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Immune events with checkpoint inhibitors

OP0194

GENERALIZED IMMUNE ACTIVATION IN STRUCTURES RELATED TO PMR OR GCA ON PET/CT ASSESSMENT DOES NOT OCCUR IN IMMUNE CHECKPOINT INHIBITOR-TREATED PATIENTS WHO DO NOT GO ON TO DEVELOP RHEUMATIC IMMUNE-RELATED ADVERSE EVENTS

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Background: The pathogenesis of rheumatic immune-related adverse events (irAEs) from checkpoint inhibitor cancer immunotherapy directed against programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) remains unknown, even though they are a consequence of pharmacologic inhibition of a specific immune mechanism. Given that some irAEs resemble polymyalgia rheumatica (PMR) or giant cell arteritis (GCA), a disease whose pathogenesis is poorly understood, observations regarding the pathogenesis of PMR-like or GCA-like irAEs are of significant interest. One proposed pathogenic mechanism involves generalized immune activation leading to a spectrum of subclinical disease. Interrogation of this hypothesis may be aided by PET/CT, which is frequently utilized for oncological staging purposes but is also useful in classical PMR or GCA diagnosis. If PMR or GCA irAEs merely represent a spectrum of generalized immune activation, low-grade subclinical PMR or GCA-related changes on PET/CT might be expected to be seen in patients who receive immunotherapy, irrespective of whether they develop clinically evident rheumatic irAEs.

Objectives: This study investigated whether such changes occurred in patients receiving immunotherapy who did not develop clinically evident rheumatic irAEs.

Methods: Consecutive patients exposed to PD-1 or PD-L1 inhibitor immunotherapy at a single center had scintigraphic uptake calculated by a nuclear medicine physician experienced in assessment of vasculitis. Patients were included if they had had 18F-fluorodeoxyglucose (18F-FDG) PET/CT imaging both within the two weeks prior to immunotherapy initiation and after at least eleven weeks of immunotherapy. Patients who went on to develop a rheumatic irAE were excluded, as were patients with scintigraphic evidence of liver metastases owing to their potential influence on scoring of uptake. Quantification of 18F-FDG uptake by maximum standardized uptake values (maximum standard unit value, SUVmax) was performed at sites relevant to PMR or GCA (17 sites relevant to PMR, 17 sites relevant to GCA) in paired scans, and the difference calculated.

Results: Twenty-four patients receiving nivolumab, pembrolizumab or avelumab met the inclusion criteria, primarily for melanoma, non-small cell lung cancer, or lymphoma. The mean age was 67 at the time of the first scan, 71% were male, and 66% had a complete or partial oncological response at best response. No statistically or clinically significant difference in SUVmax was noted at any PMR or GCA-relevant anatomical site interrogated. Latent class analysis did not reveal clusters identifiable by cancer type, best response, or presence of combination therapy.

Conclusion: Patients treated with PD-1/PD-L1 inhibitors without clinically evident rheumatic irAEs do not develop subclinical PMR or GCA-like changes on PET/CT. This supports the proposition that PMR-like and GCA-like irAEs are a distinct entity with stochastic onset, and do not simply represent generalized immune activation induced by immunotherapy.

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OP0195

PLASMA CHECKPOINT PROTEIN LEVELS AND GALECTIN-9 IN JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic Lupus Erythematosus (SLE) is the prototype for a systemic autoimmune disease. SLE is a disease of the adaptive immune system where T lymphocyte dysfunction has an important role as well. Checkpoint proteins have become an important topic in the study of T cell. The balance of T cell co-stimulatory and co-inhibitory receptors is important for the regulation of the adaptive immune system response.

Objectives: In this study we aimed to assess the checkpoint proteins in childhood SLE patients

Methods: Forty-nine jSLE patients together with 15 age- and gender-matched controls were included. Clinical features, disease activity scores and laboratory parameters were recorded both retrospectively and at the time of sampling. Patient samples were collected at their last visit, Plasma CD25 (IL-2R α), 4-1BB, B7.2 (CD86), TGF- β 1, CTLA-4, PD-L1, PD-1, Tim-3, LAG-3, Galectin-9 levels were studied by the cytometric bead-based multiplex assay panel according to manufacturer's instruction (LEGENDplex HU Immune Checkpoint Panel 1 (10-plex); catalogue number 740962, Biolegend) and analysed by Novocyte 3005 flow cytometer. Two-step cluster analysis procedure was conducted over the chosen 7 symptom status and 3 clusters were chosen for the final analysis

Results: A total of 49 patients (71.4% female) diagnosed with SLE according to the SLICC criteria and 15 healthy controls (73.3% female) were included in the study. The mean age of the patients was 17.7 ± 2.6 years and the controls was 13.3 ± 1.4 years. The median disease duration was 5.7 years. At the time of sampling fifteen of the patients had a SLEDAI score of zero (no activity), 21 of them had between 1-5 (mild activity), 7 of them had between 6-10 (moderate activity), 5 of them had between 11-19 (high activity), 1 of them had >20 (very high activity).

Galectin-9 and PD-L1 were significantly higher in SLE patients. Other checkpoint proteins and IL-2R α were also higher but did not reach statistical significance. There were significant correlations between SLEDAI and IL-2R α , Galectin-9 and PDL1. (Figure 1) There were three clinical clusters: Cluster 1 included patients with no major organ involvement, cluster 2 had predominantly haematological involvement (n=16) and cluster 3 (n=11) had predominantly renal involvement. Checkpoint proteins were not different among these three clusters.

Figure 1.

Table 1. Demographic, Clinical and Laboratory Features of Patients (n=49)

Female gender, n (%)	35 (71.4)
Mean age at diagnosis, years (mean±SD)	12.5±3.3
Mean age at the time of inclusion, years (mean±SD)	17.7±2.6
Duration of illness, years (median/IQR)	5.7 (3.0-7.0) years
Active system involvement at study, n (%)	
Renal	14 (28.5)
Skin	11 (22.4)
Musculoskeletal	9 (18.3)
Hematologic	9 (18.3)
Neurologic	1 (2.0)
Serositis	1 (2.0)
Laboratory findings (median/minimum-maximum)	
Hemoglobin, gr/dl	12.7 (7.3-18.3)
WBC, /mm ³	6.900 (2.600-26.200)
Platelet, /mm ³	252.000 (39.000-529.000)
Erythrocyte sedimentation rate, mm/hour	10 (1-71)
C-reactive protein, mg/dl	0.1 (0-21.1)
Complement 3, mg/dl	87.6 (25.4-186.0)
Complement 4, mg/dl	15.3 (0-45.8)
Anti-ds DNA, IU/ml	12.8 (0-741.7)
SLEDAI score (mean±SD)	4.69±6.69

Conclusion: Our data supports that Galectin 9 and IL-2R α are good markers for disease activity in childhood SLE. We need larger series to evaluate differences between disease clusters in SLE. We failed to show a significant correlation with checkpoint proteins and SLEDAI except for PDL1.

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The aftermath of metabolic imbalance in OA

OP0196

CIRCULATING LEVEL OF IL-6 IS ASSOCIATED WITH 10.7-YEAR KNEE CARTILAGE VOLUME LOSS AND WORSE PAIN TRAJECTORY

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Background: There is growing evidence that inflammation plays a critical role in osteoarthritis (OA) progression and its symptoms evolution. OA pain is heterogeneous and there are distinct subgroups within OA pain patients. Recently, we identified three homogeneous subgroups following distinct pain trajectories in which metabolic mechanism may be involved. Whether circulating inflammatory markers are associated with long-term knee structural changes on MRI, and whether the association between inflammatory markers and the trajectories we identified differs remain to be clarified.

Objectives: To examine whether inflammatory markers are associated with 10.7-year knee structural changes including knee cartilage volume (CV) and bone

marrow lesions (BMLs), and to assess the associations between inflammatory markers and different pain trajectories.

Methods: This study was conducted as part of a population-based older adult (mean age 63 years, 51% of females) cohort study with 1,099, 875, 768 and 563 participants attending at baseline, and 2.6-, 5.1- and 10.7-year follow-ups. Circulating levels of interleukin (IL)-6, tumour necrosis factor alpha (TNF- α) and high sensitivity C-reactive protein (CRP) were measured at baseline in 193 randomly selected participants. T1-weighted or T2-weighted MRI of the right knee was performed to measure CV and BMLs at baseline and 10.7-year. X-ray was performed to assess radiographic knee osteoarthritis (ROA). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain questionnaire was used to measure knee pain at all four visits. Data on demographic, psychological, lifestyle and comorbidities were also collected. Pain trajectories was previously identified using the group-based trajectory modelling. Linear, log-binomial and multi-nominal logistic regression modellings were used for the analyses.

Results: IL-6 was associated with both medial and lateral tibial CV loss (Medial: β =-0.51% per log pg/ml, 95%CI -0.88 to -0.15; Lateral: β =-0.34% per log pg/ml, 95%CI -0.64 to -0.04) after adjusting for age, sex, body mass index, physical activity, comorbidities, and ROA. TNF- α was not associated with either medial or lateral CV loss, but CRP was positively associated with medial tibial CV loss (Medial: β =0.27% per log mg/L, 95%CI 0.04 to 0.49), not lateral CV loss. No inflammatory markers were found to associate with medial and lateral BML size increase. Of 169 participants who had complete data at baseline, 54%, 35% and 11% of participants fell into 'Minimal pain', 'Mild pain' and 'Moderate pain' trajectory group, respectively. In multivariable analysis, IL-6 was associated with an increased risk of being a 'Moderate pain' trajectory (relative risk ratio [RRR]: 4.03, 95%CI 1.34 to 12.13) in comparison with 'Minimal pain' trajectory group. There was no significant association of TNF- α and CRP with trajectory groups.

Conclusion: IL-6 was associated with both medial and lateral tibial CV loss (Medial: β =-0.51% per log ml/pg, 95%CI -0.88 to -0.15; Lateral: β =-0.34% per log ml/pg, 95%CI -0.64 to -0.04) after adjusting for age, sex, body mass index, physical activity, comorbidities, and ROA. TNF- α was not associated with either medial or lateral CV loss, but CRP was positively associated with medial tibial CV loss (Medial: β =0.27% per log ml/pg, 95%CI 0.04 to 0.49), not lateral CV loss. No inflammatory markers were found to associate with medial and lateral BML size increase. Of 169 participants who had complete data at baseline, 54%, 35% and 11% of participants fell into 'Minimal pain', 'Mild pain' and 'Moderate pain' trajectory group, respectively. In multivariable analysis, IL-6 was associated with an increased risk of being a 'Moderate pain' trajectory (relative risk ratio [RRR]: 4.03, 95%CI 1.34 to 12.13) in comparison with 'Minimal pain' trajectory group. There was no significant association of TNF- α and CRP with trajectory groups.

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OP0197

EVALUATION OF THE RELATIONSHIP OF LEPTIN WITH THE METABOLIC PHENOTYPE OF KNEE OSTEOARTHRITIS IN THE CONTEXT OF OBESITY THERAPY

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Background: Obesity and components of the metabolic syndrome (MS) play a key role in the pathogenesis of the metabolic phenotype of osteoarthritis (OA). Obesity is a process meta inflammation due to the synthesis of proinflammatory mediators (adipokines and adipocytokines). The severity of OA depends on the presence of obesity, adipokine activity, comorbidity, and the presence of MS. The problem of treatment of metabolic OA and obesity is very relevant, in connection with the obesity pandemic.

Objectives: To evaluate the relationship of leptin with the clinical manifestations of OA and various components of MS in the context of obesity therapy.

Methods: The study included 50 female patients aged 45-65 y.o. with Kellgren-Lawrence stage II-III knee OA and obesity (body mass index (BMI)>30kg/m²). The average age of the patients was 56.5 ± 5.86 years, the average duration of the disease was 7.43 ± 3.93 years. 62% of patients were diagnosed MS. Patients were randomly divided into 2 groups for the treatment of obesity.