Intersociety Liaison Committee Concurrent Session Advances in Dermatology: Medical Dermatology

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Abstract Table of Contents

Abstracts selected by the Medical Dermatology Society Committee on Education

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1

Pruritic Skin Disease in the Elderly

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Pruritic skin eruptions are a common complaint in the elderly population and often pose a diagnostic and management challenge. We performed a chart review of 330 patients 60 years of age and over who were seen in consultation by one of the authors over a 2-year period at a complex medical dermatology practice in a large university setting. The demographics and diagnosis given to the patient were recorded. Of 330 patients with an average age of 73, 149 (45.2%) were referred with the complaint of pruritic rash. A total of 118 patient charts were retrieved and reviewed, and the morphology of the rash was characterized. A total of 75.4% of these pruritic patients had diagnoses falling into to following five diagnostic categories: eczematous dermatitis, prurigo nodularis/lichen simplex chronicus, subacute prurigo, Grover's disease, and neuropathic dermatoses. A total of 41.6% of these patients had two or more diagnoses within these five most common categories. Our data support pruritic rash as a common problem in the geriatric population. The frequency of multiple diagnoses within these five categories endorses a common underlying pathogenesis for pruritic skin disease. We hypothesize that in the aged, barrier dysfunction in combination with immunosenescence or the dominance of the TH2 immune response over TH1 function cause a clinical manifestation much like childhood atopic dermatitis with multiple features in the same patient simultaneously and over time. We propose that the five most common diagnoses in our study represent the different morphologies seen in elderly inflamed skin and suggest calling this group of skin conditions the "Eruptions of Immunosenescence." We recommend approaching the eruptions of immunosenescence as having a common underlying pathogenesis.

2

Initial Analysis of a Collaborative Web-Based Database for Skin Manifestations of Lupus Erythematosus: 102 Prospectively Enrolled Patients

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Lupus erythematosus (LE) is a potentially disabling autoimmune disease that clinically presents as a spectrum ranging from mildly affected patients with only localized discoid skin lesions to those at risk of dying from the severe systemic manifestations of LE. Skin disease, the second most frequent clinical manifestation of LE, can present with either lupus-specific (cutaneous LE (CLE)) or lupus-nonspecific findings. Lupus-specific skin manifestations are subclassified into chronic CLE (CCLE), subacute CLE (SCLE), and acute CLE (ACLE). The types of skin lesions in an individual patient can provide insight about the likelihood of underlying systemic disease. We devised this prospective study to assess disease prevalence and severity in various subsets of CLE by using outcome measures and quality-of-life measures, and to determine treatment responsiveness by establishing a web-based database of patients with CLE. A linked CLE tissue bank will enable future genetic and pathophysiologic studies. We have enrolled and followed 102 patients who met the criteria for having CLE, and presented to our outpatient clinic in a 9-month period. We used the CLE Disease Activity and Severity index (CLASI) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) to evaluate cutaneous and systemic disease, respectively. At each visit, patients completed the SKINDEX 29+3, a CLE-modified quality-of-life measure, and the SF-36, a more general quality-of-life measure. Predominant diagnosis in seven patients (6.86%) was ACLE, in 19 patients (18.62%) was SCLE, and in 69 patients (67.64%) was CCLE (55 classic DLE (25 generalized DLE, 30 localized DLE); two hypertrophic DLE, nine lupus tumidus, one chilblain LE, two lupus panniculitis), and seven patients (6.8%) had only lupus non-specific skin lesions with SLE. All of our ACLE patients were female. The female-to-male ratio in SCLE and CCLE patients was 2.8:1 and 3.92:1, respectively. The mean SKINDEX score in ACLE, SCLE, and CCLE patients at their first visit was 70.16, 82.26, and 84.89, respectively (NS). The mean CLASI activity/damage score in ACLE, SCLE, and CCLE patients was 5.42/5.14, 11.15/1.73, and 7.19/10.88, respectively. Ten patients (9.8%) were considered refractory to current therapies. This prospective web-based database is the first systematic multicenter epidemiologic study of cutaneous LE in the United States, and should allow collection of data related to disease activity, quality of life, and response to therapy at multiple centers.

3

A Systematic Review of Drug-Induced Subacute Cutaneous Lupus

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The initial appearance of subacute cutaneous lupus erythematosus (SCLE) skin lesions in conjunction with Ro/SS-A autoantibodies occurring as an adverse reaction to hydrochlorothiazide (that is, drug-induced subacute cutaneous lupus erythematosus (DI-SCLE)) was first reported in 1985. Over the past decade, an increasing number of drug classes have been implicated as triggers for DI-SCLE. Our objectives were to review the published literature on DI-SCLE and use the resulting summary data pool to develop guidelines that might be of value to clinicians in the management of DI-SCLE. A systematic review of the Medline/PubMed cited literature on DI-SCLE through June 2007 was performed. Our analysis of pooled data from the identified cases 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 quantify 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 with a mean age of 59.5 years. Triggering drugs fell into a number of different classes: calcium-channel blockers, anti-fungals, diuretics, antihistamines, chemotherapeutics, β-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 to 3.2 years) and were somewhat drug class-dependent. 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 for which such data were reported and most (83%) disappeared after resolution of the DI-SCLE. No significant differences in the clinical, histopathological, or immunopathological features of DI-SCLE and idiopathic SCLE were detected. In conclusion, it is our hope that the drug causation grading system and the drug class association summary data presented in this report can serve as a nidus for developing a consensus drug attributability algorithm for DI-SCLE. Since many of the triggering drugs are known to induce nonspecific photosensitivity states in individuals without lupus, we propose that DI-SCLE might represent a "photo-pharmacologic isomorphic response" in individuals genetically predisposed.

4

Clinical Characteristics and Treatment Response of Patients with Dermatomyositis seen at a Tertiary Dermatology Department: The Stanford Experience

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Reports on the prevalence and diagnostic parameters of patients presenting with dermatomyositis (DM) indicate variability of disease presentation and characteristics based on specialty care provider. Much of the published literature on DM reflect hospitalized cases seen by neurologists or rheumatologists, which may represent a subset of the DM disease spectrum, given that current classic DM classifications incorporate patients with skin manifestations and active muscle disease to the exclusion of hypomyopathic and amyopathic subtypes. The goal of this study was to further evaluate clinical presentation and expression of disease, as well as tolerability and treatment response, in DM patients seen in a dermatology department at an academic referral center. We hypothesized that patients with hypomyopathic dermatomyositis or amyopathic dermatomyositis would comprise a significant proportion of the patients seen in our clinic. We also hypothesized that many of these patients would present with skin biopsies that were not initially diagnostic of DM (that is, interface dermatitis), although many would eventually develop the more classic findings as the disease progressed. Finally, we suspected that skin inflammation would prove more recalcitrant to therapy than would the myositis. We conducted a retrospective chart review of patients with DM (ICD-9 code 710.3) seen in the dermatology and rheumatology clinics at our hospital between 1 January 2003 and 1 October 2007. Following chart review, patients with nonspecific or mixed connective tissue myopathic subtypes were excluded along with those who did not meet sufficient criteria for a diagnosis of probable DM. Results reflect our specific tertiary clinic population and may not be generalizable to other therapeutic settings. As a retrospective chart review, missing data and non-standardized physician-related variations will likely limit the results. In conclusion, the "classic" clinical and histopathological findings of DM are often not seen in the clinical practice of a dermatologist. As skin inflammation distinguishes DM, it is important for dermatologists to understand the spectrum of clinical and histopathological findings in DM and current therapeutic options. The challenge of treating the inflammatory skin component of this disease has been underestimated. New therapeutics and clinical trials formally assessing the efficacy of traditional therapies are needed.

5

Nephrogenic Fibrosing Dermopathy Is Associated with Expression of Transforming Growth Factor-β and Smad 2/3 without Evidence of Renin-Angiotensin System Involvement

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Nephrogenic fibrosing dermopathy (NFD) is a fibrosing disorder exclusively affecting patients with renal dysfunction, many of whom receive dialysis. Cutaneous manifestations include symmetric skin induration, particularly on lower extremities and forearms, which may progress to contractures, immobility, systemic involvement, and even death. Histologically, increased collagen, a proliferation of spindle-shaped fibroblasts, mildly increased dermal mucin and minimal to absent inflammation is seen. The exact mechanism of fibrosis in NFD is currently unknown. Leading theories postulate that CD34+ circulating fibrocytes, after being stimulated from the bone marrow, are recruited into cutaneous tissues resulting in the uncontrolled fibrosis. Transforming growth factor-β (TGF-β), a multifunctional cytokine known to have profibrotic properties, has been found in skin and fascia samples of patients with NFD by *in situ* hybridization. In other organ systems, activation of the renin–angiotensin system is shown to be profibrotic, often through upregulation of TGF-β. The first aim of this study was to confirm the expression of TGF-β in skin specimens of NFD. The second aim was to evaluate activation of the renin–angiotensin system in these same skin specimens. To investigate these aims, we evaluated the expression of TGF-β, SMAD2/3 (known second messengers of TGF-β), angiotensin-converting enzyme and angiotensin II receptor by immunohistochemistry on 12 paraffin-embedded biopsy specimens from eight previously described patients with NFD. Sections of normal skin, scar, and kidney from unaffected control patients, as well as uninvolved skin from a patient with NFD, were included as control tissues. In seven of 11 specimens tested, TGF-β was detected in the spindle cells. One NFD biopsy was not evaluated for TGF-β because of loss of tissue in the block. Additionally, five of these seven TGF-β positive biopsies demonstrated nuclear staining for the Smad2/3 nuclear transcription factor. No Smad2/3 staining was seen in the five specimens that did not show staining for TGF-β. Only faint staining for angiotensin-converting enzyme was seen in three of 12 specimens, whereas no angiotensin II receptor staining was identified in any of the specimens. We conclude that TGF-β, as well as its second messengers, Smad 2/3, appears to be associated with the fibrosis seen in nephrogenic fibrosing dermopathy. No definitive evidence of renin–angiotensin system involvement could be determined in our study.

6

The Summary of the Patients with Anti-p200 Pemphigoid

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More than 10 years ago, we have reported two cases of unique autoimmune subepidermal bullous disease, which reacted with a novel 200-kDa autoantigen by immunoblotting using normal human dermal extracts. We and Dr Zillikens in Lubeck, Germany, have designated this disease as anti-p200 pemphigoid. Thereafter, more than 50 cases of anti-p200 pemphigoid have been reported in the literature. Anti-p200 pemphigoid is associated with psoriasis or has vesicular pemphigoid-like or dermatitis herpetiformis-like clinical features. Histopathologically, anti-p200 pemphigoid shows subepidermal blisters and massive infiltrates of neutrophils. IgG antibodies in the patients' sera react with the epidermal basement membrane zone but not with vessel basement membrane zone. The IgG antibodies react with dermal side of 1 M NaCl-split skin by immunofluorescence, and with a 200-kDa antigen by immunoblotting using human dermal extracts. Immunoelectron microscopy showed that the IgG antibodies react with lower lamina lucida. Although the nature of the 200-kDa antigen has not yet been identified, p200 has been shown not to be laminin-5 or type-VII collagen by immunofluorescence using epidermolysis bullosa skin sections lacking laminin-5 or type-VII collagen. We have collected sera of many patients with anti-p200 pemphigoid and examined them by immunofluorescence and immunoblotting. In addition, we have attempted to identify the p200 by cDNA cloning by immunoscreening the cDNA library of keratinocytes. However, we have not yet identified this misterious antigen. In this review, I will summarize the clinical, histological, and immunological features of anti-p200 pemphigoid for all the patients we have collected so far, and will show the results of our attempt to identify the p200 by proteomics analysis using two-dimentional gel electrophoresis and mass spectrometry.

7

Healing of Pyoderma Gangrenosum-like Ulcers with Folate Supplementation

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Methylenetetrahydrofolate reductase is an enzyme that aids in the metabolism of homocysteine. Defects in this enzyme can lead to elevations of homocysteine and possible thrombotic complications, particularly in folate deficient individuals. We present a patient with mutations in methylenetetrahydrofolate reductase and recurrent pyoderma gangrenosum-like ulcerations on the lower extremities responsive to folate supplementation. A 12-year-old boy with a past medical history of hypothyroidism presented with a ***one and a half year history of recurrent ulcerations of the lower extremities. Prior to presentation the ulcers had been debrided and treated with culture-directed antibiotic therapy. Histopathological evaluation demonstrated nonspecific dermal and subcutaneous suppurative mixed inflammatory cell infiltrate that was non-diagnostic, but consistent with pyoderma gangrenosum. The patient had an extensive laboratory evaluation that was within normal limits except for an elevation of C-reactive protein and a positive cryofibrinogen. A repeat biopsy was refused by the patient on multiple occasions. He did report improvement in the past with dapsone, which was reinitiated; however the patient discontinued it due to headaches. He was later started on indomethacin, and was eventually lost to follow-up. The patient presented again with recurrent ulcerations, and additional laboratory work-up revealed C667T and A1298C mutations of the methylenetetrahydrofolate reductase gene. The patient was placed on 5 mg of folate daily and in 3 weeks had nearly complete healing of the ulcers. Eventually, the patient self-discontinued folate and had recurrent ulcerations. Due to clinical appearance of the patient's lesions he was placed on mycophenolate mofetil for the possibility of pyoderma gangrenosum. The patient was unable to consistently take mycophenolate mofetil due to gastrointestinal side effects, but had again restarted folate, which resulted in healing of the ulcerations. In conclusion, this case demonstrates the potential utility of folate in patients with mutations of the methylenetetrahydrofolate reductase gene. The healing of lesions with folate and the exacerbation without lends evidence to the efficacy of folate supplementation in this patient.

8

Quality of Life Evaluation in Epidermolysis Bullosa: Development of the QOLEB Questionnaire

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Epidermolysis bullosa (EB) is a group of genetic skin-blistering disorders, which causes significant pain and physical deformity. While physical impact of EB is obvious, psychosocial parameters are often overlooked. The aim of this study is to develop a valid and reliable quality-of-life questionnaire to evaluate the physical and psychosocial impact of EB. Generic quality of life and burden of disease tools have poor sensitivity for detecting disability in EB. Non-structured interviews were conducted with 44 EB patients and their families in order to generate initial items for a pilot questionnaire. Relevant experts in the field involved in the care of EB patients were also interviewed. A content analysis of the interviews was conducted, which revealed 168 items, which were compiled into a pilot questionnaire of 53 questions. After wording revisions and data reduction, a final questionnaire was developed and named the Quality of Life in Epidermolysis Bullosa (QOLEB) Questionnaire. This EB-specific tool was validated against established generic quality-of-life indices, function, and psychosocial parameters. Test–retest reliability of the final questionnaire was also conducted. In conclusion, EB is associated with considerably impaired quality of life, which varies according to disease subtype. The questionnaire developed was valid and reliable in evaluating quality of life in this cohort of EB patients. (Cronbach's alpha = 0.933) This questionnaire has potential to identify areas for intervention, and to measure the response of interventions.