Table 1. Patient characteristics

Variable	RA (n=336)	Controls (n=144)	p
Age (years), median (q25-q75)	55.5 (48-61)	53 (48-58)	0.017
Women, n (%)	311 (92.6)	134 (93.1)	NS
Disease duration (years), median (q25-q75)	7.8 (3.2-15)	-	-
BMI (kg/m²), median (q25-q75)	27.6 (25.1-31.2)	27.8 (24.9-31.5)	NS
Diabetes Mellitus, n (%)	47 (14)	14 (9.7)	NS
Dyslipidemia, n (%)	93 (27.7)	31 (21.5)	NS
Hypertension, n (%)	93 (27.7)	31 (21.5)	NS
DAS28-CRP, median (q25-q75)	3.2 (2.1-4.3)	-	-
Past or current smoker, n (%)	65 (19.3)	36 (25)	NS
Nonsteroidal anti-inflammatory drugs, n (%)	90 (26.8)	-	-
Prednisone, n (%)	195 (58)	-	-
Methotrexate, n (%)	283 (84.2)	-	-
Leflunomide, n (%)	69 (20.5)	-	-
Chloroquine, n (%)	54 (16.1)	-	-
Sulfasalazine, n (%)	59 (17.6)	-	-
Hydroxychloroquine, n (%)	34 (10.1)	-	-
Biologic DMARDs, n (%)	21 (6.3)	-	-

Table 2. Echocardiographic and carotid US findings

Echocardiography	RA (n=60)	Controls (n=28)	p
Ejection fraction, median (q25-q75)	60 (56.2-65.0)	63 (60-69)	**0.008**
Abnormal LV geometry, n (%)	21 (35)	7 (25)	NS
Abnormal LA geometry, n (%)	6 (10)	3 (10.7)	NS
Carotid US, n (%)	**RA (n=128)**	**Controls (n=110)**	
CP	38 (29.7)	25 (22.7)	*NS*
Increased cIMT	64 (50)	32 (29.1)	***0.001***
Unilateral CP	18 (14.1)	17 (15.5)	*NS*
Bilateral CP	20 (15.6)	8 (7.3)	***0.046***

Conclusion: RA patients from this clinic had lower ejection fraction, more prevalence of cIMT and bilateral CP when compared to controls. It is important that rheumatologists perform a complete evaluation of their patients, in which cardiovascular assessment should be included.

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INFLAMMATORY ARTHRITIS INDUCED BY IMMUNE-CHECKPOINT INHIBITORS: RESULTS FROM A COMBINED RHEUMATOLOGY/ONCOLOGY OUTPATIENT CLINIC

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Background: Immune checkpoint inhibitors (ICIs) has radically changed the oncology field: the blockade of co-stimulatory molecules on T cells, antigen presenting cells and tumor cells induces unchecked T cell activation with subsequent immune response targeting malignant cells. In the last years, different ICIs have been approved for the treatment of several malignancies. The stimulation of the immune response could be associated with the development of immune-related adverse events (irAEs), potentially involving every organ/system (1). Musculo-skeletal manifestations represent one of the most common irAEs developing during ICIs treatment: up to 40% of treated patients could experience arthralgia or arthritis. Moving from these evidences, the role of the rheumatologist became very important in the management of ICIs treated patients (2).
Objectives: To determine the frequency of musculo-skeletal manifestations in patients treated with ICIs in a combined rheumatology/oncology outpatient clinic.
Methods: From January 2015 we organised a rheumatology/oncology combined outpatient clinic: all patients starting an ICIs treatment were referred from oncologist to rheumatologist. Data from patients, including demographic features, date of diagnosis, comorbidities and previous and concomitant medications, smoke habit, were collected and registered into a standardized, computerized, electronically filled-in form. All the patients underwent to a physical and laboratory evaluation in order to assess the presence of tender and swollen joints. In case of joint involvement, we assessed disease activity by clinimetric evaluation (DAS28) and ultrasonographic assessment of involved joints (presence of active synovitis as for presence of power Doppler). Moreover, a laboratory evaluation including, ESR, CRP, and autoantibodies (ANA, ACPA, RF) was performed.
Results: Seventy-two patients were evaluated (M/F 48/24, median age 66.0 years, IQR 13.0; median disease duration 7 months, IQR 13.0). Concerning malignant disease, 75.1% were affected by non-small cell lung cancer, 15.3% by renal cell carcinoma, 6.9% by melanoma, 2.7% by other malignancies; all patients were treated with anti-PD-1, 67 (93.1%) with nivolumab and 5 (6.9%) with pembrolizumab. During ICIs treatment, 7 patients (9.7%) developed clinically evident synovitis (absolute risk: 0.1; incidence rate 0.01 patients/month): table 1 reports the main features of these 7 patients. According with ACR/EULAR 2010 criteria, two patients could be classified as affected by rheumatoid arthritis (RA). Six patients (85.7%) were treated by prednisone (dosage range 10-12.5mg/daily) or NSAIDs, experiencing a rapid, complete and persistent response. Patient 2, due to resistance to prednisone, was treated by methotrexate 10mg/weekly achieving remission after 6 weeks.
Conclusion: The present study represents the first attempt to apply a multidisciplinary approach involving rheumatologists and oncologists in the evaluation of patients treated with ICIs. We found a high absolute risk (10%) to develop synovitis in patients treated by ICIs. Interestingly, the majority of these patients experienced a clinically evident synovitis promptly responding to glucocorticoids and not requiring further DMARDs treatment. This could suggest a peculiar pathogenesis of such ICIs-induced arthritis.

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Table 1. Main features of seven patients experiencing synovitis.

Pt	Sex	Age	Malignancy (Treatment)	Clinical manifestations	Interval (weeks)	Autoantibody Evaluation	US	Treatment
1*	F	55	RCC (+nivolumab)	Simmetric polyarthritis	3	RF, ACPA, ANA neg	Active synovitis	PDN 12.5 mg/daily
2*	F	61	Melanoma (+nivolumab)	Simmetric polyarthritis	3	RF 22 UI/ml, ACPA >100 U/mL, ANA + 1/80, a-SSA +	Active synovitis	PDN 10 mg/daily MTX 10 mg/weekly
3	M	68	NSCLC (+nivolumab)	Monoarthritis	8	RF, ACPA, ANA neg	Synovitis	NSAIDs
4	F	72	NSCLC (+nivolumab)	Polyarthritis	18	RF, ACPA, ANA neg	Synovitis	PDN 12.5 mg/daily
5	M	77	NSCLC (+nivolumab)	Oligoarthritis	4	RF, ACPA, ANA neg	Synovitis	NSAIDs
6	M	70	NSCLC (+nivolumab)	Simmetric polyarthritis	2	RF, ACPA, ANA neg	Active synovitis	PDN 10 mg/daily
7	M	61	NSCLC (+nivolumab)	Simmetric polyarthritis	36	RF, ACPA, ANA neg	Synovitis	PDN 10 mg/daily

Legend. NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma, PDN: prednisone; MTX: Methotrexate. RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; ANA: anti-nuclear antibodies; a-SSA: anti-SSA

*These patients satisfied ACR/EULAR 2010 classification criteria for Rheumatoid Arthritis.

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