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FROM THE DESK OF CHIEF-EDITOR

'Team Quarterderm' is very happy to announce that Quarterderm has gained an ISSN Number; which is first step for getting our journal indexed in future. We are hopeful of getting the journal indexed very soon. I, as a chief editor Quarterderm would like to thank my associate editor Dr. Amit Mistry and co-editor Dr. Santosh Rathod for their prompt efforts in gaining ISSN number.

We never imagined becoming a part of Quarterderm will give all of us whole new identity. I received reviews from so many seniors, my teachers, colleagues and friends that I am certainly overwhelmed. I thank all of you who appreciate the work 'Team Quarterderm' is doing. I thank all for giving constructive feedbacks and suggestions. We will try to implement them as far as possible. Response to Quiz part of the journal is tremendous particularly PG students from all over Gujarat; reflecting the hunger for knowledge in all.

The feedbacks from members fill my heart with satisfaction of doing a good work and remind me of a poem by Sri Rabindranath Tagore whom I admire the most.

“So much of the unknown
You've made known to me
You've given me a place in so many homes
You've made the distant near, my friend,
And made stranger a brother
So much of the unknown
You've made known to me
You've given me a place in so many homes”

We will certainly see that this knowledge journey continues. We hope that you keep on reading and enjoying as much we are enjoying putting it in front of you all. Knowledge has no boundaries. In era of explosion of information, we have tried to cover certain basic and fundamental issues encompassing dermatology in a simple manner.
Keep on reading!

Dr. KRINA BHARAT PATEL
Chief Editor

INSTRUCTIONS FOR AUTHORS

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EDITORIAL ARTICLE

Immunofluorescence Simplified: How to interpret the findings in immune-bullous disorders.

Dr. Santosh Rathod

Abstract: Before a specific diagnosis of an immunologically mediated blistering disease can be made, the clinical and histologic features and the results of direct and indirect immunofluorescence studies (with use of multiple substrates in some cases) must be assessed. For both subepidermal and intraepidermal groups of blistering diseases, direct immunofluorescence testing of perilesional tissue is critical for diagnosis. For these conditions, indirect immunofluorescence testing of serum is important for diagnosis and has a role in management of selected diseases. In dermatitis herpetiformis, indirect testing of serum for IgA antiendomysial antibodies is useful for both diagnosis and management. Indirect testing of serum for IgG antibodies to intercellular substance is important for diagnosis and, in conjunction with the clinical findings, can be used as a guide for monitoring disease activity in patients with pemphigus. From a practical standpoint, however, direct and indirect immunofluorescence testing, in conjunction with clinical and histologic evaluations, is a simple, rapid, and relatively inexpensive tool for diagnosis and management.

Interpretation:

Direct immunofluorescence
In interpreting an immunofluorescence specimen, four main features of fluorescence are particularly important:

a) main site of deposition;
b) the class of immunoglobulin or type of immunoreactant;
c) the number of immunoreactants; and
d) any deposition in other sites besides the main site. Using these features, a logical and practical approach can lead to an accurate diagnosis in the vast majority of specimen

A. Intercellular Space (ICS) Deposition
Intercellular space (ICS) immunoreactant deposition is seen in pemphigus group.[2] When fluorescence is observed at the inter-cellular space, it is important to note the class of immunoglobulins deposited, their preferential binding to different levels within the epidermis and any associated deposition at other sites.
Deposition of IgG in the ICS only

Deposition of IgG in the epidermal ICS is the hallmark of pemphigus group of diseases.
Pemphigus vulgaris, pemphigus foliaceus and their variants

Positive immunofluorescence is seen in 100% patients with active disease, if an appropriate biopsy has been obtained.[3] The IgG belong to IgG1 and IgG4 subclasses. The pattern of fluorescence appears as typical linear deposition on the surfaces of keratinocytes. It resembles a "Chickenwire or net-work pattern". The epidermal ICS fluorescence seen in both pemphigus vulgaris and pemphigus foliaceus and their variants can be identical; but often fluorescence is limited to or predominant in suprabasal area in PV and the upper epidermal area in PF. However, it is not reliable enough to be used diagnostically. Complement component C3 may be seen in a pattern similar to that of IgG, but with lower frequency and intensity.[1] However, the diagnosis of pemphigus should not be made when only C3 is deposited.

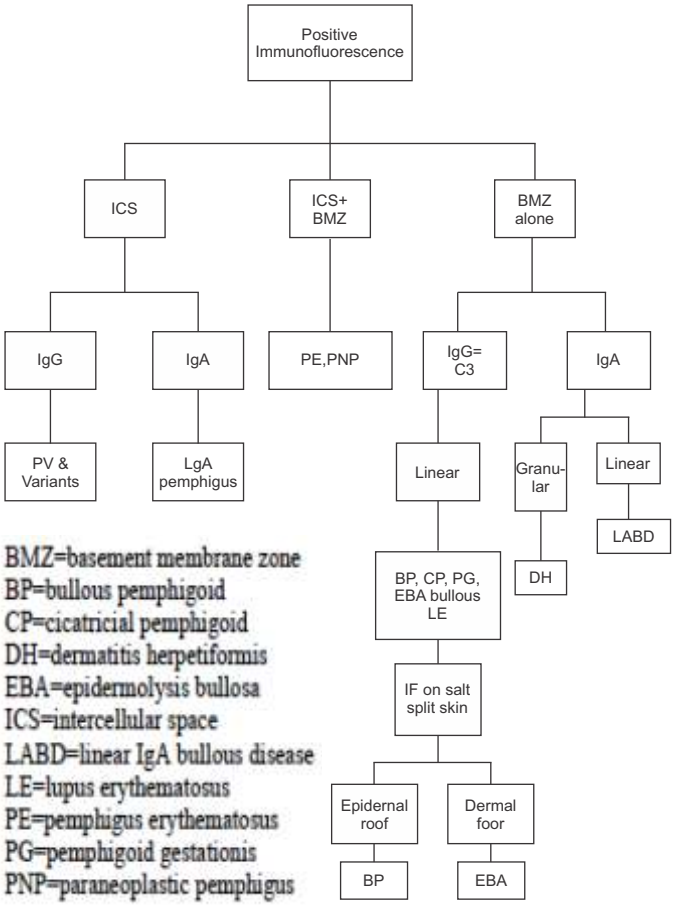

Figure: An algorithmic approach in case of direct immunofluorescence

In PV patients, negative DIF finding is a good indicator of remission, as patients with positive results of DIF had major relapses within three months of cessation of therapy.

ii) *IgA deposition in the ICS*

If the deposition of immunoreactants in the ICS consists exclusively or predominantly of IgA, the diagnosis of *IgA pemphigus* is made. Intercellular deposition of IgA is observed in the upper epidermis in subcorneal pustular dermatosis (SPD)-type and in the entire epidermis in the intraepidermal neutrophilic (IEN)-type. Patients with pemphigus having both intercellular IgG and IgA antibodies should be differentiated from IgA pemphigus. Aggregated IgA deposits in the stratum corneum in the pustules differ from the pemphigus-like deposits in IgA pemphigus.

B. Deposition in the ICS and BMZ

The presence of basement membrane zone deposition, in addition to ICS deposition of IgG, is seen in pemphigus erythematosus and paraneoplastic pemphigus. In *pemphigus erythematosus*, the fluorescence at BMZ is granular or as a fibrillar band of immune deposits, in addition to a net-work pattern at ICS.[3]

In *PNP*, IgG and C3 are deposited in the ICS and BMZ; however, false-negative DIF is more commonly noticed in PNP than in other forms of pemphigus.[11]

C. Basement Membrane Zone Deposition

When deposition of immunoreactants in the BMZ is studied, four features have to be observed, which include a) the type of immunoreactants, b) their number, c) morphologic pattern, and d) deposition present at any other site.[3]

i) *IgG or C3 deposition at the BMZ*

Deposition of IgG and/or C3, and occasionally other immunoreactants exclusively at the BMZ is seen in BP, CP, PG, EBA, and bullous LE. It is not always easy to differentiate these diseases on the basis of DIF alone. Indirect IF may be needed to confirm the diagnosis. In BP and PG the deposition consists predominantly and occasionally exclusively (especially in PG) of C3.[3] They are present in a continuous, fine and linear pattern.[3]

Bullous pemphigoid Linear deposits of IgG and C3 are observed in nearly 100% and approximately 90% of cases, respectively.[7] IgG4 is the predominant isotype. DIF on salt-split specimen shows epidermal mapping in about 50% of cases whereas it is combined in the rest. C3 is of less diagnostic significance. DIF is less sensitive in localized pemphigoid than generalized type. If the perilesional skin is not available for biopsy then anterior aspect of thigh or flexor aspect of forearm is a suitable alternative site. Biopsy specimens from the legs have a lower yield of positivity.

DIF in lichen planus pemphigoides shows C3 deposits at BMZ.

Pemphigoid gestationis Homegeneous linear deposits of C3 at the BMZ are seen in almost all active cases.[8] In 30-50% of cases, IgG (IgG1 subclass) may also be present. However, using monoclonal antibodies, IgG1 was demonstrated in all cases. Other immunoreactants infrequently reported include IgA, IgM, C1q, C4 and other complement components. DIF findings may persist for several months after the resolution of cutaneous lesions.

Cicatricial pemphigoid Linear deposits of IgG (IgG4 isotype) along with C3 are seen. IgA, IgM, fibrin are rarely seen. DIF on salt-split skin reveals usually epidermal-dermal pattern.[1,8]

EBA and bullous LE Both are characterized by tendency for multiple immunoreactant deposition at the BMZ and a different morphologic pattern of deposition.[3] In EBA, intense IgG (IgG1 and IgG4 subclasses) is almost always present, followed by C3 and then IgA and IgM with more variable and relatively weaker intensity.[3] The BMZ deposition tends to be in a thick, broad and homogeneous band.[2] In bullous LE, as in EBA, IgG is invariably present at the BMZ followed by IgA (two thirds) and IgM (one half).[3] In bullous LE, 60% cases show a pattern of deposition similar to that of EBA and in 40% the deposition is in a granular pattern similar to that of non-bullous LE. In the absence of clinical history, it is impossible to distinguish EBA form bullous LE. The only distinguishing feature between bullous LE and EBA is the presence of other serologic evidence of SLE.[3]

Differentiation of BP and EBA

DIF studies are of limited value in distinguishing between BP and EBA because both are characterized by linear deposition of complement and immunoglobulin along the BMZ. Electron microscopy, immunoelectron microscopy and Western blotting differentiate the two diseases, but these are time-consuming, expensive and are available at few centers. The use of DIF and IIF tests on either salt-split patient skin or salt-split substrate, respectively is helpful in resolving this dilemma.[15] IIF on salt-split substrate reveals epidermal binding in BP whereas dermal binding occurs in EBA. Dermal deposition is infrequently seen in anti-laminin 5 CP and protein 105 BP. Nonetheless, approximately 25% of BP patients and 50% of EBA patients do not possess detectable circulating antibodies, therefore IIF on salt-split skin is of no help for a great number of patients. In these cases DIF on salt-split skin can distinguish between BP (deposition in the epidermal roof) and EBA (deposition in the dermal floor) with certainty.[21]

Fluorescent overlay antigen mapping is another technique used to differentiate between BP and EBA. Using different fluorescent markers, mapping the known location of red-labelled type VII collagen to the unknown location of green-labelled IgG deposits is done. In BP, a nonoverlapping pattern composed of interfacing and partially merging red and green bands is seen which differs from overlapping pattern of EBA.[2] *ii) IgA deposition*

at the BMZ only
Given the clinical and histopathologic overlap that exists between DH, linear IgA disease and other subepidermal bullous diseases, the IF findings are of paramount importance in distinguishing between these disorders.

Dermatitis hepetiformis The most specific immunopathologic finding and diagnostic criterion of DH is the granular deposition of IgA in the papillary dermis of uninvolved skin.[3] Granular deposits are usually located at the tips of dermal papillae within the microfibril bundles but they may also extend as a band along the BMZ especially if the epidermis is flat. IgA belongs to IgA1 subclass, IgA2 was found in one study. J-chains and secretory components are also present, suggesting that IgA is of mucosal origin. C3 is commonly found particularly in patients who are not on gluten-free diet.

Linear IgA disease Both childhood form and adult LAD will show a linear band of IgA deposition at the BMZ. IgA belongs to IgA1 isotype and lacks J-chains and secretory component. Rarely, other immunoreactants such as C3, IgM and IgG are found with IgA by direct IF. DIF on salt-split skin gives heterogeneous pattern, dermal, epidermal and combined, all are reported.

II. Indirect Immunofluorescence (IIF)
While interpreting IIF, it is important to note a) the class of circulating antibody; and b) the site of its binding. The vast majority of circulating antibodies belong to the IgG class in BP, CP, PG, EBA and bullous LE. IgA is characteristic of LAD and IgA pemphigus. No circulating antibodies are demonstrable in DH.[3]

A. Anti-ICS antibodies

i) IgG class

Pemphigus Circulating IgG anti-ICS antibodies in a chicken wire pattern are characteristic of PV (80-90%), PF (60-80%), PE, some cases of drug-induced pemphigus and PNP.[3,11] Monkey esophagus is the sensitive and specific substrate for PV and guinea pig tissue (esophagus or lip) is the preferred substrate for PF. The titer of anti-ICS antibodies correlates with the activity of pemphigus and thus can be used to follow progress and response to therapy. [3]

Paraneoplastic pemphigus In addition to ICS, some IgG deposits are also seen at BMZ. Antibodies in PNP differ from those of other forms of pemphigus in that they bind the ICS of simple and transitional epithelia (rodent bladder) in addition to stratified squamous epithelia.[3] Immunoprecipitation studies are more sensitive than IIF but are more time consuming and expensive.[11]
ii) IgA Class
IgA pemphigus IgA anti-ICS antibodies are characteristic of IgA pemphigus.[3] These are detected in about 50% of cases. Deposition occurs in the upper epidermis in SPD-type and entire epidermis in IEN-type.

B. Anti-BMZ antibodies

i) IgG class

These antibodies are present in the sera of patients with BP, CP, PG, EBA and bullous LE. A positive result of IIF does not differentiate among the various IgG-mediated subepidermal bullous diseases, although binding tends to be broader and more homogeneous in EBA than in pemphigoid variants.[3]

Bullous pemphigoid The frequency of a positive result of IIF on intact substrates is approximately 70-80% for BP. They are not predictive of disease severity. IIF on salt-split skin, reveals circulating autoantibodies in 90% of patients, and these usually bind to epidermal roof.[3] Using monoclonal antibodies, it has been shown that serum autoantibodies are mainly anti-BP230. Serum level of anti-BP180 correlates with the disease activity and can be used as a guide for therapy.
Pemphigoid gestationis IgG (IgG1 class) serum anti-BMZ antibodies are detected in only 20% of patients but can be demonstrated in 100% of cases if monoclonal antibodies are used. HG, an avidly complement-fixing IgG antibody, is found in 50% of cases.[1,]

Cicatricial pemphigoid Circulating autoantibodies are found in 20% of cases and these give heterogeneous pattern on salt-split specimen.[1,]
Lichen planus pemphigoides IgG deposits are seen at BMZ.

Epidermolysis bullosa acquisita About 50% of patients with EBA have serum autoantibodies.[3] IIF on salt-split skin shows the dermal pattern of deposition. This is helpful in differentiating between EBA and BP.

ii) IgA class
Linear IgA disease Circulating autoantibodies are found in 80% of children and 30% of adults with LAD. These belong to IgA1 subclass. Normal human skin and monkey esophagus both can be used as substrate. IIF on salt-split substrate demonstrates epidermal, dermal and combined patterns, with epidermal being the most common.[1]

Advantages of Immunofluorescence
Immunofluorescence is a relatively simple and reproducible technique. One advantage of the technique is the short procedure time. The complete procedure including the preparation of sections, their staining and observation can be performed in one to three hours.[4]
Another characteristic is its sensitivity. The sensitivity of the direct method seems to correspond to that of the classical complement fixation test.[4] Sensitivity of the indirect or complement method is estimated to be between five and ten times higher than that of the direct

one. IIF, besides the diagnostic importance, has a substantial prognostic value, particularly for pemphigus cases.

Disadvantages of immunofluorescence
Immunofluorescence technique is based on a delicate immune reaction. Careful examination and selection of materials, and skillful observation and judgment must be made under adequate optical systems for proper evaluation. Specific fluorescence must be distinguished from nonspecific fluorescence.

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REVIEW ARTICLE

ADVANCES IN PEMPHIGUS THERAPY

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ABSTRACT

The pemphigus variants represent a group of potentially life-threatening autoimmune mucocutaneous blistering diseases. Though systemic corticosteroids have dramatically reduced the rate of disease mortality, current therapeutic options are limited by their toxicity profiles. Advancements in our understanding of the molecular mechanisms involved in the pathogenesis of pemphigus have translated into the development of novel therapies. However, few treatments have been subject to randomized controlled trials to firmly establish therapeutic efficacy. Herein, we focus on the new and emerging therapies in the management of pemphigus.

Key Words: pemphigus, autoimmune skin disease

Pemphigus represents a group of rare autoimmune mucocutaneous blistering disorders. The 2 main subtypes are pemphigus vulgaris (PV) and pemphigus foliaceus (PF), each with its own clinical variants. Less common forms include paraneoplastic pemphigus, IgA pemphigus, and pemphigus herpetiformis. Since PV is the most common subtype of pemphigus in india, it will be the focus of this article.

PV affects both genders equally and has a mean age of onset of 50-60 years. Presentation at relatively young age is common in india. Patients often present with multiple, painful erosions or flaccid bullae on the skin and/or mucous membranes. Mucosal disease precedes cutaneous involvement in the majority of the cases.[1]

The disease is mediated by circulating immunoglobulin G (IgG) autoantibodies against the desmosomal cadherins, desmogleins 1 and 3. Histopathology reveals a loss of cell-cell adhesion (acantholysis) in the suprabasilar layer of the epithelium and direct immunofluorescence (DIF) of perilesional skin reveals intercellular deposition of IgG +/– C3. As antibodies often correlate with disease activity, indirect immunofluorescence (IIF), immunoblots, and enzyme-linked immunosorbent assays (ELISA) are commonly used to quantify circulating antibody levels.

If left untreated, PV is frequently fatal with a mortality rate ranging from 60% to 90%. While systemic corticosteroid use and other therapeutic advances have reduced this mortality rate to approximately 10%, complications from treatment are now the primary cause of morbidity and mortality in this population. The goal of managing pemphigus patients is, therefore, to induce and maintain remission with the lowest possible doses of medication, so as to minimize the risk of serious and potentially fatal adverse effects.

Conventional Therapies

Systemic corticosteroids remain the treatment of choice for pemphigus as they are both effective and capable of inducing a rapid remission. However, adverse effects of corticosteroids are both time- and dose-dependent.[2] They include weight gain, diabetes, hypertension, glaucoma, cataracts, osteoporosis, avascular necrosis, peptic ulcer disease, adrenal insufficiency, electrolyte and lipid abnormalities, psychosis, immunosuppression, and increased susceptibility to infections.[2] Adjuvant therapies are, therefore, used to provide a steroid-sparing effect. As these treatments typically have a slower onset of action (i.e., 4-6 weeks), they are most beneficial as maintenance therapies. Conventional adjuvants include various immunosuppressive agents such as azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, chlorambucil and cyclopsorine, as well as anti-inflammatory agents such as gold, dapsone, colchicine and a variety of tetracycline antibiotics (Table 1).Unfortunately, these medications are often associated with significant toxicities and must be used with caution. Though the majority of patients will ultimately respond to conventional therapies, few patients develop recalcitrant disease.

Emerging Therapies

Over the years, advances have been made to expand our therapeutic armamentarium for pemphigus. Emerging therapies include intravenous immunoglobulin (IVIg), plasmapheresis, immunoadsorption (IA), extracorporeal photochemotherapy (ECP), rituximab, tumor necrosis factor-alpha (TNF-á) antagonists (infliximab and etanercept), cholinergic agonists, and other experimental therapies such as desmoglein 3 peptides and KC706.

Intravenous Immunoglobulin (IVIg)

IVIg is a fractionated and purified blood product derived from the plasma of between 1,000 and 15,000 healthy donors per batch. It contains a high concentration of IgG and has a broad range of antibodies directed against

pathogens, foreign antigens, and self-antigens.[3] Although its exact mechanism of action remains unclear, IVIg is associated with a rapid and selective decline in the serum levels of pathogenic PV autoantibodies.[4]

Drug Type	Systemic Agent	Mode of Administration	Dose
Systemic Corticosteroids	Prednisone	Oral	1-2mg/kg/d
	Dexamethasone	Oral or IV pulse	50-200mg/d for 3-5 d
	Methylprednisolone	IV pulse	500-1,000mg/d for 3-5 d
Immunosuppressive and Anti-inflammatory Agents	Azathioprine	Oral	3-4mg/kg/d
	Chlorambucil	Oral	0.05-0.2mg/kg/d
	Colchicine	Oral	1.2-1.8mg/d
	Cyclophosphamide	Oral	2-3mg/kg/d
		IV pulse	0.5-1g/m2 monthly
		Immunoablative high-dose (IV)	50mg/kg/d for 4 d
	Cyclosporine	Oral	2-5mg/kg/d
	Dapsone	Oral	50-200mg/d
	Erythromycin	Oral	1,200mg/d
	Gold	IM injection	25-50mg/biweekly
		Oral	6-9mg/d
	Leflunomide	Oral	20mg/d
	20mg/d	Oral, SC, IM or IV	5-30mg/wk
	Minocycline	Oral	100-200mg/d
	Mycophenolate mofetil	Oral	30-45mg/kg/d
	Tetracycline +/- Nicotinamide	Oral	1-2g/d1,500-2,000mg/d
Biologic Agents	Etanercept	SC injection	50mg weekly
	Infliximab	IV infusion	5mg/kg/cycle
	Intravenous Immunoglobulin (IVIg)	IV infusion	2g/kg/cycle
	Rituximab	IV infusion	375mg/m2 weekly for 4 weeks; OR 1,000mg on days 1 and 15†

Table 1: Therapeutic doses for immunomodulatory drugs used in the treatment of pemphigus.
IV = intravenous, IM = intramuscular, SC = subcutaneous
† Weight-independent dosing schedule based on unpublished observations.

Three case series and 1 retrospective analysis document the efficacy of IVIg in PV. The dosage and frequency of IVIg infusions were comparable between the studies. In all 4 studies, treatment with IVIg resulted in a rapid clinical response and a corticosteroid-sparing effect. In 2 retrospective analyses, however, IVIg demonstrated a less favorable response.[5,6] As the published studies are limited by their methodologies and small sample sizes, a Canadian multi-centre randomized controlled trial is underway to establish the role of IVIg in the management of PV patients.

Plasmapheresis

Plasmapheresis is the process by which plasma is removed from blood using a cell separator. The blood cells and an appropriate plasma substitute are then returned to the patient undergoing treatment. As antibodies are contained within plasma, plasmapheresis results in the removal of the pathogenic PV autoantibodies. In a multicenter study, PV patients (n=40) were randomized to receive prednisolone alone or prednisolone plus large-volume plasma exchange.[7] While plasmapheresis failed to demonstrate a therapeutic benefit in this study, it has been suggested that an additional immunosuppressive (i.e., cyclophosphamide) or immunomodulatory (i.e., IVIg) therapy may be required to prevent the rebound production of pathogenic autoantibodies associated with disease flares. Multiple case series have evaluated the efficacy of plasmapheresis in treating PV. Of the 28 patients evaluated in these studies, 18 (64%) experienced complete remission, 6 (33%) experienced partial remission and 4 (22%) had no clinical improvement. Adverse effects encountered included systemic infections, acute hepatitis, thrombocytopenia, anemia, hypocalcemia, nausea, dizziness, urticaria, fever, and hypotension.

Immunoadsorption (IA)

IA consists of collecting patient plasma, passing it through an adsorber column (i.e., Protein A) to remove circulating immune complexes and IgG and then returning the filtered plasma to the patient.[8] Four case series and 2 case reports document the efficacy of IA for the treatment of recalcitrant PV. Though patients were allowed to remain on concomitant immunosuppressive therapies, IA resulted in a dramatic clinical response and a rapid decline in desmoglein-specific IgG autoantibodies. In the study by Schmidt, et al., a corticosteroid-sparing effect was observed. More recently, a small case series demonstrated that IA, administered in combination with rituximab, may result in long-term remission. In all studies, IA was safe and well tolerated.

Extracorporeal Photochemotherapy (ECP)

In ECP, also known as photopheresis, a patient's white blood cells are collected (leukapheresis), exposed to 8-methoxypsoralen, irradiated with ultraviolet-A light and reinfused into the patient. The proposed mechanism of action may involve inhibition of pathogenic autoantibody production by B lymphocytes. There are only 2 small case series and 2 case reports in the literature that document the use of ECP for refractory PV.[9] Of the 9 PV patients treated with ECP in these studies, all experienced significant clinical improvement, and no adverse effects from ECP were noted.

Rituximab

Rituximab is a chimeric murine/human IgG1 anti-CD20 monoclonal antibody that targets pre-B and mature B lymphocytes, resulting in complement and antibody-dependent cytotoxicity and apoptosis. Rituximab reduces circulating B cells, thereby preventing their maturation into antibody-producing plasma cells. Multiple case reports suggest that rituximab is an effective treatment option for PV.[10] Of the 18 patients with refractory PV reviewed, 3 (17%) experienced complete remission, 4 (22%) experienced clinical remission with further therapy required and 11 (61%) experienced partial remission. Systemic infections occurred in 4 of the 18 patients, resulting in 1 fatal outcome.

The largest clinical study evaluating the use of rituximab in PV has been a case series of 14 patients with refractory PV in which 12 (86%) experienced a complete remission at 3 months after a single cycle of rituximab.This agent was also shown to be effective when used in combination with IVIg. In a series of 11 patients with extensive, recalcitrant PV, 9 (82%) experienced a clinical remission lasting between 22-27 months with combination therapy.

Tumor Necrosis Factor-alpha (TNF-á) Antagonists

TNF-á antagonists may be beneficial for the treatment of PV as experimental studies have demonstrated that TNF-á plays a role in the acantholytic process. Two case reports document the successful use of infliximab for refractory PV.[11] Two additional case reports have shown clinical improvement of PV with the use of etanercept.[44,45]Clinical trials for both infliximab and etanercept are currently underway.

Cholinergic Agonists

Research suggests that acetylcholine and its receptors are involved in the acantholytic process of pemphigus. To date, only 2 clinical studies have been performed. In a case series of 6 patients with active PV, 3 (50%) experienced clinical improvement with the cholinergic agonist pyridostigmine bromide (Mestinon®, Valeant Pharmaceuticals).Two of the 3 responders were able to control their disease with pyridostigmine bromide alone and 1 patient was able to remain in remission without any medications. In a recent double-blind, placebo-controlled trial of 3 PV patients with a total of 64 lesions, those lesions treated with 4% pilocarpine gel were found to have a significantly higher epithelialization index compared with placebo.

Other Experimental Therapies

Selective therapy using intravenous desmoglein 3 peptides was developed to suppress the production of anti-desmoglein 3 antibodies through inactivation and/or deletion of disease-associated CD4+ T lymphocytes.[12] However, an open-label phase I clinical trial of PI-0824 failed to demonstrate significant changes in anti-desmoglein 3 antibody titres following treatment with 2 IV infusions of desmoglein 3 peptides.[12]

A novel therapy, KC706 (Kémia, Inc.) is an oral allosteric p38 mitogen-activated protein kinase (p38MAPK) inhibitor. In a murine model of pemphigus, p38MAPK inhibition prevented blister formation.[13] A clinical trial is underway to determine the safety and efficacy of KC706

in the management of PV.

Conclusion

While corticosteroid therapy remains the mainstay of treatment for PV, the morbidity associated with its use is significant. Conventional immunosuppressive and anti-inflammatory therapies are further associated with serious and potentially life-threatening adverse events. With an improved understanding of PV pathogenesis, a number of novel therapies have been developed. Though many of these therapies appear promising, case reports and case series dominate the dermatologic literature. Randomized controlled trials are urgently required to establish their efficacy and safety in the management of pemphigus patients.

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REVIEW ARTICLE

DIFFERENTIAL DIAGNOSIS OF VESICULOBULLOUS DISORDERS IN CHILDREN

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The approach to the child with vesiculobullous disease is a complicated and challenging task given the vast differential diagnosis as well as the great concern a blister can evoke. The causes may range from the fairly innocuous ones, like insect bites to the far more sinister immune mediated and hereditary blistering conditions.

The classification of bullous or vesiculobullous disorders is based on clinical morphology and examination of biopsied specimens of lesional or perilesional skin by light microscopy, immunofluorescence analysis, and electron microscopy. It is well recognized that the skin of infants and children is more susceptible to blister formation than that of adults.

A few key factors in the differential diagnosis of a child or infant with a vesiculobullous disease include:

1) Whether the vesiculobullous process is a manifestation of an underlying systemic illness
2) The age of onset
3) The family history of blistering
4) The distribution of lesions
5) The morphology of lesions
6) The pattern of eruption

A few representative differentials considering the above variables are as follows:

1) Whether the vesiculobullous process is a manifestation of an underlying systemic illness:

a) Infections:
- Viral:
  - o Herpes (herpes simplex, herpes varicella zoster), cytomegalovirus,
  - o Epstein-Barr virus, coxsackievirus, poxvirus (variola, monkeypox)
- Fungal:
  - o Candidiasis (neonatal cutaneous versus congenital)
  - o Aspergillus
- Bacterial:
  - o Gram-positive organisms:
  - o Treponema pallidum
  - o Staphylococcus (impetigo neonatorum, SSSS)
  - o Streptococcus (particularly group B ? haemolytic)
  - o Bacillus anthracis
  - o Listeria monocytogenes (especially in neonates)
  - o Gram-negative organisms:
  - o Chlamydia trachomatis
  - o Escherichia coli
  - o Haemophilus influenzae
  - o Klebsiella pneumoniae
  - o Pseudomonas aeruginosa

b) Inflammatory conditions:
- Vasculitis: eg. Bullous Henoch - Schönlein purpura

c) Drug reactions:
- Bullous erythema multiforme
- Toxic epidermal necrolysis
- Acute generalized exanthematous pustulosis
- Fixed drug eruptions
- Photoallergic drug reactions
- Phototoxic drug reactions
- Bullous drug eruptions

2) The age of onset: the differentials of onset of blistering in the neonatal age group (whether at birth or during the first 72 hours of life) differ from those in older children:

a) Infection (as above)

b) Infestations:
Scabies

c) Inflammatory dermatosis:
Miliaria
Neonatal eosinophilic pustulosis
Erythema toxicum neonatorum
Transient pustular melanosis
Bullous Mastocytosis

d) Genodermatoses:
Epidermolysis bullosa
Incontinentia pigmenti
Bullous CIE

e) Autoantibody-mediated disorders:
Pemphigus vulgaris
Pemphigus foliaceus
Herpes gestationis

f) Metabolic:
Acrodermatitis enteropathica

g) Traumatic:
Sucking blisters

3) The family history of blistering:

a) Presenting at birth or in immediate postpartum period:

Mechanobullous genodermatoses:
- EB
- Junctional
- Dystrophic
- Incontinentia pigmenti
- Bullous CIE
- Kindler syndrome

Autoantibody-mediated disorders:
- Pemphigus vulgaris
- Pemphigus foliaceus
- Bullous pemphigoid

b) Delayed onset:

Mechanobullous genodermatosis
- EB Simplex

Hailey-Hailey disease (benign familial pemphigus)

Photosensitivity disorders:
- Porphyria cutanea tarda
- Porphyria variegata
- Congenital erythropoietic porphyria

4) The distribution, particularly whether the blisters are localized or generalized:

a) Localized:

Infections:
- Viral:
  - Herpes simplex
  - Herpes zoster
  - Hand-foot-mouth disease
  - Poxvirus (molluscum contagiosum)
- Bacterial:
  - Impetigo
  - Bullous cellulitis
- Fungal:
  - Candidiasis
  - Bullous tinea

Infestation

Insect bites and stings

Acute dermatitis:
- Allergic contact or irritant dermatitis
- Cheiro- or podopompholyx

Physical agents:
- Burns
- Friction
- Radiation
- Chemical irritants/agents

Inflammatory conditions:
- Fixed drug eruption
- Acropustolosis of infancy
- Acrodermatitis of Hallopeau (localized pustular psoriasis)

Photosensitivity disorders:
- Phototoxic
- Photoallergic
- Phytophotodermatitis

Coma blisters

b) Generalized:

Miliaria:
- Miliaria crystillina
- Miliaria rubra
- Miliaria profunda

EM

Pustular psoriasis

Urticaria pigmentosa

Infections: Barring those listed above

5) The morphology of lesions (flaccid versus tense blisters) and the presence of secondary changes (crusting/erosions/ulcers/scarring/milia):

a) Flaccid vesicle/bulla => Intraepidermal split:

Rupture easily

Lead to erosions, scales and crusting

Does not cause pigmentary change and scarring unless secondarily infected

Asboe - Hansen sign positive (the blister can be spread into adjacent normal skin)

Nikolsky sign positive (blistering can be induced by rubbing normal appearing skin)

b) Tense vesicle/bulla => Subepidermal split:

Not so fragile

Commonly cause pigmentary changes and/or scarring; may heal with milia Mechanobullous and Immunobullous disorders are the major groups among the de-novo, primarily blistering disorders. Representative conditions of the mechanobullous subgroup are discussed below in brief:

Mechanobullous disorders - epidermolysis bullosa:
The term epidermolysis bullosa (EB) refers to a group of inherited disorders characterize by bullous lesions that develop spontaneously or as a result of varying degrees of friction or trauma. At least 20 distinct types, based on identification of mutations in various genes encoding proteins and clinical symptoms have been described.

The current classification of EB is as follows:

a) Epidermolysis Bullosa Simplex (EBS):

EBS localized (Weber-Cockayne)

EBS generalized, other (Köbner)

EBS Dowling-Meara

EBS with mottled pigmentation

Autosomal recessive EBS (not associated with muscular dystrophy)

EBS with muscular dystrophy

EBS Ogna

EBS superficialis

Skin fragility - ectodermal dysplasia syndrome

Lethal acantholytic EB

b) Junctional Epidermolysis Bullosa (JEB):
Herlitz JEB
Non-Herlitz JEB
JEB with pyloric atresia
Laryngo-onycho-cutaneous syndrome

c) Dystrophic Epidermolysis Bullosa (DEB):
Dominant DEB
Severe generalized recessive DEB
Recessive DEB, generalized other

d) Kindler's syndrome

Now discussing each in brief:

a) Epidermolysis Bullosa Simplex (EBS):

EBS localized (Weber-Cockayne):
- o Autosomal Dominant
- o Protein defect: Keratin 5, keratin 14
- o Gene defect: KRT5, KRT14
- o Most common form of EB
- o Begins in childhood or adolescence; may occasionally present in adulthood
- o Localized to hands and feet
- o Aggravated by warm weather
- o Erythematous halo present around blisters even in absence of secondary infection
- o Hyperhidrosis common
- o May have focal keratoderma of palms and soles in adults, usually mild
- o Nails are not usually affected
- o Lesions usually heal rapidly without scarring, in absence of secondary infection

EBS generalized, other (Köbner):
- o Autosomal Dominant
- o Protein defect: Keratin 5, keratin 14
- o Gene defect: KRT5, KRT14
- o Presents with generalized blistering within the first year of life; may present at birth; Improves with advancing age
- o Blisters tend to be more common on distal extremities, especially the feet, knees, elbows and hands
- o Variable mucosal involvement
- o Nail involvement in 20% cases, usually without dystrophy
- o Focal palmoplantar keratoderma
- o Lesions usually heal rapidly without scarring, in absence of secondary infection

EBS Dowling-Meara:
- o Autosomal Dominant
- o Protein defect: Keratin 5, keratin 14
- o Gene defect: KRT5, KRT14
- o Also known as EB Herpetiformis
- o Onset in early infancy. Most severe in neonate, infant; improves beyond childhood
- o Generalized blistering present, common on palms and soles, also on face, trunks and limbs. Lesions are usually grouped - arcuate or annular patterns - with an erythematous border
- o Oral mucosa involvement present, including esophageal
- o Blisters may be even more often haemorrhagic than in other forms of EBS; milia may be a transient feature after blisters have healed.
- o Nails may be shed and regrow; a characteristic thickening may be present even during the neonatal period
- o Hyperkeratosis of palms and soles

EBS with mottled pigmentation:
- o Autosomal Dominant
- o Protein defect: Keratin 5
- o Gene defect: KRT5
- o Generalized blistering which heals without scarring or atrophy
- o The mucosae are generally not affected.
- o Blistering becomes less prominent with increasing age and may even disappear.
- o Reticulated?hyperpigmentation in the form of well - demarcated pigmented macules 2 - 5 mm in diameter, most profuse on the trunk and the proximal limbs
- o Punctate?keratoses?and?keratoderma

Autosomal recessive EBS (not associated with muscular dystrophy):
- o Autosomal Recessive
- o Protein defect: keratin 14
- o Gene defect: KRT14
- o Very rare

EBS with muscular dystrophy:
- o Autosomal Recessive
- o Protein defect: Plectin
- o Gene defect: PLEC1
- o Generalized blistering is of early onset, with an acral preponderance, atrophic scarring and nail dystrophy
- o Laryngeal involvement may give rise to considerable respiratory
- o compromise
- o Focal palmar and plantar hyperkeratosis
- o Progressive muscular dystrophy between the first year and the fourth decade of life

EBS Ogna:
- o Autosomal Dominant
- o Protein defect: Plectin
- o Gene defect: PLEC1
- o Blistering on the hands and feet predominantly and the presence of bruising
- o No neuromuscular involvement
- o Very rare

EBS superficialis:
- o Autosomal Dominant

- o Protein defect: unknown
- o Gene defect: unknown
- o Not associated with scarring, but milia and nail dystrophy may be present.
- o Very rare

Skin fragility - ectodermal dysplasia syndrome:
- o Autosomal Recessive
- o Protein defect: Plakophilin-1
- o Gene defect: PKP1
- o Characterized by sparse hair, nail dystrophy, dental abnormalities, skin fragility, focal palmoplantar keratoderma and, in some cases, reduced sweating
- o Very rare

Lethal acantholytic EB:
- o Autosomal Recessive
- o Protein defect: Desmoplakin
- o Gene defect: DSP
- o Presents at birth with generalized denudement and absence of hair and nails.
- o Frank blisters are not seen, but the skin peels in sheets. Mucosal sloughing is severe and affected neonates are born with teeth.
- o All babies to date have died in the neonatal period.
- o Very rare

b) Junctional Epidermolysis Bullosa (JEB):

Herlitz JEB:
- o Autosomal Recessive
- o Protein defect: Laminin 332
- o Gene defect: LAMA3, LAMB3, LAMC2
- o Severe form usually fatal before the age of 5years
- o Blisters appear in the neonatal period; may appear deceptively mild at onset
- o Oral mucosa is usually affected, causing failure to thrive from poor nutrition
- o Laryngeal involvement is common; may present with hoarse cry
- o Nonhealing granulation tissue (mid-face, neck, spine, ears and nail beds) is characteristic
- o Bacterial infection occurs frequently
- o Periungual and fingerpad blistering,erythema
- o Anonychia
- o Dental enamel hypoplasia,excessive caries
- o Respiratory, GI and genitourinary systems can be involved
- o Growth retardation
- o Anemia
- o Blisters heal with atrophic scarring,but no milia

Non-Herlitz JEB:
- o Autosomal Recessive
- o Protein defect: Type XVII collagen, Laminin 332
- o Gene defect: COL17A1, LAMC2
- o Less severe, but similar manifestations as Herlitz type, including dental, nail and laryngeal involvement
- o May be generalized or localized
- o Granulation tissue is rare
- o Perinasal?cicatricization
- o Less mucosal involvement
- o Alopecia
- o Dental and nail abnormalities as in JEB-H
- o Anemia, but not as severe as JEB-H

JEB with pyloric atresia:
- o Autosomal Recessive
- o Protein defect: Integrin ?6?4, plectin
- o Gene defect: ITGA6, ITGB4, PLEC1
- o Usually lethal in neonatal period
- o Generalized blistering, leading to atrophic scarring
- o The patient may be born with large areas of cutis aplasia
- o No granulation tissue
- o Pyloric atresia, GU malformations
- o Rudimentary ears
- o Dental enamel hypoplasia in survivors
- o Variable anemia, growth retardation, mucosal blistering
- o Nail dystrophy or anonychia

Laryngo-onycho-cutaneous syndrome:
- o Autosomal Recessive
- o Protein defect: Laminin ?3a
- o Gene defect: LAMA3
- o Also known as Shabbir Syndrome
- o Non - healing erosions and hoarseness with progressive course with death usually due to airway involvement.
- o Chronic wounds and granulation tissue affecting the skin, nail beds, larynx and conjunctivae
- o Described almost exclusively in Muslim families from the Punjab region

c) Dystrophic Epidermolysis Bullosa (DEB):

Dominant DEB:
- o Autosomal Dominant
- o Protein defect: Type VII collagen
- o Gene defect: COL7A1
- o Onset at birth to early infancy
- o Blistering predominates on dorsum of hands, elbows, knees, and lower legs
- o Milia associated with scarring
- o Some patients develop scar-like lesions, especially on the trunk
- o 80% have nail dystrophy
- o Although mucous membrane lesions appear in 20% of cases, they tend to be mild and not problematic.
- o The teeth and hair are generally not affected, and physical development is normal.
- o Variants include acral , pretibial, DEB pruriginosa, DDEB with only nails involved and bullous dermolysis of the newborn. All have varying prognosis

Severe generalized recessive DEB:

- o Autosomal Recessive
- o Protein defect: Type VII collagen
- o Gene defect: COL7A1
- o Present at birth with widespread blistering, scarring, milia
- o Severe involvement of mucous membranes and nails
- o Deformities: pseudosyndactyly, joint contractures alopecia
- o Growth retardation, poor nutrition
- o Anemia
- o Mottled, carious teeth
- o Osteoporosis, delayed puberty,
- o cardiomyopathy, glomerulonephritis, renal amyloidosis, IgA nephropathy
- o Predisposition to squamous cell carcinoma in heavily scarred areas

Recessive DEB, generalized other:
- o Autosomal Recessive
- o Protein defect: Type VII collagen
- o Gene defect: COL7A1

Recessive DEB, generalized other:
- o Autosomal Recessive
- o Protein defect: Type VII collagen
- o Gene defect: COL7A1
- o Generalized blisters from birth with milia, scar ng
- o Less anemia, growth retardation, mucosal but more esophageal issues with advancing age Variants include inversa, pretibial, pruriginosa, centripetalis and bullous dermolysis of the newborn

b) Kindler's syndrome:

- o Autosomal Recessive
- o Protein defect: Fermitin family homologue (kindlin -1)
- o Gene defect: FFH-1 (KIND-1)
- o Generalized progressive poikiloderma, congenital acral skin blistering, diffuse cutaneous atrophy, skin fragility, webbing of the fingers and toes, nail dystrophy, oral mucosal lesions, and photosensitivity
- o Hyperkeratosis of the palms and soles; leukokeratosis; red friable hyperplastic gums; constipation and sometimes severe colitis; esophageal, laryngeal, anal, vaginal and urethral meatal stenosis; and phimosis.
- o Photosensitivity and blistering may decrease with age, but the atrophic scarring and poikiloderma increase.
- o The incidence of squamous cell carcinoma of the acral skin or mouth is increased

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REVIEW ARTICLE

RITUXIMAB-A NOVEL BIOLOGICAL THERAPY USED FOR THE TREATMENT OF PEMPHIGUS AND OTHER AUTOIMMUNE DISEASES

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Dr.R.C.Raval (Prof.& HOD)
NHL Medical College,Ahmedabad

TRADE NAMES-Rituxan and Mab Thera

RITUXIMAB-A chimeric monoclonal IgG1 antibody targeting the B cell specific cell surface antigen CD20 approved so far for use only in CD20 B cell Non-hodgkin lymphoma(NHL), treatment resistant rheumatoid arthritis, Wegener's granulomatosis, microscopic polyangitis. It is now a newer novel therapy for treatment of pemphigus.[1]

MECHANISM OF ACTION-
CD20 is a cell surface non-glycosylated hydrophobic trans-membrane protein of 35 Kda molecular weight and appears to function as a component or regulator of voltage dependent calcium channel. Exact function is unknown. It appears to play a role in Ca^{2+} influx across plasma membranes, maintaining intracellular Ca^{2+} concentration and allowing activation of B cells.[1]

Rituximab is a chimeric monoclonal antibody against the protein CD20 which is found on the surface of immune complex B cells. The antibody is an IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids.

F*ab* portion binds to the CD20 antigen on the surface of mature B cells. F*c* portion of rituximab acts by recruitment of antibodies and complement and thus causes death of CD20 positive B cells. Thus rituximab leads to depletion of mature B lymphocytes which would transform into antibody producing short lived plasma cells. But stem cells and pro B cells are not affected as these cells reconstitute the B cell population after 6 months to 1 year.

OTHER MECHANISMS

It elicits shedding of CD23.

It down regulates the B cell receptor.

It induces apoptosis of CD20+ cells.

It increases MHC-II and adhesion molecules LFA-1 and LFA-3

Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues.

PHARMACOLOGY-
Half life - 59.8 hr(1st dose)
174 hr(4th dose)

Volume of distribution - 3.1 L
Clearance - 0.34 L/day (in RA patients)

Metabolism- Most likely removed by opsonization via the reticuloendothelial system when bound to B lymphocytes, or by human antimurine antibody production

INTERACTIONS-
Serious (use alternative)-
Certolizumab pegol

Serious (monitor closely)-
amphotericin B deoxycholate
belatacept
cisplatin
denosumab
fingolimod
ioversol
sipuleucel-t

METHOD OF ADMINISTRATION-

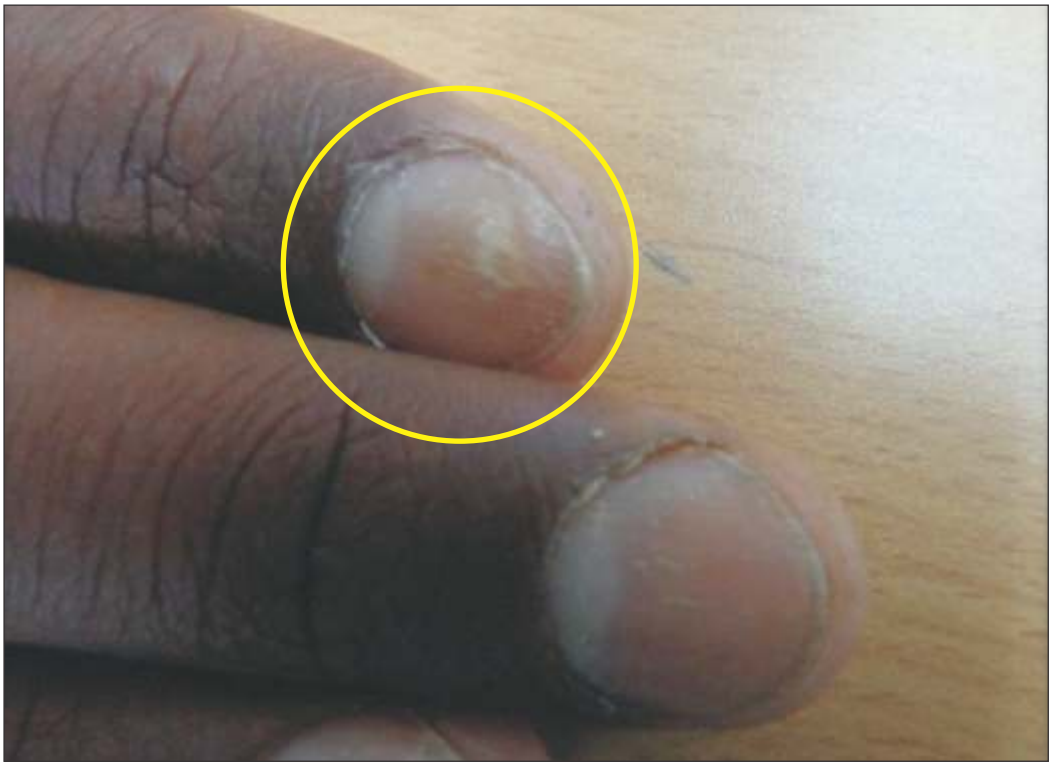
IV Preparation
Reconstitution: withdraw necessary amount of rituximab and dilute to a final concentration of 1-4 mg/ml into an infusion bag containing either NS or D5W

IV Administration
Consider premedication (consisting of acetaminophen and diphenhydramine, or glucocorticoids for RA) before each infusion of rituximab

TURN TO PAGE 23 >>

PHOTO QUIZ - 5

Dr. KRINA PATEL
GMERS Medical College, SOLA

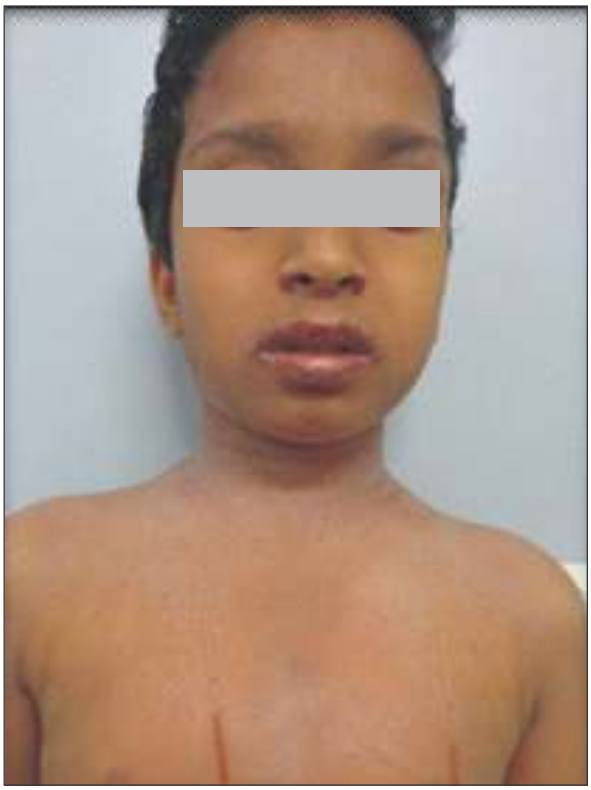


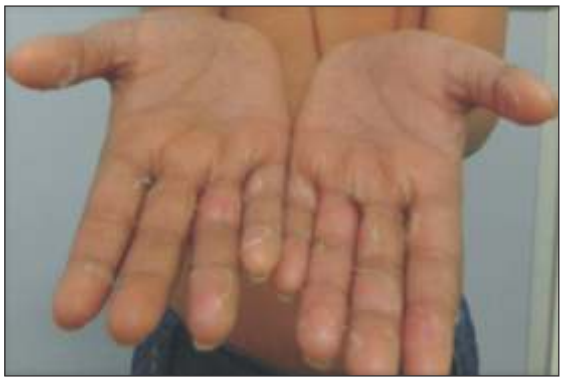
1) What is this sign known as?
2) In which dermatological disease one can see this change?

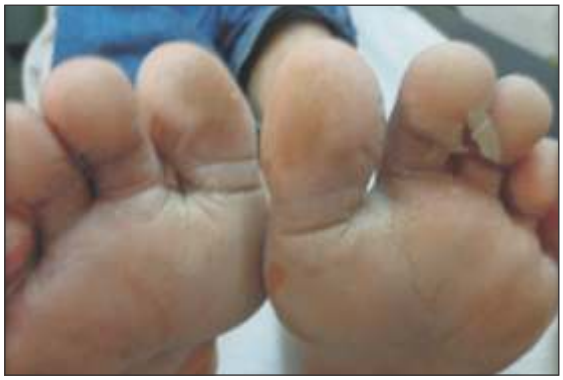
Please send your answers by
E-mail – quarterderm@mail.com
Or by post at
Dr. Krina Patel (Chief – Editor, Quarterderm)
Department of Dermatology
GMERS Medical College & Hospital, Sola,
Near Gujarat High court, SG Highway, Ahmedabad-380054.

PHOTO QUIZ - 6

Dr. KRINA PATEL
GMERS Medical College, SOLA







9- year old male suffered from high grade fever for 6 days followed by development of this rash.

1) what is the condition?
2) what is the rare but most dreaded complication of this disease?
3) what is the 1st line therapy for this condition?

What is your diagnosis?

Please send your answers on
quarterderm@mail.com by email or
on postal address mention in photoquiz 5 by post.

<< PAGE 18

Premedication may attenuate infusion-related events

Because transient hypotension may occur during infusion, give consideration to withhold antihypertensive medications 12 hr prior to rituximab infusion

First IV infusion rate: Start 50 mg/hr; increase by 50 mg/hr q30min, not to exceed 400 mg/hr

Subsequent IV infusions (standard): Start 100 mg/hr, increase by 100 mg/hr q30min, not to exceed 400 mg/hr; institutional protocols may allow faster increments.[1]

USES-

a) Non-Hodgkin's lymphoma - 375 mg/m² IV infusion according to the following schedules:

Relapsed or refractory low-grade or follicular, Cd20 positive, B-cell NHL: Once weekly x4-8 doses
Retreatment for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL: Once weekly x4 doses
Previously untreated, follicular, CD20-positive, B-cell NHL: Administer on Day 1 of each chemotherapy cycle for up to 8 doses; with complete or partial response, initiate maintenance 8 weeks following completion of combination chemotherapy as a single agent q8weeks for 12 doses
Non-progressing, low-grade, CD20-positive, B-cell NHL, after first-line CVP chemotherapy: Following completion of 6-8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses
Diffuse large B-cell NHL: Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions

b) **Chronic lymphocytic leukemia** -375 mg/m² IV infusion on day 1 of 1st cycle
For 1st cycle, administer 1 day before chemotherapy with FC, then 500 mg/m² IV on day 1 of subsequent cycles (administer on same day as chemotherapy with FC). Repeat q28 days x6 cycles

c) **Rheumatoid arthritis** -1000 mg IV infusion, repeat after 2 week (2 infusions separated by 2 week is 1 course).Repeat course q24weeks or based on clinical evaluation (but no sooner than 16 weeks)

d) **Wegener's granulomatosis** - 375 mg/m² IV qWeek x4 weeks

e) **Microscopic polyangitis** - 375 mg/m² IV qWeek x4 weeks

f) **Idiopathic thrombocytopenic purpura**

OFF LABEL USES -

a) Refractory autoimmune hemolytic anemia

b) Castleman's disease

c) Corticosteroid refractory pemphigus vulgaris

SIDE EFFECTS[(2)] -

a) Infusion reactions - fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension may occur during the first Rituximab infusion. Infusion reactions typically occurred within 30 to 120 minutes of beginning the first infusion and resolves with slowing or interruption of the infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline). The incidence of infusion reactions is the highest during the first infusion (77%) and decreases with each subsequent infusion.

b) Infections - serious infections including sepsis occurs in less than 5% of cases. The overall incidence of infections is approximately 31% (bacterial 19%, viral 10%, unknown 6%, and fungal 1%).

c) Cytopenias and hypogammaglobulinemia- lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%).

d) Cardiac complications – Myocardial infarction, arrhythmias

e) Central nervous system complications - dizziness and anxiety

f) Respiratory system complications - cough, rhinitis, sinusitis, bronchospasm and dyspnea

g) GI symptoms - nausea, abdominal pain, diarrhea, vomiting

h) Nutritional and metabolic disorders - hyperglycemia, LDH release, peripheral edema

OTHER RARE COMPLICATION WHERE CAUTION IS REQUIRED

a)Tumour lysis syndrome(TLS) - acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia

Treatment - Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care

b) Progressive multifocal leucoencephalopathy - diagnosed within 12 months of their last administration

Patient presents with new onset neurologic symptoms, consult a neurologist, brain MRI, lumbar puncture

Mostly in patients undergoing concomitant chemotherapy and immunosuppressant therapy

c) Severe mucocutaneous reactions paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis

Treatment - Discontinue Rituximab in patients who experience a severe mucocutaneous reaction.

d) Bowel obstruction and perforation- in patients receiving concomitant therapy

e) Renal toxicity- in patients receiving concomitant therapy

f) Hepatitis B virus reactivation with fulminant hepatitis - Screen patients at high risk of HBV infection before initiation of Rituximab. Closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection for several months following rituximab therapy

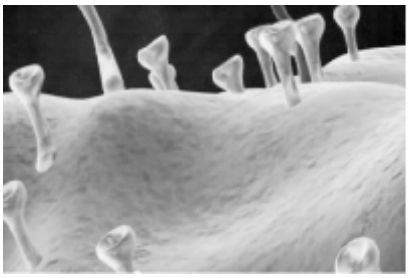
CONTRAINDICATIONS-

a) Hypersensitivity to rituximab or other murine proteins
b) Active severe infections
c) HIV infection with CD4 cell count <250 ug/ml
d) Severe heart failure

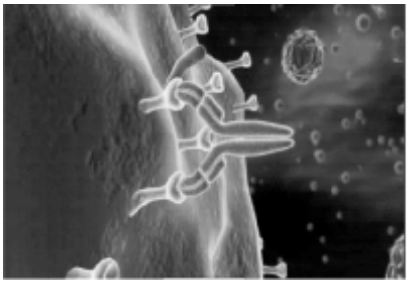
PREGNANCY AND LACTATION-

Pregnancy Category: C

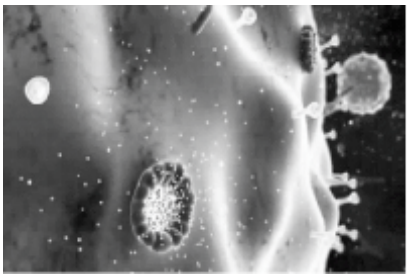
Lactation: not known if excreted in breast milk, do not nurse



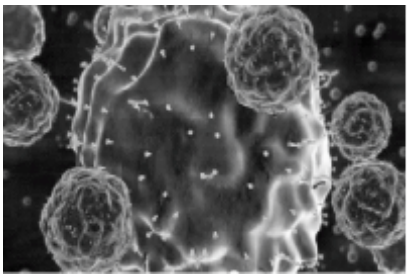
CD-20 ON B-CELL



RITUXIMAB BINDING TO CD20



COMPLEMENT DEPENDENT CYTOTOXICITY



ANTIBODY DEPENDENT CELL MEDIATED CYTOTOXICITY (ADCC)

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2. reference.medscape.com/drug/rituxan-rituximab-342243

CASE REPORT

SUCCESSFUL TREATMENT OF REFRACTORY CHILDHOOD PEMPHIGUS VULGARIS WITH RITUXIMAB – A STUDY OF 3 CASES

DR.JETA BUCH (2nd YEAR RESIDENT)
DR.R.C.RAVAL (HOD & PROF, DEPT OF DERMATOLOGY)
NHL MEDICAL COLLEGE, AHMEDABAD.

INTRODUCTION:- Pemphigus is a chronic autoimmune blistering disease commonly present in 2nd -3rd decade and rarely presents in childhood. In a study from north India, 75% of the patients were aged less than 45 years, and children aged less than 15 years accounted for 3.7% of cases.[2] Systemic steroids and immunosuppressants are the mainstay of therapy. However, substantial portion of the morbidity and mortality associated with juvenile pemphigus has been attributed to treatment (mainly steroids).We, hereby, present a study of 3 pediatric patients of extensive pemphigus vulgaris showing resistance to conventional therapy with daily stroids and treated effectively with rituximab as an adjuvant.

CASE REPORT:-

CASE-1

An 11-year old female (fig1)presented to the skin OPD with fluid filled lesions over scalp, skin and oral cavity since 4 months. Patient was diagnosed as having Pemphigus Vulgaris which was confirmed by Tzanck smear and Biopsy. Patient was given Injectable Dexamethasone 4mg i.v. twice a day which was gradually tapered along with immunosuppressant azathioprine 50mg once a day for 22 days. Despite this, new lesions continued to develop, so patient was given 1st DAP pulse. Side effects like moon face and hyperglycemia developed due to long term steroids and Inj.Insulin was given to counteract this side effect.

CASE-2

A 12- year old male (fig.2) presented to the skin OPD with fluid filled lesions over scalp and skin since 14 months and oral lesions since 6 months. Patient was diagnosed as having Pemphigus Vulgaris which was confirmed with Tzanck smear and Biopsy. Patient was given Injection Dexamethasone 4mg i.v. twice a day which was gradually tapered, along with immunosuppressant azathioprine 50mg once a day for 20 days. Despite this new lesions developed along with side effects of steroids like moon face, weight gain, cushingoid features and atrophy. So patients was given DAP pulse. On the first day of pulse therapy, patient developed side effects like tachycardia, hypertension and chest pain. So the pulse therapy was stopped and patient was considered for rituximab.

CASE-3

A 9- year old female (fig.3) presented with fluid filled lesions over scalp and body since 6 months and oral lesions since 1 month. Patient was diagnosed as having Pemphigus Vulgaris which was confirmed with Tzanck smear and Biopsy. Patient was given Injection Dexamethasone 4mg i.v. once a day which was gradually tapered over a 30 day period. New lesions continued to develop along with steroid side effects like weight gain and cushingoid features. So patient was considered for rituximab.

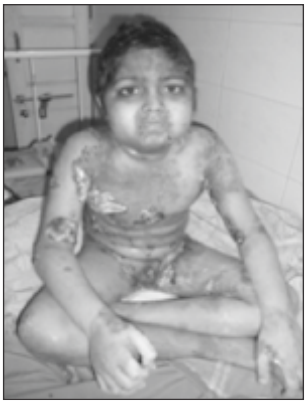


fig 1

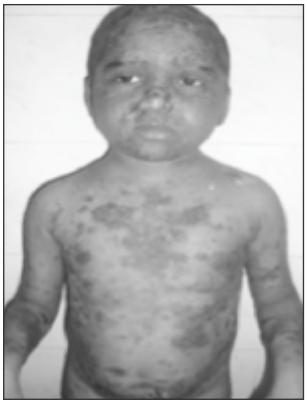


fig 2

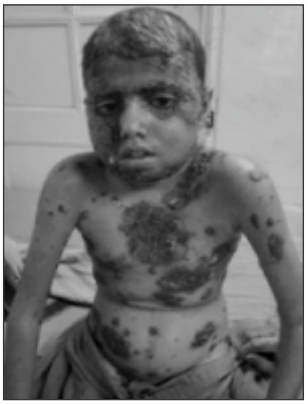


fig 3

Table 1 PRE TREATMENT DESMOGLEIN LEVELS:-

	AGE/SEX	PRE TREATMENT DESMOGLEIN LEVELS	
1	11/F	DSG 1	20.2
		DSG 3	143.4
2	12/M	DSG 1	237
		DSG 3	194.6
3	9/F	DSG 1	228
		DSG 3	229

TREATMENT SCHEDULE -
All patients were Pre-medicated 30 minutes before starting rituximab infusion with-
Hydrocortisone 100mg intravenous stat
Pheniramine maleate 22.75mg IV stat
Paracetamol 500mg orally single dose

Method-

- Pre treatment (table 1)- Dsg 1 & 3 and DIF
- 300mg i.v infusion in children over 4-5 hours duration.
- Two doses of rituximab were given at 15 days interval.
- Dsg 1 & 3 (table 2) and DIF were repeated after 1 month of 2nd dose of rituximab
- Follow up (weekly for one month , fortnightly for next two months).[1]

Table 2 POST TREATMENT DESMOGLEIN LEVELS:-

	AGE/SEX	PRE TREATMENT DESMOGLEIN LEVELS	
1	11/F	DSG 1	15.8
		DSG 3	18.7
2	12/M	DSG 1	80.54
		DSG 3	184.6
3	9/F	DSG 1	49
		DSG 3	44

- All the three patients responded well to rituximab. In follow-up patients are maintained on minimal dose steroids and immunosuppressive. Table 3 shows follow-up treatment data for all patients

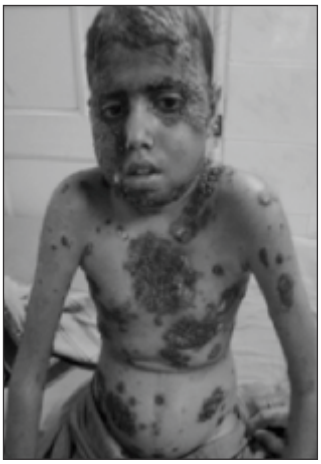
Table 3 FOLLOW -UP

CASE	MAINTENANCE DOSE OF STEROID AND IMMUNOSUPPRESSANT
1	PREDNISOLONE(5 MG)1 TABLET ALTERNATE DAY +AZATHIOPRINE(50MG)ONCE A DAY
2	PREDNISOLONE(10 MG)1 TABLET ONCE A DAY +AZATHIOPRINE(50MG)ONCE A DAY
3	PREDNISOLONE(10 MG)1 TABLET ONCE A DAY

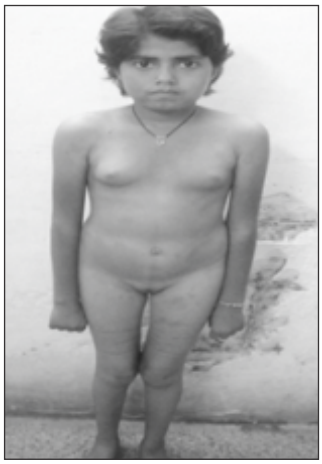
DISCUSSION:- Rituximab, a chimeric monoclonal anti-CD20 antibody, acts by cell mediated and complement dependent cytotoxicity. All cases were treated with conventional modalities before rituximab therapy. These cases were generally resistant to conventional treatments or had severe adverse effects with these therapies. None of these cases showed any serious long-term adverse effects. All 3 patients showed complete remission during the 3-month follow-up period, along with a consensual decline of the serum antidesmoglein titers

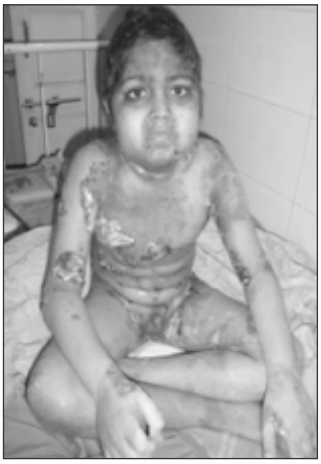
CONCLUSION:- Rituximab, can be considered as an effective adjuvant therapy when treating resistant cases of PV in pediatric patients. However, more number of patients and long term follow up is required to draw a definite conclusion

CLINICAL PHOTOGRAPHS:

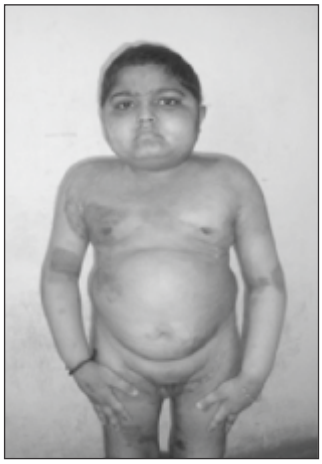


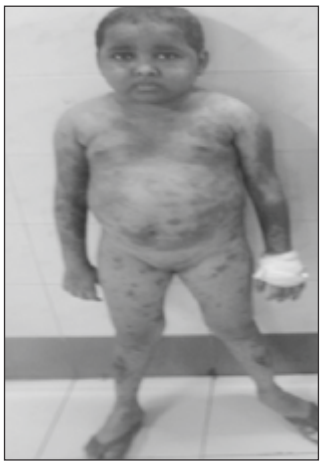
CASE-1



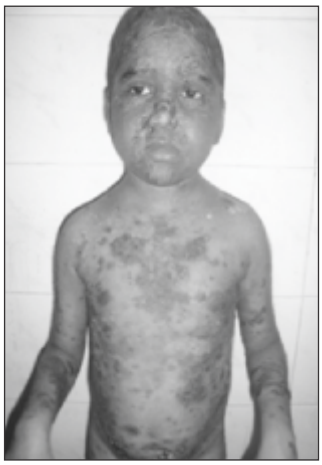


CASE-2





CASE-3



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2. Kanwar AJ, Ajith AC, Narang T. Pemphigus in North India. J Cutan Med Surg 2006;10:21-5. .

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HISOTRY SNIPPET - 3 HISTORY OF BULLOUS DISORDERS

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GMERS MEDICAL COLLEGE, SOLA
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Bullous disorders in skin have always attracted physicians since ancient times. Blisters in skin are considered so distinctive that they were worthy of special designation. 'Pemphix', 'pomphos', 'pompholyx', 'phyctama' etc were the words used by Greeks. The old testament, the Arabic literature, the Chinese texts, Latin writings all have used words which related to air or bubble, liquid, boiling etc. to describe bullous disorders of skin.

The term 'pemphigus' was first introduced by Francois (1706-1767) for all blistering disorders; not differentiating between various bullous diseases. Hippocrates mentioned it as 'Febris pemphigoides'. Sauvages described five forms of pemphigus – major, castrensis, helveticus, indicus and brasiliensis but none of this can be related to modern variants of pemphigus.

Gilbert, Sachse are other authors who published their work on cases which they considered pemphigus. Wichmann in 1791 and about half a century later Devergie gave exact clinical description of blistering diseases and even described the detachment of epidermis by shearing forces as distinguishing phenomenon which later was defined by Nikolski. Henrich Auspitz in 1880 coined the term ' acantholysis' and described the histopathology of pemphigus, stating for the first time that stratum basale remain in floor of blisters in some cases. All previous authors talked about separation of epidermis from the dermis.

Lever and Talbott tabulated the early descriptions of pemphigus and evaluated them in modern terms. Pemphigus Brasiliensis is the oldest terminology but bear no relation to fogo salvagem. Pemphigus foliaceus is the next; coined by Cazenave in 1844. Pemphigus vulgaris was introduced by Hebra in 1860. Pemphigus vegetans was later on described by Neumann. Isidor Neumann described pemphigus vegetans in 1876 referring to early description of Kaposi and Auspitz, who referred back to Alibert, Willan and Bateman, Plenck and ultimately Sauvages who all gave description related to this type of pemphigus.

Last centuries of 80s were the beginning of new era for pemphigus research. Auspitz gave a landmark findings of acantholysis in pemphigus, describing loss of intracellular cohesion responsible for blister formation and also described cylindrical basal layer at the floor of blister.. In 1884 Adolphus Duhring described ad new entity dermatitis herpetiformis. But still at this time terminology for bullous disorders were full of confusion. In 1891, Besnier and Doyon translated Kaposi's textbook into French from German with full 30 pages were devoted to bullous diseases. A decade later, Brocq used more than 100 printed pages to deal with pemphigus and its terminology. Piott Vasililevitch Nikolski described his first observation of Nikolski sign in a 44-year old woman from Professor Stoukovenkoff's department in Kiev in 1895. Originally described to represent shearing off the stratum corneum from underlying layers of epidermis. In 1900 and 1901 this phenomenon was made internationally known by Danlos and Dubreuilh. It was Ferninand Jean Darrier who considered Nikoloski sign to be due to acantholysis. In 1926 Pemphigus erythematosus was described as a new variant by Eugene Senear and Barney Usher. Pemphigus brasiliensis was described by Joao Paulo Viera from Brazil. It was Achille Civatte in 1934 who eventually emphasized the importance of acantholysis in pemphigus histopathology. Civatte also differentiated pemphigus vulgaris from dermatitis herpetiformis. Lever in 1951 gave classical description of histology of pemphigus.

Later in 1953 it was Lever only who introduced the term pemphigoid. Benign mucous membrane pemphigoid or cicatricial pemphigoid were also classified by Lever. A special variant of cicatricial pemphigoid was described by Brunsting and Perry in 1957 bearing their eponym ever since.

Herpes gestationis was termed by Milton in 1872 for pregnancy associated bullous diseases. There were many past and later workers who described bullous dermatosis in pregnancy; including Hebra, Koebner, Bunel etc. but only after immunopathological methods

became available, exact nature of herpes gestationis became known under bullous pemphigoid.

Pemphigus herpetiformis is the most recently described form of pemphigus; described by Jablonska et al in 1975.

In 1939 Hailey brothers described four patients with Pemphigus familiaris chronicus benignus. The term 'epidermolysis bullosa hereditaria' was created and introduced by Koebner in 1886 for Auspitz's acantholysis but term for historical purpose term was retained to describe mechano-bullous disorders.

Similarly if we see other terminology –
pompholyx was originally used for many bullous disorders; especially favoured by Willan as pemphigus.
Herpes another age old term used by ancient Greek physicians for various blistering eruptions.
Dermatitis exfoliativa neonatorum was originally described by Gottifried Ritter Von Rittershain in 1878 for the disease we know as staphylococcal scalded skin syndrome.
Toxic epidermal necrolysis described by Lyoll in 1956; is related to butcher's pemphigus and severe erythema exsudativum multiforme.
The term porphyria cutanea tarda was introduced by Waldenstorm in 1937.

Immunopathology in blistering diseases.

Beutner, Jordon and Collaborators gave revolutionary findings of pemphigus antibodies in 1965. Than after two years same for bullous pemphigoid was identified by same laboratory in 1967. Simultaneously Rudi Cormane of Amsterdam reported his preliminary findings of immunoglobulin deposition in skin in dermatitis herpetiformis. In 1969 his pupil, Van der Meer published the first study of IgA deposition in DH patients. In another 5 years the pathogenic concepts of the most of the major bullous diseases had revolutionized. Immunoelectron microscopy too followed and provided much needed confirmatory evidences for blistering diseases. Tissue culture studies and in vivo experiments including antibody transfer experiments soon gave more and more insights into these diverse groups of diseases.

ADOPTED AND CONCISED FROM ORIGINAL WRITINGS OF PROF. KARL HOLUBAR

JOURNAL SQUEEZE!!!

Dr. Santosh Rathod

Article 1: Journal of the American Academy of Dermatology

From the Medical Board of The National Psoriasis Foundation: Recommendations for Screening for Hepatitis B Infection Prior to Initiating Antitumor Necrosis Factor-Alfa Inhibitors or Other Immunosuppressive Agents in Patients With Psoriasis
J Am Acad Dermatol 2013 Nov 09;[EPub Ahead of Print], K Motaparthi, VStanisic, AS Van Voorhees, MG Lebwohl, S Hsu

BACKGROUND

No consensus exists regarding the optimal laboratory screening for hepatitis B infection that should be performed before initiating therapy with tumor necrosis factor-alfa inhibitors or other immunosuppressive agents.

OBJECTIVE

We sought to give guidelines on which tests to order for hepatitis B screening.

METHODS

We review the pathophysiology and serology of hepatitis B infection and provide recommendations for screening for hepatitis B infection in patients with psoriasis before beginning anti–tumor necrosis factor-alfa therapy or other immunosuppressive agents.

RESULTS

We propose the standardized use of triple serology testing: hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody in combination with liver function tests as screening.

LIMITATIONS

Conclusions based on review of available literature is a limitation.

CONCLUSIONS

All patients with psoriasis who are candidates for tumor necrosis factor-alfa inhibitor should undergo screening for hepatitis B virus infection using the triple serology: hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody. It is advisable that patients, who are candidates for ustekinumab, cyclosporine, or methotrexate undergo the same screening.

Take Home Message:
- Because there is concern for reactivation of latent hepatitis B virus (HBV) infection, the National Psoriasis Foundation (NPF) recommends that all patients treated with TNF-α inhibitors (ie, ustekinumab, cyclosporine, or methotrexate) for moderate to severe psoriasis should be first screened by the triple serology: hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody.
- Hepatitis B activation is avoidable if proper screening is performed.

Article 2: The British Journal of Dermatology

Factors Associated With the Relapse of Infantile Hemangiomas in Children Treated With Oral Propranolol
Br J Dermatol 2013 Dec 01;169(6)1252-1256, CK Ahogo, K Ezzedine, S Prey, V Colona, A Diallo, F Boralevi, A Taïeb, C Léauté-Labrèze

ABSTRACT

BACKGROUND

Although propranolol has become the first line therapy of infantile hemangiomas (IH), no study has yet investigated factors associated with the risk of relapse in children with IH treated with propranolol after treatment cessation.

OBJECTIVE

To compare factors associated with the risk of relapse in children with IH treated with oral propranolol PATIENTS AND

METHODS

We conducted a single-centre retrospective observational study. All files and photographs of patients with IH aged 5 months or less at the time of treatment initiation and who were seen between June 1(st) 2008 and December 31(th) 2011at the National Reference Center for rare skin diseases of Bordeaux were retrospectively reviewed.

RESULTS

A total of 158 children were included of whom 118 had not relapsed (R-) and 40 had relapsed (R+).52 patients were boys and 106 were girls (sex ratio M/F, 1:2), and 19 had a segmental IH (12%). When conducting multivariate analysis, only IH with a subcutaneous component and those with segmental distribution were independently associated with relapse.

CONCLUSIONS

Our study shows that segmental IH as well as hemangiomas with a deeper component are more at risk for relapse and should thus beneficiate of closer follow-up after treatment interruption and/or longer treatment.
Take Home Message:
- A retrospective analysis was conducted to determine risk factor for relapse in infantile haemangiomas (IH) treated with oral propranolol. IH with a subcutaneous component and/or segmental distribution were associated with a significantly increased risk of relapse, while propranolol dosage was not associated with the relapse risk.

Vesicobullous dermatoses: An update

Dr. Ankan Gupta, Dr. Amita Sutaria, Dr. Kirti Parmar, Dr.Bela Shah.
B.J.Medical College,Ahmedabad.

Introduction: What we already know.

Vesicobullous dermatoses are skin conditions characterised by vesicles and bullae. They are mostly autoimmune in nature and can be debilitating and fatal. They include pemphigus vulgaris, pemphigus foliaceous, paraneoplastic pemphigus, bullous pemphigoid, cicatricial pemphigoid, pemphigoid gestationalis, epidermolysis bullosa aquisita, dermatitis herpetiformis, linear IgA dermatosis.

Autoimmune Vesicobullous disorders

	Disease	Characteristic	Antigen Target	Cellular Component
1	Pemphigus vulgaris	Usually starts in the oral mucosa followed by blistering of the skin, which is often painful	Desmoglein 3,1 and 4 Desmocollin 31	Desmosomal Cadherins
2	Pemphigus foliaceous	Scaky, crusted lesion on an erythematous base present in seborrhoeic distribution.	Desmoglein 1, 4	Desmosomal Cadherins
3	Paraneoplastic pemphigus	Associated with neoplasms, most commonly of lymphoid tissue, but also Waldenström's macroglobulinemia, sarcomas, thymomas and Castleman's disease	Desmoglein 3 Desmoplakin, Envoplakin, periplakin	Desmosomal Cadherins Desmosomal Plaque proteins
4	Bullous pemphigoid	Characterized by large, tense bullae, but may begin as an urticarial eruption.	Bullous pemphigoid Antigen 1/ Bp230	Hemidesmosomal plaque proteins
			Plectin	Hemidesmosomal plaque proteins
			Collagen XVII/ Bp180	Hemidesmosomal transmembrane proteins
			a6ß4 integrin	Hemidesmosomal transmembrane proteins

5	Cicatricial Pemphigoid	Presents with severe, erosive lesions of the mucous membranes with skin involvement in one third of patients focused around the head and upper trunk	Plectin	Hemidesmosomal plaque proteins
			Collagen XVII/ Bp180	Hemidesmosomal transmembrane proteins
			a6ß4 integrin	Hemidesmosomal transmembrane proteins
6	Pemphigoid gestationalis	Blistering disorder occuring during 2nd-3rd trimester with an abrupt onset of extremely pruritic urticarial papules and blisters on the abdomen and trunk	Collagen XVII/ Bp180	Hemidesmosomal transmembrane proteins
7	Linear IgA dermatosis	Clinically similar to dermatitis herpetiformis, but it is not associated with gluten-sensitive enteropathy	Collagen XVII/ Bp180	Hemidesmosomal transmembrane proteins
			Ectodomain of Collagen XVII	Anchoring filament proteins
8	Epidermolysis bullosa aquisita	Characterized clinically by blisters, scars, and milia primarily at the trauma-prone areas	Collagen VII	Anchoring fibril proteins
9	Subcorneal Pustular dermatosis	Benign, chronic relapsing sterile pustular eruption typically involving the flexural sites of the trunk	Desmocollins	Desmosomal Cadherins
10	Dermatitis herpetiformis	Intensely pruritic and chronic, characterized by papulovesicles and urticarial wheals on the extensor surfaces in a grouped or herpetiform, symmetric distribution	Epidermal transglutaminases	Epidermal enzyme

The pathogenesis of autoimmune vesicobullous diseases is still to be completely deciphered. Headway growth has been seen after the recognition of autoantibodies and demonstration of acantholysis as the primary pathology in a majority of intraepidermal bullous diseases. An immense research is still going on in the diagnostics, immunopathology and their treatment but we still have a long way to go as these disorders are still associated with significant morbidity, considerable mortality and impaired quality of life[2]. Pemphigus, the most common intraepidermal vesicobullous disease has a worldwide prevalence of 0.1-0.5 per 100,000 population, as high as 3.2 per 100,000 in Ashkenazi jews[3]

What's new in immunopathology?

I. PEMPHIGUS VULGARIS(PV) AND PEMPHIGUS FOLIACEOUS(PF)

Acantholysis occur in genetically predisposed on exposure to certain environmental triggers. But acantholysis does not explain the mechanism by which disruption of adhesion between keratinocytes occurs. The three theories postulated are:

- Binding of autoantibodies to their antigens can disrupt adhesion of the bound antigens by steric hindrance.
- Production of plasminogen activator by the antigen antibody complex, which in turn leads to the production of active plasmin culminating in cell dissociation.
- Reorganization of the keratinocyte cytoskeleton, leading to cellular shrinkage and separation of keratinocytes[4].

Although electron microscopy showed widening of the intercellular space and the absence of half desmosomes in acantholytic skin, supporting the "basal cell shrinkage theory" with no reference to steric hindrance[5] but by using atomic force microscopy, it is seen that the molecular mechanisms in pathogenesis of PV and PF differ.

- PV-IgG directly interferes with homophilic Dsg 3 transinteraction[6] whereas
- Neither PV-IgG nor PF-IgG directly interact with homophilic Dsg 1. They reduce Dsg1 transinteraction indirectly via cellular mechanisms.

Few recent studies have also reported profound changes in actin organization to accompany acantholysis in PV[7]. Genetic polymorphisms is also seen in genes encoding co-stimulatory receptors (viz. cytotoxic T-lymphocyte antigen 4 (CTLA4) and inducible T-cell co-stimulator (ICOS) - on T cells) in PV and PF[8]. Some newer autoantibodies have also been postulated like approximately 85% of the pemphigus patients develop antibodies against keratinocyte acetylcholine receptors (AChR) - AChR α9 and Pemphaxin[9]. PV-IgG binding to AChR α9 may block Ca++ influx involved in desmosome assembly and in protein kinase C (PKC) activation weakening the intercellular adhesions between keratinocytes via inactivation of the cholinergic receptor-mediated physiologic control of cadherin (Dsg) expression causing acantholysis. One of the earliest pathogenic events in PV is the activation of protein kinases, the protein kinase R (PKR) -like endoplasmic reticulum kinase (PERK). Decreased expression of PERK *in vivo* has been shown to reduce the effects of PV serum on the cell cycle and keratinocyte viability, two key events in PV pathophysiology[10]. The role of IL-10 and CD-28 is still unclear but research is going on in the role of cellular immune system in PV and PF.[11]

II. BULLOUS PEMPHIGOID

Recently, plectin has been shown to be a minor pemphigoid antigen with an immunodominant epitope located on the central rod domain[12].

Newer types of Autoimmune vesicobullous disorders

A newer morphologic variant of PV, dyshidrosiform PV, presenting as a pompholyx-like eruption on the soles has also been described[13]. In 1996, a new entity by the name of paraneoplastic autoimmune multiorgan syndrome (PAMS) was described where, in addition to skin and upper digestive and respiratory tract mucosa, deposits of autoantibodies are present in the kidney, urinary bladder and smooth as well as striated muscle[14]. PNP is now considered as an epithelial variant of PAMS. Clinically, PAMS may present with pemphigus-like, pemphigoid-like, graft versus host disease-like, erythema multiforme-like or lichen planus-like eruptions and may be associated with leukemias and lymphomas, Castleman's disease, thymoma, retroperitoneal sarcoma and other malignancies.

A new subepidermal blistering disease has been described where the circulating autoantibodies did not react to any known autoantigen but to a 200-kDa molecule (p200) from dermal extracts[15]. Recently, the identity of p200 has been unmasked as laminin γ1, an extracellular matrix glycoprotein composed of several forms of laminin heterotrimers. Hence, it has been renamed as anti-laminin γ1 pemphigoid[16]. where patients approximately 50-70 years old, often having pre-existing psoriasis[16] develop tense blisters and urticarial eruptions closely resembling BP. On indirect immunofluorescence microscopy on 1 mol/L NaCl-split skin, anti-laminin γ1 pemphigoid IgG reacts with the dermal side of the basement membrane, whereas BP IgG shows reactivity with its epidermal side.

A case of congenital EBA due to transplacental passage of autoantibodies, which was self-limiting in nature, has been reported[17]. Among the drug-induced bullous disorders, biologic response modifiers like adalimumab

have been reported to cause both BP and PV[18].

Another area of interest is the association between BP and neurological disorders. The risk factors for developing BP are presence of neurological disorders, particularly dementia and Parkinson's disease, psychiatric disorders, bedridden condition and chronic use of several drugs[19]. In a study at least one neurologic diagnosis was present in 42/91 (46%) BP patients compared with 16 controls (11%)[20]. Four major neurologic diagnoses were observed (cerebrovascular disease, dementia, Parkinson disease and epilepsy), with a highly statistically significant association for cerebrovascular disease and dementia[20].

What's new in diagnostics of autoimmune vesicobullous disorders?

Direct immunoflourescence (DIF) microscopy from perilesional skin remains the gold standard for diagnosing vesicobullous disorders.

- DIF on telogen hair root sheath has shown promising results in diagnosis and follow-up in cases of pemphigus[21].
- Several enzyme-linked immunosorbent assays (ELISAs) using extracts of bovine skin and recombinant portions of Dsg 3 and 1 expressed in E. coli have been developed to detect circulating autoantibody levels and have been found to be superior to IIF microscopy due to less interpreter dependency and greater standardization[22].
- The efficacy of a novel ELISA system using ectodomains of Dsg 3 and 1 expressed in human cell lines (HEK293) as target antigens has been analysed and has been found to be sensitive and specific in both the diagnosis and monitoring of PV and Pf[23].
- Similarly, the BP180 NC16a ELISA has been found to be highly sensitive and specific in differentiating PG from polymorphous eruptions of pregnancy[24].
- Measurement of B-cell activating factor (BAFF) belonging to the tumor necrosis factor (TNF) family may be a useful marker to detect early activation of an autoimmune diathesis as it is thought to play a critical role in triggering activation of self-antigen-driven autoreactive B cells in Bp[25].
- C3d immunohistochemistry has been devised as a valuable tool for the diagnosis of BP and Pv[26].
- Collagen (COL) VII-NC1 ELISA has been used in the diagnosis of EBA and found to be a powerful tool in diagnosing EBA with COL VII-specific IgG correlating with disease activity, and IgG reactivity was found to be associated with T-cell recognition of identical subdomains of COL VII-NC1[27].
- Commercially available ELISA assays are now used to detect autoantibodies against p-200 antigen[28].

New in treatment: Immunomodulation!

There is no treatment protocol till now with systemic glucocorticosteroids in combination with different immunosuppressants being a time-tested treatment[29]. A therapeutic ladder has been proposed for treating pemphigus, initially with a combination of oral prednisolone and mycophenolate mofetil[30]. Cyclophosphamide, intravenous immunoglobulins (IVIg) or rituximab were used in cases of treatment failure. But the ladder has not been universally accepted.

High-dose IVIg (2g/Kg over 3-5 days every 4 weeks) in treating recalcitrant pemphigus works by selectively[31] and rapidly decreasing the circulating levels of pathogenic antibodies by more than half within 1-2 weeks of initiation of treatment. and results in clinical improvement within days of its initiation[32]. The effectiveness of IVIg improves with the concomitant administration of cyclophosphamide or azathioprine[33]. A consensus statement has been published on its use in the treatment of autoimmune mucocutaneous blistering diseases[34].

Rituximab, which is an anti-CD20 humanized monoclonal antibody, originally developed for the treatment of non-Hodgkin's lymphoma has been used at a dose of 375 mg/m^2 weekly for 4 weeks[35,36]. In most patients, resistant lesions cleared within 1-4 months.

Etanercept, a TNF-α antagonist, has also shown encouraging results in the treatment of pemphigus[37].

Pimecrolimus 1% cream is effective adjuvant to steroids and azathioprine in the treatment of Pv[38].

Systemic tacrolimus is also found to be effective in the treatment of recalcitrant PV in two patients[39].

Daphentin, a novel antimalarial agent, has also shown promising initial results[40].

Allogenic hematopoietic stem cell transplantation following non-ablative conditioning regimen has been reported to be effective[41].

Intravenous administration of high-dose Dsg 3 peptides selectively blocks the acantholytic activity of pemphigus antibodies with cholinergic agonists such as pyridostigmine bromide[42].

Caspase inhibitor Ac-DEVD-CMK in BALB/c has been studied to block apoptosis and prevent blistering[43].

On induction of the hyperadhesive state with the PKC inhibitor Go6976 it reduces both the acantholysis rate and the processing of cell adhesion molecules induced by PV serum[44].

Newer modalities of therapy in bullous pemphigoid and epidermolysis bullosa acquisita include IVIg, rituximab and daclizumab.

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Answers to Photoquiz 1 to 4 and correct entries.

(first two names in bold are winners)

Photo Quiz 1

Answer – Nodular Bullous Pemphigoid

1) Vidushi Jain **2) Deep Joshipura**
3) Jigisha Jhalu 4) Sweta Patel
5) Pooja Koyani 6) Sanjay Pancholi

Photo Quiz 2

Answer – Juvenile xanthogranuloma (Of adult onset)
No correct entry received

Photo Quiz 3

Answers – 1) Aplasia Cutis Congenita
2) Hair collar sign around scalp lesion
3) Fetus papyrus
1) Dr. Ritu Marfatia 2) Dr. Ranjan Rawal

Partly correct entries
1) Dr. Kishan Nimama 2) Dr. Priyanka Patil
3) Dr. Kiran Gopichandani

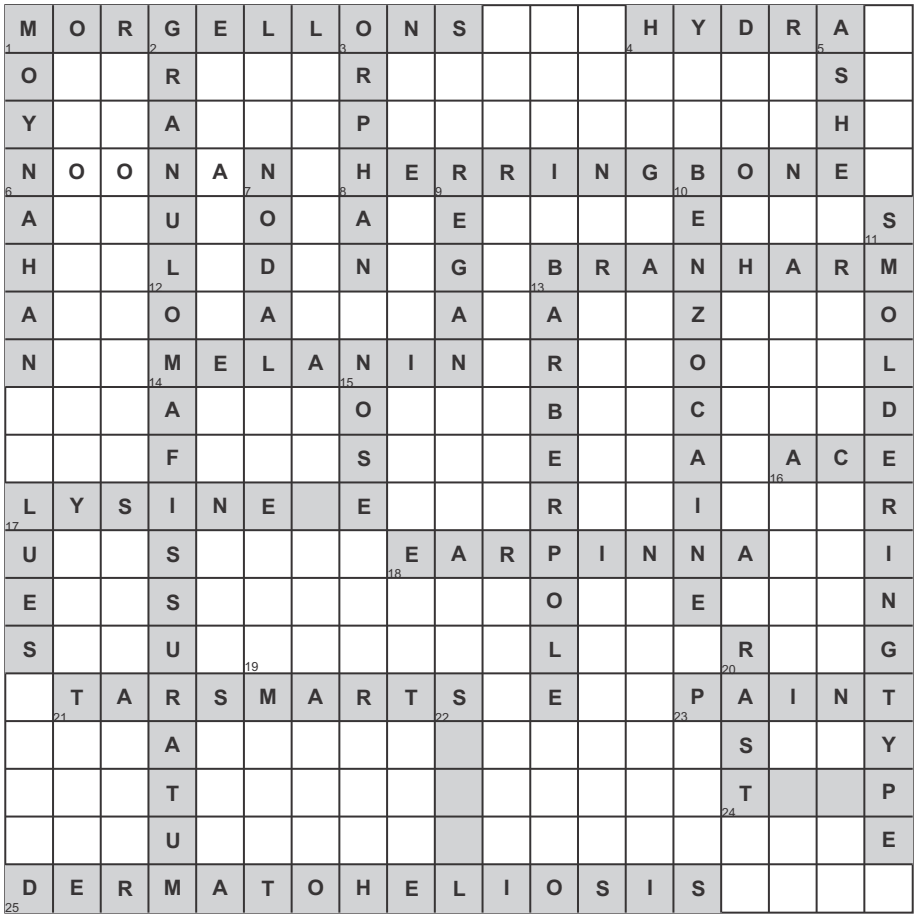
Quiz 4

Answer – Fordyce spots
1) Dr. Kishan Nimama 2) Dr. Priyanka Patil
3) Dr. Sweta Pastagia 4) Dr. Bharat Dabhi
5) Dr. Ranjan Rawal

Answers to Pediatric dermatology MCQ (Issue 2)

1. C
2. B
3. C
4. D
5. A
6. D
7. D
8. C
9. B
10. B
11. A
12. C
13. B
14. C
15. D

ANSWERS TO CROSSWORD 1



ANSWERS TO CROSSWORD 2

		EXCORIATE								
		X			X			C		R
INCLUSION										Y
		O						E		T
PURPURA										H
		I			A			M		E
S		A			L			A		M
O		T			E			C		A
L		I			NEVUS					
ATOPY								L		
R		N			ECZEMA					

NEWS & POSTS

1. Dr. Krina Patel thanks all members of
Gujarat IADVL for whole hearted l support in
IADVL election 2013-14 as Joint Secretary IADVL

2. Gujarat IADVL congratulates following recipients of
International society of dermatology - Global education award (ICD Delhi 2013)

Dr. Hardik Pitroda
Dr. Yogiraj Rathod
Dr. Deep Joshipura
Dr. Smita Nagpal
Dr. Smriti Naswa