

Predicting and preventing autoimmunity, myth or reality ?

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Many autoimmune diseases are chronic conditions that progress over the course of years, and are characterized by the presence of autoantibodies that precede the overt disease by months or years. As examples, the presence of two islet-cell antibodies are associated with a 50% risk of developing diabetes mellitus in 5 years, anti-cyclic citrullinated (anti-CCP) antibodies are found in the sera of rheumatoid arthritis patients a median of 4.5 years before the overt disease, and in systemic lupus erythematosus, patients accrue antibodies throughout a foreseen course during the 3-4 years prior to the clinical symptoms. This ability to predict autoimmune diseases, or rather their clinical manifestations, leads to the prospect of screening healthy individuals for autoantibodies. The importance of such a notion lies not only in the ability to prevent life-threatening manifestations such as Addisonian's crisis and thyroid storm, but also in the ability to treat and even prevent overt autoimmune diseases. Among such documented treatment modalities are administration of aspirin in antiphospholipid syndrome, ursodeoxycholic acid in primary biliary cirrhosis, vitamin D in systemic lupus erythematosus and autoimmune thyroid diseases, and more. Although additional studies are still needed to fully assess these notions, as well as the appropriate screening strategies to apply them, one cannot ignore the prospect of predicting and preventing autoimmunity.

Regulatory T cells for self-tolerance and immune homeostasis

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Naturally arising CD25⁺CD4⁺ regulatory T cells (Tregs) are engaged in the maintenance of immunological self-tolerance and immune homeostasis by suppressing aberrant or excessive immune responses, such as autoimmune disease and allergy. Tregs specifically express the transcription factor Foxp3, a key regulator of Treg development and function. Ectopic expression of Foxp3 in conventional T cells is indeed sufficient to confer suppressive activity, repress production of cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN- γ), and up-regulate Treg-associated molecules such as CD25, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), and glucocorticoid-induced TNF receptor family-related protein (GITR). How Foxp3 controls these molecular events has, however, yet to be elucidated. Here we show that the transcription factor AML1/Runx1, which is crucially required for normal hematopoiesis including thymic T cell development, activates IL-2 and IFN- γ gene expression in conventional CD4⁺ T cells through binding to their respective promoters. In natural Tregs, Foxp3 physically interacts with AML1. Several lines of evidence support a model whereby the interaction suppresses IL-2 and IFN- γ production, up-regulates Treg-associated molecules, and exerts suppressive activity. Besides Foxp3 expression, another prominent feature of natural Treg is their high dependency on

exogenous IL-2 for their survival. IL-2 neutralization for a limited period is indeed sufficient to cause autoimmune disease. This indicates that CD25, which is the IL-2 receptor α -chain, is not a mere marker for Treg but also an essential molecule for their function. Based on these and other findings on the molecular basis of Treg development and function, I plan to discuss how Treg contribute to the maintenance of immunological self-tolerance and immune homeostasis, and how they can be exploited to control physiological and pathological T cell-mediated immune responses.

"SCLE -- A Paradigm for Bedside-to-bench Patient-oriented Translational Clinical Investigation"

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At the 1st International Conference on Cutaneous LE at Düsseldorf in September 2004, I was afforded the distinct honor of reviewing the first-quarter century of progress that has been made on understanding the clinical significance of subacute cutaneous LE (SCLE) skin lesions. During this presentation, I would like to explore in greater depth a clinical aspect of SCLE that has only recently come into better focus - drug-induced SCLE (DI-SCLE). I will then conclude by discussing new approaches for treating refractory cutaneous LE that might become available in the future as a result of recent progress that has been made in our understanding the cellular and molecular pathogenesis of the lichenoid tissue reaction/interface dermatitis (LTR/IFD).

The appearance of SCLE skin lesions in conjunction with Ro/SS-A autoantibodies occurring as an adverse reaction to hydrochlorothiazide (HCTZ) was first reported in 1985 by Reed and colleagues in the Department of Dermatology at the University of Colorado. Over the past decade an increasing number of drugs in different chemical classes have been implicated as triggers for DI-SCLE. We felt it was timely to review the published literature on DI-SCLE with the hope of developing guidelines that might be of value to clinicians in managing such patients.

A systematic review of the Medline/PubMed cited literature on DI-SCLE through

June, 2007 was performed. Our data collection and analysis strategies was prospectively designed to answer a series of questions related to the clinical, prognostic, and pathogenetic significance of DI-SCLE. A drug causation grading scale was developed in an effort to estimate the strength of association of individual drugs as triggers for SCLE.

Seventy four cases of DI-SCLE were identified and reviewed. A large majority of the cases were Caucasian females and the mean overall age was 59.5 years. Triggering drugs fell into a number of different classes: calcium-channel blockers, anti-fungals, diuretics, antihistamines, chemotherapeutics, beta-blockers, antiepileptics, immune modulators (listed in decreasing strength of class association). Time intervals ("incubation period") between drug exposure and appearance of DI-SCLE varied greatly (2 weeks-3.2 years) and were somewhat drug class dependent. The mean duration to clearance of lesions when drug was stopped and no active treatment was given was 5.76 weeks. The range of time required for spontaneous resolution was 1 week for one case of ranitidine/HCTZ associated SCLE, up to 24 weeks for one case of ranitidine associated SCLE. An attempt was made to quantify the strength of association of a suspected triggering drug by employing a drug causation grading system. Ro/SS-A autoantibodies were present in 82% of the cases in which such data were reported and most (83%) were still present after resolution of the DI-SCLE. No significant differences in the clinical, histopathologic, or immunopathologic features of DI-SCLE and idiopathic SCLE were detected.

There is now adequate published experience to argue that DI-SCLE should be recognized as a distinct clinical constellation differing clinically, epidemiologically, and immunologically from the classical form of drug-induced SLE. It is our hope that our proposed drug causation grading system and drug class association summary data can serve as a nidus for developing a consensus drug attributability algorithm for DI-SCLE.

As a number of drugs that can trigger SCLE are from different pharmacologic classes, it is challenging to envision a unifying pathogenetic mechanism for DI-SCLE. Many of the triggering drugs are known to induce nonspecific photosensitivity states in individuals without lupus. We propose that many cases of DI-SCLE might represent a "photo-pharmacologic isomorphic/Köebner response" in individuals who are genetically predisposed to developing SCLE.

Recent work has suggested that a number of different LTR/IFD skin disorders including LE-specific skin disease share a common inflammatory signaling pathway involving plasmacytoid dendritic cell-derived interferon- α . Interferon- α expression in the skin supports the local production of a cascade of chemokines including CXCL9, CXCL10, CXCL11. These chemokines contribute to the recruitment and activation of CXCR3(+) CD8(+) cytotoxic T cells that produce injury to the epidermal basal cell compartment via apoptosis and necrosis. Such a pathogenetic effector mechanism suggests new approaches to controlling LTR/IFD skin inflammation including: neutralizing monoclonal antibodies to interferon- α (eg, MEDI-545 [Medimmune, Inc.]), costimulatory pathway inhibiting monoclonal antibodies (e.g. efalizumab [Raptiva-Genentech]), and small molecule inhibitors of CXCR3.

1.

Frontiers in the immunopathogenesis of primary cicatricial alopecia in cutaneous autoimmunity

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While lichen planopilaris (LPP) and its variants may be the predominant cause of primary cicatricial alopecia (CA), classical cutaneous autoimmunity, such as in CDLE and SLE, can also cause CA. The irreversible nature of and cosmetic disfigurement caused by CA as well as the still rather unsatisfactory therapeutic options available to-date all serve as motivation to better characterize the obscure pathobiology of CA in cutaneous autoimmunity in order to define new therapeutic targets and to develop new management strategies. Whatever the unknown trigger factor may be, the follicular inflammatory changes induced by it e.g. in CDLE patients with CA (e.g. lymphocytic perifollicular infiltrate, immunoglobulin and complement deposition) must cause the destruction of epithelial hair follicle stem cells in the bulge region of the outer root sheath in order to abrogate the hair follicle's astounding capacity for regeneration and self-repair. Recent indications that the bulge region represents a second site of relative hair follicle immune privilege (IP), raises the question whether IP collapse is an important element in the pathobiology of LE-associated CA, and whether future CA management may need to focus on bulge IP restoration. However, as suggested from deletional mouse mutants, stem cell destruction alone does not yet explain the scarring nature of CA in cutaneous autoimmunity so that additional pathobiology elements must be at play. On this background, we discuss why recent insights from the murine system into the potential role of PPAR gamma-mediated signaling in LPP pathogenesis (Mirmirani and colleagues) and of stress-induced perifollicular neurogenic inflammation (Arck & Paus) may be relevant in this context. After defining key open questions in CA pathogenesis (e.g. on the role of "programmed organ deletion [POD]"), of the sebaceous gland, of follicular basement membrane function, and of innate hair follicle immunity), we delineate selected future research avenues that promise to shed new light onto CA immunopathogenesis.

2.

Epidemiology and hair loss patterns of Korean LE patients

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Objectives: To evaluate epidemiology and characteristics of lupus erythematosus (LE) patients visiting dermatology unit, we analyzed and classified 117 LE cases with cutaneous lesions diagnosed by clinical manifestations, skin biopsy result, and laboratory findings. In addition, to evaluate the hair loss pattern in systemic LE (SLE) during the course of the disease, 122 patients with SLE were evaluated by questionnaire format and physical examination by dermatologists.

Results: Among LE patients, 53% had chronic cutaneous LE (CCLE), 35% had acute cutaneous LE (ACLE), and 9% had subacute cutaneous LE (SCLE). Only 3% of patients were diagnosed as LE with nonspecific skin lesions. The female:male ratio was high especially in ACLE (9.2:1). LE nonspecific features and laboratory abnormalities including positive autoantibodies and complements were commonly found in ACLE patients. Also, 92.7% of ACLE patients satisfied the criteria for definite SLE during follow up period, while only 27% and 6.4% of patients had definite SLE in SCLE and CCLE, respectively. We found that 104 SLE patients experienced at least one hair loss event before or during the course of the disease. The most common pattern of hair loss was diffuse hair loss (65.1%) and, interestingly, 18 patients (14.8%) experienced non-scarring patch alopecia similar to alopecia areata, which was not documented so far.

Conclusion: Our results suggest that CCLE was the most frequently seen in dermatology unit, in which the development of SLE was very rare. Finally, non-scarring patch alopecia is also an important pattern in SLE that should be included in the differential diagnosis of alopecia areata.

3.

Animal models of the lichenoid tissue reaction: Relevance to cutaneous lupus

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Lichenoid tissue reactions (LTR) form a pattern of tissue injury common to several autoimmune and immune mediated skin disorders in which inflammation is principally mediated by T cells. The lichenoid tissue reaction is a pattern of tissue injury and inflammation present in the three forms of lupus erythematosus-specific skin disease: Acute cutaneous lupus, subacute cutaneous lupus and discoid lupus erythematosus. A study of this tissue injury pattern may enhance our understanding of the pathogenesis of cutaneous lupus. Animal models of the LTR include T cell mediated skin inflammation mediated by the generation of auto-reactive T cell receptor bearing transgenic T cells, models of altered keratinocyte cytokine and antigen expression, and murine graft versus host disease. The use of these models to better understand the pathophysiology of cutaneous lupus and the therapy of cutaneous lupus will be discussed.

4.

Ultraviolet light mediated induction of systemic lupus erythematosus-like disease in NOD mice: A model of environmentally induced autoimmunity

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The role of environmental precipitants in autoimmunity such as systemic lupus erythematosus (SLE) remains unclear. Here we demonstrate that ultraviolet light B (UVB) with or without topical application of synthetic Toll like receptor 7 ligand (imiquimod) induces SLE like disease in auto-immune prone non-obese diabetic (NOD) mice but not in the related NOR strain. Repeated weekly exposures of mice to UVB alone (≥ 7500 J/m²) or combined with topical imiquimod (250 ug) induced high levels of auto-antibodies against chromatin, dsDNA, sm-RNA or RNP detectable by indirect immunofluoresence using HEP-2000 cells and antibody against the cutaneous antigen desmoglein 3 (Dsg3) by ELISA. This treatment also resulted in glomerulosclerosis with immune complex deposition. The incidence of apoptotic keratinocytes was significantly increased in the skin 24 hours following UV irradiation. IFN α inducible myxovirus protein A (MxA) expression was detectable in the skin of UV treated mice with or without TLR7 agonist. High mobility group box 1 (HMGB1), a chromatin protein, has been implicated in immune complex mediated autoimmune pathogenesis. In our studies increased HMGB1 was expressed extracellularly in the dermis of skin after treatment with UVB and imiquimod but not in normal control mice. Systemic immune activation was detected following combination (UVB and imiquimod) but not single therapy as evidenced by IL-6 and TNF α production in serum. Combined treatment induced up-regulation of TLR-7 in IgM positive peripheral blood B cells. These studies demonstrate UV induction of systemic autoimmunity in an autoimmune prone mouse strain and suggest synergistic roles of UV induced local inflammation and TLR7 engagement.

5.

CD40L-induced systemic autoimmunity in mice is mediated in part by S100A8 and A9 proteins in CD8+ T cells

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CD40-CD40L signaling is involved in the development of autoimmunity. Within the skin, transgenic (tg) overexpression of CD40L in basal keratinocytes spontaneously leads to systemic autoimmunity as evidenced by autoantibodies, nephritis, proteinuria, and autoimmune dermatitis, which can be adoptively transferred by injecting CD8+ T cells into naïve recipient mice. To identify genes involved in the development of MHC class I-restricted autoreactivity gene expression profiling of sorted CD8+ T cells from CD40L tg mice before and after onset of disease was performed. Surprisingly, an increased expression of S100A8 and A9 genes both members of the S100 family of Ca-binding proteins was detected in CD8+ T cells after onset of autoimmune disease. Elevated mRNA levels of S100A8/A9 in CD8+ T cells from CD40L tg mice compared to controls were confirmed by quantitative realtime PCR. To determine the functional relevance of S100A8/A9 expression for the development of autoimmunity *in vivo*, CD40L tg mice were crossed to S100A8/A9^{-/-} mutants. Interestingly, CD40LxS100A8/A9^{-/-} mice showed significantly reduced autoimmune dermatitis and markedly decreased numbers of skin lesion infiltrating lymphocytes. Since CD40L tg mice are characterized by renal IgG/IgM depositions, glomerulonephritis, and proteinuria, renal function was analyzed in CD40LxS100A8/A9^{-/-} mice. CD40LxS100A8/A9^{-/-} mice showed a rescue of renal function. Additionally, the activation status of splenic and lymph node CD8+ T cells was determined in CD40LxS100A8/A9^{-/-} mice demonstrating a decreased expression of cytotoxic/autoreactive markers like CD43, CTLA-4, granzyme B, and IFN-gamma secretion. Furthermore, CD8+ T cells isolated from CD40LxS100A8/A9^{-/-} mice produced significantly reduced amounts of IL-17 a cytokine which has been suggested to mediate the inflammation associated with several autoimmune diseases. To emphasize the relevance of S100A8/A9 expression in T cells for the development of an autoreactive phenotype CD8+ T cells were purified from peripheral lymph nodes of CD40L tg and CD40LxS100A8/A9^{-/-} mice and adoptively transferred into naïve wildtype recipients. Interestingly, in contrast to T cells isolated from CD40L tg mice CD8+ T cells purified from CD40LxS100A8/A9^{-/-} mice failed to induce systemic autoimmunity in the recipients. These data indicate that the expression of S100A8/A9 proteins may be critically involved in the pathogenesis of autoreactive CD8+ T cells in CD40L-induced systemic autoimmunity.

6.

The effects of etretinate on the skin of murine models for collagen diseases such as MRL mice and bleomycin-Induced scleroderma mice

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Retinoids are known to inhibit the proliferation of skin fibroblasts and collagen synthesis, modulate immune responses, and induce apoptosis by Fas ligand upregulation in skin fibroblasts. We previously demonstrated that a vitamin A derivative etretinate had clinical efficacy for skin disorders in patient with systemic sclerosis (SSc).

We examined changes in dermal thickness and appearance of skin disorders in 5 months old MRL/Mp-*lpr/lpr* (MRL/*lpr*) mice by oral treatment with etretinate every other day for 2 months. MRL/*lpr* mice are characterized by the disorder of apoptosis by the defects in Fas antigens and symptoms including spontaneous LE-like skin lesions. MRL/Mp-*+/+*(MRL/*n*) mice do not carry the defect of *lpr* mutation and do not exhibit skin disorders during the first 6 months of life. Etretinate-treated MRL/*lpr* mice did not have skin lesions or dermatopathological characteristics including an increase in cells infiltrating the dermis. The mean dermal thickness of MRL/*lpr* and MRL/*n* mice treated with etretinate decreased significantly and apoptotic cells density in the dermis of MRL/*lpr* mice with etretinate was significantly higher compared with the control group ($p < 0.05$) although MRL/*lpr* mice have a defect in the Fas antigen. It suggested that etretinate reduced dermal thickness and suppressed the appearance of skin lesions by inducing apoptosis.

We also investigated whether the oral treatment with etretinate for a month improved sclerosis in bleomycin (BLM)-induced sclerotic skin mice. The significant decrease was seen in mean dermal thickness ($P < 0.05$) and there were changes in collagen bundles in the etretinate-treated mice group compared to controls. The density of TUNEL-positive cells in the dermis of etretinate-treated mice for a 14-day period was significantly increased ($P < 0.05$). The ratio of procollagen $\alpha 1$ (I) chain to β actin mRNA from etretinate-treated mice for a 1-day period decreased significantly compared to that of the control mice, but the ratio from etretinate-treated mice for a 14-day period increased significantly ($P < 0.05$).

These results suggest that etretinate can be applied to the treatment for the skin disorders of human collagen diseases such as cutaneous lupus erythematosus and scleroderma.

Classification of lupus erythematosus based upon Japanese patients

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The present difficulties in classification of lupus erythematosus (LE) have been caused by the varieties of standpoints used for diagnosis. Discoid LE (DLE) and LE profundus are diagnosed according to the skin manifestation, namely from the morphological standpoint. On the other hand, systemic LE (SLE) is a disease diagnosed from the symptomatic standpoint. Because DLE, subacute cutaneous LE (SCLE) and SLE are entities diagnosed from different standpoints, we should not make differential diagnosis for these entities.

If we continue to use the term of SLE diagnosed by the ACR criteria, we should use the terms for diagnosis consistently such as cutaneous-limited LE (CLE), intermediate LE (ILE) and SLE. CLE is an entity which has only cutaneous manifestation, and ILE has mild systemic manifestations. DLE, LE profundus and SCLE et al. should be used as terms for types of skin manifestations only.

Using the terms for diagnosis (CLE, ILE, SLE) and eruption (DLE, LE profundus, SCLE et al.) separately, we analyzed 195 LE patients at the Department of Dermatology in Tokyo University Hospital from 1979 to 1989. Then we proposed a system for consistency in classification of LE in 1990. Adding the data in the recent 15 years, the significance of this classification will be presented.

Systemic lupus erythematosus: a genetic epidemiology study of 695 patients from China

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Our purpose was to explore potential genetic models for systemic lupus erythematosus (SLE) and analyze genetic epidemiologic characteristics of SLE in a Chinese population. Data for 695 patients with SLE were obtained by using a uniform questionnaire. Patients, clinical characteristics and their family history were analyzed using software. A complex segregation analysis was conducted to propose potential genetic models for SLE. The mean \pm SD age of onset were 30.2 ± 10.5 years and mean time to progression to SLE was 32.5 ± 44.4 months. The most frequent initial manifestations were malar rash (61.3%). During the evolution of the disease, the main clinical features were arthritis in 73.6% of our patients, followed by malar rash (68.1%), and renal involvement (56.7%). As the first symptom, the late-onset group (onset of disease beyond the age of 50 years) less often showed malar rash (45% vs. 63.4% in the early-onset group; $p = 0.001$). There were no significant differences in the other cumulative clinical symptoms between late-onset and early-onset group, except for a lower prevalence of malar rash, photosensitivity and alopecia and a higher prevalence of mucosal ulcers in the late-onset group. A positive family history of SLE was obtained in 50 patients (7.2%). There were no statistical differences in clinical characteristics between familial SLE and sporadic SLE patients. The heritability of SLE was 43.6%, the genetic model of SLE could be polygenetic model and major gene mode is the best fitted one. SLE could be a multifactorial disease with polygenetic model.

Clinical and histopathological features of livedo lesions

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Thirty three patients (four men and 29 women) with livedo lesions were evaluated in our department from July 1997 to August 2004. Mean onset age was 42.6 years (range 14-87 years). Lesions were located on legs in 21 patients, feet in 15 patients, forearms in 10 patients, and thighs in 8 patients. All of the skin lesions showed incomplete network, having branched, wedge-shape, linear, or round configurations. The histopathological findings classified the lesions into two main categories: vasculitis or thrombotic vasculopathy. Although livedo lesions are generally found on legs, we found lesions associated with rheumatic arthritis on upper extremities and trunks as well, while those with cholesterol embolism and antiphospholipid syndrome were distributed on legs and feet. Clinical diagnosis of livedo lesions associated with rheumatic arthritis, some collagen diseases, and cholesterol embolism were relatively easy. We think a livedo lesion is a symptom of a core disease and thus histopathological, blood, or a comprehensive physical examination to confirm the core disease is important.

The presence of anti-phosphatidylserine-prothrombin complex antibodies associated with cutaneous polyarteritis nodosa

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To investigate the possible correlations between antiphospholipid antibodies (aPL) and cutaneous polyarteritis nodosa (CPN), we measured serum lupus anticoagulant (LAC), IgG and IgM anti-cardiolipin (aCL) and anti-phosphatidylserine-prothrombin complex (aPS/PT) antibodies, and anti- β_2 -glycoprotein I-dependent cardiolipin ($\alpha\beta_2$ GPI/CL) antibodies in the 16 CPN patients, 8 microscopic polyangiitis (MPA) patients, 33 systemic lupus erythematosus (SLE) patients, and 23 healthy controls. LAC was determined according to the Subcommittee on Lupus Anticoagulant/Phospholipid Dependent Antibody guidelines. aPS/PT, aCL, and $\alpha\beta_2$ GPI/CL antibodies were measured by enzyme-linked immunosorbent assay. aPS/PT antibodies and/or LAC were detected in all CPN patients, but not in any controls. Serum IgM aPS/PT antibody was found in 13 (81.3%) CPN patients. The mean \pm SD serum aPS/PT IgM level (19.9 ± 12.4 units/ml) in CPN patients was significantly elevated compared with SLE patients (5.7 ± 5.9 units/ml). IgG aPS/PT antibody was detected in 5 (31.3%) CPN patients, but not in any controls. The IgG aPS/PT antibody titers were similar in CPN patients (12.3 ± 12.0 units/ml) and SLE patients (13.8 ± 14.3 units/ml). LAC was detected in 7 (43.8%) CPN patients. Three (18.8%) CPN patients were positive for IgG aCL antibody and 2 (12.5%) for IgM aCL antibody. No MPA patients had aPL. CPN skin manifestations included livedo reticularis (14 [87.5%]). Direct immunofluorescence revealed C₃ within the affected vessels in 7 (77.8%) of 9 CPN patients. Our study demonstrated that presence of aPS/PT antibodies and/or LAC could serve as markers in CPN patients. CPN could be dependently associated with the presence of aPS/PT antibody. The association between microvascular occlusions and cutaneous vessel vasculitis could have a predictive value for livedo reticularis pathogenesis in patients with CPN. We believe that aPS/PT antibodies will become widely recognized as a new factor when diagnosing CPN.

Severe digital gangrene in systemic lupus erythematosus

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Case 1: A 35-year-old woman was diagnosed as having systemic lupus erythematosus (SLE) at the age of 20 in 1993. She has had multiple indurated plaques and subcutaneous nodules on her trunk and extremities since 1997, which were diagnosed as lupus erythematosus profundus and subcutaneous calcification respectively. Since 2005, she has suffered from recurrent digital ulcers and gangrene on her fingers accompanied by severe pains. Anti-beta2-glycoprotein-I-dependent cardiolipin (β 2GP-I/CL) antibodies and lupus anticoagulant (LAC) were negative, however, anti-phosphatidylserin/prothrombin (PS/PT) complex antibodies were highly elevated.

Case 2: A 50-year-old woman was diagnosed as having SLE when she was 35-years-old. She developed CNS lupus and was treated with steroid pulse therapy in 1993. A perforation of the small intestine occurred in 2005, which was suspected to be associated with lupus colitis. She had multiple erythema with atrophie blanche and small skin ulcers on her trunk and extremities. Anti β 2GP-I/CL antibodies, LAC and anti PS/PT antibodies were negative. Digital gangrene developed on her left third finger in 2008.

Case 3: A 28-year-old woman with an 11 year history of SLE presented with digital gangrene on her left second finger in 2007. She had been treated with prednisolone and immunosuppressive agents. Positive anti β 2GPI/CL antibodies and LAC were noted. Despite several conservative treatments for her digital ulcer, no significant improvement has been obtained.

None of our patients revealed any symptoms of other connective tissue diseases. The etiology of skin ulcers or digital gangrene is complex, and there may be unknown causes other than vasculitis and thrombosis.

Recent advance in ANCA-associated vasculitis

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Among small-vessel vasculitides, microscopic polyangiitis (MPA), Wegener's granulomatosis (WG), and allergic granulomatous angiitis (AGA) are known collectively as ANCA-associated vasculitis (AAV) because of the involvement of anti-neutrophil cytoplasmic antibodies (ANCA) as the common pathogenesis. Major target antigens of ANCA associated with vasculitis are myeloperoxidase (MPO) and proteinase 3 (PR3). MPO-ANCA is related to MPA and AGA, and PR3-ANCA is the marker antibody in WG. MPO-ANCA-associated vasculitis is more frequent in Japan, whereas PR3-ANCA-associated vasculitis is more common in Europe and USA. Untreated patients with severe AAV with multi-organ involvement have a poor prognosis, which is improved by combination therapy with cyclophosphamide and high-dose corticosteroid. Regarding the induction and maintenance of remission of AAV, several randomized controlled trials have been performed in Europe and USA, and provided good evidence. These data, however, were obtained mostly in patients with positive PR3-ANCA. Therefore, caution must be taken in applying these findings to Japanese patients, most of whom are positive for MPO-ANCA. To establish evidence for Japanese patients with MPO-ANCA-associated MPA, the efficacy and safety of the standard protocols has been evaluated in a prospective, open-labeled, and multi-center manner (JMAAV trial). In this trial, patients with newly diagnosed MPA were stratified based on their severity. Patients received the regimen according to the therapy protocol, and were followed up for 18 months. The primary end point was the induction of remission. Furthermore, transcriptomic analysis of peripheral blood was performed in order to reveal genes associated with outcome. The enrollment was completed in September 2006, and 51 patients were enrolled. In this seminar, the current results of the JMAAV study will be reported.

13.

History of Seishu Hanaoka, Wakayama and Kyoto in modern medicine

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I will introduce the impact of Seishu Hanaoka in the modern medicine.

Following is from **Wikipedia, the free encyclopedia**.

Seishu Hanaoka (華岡青洲 Hanaoka Seishu November 30, 1760 - November 21, 1835) was a Japanese physician, who was the first to perform surgery using general anaesthesia, almost forty years before Dr. Crawford Williamson Long operated in Danielsville, Georgia using anaesthesia. Hanaoka performed a breast cancer operation in 1804 using a compound he called Tsusensan, based on a concoction of the plants Datura Metel, Aconitum and others. His patient was 60 year-old Kan Aiya (藍屋勤), whose family was beset by breast cancer - Kan being the last of kin alive. Seishu Hanaoka learnt traditional Japanese medicine as well as Dutch-imported European surgery. The imported knowledge was very difficult for him and other Japanese physicians to learn, as few foreign medical texts were permitted brought into Japan due to the nation's self-imposed isolation policy of Sakoku. The national isolation policy of the Tokugawa Shogunate prevented Hanaoka's achievements from being publicized until after the isolation ended in 1854. The delay meant anaesthesia in the rest of the world had to develop independently. The famous Japanese author Sawako Ariyoshi wrote a novel entitled, The Doctor's Wife (Japanese 華岡青洲の妻), based on the actual life of Seishu Hanaoka mixed with a fictional conflict between his mother and his wife.

14.

New Clinical and Pathophysiological Aspects of Cutaneous Lupus Erythematosus

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Cutaneous lupus erythematosus (CLE) is an inflammatory autoimmune disorder, comprising a broad spectrum of clinical manifestations. A detailed patient's history, evaluation of the activity and damage, histological analysis of skin biopsy specimens, phototesting, and serological investigations support the diagnosis of the disease. A Core Set Questionnaire was recently developed by EUSCLE e.V. with the aim of gaining a broad, comparable data collection from patients with CLE at different European centers. Various environmental factors influence the clinical expression of CLE and a striking relationship has emerged between sunlight exposure and the various subtypes of the disease. Although the mechanism by which ultraviolet (UV) irradiation activates the autoimmune response is not fully understood, recent studies addressing the molecular mechanisms underlying UV-induced apoptosis contribute to a better understanding of the disease pathogenesis. In the past years, CD4⁺CD25⁺ regulatory T cells (T_{reg}) have also emerged as an important factor in our understanding of the mechanisms underlying the development of autoimmunity. Recently, a decrease of Foxp3⁺ T_{reg} in skin lesions of patients with CLE compared to other chronic inflammatory skin diseases, such as lichen planus, atopic eczema, and psoriasis, was observed. This reduction of T_{reg} in the dermal infiltrate was independent of the disease subtype; however, patients with CLE did not show a general T_{reg} defect as supported by a normal frequency of peripheral T_{reg} subpopulations, a normal sensitivity of T_{reg} toward CD95L-mediated apoptosis, and a similar activity of T_{reg} in CLE patients and healthy controls. These data suggest an organ-specific abnormality of T_{reg} in skin lesions of patients with CLE and differ from a global peripheral dysfunction in patients with an active flare of a systemic organ manifestation of the disease. Further elucidation of the relevant pathogenic factors of the disease will lead to the development of effective strategies to prevent abnormal humoral and cellular reactivity in patients with CLE.

TNF- α production in the skin

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Upregulation of TNF α is a key early response by keratinocytes (KCs) in response to UVB, and represents an important component of the inflammatory response in skin. UVB irradiation induces TNF α expression in both KCs and dermal fibroblasts, with TNF α mRNA induction seen as early as 1.5 hours after UVB. We previously reported that the effects are wavelength-specific: TNF α expression and secretion are induced by UVB (290-320nm), but not by UVA (320-400nm). Moreover, we found that IL-1 α , a cytokine also present in irradiated skin, substantially and synergistically enhances the induction of TNF α by UVB, and the induction of TNF α by this combination of UVB with IL-1 α is mediated through increased TNF α gene transcription. We investigated the molecular basis for UVB-induction of the TNF α promoter with a series of TNF α promoter constructs, ranging from 1.2 kbp (from -1179 to +1 with respect to the TNF α transcription initiation site) down to 0.1 kbp (-109 to +1), each driving expression of a CAT reporter. Our results showed a persistent 9-10 fold increase of CAT activity in all TNF α promoter/reporter constructs in response to UVB (30 mJ/cm²) exposure. These results indicate the presence of UVB-responsive *cis*-element(s) located between -109 and +1 of the TNF α promoter, a region that contains a putative AP-1 site and a putative NF κ B site. UVB-induction was abolished when the TNF α promoter was mutated by one base pair at the AP-1 binding site. Cells treated with SP600125, an AP-1 inhibitor that inhibits JNK (c-Jun N-terminal kinase), showed suppression of the 0.1 kbp TNF α promoter/reporter construct. The authentic endogenous gene in untransfected cells also was blocked by the inhibitor. Electrophoretic Mobility Shift Assay indicated new complexes from UVB-treated nuclear extracts and anti-phospho-c-Jun, a regulatory component of the AP-1 transcription factor, creating a supershift. In conclusion, UVB specifically induces TNF α in skin cells, in large part through activation of the AP-1 site in the proximal region of the TNF α promoter. Keratinocyte-derived TNF α is a component of the early induction phase of the inflammatory cascade.

Activated innate immune response pathways support the type I interferon-associated cytotoxic inflammation in CLE skin lesions

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Background: Chronic discoid lupus erythematosus (CDLE) is an autoimmune skin disorder that is characterized by a cytotoxic immune response invading the basal epidermal layer accompanied by hydropic degeneration and apoptosis of keratinocytes ("interface dermatitis"). Recent studies provided evidence for an important pathogenic role of the type I interferon system in this skin disease, but the detailed components of the proinflammatory network remained undiscovered.

Methods: Laser microdissection of cryofixed LE skin biopsies taken from 6 patients with CDLE with active disease was performed. Epidermal, junctional and dermal cells were extracted. mRNA was isolated, amplified and used for microarray gene expression analyses. Immunohistochemistry was performed to confirm the results on the protein level. In situ hybridization for IFN α 1 and IFN β was established to identify lesional IFN producing cells in the skin.

Results: Our analyses demonstrated a strong activation of innate immune response pathways (TLR, JAK/STAT, MAP-kinase, NF κ B) accompanied by a lesional cytokine-storm (e.g. CCL5, CCL20, CCL22, CXCL9, CXCL10, CXCL11, IL3, IL7, IL12, IL18), recruitment of cytotoxic immune cells (granzyme B, perforin, Tia, NKG2D) and induction of keratinocytic apoptosis. In the skin of CLE patients we identified an "interferon-signature" (e.g. IFIT1, IFITM2/3, AIM2, IRF7, STAT1) that closely resembles the expression pattern described in the blood of patients with active systemic disease (SLE). Additionally we were able to show that keratinocytes are producers of type I IFN in cutaneous LE skin lesions.

Conclusion: Our results demonstrate that inappropriately activated innate immune pathways are involved into the pathogenesis of CDLE skin lesions. We assume that these mechanisms drive a cytotoxic cellular immune response, which is responsible for the tissue destruction and the scarring character of this disease.

Specific Species of Glycosaminoglycans Accumulate in Skin in Cutaneous Lupus Erythematosus

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Elevated glycosaminoglycans (GAGs) have been observed on Hale's stain of skin in cutaneous lupus erythematosus (CLE). Hale's stain, however, cannot distinguish among different GAG species, which have distinct effects on recruitment and activation of immune cells and stimulation of cytokine production. Thus, we used immunohistochemistry to examine two GAG species, hyaluronic acid (HA) and chondroitin sulfate (CS), in CLE, UVB-irradiated SCLE and healthy skin. Skin sections from patients with one of several types of CLE (subacute cutaneous, SCLE; discoid, DLE; and tumid, TLE), healthy controls, and UVB- or sham-irradiated subjects were separately stained with HA binding protein and the anti-CS antibody CS-56. Total and upper dermal staining among disease subtypes and controls was graded in a blinded fashion from 0 (absent) to 4 (high). DLE exhibited higher total dermal HA (3.8 ± 0.22 vs. 2.4 ± 0.27) and CS (3.4 ± 0.67 vs. 1.2 ± 0.22) compared to controls (means \pm SEM, $n=5$, $p<0.05$), whereas TLE only showed an upper dermal increase in HA (3.8 ± 0.22 vs. 2.8 ± 0.22 , $n=5$, $p<0.05$). No significant increase in HA or CS was found in SCLE patients. Among UVB-irradiated samples, HA decreased in the upper dermis 48 hours post-irradiation but returned after 72 hours in both SCLE ($n=2$) and healthy skin ($n=3$) compared to sham-irradiated skin. In contrast, upper dermal CS increased in both SCLE and healthy skin 48 to 72 hours post-irradiation compared to sham-irradiated skin. Thus, HA and CS exhibited distinct patterns of altered staining, depending on the condition. We speculate that the increase in HA in DLE and TLE patients may be part of the local inflammatory response. The biologic role for the increase in CS in DLE and UVB-irradiated skin is unknown. Importantly, the decrease in HA 48 hours after UVB-irradiation may indicate HA fragmentation, which could augment photosensitivity.

Anti-laminin 1 antibodies in cutaneous lupus patients.

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Although the lupus band test is widely used for the diagnosis of lupus erythematosus (LE), the target antigen of the lupus band is still unknown. Recently it has been shown a partial colocalization of the lupus band with laminin-1. It has been shown that antibodies against the VRT101 laminin-1 epitope correlate with human systemic LE disease activity. However, the presence of anti-laminin-1 autoantibodies in cutaneous LE (CLE) has never been tested.

In the present study, the sera of 13 patients with CLE (8 discoid LE, 2 subacute CLE and 3 acute CLE), 3 with dermatomyositis, 3 with systemic sclerosis, 3 with bullous pemphigoid, 3 with Senear-Usher syndrome, 3 with cicatricial alopecia and 10 healthy controls were tested. Cryostat sections of rat stomach (the best available substrate to detect anti-laminin-1 antibodies) and of human salt split skin was used as substrate for indirect immunofluorescence (IIF) assay. Subsequently, all the sera were tested with an immunoblot assay using both 400 and 220-230 kDa subunits of laminin 1 purified from Engelbreth-Holm-Swarm tumor.

Using anti IgM antibodies, IIF was positive with both substrates in 3 CLE patients, 1 dermatomyositis patient, 1 Senear-Usher syndrome patient, and in the 3 patients with bullous pemphigoid. The sera of 11 CLE patients (7 discoid CLE, 2 subacute CLE and 2 acute CLE), 1 dermatomyositis patient and 1 systemic sclerosis patients demonstrated reactivity against both laminin 1 subunits, while the sera of the healthy controls and of the other patients did not.

In conclusion, our data suggest that anti-laminin-1 antibodies are present in patients with CLE. It still remain to be determined whether the IgM antibodies located at the basement membrane zone in CLE lesions are directed against laminin-1.

High concomitance of disease marker autoantibodies in anti-DFS70/LEDGF autoantibody-positive patients with autoimmune rheumatic disease

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Autoantibodies against DFS70 (dense fine speckles 70) are found in 10% of healthy people, but only in a tiny population of patients with autoimmune rheumatic disease (ARD). The antibody may thus be a marker of ARD negativity. To investigate this possibility, we examined the presence of various disease-marker autoantibodies in anti-DFS70 antibody-positive patients with ARD. Serum samples from 500 patients with various types of ARD were examined for anti-DFS70 antibodies by indirect immunofluorescence and immunoblotting. Various disease-marker autoantibodies were measured by ELISA. Twenty-two patients were positive for anti-DFS70 antibodies. Eighteen patients also had disease-marker autoantibodies including anti-double stranded DNA, anti-cardiolipin, anti-SS-A, or other antibodies. In one patient with Sjögren syndrome and two patients with dermatomyositis, no disease-marker antibodies were found; however, one dermatomyositis patient had a concomitant anti-cytoplasmic antibody. All seven systemic lupus erythematosus patients fulfilled the classification criteria for this disease even if ANA-positive findings were excluded. One morphea patient had high titer anti-single stranded DNA antibody. According to this and previous studies, patients with only anti-DFS70 antibody are very rarely diagnosed as ARD. Recognizing DFS patterns in ANA tests is thus very important for analysis of laboratory results in rheumatology clinics.

Following values of circulating immune complexes (CIC) in the blood of patients with systemic (SLE) and discoid lupus erythematosus (DLE)

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INTRODUCTION and AIM: SLE and DLE are heavy and complex diseases which have to be followed constantly with measuring of many important immunological parameters, to detect small changes which can lead to progressing of the disease or inadequate therapy. So we decided to look at the values of CIC (especially IgG fraction) which are important in the prognosis and therapy.

PATIENTS AND RESULTS: The values of CIC in the blood of patients suffering from SLE and DLE were measured constantly during one year every 3 months. The clinical state of 8 patients with SLE was also evaluated with other specific tests such as DIF, IIF, ANA, anti ds-DNA, complement, C3 and C4 components. The values of CIC were the main parameters for monitoring clinical changes and also therapeutic effect of immunosuppressives and antimalarics. In 6 out of 12 patients suffering from DLE constantly increased values of CIC (especially IgG fraction) were found. One patient developed SLE and 2 patients were under constant control because of positive ANA test.

The measuring was conducted from year 1989 till 1992 when we discontinued examinations because of the war in Croatia. We started again in year 2002. From our group of patients with SLE only 2 were still alive. So we have taken another group of 6 patients with SLE and again found the same changes in CIC as before. We also included 5 old patients with DLE again and added 8 new ones. In our old group one patient developed subacute form of SLE and in a new ones 3 are showing the increased IgG fraction in CIC with values of 180-356 mg/L (normal 130 mg/l). CIC was repeated every 3 months and other immunological tests every 6 months.

CONCLUSION: We can conclude that values of CIC, but only in LONGITUDINAL follow up, can make indicate developing of SLE and show us a results of therapy in patients with DLE. High values of CIC can also warn us on great possibility of depositing in tissues and cause damages. By using CIC, which is a common and cheap test for follow up of patients, we can reduce the frequency of performing other immunological tests.

Clinical Significance of Anti-U1RNP Antibodies in Cerebrospinal Fluid from SLE and MCTD Patients with Active Central Nervous System Involvements

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Objective. To determine the clinical significance of anti-U1RNP antibodies (Abs) in cerebrospinal fluid (CSF) from Japanese connective tissue disease patients with central nervous system (CNS) involvements.

Methods. In 19 patients with systemic lupus erythematosus (SLE) and 4 with mixed connective tissue disease (MCTD), who had clinically active or inactive CNS involvements, anti-nuclear Abs including anti-U1RNP Abs were determined both in sera and CSF by RNA-immunoprecipitation assay using HeLa cell extracts and ELISA.

Results. In CSF, the detected Abs were limited to anti-U1RNP (43%), anti-SS-A/Ro (23%), and anti-dsDNA (9%) Abs. Anti-U1RNP Abs were found more frequently in CSF from patients with active neuropsychiatric manifestations associated with SLE and MCTD than in CSF from inactive CNS involvements (70% vs. 10%, $P<0.05$). Anti-U1RNP ratio ($=[\text{CSF-anti-U1RNP Ab titer}/\text{CSF-total IgG concentration}]/[\text{serum-anti-U1RNP Ab titer}/\text{serum-total IgG concentration}]$) was significantly higher in patients with active ($=6.8\pm 4.6$) than with inactive CNS involvements ($=2.2\pm 1.6$) ($P<0.05$). The anti-70K ratio ($=3.08\pm 1.75$) was higher than anti-A ($=1.52\pm 1.18$) and anti-C ($=0.87\pm 0.67$) ratios calculated using samples from anti-U1RNP Ab-positive patients with active CNS involvements.

Conclusions. Determination of CSF-anti-U1RNP Abs is useful to define activity of CNS involvements in patients with anti-U1RNP Ab-positive SLE and MCTD. The elevated anti-U1RNP ratio with the unequal detection of anti-70K, A, and C Abs suggests that anti-U1RNP Abs in CSF are not always attributable to the increased blood brain barrier permeability.

Clinical photobiology of lupus erythematosus

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Photosensitivity is a characteristic feature of all forms and subsets of LE that has been recognized since the first phenomenological descriptions of this disease in 1881 by Cazenave. Despite the numerous anecdotal reports and clinical evidence, systematic studies on photobiological reactivity in patients with LE started only after 1980. Experimental test protocols were developed in order to phototest LE patients on a routine basis. Reproduction of skin lesions were successful using UVB as well as UVA irradiation in the repeated exposure technique. This testing regimen received much attention because the reproduction of lesions is an optimal model for clinical and experimental studies.

Overall, in 45% of all LE subsets characteristic lesions can be induced experimentally. LE tumidus type is the most photosensitive subtype (79% positive reactions), followed by subacute cutaneous LE (65%), discoid LE (45%), and others like LE profundus and chilblain LE (41%). In contrast to other photodermatoses, such as PLE, the development of skin lesions in LE shows a latency of several days up to three weeks and longer and might persist for several weeks to months. This may explain the fact that LE patients are sometimes not aware of their photosensitivity.

By now we have been able to phototest over 500 patients with this standardized protocol and could clinically characterize the LE subset with the highest photosensitivity, namely LE tumidus.

Cell Death in Photosensitive Lupus: Past, Present and Future

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Statement of the Problem: Cell death plays an important role in the skin disease and systemic disease of patients with multiple clinical variants of photosensitive lupus.

Study methods: This is a literature review summarizing 25 years of evolving research in cytotoxic mechanisms in photosensitive lupus

Results and Conclusions: Past An early model of cell death in photosensitive lupus deduced that in SCLE, SSA/Ro-specific antibodies binding to ultraviolet (UV)-treated LE patient keratinocytes could induce significant cell death through antibody dependent cellular cytotoxicity (ADCC) mediated by mononuclear effectors. During the past 15 years, there has been a revolution in thinking about the mechanisms of cell death, and it is now dogma that apoptosis and necrosis are two types of cell death that are nearly opposite in mechanism. UV is a significant inducer of apoptosis and necrosis. It was soon recognized that apoptosis is an important aspect of photosensitive lupus, involved in antigen translocation and processing, in the failure to destroy auto-reactive T cells, and also in tissue damage. Apoptosis of basal keratinocytes is seen in CCLE, while in SCLE apoptosis is seen in midlevel keratinocytes and necrosis in basal keratinocytes. Regulation of UV-induced apoptosis in keratinocytes in LE patients appears to be determined by genetic polymorphisms such as in TNF- α gene.

Present Immunologists have rediscovered the lichenoid tissue reaction as an important immunologic mechanism characterized by basal keratinocyte apoptosis and question its relation to photosensitive lupus and dermatomyositis.

Future The precise role of different cytotoxic T cells subsets, plasmacytoid dendritic cells, T regs, and autoantibodies in cutaneous lupus, and the type of keratinocyte damage produced will be a fertile area of investigation in the near future. Genetic determinants of faulty antigen processing, of UVR-induced cell death, and of faulty elimination of auto-reactive T cells will surely be a major direction of research in photosensitive LE.

Abbreviations:

SCLE: subacute cutaneous lupus erythematosus, CCLE: Chronic cutaneous lupus erythematosus (discoid)

SCLE in Sweden, novel findings

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Objectives. Our aim was to study the epidemiology of subacute cutaneous lupus erythematosus (SCLE) in Stockholm, Sweden, to characterize Ro/SSA-positive patients clinically and serologically, and to investigate the Ro52 antigen as target for the autoimmune inflammatory process in the skin.

Results: By studying serology-based registers of Ro/SSA autoantibody positive patients together with questionnaires, we could estimate the incidence of Ro/SSA-positive SCLE to 0.7 per 100000 persons per year and the prevalence to 6.2-14 per 100000 persons. PLE and smoking were more common than in the general population. ELISA revealed higher levels of Ro52 and La-autoantibodies in CLE patients with systemic manifestations compared to those with disease confined to the skin. At follow-up after 2 years, new or additional autoimmune disease as well as drug-induced SCLE were found. Immunohistochemical studies of skin biopsies revealed increased cytoplasmic and extracellular expression of the proinflammatory cytokine high mobility group box chromosomal protein (HMGB-1) in both spontaneous and experimentally UV-induced CLE. TNF- α and IL-1 β were also expressed, these together with HMGB-1 can result in sustained inflammation in CLE. The Ro52 antigen was overexpressed in SLE and Sjögren's syndrome patients and was shown to function as an E3-ligase regulating proliferation and apoptosis. Ro52 was upregulated in the epidermis of spontaneous and UV induced CLE lesions. Dermal infiltrates showed strong Ro52 expression. *In vitro*, UV-irradiated keratinocytes displayed upregulation of Ro52 in the cytoplasm, perinuclear accumulation and translocation to the nucleus.

Conclusion: SCLE is a rare subset of lupus but CLE as a group was estimated to be a more prevalent disease than SLE. Guidelines of care should include counselling concerning smoking cessation, sun-protection and avoidance of photosensitizing drugs. HMGB-1 is a potential therapeutic target in the skin, and Ro-52 dysfunction can be a pathogenic factor in CLE.

The Clinical Spectrum of Neonatal Lupus

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Objective: to review the cutaneous manifestations of neonatal lupus, primarily from cases in the United States, and to review briefly possible associated extracutaneous findings

Results: Cutaneous neonatal lupus lesions usually begin at a few weeks of life, but may be present at birth. Although males are commonly affected, there is a female predominance. Lesions are erythematous plaques, often round with central clearing. Lesions are found most often on the face and scalp, but may affect any area of the skin. The periorbital skin is a characteristic location. Sun exposure may initiate or exacerbate. Cutaneous lesions resolve within weeks or months. In most cases, there are no residua, but there can be persistent dyspigmentation or telangiectasia. Atrophy is unusual but has been reported.

In most cases of cutaneous lupus, the skin is the only organ noted to be affected. A significant number of cases, however, have other organs involved. These are mainly heart (congenital heart block, with or without cardiomyopathy), liver (cholestatic jaundice, elevated transaminases, or rapidly progressive liver failure with a phenotype of neonatal hemochromatosis), or blood (thrombocytopenia, neutropenia, anemia).

The Neonatal Lupus Registry (USA) reported 7 of 49 children who had neonatal lupus developed autoimmune disease of some type in childhood or adolescence (e.g., 2 had juvenile rheumatoid arthritis), and 2 of their 45 unaffected siblings developed a positive ANA without associated symptoms.

Conclusion: Cutaneous neonatal lupus is a transient condition but may occasionally be associated with severe extracutaneous disease. Children who have neonatal lupus are probably at increased risk for autoimmune diseases later in childhood or adulthood. The magnitude of that risk is uncertain.

Anti-Ro/SSA and La/SSB associated annular erythema and neonatal lupus

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Sjogren-associated annular erythema was first reported in Japanese literature almost 30 years ago. Association with anti-SSA and SSB was suggested several years later. Since then, a number of similar cases have accumulated, but such lesions are very rare in American Caucasian or Black anti-SSA positive patients. The Sjogren-associated annular erythema can be distinguished clinically and histologically from the annular-polycyclic lesion of SCLÉ. Two major points are: absence of epidermal changes, and remarkable lymphocytic infiltration around sweat glands in Sjogren-associated annular erythema. The erythema disappears within several weeks, and often, does not respond to topical corticosteroids. Treatment depends on severity of skin lesions and systemic manifestations of each patients. Complications we have observed in our 10 patients are: thyroid disease, aseptic meningo-encephalitis and one woman had babies with cutaneous neonatal lupus. Very recently, one patient developed cutaneous B-cell lymphoma after the follow-up period of 20 years.

There are racial differences as well as similarities in the clinical features and immunogenetic backgrounds of Japanese and Caucasian patients with neonatal lupus. The majority of Japanese infants with cutaneous neonatal lupus develop annular, erythematous or edematous lesions which have also been reported in association with Sjögren's syndrome. The frequency of isolated congenital heart block (CHB) is about 50% in Japanese anti-Ro/SSA positive neonatal lupus infants; this is similar to the frequency among Caucasians. The HLA-DR3 phenotype, which is found in the great majority of Caucasian mothers, is absent in Japanese mothers. Finally, both Japanese and Caucasian children with CHB are often identical to their mothers in their alleles of HLA-DRB1, DQA1 and DQB1 loci.

Neonatal lupus erythematosus in Japan : a case report and review of the literature

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Neonatal lupus erythematosus (NLE) is characterized by transient annular erythema, autoantibodies, and possible development of congenital heart block. We report a 2-month-old female baby with NLE. She developed annular erythema on the cheek one month after her birth. She had abnormal liver function tests, but there was no thrombocytopenia nor ECG abnormality. Skin biopsy specimen from her left cheek revealed perivascular and periappendageal patchy lymphocytic infiltrations in the dermis with liquefaction degeneration, however, immunofluorescence test (lupus band test) was negative. Her ANA titer was elevated at 1:40 (speckled pattern), and anti-SS-A/Ro and anti-SS-B/La antibody were positive. Her mother had symptoms of dry eye and dry mouth, and also had positive ANA titer of 1:640 and positive anti-SS-A/Ro and anti-SS-B/La antibody, which suggested her mother had Sjogren syndrome. The eruption of the patient faded completely in four month in parallel with disappearance of serum anti-SS-A/Ro and SS-B/La antibody. In addition to this case description, we also report literature review of recent Japanese cases with NLE.

Histopathologic features of cutaneous lupus erythematosus

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Cutaneous lupus erythematosus (LE) comprises a broad spectrum of histopathological signs, most being the expression of the developmental stage of the lesions; some are common to all stages (e.g. mucin deposits). Distinction is made between *early type*, *full-blown* and *late type* LE; plus a group of special manifestations. Histopathology of LE skin lesions depends only on their stage, irrespective of the presence or not of systemic signs. The sequence of events in developing cutaneous LE lesion is:

- sparse superficial perivascular lymphocytic infiltrates, neutrophils and nuclear dust beneath the dermoepidermal junction
- perivascular and periappendageal lymphocytic infiltrates
- interface dermatitis: "smudging" of junction zone, vacuolar degeneration of basal layer, cytooid bodies, pigmentary incontinence
- thinning of epidermis, hyperkeratosis, follicular horny plugs, follicular atrophy
- basal membrane thickening
- fibrosclerosis and atrophy

Special manifestations comprise *bullous LE* (subepidermal cleavage, linear array of leucocytes at dermoepidermal junction zone, perivascular lymphocytic infiltrates); *LE tumidus* (no epidermal changes, hair follicles unaffected, prominent perivascular infiltrates, prominent mucin); *lichenoid LE* (lichenoid junctional infiltrate); *verrucous (hypertrophic) LE* (pseudoepitheliomatous epidermal hyperplasia, prominent basal lamina, prominent perifollicular infiltrates); *chilblain LE* (orthohyperkeratosis, dermal edema, superficial and deep lymphocytic infiltrates); and *LE panniculitis* (prominent infiltrates of reticular dermis, lobular and septolobular panniculitis, lymph follicles, abundant mucin).

Differential diagnoses of cutaneous LE comprise dermatomyositis and dermatitis herpetiformis (early LE), lichen planus (lichenoid LE), erythema anulare centrifugum and polymorphous light eruption (LE tumidus) and squamous cell carcinoma.

Drug-induced lupus erythematosus

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Drug-induced lupus erythematosus (DILE) is as a lupus-like syndrome temporally related to continuous drug exposure (from one month to as long as over a decade) which resolves after discontinuation of the offending drug. Similarly to idiopathic lupus, DILE can be divided into systemic (SLE), subacute cutaneous (SCLE) and chronic cutaneous lupus (CCLE). Systemic DILE is rare and it is characterized by typical general lupus-like symptoms, skin involvement and mild systemic involvement (serositis). Anti-nuclear and anti-histone Abs are common, whereas anti-dsDNA and anti-ENA Abs are rare. High risk drugs include hydralazine, procainamide and isoniazid. Usually, years of exposure to the offending drug are required for the development of this syndrome, which resolves within weeks of drug discontinuation. Instead exposure to low levels of certain drugs (antibiotics, NSAIDs, anticonvulsant and estrogens) for relatively short periods may exacerbate underlying SLE, which remains or recurs after withdrawal of the implicated drug. Drug-induced SCLE is very similar to idiopathic SCLE in terms of clinical and serologic characteristics, and it is more common than the systemic form of DILE. Drugs associated with SCLE include calcium channel blockers, angiotensin-converting enzyme inhibitors, interferons, thiazide diuretics and terbinafine. Drug-induced CCLE is very rare and usually refers to fluorouracil agents or NSAIDs. Recently, DILE has been reported with anti-TNF α agents (etanercept and infliximab). These cases present with disparate clinical features including arthritis/arthralgia, skin rash, serositis, cytopenia and variable laboratory abnormalities. DILE secondary to anti-TNF α agents differs in several ways to classic DILE: the incidence of rashes and visceral involvement (renal) is higher whereas myalgias are less common. Low serum complement levels and ENAs are rarely associated with classic DILE, while they are reported in half the cases of anti-TNF α DILE. Finally, anti-dsDNA aAbs occur more frequently in anti-TNF α DILE than in classic DILE, and anti-histone Abs are described in classic DILE more often than in anti-TNF α DILE. Recognition of DILE in patients receiving anti-TNF α therapy can be difficult due to the symptoms of their underlying disease. A temporal association of the offending drug with characteristic or suggestive symptoms, and resolution of symptoms on withdrawal of the drug is the best evidence for this diagnosis.

Anti SS-A/Ro antibody: risk factor of fluorouracil and paclitaxel-induced acral erythema, lupus-like and annular lesions

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Background: It is well known that fluorouracil (FU) agents frequently induce discoid lupus erythematosus (DLE)-like eruptions and acral erythema in Japan. However, the etiology of these drug eruptions caused by chemotherapy has not been clarified yet.

Objective: To determine if the existence of anti-SSA/Ro antibody may be a risk factor for chemotherapy-induced drug eruptions showing LE-like eruptions and acral erythema.

Patients and Methods: Six patients with FU agents-induced drug eruptions showing LE-like eruptions and acral erythema and 2 patients with paclitaxel-induced annular lesions were enrolled in this study. The titers of anti-SSA/Ro antibody in the sera and histopathology of the skin lesions were examined.

Results: Biopsy specimens from DLE-like eruptions, acral erythema and annular lesions in all examined cases showed lichenoid change of the basal keratinocytes. Direct immunofluorescence studies revealed that deposition of immunoglobulins along the basement membrane zone in the lesions of both DLE-like eruptions and acral erythema. Further, all 8 cases had high titers of serum anti-SSA/Ro antibody, which did not decline within 6 months after cessation of the causative drug.

Conclusion: We propose that anti-SSA/Ro antibody may be a risk factor for chemotherapy-induced acral erythema, DLE-like eruptions and annular lesions

Autoimmune disease as sequelae of drug-induced hypersensitivity syndrome

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Drug-induced hypersensitivity syndrome (DIHS/DRESS) is a life-threatening multiorgan system reaction induced by specific drugs such as anticonvulsants: this syndrome is characterized by reactivation of human-herpesvirus-6 (HHV-6), but other herpesviruses such as Epstein-Barr virus (EBV) can be also reactivated in a sequential manner during the course. After withdrawal of the causative drug, this syndrome has the protracted clinical course associated with several sequelae, such as type 1 diabetes mellitus and thyroiditis, and their development may be recognized only months or years later. In this regard, we have recently found that regulatory T (Treg) cells detected in the resolution stage of DIHS are functionally impaired in their in vitro suppressive activity despite their normal frequencies in blood, regardless of whether the patients have developed autoimmune diseases. Consistent with this finding, some recent studies have demonstrated the existence of Treg cells with a reduced in vitro suppressive function in patients with type 1 diabetes mellitus and other autoimmune diseases. Indeed, we have recently experienced an interesting case who developed systemic lupus erythematosus (SLE) 4 years after the resolution of DIHS. This patient presented with bilateral enlarged lymph nodes, consistent with the diagnosis of Kikuchi-Fujimoto's disease, which is a benign and self-limited lymphadenitis. Within 2 weeks, he developed clinically evident SLE. Expression of EBV-encoded RNA was detected in the lymph node. EBV repeatedly reactivated during the course of DIHS and again at the time of the lymphadenitis might have contributed to the induction of SLE in this patient. Our case suggests the importance of recognizing DIHS at a risk of eventually developing autoimmune diseases. To ensure an early diagnosis of possible development of autoimmune diseases, patients with DIHS should be carefully followed up even long after resolution.

Dermatologic manifestations of the antiphospholipid syndrome

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Since the first description of antiphospholipid syndrome (APS), a wide variety of dermatologic manifestations have been reported. They may be the presenting feature of the APS syndrome. They are extremely diverse and heterogeneous, ranging from minor signs to life-threatening conditions. Some of them are now considered as clinical criteria according to classification criteria for definite APS which were revised in 2006. Livedo reticularis (LR) is the most common skin lesion, present in 16 to 25% of cases. When it is the sole cutaneous manifestation, its clinical features, although non-specific, is rather suggestive of APS. Its mechanism remains subject of debates. Indeed, thrombosis is rarely observed from biopsies of LR except in the catastrophic APS. A direct effect of antiphospholipid antibodies was suggested. A significant association between LR and cerebral or ocular ischemic arterial events, seizures, all arterial events, heart valve abnormalities detected on echocardiography, and arterial systemic hypertension was demonstrated. Conversely, LR was less frequently observed in patients with only venous thrombosis. The pseudovasculitis lesions may mimic cutaneous vasculitis and may be misdiagnosed if skin biopsies are not performed, especially in patients with SLE. Clinical features of widespread superficial cutaneous necrosis within APS are similar to those observed in other thrombophilic states. Treatment of patients with skin lesions must be considered according to both the different dermatological manifestations and the presenting clinical situation. Prevention of recurrence of skin lesions depends not only on their severity, but also on the other features of the disease. Scientific data are required to determine the optimum management of these patients, who might benefit from recently developed antithrombotic agents.

Antiphospholipid Syndrome and Pro-Atherogenic Oxidized Low-Density Lipoprotein/ β 2-Glycoprotein I Complexes

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Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of a heterogeneous group of "antiphospholipid antibodies", associated with arterial and/or venous thrombotic events, or with pregnancy morbidity. Arterial involvement in APS includes coronary vascular disease, stroke, and peripheral vascular disease, all with common underlying features of atherosclerosis and thrombus formation. It is now generally accepted that clinically relevant so-called "antiphospholipid" antibodies recognize phospholipid binding plasma proteins, such as β 2-glycoprotein I (β 2GPI) complexed to negatively charged phospholipid. β 2GPI also binds to oxidized LDL (oxLDL) and oxLDL/ β 2GPI complexes.

Circulating oxLDL/ β 2GPI complexes (which are originally formed in atherosclerotic plaques) are detected in sera of patients with chronic inflammatory and systemic autoimmune diseases associated with atherosclerotic complications, such as systemic lupus erythematosus, APS, systemic sclerosis, as well as type 2 diabetes mellitus, chronic nephritis, and acute coronary syndrome. On the other hand, anti- β 2GPI antibodies reacting with oxLDL/ β 2GPI complex are also frequently present in SLE/APS patients. We have demonstrated that the *in vitro* macrophage uptake of oxLDL/ β 2GPI complexes is increased significantly in the presence of IgG anti- β 2GPI antibodies and that IgG immune complexes with oxLDL/ β 2GPI up-regulate the surface expression of Fc γ receptor and CD36, a scavenger receptor, and antigen presentation to oxLDL/ β 2GPI specific T cells. These observations strongly suggested that oxLDL/ β 2GPI complexes and APS-derived anti- β 2GPI antibodies are "pro-atherogenic".

Antiphospholipid Syndrome: Why sticky blood?

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Antiphospholipid antibodies (aPL) are a large and heterogeneous family of circulating immunoglobulins found in a wide range of infectious and autoimmune diseases. Since the early 80s, the interest on these antibodies has exponentially increased due to their associations with thrombotic events and pregnancy morbidity in the antiphospholipid syndrome (APS).

Intensive research works have greatly advanced our knowledge of the mechanisms that explain why these antibodies may play a direct role in clot formation. Nowadays, it is worldwide recognized that many of the autoantibodies associated with the APS are directed against phospholipid-binding plasma proteins such as β 2glycoprotein I (β 2GPI) and prothrombin or phospholipid-protein complexes, expressed on, or bound to, the surface of vascular endothelial cells, platelets or other cells.

Tissue factor (TF), the major initiation of the coagulation system, is induced on monocytes by aPL *in vitro*, explaining, in part, the pathophysiology of APS. However, little is known regarding the nature of the aPL-induced TF expression. We investigated aPL-induced genes in PBMC using cDNA array system and real-time PCR. Our results indicated that mitogen-activated protein kinase (MAPK) pathway was related to TF expression when PBMCs were treated, in the presence of β 2GPI, with human monoclonal anti- β 2GPI antibodies [β 2GPI-dependent anti-cardiolipin antibodies (aCL/ β 2GPI)]. Western blotting studies using monocyte cell line demonstrated that p38 MAPK protein was phosphorylated with nuclear factor κ B (NF- κ B) activation by monoclonal aCL/ β 2GPI treatment, and that SB203580, a specific p38 MAPK inhibitor, decreased the aCL/ β 2GPI-induced TF mRNA expression. The p38 MAPK phosphorylation, NF- κ B translocation and TF mRNA expression triggered by aCL/ β 2GPI were abolished in the absence of β 2GPI. These results demonstrated that the p38 MAPK signaling pathway plays an important role in aPL-induced TF expression on monocytes and suggest that the p38 MAPK may be a possible therapeutic target to modify a pro-thrombotic state in patients with APS.

35.

Calcineurin inhibitors in the treatment of cutaneous lupus erythematosus

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Cutaneous lupus erythematosus is a chronic autoimmune inflammatory skin condition. It is usually localized on sun-exposed areas resulting in sharply demarcated, erythematokeratotic plaques with frequent atrophic scar formation and subsequent loss of hair follicles, being a therapeutic challenge for dermatologists. Calcineurin inhibitors are immunosuppressive macrolides blocking T cell activation in the skin. These molecules bind to macrophilin 12 to form a complex being capable of blocking calcineurin, a protein which physiologically dephosphorylates (and therefore activates) the cytoplasmic subunit of nuclear factor of activated T cells (NF-AT). Thus NF-AT cannot enter the nucleus and interact with the promoter regions of many cytokine genes. In addition to T cells, calcineurin inhibitors were also shown to inhibit the activation of a number of other cell types of the skin immune system including eosinophils, basophils, and Langerhans cells. These drugs are highly effective even in monotherapy resulting in rapid, progressive, and sustained improvement, are well tolerated for long-term treatment, and there are no contraindications when using on face, eyelids, flexural skin, or mucous membranes. Although being immunosuppressants, no significantly increased incidence of infections can be detected during therapy. In this presentation, the current treatment options of all clinical subtypes of cutaneous lupus erythematosus will be reviewed. Therapy with calcineurin inhibitors will be emphasized, advantages and drawbacks, effects and side effects, treatment protocols, dosage, and expected outcome will be discussed in detail.

36.

Biologics: a new therapeutic strategy in lupus erythematosus

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The main treatment modalities of Lupus erythematosus consist of several immunosuppressive strategies which are not consistently effective in reducing SLE associated morbidity and frequently are associated with significant limiting side effects. Recent developments in our understanding of the pathophysiology of SLE and advances in biotechnology have permitted to develop targeted highly active agents. Accordingly, biologics targeting soluble mediators, cell surface molecules and cell-cell interaction have been developed and are being tested in clinical trials. Treatment with antibodies, which affect the activation of potentially auto-reactive B cells such as Anti B-lymphocyte stimulator (LymphoStat B, Belimumab), Anti-CD20 (Rituximab, Tositumomab) and Anti-CD22 (Epratuzumab) in first clinical trials appear to be promising. Clinical studies using CTLA-4Ig (Abatacept, Belatacept) to block co-stimulation of T-cells and Anti-CD40L (Daclizumab, Ruplizumab) which blocks T-B-cell crosstalk are currently ongoing. Preliminary reports indicate that blocking T-cell co-stimulation with an Anti CD11b antibody (Efalizumab) or a fusion protein targeting T-cell co-stimulation and adhesion to endothelial cells (Alefcept) appear to be promising. Since several cytokines such as Interleukin 1 (IL-1), IL-6, IL-10, IL-15, IL-18, tumor necrosis factor alpha (TNF alpha), interferons, and more recently IL-23 as well as IL-17 have been implicated in the pathogenesis of SLE several biological medications (biologics) targeting these pathways have been developed or are under investigation. Clinical trials are currently performed with antibodies against IL-6 and IL-6R (Atlizumab) are currently being performed. A monoclonal antibody that prevents the cleavage of terminal complement components (anti-C5b, eculizumab) may provide a further potentially successful approach to treat SLE. In the future novel strategies including small molecules and compounds targeting intracellular messenger molecules may eventually result in more effective and safe medications for the treatment of SLE.

Anti-IL-6 receptor antibody therapy for autoimmune diseases

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Recent progress in understanding pathological roles of cytokines in autoimmune inflammatory diseases has facilitated a therapeutic concept to restore the disequilibrium of cytokines and their inhibitors.

Interleukin-6 (IL-6) is a multifunctional cytokine that regulates immune response, inflammatory reaction and hematopoiesis. Overproduction of IL-6, however, causes not only inflammatory manifestations such as fever and fatigue but also laboratory abnormalities including hyper- γ -globulinemia, emergence of autoantibodies, and increase in serum acute phase proteins. Overproduction of IL-6 is involved in complications such as mesangial proliferative glomerulonephritis in the kidney, interstitial pneumonia in the lung. Therefore, inhibition of IL-6 actions can be a therapy for autoimmune inflammatory diseases, in which IL-6 is overproduced.

The application of molecular biology techniques to design monoclonal antibodies as therapeutic biologic agents made it possible to regulate the IL-6 signal for the treatment of the diseases utilizing monoclonal antibody. Tocilizumab is a humanized anti-IL-6 receptor antibody that specifically inhibits IL-6 actions. In a series of clinical trials, tocilizumab has been proven to be safe and therapeutically effective for patients with chronic inflammatory diseases such as rheumatoid arthritis, systemic juvenile idiopathic arthritis, Castleman's disease, and Crohn's disease.

Increase in IL-6 expression is associated with murine models of SLE and inhibition of IL-6 actions improves them. Lupus patients show elevated levels of serum IL-6 that correlated with disease activity. Therefore, blocking IL-6 action may be effective for lupus patients. On the basis of these findings, phase I study for patients with systemic lupus erythematosus has been conducted in the USA. A paradigm of IL-6 research from bench to bedside will be discussed.

Reconstructive surgery for deformities of the hemifacial atrophy (Romberg 's disease)

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Romberg's disease was first described by Parry in 1825 and later by Romberg in 1846. The disease is a progressive hemifacial atrophy of unknown etiology. The disease manifests variable involvement of the skin, soft tissue and underlying craniofacial skeleton. The initial sign is a slow wasting of the subcutaneous tissue on the lateral aspect of the face. The atrophy of the soft tissue progresses over a period of several years. The disease appears during first decade of life, the skeletal deformity on one side may appear. The etiology of the Romberg's disease remains poorly understood but may be a localized form of scleroderma. The two diseases are differentiated histologically by the preservation of elastin in Romberg's disease.

The purpose of this study is to present our experience in treating Romberg's disease and localized scleroderma with de-epithelized free flaps and facial bone osteotomy. We reviewed all the cases over 10 years at our hospital. Five females and 2 males with those disease underwent transfer of free flaps and several reconstructive procedures. Our patients were classified as mild, moderate or severe according to the severity of the disease. The cases were classified as mild when the atrophy of the skin and fat tissue affected the small area of the face. The cases were classified as moderate the atrophy of the soft tissue affected the two trigeminal territories. Finally when the disease involved boney atrophy, the cases were classified as severe.

For mild case, a free dermal fat graft was better than lipoinjection because the volume of the former was left more than the latter. For moderate case, the groin flap was first option because the donor area was ideal for leaving an inconspicuous scar. If the groin flap was not suitable, a scapular dermis-fat free flap was chosen. Severe cases with bone involvement required all the procedures mentioned herein and in addition orthognathic surgery. We recommended therapeutic strategy combing reconstructive microsurgical and craniofacial surgical techniques in these patients.

Relation between cytomegalovirus reactivation and dermatomyositis

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Cytomegalovirus (CMV) is one of the most common opportunistic pathogens complicating the course of autoimmune diseases. Because it is currently believed that protracted use of immunosuppressive drugs is a risk factor for the subsequent development of CMV disease, special attention has not been focused on the pathogenic role of CMV in autoimmune diseases. We have recently detected CMV reactivation using CMV-pp65 antigenemia and real-time PCR assays in five patients with dermatomyositis (DM), coincident with the onset of unexplained manifestations during the course of the disease, such as slight deterioration of DM symptoms, cutaneous ulcers, an increase in levels of hepatic enzymes, and a low-grade fever. All patients had been treated with systemic prednisolone (PSL) 0.8~1.4mg/kg daily without any immunosuppressive agents at the time of the reactivation; the interval between the initiation of PSL and the detection of CMV reactivation ranged from 13 days to 1 year. Two patients had a recurrence of CMV antigenemia. Despite subtle manifestations, all patients were given gancyclovir without any tapering of PSL with beneficial outcomes. Our results indicate that CMV reactivation much more frequently occurs without overt clinical symptoms in DM than in other autoimmune diseases, and suggest that CMV reactivation may have a strong impact on the pathological outcomes of this disease. Our prompt initiation of anti-viral agents to manage CMV reactivation could prevent from developing not only severe CMV diseases but also unexplained inflammations during the course of DM. Close monitoring of CMV reactivation during the course of the disease would elucidate the role of CMV in the pathogenesis of DM.

Autoinflammatory syndromes with a dermatological perspective

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The autoinflammatory syndromes describe a distinct group of systemic inflammatory diseases apparently different from infectious, autoimmune, allergic and immunodeficient ones. Originally, it was almost the synonym with clinically defined hereditary periodic fever syndromes, including familial Mediterranean fever (FMF), hyper IgD syndrome with periodic fever (HIDS) and tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS). Similar but distinct periodic fever syndromes accompanied with urticarial rash, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and chronic infantile neurological cutaneous articular syndrome (CINCA), have all been reportedly associated with *C1AS1* mutations and are collectively called as cryopyrin-associated periodic syndromes (CAPS). Consequently, the concept of "autoinflammatory syndromes" has been spread to contain other systemic inflammatory diseases: rare hereditary diseases with or without periodic fevers, such as pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome (PAPAS), Blau syndrome and chronic recurrent multifocal osteomyelitis (CRMO), and more common "collagen disease-like" diseases, such as Behçet's disease, Crohn's disease, sarcoidosis and psoriatic arthritis. These diseases are all caused by or associated with mutations of genes regulating innate immunity and have common clinical features accompanied with activation of neutrophils and/or monocytes/macrophages. In this poster, major autoinflammatory syndromes are summarized and pathophysiology of related skin disorders is discussed in association with dysregulated innate immune signaling.

41.

An interferon-associated cytotoxic cellular immune response against viral-, self- or tumor- antigens is a common pathogenetic feature in "Interface Dermatitis"

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Cytomegalovirus (CMV) is one of the most common opportunistic pathogens complicating the course of autoimmune diseases. Because it is currently believed that protracted use of immunosuppressive drugs is a risk factor for the subsequent development of CMV disease, special attention has not been focused on the pathogenic role of CMV in autoimmune diseases. We have recently detected CMV reactivation using CMV-pp65 antigenemia and real-time PCR assays in five patients with dermatomyositis (DM), coincident with the onset of unexplained manifestations during the course of the disease, such as slight deterioration of DM symptoms, cutaneous ulcers, an increase in levels of hepatic enzymes, and a low-grade fever. All patients had been treated with systemic prednisolone (PSL) 0.8~1.4mg/kg daily without any immunosuppressive agents at the time of the reactivation; the interval between the initiation of PSL and the detection of CMV reactivation ranged from 13 days to 1 year. Two patients had a recurrence of CMV antigenemia. Despite subtle manifestations, all patients were given gancyclovir without any tapering of PSL with beneficial outcomes. Our results indicate that CMV reactivation much more frequently occurs without overt clinical symptoms in DM than in other autoimmune diseases, and suggest that CMV reactivation may have a strong impact on the pathological outcomes of this disease. Our prompt initiation of anti-viral agents to manage CMV reactivation could prevent from developing not only severe CMV diseases but also unexplained inflammations during the course of DM. Close monitoring of CMV reactivation during the course of the disease would elucidate the role of CMV in the pathogenesis of DM.

42.

Clinical Entity of Lupus Erythematosus Panniculitis/ Lupus Erythematosus Profundus

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Objectives: Lupus erythematosus profundus (LEP) has been classified as a type of erythematosus in which subcutaneous tissue is the principal focus of inflammation. However, there is controversy concerning the diagnostic criteria, whether LEP is a variant of erythematosus, etc. We therefore reexamined the results of the antinuclear antibody titers and direct immunofluorescence lupus band tests in 44 cases diagnosed as LEP clinically and histopathologically in our department in the 37-year period from 1970 to 2007, and discussed the pathology and classification of this disease.

Results: The 44 LEP patients consisted of 7 males and 37 females, and their mean age at diagnosis was 36.3 years (range 14-79 years). There were 27 cases of LEP alone, and 17 cases complicated by a systemic collagen disease (SLE in 15 cases, Dermatomyositis in 1 case, and Systemic sclerosis in 1 case). The most common sites of LEP were the face (26 cases) and upper limb (16 cases), and there were more cases of multiple lesions (29) than of solitary lesion (15). In the 27 cases of LEP alone, the antinuclear antibody was positive in 90.5% (19 of 21 cases tested) and the direct immunofluorescence lupus band test was positive in 84.2% (16 of 19 cases tested). There were no morphological differences between the cases of LEP according to whether they were complicated by a systemic collagen disease.

Conclusion: It is appropriate to classify LEP as a variant of erythematosus, and the clinical and histopathological findings together with the results of the antinuclear antibody titer and direct immunofluorescence lupus band test are important elements in making the diagnosis of LEP.

Are there any race differences of photosensitivity in cutaneous lupus erythematosus such as SCLE and LET ?

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Skin lesions are variable in cutaneous LE such as SLE, DLE, SCLE, lupus erythematosus profundus (LEP) and lupus erythematosus tumidus (LET). Although there are a few exceptional reports, many Japanese dermatologists feel some differences of typical skin lesions of lupus erythematosus between Asian patients and Caucasian patients.

Especially, we have to discuss the photo-induced skin eruptions. In Japanese patients with SLE, skin lesions are present in at least 80%, and are the primary sign in about 25% of them. Our survey of Japanese patients revealed that 59% (49/83 cases) of SLE and 39% (12/31 cases) of DLE patients had photosensitivity, which was determined by standard clinical examinations. The positive ratio of the *in vivo* phototest for SLE patients was 33%, but there was no statistically significant association between clinical photosensitivity and the *in vivo* photo test. There are no associations between anti-SS-A/Ro antibodies and photosensitivity. Similar differences are present in the incidence of SCLE and LET which are characterized by photosensitivity

This discrepancy may depend on the genetic background, the investigators, the form of questioning and the patients' age. Hence, new and more reliable methods should be developed for the examination of so-called photosensitivity.

A Cutaneous Lupus Erythematosus Database: Review of The First 116 Prospectively Enrolled Patients

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The skin findings seen in Lupus Erythematosus (LE), can present with either lupus-specific (Cutaneous LE [CLE]) or lupus-nonspecific findings. CLE is subclassified into chronic CLE (CCLE), subacute CLE (SCLE), and acute CLE (ACLE). This prospective study was designed to assess disease severity in various subsets of CLE by using outcome and quality of life (QoL) measures, and to determine treatment responsiveness by establishing a web-based database of patients with skin manifestations of LE. We enrolled and followed 116 patients who met the criteria for having CLE or lupus-nonspecific disease and presented to our outpatient clinic in a one-year period. We used the CLE Disease Activity and Severity index (CLASI) to evaluate cutaneous disease. At each visit, patients completed the SKINDEX 29+3. Predominant diagnosis in 8 patients (6.9%) was ACLE, in 21 patients (18.1%) was SCLE, and in 79 patients (68.1%) was CCLE (58 Classic DLE [24 generalized DLE, 36 localized DLE], 2 hypertrophic DLE, 13 lupus tumidus, 1 chilblain LE, 3 lupus panniculitis), and 8 patients (6.9%) had SLE with lupus-nonspecific skin lesions or only lupus-nonspecific skin lesions. The mean SKINDEX score in ACLE, SCLE, and CCLE patients at their first visit was 81.9, 79.4, and 81.6, respectively (ns). The mean baseline SKINDEX score in generalized and localized DLE was 90.7 and 75.5, respectively. The mean baseline CLASI activity/damage score in ACLE, SCLE, and CCLE patients was 5.6/4.5, 11/1.6, and 7.3/10.1, respectively. Eleven patients (9.5%) were considered refractory to current therapies. This web-based database is the first systematic multi-center epidemiologic study of cutaneous LE in the United States, and should allow collection of data related to disease activity, QoL, and response to therapy at multiple centers.

EUSCLE Core Set Questionnaire: A Database Analysis of 50 Patients with Cutaneous Lupus Erythematosus

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Due to the lack of standardized guidelines for the assessment and treatment of cutaneous lupus erythematosus (CLE), the European Society of Cutaneous Lupus Erythematosus (EUSCLE) developed a Core Set Questionnaire for the evaluation of patients with this multifaceted autoimmune disease. In this study, disease subsets were evaluated in 50 patients (42 female, 8 male) from two European centers (Germany and Sweden) by means of the EUSCLE Core Set Questionnaire and an associated database. Acute CLE (ACLE) was diagnosed in 5 patients, subacute CLE (SCLE) in 12 patients, chronic CLE (CCLE) in 14 patients, and intermittent CLE (ICLE) in 19 patients. 24 of the 50 patients fulfilled 4 or more of the ACR criteria for the classification of systemic lupus erythematosus; however, only 10 of them had severe organ manifestations, such as kidney involvement. Malar rash and arthritis were significantly ($p < 0.05$) more frequent in ACLE than in all other subtypes of CLE. Furthermore, antinuclear antibodies occurred significantly ($p < 0.05$) more often in patients with ACLE than in patients with ICLE. The presence of different types of antibodies, such as anti-Ro/SSA and anti-La/SSB antibodies, revealed further significant differences between the various CLE subtypes. The predominantly used treatments included sunscreens (47 patients), topical steroids (46 patients), topical calcineurin inhibitors (21 patients), chloroquine (22 patients), hydroxychloroquine (17 patients), and systemic steroids (15 patients). In conclusion, the EUSCLE Core Set Questionnaire with its database provides a useful tool for a standardized collection and evaluation of data on CLE in clinical practice. It further enables the clinician to characterize the different skin manifestations involved in CLE and to evaluate diagnostic parameters and reasonable treatment modalities.

Ectopic expression of CD40 ligand on B cells abrogates clonal deletion of double-stranded DNA-reactive B Cells and induces lupus-like autoimmune disease

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by production of autoantibodies to nuclear components such as DNA. CD40 ligand (CD40L) is ectopically expressed on B cells in patients with SLE and lupus-prone BXSB mice. To assess the role of the ectopic CD40L expression in breakdown of self-tolerance and development of SLE, we have established transgenic mice expressing CD40L on B cells. When these mice were crossed with mice transgenic for anti-DNA IgM heavy chain, self-tolerance of dsDNA-reactive B cells was specifically perturbed probably by abrogation of clonal deletion in the periphery. Moreover, some of the CD40L-transgenic mice spontaneously produced autoantibodies including anti-DNA antibodies and developed lupus-like glomerulonephritis. Taken together, ectopic CD40L expression on B cells can break down self-tolerance of dsDNA-reactive B cells and induce development of SLE.

Involvement of gaseous low molecular monoxides in the cutaneous reverse passive Arthus reaction

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The deposition of immune complexes (IC) induces an acute inflammatory response with tissue injury, for which the involvement of nitric oxide (NO) and carbon monoxide (CO) has been suggested. They are gaseous low molecular monoxide. NO is induced by NO synthase (NOS) and CO is generated by heme oxygenase (HO) in the process of heme metabolism. Among HO isoenzymes, HO-1 is an induced type. To assess the role of NO and CO in the pathogenic process, the cutaneous reverse passive Arthus reaction was examined using NOS inhibitor, HO-1 stimulator and HO-1 inhibitor. Edema, tumor necrosis factor- α , interleukin-6 and neutrophil number were used for the evaluation of the cutaneous reverse passive Arthus reaction. The values of above four parameters were significantly reduced and furthermore, the level of interleukin-10 was significantly increased, which was an anti-inflammatory cytokine, in mice treated with HO-1 stimulator as compared to positive control mice. Quite the reverse changes in these parameters were recognized in mice treated with HO-1 inhibitor. Meanwhile, NOS inhibitor did not cause any improvement in the values of these parameters. The results of this study indicate that HO-1/CO signaling pathway may play an important role in the improvement of the cutaneous reverse passive Arthus reaction, and suggest that HO-1/CO signaling pathway is a therapeutic target for human IC-mediated disease.

Decreased number of peripheral nTreg in an asymptomatic mother of an infant with NLE

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Objectives: Mothers of infants with neonatal lupus erythematosus (NLE) are often asymptomatic initially, but most of them develop symptoms of autoimmune disease eventually, such as systemic lupus erythematosus (SLE) and Sjögren's syndrome. Several recent studies revealed decreased frequencies of nTreg in periphery blood of patients with active SLE. Here we present a case of asymptomatic mother with decreased number of peripheral natural occurring regulatory T cells (nTreg) and her female infant with NLE and her. **Results:** At 9 weeks after birth, the infant had several sporadic annular erythemas on her cheek, forearm and buttocks. The lesion lasted for 3 months and then resolved. Findings with echocardiography, electrocardiogram and hematologic tests were within normal range. Both mother and infant were positive for antinuclear antibody (ANA), anti-Ro antibody and anti-RNP antibody. Anti-La antibody and anti-DNP antibody were found only in the mother. At the time of her pregnancy and three months after delivery, the mother had been asymptomatic and without observable skin lesion. The frequency of her CD4+CD25+ T cells in periphery blood (4.17% of CD4+ T cells) was higher than normal control (3.82%) but CD4+CD25+FoxP3+ nTreg (68.35% of CD4+CD25+ T cells) were lower than normal control (75.43%). In the follow-up examination two months after first consultation, S/CO rate of ANA in the mother was elevated by 1.26 folds, and erythema angiectaticum was observed on her cheek. **Conclusion:** This case report indicates that testing for frequency of nTreg may be valuable in evaluating prognosis of asymptomatic mother with an infant of NLE.

High Expression of Ro52 in Skin Lesions in Cutaneous Lupus Erythematosus

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Background: Autoantibodies against Ro52 are associated with photosensitivity and subacute cutaneous lupus erythematosus (SCLE). Our aim was to study expression of Ro52 in the autoimmunity target Organ.

Objectives: To study Ro52 expression in spontaneous, UV induced lesions and normal skin of CLE patients and healthy controls; to investigate effect of UVB irradiation on expression and subcellular localization of Ro52 in CLE patients' keratinocytes and fibroblasts *in vitro*.

Methods: Skin biopsies (totally 43) collected from spontaneous, UV-induced active and fading CLE lesions, control patients and healthy individuals skin were stained by immunohistochemistry using a novel panel of anti-Ro52 monoclonal antibodies. Keratinocytes and fibroblasts derived from CLE patients skin biopsies were cultured and irradiated by UVB (50-60mJ/cm²), incubated for 24h and stained for Ro52.

Results: Ro52 was highly expressed in all CLE lesions. About 50% of keratinocytes within epidermis of spontaneous lesions stained for cytoplasmic Ro52, significantly more than in patients and healthy controls. Expression of nuclear Ro52 did not differ between lesional and control skin. Around half of the cells in dermal infiltrates were strong Ro52 expressers. Ro52 was similarly highly expressed in the epidermis and dermal infiltrates of UVB induced active lesions, and reduced in the fading ones. *In vitro*, irradiation with UVB induced Ro52 upregulation and suggestive nuclear translocation in keratinocytes. Fibroblasts responded by downregulation and protein collection perinuclearly.

Conclusion: Ro52 is highly expressed in the skin of CLE lesions, and its levels can be enhanced by UVB irradiation, thus circulating anti-Ro52 autoantibodies could bind to their antigen locally and promote skin inflammation.

Expression of histamine receptors on mast cells in lupus skin lesions

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In skin lesions of systemic lupus erythematosus (SLE), the histamine-N-methyltransferase (HMT) activity is much lower than that of controls, and the decreased activity plays a particular role in the development of immune-complex-mediated skin lesions (Furukawa, *Dermatologica* 1989). Th1 cells mainly express the histamine H1 receptor (H1R) and produce IFN-gamma; and Th2 cells mainly express H2R and induce immune-tolerance. We reported the expressions of H2R in the skin lesions from MRL/lpr (l) mice at preceding SID meeting. T cell receptor alpha; chain knock out mice treated with 5-fluorouracil and UVB irradiation, which is a model of drug-induced cutaneous lupus erythematosus (CLE) established by us. The expressions of H2R were seen on both of CD4 lymphocytes and mast cells in the skin lesion of the CLE model by immunohistochemical staining. The expression of H2R was also strongly seen in the lesional skin by RT-PCR method. The expression of H1R was not seen in both of lesional and non-lesional skin.

In addition, we investigated the relationship between human lupus skin lesions and the expressions of HRs. Biopsy specimens of the involved and non-involved skin of lupus patients (7 SLE patients and 2 DLE patients) were provided for the study. Mast cells infiltration was assessed by toluidine blue staining and the expressions of CD4, CD8, H1R and H2R in the skin lesions were assessed by immunohistochemical staining. Infiltration of a number of mast cells in involved lesions of lupus patients were observed compared with those of non-involved skin. The expressions of HRs in skin lesions of human lupus and the difference between the expression pattern of HRs in lupus model mice and human lupus skin lesions are now under investigations.

Alterations in the basement membrane zone in cutaneous lupus erythematosus(CLE) as demonstrated by immunohistochemistry

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Background. Lupus Erythematosus is characterized histologically by interface dermatitis with epidermal, basement membrane zone (BMZ) and dermal pathological changes. The clinical subsets of lupus erythematosus cannot easily be distinguished by histology alone. Despite this, discoid lesions scar, whilst sub-acute and acute systemic lesions heal without scarring.

Objectives To investigate the alterations in the basement membrane zone (BMZ) in CLE by immunohistochemistry.

Methods Skin biopsies from twenty seven patients with CLE (17 from DLE and 10 from SCLE) and ten normal controls were studied by immunohistochemistry with a panel of antibodies to the following BMZ components: CK5, CK14, PB230, PB180, plectin, laminin 5, collagen IV and collagen VII.

Results Using immunohistochemistry, there was an increased expression with antibodies to components of the lamina lucida, lamina densa and anchoring fibrils in DLE, whereas the expression in SCLE, scarred tissues and normal controls was normal. In addition, DLE showed more expression of the hemidesmosome-associated antigens (BP230 and plectin) than SCLE, scarred DLE and controls. The expression of other antibodies (BP180, CK5 and CK14) was similar in all examined tissues.

Conclusions These alterations to structural components of the BMZ in DLE suggest that the BMZ reacts in a different way from the non scarring type of LE (SCLE); the BMZ remodels itself in different ways in these different clinical types. As well as having important messages for pathogenesis, these differences in immunohistochemical staining between DLE and SCLE may provide a new method of differentiating between them.

Decreased serum concentration of 25-hydroxyvitamin D in patients with lupus erythematosus

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Patients with cutaneous and systemic lupus erythematosus are photosensitive. UV irradiation can exacerbate cutaneous and internal organ lesions. Photoprotection and corticosteroids can diminish vitamin D levels. Population based studies indicate that vitamin D deficiency is a strong risk factor for autoimmune diseases. Serum 25hydroxyvitamin D [25(OH)D] is the preferred indicator of vitamin D status, because it reflects both dietary intake and skin photosynthesis of vitamin D status. Objectives were to evaluate vitamin D status of SLE patients using serum 25- hydroxyvitamin concentration and assess the correlations between the vitamin D level and clinical, laboratory and demographic data. Materials and methods: The study covered 63 patients with lupus erythematosus, 50 females and 13 males, aged 21-80. Serum 25(OH)D was measured with automated electrochemiluminescence immunoassay platform (Elecsys 2010 Roche Diagnostic GmbH) under DEQAS control system. Results: The mean concentration of 25(OH)D was significantly decreased both in patients with SLE (11.99 ng/mL) and DLE (12.16 ng/mL) as compared to replete status. Mild vitamin D deficiency (20-30 ng/mL) was found in 15.8%, moderate deficiency (10-20 ng/mL) in 34.9% and severe (<10 ng/mL) in 47.6% of patients. No significant difference in serum 25(OH)D level was shown between DLE and SLE groups. Serum 25(OH)D concentration was decreased in LE patients who used regularly sunscreens ($p<0.05$) but higher in smoking subjects ($p<0.05$). Decreased levels of 25(OH)D did not correlate with disease duration, age, gender, skin phototype, SLAM score, alcohol consumption, cumulative antimalarials and glucocorticoid dose. Conclusion: Our results shows vitamin D deficiency in LE patients and emphasize the need of appropriate vitamin D supplementation that is particularly important due to its possible immunomodulatory effects.

Hair follicle stem cells in the pathogenesis of the scarring process in cutaneous lupus erythematosus

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Background: Discoid lupus erythematosus (DLE) is a scarring disease, and scarring may occur at any site, particularly the scalp, which is involved in more than half of patients with DLE. The pathogenesis behind this scarring process is not well known. The fact that inflammation in DLE generally involves the bulge area of the hair follicle raises the possibility that the death of stem cells located there may lead to permanent loss of the follicle. We carried out this study to define better the possible pathogenic role of the follicular stem cells in the scarring process in CLE.

Methods: We studied the reactivity of an antibody to the CD8 antigen (C8/144B), recognizing CK15, which preferentially immunostains hair follicle stem cells, on skin biopsies (scalp and body) from thirty-six CLE patients with discoid lesions and ten with subacute lesions. Normal scalp biopsy specimens served as controls. Using this antibody as a marker of the stem cells of bulge region, we could correlate the degree of the cytotoxic inflammatory cells infiltrate (CD8+) and the expression of the stem cells. Results were analysed using semiquantitative criteria.

Results: The expression of CK15 was variable in DLE lesions; there was normal to moderate CK15 expression at the bulge region of hair follicles which were surrounded by mild or moderate inflammatory infiltrate (CD8+), but in cases of severe inflammation, CK15 expression was weak or absent, indicating damage to or differentiation of the stem cells.

Conclusion: The bulge region is involved in this disease as a part of broader involvement of the hair follicle; it is secondarily affected by the surrounding inflammatory cell infiltrate. If the stem cells are damaged, rather than differentiating, the hair loses its potential of regrowth with resulting scarring alopecia.

Finnish patients with systemic lupus erythematosus share predisposing genetic risk factors with other populations

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We have recruited a population-based sample of lupus erythematosus (LE) patients, comprising altogether 338 patients with systemic LE (SLE) and 177 with discoid LE, and 808 population-based controls. In this cohort, we have studied 8 published candidate susceptibility genes for SLE. After careful review of recent literature, we selected for genotyping 18 risk allele tagging SNPs in these 8 genes with the strongest evidence of susceptibility, including the most strongly replicated gene interferon regulatory factor 5 (IRF5). The samples were genotyped using the Sequenom iPLEX assay system with allele detection by mass spectrometry. Preliminary data analysis was performed for the families multiply affected by SLE using PDTPhase. In accordance with previous reports, we confirmed the association of SLE to *IRF5* and *programmed cell death 1 (PDCD1)*. Preliminary analyses suggested allelic heterogeneity for *cytotoxic T-lymphocyte-associated protein 4 (CTLA4)* compared to the previous report on UK population. We conclude that LE susceptibility genes and their SNPs suggested in the recent literature are also important in the Finnish patients. We are currently performing gene-gene interaction studies to assess the risk of SLE in carriers of multiple independently confirmed susceptibility genes.

Cutaneous manifestations in 126 patients with systemic lupus erythematosus

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Objectives. Three of the ACR criteria for SLE diagnose are cutaneous. Our aim was to review clinical and serological features in 126 (115 female) patients with cutaneous manifestations, out of a well-defined cohort of 270 SLE patients. Previous to inclusion they had met the following cutaneous ACR criteria: photosensitivity n=97 (77%), malar rash n=76 (60%) and discoid lesions n=35 (28%).

Results. Clinical examination, history and chart review showed LE-specific lesions in 47 (37%) patients: DLE n=25 (20%), SCLE n=18 (14%), ACLE (all non-facial) n=5 (4%), chilblain lupus n=8 (6%), LE tumidus n=1 and LE panniculitis n=1. Malar rash was diagnosed clinically or by history in 75 patients. LE-non-specific lesions were present in 93 (74%) patients: Raynaud's phenomenon n=65 (52%), non-scarring alopecia and vasculitis n=21 (17%), urticaria n=15 (12%) and livedo reticularis n=5 (4%). Arthritis and nephritis were found in 110 (87%) respectively 50 (40%) patients. Four of 126 patients did not fulfil 4 or more ACR criteria if "malar rash" was excluded from their criteria for SLE diagnosis. The following autoantibodies were found in the 126 patients: ANA 99%, ds-DNA 59%, Ro/SSA 44%, La/SSB 26%, cardiolipin IgG 40% and IgM 18%, RNP 14% and Sm in 8% of the patients. SCLE patients (n=18) had anti-Ro/SSA in 72% and anticardiolipin IgG in only 11% while patients without SCLE (n=108) had lower prevalence of anti-Ro/SSA (40%) and more often anticardiolipin IgG (44%) (p=0,01).

Conclusions. We found LE-specific skin lesions excluding malar rash in 17% of 270 SLE patients. SLE diagnose was rarely dependent on the malar rash criterion, which was commonly based only on clinical data contrary to non-facial ACLE lesions which were histopathologically specific. SCLE is clinically and serologically distinct from other SLE. The low percentage of cardiolipin antibodies in these patients might contribute to a better prognosis.

Clinical and laboratory manifestations in systemic lupus erythematosus patients with and without antiphospholipid antibody

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To investigate the association of antiphospholipid antibodies (aPLs) with the clinical and laboratory manifestations in patients with systemic lupus erythematosus (SLE). Sixty-nine SLE patients were included in this retrospective study. Patient files, questionnaire data, and a cumulative database were used to collect patients' medical histories. Anti-cardiolipin antibody (aCL), anti- β_2 -GPI glycoprotein I antibody (a β_2 -GPI), and lupus anticoagulant (LA) were measured according to international recommendations. Criteria of antiphospholipid syndrome (APS) were fulfilled by 21 patients (30.4%). Twenty-six patients (37.7%) were positive for at least one of aPLs but were not diagnosed as APS. Twenty-two patients (31.9%) had neither aPLs nor thrombosis. Among SLE patients with APS, LA, aCL, and a β_2 GPI were detected in 16 patients (76.2%), 3 patients (14.3%), and a patient (4.8%), respectively. There was no significant difference in the positive rate of each aPL between patients with APS and without APS. The patients who were positive for aCL or a β_2 -GPI showed a tendency to have livedo reticularis compared with patients without it. However, other skin and systemic manifestations related to SLE or APS, laboratory findings, past treatment were not associated with the existence of any aPLs. Thus, there was no obvious difference in the clinical and laboratory findings between SLE patients with and without aPLs. However, our findings indicate that aCL or a β_2 -GPI may associate with the development of livedo reticularis in patients with SLE. Further prospective studies in larger populations will be needed to determine these findings.

Statistical Evidence of Lupus Erythematosus Tumidus as a Separate Entity

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Cutaneous lupus erythematosus (CLE) is a rare skin disorder presenting with great clinical variation. Until today, the classification of CLE is not evidenced by epidemiological data. The aim of this study was to compare characteristics of the different CLE subtypes and to analyze statistically whether LE tumidus (LET) can be identified as a separate entity in the classification system of this disease. The study involved 45 patients with CLE from two centers in Germany including 24 patients with LET, 12 with discoid LE (DLE), and 9 with subacute CLE (SCLE). The mean age at first diagnosis was not significantly different between the subtypes but was slightly lower in patients with LET (39.7 years) compared to SCLE (46.9 years) and DLE (45.9 years). Several significant differences between LET and the other subtypes were found with regard to clinical, histological, laboratory, and other relevant parameters. For example, skin lesions on the ears occurred significantly less often in patients with LET than in patients with the other CLE subtypes ($p < 0.05$). Further characteristic clinical features, such as dyspigmentation, scarring, and photosensitivity, were also confirmed to be different in LET. The activity score was significantly lower in LET than in DLE ($p < 0.05$) and the damage score was significantly lower in LET than in SCLE ($p < 0.05$) and DLE ($p < 0.05$). Moreover, hyperkeratosis/parakeratosis, vacuolar alteration at the dermoepidermal junction, and affection of hair follicles were significantly ($p < 0.05$) less frequent in LET than in SCLE and DLE. In contrast, interstitial mucin deposition was found significantly ($p < 0.05$) more often in skin specimens from patients with LET compared to the other CLE subtypes. In summary, these data strongly support the definition of LET as a separate entity in the classification system of CLE.

Lupus erythematosus telangiectoides

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Patients with lupus erythematosus (LE) manifest various cutaneous lesions. We describe SLE patient who presents with the lupus erythematosus telangiectoides concomitantly with *urticarial vasculitis*. A fifty-three year old Caucasian female developed with skin lesions after sun exposure. Typical facial butterfly erythema was noted along with superficial ulcerations on mucous membranes. Dark-red, purplish papules and plaques with adherent scale were noted on the V area of her trunk, extensor arms and back. Asymptomatic, long-lasting erythematous wheals were observed all over her body. Additional manifestations were anaemia, leucopenia, thrombocytopenia, proteinuria, low C3 and C4 levels, and elevated autoantibody titers (1:1260; anti-dsDNA and anti-RNP). These findings along with evidence of arthritis, photosensitivity and Raynaud phenomenon indicated a diagnosis of SLE. She was treated with antimalarials. The addition of systemic corticosteroids led to resolution of the malar rash and oral ulcerations after a few weeks. Her anemia, leukopenia, thrombocytopenia, proteinuria, and C3 and C4 complement levels returned to normal ranges within 6 months. The urticarial lesions cleared 1 week after dapsone was initiated. Despite continued treatment (corticosteroids, antimalarials, dapsone), the chest and back lesions persisted for 12 years and evolved into inflamed erythematous patches covered with grayish adherent scale. Telangiectasias were noted within these lesions. Some of them healed with atrophic scarring. Biopsies of these lesions revealed an atrophic epidermis, dilatation of superficial blood vessels and mononuclear inflammatory infiltration of the papillary dermis. Immunohistochemical staining revealed abundant CD31 and CD34 positive cells (endothelial cell marker). Urticarial vasculitis reappeared each time that an attempt was made to discontinue the dapsone therapy. Histologic findings from urticarial vasculitis skin lesions revealed dermal edema and perivascular infiltrate predominantly consisting of lymphocytes T.

Different clinical appearance of cutaneous lupus erythematosus

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Summary of the objectives: Lupus erythematosus differs from patient to patient as a disease continuum ranging from skin changes alone to life threatening systemic disease. Mostly appears as slightly indurate erythematous plaques and slightly edematous erythema. Less common subtypes present as hypertrophic or verrucous LE where the hyperkeratosis is greatly exaggerated, and other variants as LE profundus, LE panniculitis, chilblain LE, LE tumidus and vesiculobullous LE. The course and prognosis varies from complete remission even on mild treatment modalities. In other patients very disfiguring and cicatricial lesions appears in spite of more aggressive treatment.

Results: One of our patients is very interesting and we follow her for last 20 years. At 18 years, previously healthy girl, presented with DLE on her face. One year later she developed SLE, and after 7 years LE profundus appears on her arms, buttocks and thighs. Unsatisfied with treatment and course of her disease, patient stopped with any treatment. Very soon skin changes started to heal leaving atrophic scars and all laboratory findings for SLE became negative. In last 10 years patient is healthy with no sign of LE.

Conclusion: It can be said that follow up treatment efficacy assessment and long-term follow-up studies are recommended to determine the true risk for the cutaneous lupus erythematosus patients.

A case of lupus erythematosus in childhood

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We report a case of 9-year-old boy who developed erythematous-lesion on the cheeks, palms and fingers. He was also suffering from oral ulcer and mild joint pain in the knees. Family history was unremarkable. A skin biopsy specimen obtained from a lesion of the right cheek showed hydropic degeneration of the basal cell layer. There was also pronounced inflammatory infiltrate composed predominantly lymphocytes surrounding blood vessels and appendages. Direct immunofluorescence on lesional skin showed granular IgM deposits at the dermoepidermal junction. Laboratory investigations revealed the presence of anti-nuclear antibody (ANA) at a titer of 1:160. All other immunological screening results were negative or normal; these included anti-ds DNA, anti-ss DNA, anti-SS-A, anti-SS-B, anti-Jo-1, and complement components (C3, C4, CH50). Blood cell counts, blood chemistry tests, and urinalysis was within normal limits. His symptoms were disappeared by treatment with photo-protection and topical corticosteroids, leaving dyschromic change on the cheeks. In our patient, cutaneous lesions were clinically main manifestation. However, recent reports suggest that the severity of childhood-onset lupus erythematosus is usually greater than adult-onset. Continuous follow up is necessary to detect his systemic features.

A Case of Systemic Lupus Erythematosus with Fulminant Manifestation

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A 76-year-old woman was referred to our department because of the appearance of facial and truncal eruption at August 2006. She had been diagnosed as systemic lupus erythematosus at May 2006 because of arthralgia, positive antinuclear antibodies and pancytopenia, She had been treated with oral predonisolone at 15 mg per day. She found multiple erythema and erosion including periorbital area, chest and back after the sun exposure. She had been also treated with antidepressant drugs. The case was clinically suspected as drug-induced eruption caused by antidepressant drugs or lupus erythematosus. Histological examination revealed basal liquefaction, mucin deposit in the upper dermis and microabscess formation composed of neutrophils infiltration in subcorneal areas of the lesional skin. Diffuse lymphocytes and neutrophils infiltrations were also detected in the dermis. The eruption gradually improved by the increase of oral predonisolone upto 45 mg per day.

Linear Cutaneous Lupus Erythematosus in the Lines of Blaschko

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Discoid lupus erythematosus (DLE) is uncommon in children. A 3-year-old Japanese boy was reported. He was referred to our Department because of a 5-month history of asymptomatic linear erythematous lesion measuring 10 x 3 cm on the center of the forehead. He had no previous history of trauma or frequent exposure to sunlight. He had no family history of connective tissue diseases. Full blood cell count was normal and antinuclear antibody was negative. A biopsy specimen from the lesion showed follicular hyperkeratosis, vacuolar alteration of the dermoepidermal junction and the hair follicles, and dense perivascular and periappendageal infiltrate of mononuclear cells. The histopathologic diagnosis was DLE. Direct immunofluorescence testing was not performed. He was followed as linear cutaneous lupus erythematosus (LGLE), and treated with flurandrenolide tape which resulted in significant improvement of the lesion after 2 months. A review of the literature is presented and the clinical and histological features of LCLE are discussed.

An Unusual Case of Cutaneous Lupus Erythematosus with Degos'-like Skin Lesions

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Degos'-like skin lesions have rarely been associated with autoimmune conditions such as lupus erythematosus and dermatomyositis. We describe a 41 year old Chinese man presenting with multiple erythematous papules over the face, shoulder, trunk, back and thighs for 3 years. The most striking clinical findings were the multiple porcelain-like atrophic white scar-like papules and plaques over the back with dusky erythematous borders. In addition, there was a photo-distributed facial erythema with scattered erythematous scaly papules with areas of follicular plugging over the face and forearms. Histological examination from the lesions on the back revealed a central portion of compact hyperkeratosis and atrophy with an underlying a wedge-shaped area of degeneration and infarcted collagen, extending up to the mid dermis, suggestive of Degos' disease. There was also a perivascular and perifollicular lymphocytic infiltrate in the dermis, associated with increased deposits of dermal mucin around the infarcted area. Direct immunofluorescence studies were negative. The anti-nuclear antibody titre was positive at 1:400, with a speckled and homogenous pattern. The rest of the autoimmune markers were negative. Systemic review and examination were non-contributory. A final diagnosis of discoid lupus erythematosus with prominent degos'-like skin lesions was made. He was commenced on hydroxychloroquine and low dose aspirin with good clinical response. At his last review 1 year post-diagnosis, he remained systemically well with no new or active skin lesions. This case highlights the rare clinical findings of degos'-like skin lesions that may be an unusual clinical manifestation of underlying cutaneous lupus erythematosus. The risk of gastrointestinal infarcts or systemic vascular occlusion is unknown for such cases but appears to be low, as seen in this case.

Lupus erythematosus profundus associated with haemophagocytic syndrome

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A 36-year-old male presented with fever and erythematous plaques on the trunk. He had been treated with corticosteroids for systemic lupus erythematosus since he was 16 years old. On examination, there were well-defined, palm-sized, erythematous lesions and hen's egg-sized, subcutaneous nodules on his back. In addition, he had discoid lesions consisting of atrophic erythematous plaques with scaling on the cheek and upper extremities. On histology, the subcutaneous nodules were found to have a panniculitic cellular infiltrate consisting of lymphocytes and histiocytes, with haemophagocytosis around hyalinized fat lobules in the subcutaneous tissues. There was also a periappendageal mononuclear cell infiltrate in the entire dermis. The lupus band test was positive. The patient had a thrombocytopenia, as well as increased serum LDH, AST, ALT, triglyceride, ferritin, and soluble IL-2 receptor levels. There was no evidence of viral infections and/or reactivations, including cytomegalovirus, EB virus, and human parvovirus B19. On bone marrow aspiration biopsy, erythrophagocytosis was noted, which confirmed the diagnosis of haemophagocytic syndrome. The patient was successfully treated by increasing his oral corticosteroid dose. The prominent phagocytic features found in the skin lesion of the lupus panniculitis were associated with the concomitant occurrence of haemophagocytic syndrome related to systemic lupus erythematosus.

Lupus erythematosus profundus:clinical and pathological features of 12 cases

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We had 12 cases of LEP in the period from 2006-2008. Ten of them were female, and the rest were male. Their median age was 24 years (range, 10-55 years). We investigated their clinical and pathological features.

Anetoderma accompanying microscopic panniculitis in a patient with antiphospholipid syndrome and systemic lupus erythematosus

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Anetoderma is a rare cutaneous disease characterized by a loss of normal elasticity that presents as localized areas of wrinkled or flaccid skin. Primary anetoderma is known to be often associated with positive antiphospholipid antibodies (APAs) in the diseases such as antiphospholipid syndrome (APS), systemic lupus erythematosus (SLE), HIV, or other autoimmune disease, however its etiology is still unknown. We present a case of anetoderma accompanying microscopic panniculitis in a patient with APS and SLE. An 18-year-old Japanese girl was referred to us for evaluation of skin lesions on her neck. She had been diagnosed as SLE complicated with APS for 6 years. Physical examination revealed multiple flaccid, protuberant skin lesions measuring 5 to 30mm in diameter on the right side of the neck along the direction of its wrinkles, which she had noticed 10 days before the consultation. Histopathological examination of the lesion revealed depletion of elastic fibers without inflammation. Further, the subcutaneous fat demonstrated lipomembranous changes concomitant with giant cells. Interestingly, she had other panniculitis with mild tenderness on the upper back and the right cheek in recent 6 months, confirmed by histopathological examination. We speculated that anetoderma and panniculitis might share common pathogenic mechanisms, mediated by ischemic changes due to APAs. Alternatively, anetoderma could be secondary to inflammation expanded from lesions of panniculitis.

A case of lupus erythematosus profundus with multiple annular erythematous plaques on the scalp

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A 26-year-old Japanese female was presented to us in August 2007 with a two-year history of multiple erythematous plaques on the scalp. A physical examination revealed an arc-shaped indurated erythema on the right side of the forehead, and multiple annular erythematous plaques with hair loss on the scalp. She had no other symptoms, such as fever, arthralgia and general fatigue, and had no signs of Sjögren syndrome. Histopathological examination of the lesions on the forehead and the vertex, showed perivascular lymphocytic infiltrations in the dermis, and lobular and septal panniculitis with prominent lymphocytic infiltrations, but not liquefaction degeneration. Alcian blue staining revealed accumulation of acid mucopolysaccharides in the dermis and the subcutaneous tissue. Direct immunofluorescence examination of the biopsy specimens showed granular deposits of IgG in the basement membrane zone. Laboratory data including blood cell count, liver function, renal function, complements and urinalysis were within normal limits. Antinuclear antibody titer was 1:1280 with a speckled pattern and anti-SS-A antibody was 12.3 IU/ml. Anti-double-stranded DNA, anti-single-stranded DNA antibodies and anti-Sm antibody were not detected. These findings were consistent with the diagnosis of lupus erythematosus profundus. The treatment was initiated with oral prednisolone of 20 mg/day. Significant improvement was observed in two weeks, and all the erythematosus lesions and hair loss almost disappeared without scar formation in four months. There has been no recurrence with oral prednisolone of 13mg/day so far. Multiple annular erythematous plaques on the scalp observed in this case are rare clinical manifestation as lupus erythematosus profundus.

Tuberculous cellulitis in a systemic lupus erythematosus patient

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A 67 year-old female systemic lupus erythematosus patient has been treated with 10mg of prednisolone since March 2005. Because she controlled the dose of prednisolone by herself, the symptom exacerbated and she admitted to our hospital on June 2005. The dose of prednisolone was increased to 30mg for two weeks, and then 500mg of methyl prednisolone was infused for three days. Two weeks after, her right thumb got severe erythematous swelling and bulla with local fever under 50mg of prednisolone. At the same time, her body temperature increased to 39 degrees centigrade. The bacterium culture from her right thumb showed negative and some kinds of antibiotics or acyclovir were ineffective. After then, microscopic findings revealed positively to mycobacterium tuberculosis in an urinary examination and the typical findings of miliary tuberculosis on lung was obtained by computer tomography. We diagnosed this case as miliary tuberculosis. Biopsy was performed on her right thumb. Positive reaction was obtained to Ziehl-Neelsen stain and DNA polymerase chain reaction of mycobacterium tuberculosis. Thus, we thought the swelling of her thumb as tuberculous cellulitis and gave her the antituberculous drugs. Although the erythematous swelling improved within 2 weeks, the bacterium culture was positive reaction to mycobacterium tuberculosis from her sputa and her body temperature did not reduced. She went to another hospital which accommodate the mycobacterium tuberculosis patients only.

In our country, the number of tuberculous patients was over 50% of whole citizens until the second world war. After the war, the public health policy was carried out strongly and the number of tuberculous patients were decreased dramatically. However, almost people who were born before the war, exposed tubercle bacillus. This fact means that inactivated these micro organisms may be scattered in their body. In immunosuppressive status such as aging, drugs or some kind of disorders, tubercle bacillus are reactivated. We speculate our case was induced by steroid especially steroid pulse therapy. There are few literatures about tuberculous cellulitis in the world. This time, we report and alarm such important infectious disorder for the patients who are given immunosuppressive drugs.

A case of idiopathic thrombocytopenic purpura suggesting an initial manifestation of systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a multisystemic disorder, but sometimes it may involve only one organ system at onset and additional manifestations occur later. Mild thrombocytopenia is common, but severe thrombocytopenia with bleeding and purpura occurs in only 5% of the patients. Here we report a case who was at first diagnosed as idiopathic thrombocytopenic purpura (ITP), then cutaneous lesions suggesting the vasculitis became obvious 1 year after.

A 13-year-old Japanese girl visited our hospital with 1-month history of purpura on her extremities. Her platelet count was as few as 7,000/mm³. A bone marrow examination showed no atypical cells but the number of megakaryocytes increased. At that time she was diagnosed as ITP. Intravenous immunoglobulin therapy was ineffective and mild leukopenia and anemia became obvious. Therefore prednisolone of 60 mg/day (=1.5 mg/kg/day) was started and the condition was fortunately controlled in short order. In next winter, she developed chilblains on her hands. Her platelet count as well as complement was falling down. Palpable erythemas appeared around her nails and on her palms and knees. Skin biopsies from the knees showed a mild lymphocytes infiltration around the vessels and appendages in the dermis. The direct immunofluorescent staining showed immune deposits at the superficial dermal blood vessel walls in the skin lesion and also along the dermoepidermal junction in both of the affected lesion and non-sun-exposed normal skin. Serological evaluations showed an elevation of anti-dsDNA but a negative for anti-SSA/La and anti-SSB/Ro. We think histological features of the cutaneous lesions were compatible with SLE. However the patient did not have any skin symptoms that fulfilled the criteria of the American Rheumatism Association for SLE. Because some reported the cases of ITP as the first manifestation of SLE, we carefully see what is going on with her.

Subacute cutaneous lupus like rash following immunotherapy for renal cell carcinoma

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Objective : We describe a case of Subacute Cutaneous Lupus like rash following immunotherapy for renal cell carcinoma and highlights the potential role of interferon alpha-2b in its pathogenesis.

Results : The patient is a 63 year old man diagnosed with metastatic renal cell carcinoma. He was started on adjuvant treatment with recombinant alpha-2b interferon immunotherapy. During the fifth month of therapy, he developed scattered erythematous scaly plaques which were photodistributed over his face, neck and upper limbs.

Lesional skin histology and immunofluorescence was consistent with lupus erythematosus Serological tests were positive for ANA with a titre of 1 : 400 with a speckled pattern. Double-stranded DNA, anti-Ro, Anti-La antibodies and rheumatoid factor were negative

Clinical examination and other investigations did not reveal systemic involvement.

A diagnosis of subacute cutaneous lupus erythematosus was made and he was given emollients. IFN treatment was stopped later that month, following completion of a 6 month treatment cycle. He has since recovered with areas of post-inflammatory hyperpigmentation.

Conclusions

The alpha interferons are a family of cytokines with multiple immunomodulatory effects and are widely used in the treatment of malignancies and chronic hepatitis. They have been associated with the induction or exacerbation of autoimmune and inflammatory disorders including systemic lupus erythematosus. Levels correlate with presence of cutaneous manifestations of SLE. Unlike classical drug induced SLE, our patient did not have systemic features nor histone antibodies.

The fact that the rash started while on IFN treatment and resolved on completion implicates IFN as the likely trigger. Although SCLE has been reported in association with various malignancies, it is unlikely to be the cause as the rash resolved despite the progression of his malignancy.

B cells depletion for therapy-resistant cutaneous manifestations in systemic lupus erythematosus (SLE)

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Background: Skin involvement is one of the most common manifestations of SLE. While cutaneous lupus erythematosus (CLE) is not life-threatening, it may result in considerable morbidity. CLE may be difficult to manage with both topical and systemic therapies. B-cell depletion using anti-CD20 monoclonal antibody (rituximab) is currently investigated in the management of autoimmune diseases. Rituximab may induce remission in SLE, its value in controlling CLE is, however, unclear.

Aim and intervention: To test the efficacy of rituximab in two patients with long-lasting SLE with CLE manifestations refractory to a variety of topical and systemic therapies (steroids, calcineurin inhibitors, antimalarials, immunosuppressants). Both patients received four weekly infusions of 375mg/m² of rituximab. The usual immunosuppressive therapy was continued.

Results: In both cases, B cell depletion led progressively to a significant improvement of their skin manifestations. Furthermore, prednisone dosage could be reduced (from 20 to 2.5 mg/d and from 30 to 10 mg/d, respectively). During the period of B depletion, no serious side effects were observed. In one case, 17 months after anti-CD20 treatment a relapse was observed, which occurred concomitantly with the reconstitution of B cell numbers. Two additional doses of rituximab (375mg/m², at 1 week of interval) controlled her skin involvement. At present both patients show no or weak cutaneous activity, seven and six months after the last infusion, respectively.

Conclusion: Our results suggest that B cells depletion represents a viable option for the treatment of therapy-resistant cutaneous involvement in LES.

Successful treatment of subcutaneous calcinosis of systemic lupus erythematosus with intravenous alprostadil

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Subcutaneous calcinosis is one the most refractory cutaneous anifestation of connective tissue diseases. It is most commonly observed in systemic sclerosis and dermatomyositis but also seen in systemic lupus erythematosus. We had two patients with systemic lupus erythematosus who suffered from refractory calcinosis cutis, which did not respond to diltiazem and other oral medications. Alprostadil is intravenous Prostaglandin E1 approved as a treatment of cutaneous ulcer in patients with systemic lupus erythematosus in Japan. Our patients had intractable skin ulcers at the site of calcinosis cutis, and alprostadil was infused intravenously five day a week for four weeks and then twice a week for eight weeks as an adjunctive treatment for the cutaneous lesion. Improvement of the subcutaneous lesion was observed in both patients over the three months. The mechanism of the effect is not well-known but augmentation of local vascular circulation with facilitated absorption of the calcium deposits is one of the possibilities. The adverse reactions of alprostadil infusion are reported based on a post-marketing surveillance, where, among 12747patients, 472 patients (3.7%) experienced side effects including abnormalities of liver function tests (0.84%), nausea (0.65%), abdominal pain (0.65%), fever (0.33%), vascular pain (0.31%). Since there is no established effective therapy for calcinosis cutis, a new medical treatment needs to be investigated. The potential efficacy and the superb safety profile of alprostadil make a clinical trial reasonable.

Effective treatment of intractable ulcers using allogeneic cultured dermal substitutes with systemic lupus erythematosus

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In Japan, to establish new treatment for intractable skin ulcers, clinical trial on allogeneic cultured dermal substitutes (CDS), which was newly developed at the R&D Center for Artificial Skin of Kitasato University, has been carried out in medical centers across Japan with the support of the Millennium Project of the Ministry of Health, Labor and Welfare. This CDS was prepared by culturing fibroblasts on a two-layered spongy matrix of hyaluronic acid and atelo-collagen. Allogeneic CDS fails to live permanently on the wound surface, but is able to produce tissue growth factor and extracellular matrix components which are necessary for wound healing. A characteristic of this CDS is that the spongy matrix itself, as well as the various cytokines released from the allogeneic CDS, effectively promote the healing of severe skin defects. On the other hand, ulcers occurred in systemic lupus erythematosus (SLE) patients are highly intractable, because various factors including vasculitis, medication of prednisolone impair wound healing. In our study, we applied CDS to 3 cases of intractable ulcers with SLE. The allogeneic CDS rinsed with lactated Ringer's solution after thawing was placed cell-seeded side down on the wounds. A conventional ointment-gauze dressing was used to protect the CDS. The CDS was applied repeatedly at intervals of 3-7days. In all cases, healthy granulation tissue was formed within 6 weeks, and skin graft was successfully performed. These results indicate that the allogeneic CDS provides a new therapeutic alternative as the topical therapy for intractable ulcers involving SLE.

Clinical characteristics of annular erythema associated with Sögren's syndrome ~ Long-term follow up

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OBJECTIVE: It is now well known that annular erythema (AE) is a characteristic skin eruption of Sögren's syndrome (SS). The purpose of our clinical study was to clarify the pattern of progression of AE, the frequency of its association with other eruptions, and the systemic symptoms in SS patients with AE on long-term follow up.

METHODS: The clinical study was conducted on 30 patients of primary SS who developed AE. The patients (8 men, 22 women; age range, 8-69 years; mean, 35.0 years) were followed over a 5-year period (longest; 32 years) at our department.

RESULTS: AE in our cases of primary SS manifested in various shapes (ring erythema, horseshoe-like erythema, double- ring erythema, etc) and sizes. Although AE often developed multi-focally, it appeared most often on the face (77%). The erythema lasted for an average of 2 months (range, several days to 10 months), and most occurred repeatedly (93%). The period to repeat was about 6 or 7 years (range, 1 to 26 years). The most frequent complications included chilblains (77%), papular erythemas like insect bite (73%), pyrexia (60%), and parotid swelling (30%). AE tended to develop in the early stages of SS with mild sicca (37%), which clearly deteriorated over several years (87%). Although AE sometimes remitted spontaneously, oral steroid treatment was necessary in some cases with severe complications or erythema.

CONCLUSION: AE is often the initial manifestation of the onset of SS. It recurs multiple times over several years with some complications, until final spontaneous remission.

Amyopathic dermatomyositis as a therapeutic problem

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A female patient now aged 47 presented for the first time to our Department 10 years before with butterfly erythema on her face. Shortly thereafter, erythema appeared on both dorsa of her hands. One year later erythema appeared on her chest and buttocks. Biopsy performed in 1998 showed some elements of lupus erythematosus, thus prednisolone 50 mg and Resochin were introduced. She came to our Department at the end of 1999 for periorbital erythema, erythema on her hands (Gottron's papules) with periungual erythema, and on her arms and buttocks. She did not complain of muscle weakness. Her laboratory findings including muscle enzymes were within the normal values, whereas biopsy showed elements of dermatomyositis. EMNG was normal. In 2001 she got pregnant and gave birth to a healthy child at the end of 2001. During pregnancy, there was no worsening of the disease. Two months after delivery, she felt muscle weakness and her muscle enzymes slightly increased. She was administered prednisolone 30 mg and felt much better for some time. Her skin finding has slowly worsened over years; now her face is erythematous, with some violaceous areas; her body is poikilodermic; and she has Gottron's papules and periungual erythema. Now her muscle weakness has resolved and her muscle enzymes are normal. However, the choice of appropriate therapy for her skin to improve remains a problem as yet impossible to solve.

Study of dermatological and dermatopathological feature of anti-phospholipid syndrome compared with cutaneous polyarteritis nodosa

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【Objectives】 A little is reported about dermatological feature indicated primary antiphospholipid syndrome (PAPS) and association of cutaneous polyarthrits nodosa (PNC) and livedoid vascuopathy (LV).

【Material & Methods】 Patients were 6 cases of PAPS and 6 cases of PNC /LP. A series of antiphospholipid antibodies, protein C, protein S, factor 12 were measured. Exploration of whole body including dermatopathological examination has done.

【Results】 Painful subcutaneous nodule and erythematous macules were more specific to PAPS. Four cases of asymptomatic cerebral infarction and 2 cases of necrotizing vasculitis were detected in PAPS whereas no asymptomatic cerebral infarction was detected in LP/PNC. Detection of antiphospholipid antibodies and abnormality of coagulation factor were observed in LV/PNC. Interestingly abnormality of coagulation factor was observed in PAPS.

【Conclusion】 PAPS and LP/PNC bear similarity to pathogenesis in laboratory and pathological findings.

Cutaneous Polyarteritis Nodosa: Revisit of Definition and Diagnostic Criteria

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Cutaneous polyarteritis nodosa (CPN) has been described as having a benign and chronic course without systemic involvement in many case reports. However, it has been a matter of controversy, whether or not CPN progresses to systemic PN. In this study, we retrospectively analyzed 21 cases diagnosed as CPN over the last 10 years in Japan and collected clinicians' opinion on that matter, to re-define the clinical entity of CPN and to propose the appropriate diagnostic criteria. The cases comprised 18 women and 3 men. None of them progressed to systemic PN or death during the 7 months to 13 years' follow up. Notably, 6 patients were followed for more than 3 years. These results suggest that CPN is a distinct clinical entity from systemic PN. Of the 21 patients, 6 (29%) had clinical evidence of peripheral neuropathy and 13 (62%) showed any extracutaneous symptoms such as peripheral neuropathy, myalgia, and arthralgia, without any visceral involvement. Regarding the interpretation of these extracutaneous symptoms, two opinions have been claimed; (1) The disease is systemic PN when the extracutaneous symptoms are directly caused by arteritis. (2) The disease is CPN when the extracutaneous symptoms are limited in the affected skin lesions, even though they are directly caused by arteritis. Our study has revealed that many dermatologists sustain the latter opinion. However, the diagnostic criteria for systemic PN, which were established by Ministry of Health, Labour and Welfare, seem to be based on the former one, without mentioning CPN, and can mislead the diagnosis of CPN with any extracutaneous symptoms to systemic PN. Considering the latter opinion as the latest consensus, here we present drafts of diagnostic criteria for CPN and for systemic PN, to clearly distinguish these diseases.

Treatment of SLE based on syndrome differentiation in traditional Chinese medicine

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Traditional Chinese medicine (TCM) has a unique theoretical system and is clinically effective. Over the past few decades it has attracted increasing attention from all over the world. In order to understand and treat diseases, the TCM physicians determine syndrome differentiation, a unique diagnostic system of TCM, as well as disease differentiation. The disease differentiation aims to identify different diseases, while the syndrome differentiation aims to identify different patterns of one disease and to provide a specific treatment plan. The syndrome differentiation emphasizes different stages of the disease and the present struggle between the anti-pathogenic qi and pathogenic factors. Therefore it modifies the treatment method at different condition of a patient.

In systemic lupus erythematosus (SLE), the syndromes are differentiated in the following five patterns; 1.Ying-nutrient phase syndrome, in which pathogenic heat scorches inside the body and disturbs the heart-mind. 2.Qi and yin deficiency, which obstructs circulation of the blood. 3.Spleen and kidney deficiency, which deteriorates deficiency of qi, blood, imbalance of yin-yang. 4.Spleen deficiency and liver stagnation, which leads to blood stasis due to qi stagnation. 5.Wind-damp Bi, in which retention of wind, dampness and heat in the meridians obstructs the flow of qi and blood.

Generally, the following 3 factors are considered as the etiology of SLE; 1.Congenital weakness and deficiency, leading to deficiency of qi, blood, yin and yang of zan-fu organs (internal organs and digestive tracts), 2. Overstrain damaging the five-zang organs (lung, heart, liver, spleen and kidney), leading to deficiency of qi and blood, 3. Irradiation and six external pathogenic factors (wind, cold, heat, dampness, dryness and fire). Based on the each syndrome determined, the specific pathogenesis or the root cause of each patient's disease can be understood to apply the specific medication.

In this poster, we introduce detailed contents of the medication based on each syndrome in SLE.

Investigation of the usefulness of etidronate in patients treated for dermatological disorders with oral glucocorticoids

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[Purpose]

The usefulness of etidronate was investigated for prevention of steroid-induced osteoporosis in patients suffering from collagen diseases treated with oral glucocorticoids (GCs).

[Methods]

The patients basically received Vit D3 and Ca preparations and were randomly allocated to the etidronate-added group (E group) and the control group (C group). A 16-month multicenter, parallel-group, open-label study was conducted. The main evaluation items were a resorption marker, deoxypyridinoline (DPD), and a bone formation marker, bone specific alkaline phosphatase (BAP, Bone Alp). Of the 110 total patients, ITT analysis was conducted in 87 (38; E group, 49; C group) who could be followed for at least 3 months.

[Results]

DPD increased over time in the C group at 1 year or more after the start of administration, showing significant increases at 12 and 16 months ($p=0.0349$ at 12 months, $p=0.0496$ at 16 months) while baseline levels were maintained in the E group. This tendency was more evident in females on stratified analysis. BAP did not differ significantly between the E and C groups.

[Discussion]

Bone metabolism should be monitored in patients given oral GCs, particularly females receiving treatment for dermatological disorders. Our observations suggest increasing use of bisphosphonates to be beneficial in such female patients.

**Relapsing polychondritis associated with SLE
-Serum levels of anti-type II collagen antibodies correlated with the disease
activity of relapsing polychondritis.-**

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A 39-year-old woman presented with erythema on right cheek in 1999. She had had photosensitivity and gradually developed arthritis. Laboratory tests revealed positive ANA, anti-dsDNA and anti-SS-A antibodies. She fulfilled with ARA diagnostic criteria of SLE and was treated with oral prednisolone and azathioprine. She had developed recurrent auricular chondritis, polyarthritis, episcleritis and iritis since February 2002. She was finally diagnosed with relapsing polychondritis (RP). Serum levels of anti-type II collagen antibodies were positive and correlated with the disease activity of RP. We also reviewed ten cases of RP in our department and investigated their association with other collagen diseases, serum levels of anti-type II collagen antibodies.