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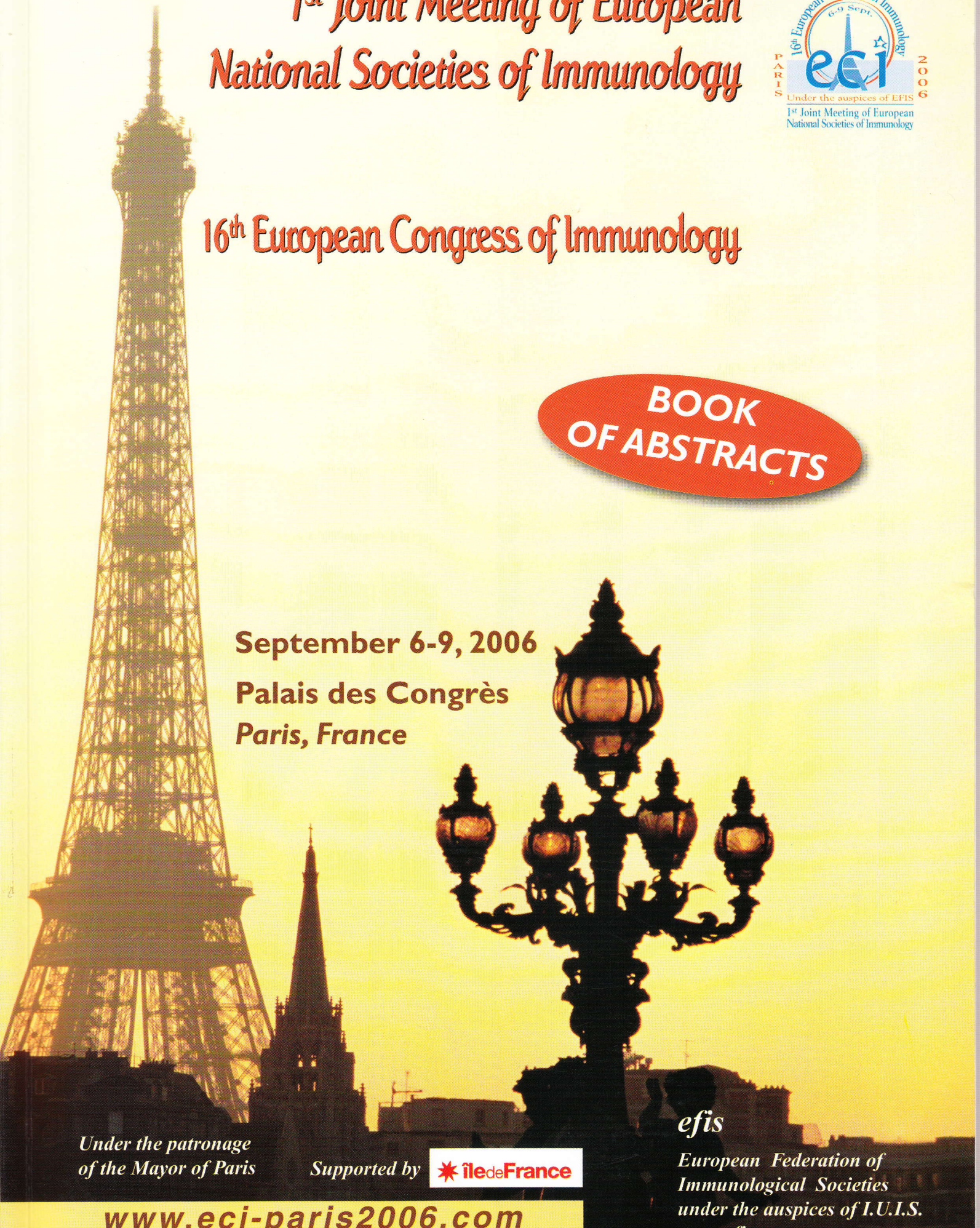
BOOK OF ABSTRACTS



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THYROID FUNCTION AND ANTITHYROID AUTOANTIBODIES IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Autoimmune thyroid disease (ATD) has been described in patients with connective tissue diseases. The aim of this study was to estimate and to compare the prevalence of ATD in a group of 53 systemic lupus erythematosus (SLE) patients and age and sex maches control group (34 healthy blood volunteers). Serum levels of free thyroxine (FT4), thyroid stimulating hormone (TSH), as well as thyroid autoantibodies (Abs) specific for thyroperoxidase (TPO) and thyroglobulin (TG) were examined. FT4 and TSH concentrations were measured using ***CIS Biointernational*** kits with the normal range 7-18 pg/ml and 0.25-4.0 μIU/ml, respectively. Anti-TPO Abs were detected using competitive radioligand (TPO-AB-CT) assay, and anti-TG Abs using the immunoradiometric (ELSA-AB-hTG) assay. SLE patients had significantly higher number of thyroid dysfunction than the control group (22.63 vs 2.94, $p<0.05$). Hypothyroidism was detected in 15.09% and hyperthyroidism in 7.54% SLE patients. Anti-TPO Abs were detected in a significant number of SLE patients (22.64%) when compared to the control group (5.88%). It was also found that a higher number of SLE patients (11.32%) had positive anti-TG Abs, when compared to the control group (2.94%). In conclusion, the presence of hyperthyroidism and particularly hypothyroidism in SLE patients is associated with a higher prevalence of antithyroid, predominantly anti-TPO Abs, indicating the coexistence of SLE and ATD in these patients. According to these results, intermittent screening of thyroid function and antithyroid autoantibodies in patients with SLE could be recommended.
Key words: systemic lupus erythematosus, hyperthyroidism, hypothyroidism, TPO, TG, autoantibodies

GLOBAL NATURAL REGULATORY T CELL DEPLETION IN ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS

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The Immune defect that could account for the multi-systemic involvement that characterizes Systemic Lupus Erythematosus (SLE) remains unknown. We hypothesized that iterative disease flares correspond to a recurrent defect in the peripheral immune suppression exerted by naturally occurring T regulatory cells (Tregs). Surprisingly, Tregs isolated from lupus patients show the same phenotypic and functional characteristics as corresponding cells found in healthy controls. A decrease in the proportion of circulating Tregs among other CD4+ T cells is nevertheless evidenced in active patients when this group is compared to healthy controls (0.57 ± 0.24 %, n=45 vs 1.29 ± 0.38 % n=82, $p<0.0001$) or to inactive patients (1.22 ± 0.67 %, n= 62, $p<0.0001$). In contrast, the proportion of Tregs in other systemic autoimmune diseases such as primary Sjögren Syndrome (pSS) and Inflammatory Myopathy (IM) does not significantly differ from controls' values (1.15 ± 0.46 %, n=21, p=0.09 and 1.16 ± 0.44 %, n=16, p=0.43, respectively).
Lupus Tregs do not accumulate in either the lymph nodes or the diseased kidneys, are not killed by a circulating soluble factor but demonstrate ***in vitro*** a heightened sensitivity to Fas-induced apoptosis. Finally, we show that the extent of Treg depletion correlates with the clinical severity of the flare. SLE flares are therefore associated with a global Treg depletion and not with a phenomenon of tissue redistribution. In summary, we suggest that the physiopathology of SLE could be tied to a defect in the homeostatic control of the Treg subpopulation.

CLINICAL AND IMMUNOLOGICAL ASPECTS IN ANTIPHOSPHOLIPID ANTIBODIES SYNDROME

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Introduction. The antiphospholipid antibodies syndrome (AphL) is a disorder characterized by multiple different antibodies against negatively charged phospholipides that are associated with both artherial and venous thrombosis. **Aim**. The purpose was to study the incidence of certain antibodies in systemic lupus erythemathosus (SLE) patients with antiphospholipid antibodies syndrome secondary (AphLS) and in patients with infectious condition (chronic viral hepatitis C) for to evaluate their significance as serological markers of AphL syndrome. **Patients and methods.** Sera from 40 SLE patients with AphLS – group 1 and 36 with hepatis C- group 2 were investigated for presence of antinuclear (ANA), anticardiolipin (aCL) and anti-beta 2 glicoprotein (anti beta 2 glp) antibodies. Results obtained were analysed versus a control group (20 healthy persons) For the quantitative determination of antibodies was utilised ELISA technique (DRG Instruments GmbH-Germany and IMMCO Diagnostics – USA, kits). **Results.** In group 1 high titers of aCL were detected in 55% and anti-beta 2 glp in 20% of patients. The prevalences of aCL class antibodies were: IgG (40,9%), IgA(45,45%) and IgM (18,1%). IgG and IgA isotypes were more closely associated with AphL syndrome than IgM isotype. Isotype IgG, was associated with increased incidence of ANA and correlated strongly with trombotic events, more in male patients. In group 2 occurred low levels anticardiolipin antibodies, of IgM class. Anti beta 2 glp 1, aCL and antinuclear antibodies were not detected in patients with chronic hepatitis C and in healthy persons. **Conclusions**. The diagnosis of antiphospholipid syndrome should be made when the aCL(IgG) test results are moderately or highly positive. Anti aCL antibodies were useful serological markers since they associated more frecvent to the AphLS-common in group of SLE patients. Is important to mentione that SLE male patients with IgG aCL antibodies and without thromboembolic manifestations may benefit of antiplatelet prophylaxis.

TNF-ALPHA INDUCES THE RELEASE OF MEMBRANE-BOUND BAFF FROM NEUTROPHILS

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B cell activating (BAFF) is a novel member of the tumour necrosis factor (TNF) superfamily of ligands. It is essential for B cell survival and maturation, and is implicated in the pathogenesis of autoimmune inflammatory diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In the study presented here, we investigated the subcellular localisation and mechanism of the release of BAFF in human neutrophils. We show that neutrophils constitutively express BAFF both on the cell membrane as well as in intracellular stores. However, BAFF release from these sites was regulated independently and among a range of proinflammatory cytokines, only TNF-α triggered the release of BAFF from the neutrophil membrane. The mechanism occurs via the activity of furin, following ligation of TNFR, leading to the production of large quantities of soluble BAFF. The expression of membrane-associated furin also increased by TNF-α. In contrast, G-CSF increased the release of BAFF from intracellular stores without changing the membrane level of the protein. In patients with active SLE, the serum level of TNF-α correlated positively with that of BAFF, but no correlation was seen with serum G-CSF levels. Ωε χονχλυδε, τηατ δεπενδινγ ον τηε ινφλαμματορψ στιμυλυσ, ΒΑΦΦ χαν βε ρελεασεδ φρομ ειτηερ τηε μεμβρανε ορ τηε ιντραχελλυλαρ στορεσ οφ ηυμαν νευτροπηιλσ. Νευτροπηιλ μεμβρανεσ τηυσ ρεπρεσεντ α σιγνιφιχαντ ρεσερϖοιρ οφ ΒΑΦΦ, ωηιχη χαν βε ρελεασεδ ραπιδλψ βψ ΤΝΦ–α stimulation and may therefore contribute to the raised levels of serum BAFF seen in some SLE patients or in the synovium of RA patients.

CD8 T CELL INVOLVEMENT IN A PATIENT WITH CGVHD-LIKE DISEASE IN THE SETTING OF MATERNAL MICROCHIMERISM

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Chronic GVHD (cGVHD) shares features with systemic sclerosis (SSc), including T cell activation and excess collagen deposition in tissues. Oligoclonal T cell expansion has been observed in skin and lungs of SSc patients, suggesting that chronic antigenic stimulation may contribute to pathogenesis of SSc. Microchimeric cells of foetal or maternal origin, whose presence in SSc patients has been established, may represent a source of allogeneic peptides.
We studied a male patient who developed lung, skin and bowel lesions characterized by prominent lymphocytic infiltration and fibrosis, after professional exposure to organic solvents, and in whom female microchimerism, presumably of maternal origin, was demonstrated in peripheral blood using FISH. Investigation of TCR Vβ families in peripheral blood by spectroscopy and flow cytometry revealed oligoclonal expansion of CD8+ T cells, with a striking majority belonging to Vβ7 (35%) and Vβ17 (21%) families. This result led us to further explore CD8+ T cells in blood and in bowel biopsies.
The surface phenotype and intra-cytoplasmic expression of cytokines and perforin by CD8 T cells belonging to both Vβ families were examined by flow cytometry. Cells from both families obtained negatively for CD27, CD28, CD62L and CCR7, and were $CD57^{pos}$. They spontaneously contained large amounts of perforin, and were shown to produce IFN-γ and TNF-α, but not IL-2, IL-4, IL5, IL-10 nor IL-13, following polyclonal stimulation in vitro. We were unable to induce them to proliferate using PHA, PMA combined with an ionophore (A23187), or by adding IL-2 in these conditions. These results suggest that the Vβ7+ and Vβ17+ CD8 cells are terminal effectors with a cytotoxic Tc1 profile. Interestingly, approximately half of the Vβ7+ CD8 cells express CCR8, which is hardly found on circulating T cells in normal subjects, and is thought to be involved in immune surveillance in skin. Immunohistochemistry on gastrointestinal biopsies showed an overwhelming presence of CD8 T cells, and some $perforine^{pos}$ cells, but no CD4 T cells. These findings suggest a key role of CD8+ T cells in the pathogenesis of disease in this patient, which may be relevant for understanding the overlap between environmental systemic sclerosis, cGVHD and foeto-maternal microchimerism.

ANTICARDIOLIPIN ANTIBODIES, FACTOR V LEIDEN AND 20210 G - A MUTATION OF PROTHROMBIN GENE IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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We studied a group of 110 APS patients: 80 with deep vein thrombosis (DVT), 54 of them with pulmonary thromboembolism (PTE), 30 with systemic lupus erythematosus (SLE) and a control group of 80 healthy persons for the prevalence of IgG and IgM anticardiolipin antibodies (ACL) and anti-beta 2 GP1 – using an ELISA method, Factor V Leiden mutation and 20210 G – A mutation – by using polymerase chain reaction. High levels of IgG and/or IgM ACL were found in 26.5% of the DVT and/or PTE patients, 50% of the SLE group and in none of the healthy controls. Factor V Leiden was found in 25% of the DVT/PTE group, 5% of the SLE patients and in 11% of the healthy controls. 20210 G - A mutation was detected in 25% of the DVT/PTE group, 8.8% of the healthy controls and in none of the SLE patients. Conclusions: 1) In our population there is a high prevalence of mutations associated with increased thrombotic risk: factor V Leiden and 20210 prothrombin gene mutation. 2) In DVT and/or PTE patients the thrombosis could be associated not only APS but also with these two common mutations. 3) Thrombotic incidents in SLE patients are associated mainly with APS.