FRI0583 IGG4-RELATED DISEASE AMONG PATIENTS PREVIOUSLY DIAGNOSED WITH IDIOPATHIC RETROPERITONEAL FIBROSIS. A NATIONWIDE DANISH STUDY

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Background: IgG4-related disease (IgG4-RD) is a recently recognized systemic disease of unknown etiology and prevalence [1]. Retrospective single center series have provided evidence that 13–63% of patients with idiopathic retroperitoneal fibrosis (IRPF) could be reclassified as IgG4-RD. Since immunesuppressants or B-cell targeted therapies may halt or reverse progression, early diagnosis and treatment is important to prevent terminal fibrosis.
Objectives: To estimate the occurrence of IgG4 related retroperitoneal fibrosis (RPF) in Danish patients diagnosed with IRPF.
Methods: The National Danish Pathology Register was searched for biopsy codes relating to retroperitoneal tissue and inflammation from 01.01.2004 through 31.12.2013. Patients below 18 years of age, secondary causes, malignancies, infections, and specimens with multinucleated giant cells or granulomas were excluded. Among 724 candidate cases 68 were identified with IRPF. Among these 25 were left out due to small tissue samples, unavailable patient files or lack of consent. Clinical, laboratory data and imagings were reviewed. Paraffin-embedded tissue blocks were retrieved from 18 pathology departments. Four sections were prepared and stained with hematoxylin-eosin, Weigerts elastin and IgG4 immunostaining. Histopathologic features suggesting an IgG4-RD background were recorded (table). Cut-off levels for IgG4 positive cells at $\geq$30 per HPF and IgG4: total IgG ratio at $\geq$40% were applied. Patients were categorized as IRPF, definite or possible IgG4-RD according to international consensus [2]. Intergroup comparisons were done using Mann-Whitney U test or Chi square test.
Results: Forty three patients (29 males), median age 56 years were included among which 19 (44%) met the criteria for IgG4-RD comprising 7 with definite, 12 with possible IgG4-RD and 24 with IRPF. Biopsies were available from all participants. Extraretroperitoneal manifestations, standard laboratory measures and serum IgG4 (in 5 individuals) did not differ significantly between RPF subsets. Patients with an IgG4: total IgG ratio $\geq$40% had significantly more histopathologic features of IgG4-RD compared to a ratio $<$40% (table). Patients with $\geq$30 IgG4 positive cells per HPF had higher numbers of tissue eosinophils than those with lower IgG4+ cell counts.

Table 1. Histopathologic findings in RPF biopsies (N=43) according to IgG4: total IgG ratio

	IgG4/IgG ratio $\geq$40% N=21	IgG4/IgG ratio $<$40% N=22	p-value
Lymphoplasmacytic infiltrate	21	13	0,002
Storiform fibrosis	12	3	0,004
Obliterative phlebitis	5	1	0,078
Phlebitis without obliteration	4	2	0,378
Increased numbers of eosinophils	13	6	0,030

Conclusions: A total of 44% of IRPF patients was diagnosed with IgG4-RD, 16% with definite and 28% with possible IgG4-RD. This estimate may be conservative because specimens with multinucleated giant cells or granulomas were excluded. The closer association of IgG4: total IgG ratio $\geq$40 vs. lower ratios with histopathologic findings supports a direct pathogenic role by IgG4 bearing cells or IgG4 in IgG4 RPF.
References:
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FRI0584 RHEUMATIC AND MUSCULOSKELETAL DISORDERS RELATED TO IMMUNE CHECKPOINT INHIBITORS IN CANCER PATIENTS: A PROSPECTIVE SINGLE-INSTITUTION STUDY

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Background: Immune checkpoint inhibitors (ICI) targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) axis have been a major advance in cancer immunotherapy. By enhancing T cell activity, unprecedented long-lasting tumour responses are observed in selected cancers but some patients experience immune related adverse events (irAE).
Objectives: To evaluate the prevalence and type of rheumatic and musculoskeletal disorders in patients receiving ICI at a single institution (University Hospital of Bordeaux, France).
Methods: All cancer patients with musculoskeletal disorders while receiving ICI were referred to our rheumatology department. For each referred patient, an experienced rheumatologist performed a comprehensive clinical evaluation. Blood tests (inflammatory markers, serum creatine kinase, autoantibodies) and imaging (X-rays, ultrasound) were obtained according to clinical findings. HLA-DR phenotyping was also performed for some patients to search for shared epitope.
Results: From September 2015 to December 2016, 329 patients received ICI (anti CTLA-4: n=38; anti PD-1: n=251; anti PD-L1: n=29; combination anti CTLA-4/anti PD-1: n=11) and 21 patients were referred to our rheumatology department (6.4%). Mean age was 65 years and cancer types included melanoma (n=10), non small cell lung cancer (n=9), Merkel carcinoma (n=1) and renal carcinoma (n=1). All musculoskeletal disorders occurred in patients receiving anti PD-1 (nivolumab: n=12; pembrolizumab: n=6) or anti PD-L1 (avelumab: n=2; atezolizumab: n=1), with a median exposure time of 90 days (range: 1–650 days). There were two distinct clinical presentations: 1) inflammatory arthritis (IA) mimicking either rheumatoid arthritis (n=5) or polymyalgia rheumatica (n=8) and, 2) non-inflammatory musculoskeletal conditions (n=8). Of note, one patient was anti-CCP positive but negative for RF. Shared epitope HLA-DRB1 *01:01 was present in 4 patients. Eleven patients required corticosteroid therapy with a median dose of 15mg/day (range: 7–30 mg/day). Non-inflammatory disorders were easily managed with NSAIDs, analgesics and/or physiotherapy. ICI treatment was temporarily discontinued in one patient only, in line with the clinical trial protocol. To date, there was a partial or complete tumour response to ICI in 10 patients whereas 3 had stable disease and 7 had progressive disease. Tumour response or stable disease was observed in 11 of 12 patients with IA but only in 2 of 8 patients with non-inflammatory conditions.
Conclusions: In our series, patients with immune-related IA mimicking rheumatoid arthritis and polymyalgia rheumatica were responsive to low-to-moderate dose of prednisone and did not require ICI discontinuation. Furthermore, tumour response was frequently observed in such patients.
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FRI0585 FREQUENT, UNUSUALLY SEVERE, LONG LASTING, LOCAL AND SYSTEMIC PNEUMOCOCCAL VACCINE REACTIONS IN PATIENTS WITH CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS): RESULTS OF A PROSPECTIVE REGISTRY BASED STUDY

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Background: Pneumococcal, tetanus and influenza vaccinations are recommended for patients with Cryopyrin-Associated Periodic Syndromes (CAPS) when treated with immunosuppressive medication.
Objectives: This study aims to report the safety of pneumococcal and other vaccinations administered to CAPS patients.
Methods: All CAPS patients followed in the β-CONFIDENT (Clinical Outcomes and Safety Registry study of Ilaris® patients) registry between 07/2010 and 12/2015 were analysed if they had received a vaccination. The β-CONFIDENT registry is a global, long-term, prospective, observational registry, capturing and monitoring CAPS patients treated with canakinumab [1].
Results: 68 CAPS patients (56% female, age range 3.5–73 years) had received a total of 159 vaccine injections, 107 injections against influenza, 19 pneumococcal vaccinations (15 pneumococcal polysaccharide vaccines [PPV], 2 pneumococcal conjugate vaccines [PCV], 2 unknown), 12 against tetanus/diphtheria antigens and 21 other vaccinations.
A reaction was observed in 22 vaccine injections (14%) administered to 18 patients. 13 vaccine reactions (68% of all pneumococcal vaccine injections) occurred in 12 patients receiving pneumococcal vaccines. 12 PPV injections (80% of all PPV injections) elicited a vaccine reaction while none was elicited by the PCV injections The high frequency of pneumococcal vaccine reactions contrasted with that of the reactions to other vaccine types: only 17% and 7% of the tetanus/diphtheria and influenza vaccinations, respectively, elicited a vaccine reaction. The odds ratios to react to the pneumococcal vaccines compared to influenza and tetanus/diphtheria vaccines were 31.0 (95% confidence interval (CI) 8–119) and 10.8 (95% CI 2–74).
Vaccine reactions after pneumococcal vaccinations were more severe and lasted significantly longer compared to the reactions after other vaccinations. Fever was elicited by almost half of all PPV injections. All symptoms after pneumococcal vaccination were observed very rapidly, usually within hours. Unlike the symptoms observed after influenza and tetanus/diphtheria vaccination, which resolved rapidly, the symptoms related to PPV were much more prolonged and in some cases lasted more than 3 weeks. In 2 patients, pneumococcal vaccination also elicited symptoms consistent with systemic inflammation due to CAPS reactivation. All 5 vaccine related serious adverse events were associated with pneumococcal vaccination.