WEDNESDAY, 14 JUNE 2017

Controlling the balance between cancer and autoimmunity

OP0003 RHEUMATIC IMMUNE RELATED ADVERSE EVENTS OF CHECKPOINT THERAPY FOR CANCER: CASE SERIES OF AN EMERGING NOSOLOGIC ENTITY

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Background: Immune checkpoint therapy is a major advance in the field of oncology. Agents targeting CTLA-4, programmed cell death protein 1 (PD-1) and PD-ligand 1 have produced significant survival benefits in patients with malignancies. With these therapies have come a unique spectrum of adverse events related to over-activation of the immune system with resultant autoimmune disease. To date reports of rheumatic immune related AEs (irAEs) have not been adequately characterized, as they are infrequently reported in clinical trials. We describe the largest series of rheumatic irAEs secondary to checkpoint inhibitors to date.
Objectives: To report our 22 month experience with 19 patients evaluated in the Cleveland Clinic Rheumatology department.
Methods: A retrospective chart review was performed on 19 patients, 16 without pre-existing autoimmune disease (AID) and 3 with pre-existing AID, seen in our rheumatology department February 2015-December 2016. 2 designated rheumatologists evaluated all patients. Recorded information included gender, age, age at malignancy diagnosis, malignancy details, checkpoint inhibitor, nature of rheumatic irAE, time of onset, diagnostic data, treatment of irAE and response to treatment.
Results: In the group without pre-existing AID 56% developed a rheumatic irAE within 16 weeks of starting immunotherapy, with median time to onset of 14.5 weeks (table 1). Of the 3 patients with pre-existing AID, 1 experienced a disease flare after starting immunotherapy.
Conclusions: Rheumatic irAEs is a new field that will continue to grow. At this stage we have more questions than answers regarding their epidemiology, natural history and pathophysiology. Our findings reinforce that rheumatic irAEs are complex, at times require aggressive immunosuppression and can impact checkpoint inhibitor therapy for the underlying malignancy.
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OP0004 RHEUMATOID ARTHRITIS OCCURING AFTER IMMUNE CHECKPOINT INHIBITORS

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Background: Immune checkpoints inhibitors (ICIs) targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and Programmed cell death protein 1 (PD-1) have demonstrated survival improvement in multiple cancers. Immune Related Adverse Events (IrAE) have been described with ipilimumab and anti PD1. Relapse or flare of preexisting auto-immune diseases has been reported but occurrence of new auto-immune diseases seems to be less frequent. A series of 13 patients with non-classified rheumatic IrAE has been published: 9 patients developed non-specific inflammatory arthritis but no seropositive rheumatoid arthritis (RA) and 4 presented with sicca symptoms but did not fulfill criteria for Sjögren syndrome [1].
Objectives: We did a retrospective study for collecting patients who developed seropositive rheumatoid arthritis (RA) after exposition to ICIs.
Methods: We used the "Club Rhumatismes et Inflammation (CRI)" network, a section of the French Society of Rheumatology and the Gustave Roussy Cancer

Abstract OP0003 – Table 1. Demographic features, cancer types, immunotherapy and rheumatic irAEs

Patient	Age	Sex	Malignancy	Immunotherapy	irAE	Serology	Time to onset (weeks)	Treatment	Improvement	Immunotherapy held for irAE
1	74	F	NSCL	Nivo	Arthritis	ANA 1:160 Anti-dsDNA 77	7.3	Prednisone 40 mg	Significant	Y
2	49	F	Melanoma	Ipi Pembrolizumab	Arthritis		52.7	Prednisone 20 mg HCQ	Moderate	Y
3	42	F	RCC	Ipi/Nivo	Arthritis		3	Prednisone Infliximab, MTX Etanercept	Moderate	N
4	57	M	RCC	Ipi/Nivo	Arthritis	RF 214	48.4	Prednisone, MTX Etanercept Adalimumab	Significant	N
5	59	F	Melanoma	Ipi/Nivo	Arthritis		21.7	Prednisone 60 mg	Minimal	N
6	81	M	Melanoma	Ipi/Nivo	Arthritis	ANA 1.5	13.1	Prednisone 15 mg	Moderate	Y
7	59	M	RCC	Ipi/Nivo	Arthritis	ANA 1.8	56	Prednisone 10 mg	Minimal	N
8	53	M	Melanoma	Ipi/Nivo	Arthritis		16	Methylprednisolone 80 mg IM	Minimal	Y
9	63	59	NSCL	Nivo	Arthritis	ANA 1:160	38	Prednisone 30 mg Methorexate	Minimal	Y
10	57	F	Melanoma	Ipi/Nivo	Arthritis Sicca	ANA 1:320 6.7	6.7	Prednisone 30 mg	Significant	Y
11	61	M	Melanoma	Ipi/Nivo	Sicca		5.3	Prednisone 60 mg*	Significant	Y^
12	63	M	RCC	Atezolizumab	Sicca		21.9	Prednisone 60 mg*	Significant	Y^
13	68	M	Melanoma	Ipi/Nivo	Sicca PMR	ANA 1:1280 SSA	8.1	Prednisone 30 mg	Significant	Y
14	79	M	Melanoma	Nivo	PMR Sicca		2	Prednisone 20 mg	Moderate	Y
15	63	M	RCC	Nivo	PMR		213	Prednisone 40 mg Infliximab Tocilizumab	Moderate	Y
16	68	M	NSCL	Tremelimumab Durvalumab	Myositis		4.6	IV methylpred 60 mg Prednisone 60 mg	Moderate	Y

NSCL non-small cell lung cancer, RCC renal cell carcinoma, Ipi ipilimumab, Nivo nivolimumab, RF rheumatoid factor HCQ hydroxychloroquine, MTX methotrexate, *Prednisone given for hypophysitis. ^Immunotherapy held for hypophysitis.

Abstract OP0004 – Table 1

Patients	Sex/age	Type of cancer	ICI	Date of first ICI exposure	Date of IrAE	Type of rheumatic IrAE	IrAE response to treatment	Autoantibody results
1	F 55 y	Squamous cell carcinoma of the vagina	nivolumab	October 2015	October 2015	RA	resolution with NSAIDS	anti-CCP: 671 U/ml RF: 18 UI/ml
2	F 66 y	Endometrial adenocarcinoma	pembrolizumab	March 2016	April 2016	RA	resolution with corticosteroids prednisone 10 mg/day	anti-CCP: 233 U/ml RF:180 UI/ml
3	M 59 y	Lung adenocarcinoma	nivolumab	May 2016	July 2016	RA	resolution with prednisone 10 mg/d tapered to 5 mg/d 1 months later	anti-CCP: 61 U/ml RF: 47 UI/ml
4	F 56 y	Metastatic melanoma	pembrolizumab	August 2015	September 2015	RA	resolution with hydroxychloroquine 400mg/day and NSAIDS	anti-CCP: 22UI/ml
5	M 80 y	Metastatic melanoma	nivolumab	April 2016	April 2016	RA	Resolution with prednisone 15mg/day (tapered) and hydroxychloroquine 200mg/day	anti-CCP:42 UI/ml
6	M 68 y	Lung adenocarcinoma	nivolumab	June 2015	July 2015	RA	Resolution after stopping nivolumab and after 1 month of methotrexate 10 mg/w (maintained 3 months)	anti-CCP >300U/ml RF: 246 UI/ml

Center register of safety of ICI for collecting patients treated with an ICI and who developed symptoms of arthritis with diagnosis of RA.
Results: We report 6 patients without any previous rheumatic disease, who developed seropositive rheumatoid arthritis (RA) after exposition to ICIs, all of them after anti-PD1.
Conclusions: This is the first description of RA occurring after anti-PD1 treatment for cancer. All cases responded to corticosteroids or with immunosuppressive therapy. This suggests that the PD1/PDL1 axis plays a role in RA pathophysiology. The combined expertise of oncologists, immunologists and rheumatologists is crucial in the successful management of these patients.
References:
[1] 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.
Disclosure of Interest: None declared
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Fibromyalgia: a disease of the peripheral or central nervous system

OP0005 FIBROMYALGIA IN PATIENTS WITH RHEUMATOID ARTHRITIS IN A 10-YEAR PERSPECTIVE

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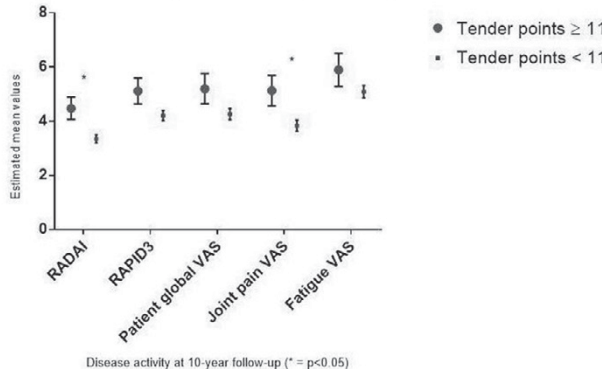
Background: Approximately 10% of patients with rheumatoid arthritis (RA) have coexisting fibromyalgia (FM). Little is known of the cross-sectional and longitudinal relationship between FM and RA disease activity.
Objectives: To examine the cross-sectional and longitudinal relationship between FM and RA disease activity.
Methods: Oslo RA register (ORAR) was established in 1994 as a prospective, observational, longitudinal nested cohort study. The inclusion criteria were RA according to the 1987-ACR classification criteria and a residential address in Oslo. 636 patients in ORAR were asked to participate in a clinical examination in 1999. A trained study-nurse systematically assessed the 18-tender point count and performed 28-tender and 28-swollen joint counts (TJC/SJC). Patients self-reported disease activity and pain related to RA, and completed the Stanford Health Assessment Questionnaire (HAQ). RA disease activity was calculated as DAS28. Fibromyalgia was diagnosed if $\geq$11 tender points were reported. FM associated variables; fatigue, muscular tenderness, headache, abdominal pain and difficulties concentrating were also scored (0–10 VAS).
At the 10-year follow-up patients completed a questionnaire that included RA Disease Activity Index (RADAI) and Routine Assessment of Patient Index Data (RAPID-3).
In cross-sectional and longitudinal analyses RA disease activity, FM associated variables and health status were compared between patients with $\geq$11 and $<$11 tender points. Level of significance was calculated using ANCOVA models corrected for age, gender, BMI and level of education. The FM associated variables at baseline were also corrected for baseline SJC 28 and C-reactive protein (CRP). The variables in the longitudinal study were corrected for the same variables as the cross-sectional analyses, but additionally for baseline values of the dependent variable when available.
Results: 488 patients agreed to participate in the baseline data-collection and 192 participated at the 10-year follow-up. The mean (SD) age was 59.5 (12.5) years, and 87% were female. There were no significant differences in age, disease duration or participation at follow-up between patients with and without FM, but only women had FM.
Patients with FM in addition to RA had higher DAS28, SJC, TJC, pain and patient global VAS, but also higher levels of fatigue, abdominal pain and concentration difficulties (table 1).

Table 1. Baseline cross-sectional associations

Variables Tender points $\geq$11 Mean (SD)	Tender joint count $<$11 n=40	Adj. Bivariate n=440	p
RA disease activity			
RA disease duration (years)	16.3 (8.9)	14.9 (9.3)	0.31
CRP (mg/L)	17.4 (24.4)	14.5 (13.4)	0.08
DAS28	5.3 (1.0)	4.4 (1.3)	0.002
PainVAS	4.5 (2.2)	3.5 (2.3)	0.03
SJC	9.8 (5.7)	6.8 (5.1)	0.04
TJC	13.3 (5.6)	7.4 (6.5)	$<$0.001
Patient disease activity VAS	4.7 (2.2)	3.7 (2.3)	0.03
Fibromyalgia related variables			
Muscular tenderness VAS	5.9 (2.7)	3.2 (2.6)	$<$0.001
Fatigue VAS	6.6 (2.7)	4.4 (2.7)	$<$0.001
Headache VAS	2.0 (2.4)	1.4 (2.1)	0.25
Abdominal pain VAS	3.7 (3.5)	1.9 (2.3)	$<$0.001
Difficulty concentrating VAS	2.9 (2.7)	1.7 (1.1)	0.003
Health Status			
HAQ	1.2 (0.1)	1.0 (0.0)	0.09

At the 10-year follow-up patient with FM had significantly higher levels of RA disease activity and pain (figure 1).

Figure 1 Longitudinal analyses
Disease activity at 10-year follow-up grouped according to baseline presence of FM



Conclusions: Presence of FM in patients with RA was associated with significantly higher levels of RA disease activity both in the cross-sectional and longitudinal perspectives. Secondary FM should be considered in patients with RA not reaching remission.
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OP0006 INFLUENCE OF AUTONOMIC NERVOUS SYSTEM DYSFUNCTION IN THE GENESIS OF SLEEP DISORDERS IN FIBROMYALGIA PATIENTS

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Background: Fibromyalgia (FM) is characterised by chronic musculoskeletal pain, autonomic nervous system (ANS) dysfunction, and disturbed sleep.
Objectives: The aim of this study was to evaluate the influence of ANS dysfunction on the genesis of sleep disorders.
Methods: Fifty consecutive Caucasian women (age 51.2±7.3 years) whose FM had been diagnosed on the basis of the 2010 ACR classification criteria were compared with 45 healthy female controls matched for age and body mass index.All of the FM patients underwent a clinical, polysomnographic and autonomic profile evaluation at rest and during a tilt test to determine muscle sympathetic nerve activity (MSNA), plasma catecholamine levels, and the spectral indices of cardiac sympathetic (LF_{RR}) and vagal (HF_{RR}) modulation computed by means of the spectrum analysis of RR during sleep.
Results: The FM patients had more tender points ($p<0.001$), a higher ESS score ($p<0.001$), and more signs and symptoms of orthostatic intolerance ($p<0.001$) than the controls. They also had a higher heart rate (HR), more MSNA and a higher LF/HF ratio, and lower HF_{RR} values at rest. The increase in tilting-induced MSNA was less in the FM patients (2±1 *vs* 16±3.1 bursts/min, $p<0.05$; 2±1 *vs* 12±2.8 bursts/100 $p<0.05$), whereas the trend in the spectral indices of the cardiac autonomic profile (LF_{RR} and the LF/HF ratio) and plasma catecholamine levels were similar in the two groups; furthermore, the decrease in the index of cardiac vagal modulation (HF_{RR}) was also less in the patients (HF_{RR}NU -17.3±3.2 *vs* -32.4±4.8, $p<0.05$; $HF_{RR}ms^2$ -148±50 *vs* -857±374, $p<0.05$). The stepwise tilt induced syncope or pre-syncope in 23 of the 50 patients (46%) and two of the 45 controls (5%) ($p<0.001$),Their sleep was less efficient ($p<0.01$), and they had a higher proportion of stage 1 non-REM sleep ($p<0.001$), experienced many arousals and periodic limb movements (PLMs) per hour of sleep ($p<0.001$) and a high proportion of periodic breathing (PB%) ($p<0.0001$). Their cyclic alternating pattern (CAP) rate was significantly increased ($p<0.001$).During sleep, the patients had a higher HR, and LF/HF ratio, and lower HF_{RR}, differences that were more marked during non-REM sleep, as were the presence of CAP, PB and PLMs. PLMs were mainly observed during CAP subtype A2 and A3. As in the tilt test, there was also a decrease in the index of cardiac vagal modulation during sleep: the decrease in HR_{RR} during sleep and in comparison when awake was less in the FMS patients than the controls (11.6±4.2 *vs* 31.1±5.3 NUs, $p<0.01$; 45±38 *vs* 403±281 ms^2, $p<0.0001$)
The number of tender points, pain VAS, the CAP rate, the PB% of sleeping time and the PLMI all seemed to correlate positively with HR and the LF/HF ratio, and negatively with HF_{RR} during sleep
Conclusions: Our data confirm that the FM patients have an autonomic nervous system dysfunction that is consistent with sympathetic over-activity due to the