Pemphigus vulgaris: A review

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Abstract
Pemphigus is an autoimmune inter epidermal blistering disorder. it is characterized by mucosal and cutaneous vesicles, bullae, erosions. It has an array of maifesations and symptoms. Systemic corticosteroids have remained the mainstay of treatment for pemphigus, recent years are focusing on use of other immunomodulators as well. This review looks at the etiology, clinical features, management, complications of the condition.

Keywords: Pemphix, Rheumatoid arthritis, Myasthenia gravis.

Introduction
The word pemphigus is as old as the medicine, with first description in literature by Hippocrates (460-370 BC) as "pemphigoides pyertoi" to describe fever associated with blisters. The term 'Pemphigus', derived from the Greek word "***pemphix***" meaning bubble or blister.[1] It refers to a group of life threatening autoimmune intraepidermal bullous diseases of the skin and mucous membranes with antibodies directed against keratinocytes, thereby causing loss of adhesion or acantholysis. The incidence of pemphigus in India is relatively common, earliest reported literature in India is dated back to 1960 by Desai and Rao who described 21cases of pemphigus.[2] Pemphigus is classified based on histological & clinical features, major categories being pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, IgA pemphigus, drug induced pemphigus and recently identified variants being pemphigus herpetiformis and IgG/IgA pemphigus.[3] However, only pemphigus vulgaris (PV) and paraneoplastic pemphigus (PNP) typically have oral involvement, this contribution focuses on pemphigus vulgaris being the protypical form of this disease.

Epidemiology
Incidence of pemphigus worldwide has been reported to be 1 to 16 per million people per year[4] with 70% cases reported from South East Asia, Middle East Asia & China.[5] Pemphigus Vulgaris being the most common variant mean incidence being 0.1 to 0.5 per 100,000 with incidence in India being 75 and 92% of all cases of pemphigus.[6,2] The mean age of occurrence being 50 and 60 years in European countries and between the ages of 30 and 50 in rest of world. [7] In India the age of patients being less than 40 years of age constitute approximately 50% patients. [2,8] A higher incidence in female population has been reported with Male: Female ratio being 1:1.1–2.25. [9] however few studies in India have reported a higher incidence in males with Male: Female ratio being 3: 1, 3: 2. [8]

Aetiology
A strong genetic background has been linked with pemphigus vulgaris owing to higher incidence in certain ethnic groups (Mediterranean and South Asian population and Ashkenazi Jews). There are also associations with HLA, particularly with HLA-DR4 (DRB1*0402) in Ashkenazi Jews and, in Europeans and Asians, with DRw14 (DRB1*1041) and DQB1*0503.; [10-14] early age of onset in Indian population has been related to occurrence of DRB1*1404, DQA1*0101, DQB1*0503 allele. [2,8] Recently ST18, a gene regulating apoptosis and inflammation, has been suggested in predisposing individuals to pemphigus vulgaris in Jeweish and Russian population.[15] Most cases the precipitating factor is usually unknown and pemphigus is considered to be idiopathic ostensibly certain trigger agents such as diet, drugs, contact allergens, stress or viruses have been identified.[1,16]

Pathogenesis
In pemphigus vulgaris, IgG autoantibodies are targeted against desmogleins, the cell adhesion molecules of the desmosome, leading to loss of cell to cell adhesion resulting in acantholysis. Desmoglein-1 (Dsg-1) is expressed in all layers of the epidermis with a higher concentration in the subcorneal layer and desmoglein-3 (Dsg-3) expressed in the parabasal and basal layers. The mucosa expresses both Dsg-1 and Dsg-3 however, the mucosa has lower concentrations of Dsg-1.[12] In

mucocutaneous pemphigus vulgaris autoantibodies are directed against Dsg-1 and Dsg-3 whereas in only mucosal disease antibodies are exclusively against Dsg-3.

Pemphigus autoantigen

With advances in diagnostic pathology target antigens have been recognized in pemphigus. The reported "pemphigus antigens" include over 40 protein bands with apparent molecular weights (MWs) of 12, 18, 25, 30, 33, 35, 38, 40, 45, 47, 50, 52, 55, 57, 59, 60, 62, 66, 67, 68, 70, 75, 78, 80, 85, 95, 100, 102, 105, 110, 112, 120, 130, 140, 160, 170,180, 185/190, 210, and 260 kD. Various self-antigens recognised by pemphigus IgG include adhesion molecules, cell membrane receptors, annexins, immunologic/hematologic antigens, neuronal/oncologic antigens and thyrogastric cluster antigens [19]

It is known that antibodies play an important role in pathogenesis of pemphigus however the exact pathogenesis of these antibodies is not known. Various theories have been proposed for the pathogenesis of pemphigus including the desmoglian compensation theory, the multiple hit hypothesis, antibody induced apoptic theory, steric hinderance and basal cell shrinkage hypothesis.[20-23]

Clinical features

Oral mucosa is typically involved, 80% patients have oral lesion as first sign of pemphigus vulgaris[6, 24-25] and 50% of patients with pemphigus vulgaris have isolated oral lesions. Oral lesion of pemphigus in children are rarely seen.[26-27] Most commonly involved site being buccal mucosa, palate, ventral surface of tongue, labial mucosa and gingiva. Lesions occur as flaccid vesicles & bullae of oral cavity associated with ulcers, desquamative gingivitis or dysphagia. [16, 17] Gingival lesions appear later in disease, presenting as isolated blisters or erosions of marginal gingiva and attached gingiva in advanced cases.[29-31] Nikolsky's sign is a common examination finding. The direct Nikolsky sign refers to direct application of pressure on a blister, causing the extension of the blister. The indirect Nikolsky sign is when the application of friction on clinically normal skin induces a blister. [32] Any mucosal surface, including conjunctiva, nasal mucosa, larynx, oropharynx, esophagus, urethra, vulva, and cervix may be involved.[33-40] Painful but rarely pruritic flaccid bullae and erosions of body accompany oral manifestations involving face, trunk, axilla and groin.[40,41] Other clinical findings include nail dystrophy, paronychia, and subungual hematomas. Nail involvement in pemphigus was first documented by Sinclair and colleagues in 1998, has been reported to be present in 34.2% patients and can precede skin findings. They can manifest as paronychia, onychomadesis /Beau line or onycholysis and nail involvment has been associated with poor prognosis.[42-44] Scalp is frequently involved in pemphigus, hair involvement in pemphigus may differentiate it with other vesiculobullous disorders. It is associated with anagen effluvium with and without alopecia[22] and is considered as Nikolsky's sign of the scalp and can be used to verify disease activity. It has been propose d that the scalp is the first site of clinical manifestation of disease.[45-47]

Association with other disorders

PV may occasionally be associated with other autoimmune disorders, particularly rheumatoid arthritis, myasthenia gravis, thyroid disorders, lupus erythematosus, vitiligo or pernicious anaemia. [48-50]

Diagnosis

Clinical examination and diagnostic modalities aid in the diagnosis of pemphigus. Direct and indirect immunofluorescence, enzyme linked immunosorbent assays (ELISA) and immunoblot are helpful in distinguishing the different subtypes of pemphigus. Light microscopy is an important modality in the diagnosis of the pemphigus demonstrating typical suprabasal cleft in epithelium of pemphigus vulgaris patients. Demonstrates intercellular deposition of IgG, IgA, IgM and C3. The immune deposits precede clinical appearance hence it is considered more sensitive than histopathology. DIF of plucked hair can be a useful test in the diagnosis of pemphigus, sensitivity ranging from 85 to 100%. Also can be used to assess disease activity with accuracy of 73.3%.[51] Indirect immunofluorescence demonstrates serum autoantibodies against desmosomal antigens causes staining of IgG antibodies in typical "Fishnet pattern" or "Chicken wire appearance" positive predictive value of 90% in active pemphigus vulgaris patients and sensitivity of 75% with specificity of 83%.[52-53] ELISA can demonstrate IgG antibodies to Dsg1 and Dsg3. Advantage being its simplicity and highly sensitive approach to confirm the initial diagnosis of PV with overall accuracy for diagnosis of PV 93.7% and sensitivity of 92- 100%. [54] Immunoblot is recently developed technique which can differentiate between PV and PF or clinical phenotypes of PV demonstrating antibodies against 130 kda and 160 kda in mucocutaneos type, for mucosal type at 130 kda and in

pure cutaneous type 160 kda. Diagnostic accuracy of 95.7% and sensitivity of 95.7% has been reported.[54]

Comorbidities

Complications of pemphigus include sepsis, malnutrition and dehydration. However, with advent of corticosteroid in management of pemphigus mortality from pemphigus vulgaris has reduced from 90% to present rate of 5-6%.[55,56] The side effects of immunosuppressive agents being the most common cause of morbidity and mortality. Dental complications owing to inadequate oral hygiene maintenance with active lesions due to pain and / or hemorrhage leading development and / or progression of periodontal disease.[57,58]

Remission rate

A high remission rate has been described in US being 94.6% with drug free remission in 25%, 50% and 75% of patients after 2, 5 and 10 years. In Korea remission rate has been reported to be 77% at 5 years and 94% at 10 years. In India, there is only one such study available which reported remission of 34.6% in patients on dexamethasone-cyclophosphamide pulse cycle at the duration of 3. 33 years.[59]

Management

Various treatment modalities for management of pemphigus available are

1. Topical therapy
2. Systemic therapy
3. Pulse therapy
4. Plasmapheresis

European dermatology forum in 2014 has suggested guidelines for management of pemphigus. The workup recommended before initiation of systemic therapy includes complete blood count, creatinine and blood electrolytes levels, transaminases, alkaline phosphatase, total serum protein, albumin levels, fasting serum glucose and chest X-ray also infection like T. B., Hepatitis B, C and HIV should be ruled out. Recommended investigations indicated based on therapeutic used in management, including serum IgA levels to rule out IgA deficiency prior to IVIG treatment; also thiopurine methyltransferase (TPMT) activity should be determined when azathioprine is being used; Quantiferone or PPD is recommended in case of elevated risk for TB; G6PD serum activity, bilirubin, reticulocyte count if dapsone planned; pregnancy should be excluded; prior to corticosteroid treatment osteodensitometry and ocular examination for glaucoma or cataract is recommended.[60]

Topical therapy

Topical agents is indicated for mild oral lesions. Topical anaesthetic rinses, provide temporary relief and high-potency topical corticosteroids in forms of rinses, pastes, gels used as monotherapy or in conjunction. Topical tacrolimus is beneficial for recalcitrant lesions. Intralesional corticosteroid injections for isolated lesion, but has been associated with scarring and / or mucosal atrophy.[9,60]

Systemic corticosteroids

First-line systemic treatment for moderate to severe pemphigus. An effective initial dose of corticosteroids has been suggested to be 1 mg/kg/d[56,61] however there is no universal consensus regarding the same. Initial oral prednisolone dose of 40-60 mg/d has been recommended by some author whereas others have reported an initial dose up to 120mg/day to be more effective.[61] However, Benjamin S Daniel;(2015), have concluded though higher doses (120 mg/day) result in a more rapid control of disease than lower doses (60 mg/day), there is no evidence that the higher doses are beneficial in the long term. The corticosteroids are tapered to 2.5 mg per month.[62]

Managing pemphigus usually requires a prolonged corticosteroids course (>3 months), the preventive measures for glucocorticoid-induced osteoporosis must be considered including oral bisphosphonates, along with 800 international units of vitamin D and 1200 mg calcium. Bisphosphonates are indicated in postmenopausal women, elderly males with a high fracture risk, on a dose of prednisone >7.5 mg daily for three months.[63] Also symptoms of adrenal insufficiency, hypertension, diabetes mellitus, infections, gastrointestinal ulcers, steroid myopathy, and mood instability should be looked for.

Immunomodulators in management of pemphigus

Numerous studies have reported and recommended use of immunomodulators as adjuvant to systemic steroids to minimise the side effects of corticosteroids use. Immunosuppressant popularly used in past were gold, dapsone and methotrexate however they were associated with severe side effects especially at higher dose. Ongoing studies have opened new horizons for therapeutic options in managing pemphigus mycophenolate mofetil, azathioprine and intravenous cyclophosphamide pulse therapy are being the most popular choices for adjuvant therapy.

Azathioprine

A Purine synthesis inhibitor promotes inhibition of DNA synthesis in proliferating B and T cells has

shown a superior steroid-sparing effect when compared to other adjuvant therapies. The recommended dose being 1-3 mg/kg daily. The combined prednisolone and azathioprine protocol proved to be the most effective in terms of disease mortality and remission[41] Cochrane review suggests that glucocorticoids dosage can be decreased when combined with azathioprine or cyclophosphamide.[64]

Mycophenolate mofetil:

Has been indicated as combination therapy and monotherapy in dosage of 1-3 g/day. It has shown improved time to and duration of response also studies have shown it to be more effective in disease control than azathioprine.[42] Decrease time required for healing. The Cochrane review, Beissert et al.;(2010) have demonstrated in a randomized clinical trial that, in comparison to corticosteroids used as monotherapy, the addition of mycophenolate mofetil may be advantageous, since it achieved a faster and longer lasting response than corticosteroids alone.[65] A study of 18 patients attempted to determine a standard treatment regimen based on a retrospective chart review. Complete disease control was achieved in 89% patients. In 14 of these patients, complete control was reached with mycophenolate mofetil at 1 gram BID and prednisone at 1 mg/kg daily. Prednisone was held steady, mycophenolate mofetil was increased by 0.5 grams every month, until a maximum dose of 3 grams daily was reached. The other 2 patients required further treatment with rituximab.[66] Daniell B et al.; 2014, have reported similarities in efficacy and side effect profiles, azathioprine or MMF as first-line therapy hence no study has been able to prove one to be more effective than the other. [67] Sinha AA; (2015), have reported that mycophenolate mofetil has been shown to have a rapid effect in lowering pemphigus antibody titers and disease activity and has fewer side effects than azathioprine.

However, mycophenolate mofetil was inferior to azathioprine and cyclophosphamide in regards to steroid-sparing effect.[46]

Cyclophosphamide

Alkylating agent that selectively inhibits lymphopoietic cells while sparing hematopoietic cells and inhibits antibody-producing B cells. Has shown faster onset and more sustained remission. The recommended dose being Dose: 2-2.5 mg/kg daily.[47] Benjamin S. Daniel; 2014 reported RCT by Chams-Davatchi C, which showed similar efficacy with azathioprine, mycophenolate mofetil (MMF), and intravenous cyclophosphamide. The steroid-sparing effect was demonstrated only when all three agents were pooled together as one group.[67]

Cyclosporine

Several randomized controlled trials have failed to demonstrate a beneficial effect of oral cyclosporine either alone or as adjuvant therapy. One study compared cyclosporine plus steroids, cyclophosphamide plus steroids and steroids alone. Remission and relapse rates were similar in all three groups, and there was no clear benefit of using a combination.[68-70]

Methotrexate

Immunosuppressive agent that decreases autoimmune disease pathogenesis. Decreases disease activity and remission time recommended in dose of 15 mg/week or 1 mg daily.[48,49]

Dapsone

As an adjunctive recommended dose being 100-300 mg daily. However several studies have concluded the effect of dapsone on remission and withdrawal to be inconclusive.[71-74]

Intravenous immunoglobulin

IVIG selectively removes the pathogenic antibodies without affecting the level of "normal" antibodies. IVIG also alters the expression and function of Fc receptors, affects activation, differentiation and effector functions of T cells and B cells and works to decrease the response to autoantibodies by interfering with the complement pathway and cytokine activation.[75] Single cycle of high dose IVIG of 2 g/kg divided into 2 or 3 equal doses, given on 3 consecutive days, repeated every 4 weeks. A multicenter RCT by Amagai et al; compared various doses of IVIg found patients treated with a higher dose of IVIg had a better outcome Patients received one of three doses of 0 mg/kg per day, 200 mg/kg per day and 400 mg/kg per day. There was a dose-response relationship with more patients benefiting from the higher dose and objectively.[76]

Rituximab

Antibodies against CD20, a protein expressed by most developing and memory B cells has been considered as the most promising agent for complete or partial remission however relapses are common and is indicated mainly for patients with PV refractory to at least two therapeutic modalities.[77] It has also been used as a first-line treatment with favourable outcomes. Two dosing schedules have been suggested

the lymphoma protocol of weekly IV infusions of 375 mg/m2 once weekly for 4 weeks and a rheumatoid arthritis protocol of two 1 g infusions, administered 2 weeks apart. High-dose (≥ 2,000 mg) Rituximab was associated with longer complete remission compared with low-dose Rituximab (<1,500 mg). In report by Cianchini et al; 2007 11 patients with refractory PV, patients received a combination of high-dose IVIG and 2 cycles of rituximab once weekly for 3 weeks followed by 4 consolidation rituximab infusions monthly for 4 months This regimen resulted in a sustained complete remission in 82% of patients after only 7-9 weeks, lasting an average of 31.1 months. A larger study consisting of 21 patients found that 86% of patients (18 out of 21) with severe pemphigus on prednisone achieved complete remission at 3 months after receiving single cycles of rituximab once weekly for 4 weeks.[78] Current evidence supports the efficacy of RTX in treating patients with pemphigus, with 76% remission. Although the long-term efficacy of many of the therapies in pemphigus has not been evaluated Colliou N, (2013) have reported it to be 60% of patients with severe pemphigus treated with rituximab were in long-term remission of 6 years.[79] In comparison, the remission rates for patients managed in the Ratnam;5-year study were 36% with a dose of 120 mg/kg per day and 9% with a starting dose of 60 mg/kg per day.[53] Meta analysis by Wang et al.;2015, supports the efficacy of Rituximab in treating patients with pemphigus, with 76% of patients achieving complete remission. Mean remission duration was 14.5 months, with an overall relapse rate of 40%.[78]

Dexamethasone cyclophosphamide pulse (DCP) regimen

First developed by Pasricha and Ramji in 1982 for treatment of psoriasis patients. It has been extensively used in India owing to its low cost of therapy and considerably less side effects of pulsed steroids. It consisits of four phases. Phase I: DCP therapy given in the presence of signs and symptoms. Patients receive monthly doses of 100 mg of dexamethasone dissolved in 500 mL of 5% dextrose by slow intravenous infusion over 2 hour on three consecutive days along with 500 mg of cyclophosphamide in the infusion on day 2. In between, the patients received 50 mg of oral cyclophosphamide daily. Phase II: Patients were in remission but monthly DCP therapy and daily oral cyclophosphamide were continued for 9 months. Phase III: Only oral cyclophosphamide 50 mg is given to patients for an additional 9 months. Phase IV: All treatments are withdrawn and patients. [80,81]

Parmar N V et al.; (2013) found no difference in the clinical outcome between patients receiving nine DCPs in phase II and patients shifted directly from phase I to III. [82] A randomized control trial of 20 patients showed that pulsed oral dexamethasone (300 mg/d for 3 days) in addition to oral prednisolone and azathioprine does not improve time to remission, duration of remission or mortality. This study concluded that prednisolone, 80 mg/day on a tapering schedule to 0 mg in 19 weeks with azathioprine sodium, 3 mg/kg continued for a year after tapering, is the most effective regimen for patients with new disease activity.[83]

Meta analysis by Atzmony et al.;2015 Remission was reported in 6 trials including 378 patients treated with Oral glucocorticoids and MMF (n = 112), Azathioprine (n = 58), Cyclophosphamide (n = 40), Cyclosporine (n = 24), Oral glucocorticoides alone (n = 144). The addition of adjuvants was not associated with an increase in remission patients.

Disease control was reported in 8 trials including 190 patients treated with azathioprine (n = 28), MMF (n = 24), cyclophosphamide (n = 44), IVIG (n = 41), cyclosporine (n = 24), plasma exchange (n = 19), or infliximab (n = 10) compared with 149 patients treated with oral GCs alone. The addition of adjuvants was not associated with acheiving disease control. Relapse was reported in 7 trials including 338 patients treated with MMF (n = 92), Cyclophosphamide (n = 57), Azathioprine (n = 39), Cyclosporine (n = 24), Compared with 126 patients treated with oral GCs alone. The addition of adjuvants resulted in a significantly lower Relapse in patients.Specifically MMF, azathioprine, and cyclophosphamide were shown to decrease relapses.

A study concluded that prednisolone, 80 mg/day on a tapering schedule to 0 mg in 19 weeks with azathioprine sodium, 3 mg/kg continued for a year after tapering, is the most effective regimen for patients with new disease activity.[84]

European guideline for autoimmune bullous disease; 2014 has recommended first line therapeutics for management of pemphigus Azathioprine in Dose: 1-3 mg/kg/day to be started on first week 50 mg /day and raised to desired dose or mycophenolate mofetil at Dose of 2g/day or Mycophenolic acid (1440 mg/day) Raise daily dose by 1 capsule per week. The second line adjuvant being Rituximab 2 x 1g i.v. (2 weeks apart) 4x375 mg/m2 (each 1 week apart) or intravenous immunoglobulins at dose of 2g/kg/month or Immunoadsorption at 2 cycles à 4 days, 4 weeks apart. Cyclophosphamide at dose of 500 mg as i.v. bolus or Orally as 2 mg/kg/day. Methotrexate at 10-20

mg/week or Dapsone Dose: 100 mg/day or up to ≤ 1.5 mg/kg/day

Conclusions

Systemic corticosteroids are the mainstay of treatment for pemphigus. Much of the recent research has been assessing the efficacy of steroid-sparing agents, most commonly azathioprine, MMF, Rituximab, methotrexate, IVIg, and cyclophosphamide. Although strong evidence in the form of RCTs is lacking, because of the rarity of the disease, studies are often underpowered and fail to demonstrate a statistically significant difference between the active and control groups. The evidence to date indicates that adding an adjuvant to steroids has a significant steroid-sparing effect, reducing the cumulative exposure to steroids. Azathioprine and MMF are often considered first-line therapies for PV with good improvement. Rituximab is beneficial in patients who have poorly controlled disease despite high-dose steroids or steroid-sparing agents (or both) or are contra-indicated for receiving steroids. IVIg in short-term studies is effective for recalcitrant cases but its duration of treatment needs further investigation and further research with larger RCTs is required.

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Reference

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