THU0615 IMMUNE RELATED ADVERSE EVENTS (IRAEs) ASSOCIATED WITH CHECKPOINT INHIBITORS: 12 CASES FROM A SINGLE CENTRE

D. Ennis, F. To, S. Jamal. *Rheumatology, University of British Columbia, Vancouver, Canada*

Background: Immune checkpoint inhibitors (ICI) have made a significant impact on the treatment of many advanced malignancies. There is little data on the rheumatologic complications of these treatments.

Objectives: We describe 12 cases of rheumatologic IRAEs following ICI treatment to further characterise the spectrum of disease and treatment responses.

Methods: We report patients evaluated in a general Rheumatology outpatient clinic from 2014 to 2017. Cases were defined as those with new rheumatologic symptoms following treatment with an ICI. Alternative explanations for the presenting syndrome were excluded clinically. Clinical data was extracted by retrospective chart review.

Results: This case series includes 12 patients (6 female, 6 male) with a mean age at IRAE onset of 63.9 years (range 33–79). Multiple cancers were represented including melanoma (n=9), Hodgkin's lymphoma (n=1), squamous cell lung cancer (n=1), and adenocarcinoma of the lung (n=1). 5/12 patients received Nivolumab, 8/12 received Pembrolizumab, and 2/9 received Ipilimumab. ICI exposure was associated with various rheumatologic IRAEs including PMR-like syndrome (n=4), symmetric polyarthritis (n=6), psoriatic arthritis (n=1), oligoarthritis (n=1), and erythema nodosum (n=1). Other IRAEs were also noted including vitiligo (n=1), pulmonary capillaritis (n=1), ulcerative colitis flare (n=1), inflammatory seborrheic keratosis and psoriasis (n=1). The mean time of onset of the IRAE from the first exposure to an ICI was 6.8 months (range 0–21 months). In 7 cases, rheumatologic symptoms worsened with each ICI dose. Laboratory investigations demonstrated elevated CRP in 7 cases (mean 75.6; range 3.7–290.1), RF positivity in 2 cases, weak positive ANAs in 4 cases (1:80), SSA positivity in 2 cases, and a single case where a pre-existing anti-CCP antibody was identified. Steroids were used in 11 cases at a mean starting dose of 36 mg (range 10–50 mg) by mouth daily for an average duration of 6.1 months (range 1–12 months). Other DMARDs were necessary in some cases (Hydroxychloroquine n=1; Methotrexate n=5). While 6 patients experienced rapid improvement, 4 experienced gradual improvement. Most patients achieved partial resolution of symptoms (n=6) while only 4 achieved complete resolution. Tumour response was observed in all 12 patients.

Conclusions: This case series of IRAEs associated with ICI treatment suggest that symmetric polyarthritis and PMR-like syndromes are the most common rheumatologic IRAEs, although the spectrum is broad. IRAEs seem to develop around 6 months after first exposure, worsen with ongoing doses of ICI administration, and respond to treatment with corticosteroids. Treatment doses and duration were higher than expected for phenotype, with few patients achieving significant improvement with short courses. Those with IRAEs tend to have good tumour response, despite concurrent use of immunosuppressants. MTX and HCQ appear to be safe and effective, but more experience with these and other DMARDs/biologics is required in these patients.

Disclosure of Interest: None declared

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THU0616 ELEVATED THYROID STIMULATING HORMONE AS A POTENTIAL BIOMARKER FOR RHEUMATIC IMMUNE-RELATED ADVERSE EVENTS FOLLOWING PD-1 INHIBITOR THERAPY

D.F.L. Liew^{1,2,3}, J.L.Y. Leung^{1,3}, C. McMaster², F. Djukiadmodjo², B. Liu¹, J. Cebon⁴, A.G. Frauman^{2,3}, R.R.C. Buchanan^{1,3}. ¹*Rheumatology*; ²*Clinical Pharmacology and Therapeutics, Austin Health, Heidelberg*; ³*Medicine, University of Melbourne, Parkville*; ⁴*Olivia Newton-John Cancer Wellness and Research Centre, Heidelberg, Australia*

Background: Programmed cell death protein (PD-1) inhibitor immunotherapy is being increasingly used in oncology, but may cause immune-related adverse events (irAEs) resembling classical rheumatic and non-rheumatic autoimmune diseases. While oncological response to therapy has been associated with the development of rheumatic irAEs, no biomarker to predict the development of rheumatic irAEs has yet been identified. Thyroid stimulating hormone (TSH) is readily available in clinical practice and is frequently tested prior to the administration of PD-1 inhibitors to screen for existing thyroid disease.

Objectives: To investigate whether thyroid stimulating hormone, or changes to it, are associated with the development of immune-related adverse events (irAEs) following PD-1 inhibitor therapy for cancer.

Methods: This was a retrospective chart review of all patients at a single centre who had a TSH level before in the institutional laboratory prior to the patient being dispensed nivolumab or pembrolizumab before January 1, 2017, with follow-up until July 1, 2017. TSH levels before and during PD-1 inhibitor therapy were recorded. Patients with any diagnosis of a rheumatic irAE or any non-

cutaneous irAE were identified. Linear regression was performed to determine the relationship between TSH and the development of irAEs. Youden's index was used to derive the optimal cut-off point. Recursive partitioning methods with imbalanced prior probabilities were used to create a decision tree model.

Results: There were 213 episodes of therapy which met criteria, of which a non-cutaneous irAE occurred in 62 episodes (29.1%), thyroid irAEs occurred in 22 episodes (10.3%) and rheumatic irAEs were diagnosed in 16 episodes (7.5%). Even when corrected for duration of exposure to PD-1 inhibitor therapy, elevated TSH levels (>4.2 mU/L) were statistically significantly associated with the development of rheumatic irAEs (adjusted OR 6.08, 1.53–24.22), and this was not weakened by excluding patients who went on to develop thyroid irAEs. There was no significant association between elevated TSH levels and the development of any non-cutaneous irAE. Change in TSH levels with PD-1 inhibitor therapy was also not associated with the development of non-cutaneous irAEs or rheumatic irAEs specifically. Using a TSH level >2.4 to predict rheumatic irAEs led to a positive predictive value of 25% and a negative predictive value of 93% in our cohort. A decision tree model to predict rheumatic irAEs combining a pre-PD-1 inhibitor TSH level >2.4 and an oncological response to therapy led to a positive predictive value of 50% and a negative predictive value of 94% in our cohort.

Conclusions: Elevated TSH levels may be a potential biomarker for the development of rheumatic irAEs. In particular, a pre-PD-1 inhibitor TSH level of >2.4 mU/L, in combination with oncological response to therapy, may identify patients at risk of rheumatic irAEs. Associations observed in this cohort should be examined in larger cohorts to determine the clinical utility of TSH in predicting rheumatic irAEs.

Disclosure of Interest: None declared

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THU0617 IS THE NUMBER OF IGG4+ PLASMA CELLS SEEN BY IMMUNOSTAINING USEFUL BEYOND ITS DIAGNOSTIC UTILITY IN IGG4-RELATED DISEASE?

E. Martín Nares¹, J. Guerrero Castillo², A. Angeles Angeles², G. Hernández Molina¹. ¹*Immunology and Rheumatology Department*; ²*Pathology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*

Background: The histopathological findings in IgG4-related disease (IgG4-RD) includes the presence of marked IgG4 + plasma cell infiltration seen by immunostaining and it has been used in clinical practice only as a diagnostic tool. Whether the number of IgG4 + plasma cells in tissue is associated with any clinical or serological feature of the disease has not been previously evaluated.

Objectives: To evaluate if the number of IgG4 + plasma cell infiltration is associated with any clinical or serological outcome.

Methods: We included 30 patients with biopsy proven IgG4-RD according to the Comprehensive Diagnostic Criteria for IgG4-RD who regularly attended a tertiary referral centre in Mexico City (2000–2017). We collected demographics, clinical (organ involvement, relapses and the disease activity assessed by the IgG4-RD Responder Index [IgG4-RD RI] at baseline) as well as baseline laboratory data (C3, C4, total eosinophil count, IgG4 levels). Patients were divided in three groups according to the number of IgG4 + plasma cells seen by immunostaining as follows: <50 IgG4 + plasma cells/HPF, 50–100 IgG4 + plasma cells/HPF, and >100 IgG4 + plasma cells/HPF.

Results: We included 30 patients, 17 (56.6%) women, mean age 53±13.9 years and median disease duration 13 months. The biopsies were from the following tissues: lacrimal gland (n=6), pancreas (n=5), orbit (n=4), kidney (n=4), lymph node (n=3), mediastinum (n=2), salivary gland (n=2) and other tissues (n=4). Eleven patients (36.6%) had <50 IgG4 + plasma cells/HPF, 9 patients (30%) 50–100 IgG4 + plasma cells/HPF and 10 (33.3%) patients >100 IgG4 + plasma cells/HPF. We did not find any difference regarding age, gender, time of follow up, number of involved organs and relapses. The median basal IgG4-RD RI was 9, 6 and 15, for the <50 IgG4 + plasma cells/HPF, 50–100 IgG4 + plasma cells/HPF, and >100 IgG4 + plasma cells/HPF groups respectively, however, they did not reach statistical significance. The group with >100 IgG4 + plasma cells/HPF had more frequently lymphadenopathy when compared with the other groups (36.4%, 66.7% and 80%, p=0.02; respectively) while the proportion of involvement of the other anatomic sites were similar. We found a statistical difference in serum C3 levels (99.5 mg/dl, 159 mg/dl, 78.5 mg/dl, p=0.04) and a tendency for serum C4 levels (20 mg/dl, 27 mg/dl, and 6 mg/dl, p=0.08) among the groups, whereas the levels of serum IgG4 (60.8 mg/dl, 196 mg/dl, 245 mg/dl, p=0.35) and the eosinophil count (284/mm³, 189/mm³, 283/mm³, p=0.46) were similar. The C3 and C4 serum levels negatively correlated with the basal IgG4-RD RI (τ = -0.48, p=0.005 and τ = -0.58, p=0.001).

Conclusions: Our results show that the number of IgG4 + plasma cells seen by immunostaining in IgG4-RD may be of value in identifying a subset of patients with hypocomplementemia, lymphadenopathy and probably higher basal disease activity. The finding of an association between hypocomplementemia and higher tissue infiltration by IgG4 + plasma cells expands the evidence that complement activation may contribute to the pathogenesis of IgG4-RD.

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THU0618 HYPOPHOSPHATASIA IN FRENCH TERTIARY CARE HOSPITALS

E. Ebstein¹, T. Thomas², B. Cortet³, K. Briot¹, C. Roux¹. ¹Rheumatology, Hôpital Cochin, Paris; ²Rheumatology, CHU Saint Etienne, Saint Etienne; ³Rheumatology, CHRU Lille, hôpital Roger Salengro, Lille, France

Background: Hypophosphatasia is a rare heritable metabolic disorder. Its prevalence is estimated at 1: 1 00 000. Its diagnosis can only be established after genetic confirmation. A low serum total alkaline phosphatase (ALP) level is the hallmark for the diagnosis of hypophosphatasia. Its prevalence is 0.05% in the general population and may be associated with symptoms similar to those of adult forms of hypophosphatasia: excess of joint pathology (chondrocalcinosis, osteoarthritis), periarticular disorders (calcifications, tendinopathies enthesopathies), and disorders of bone mineralization (risk of fracture).

Objectives: The aim of this study was to assess the recognition of persistent low ALP in 3 tertiary care hospitals in France.

Methods: All of the ALP assays of 3 tertiary care hospitals measured in 2013 were reviewed. Persistent hypophosphatasemia was defined by at least one assay <30 IU/L without any assay >40 IU/L. Selected records were analysed to eliminate secondary causes of hypophosphatasemia. A telephone questionnaire was conducted with included patients from the rheumatology and internal medicine departments.

Results: In 2013, 288,851 PAL assays were performed in 1 24 044 patients. Excluding emergency and intensive care unit services, 216,817 PAL assays were performed in 83 657 patients. 716 patients had a value ≤30 IU/L. Of these, 174 had 1 single dosage, 542 multiple dosages, of which 186 never had value >40. 31 patients were excluded due to secondary hypophosphatasemia: severe caloric restriction (n=10), massive surgery (n=6), cancer/hemopathy (n=8), acute pathology -sepsis/voluntary drug intoxication (n=4), high-dose corticosteroid therapy (n=3)). 155 patients were selected; the prevalence of hypophosphatasemia in hospitals is therefore 0.124%. Hypophosphatasemia was noticed in the summary discharge in 1,3%. 4 patients received bisphosphonates despite low PAL (before treatment) and 2 patients had a fracture under treatment. Of the 155, 38 were followed in the rheumatology and internal medicine departments and 33 answered a standardised telephone questionnaire (78% women, average age 43.8 years). 11 patients reported a history of fracture, 2 patients had a history of rickets in childhood, and 1 had known hypophosphatasia in the family. 9 patients had tooth enamel disorders, 7 had gingival recession, 3 had spontaneous tooth loss, and 1 had lost their deciduous teeth by the age of 3 years.

Conclusions: The prevalence of hypophosphatasemia is higher in hospitals than in the general population. This biological anomaly is almost never recorded in the files. However, the existence of hypophosphatasemia should be systematically reported as it is a contraindication to anti-resorptive therapy because of the risk of atypical femoral fracture.

Disclosure of Interest: None declared

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THU0619 THE FREQUENCY OF EXON-10 MUTATIONS IN MEFV GENE IN "PROBABLE" DIAGNOSED FMF PATIENTS ACCORDING TO TEL HASHOMER CRITERIA

F. Cosan¹, S. Arda¹, O.M. Gedar Totuk². ¹Department of Internal Medicine, Division of Rheumatology; ²Department of Ophthalmology, Bahcesehir University, Faculty of Medicine, Istanbul, Turkey

Background: Familial Mediterranean Fever (FMF) is characterised with recurrent inflammatory attacks with serosal inflammation. The clinical findings of FMF is seen in a large spectrum. Tel Hashomer criteria are widely used for classifying FMF. According this criteria set FMF is classified as 'definite' and 'probable' disease.

Objectives: We aimed in this study to investigate the frequency of exon-10 MEFV mutations in 'probable' FMF patients according to Tel Hashomer criteria.

Methods: The study group consisted of 117 patients (79 male, 38 female, median age:31±11, ¹²⁻⁶⁹ which is classified as 'probable' FMF according to Tel-Hashomer criteria. The 12 frequently seen mutations in Turkey analysed in all blood samples and compared with the previous reported 'definite' FMF data from Turkey.

Results: We found in probable FMF group single mutation in 36 patients (%30,8), two mutations in 56 patients (%47,9), 3 mutations in 5 patients (%4,3) and no

mutations in 20 patients (%17,1). The distribution of exon 10 mutations showed single exon-10 mutation in 46 patients (%39,3) and two exon-10 mutations only in 23 patients (%19,7). The detailed distribution of MEFV mutations in 'probable' FMF group is shown in table 1.

Abstract THU0619 – Table 1. The Distribution of MEFV gene mutations in 'probable' FMF group

	Homozygout	Heterozygout	Negative
M694V	5 (4,3%)	42 (35,9%)	70 (59,8%)
M680I	2 (1,7%)	18 (15,5%)	82,8 (96%)
V726A	1 (0,9%)	12 (10,3%)	104 (88,9%)
M694I	-	3 (2,6%)	114 (97,4%)
R202Q	2 (1,7%)	35 (29,9%)	80 (68,4%)
E148Q	1 (0,9%)	15 (12,8%)	101 (86,3%)
P369S	-	3 (2,6%)	114 (97,4%)
R761H	1 (0,9%)	6 (5,1%)	110 (94%)
K695R	-	2 (1,7%)	115 (98,3%)
A744S	-	2 (1,7%)	115 (98,3%)

Conclusions: We found decreased frequency of exon 10 mutations in the MEFV gene in "probable FMF" group according to Tel-Hashomer criteria in comparison previous reported MEFV mutations data. The distribution of non-exon 10 mutations were similar in the definite FMF group. It is needed more clinical studies with large patient group for the clinical significance of non-exon 10 mutations in "probable" FMF patients.

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THU0620 ON DEMAND USE OF ANAKINRA FOR THE ATTACKS OF FAMILIAL MEDITERRANEAN FEVER (FMF)

H. Babaoglu¹, O. Varan¹, H. Kucuk², N. Atas¹, H. Satis¹, R.B. Salman¹, M. A. Ozturk¹, B. Goker¹, S. Haznedaroglu¹, A. Tufan¹. ¹Department of Internal Medicine, Division of Rheumatology, Gazi University Hospital, Ankara; ²Department of Internal Medicine, Division of Rheumatology, Erzurum Research and Training Hospital, Erzurum, Turkey

Background: IL-1 blocking agents have been shown to be effective in the prevention of attacks in colchicine-resistant FMF (crFMF) patients by their regular use. However, their high cost, side effects and treatment noncompliance limit their use which might be overwhelmed by on-demand use of them which has not been reported in FMF patients. Herein, we evaluated the efficacy of on demand use of anakinra in crFMF patients.

Methods: Data were derived from Gazi FMF cohort which was established in the year 2010. From that date patients with FMF who were diagnosed according to the Tel Hashomer criteria were registered. Co-morbidities, detailed attack characteristics, type, duration, severity, treatments, laboratory parameters and impact of FMF on their life in terms of quality of life and work productivity were recorded either by FMF diary or a mobile phone application (FMF AIDD free to download from AppStore and Android market). A retrospective cohort analysis was made from records of patients who have ever been treated with IL-1 inhibitors.

Results: A total of 60 patients were treated with anakinra in our cohort and 15 patients were identified who were received on demand anakinra protocol. Rationale for on demand use of anakinra was prominent prodrome or trigger for attacks and patients' personal claim. Six patients were switched from regular use and 9 were directly started as on demand use. All were using background colchicine in maximum tolerated doses. None of patients had evidence of persistently elevated acute phase reactants or proteinuria. The median duration of on demand anakinra use was 6 (min 3- max 36) months. Pre- and post- on demand anakinra periods were compared (table 1). Patient reported attack severity (p=0.002), duration (p=0.001), absenteeism (p=0.001) and presenteeism (p=0.002) were significantly