Clinical characterization of hidradenitis suppurativa in Down syndrome: Retrospective analysis of 16 patients

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Background: Hidradenitis suppurativa (HS) is a debilitating chronic cutaneous condition of unknown etiology affecting approximately 1% of the general population. It occurs most commonly in the axilla and groin, and is characterized by recurrent inflammatory nodules, sinus tracts, and scarring. It is known to be associated with Down syndrome, but the characterization of this association is poor. We aimed to provide a clinical characterization of HS presentation in individuals with Down syndrome, including: sex, race, age of onset, age of presentation, BMI, and disease location and severity. Methods: We conducted a retrospective chart review examining all patients with HS and Down syndrome seen by our Dermatology service between January 1st, 1992 and October 1st, 2014. Patients were identified as having HS by billing records utilizing ICD 9 code 705.83, and diagnosis of both conditions was confirmed with manual examination of patient medical records. Results: Of the 667 patients with HS seen at our institution during this time period, 16 (2.4%) had a diagnosis of Down syndrome. There were 11 females and 5 males, with a racial distribution of 9 African Americans, 6 Caucasians, and 1 Indian individual. Our patients had a median age of HS symptom onset of 14.5, a mean age at presentation to our service of 17.9, and a mean BMI of 36.5 kg/m². The majority of patients had axilla or inguinal involvement, 10 with mild disease and 6 with moderate disease. Additionally, 2 of the 16 patients had a positive family history of HS. Conclusions: The 2.4% prevalence rate of Down syndrome seen in our population of HS patients was approximately 29 times higher than the 0.083% prevalence of Down syndrome seen in the general population. Additionally, HS symptom onset appeared to occur at a younger age in our patients with Down syndrome, as large population studies have shown the mean age of HS symptom onset in the general HS population to be closer to age 20 (vs. 14.5 in our patients). If true, this earlier age of onset would argue in favor of a genetic component driving HS development in Down syndrome patients. The enrichment in prevalence of Down syndrome patients in our HS population, and possible earlier age of onset, are both highly intriguing and warrant future investigations into the nature of the relationship between these two disease entities.

Successful use of a modified Goeckerman regimen in the treatment of chronic, severe atopic dermatitis

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Background: Atopic dermatitis (AD) is a chronic, inflammatory dermatosis that affects up to 25% of children and 2-3% of adults. Despite the current assortment of available therapies, a significant portion of patients with AD remains undertreated relative to the severity of their disease. This is problematic in patients with severe, chronic AD who frequently require systemic anti-inflammatory agents that are associated with serious side effect profiles. The Goeckerman regimen, consisting of the application of crude coal tar and exposure to ultraviolet radiation, offers a promising alternative regimen that is safe and effective for patients with chronic, severe AD. Objective: To prospectively determine the efficacy of Goeckerman therapy for the resolution of chronic, severe AD. Methods: Five patients with chronic, severe AD were treated with an outpatient modified Goeckerman regimen 5 days per week at the University of California, San Francisco between September 2014 and April 2015. All patients had previously failed standard narrowband or broadband UVB therapy. The Goeckerman regimen consisted of daily multiple-step broadband UVB therapy followed by application of crude coal tar and topical corticosteroids under occlusion for 4 hours each day. Patients were instructed to apply liquor carbonis detergens and topical corticosteroids at home following each session. Treatment was discontinued when satisfactory clinical response was achieved. Disease activity was measured prior to the initiation of treatment and weekly thereafter using the Scoring Atopic Dermatitis (SCORAD) instrument, investigator global assessment (IGA), and 5-D itch scale. Results: All five patients successfully completed the full course of Goeckerman therapy. The average SCORAD improved from 60.9 at baseline to 15.9 at final assessment (p= 0.0015), with a mean percent reduction in SCORAD of of 73.8%. Mean IGA at baseline was 4.2. All patients achieved an IGA of 1 at final assessment. The only adverse events were mild phototoxic reactions that were easily managed by reduction of the broadband UVB dose. Conclusion: A modified Goeckerman regimen may be an effective treatment for chronic, severe AD. Further data from larger studies are necessary to confirm the favorable efficacy and safety profile demonstrated in this study.
Characteristics and treatment of antimalarial refractory cutaneous lupus erythematosus: A tertiary care experience of 34 patients

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Background: Cutaneous lupus erythematosus (CLE) is an autoimmune skin disease that can result in severe disfigurement. Although antimalarial therapy is considered first-line systemic treatment for CLE, up to 55% of patients are refractory to hydroxychloroquine. Several systemic therapies have been studied individually for recalcitrant CLE; however, there is a paucity of data regarding overall treatment experience of refractory CLE. Methods: Utilizing a query based on the CLE ICD-9 code 695.4 and a CLE-related natural language search, we searched two institutional electronic medical record systems to identify patients with CLE seen at a large tertiary care center over a 4-year period. Only patients refractory to or intolerant of an antimalarial medication were included. Data were extracted on demographics, disease presentation, and treatment outcomes. Results: We identified 34 patients with CLE who were intolerant of or refractory to at least one antimalarial medication. Mean age at CLE diagnosis was 35.6 years; 85% of patients were female. All patients had involvement above the neck; 68% (n=23) below the neck. Systemic regimens included an alternative antimalarial, or the addition of quinacrine and/or methotrexate, mycophenolate mofetil, thalidomide, lenalidomide, belimumab, prednisone, rituximab, or dapsone. Sixty-eight percent (n=23) were treated with an alternative antimalarial or the addition of quinacrine; 50% (n=9) experienced a substantial to complete response. Regarding non-antimalarial treatments, belimumab, thalidomide, and methotrexate demonstrated the greatest efficacy with 50%, 50% and 42% of patients, respectively, experiencing a substantial to complete response. Mean follow up was 10.6 years. Conclusions: To our knowledge, this pilot study represents the largest study to date to describe overall treatment response of antimalarial refractory CLE within a large tertiary care center. Cutaneous involvement below the neck was present in the majority of patients, likely reflective of the referral-based nature of this academic center. Alternative antimalarial therapy was effective in 50% of patients, consistent with existing literature. Overall, cutaneous disease not responsive to antimalarial agents was recalcitrant to subsequent immunomodulatory therapy, with methotrexate, thalidomide, and belimumab demonstrating the greatest efficacy. Further study is needed to develop an appropriate therapeutic algorithm for antimalarial refractory CLE.

Reliability of the cutaneous dermatomyositis disease area and severity index among dermatologists, rheumatologists, and neurologists

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Background/Purpose: Previous studies have shown that skin lesions in dermatomyositis (DM) are best assessed using the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI). Although the CDASI has been validated for use by dermatologists, it has not yet been validated for use by other specialists such as rheumatologists and neurologists, who also manage DM patients and evaluate their skin in clinical trials. The purpose of this study is to assess the inter-rater and intra-rater reliability of the CDASI and extend the validation of the CDASI to rheumatologists and neurologists. Methods: Five dermatologists, five rheumatologists, and five neurologists specializing in neuromuscular medicine individually assessed 15 patients with cutaneous DM using the CDASI and the Physician’s Global Assessment (PGA). All physicians received a 30-minute training session on the CDASI and PGA prior to evaluating patients. Each physician also re-rated three patients. Intraclass correlation (ICC) scores >0.5 were considered poor, 0.50 to 0.70 moderate and minimally acceptable, 0.70 to 0.81 good, and >0.81 excellent. Results: Inter-rater reliability yielded an ICC for CDASI activity that was good for dermatologists and rheumatologists (0.73 and 0.74, respectively) and moderate for neurologists (0.56). The ICC for CDASI damage was excellent for all physicians (dermatologists 0.83, rheumatologists 0.82, and neurologists 0.85). For PGA activity, the ICC was moderate for dermatologists (0.61) and rheumatologists (0.69) but poor for neurologists (0.44). The ICC for PGA damage was excellent for neurologists (0.85), good for rheumatologists (0.75), and moderate for dermatologists (0.58). Intra-rater (test-retest) reliability for CDASI activity was excellent for all physicians (dermatologists 0.94, rheumatologists 0.88, and neurologists 0.82). For CDASI damage the scores were excellent for dermatologist and rheumatologists (0.92 and 0.91, respectively) and moderate for neurologists (0.66). For the PGA activity and damage the intra-rater reliability was excellent for dermatologists (0.89 and 0.91, respectively) and good for rheumatologists (0.75 and 0.75, respectively). For neurologists, the PGA activity was good (0.74), but the PGA damage was poor (0.39). Conclusion: Our data confirm the reliability of the CDASI when used by dermatologists and support the CDASI as a reliable instrument for use by rheumatologists. The data was not as robust for its use by neurologists.
Use of colchicine in reducing granulation tissue in junctional epidermolysis bullosa

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Junctional epidermolysis bullosa (JEB) is a recessive type hereditary vesiculobullous eruption. A 41-year-old female with intermediate, generalized JEB due to two different LAMB3 mutations, who had given birth to two unaffected children, had been well with only limited erosions, controlled with gentian violet. After the National EB dressing scheme was established, she began using silicone dressings and developed exuberant granulation tissue under the dressings. She had failed to respond to changes to her silicone dressing regime and was unable to wean off dressings. She became profoundly anemic with Hb of 78g/L recurring despite transfusions and antibiotics. On the basis that colchicine may inhibit cell proliferation and be anti-inflammatory, this was initiated. After colchicine, her EBDASI activity score reduced from 30 to 23 and the EBDASI damage score reduced from 76 to 37 over the 6 month period. The QOLEB score improved from 35 to 24, and her haemoglobin level improved from 95g/L to 128g/L. Colchicine has been used in a various dermatological conditions, mainly in treating neutrophilic dermatoses. A small case study on its use in EB acquisita (EBA) but not in EB has been documented in the literature. The exact mechanism of colchicine in assisting reduction of the blistering, erosions, and granulation tissue in JEB is unclear. The anti-inflammatory and anti-mitotic properties of colchicine may be partially responsible for this process.

Novel targeting and prognostic significance of inositol polyphosphate 5-phosphatase in squamous cell carcinoma

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Squamous Cell Carcinomas (SCC) are one of the most common human malignancies. In recent years, there has been an increasing health and economic burden due to cutaneous SCC. Current treatment for early stage disease is surgical excision and treatment of advanced disease remains challenging. Therefore, better characterization of SCC; its risk factors, as well as novel therapeutics are of high importance. Inositol Phosphate 5-Phosphatase (INPP5A) gene is lost in a significant number of cutaneous and oropharyngeal SCC. INPP5A gene expression is lost in 24% of primary SCC and protein expression is reduced in 72% of primary tumors as well as 92% of primary tumors with metastasis. Similarly, INPP5A protein expression is diminished in 55% of primary oropharyngeal SCC and 61.5% of matched lymph node metastasis. INPP5A expression increases with keratinocyte differentiation and expression of INPP5A as well as treatment with IP6 induce apoptosis in an oral SCC cell line. Current studies with lentivirus transfection of INPP5A as well as models of forced differentiation are underway to provide granularity to the localization and role of INPP5A in SCC initiation and proliferation. The utility of INPP5A as a prognostic marker has not been evaluated. In order to answer this question, we created a large, detailed SCC database, modeled after melanoma, to collect and house key variables of potential prognostic importance. Using the two above datasets, we present our novel scoring system for INPP5A expression as well as preliminary data of INPP5A as a potential prognostic marker in cutaneous SCC.

Granulomatous post-herpetic isotopic response in immunocompromised patients: A report of 5 cases and review of the literature

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Wolff’s isotopic response is the phenomenon of a new skin disease presenting at the site of a healed, unrelated skin disease. The most commonly observed inciting cutaneous lesions prior to a Wolff isotopic response are those caused by herpes viruses, while the most common post-herpetic isotopic response (PHIR) is a granulomatous dermatitis (GD). We conducted a retrospective study of 5 immunocompromised patients diagnosed with PHIR-GD in our department between 2008 and 2015 and reviewed all published cases of PHIR-GD. A prior published assessment of isotopic granuloma annulare had identified 12 immunocompromised and 20 non-immunocompromised cases, while our literature review identified an additional 15 immunocompromised and 20 non-immunocompromised PHIR-GD cases. We found granulomatous PHIR to be more common than previously reported in immunocompromised patients (42% overall, 44% with GD) and chronic lymphocytic leukemia (CLL) was by far the most common cause of immunosuppression in these patients (46% overall, 50% with GD). Further, immunocompromised men appear to be particularly susceptible to granulomatous PHIR independent of their higher incidence of CLL, while granulomatous PHIR in immunocompetent patients is far more frequent in women. These observations suggest male gender, CLL, and immunosuppression in general may be distinct risk factors for granulomatous PHIR. While future mechanistic investigations into granulomatous PHIR in these at risk groups may provide needed insight into both PHIR and granulomatous dermatitides, the immediate application of our observation of an increased M:F ratio in immunosuppressed PHIR-GD may lead to earlier identification of immunosuppression in male patients.
Development of PRN1008, a novel, reversible covalent BTK inhibitor in clinical development for pemphigus


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Background/Purpose: Bruton’s Tyrosine Kinase (BTK) is a target for the treatment of multiple autoimmune diseases. Principia is developing a potent, selective, reversible, covalent inhibitor of BTK for pemphigus. We characterized the pharmacology of PRN1008 and tested the human safety, tolerability and PK/PD profile of PRN1008 in a phase 1 clinical trial. Clinical efficacy of a surrogate BTK inhibitor molecule, possessing a similar kinase inhibition profile and with good canine oral bioavailability, PRN473, was investigated in 7 cases of naturally occurring, canine pemphigus foliaceus (PF). Methods: PRN1008 was tested for potency, durability and selectivity in biochemical and cell-based functional assays. The in vivo efficacy of PRN1008 was tested in a rat model of collagen-induced arthritis (CIA). The first-in-human study (N=80) included four multiple dose cohorts with 10 days treatment (300mg and 600mg QD, 300mg and 450mg BID). PRN1008 pharmacodynamics was assessed by BTK occupancy in PBMCs. Canine PF cases were administered a dose of 15mg/kg QD of PRN473 as monotherapy, designed to achieve trough BTK occupancy of 50-70% 24 hours after the first dose. Skin disease activity was measured with a modified, canine pemphigus disease activity index (cPDAI). Results: PRN1008 was very potent against BTK in vitro (IC50=1.3±0.5 nM). Human B cell proliferation and activation (CD69 expression) were inhibited by PRN1008 with IC50 of 5±2.4 nM and 123±38 nM, respectively. Dose-dependent efficacy in rat CIA was observed at trough BTK occupancies of 16-79%. PRN1008 was safe and well-tolerated in the human clinical trial with mean (±SD) BTK occupancy of 90±6% and 93±2% 4 hours post-dose on Days 1 and 10, respectively. BTK occupancy at trough on day 10 ranged from 54±15 to 77±7%. Seven of 7 dogs with PF had an initial reduction in skin disease activity with mean cPDAI 55±29 at baseline vs. 27±16 at Week 2. BTK occupancy 24 hours after the first dose ranged from 50-77%. Four of 7 dogs went on to a full or near-full remission without the use of corticosteroids. Retreatment, 9 days and 4 months after PRN473 cessation, resulted in repeat, complete responses in 2 of 2 cases. Conclusions: Treatment of canine PF with PRN473 confirmed that a trough BTK occupancy of ~50% is adequate to achieve efficacy. Humans in the phase 1 trial were safely dosed to above this target. A similar BTK occupancy target is being used to guide a phase 2 clinical trial of PRN1008 in human pemphigus vulgaris.

The role of hypercoagulability in calciphylaxis

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Introduction: Calciphylaxis is a rare and often fatal skin disease characterized by calcium deposition in the media of small vessels, leading to tissue ischemia and necrosis. It most commonly affects patients with end-stage renal disease (ESRD). While calciphylaxis has been well-described clinically and histologically, the pathogenesis remains unclear. Hypercoagulability is believed to play a role in the pathogenesis of calciphylaxis. In this study, we assess the prevalence of abnormalities in coagulation in patients with uremic calciphylaxis and compare these abnormalities to matched controls. Methods: We conducted a retrospective review of the medical records for adult patients with calciphylaxis and ESRD at the Massachusetts General Hospital and Brigham and Women's Hospital from 2006 to 2014. Three control patients also with ESRD were matched to each case by age, sex, and race. Results: Fifty-five adults with calciphylaxis were matched to 165 controls. Mean age was 60 years old, with females representing 60% of cases and 55.2% of controls. About half were Caucasian (49.1% cases, 57.6% controls) and almost one-fifth were African-American (20% cases, 13.2% controls). The odds of having diabetes mellitus type II, cardiovascular disease, obesity, and hyperparathyroidism were all significantly greater among cases as compared with controls (p<0.05 for all). Hypercoagulable tests were positive for 59.3% of cases and 15.1% of controls, with an increased odds ratio of 6.5 for hypercoagulability in cases as compared with matched controls (p<0.0001; 95% CI 3.3 to 13.0). Increased odds of hypercoagulability among cases included anti-thrombin III deficiency (OR=14.4, p<0.0001), elevated anti-cardiolipin antibodies (OR=4.2, p<0.005), hyperhomocysteinemia (OR=2.5, p<0.03), lupus anticoagulant (OR=24.0, p<0.0001), and protein C or S deficiency (OR=20.8, p<0.0001). Discussion: The results of this analysis indicate that those with calciphylaxis have an estimated 6.5 increased odds of hypercoagulability as compared to those without calciphylaxis. There was no significantly increased odds of having Factor V Leiden or heparin-induced thrombocytopenia among cases and controls. These results could inform clinical guidelines to identify at-risk patients for calciphylaxis and support the use of non-warfarin anticoagulation such as apixaban for these patients. Additionally, further analysis could aid in the understanding of the pathogenesis of calciphylaxis.
Clinical epidemiology of reactive keratoacanthoma on the legs
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Background: Keratoacanthoma’s (KA) are neoplasms of the squamous epithelium that have a characteristic growth pattern of rapid proliferation followed by spontaneous regression. Keratoacanthoma-like lesions occur following trauma and with targeted therapeutics such as BRAF inhibitors. UV-induced mutations in Ras within the MAPK pathway and altered TGFβ signaling are likely key events in the pathogenesis of KAs. The purpose of this study is to characterize a subset of keratoacanthoma-like tumors occurring on the legs. Methods: A retrospective chart review of pathology-confirmed KAs located on the legs at a single academic dermatology center was performed. Cases were identified with a pathology query from the prior 6 months and referral from practitioners. Results: Nine patients with 21 KAs on the legs were identified. The mean patient age was 74 years. More females had KAs on the legs (male:female ratio 3:6), however men had a greater number of tumors (14:7 tumors). Mean tumor size was 1.28cm (range 0.7-2.0cm). The lesion was present an average of 4.8 weeks prior to biopsy (range 4-8weeks). All cases with clinical photographs were noted to occur on a background of photodamaged skin. Four KAs developed at the site of trauma: a thermal burn, biopsy for an unrelated lesion, Mohs micrographic surgery, and blunt trauma. Two patients with four KAs had a history of PUVA therapy for cutaneous T-cell lymphoma. Four patients had multiple KAs on the legs (range 2-9) and the patients with ≥3 KAs also had a history of melanoma, keratinocyte carcinoma and KAs on the upper extremities. Most lesions were treated surgically, but 3 KAs on the legs resolved without treatment. Conclusion: KA-like lesions occur on photodamaged legs in elderly patients and frequently develop in the setting of a triggering event such as surgery, burn or blunt trauma to the shin. In our cohort KAs are more common on the legs versus other sun-exposed areas. While we identified more females with KA on the legs, our male patients had a higher number of tumors and were more likely to have KAs on the upper extremities. Excessive sun damage, particularly continued sun exposure, a history of PUVA therapy, and development of multiple types of skin cancers, appears to correlate with ≥3 KAs on the legs. 14% of the KAs regressed after the biopsy and did not recur upon follow-up, suggesting that conservative management for some lesions may be reasonable.