifies the challenges in the treatment of immune-mediated adverse events of inhibitors of the PD-1 signaling pathway and the need for collaboration in the multidisciplinary team to achieve optimal results. The patient developed de novo rheumatoid

arthritis with the onset of arthritis in the knee and ankle joints, elevated inflammatory markers, and the presence of RA-specific autoantibodies, including anti-MCV and RF IgM. The relationship between the initiation of the PD-1 inhibitor Nivolumab and the initial onset of symptoms, the initial response to corticosteroid therapy, and the absence of a previous history of rheumatoid arthritis are significant factors supporting the theory of immune-mediated RA as an adverse event of Nivolumab administration. Cases of rheumatological immune-mediated adverse events with varying frequency are increasingly reported in the literature, but the pathophysiology of these conditions is not fully understood [11]. Processes such as impaired immune tolerance, disinhibition of T-cell function, and autoimmunity have been suggested to be involved when blocking the PD-1/PD-L1 signaling pathway [11], but studies are needed to elucidate the specific mechanisms and to establish predictive and prognostic biomarkers for occurrence of rheumatological complications.

The treatment of this patient is particularly challenging due to the need to balance the control of rheumatologic manifestations and the preservation of the effect of antitumor therapy. After a temporary interruption of Nivolumab therapy and initiation of corticosteroids and methotrexate, a significant clinical improvement was achieved, which also led to a discussion

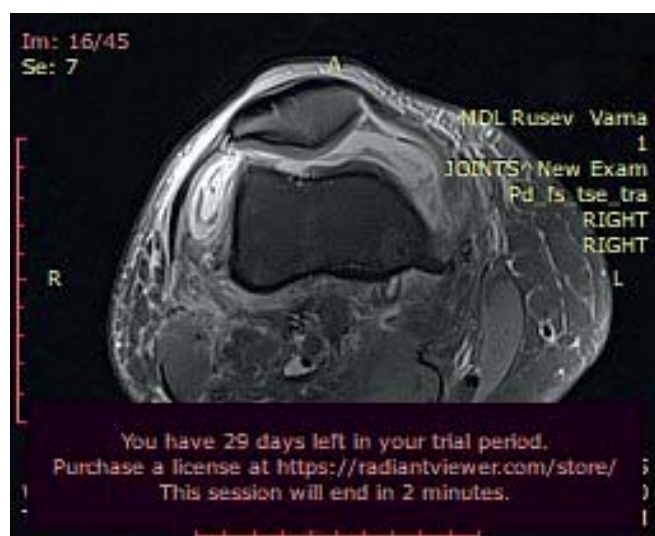


Fig. 1. MRI image of the right knee joint (transversal slice)

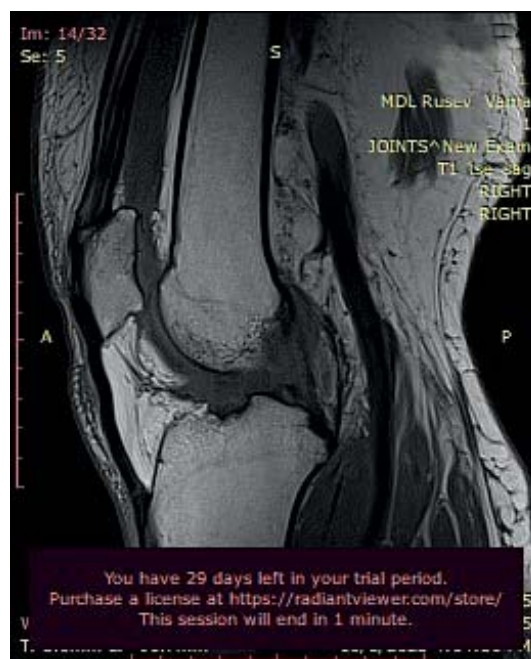


Fig. 2. MRI image of the right knee joint (sagittal slice)



Fig. 3. MRI image of the right knee joint – hydrops and synovitis suprapatellaly

in the direction of resuming treatment with the PD-1 inhibitor. This decision is supported by international recommendations when there is a clear clinical benefit of continuing Nivolumab therapy and resolution of RA complaints [12], but should be done with careful re-evaluation of the condition due to the risk of recurrence of immune-mediated toxicity [12]. Prospective studies on the combined use of immunosuppressive drugs and PD-1 inhibitors are lacking, but retrospective analyzes have reported a reduced efficacy of antitumor immunotherapy with concomitant administration of corticosteroids and second-line drugs such as methotrexate together with checkpoint inhibitors [13]. Newly published data indicate that checkpoint inhibitor therapy used in cancer immunotherapy may play a role in the pathogenesis of newly emerging syndromes with clinical symptoms similar to polymyalgia rheumatica and giant cell arteritis [14]. However, the literature does not provide further clarity regarding combination treatment with conventional synthetic disease-modifying antirheumatic drugs. The use of methotrexate in the case described by us, as well as in patients undergoing treatment with checkpoint inhibitors, has both potential benefits and risks and requires dynamic control of both conditions by medical oncologists together with rheumatologists.

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✉ *Адрес за кореспонденция:*

Д-р Владимира Бояджиева, дм

e-mail: vladimira.boyadzhieva@gmail.com

✉ *Correspondence address:*

Vladimira Boyadzhieva, MD

e-mail: vladimira.boyadzhieva@gmail.com