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SATURDAY, 15 JUNE 2019

Lessons learned from checkpoint inhibitors

OP0335

A PROSPECTIVE CLINICAL AND MRI STUDY OF IMMUNE CHECKPOINT INHIBITOR (ICI)-INDUCED MUSCULOSKELETAL MANIFESTATIONS MYO-FASCIITIS AND NOT SYNOVITIS IS THE PROMINENT IMAGING FINDING

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Background: Immune check point inhibitors (ICI) were a breakthrough in cancer therapeutics. These agents target certain "brakes" of the immune system aiming at activating T cells to fight cancer. Taking into account their mechanism of action it is no surprise that they have been associated with immune related adverse events

Objectives: To assess the prevalence, clinical and imaging characteristics of ICI-induced musculoskeletal manifestations in a prospective manner

Methods: This is a prospective, clinical and MRI study conducted from Jan 2016 to Oct 2018. All patients treated with ICI who developed musculoskeletal manifestations were referred to the Rheumatology Department and subjected to a full clinical assessment and laboratory workup. An MRI of the involved area(s) was performed within one week of the initial clinical evaluation. In 2 patients MRI was not performed due to claustrophobia (n=1) and presence of non compatible metal implant (n=1).

Results: During the study period a total of 130 patients were treated with ICI. Of those, 10 (7.7%) developed ICI-induced musculoskeletal manifestations. They suffered from lung (n=4), bladder (n=3), renal cancer (n=2) or melanoma (n=1) and received treatment with nivolumab (n=7), pembrolizumab (n=1), durvalumab (n=1) and atezolizumab (n=1). They were mostly male (n=8) with a mean $\pm$ SEM age of 66.7 ± 2.6 years. The median (range) time from ICI treatment since development of symptoms was 2.5 (1-22) months. Autoantibodies (RF/ACPA/ANA) were negative in all patients and only 3/10 had a mild/moderate increase of inflammatory markers at disease onset. Three different patterns of musculoskeletal manifestations were found: i) Prominent joint involvement (n=3). Areas involved were the small joints of the hands (n=2) and knee/ankle (n=1). The MRI of the latter patient depicted not only synovitis but also myositis of the muscles surrounding the involved joints, ii) Prominent "periarticular" involvement (n=4). These patients had diffuse swelling of the hands (n=4) feet (n=3) or knees (n=1). Joints retained a good and relatively painless range of motion. MRI depicted mild synovitis with more prominent myositis and/or fasciitis in the surrounding tissues in all cases, iii) Myo-fasciitis (n=3). In all 3 such cases the involved area was the knee. Clinically, these patients presented with pain in the knee and either no objective signs of arthritis (n=2) or swelling with non inflammatory synovial fluid. MRI depicted myo-fasciitis of the surrounding muscles in all cases; a partial tear of the quadriceps tendon was also found in the patient with knee swelling. Overall, symptoms were mild/moderate and responded well to treatment (low dose steroids in 6 and NSAIDs/analgesics in 4) with no need for ICI discontinuation.

Conclusion: In our cohort ICI-induced musculoskeletal manifestations were not uncommon and developed in 7.7% of patients. Imaging evidence of myo-fasciitis was found in all patients indicating that the muscle/fascia is more frequently involved than the synovium. Our clinical and imaging data point to the direction that ICI-induced musculoskeletal manifestations mostly involve periarticular structures and associate mainly with myo-fasciitis and not synovium based pathology

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OP0336

COMMONLY USED DRUGS IN RHEUMATOLOGY MAY ALTER ANTI-TUMORAL RESPONSE TO IMMUNE CHECKPOINT INHIBITORS

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Background: Immune checkpoint inhibitors (ICIs) are revolutionizing the treatment of some advanced cancers. Gut microbiota has emerged as an important component of anti-tumoral response and can also be related to the occurrence of immune-related adverse events (irAEs). It has recently been shown that antibiotic treatment given at the initiation of ICI therapy had a dramatic impact on microbiota that compromised the anti-tumoral effect of ICIs (1).

Objectives: To evaluate whether co-medications known to have a potential impact on gut microbiota may alter ICI efficacy and/or irAE occurrence when given at ICI onset.

Methods: This was a retrospective cohort study including all cancer patients who received ICIs at our institution from May 2015 to September 2017. Co-medications given to the patients within one month before or one month after the first administration of ICI were extracted from medical records on the basis of a predefined list of medications known to impact gut microbiota. The tumour response, occurrence of irAEs and patient outcomes were assessed on a regular basis. Overall survival (OS) has been considered from the start of ICI therapy.

Results: 635 patients (70% male, mean age 64.5 years) were included, of whom 293 had melanoma, 150 had advanced non-small cell lung cancer and 83 had renal carcinoma. A previous autoimmune disorder was present in 8% of patients, mainly rheumatic and endocrine diseases. Psychotropic drugs (41.1%), proton pump inhibitors (PPIs) (37.3%), angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) (32%), glucocorticoids (GC) (24.2%), antibiotics (21.4%), statins (20.8%) and morphine (20.6%) were the most co-prescribed medications. Baseline GC use, when ≥ 10 mg of prednisone equivalent, was associated with a significant decrease in OS (median 4.5 months versus 24.3 months; $p < 0.0001$) and a less frequent tumour response (55% versus 73%; $p = 0.0001$). When given after ICI onset for the management of irAEs, GC did not influence ICI efficacy (Figure A). Baseline PPIs use also altered both OS (median 10.9 versus 24.3 months; $p < 0.0001$) and tumour response (62% versus 71%; $p = 0.02$) (Figure B). We confirmed the detrimental impact of antibiotics when given at ICI onset, and also found worse outcomes for patients receiving baseline psychotropic drugs (median OS 9.3 versus 19.4 months; $p = 0.0001$). No significant difference was observed with baseline use of NSAIDs, aspirin, statins and ARBs/ACE. Furthermore, co-medication with antibiotics, GC, PPIs, morphine, NSAIDs, aspirin and psychotropic drugs was associated with decreased occurrence of irAEs.

Conclusion: As many of these treatments are used by rheumatologists, one should be aware of their potential detrimental effect when used at ICI initiation, that sometimes could have been avoided.

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Orthotic treatment: is it in or out?

OP0337-HPR

EFFECTIVENESS OF CUSTOMIZED INSOLES IN PATIENTS WITH MORTON'S NEUROMA: A RANDOMIZED, CONTROLLED, DOUBLE-BLIND CLINICAL TRIAL

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Background: Morton's neuroma (MN) is a benign enlargement of the third common digital branch of the medial plantar nerve. The most common symptom is burning pain in the plantar foot, located between the metatarsal heads, often radiating to the two corresponding toes. Treatment can be surgical or conservative, which consists of decreasing nerve pressure and irritation through therapies that promote analgesia, patient education, and plantar orthosis. The custom insole prescriptions are aimed at relieving the pressure in the MN region, and to redistribute pressure throughout the sole of the foot. There is no study evaluating the effect of insoles in patients with MN.

Objectives: The aim of the present study was to assess the effectiveness of a customized insole with metatarsal and arch support on pain in patients with Morton's neuroma and the impact of this insole on function, load distribution in the plantar region, gait, quality of life and satisfaction with insole use.

Methods: A randomized, controlled, double-blind, clinical trial was carried out with intent-to-treat analysis. Seventy-two patients with NM were randomly allocated into a study group (n=36) and control group (n=36). One week following the baseline evaluation, the study group received a customized insole with metatarsal and arch support made of ethyl vinyl acetate and the control group received a flat insole of the same material, color and density. The groups were evaluated after 6, 12 and 24 weeks of insole use. The following assessment parameters were employed: pain when walking, on palpation and at rest (END); paresthesia (ENP); quality of life (SF-36); foot function (FFI and FHSQ); six-minute walk test (6MWT) and foot pressure analysis using the AM Cube FootWalk Pro program.

Results: The groups were homogeneous regarding the majority of variables at baseline. In the comparisons over time, statistically significant differences between groups were found for pain when walking (p=0.048), in the general health domain (p<0.001) and physical activity (p=0.025) in the FHSQ questionnaire, in the general FFI questionnaire score (p=0.012) and in the functional capacity domain of the SF-36 questionnaire (p=0.046). For pain at rest and palpation, in the domains of the FFI, some parameters of the FHSQ (vigor, pain, function and general health of the foot) and quality of life (limitation by physical aspects, bodily pain and vitality), we observed improvement in both groups with no statistically significant difference between them. No change was observed in the baropodometry parameters with the use of the insole.

Conclusion: A customized insole with metatarsal and arch support reduce pain when walking and improve function of patients with NM.

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Current treatment of vasculitis

OP0338

LOW-DOSE IL-2 SELECTIVELY RESTORES REGULATORY T CELLS IN PATIENTS WITH BEHCET'S DISEASE

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Background: The lack of CD4+CD25+Foxp3+ T regulatory cell (Treg) has been associated with human systemic autoimmune diseases, such as rheumatoid arthritis (RA). IL-2 is an essential growth and survival factor for Treg cells. However, the significance of Treg cells in the pathogenesis and the effect of low dose IL-2 on Behcet's disease (BD) are rarely reported.

Objectives: To investigate the significance of Treg cells and the effect of low dose IL-2 on BD.

Methods: Eighty patients with BD and seventy healthy donors were enrolled. CD4⁺T cell subsets in peripheral blood mononuclear cells from these people were measured by multicolour flow cytometry. Twenty-six patients were treated daily with subcutaneous injections of 0.5 million IU of human IL-2 for five consecutive days. CD4⁺T cell subsets were analysed before and after treatment by flow cytometry.

Results: Compared to health control, the absolute counts of circulating Treg cells were significantly decreased in patients with BD (median:29.93 cells/ul VS median:33.16 cells/ul, $P=0.039$) and it is negative correlation with disease activity. While the ratios of Th17/Treg in patients with BD (median:0.29) were significantly higher than those of health control (median:0.2). No difference in the absolute counts of circulating Th17 cells (CD4⁺IL-17⁺) between patients with BD and health control. Treatment of patients with BD with a low-dose IL-2 selectively increased the absolute counts of Treg cells, from a median of 18.97 cells/ul to 74.68 cells/ul (at 5 days) ($P<0.001$). No significant difference was observed in the absolute counts of circulating Th17, Th1 and Th2 cells after IL-2 treatment.

Conclusion: Th17/Treg cells may play a role in the pathogenesis of patients with BD, low-dose IL-2 proposes a selective biological treatment strategy by restoring immune tolerance.

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OP0339

TOCILIZUMAB IN GIANT CELL ARTERITIS. MONOTHERAPY VERSUS COMBINED WITH CONVENTIONAL IMMUNOSUPPRESSIVE DRUGS

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Background: Giant cell arteritis (GCA) can be refractory to corticosteroid therapy. Tocilizumab (TCZ) has been approved in the treatment of GCA. There are no studies comparing the efficacy and safety when using TCZ as monotherapy or in combination with conventional immunosuppressive drugs in GCA.

Objectives: Our aim was to compare efficacy and safety of TCZ combined or in monotherapy in GCA.

Methods: Multicenter study on 134 patients with refractory GCA who received TCZ therapy as monotherapy or combined with conventional immunosuppressants. Prolonged remission, absence of clinical symptoms and signs and normalization of the acute phase reactants for at least 6 months. Relapse, recurrence of signs or symptoms of GCA and/or ESR >20 mm/h in men or >25 mm/h in women, and/or serum CRP >0.5 mg/dL related to GCA, both before and after starting TCZ therapy.

Results: We evaluated 134 patients (101 w/33 m) with a mean age of 73.0±8.8 years. TCZ was prescribed as monotherapy in 82 (62.2%) cases and combined with conventional immunosuppressants in 52 (38.8%) patients: MTX (n=48), AZA (n=3), and LFN (n=1). A comparative study between both groups is summarized in **TABLE**. Patients who received combined TCZ were younger and had a higher C-reactive protein (CRP) and a higher presence of aortitis in imaging techniques. After TCZ was started, prolonged remission was reached with combined therapy (statistical significance at 12 and 24 months). The corticosteroids sparing effect