THU0585 DISTINCT CLINICAL FEATURES DISTINGUISHING IGG4-RELATED DISEASE AND MULTICENTRIC CASTLESMAN'S DISEASE

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Background: IgG4-related disease (IgG4-RD) is a fibro-inflammatory disease with multiple-organ involvement characterized by infiltration of $IgG4^+$plasma cells and elevated serum IgG4 concentrations. However, similar findings are observed in multicentric Castleman's disease (MCD)[1], thereby making it difficult to differentiate one disease from the other.
Objectives: The aim of this study was to clarify the differences of clinical characteristics and laboratory findings in IgG4-RD and MCD for differential diagnosis.
Methods: All consecutive patients with IgG4-RD and MCD who visited the Rheumatology or Hematology department in our institutes from January 2000 to November 2015 were retrospectively reviewed. Patient characteristics and laboratory data at the time of diagnosis were compared.
Results: Forty-nine patients with IgG4-RD and 48 patients with MCD were included. Patients with IgG4-RD were older compared to MCD (57.4 vs 47.3 years, $p<0.0001$) and there was no difference in gender distribution. While lymph nodes were affected less frequently in IgG4-RD compared to MCD (49% vs 100%, $p<0.0001$), lacrimal glands, salivary glands and pancreas were affected only in IgG4-RD. The levels of serum IgG, IgA and IgM were significantly lower in patients with IgG4-RD compared to MCD (IgG: 1945.6 mg/dl vs 4317.5 mg/dl, $p<0.0001$, IgA: 172 mg/dl vs 669 mg/dl, $p<0.0001$, IgM: 83 mg/dl vs 279 mg/dl, $p<0.0001$), whereas no difference was observed in serum IgE levels. Although level of serum IgG4 was also equivalent between IgG4-RD and MCD (607 mg/dl vs 353 mg/dl, $p=0.211$), IgG4/IgG ratio was significantly higher in IgG4-RD compared to MCD (0.30 vs 0.09, $p<0.0001$). In addition, atopic history was more frequent (71.4% vs 16.7%, $p<0.0001$), and the proportion of eosinophils (6.4% vs 2.7%, $p<0.0001$) was significantly higher in IgG4-RD compared to MCD. The level of serum C-reactive protein (0.3 mg/dl vs 5.4 mg/dl, $p<0.0001$) and erythrocyte sedimentation rate (35.9 mm/hr vs 110.7 mm/hr, $p<0.0001$), the prevalence of anemia (10.2% vs 50.0%, $p<0.0001$) and thrombocytosis (2.0% vs 31.3%, $p<0.0001$) were significantly higher in MCD compared to IgG4-RD.
Conclusions: The involvement of lacrimal gland, salivary gland and pancreas was unique for IgG4-RD. While allergic reaction such as hypereosinophilia and atopic history was more frequently observed in IgG4-RD, intense inflammation was the distinct characteristics for MCD. The distribution of organ involvement and marked inflammatory reaction represented by elevated serum CRP, anemia and thrombocytosis were important features to distinguish between IgG4-RD and MCD.
References:
[1] Y. Sato et al. Systemic IgG4-related lymphadenopathy: a clinical and pathologic comparison to multicentric Castleman's disease. Mod Pathol 2009;22:589–599.
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THU0586 AGREEMENT OF PATIENT AND PHYSICIAN GLOBAL ASSESSMENT OF DISEASE ACTIVITY IN ADULT ONSET STILL'S DISEASE

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Background: There is not valid outcome measures for assessment Adult onset Still's disease (AOSD) activity. The patients or physicians global view is relevant way to assess this kind of complex diseases. However, it is well known that there is discordance between patient and physician perspective for disease activity in different inflammatory diseases.
Objectives: Objective of this study was to evaluate agreement of patient and physician perspective in AOSD patients.
Methods: We conducted a cross-sectional, multicenter study for assessment of disease activity in AOSD patients. All AOSD patients were fulfilled Yamaguchi criteria. For every center, at least 20% of AOSD patients had to be an active state according to physician assessment. Age, sex, disease duration, current disease symptoms was recorded. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leucocyte, and ferritin level also recorded. Visual analog scale (VAS) (0–10 cm) used for physician and patient global assessment of disease activity. Disease activity status were also assessed by likert scale (as remission, low, moderate, severe, and more severe disease activity) for both patients and physician perspective. Patient global assessment VAS and physician global assessment were correlated by correlation coefficient (r). Agreement of disease activity level for patient and physician perspective were calculated with kappa. Kappa >0.6 was accepted as significant.
Results: One hundred thirty (83, 63.4% female) AOSD patients were enrolled. Mean age was 38 (14) years old and median disease duration was 3 years (0–29). Currently AOSD symptoms followed; fever 34 (26.2%), rash 28 (21.5%), arthritis 31 (23.8%), arthralgia 60 (46.2%), sore throat 28 (21.5), myalgia 42 (32.3), lympadenopathy 12 (9.2%), splenomegaly 17 (13.1%), hepatomegaly 7 (5.4%), pleuritic 3 (2.3%), hemophagocytic syndrome 2 (1.5%). ESR 47.7%, CRP 43.8%, ferritin 27.0%, and leucocyte 43.1% were higher than upper limit. Mean patient global assessment VAS was 3.53 (3.25), and mean physician global assessment VAS was 2.71 (2.95). Correlation coefficient (r) of patient and physican global VAS was 0.89. There was excellent agreement according to severe/more severe disease activity at patient and physician level (kappa 0.88 (CI 95% 0.79–0.98). There was also good to excellent agreement according to low disease activity/remission at patient and physician level (kappa 0.74 (CI 95% 0.62–0.86).
Conclusions: Although, features of AOSD seems more complex with constitutional symptoms, joint or reticuloendothelial system involvement, patients and physicians assess level of disease activity similarly. We thought, this results will be helpful for procedure of new composite index in AOSD.
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THU0587 CLINICAL CHARACTERIZATION OF CASTLEMAN'S DISEASE IN A GROUP OF PEDIATRIC PATIENTS

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Background: Castleman's disease (CD) is a rare lymphoprolipherative mostly benign disorder presenting in two major forms: localized (unicentric) and systemic (multicentric). Based on pathomorphological finding it is classified as hyaline-vascular, plasma cell or mixed type. The age of onset can differ greatly from infancy to adulthood. Except for lymph node hyperplasia, patients with CD can also develop such symptoms as anemia, fatigue, hepatosplenomegaly, low-grade fevers and other systemic symptoms.
Objectives: Analysis of clinical manifestations, pathomorphology and treatment efficiency in a group of pediatric patients.
Methods: We conducted a retrospective analysis of 12 patients (11 boys and 1 girl) with histologically confirmed cases of Castleman's disease.
Results: Age of onset varied from the moment of birth to 16 years (median 8,5 years) 8 patients had unicentric form of disease, 3 had multicentric form and one patient had two groups of lymph nodes affected, thus could not be precisely classified. The majority of the patients (9 patients) had hyaline-vascular variant of CD, one patient had plasma-cell type and two patients had the mixed pathomorphological type. The reason for seeking medical attention in three patients was visible unilateral enlargement of neck lymph nodes, four patients initially presented with anemia, fatigue, fever and laboratory signs of inflammation, and in 4 patients enlarged lymph nodes were incidentally visualized during control X-ray, and no other symptoms of CD were present. Interestingly, of 3 patients with multicentric form of CD, two had underlying primary immunodeficiency – Wiskott-Aldrich syndrome (WAS). They presented with plasma cell type and mixed type of CD, respectively. No immunodeficiency has been proven in other patients. We have conducted tests to indicate HHV VIII in affected lymph node biopsies and blood samples via PCR in half of the patients and none occurred to be positive.
Treatment: The affected lymph nodes were completely excised surgically in 7 patients with unicentric form, with no relapse of the disease on follow-up. Both patients with WAS received rituximab treatment followed by bone marrow transplantation, which was originally planned as a treatment of WAS, with remission on follow-up at 3 month and 2 years, respectively. Third patient with multicentric form received several courses of anti-cytokine and immunosuppressive treatment including tocilizumab, cyclophosphamide, vincristine and prednisolone (total of 5 blocks), rituximab (6 infusions) with partial effect, then surgical excision of large conglomerates of lymph nodes followed by bortezomib and bendamustine (total of 6 blocks) with positive effect. However at the one year follow-up patients demonstrated enlarged lymph nodes again, so she was started on JAK tyrosine kinase inhibitor ruxolitinib. Follow-up results are pending.
Conclusions: Our analysis of a group of pediatric patients demonstrates great variability in symptoms and severity of the disease. Castleman's disease is a disorder with poorly studied pathogenesis. Based on our experience, the role of primary defects of immune system in development of CD requires further investigation.

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THU0588 IGG4-RELATED DISEASE: FEATURES AND TREATMENT RESPONSE IN AN ASIAN COHORT

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Background: Most descriptions of IgG4-related disease (IgG4-RD) have been from Japanese and Caucasian populations.
Objectives: To describe the clinical, laboratory, histological features and treatment outcomes of IgG4-RD in multi-ethnic Asian patients in Singapore.
Methods: Patients diagnosed with IgG4-RD were identified from a Rheumatology and Gastroenterology patient database in a tertiary hospital. Demographics, clinical manifestations, laboratory results, disease activity, clinical outcomes and therapeutics used were derived from medical records. Disease activity was assessed by the IgG4-RD Responder Index.
Results: 42 patients (76% male) were included; all had a diagnosis of IgG4-RD made by a rheumatologist or gastroenterologist experienced in IgG4-RD. 79% and 17% fulfilled the 2011 comprehensive diagnostic criteria for IgG4-RD[1] for definite and probable IgG4-RD respectively. 81% were Chinese and 19% were Malays. Mean age of the cohort was 62.7 ± 13.1 years. Mean age of diagnosis was 57.5 ± 12.8 years. Mean duration of disease was 4.5 ± 3.5 years. Common initial manifestations included jaundice (52%), abdominal pain (36%), swollen salivary glands (26%) and constitutional symptoms (21%). Only 36% had a history of allergy. 83% had ≥1 organ involvement, including autoimmune pancreatitis (67%), lymphadenopathy (45%), sclerosing cholangitis (43%), sialadenitis (31%) and dacryoadenitis (21%). 86% (6/7) of patients with isolated lesions involved only the pancreas. There was no gender difference in type of organ involvement. Erythrocyte sedimentation rate (ESR), IgG1, IgG2, IgG3, IgG4 levels were elevated in 83%, 22%, 74%, 37%, 41% of patients respectively. IgG4 levels did not correlate with ESR, age, disease duration, IgE levels and number of organs involved. The most common histopathological feature was that of >10 IgG4+ cells per high power field (66%), followed by lymphocytic infiltration (51%) and storiform fibrosis (51%). Only 7% had obliterative phlebitis. 94% (34/36) of patients were treated with moderate to high doses of glucocorticoids, including 17 patients with combination immunosuppressants. Of these, all patients responded to therapy by 3 months. With a mean follow-up of 4.8 ± 3.1 years, 69% (25/36) needed low dose of glucocorticoids to maintain disease remission. 26% had relapse of disease, of which 82% had disease recurrence in the same organs.
Conclusions: Pancreatitis, lymphadenopathy and cholangitis were the commonest manifestations in Asians with IgG4-RD. All patients responded to glucocorticoid therapy by 3 months, two-thirds required maintenance therapy with glucocorticoids, and one-quarter developed relapse of disease.
References:
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THU0589 INFLIXIMAB THERAPY FOR NEURO-, VASCULAR, AND INTESTINAL BEHÇET'S DISEASE: EFFICACY, SAFETY, AND PHARMACOKINETICS IN A MULTICENTER PROSPECTIVE STUDY

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Background: Behçet's disease (BD) is a multisystem disease characterized by mucocutaneous, ocular, neurologic, vascular, or gastrointestinal manifestations. Involvement of the neuronal (NBD) and vascular (VBD) systems and intestinal tract (intestinal BD) is rare, although such cases tend to have a poor prognosis.
Objectives: We conducted a prospective multicenter clinical trial to determine the efficacy, safety, and pharmacokinetics of infliximab (IFX) in BD patients with these serious complications who had displayed poor response or intolerance to conventional therapy (ClinicalTrials.gov, NCT01532570).
Methods: IFX at 5 mg/kg was administered to 18 patients (3 NBD [2 acute and 1 chronic progressive], 4 VBD, and 11 intestinal BD) at Weeks 0, 2, and 6 and every 8 weeks thereafter until Week 46. In patients who showed inadequate responses to IFX after Week 30, the dose was increased to 10 mg/kg. We then calculated the percentage of complete responders according to the predefined criteria depending on the symptoms and results of examinations (ileocolonoscopy, brain MRI, CT angiography, positron emission tomography, cerebrospinal fluid, CRP, or ESR), exploring the percentage of complete responders at Week 30 as the primary endpoint.
Results: The percentage of complete responders was 61% (11/18) at both Weeks 14 and 30 and remained the same until Week 54. By BD type, the percentage of complete responders at Week 30 was 33% (1/3) among NBD patients, 100% (4/4) among VBD patients, and 55% (6/11) among intestinal BD patients. In acute NBD patients, IFX lowered the cell count and IL-6 concentrations in the cerebrospinal fluid and inhibited the onset of attacks. In a chronic progressive NBD patient, IFX lowered cerebrospinal fluid IL-6 concentrations along with inhibition of progression of clinical symptoms and brainstem atrophy. VBD patients showed improvement in clinical symptoms at an early stage (Week 2) with reductions in serum CRP levels and ESR. Accordingly, positron emission tomography/CT imaging studies showed reversal of inflammatory changes in three of the four VBD patients. Intestinal BD patients also showed improvements in clinical symptoms along with decrease in serum CRP levels after Week 2. Consistently, scarring or healing of the principal intestinal ulcer in each patient was found in more than 80% of these patients after Week 14. Irrespective of the type of BD, all patients achieved improvements in visual analogue scale and Short Form 36 scores, leading to the dose reduction or complete withdrawal of steroids. IFX dose was increased to 10 mg/kg in three intestinal BD patients, resulting in improvement of clinical symptoms, CRP level, and visual analogue scale score. Safety and pharmacokinetics profiles were comparable to those in patients with rheumatoid arthritis or Crohn's disease.

Table Proportion of complete responders

	Complete responders					
		NBD			VBD	Intestinal BD
	All three types	All NBD	Acute NBD	Chronic progressive NBD		
Week 14	61% (11/18)	33% (1/3)	0% (0/2)	100% (1/1)	100% (4/4)	55% (6/11)
Week 30 (Primary endpoint)	61% (11/18)	33% (1/3)	0% (0/2)	100% (1/1)	100% (4/4)	55% (6/11)
Week 54	69% (11/16)	50% (1/2)	0% (0/1)	100% (1/1)	100% (4/4)	60% (6/10)
Final point of 5 mg/kg therapy	67% (12/18)	33% (1/3)	0% (0/2)	100% (1/1)	100% (4/4)	64% (7/11)

NBD, neuro-Behçet's disease; VBD, vascular Behçet's disease; intestinal BD, intestinal Behçet's disease

Conclusions: The results demonstrate that IFX is effective and well tolerated in the treatment of recalcitrant NBD, VBD, and intestinal BD with poor response or intolerance to conventional therapy. IFX may therefore represent a promising new therapeutic option for use in BD patients with these serious complications.
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THU0590 RISK FACTORS FOR CYTOMEGALOVIRUS REACTIVATION IN PATIENTS WITH CONNECTIVE-TISSUE DISEASES

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Background: Intensive immunosuppressive treatment for remission induction in connective tissue diseases (CTDs) sometimes causes serious infection. Cytomegalovirus (CMV) is a herpesvirus remaining latent after primary mild or asymptomatic infection, and the reactivation of CMV is one of the problematic opportunistic infections in immunocompromised patients. However, little is known