Current Best Evidence

Current best evidence in dermatology literature

Takeuchi S, Soma Y, Kawakami T. IgM in lesional skin of adults with Henoch-Schonlein purpura is an indication of renal involvement. J Am Acad Dermatol 2010;63:1026-9.

Henoch-Schonlein purpura (HSP) is a multisystem disease believed to be the consequence of the entrapment of circulating IgA-containing immune complexes (ICs) in the blood vessel walls of the skin, kidneys, and gastrointestinal tract. Adults with HSP have more pronounced skin lesions and more frequent renal involvement than children. Although the cause is unknown, it is clear that IgA plays a pivotal role in the immunopathogenesis of HSP. For study purposes, records of 25 adult patients with HSP were retrieved. The basis for diagnosis of HSP were non-thrombocytopenic palpable purpura, typical distribution on the extensor surfaces of the lower limbs, no accompanying connective tissue disease, leukocytoclastic vasculitis in the skin biopsy specimen, and evidence of IgA deposition on direct immunofluorescence (DIF). Renal involvement was defined as microscopic proteinuria, hematuria or both, which was noted in 12 patients (48%). IgM deposition was noted in the vascular walls of the papillary dermis and / or subpapillary dermal plexus of the vessels, in 15 of the 25 patients (60%). DIF revealed C3 within the affected dermal vessels in 22 of the 25 patients (88%). There was a significant correlation between IgM deposition on the DIF of the skin biopsy specimen and renal involvement ($P = 0.022$). Similarly, the IgM and C3 deposition on DIF showed a close relationship ($P = 0.024$). Thus, IgM deposition in palpable purpura, as shown by direct immunofluorescence, provided an indicator of nephritis in adult Henoch-Schonlein purpura. IgM deposition could be related to the pathogenic factors that triggered the development of renal involvement in adult Henoch-Schonlein purpura.

Comments: Henoch-Schönlein purpura (HSP) is a systemic, vasculitic disorder, mainly affecting the skin, joints, gastrointestinal tract, kidneys, and sometimes, other organs. Although HSP can occur at all ages, it predominantly affects children younger than 10 years of age, and is generally a benign, self-limited disorder that follows an intercurrent illness, usually of the upper respiratory tract. It may also be precipitated by other infections, medications, or miscellaneous conditions. There is age-related organ severity with a higher prevalence of skin involvement in children, and kidneys in adults. Renal involvement is a common, but inconstant manifestation of HSP, and its incidence varies from 33% in children to 63% in adults with HSP. Heamaturia is often macroscopic, but may be microscopic. It is transient, persistent, or recurrent, and may accompany relapses of purpura or recur long after the extrarenal manifestations have resolved. The associated proteinuria is of variable intensity. The frequency of the nephrotic syndrome is also extremely variable. Deterioration of the glomerular filtration rate (GFR) may occur, and azotemia or end-stage renal failure may ensue. It is controversial whether there is a correlation between the intensity of the extrarenal manifestations and the severity of the nephropathy. The pathogenesis of HSP remains unknown; however, it is generally considered to be an immune complex-mediated disease, characterized by the presence of polymeric IgA1 (pIgA1)-containing immune complexes, predominantly in the dermal, gastrointestinal, and glomerular capillaries. Earlier studies have shown pathognomonic granular IgA and C3 deposits in the mesangium, in renal biopsies. The present study, however, demonstrates the co-occurrence of IgM in palpable pupuric lesions, along with IgA and C3, and its relation to the appearance of nephritis in the patients. It lacks the definitive evidence of renal biopsies, confirming glomerular injury by IgM deposits. Another, limiting factor of this study is the small sample size. However, detection of IgM on skin biopsy in the early stages of HSP, in adults, may predict a later development of nephropathy and an early efficacious treatment can be initiated. In both cryoglobulinemic vasculitis and HSP, the common features are skin and kidney involvement with IgM and C_3 deposits. Whether IgM and C_3 deposition are somehow related to the pathogenesis of nephropathy needs to be known.

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Cerroni L, Argenyi Z, Cerio R, Facchetti F, Kittler H, Kutzner H, *et al*. Influence of evaluation of clinical pictures on the histopathological diagnosis of inflammatory skin disorders. J Am Acad Dermatol 2010;63:647-52.

During routine practice, dermatopathologists often ask the referring physicians for clinical information before providing any definitive histological diagnosis of skin disorders. Clinical information on the histological referral sheets is usually very limited. This problem is compounded by the fact that more surgical biopsies are performed by physicians without formal dermatological training, and the proposed clinical diagnoses are often imprecise. On the other hand, a clinical image can be considered as 'gross macroscopy' of dermatopathology. This study was undertaken to assess whether evaluation of a clinical picture increases the diagnostic accuracy on dermatopathology, for inflammatory skin disorders.

In this retrospective study, the authors chose 100 cases of varied inflammatory skin disorders, for which clinicopathological correlation was required for definitive diagnosis. The biopsy specimens of these cases were digitalized and stored on three DVDs, along with the clinical information available on the original biopsy request slips. These cases were then evaluated by nine independent dermatopathologists, initially without looking at the clinical pictures and subsequently after checking them. Each observer provided a main diagnosis, up to a maximum five differential diagnoses and a 'level of confidence' on a 100-point scale, for the main diagnosis. All the diagnoses were finally compared with the 'reference' diagnosis, established in one single institute, and the results were statistically analyzed. The results of the study showed improvement in the correct histopathological diagnosis of the skin disorders after evaluation of the clinical images. The total percentage increase in the correct diagnosis was 16.6%, decrease in the number of differential diagnoses was from 1.22 per case to 0.44 per case and increase in the mean level of confidence of the dematopathologists, with regard to the histological diagnoses, was increased from 61.8 to 80.8. Thus, the study clearly showed that clinical pictures should be added to the biopsy request slips of inflammatory skin disorders whenever possible.

Comments: Dermatopathology, as described as a subspeciality of dermatology and surgical pathology, nowadays encompasses both microscopic and macroscopic dermatopathology. Microscopic dermatopathology encompasses both diagnoses of cases, by examining the skin biopsies as well as by studying the cause or the pathogenesis of skin diseases at the cellular level. Macroscopic dermatopathology includes digital photography. Dermatologists and dermatopathologists work in close association with each other. Dermatologists recognize most skin diseases based on their appearance, distribution on the body, evolution with time, and so on, but sometimes these criteria are not enough to reach a particular diagnosis and a skin biopsy is taken to clarify the diagnosis. Incomplete or incorrect description of clinical information in the histopathology request forms diverts the concerned dermatopathologist to varied differential diagnoses, and either the clinical correlation is asked for or higher and more expensive investigations, or at times, even re- biopsy are suggested, to reach any definitive single diagnosis. In such a case, digital photographs may help to narrow down the differential diagnosis to the most probable diagnosis. This study clearly, shows that the evaluation of clinical pictures increases the accuracy of dermatopathological diagnosis of skin disorders. This of course, implies a decrease in the cost of management for a given patient. This aspect is even more important if we consider that the cost of providing clinical pictures is negligible, as small inexpensive cameras can be used for taking pictures of thousands of patients. The study also encourages the introduction of digital photography as a supplement in dermatopathology teachings, to improve the quality of information provided in histopathology request forms. Although digital photography is computerized and is different from real life examination, the study encourages the practice of attaching the digital photographs of the individual cases to the histopathology request forms.

Haeck IM, Rouwen TJ, Timmer-de Mik L, de Bruin- Weller MS, Bruijnzeel, Koomen CA. Topical corticosteroids in atopic dermatitis and the risk of glaucoma and cataracts. J Am Acad Dermatol 2011;64:275-81.

Atopic dermatitis (AD) is a relapsing chronic inflammatory disease, often affecting large skin areas. Topical corticosteroids are the most important treatment modality for AD. With topical corticosteroids, there is concern about the development of glaucoma and cataracts in patients with AD. The present study evaluates the risk of glaucoma and cataract development in patients with AD, whether the risk is associated with a cumulative dose of topical steroids or the use of topical corticosteroids on the eyelids and periorbital region. It is a retrospective study, in which

88 patients with moderate-to-severe atopic dermatitis, with an average age of 37.2 years, were recruited. The use of corticosteroids in at least the previous two or possibly five years was obtained from the pharmacy records of the patients, as also the total cumulative dose of topical corticosteroids. The classification of the potency of topical corticosteroids used was according to the US classification. It was found that most of the patients used class III and IV of the topical steroids on the eyelids and periorbital region. In all, 37 of the 88 patients had used topical corticosteroids (class III and IV) on the eyelids and periorbital region, with an average frequency of 3.9 days per week and 6.4 months per year for 4.8 years. A complete ophthalmological examination was performed for the presence of glaucoma and cataracts. Results of the study showed that out of the 88 patients, one patient had transient ocular hypertension and one patient had optic disc cupping, without any glaucomatous defects in his visual field. Seven patients were diagnosed with cataracts, one (1.1%) was AD-related, two (2.3%) corticosteroid-induced, and four (4.5%) age-related. Both patients with corticosteroid-induced cataracts had also used systemic corticosteroids. The one patient who showed ocular hypertension, had the increased ocular pressure (IOP) normalized, despite continued use of class III topical corticosteroids on the eyelids, thus suggesting that there was no relation between the high IOP and the use of topical corticosteroids. Although, the study showed that application of topical corticosteroids to the eyelids and periorbital region, even over longer periods of time, was not related to the development of glaucoma or cataracts; the authors still recommended regular ophthalmological examination for patients on long-term steroids, given by any route, to prevent vision loss and the morbidity associated with it.

Comments: Besides the skin manifestations of atopic dermatitis, many ocular signs are also associated with it, like allergic conjunctivitis, anterior subcapsular cataract, retinal detachment, keratoconus, and retinal tears. The chronicity of the disease is the major morbidity factor and use of long-term treatment is required in such patients. Although, the first-line treatment in atopic dermatitis is emollients and other topical products, for maintaining skin barrier functions, corticosteroids form an integral part of the treatment of both the acute and chronic stages of the disease. The ocular side effects of steroids are mainly cataract (posterior subcapsular cataract) and glaucoma. The exact route of the entry of steroids in eyes after topical application is not known. Few proposed mechanisms are direct absorption through the skin of the eyelid, absorption from spills of corticosteroid ointment over the lid margin or systemic absorption of topical corticosteroids with distribution to the eyes. Thus far, there have been only few case reports of development of cataract or glaucoma in patients using topical corticosteroids for eyelid or periorbital eczema. This study has evaluated the data of 88 patients using topical corticosteroids for eyelid and periorbital dermatitis, and has shown negligible risk of development of glaucoma and cataract in these patients. There are some limitations to the study, like small sample size, and the difficulty of standardizing the amount and frequency of use of steroid creams in a retrospective study of longer duration. Therefore, caution needs to be exercised while applying corticosteroids topically, especially on the eyelids for a longer duration, in AD patients who are predisposed to ocular involvement *per se*.

Halevy S, Kardaun SH, Davidovici B, Wechsler J, for the EuroSCAR and RegiSCAR study group. The spectrum of histopathological features in acute generalized exanthematous pustulosis: a study of 102 cases. Br J Dermatol 2010;163:1245-52.

Acute generalized exanthematous pustulosis (AGEP) is an uncommon, severe, acute pustular reaction pattern, characterized by the appearance of sterile, non-follicular, pinhead-sized pustules arising on an erythematous, edematous skin, in a widespread manner, with a predilection to body folds. Several pustular conditions, including IgA pemphigus, necrolytic migratory erythema, Sweet's syndrome, bowel bypass syndrome, and so on, can be differentiated from AGEP both clinically and histopathologically. However, a clinical and histopathological differentiation from pustular psoriasis (PP) may be difficult. The histopathological features of AGEP have been widely described in clinical studies and case reports, and are quiet variable. This study aims to compile the various histological features of AGEP. It is a retrospective review of the histopathology of 102 cases of AGEP selected from two previous multinational studies EuroSCAR and RegiSCAR. Out of the 102 cases, 16 cases had a history of psoriasis.

The results of the study showed that the epidermal changes mainly consisted of sub- or intracorneal pustules in 41%, intraepidermal pustules in 20% or combinations of them in 38% of the biopsies.

Follicular pustules were observed in 23% of the patients. The pustules were usually large, more than the size of 15 keratinocytes, and these regularly contained eosinophils. Spongiform features were less prominent in the sub- or intracorneal pustules, when compared with the intraepidermal pustules, as seen in 44 and 95% of the biopsies, respectively. The other epidermal features were necrotic keratinocytes in 67%, spongiosis in 80%, with neutrophil exocytosis in 77% of the biopsies. The main dermal features were papillary edema in 88% of the cases, mixed superficial, interstitial, and mid- or deep-dermal infiltrates in 100, 93, and 81% of the biopsies, respectively. The infiltrates were mainly composed of neutrophils and eosinophils. Vasculitis was generally absent. The classical features of plaque-type psoriasis were infrequent and there was no significant difference in the histopathologies between a subgroup of 16 cases with a history of psoriasis and 86 cases without it. The study thus tried to show the prevalence of various histopathological features of AGEP and claimed to provide the unique diagnostic clues to support the diagnosis of AGEP.

Comments: AGEP is a type of pustular reaction, which has been mainly reported in association with various drugs, although other etiologies such as viral infections due to human parvovirus B19, cytomegalovirus and Coxsackie B4, hypersensitivity to mercury, and spider bite have also been implicated. The main differential diagnosis of AGEP is pustular psoriasis. The two main histopathological features of AGEP, which have been described in literature, are a toxic pustuloderma with spongiform intraepidermal pustules, papillary edema, and a mixed upper dermal perivascular inflammatory infiltrate, or a leukocytoclastic vasculitis with neutrophil collections both below and within the epidermis, suggesting passive neutrophil elimination via the overlying epidermis. This study has tried to describe various histopathological features of AGEP after studying a large number of cases. It favors the earlier theory of toxic pustuloderma like histology, while the observation of the absence of vasculitis is contrary to the previous reports.

As leukocyte extravasation was observed in 54% of the cases, the previously reported high incidence of vasculitis could have been due to the misinterpretation of erythrocyte extravasation and / or leukocytoclasia as vasculitis, or a diagnostic confusion of AGEP with pustular vasculitis. Although there were some overlaps between the histopathological features of AGEP and PP, the classical features of PP, like the Munro's microabscess, absence of a granular cell layer, parakeratosis, suprapapillary thinning, tortuous, dilated vessels, and so on were uncommon. As shown by the earlier studies, this study also favored the idea of the different histological features of AGEP, according to the stage of the disease; like in the biopsies of the early lesions marked as moderate papillary dermal edema, a mixed dermal inflammatory infiltrate, often with erythrocyte extravasation, and some leucocytoclasia was seen, whereas, biopsies of well-developed lesions showed spongiform pustules within the epidermis and occasional dyskeratotic cells with residual perivascular dermal edema. The study also explained the eitopathogenesis of AGEP, based on the various histological features like eosinophils in skin biopsies in contrast to PP, which suggested that AGEP is a drug-induced hypersensitivity reaction; the necrotic keratinocytes in the biopsies suggested cytotoxic, drug-specific, T-cell damage; the dermal neutrophilic infiltrates pointed to the potent neutrophil attracting the chemokines secreted by the drug-specific T-cells and thus helping in sterile pustule formation. Thus, overall this study has enhanced our knowledge about the histopathological features of AGEP and provided us with vital clues to diagnose this particular condition, which is an important differential diagnosis of widespread pustular eruptions.

Van Velsen SG, Knol MJ, van Eijk RL, de Vroede MA, de Wit TC, Lam MG, *et al*. Bone mineral density in children with moderate-to-severe atopic dermatitis. J Am Acad Dermatol 2010;63:824-31.

Although topical corticosteroids represent the mainstay of treatment for atopic dermatitis (AD), there is widespread concern about their adverse effects. Systemic use of corticosteroids in children is known to be associated with a decrease in bone mineral density (BMD) and bone turnover. A high incidence of low bone mineral density has been observed in adults with moderate-to-severe AD. Topically applied corticosteroids have been observed to exert a systemic effect through percutaneous absorption, one of them being osteoporosis. Other than iatrogenic causes, intolerance or allergy to cow's milk and interference of physical activity in children with moderate-to-severe AD may also be the causes of low BMD. This study aims to determine the prevalence of low BMD in children with moderate-to-severe AD and the relationship between BMD and the treatments for AD. Lumbar spine BMD was measured by dual-energy X-ray

absorptiometry and was studied in 60 children, of age between 5 and 16 years. Inclusion criteria were scoring atopic dermatitis (SCORAD) greater than 20, more than four visits to the hospital on an outpatient basis in one year, inpatient treatment ever for AD, or current use of a potent topical corticosteroid, and a history or current use of prednisolone and / or cyclosporine. Several other factors that could affect bone health were the exclusion criteria. Information on lifestyle parameters and bone fractures was collected by a standardized questionnaire. The cumulative dose of corticosteroids, topical, inhaled, or oral, and cyclosporine therapy, was calculated using the pharmacy records for the previous five-year period. The results of the study showed that three patients (5%) had low BMD (Z - score < 2 without a significant fracture history); and one patient (1.7%) had osteoporosis (Z - score < 2 with a fracture history). The observed prevalence of low BMD in this study did not differ from the expected prevalence of low BMD in the general population. Thus, the authors concluded that overall, the use of topical corticosteroids in the previous five years was not associated with a decrease in BMD. When children received additional systemic treatment (oral corticosteroids and / or cyclosporine) in the previous five years, the BMD decreased, although the decrease was not statistically significant. Correction of lifestyle parameters did not change these associations.

Comments: Bone mineral density is used as an indicator of osteoporosis and fracture risk. Measurements are most commonly made over the lumbar spine and over the upper part of the hip. The value is usually studied in Z-scores, that is, the number of SD above or below the mean value of an age- and sex-matched reference population. During childhood and adolescence, the bone mineral density increases until a peak bone mass is reached. The peak bone mass and subsequent bone loss are important determinants of osteoporosis later in life. There are many factors that influence BMD in individuals, the most important being dietary intake of calcium and dairy products. The other significant factor that is known to have an association with low BMD is the long-term use of systemic corticosteroids. The association of topical corticosteroids with BMD has not been not studied. However, low BMD in adult population with atopic dermatitis is known. This study has estimated low BMD in atopic dermatitis children, but the incidence iss comparable to the general population of the same age group. No association has been found between low BMD and the use of topical corticosteroids in AD children. The limitations of the study are the small sample size and inaccuracy in the quantification of topical corticosteroids by the pharmacy records.

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