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International Journal of Pharmaceutical and Biological Science Archive 1 (2) 2013, 01-07

REVIEW ARTICLE

A REVIEW ON PEMPHIGUS VULGARIS: RARE BUT A SEVERE AUTO IMMUNE DISORDER

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Received 28 August 2013; Revised 1 September 2013; Accepted 5 September 2013

ABSTRACT

This manuscript was prepared as a review presentation of Pemphigus. Pemphigus is a rare skin disease that causes by autoimmune disorders when body's defense attacks its own tissues and cells. Patient affected by pemphigus vulgaris will occasionally present with associated and characteristic nail changes. Article describing pemphigus vulgaris, it's complied, reviewed and pertinent information was extracted to provide a concise analysis. The diagnosis can be made by histologic identification or by presence of IgG and C3 with direct immunofluorescence testing. Systemic treatment is required and highly effective: It includes a tailored combination of anti-inflammatory medication, immunosuppressive agents or immunomodulatory treatments. The literature on this topic is still maturing. Here we have the summarized information of rare but sever auto immune disorder i.e. Pemphigus Vulgaris; its type, symptoms, etiology, pathophysiology, diagnosis, treatment and its after effects or complications associated with as treatment persist for long duration.

KEYWORDS: Pemphigus Vulgaris, Auto immune disorder, Rituximab.

INTRODUCTION:

It is a rare group blistering disease that affects the skin and mucous membranes[1]. In pemphigus, auto antibodies form against desmoglegin. Desmoglegin forms the "glue" That attaches adjacent epidermal cells via attachment points called Desmosomes. When autointibodies attacks desmoglegins, the cells become separated from each other and the epidermis become "unglued" A phenomenon called Acantholysis. This causes blisters that slough off and turn into sores. In some cases, these blisters can cover a significant area of skin. In 1964 the historic paper published about Pemphigus [2], In 1971 It was declared it comes under autoimmune disorder category.[3]An autoimmune disorder is a condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue. There are more than 80 different types of autoimmune disorders.

Normally the immune system's white blood cells help protect the body from harmful substances, called antigens e.g. bacteria, viruses, toxins, cancer cells and blood or tissues from another person or species. The immune system produces antibodies that destroy these harmful substances. But in patient with an auto immune disorder, the immune system cannot tell the difference between healthy body tissue and antigens. The result is an immune response that destroys normal body tissues. The response is a hypersensitivity reaction similar to the response in allergic conditions. In allergies, the immune system reacts to outside substances that it normally would ignore. With auto immune disorders, the immune system reacts with normal body tissues that it would normally ignore.

An auto immune disorder may result in:

- The destruction of one or more types of body tissue
- Abnormal growth of an organ
- Changes in organ function

Pemphigus vulgaris is a potentially fatal blistering muco cutaneous autoimmune disease that affects the skin and the oral cavity and other mucosal surfaces. The lesion is characterized by intraepidermal vesicles with acantholysis and an intact basal layer.[4]

Pemphigus is a rare skin disease that causes by autoimmune disorders when body's defense attacks its own tissues and cells. Autoantibodies is antibodies attack one's own cells. The part of the cells that are attacked in pemphigus are proteins called desmogleins. Desmogleins form the glue that attaches skin cells together, keeping the skin intact. When autoantibodies attack desmogleins, the cells become separated from each other. when skin becomes unglued. This causes burn-like lesions or blisters that do not heal. In some cases, these blisters occur a significant area of the skin.[5] It is unclear why the immune system goes wrong in this way. PV could be caused by a

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combination of both genetic and environmental factors. What is known is that PV is not contagious and cannot be passed from one person to another.

SIGN AND SYMPTOMS OF PEMPHIGUS

- Blister on mouth and skin (Fig.1)
- Oral mucous membrane lesions (Fig.2)
- Lesions usually start upper trunk and back. Gradual extension on face, groin, and maxillae.
- In most people with PV, blisters first appear in the mouth, and may later affect the skin. Blisters in the mouth turn into sores, making eating, drinking and brushing teeth very painful. If they spread to the larynx (voice box), the voice can become hoarse. If the skin is affected, PV will cause delicate blisters to appear all over the skin. These blisters easily burst to reveal red sores. The sores can crust over and form scabs, which can eventually discolor the skin. Sores may join together to form large areas of raw-looking skin.

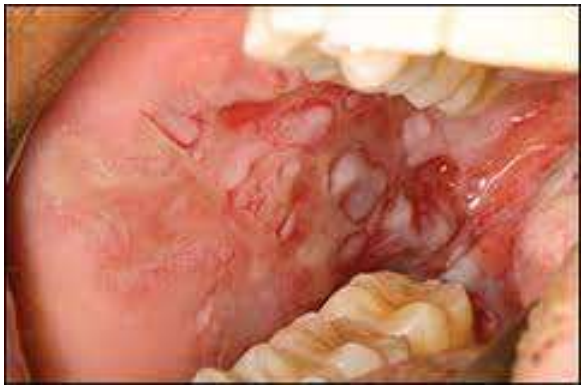

Figure 1: Blisters in mouth

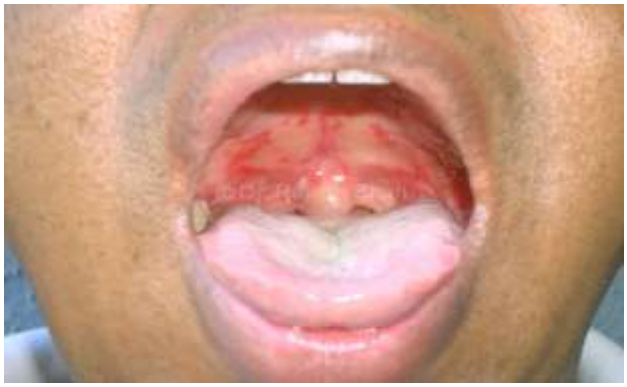

Figure 2: Lesions in oral cavity

CLASSIFICATION:

Pemphigus vulgaris (PV): Most common type of Pemphigus found majority in Middle East. Sore in the mouth, difficult to eat. Occur in mid to late adult life (46 of age).[6, 7]

Pemphigus foliaceus: Body's immune system destroyed protein caused crusty sores, then move to chest, back, and face. and is often mis-diagnosed as dermatitis or eczema.

Paraneoplastic pemphigus: is disease that causes 50% of chance of inheriting the disorder by parents have HHD.

ETIOLOGY AND PATHOPHYSIOLOGY:

The mucocutaneous symptoms of pemphigus vulgaris are caused by the binding of IgG autoantibodies to desmosomal associated glycoprotiens, desmoglein 1, and desmoglein 3. [8-10] This autoimmune reaction leads to acantholysis (Fig 3 and 4), or disruption of cell to cell interactions, that manifestes as painful blisters and erosive lesions. In the case of PV, the immune system produces antibodies that damage the cells in the skin and mucous membranes (the lining of the mouth, nose, throat and genitals).[9] The lesions can become quite extensive. The pathogenesis of the disease involves autoantibodies against desmosome proteins, separating keratinocytes from the basal layer of the epidermis. On histology, the basal keratinocytes are usually still attached to the basement membrane leading to the appearance and thus the term, "tombstoning".

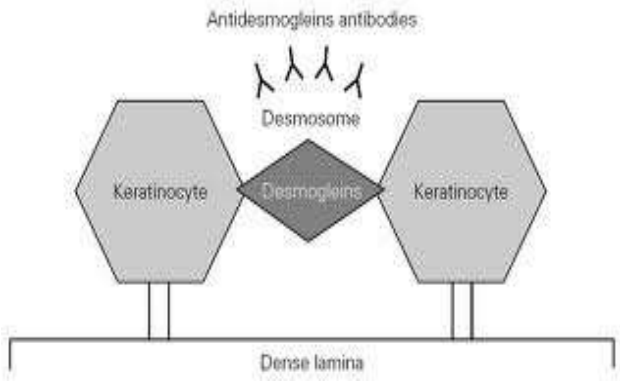

Figure 3: Pathogenesis of Acantholysis

Transudative fluid accumulates in between the keratinocytes and basement membrane (suprabasal split), forming a blister and resulting in what is known as a positive Nikolsky's sign. This is a contrasting feature from bullous pemphigoid, where the detachment occurs betweenthe epidermis and dermis.[10]

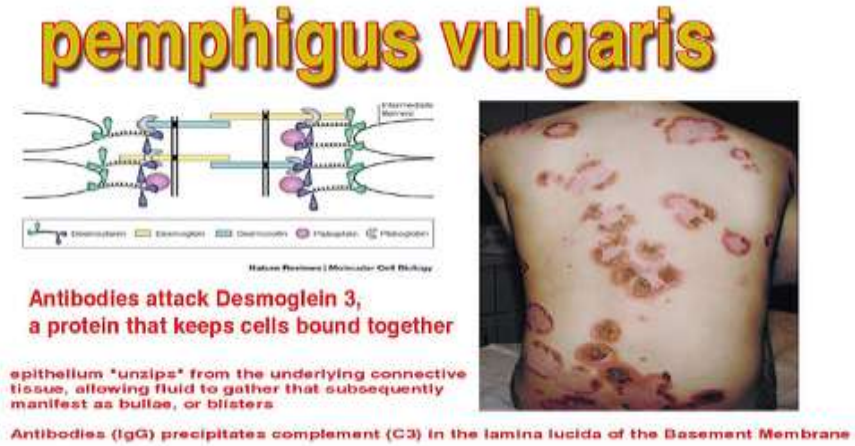

Figure 4: Pathophysiology of pemphigus vulgaris, throughout the body

Whether Pemphigus is hereditary?

Pemphigus is not passed down through families, and it is very unusual for more than one person in a family to have PV. However, recent evidence suggests that the genes a person inherits from their parents, while not directly causing PV, may make them more susceptible to the disease. Two genetic mutations (where the instructions found in all living cells become scrambled in some way) called DR4 and DRw4 are common in people with PV. Most experts believe it also takes an external factor or combination of factors to trigger PV. This could be a bacterial or viral infection or something in the environment, such as a pollutant.

DIAGNOSIS:

Pemphigus vulgaris (PV) is so rare, many patients could not come across it before. If any suspects PV, he should be referred to dermatologist (skin specialist).

A dermatologist will confirm the diagnosis and prescribe appropriate treatment.

PV should always be suspected in anyone who has sores inside the mouth that do not heal. The mouth is affected in many cases of PV, and sores may also be seen in other places, such as the genital organs on the skin.

The diagnosis of PV can be confirmed by doing a skin Biopsy, in which a sample of an unbroken blister is sent to a laboratory. The sample is examined under a microscope to see whether the skin cells are breaking apart, which could indicate PV.[11]

To confirm the diagnosis of PV further, a technique called Immunofluorescence can be used.

- In direct Immunofluorescence the skin Biopsy is stained with dye to detect PV antibodies in the cells. Specific direct immunofluorescences (DIF) testing of cells biopsy is only indicated in cases of chronic paronychia or onychomadesis that precede mucocutaneous lesions[12] In this cases chronic immunosuppressive therapy is omitted. [13]
- If DIF is positive, the diagnosis can be confirmed by conducting subsequent indirect immunofluorescesnce testing using the patient's serum. In indirect Immunofluorescence the levels of PV antibodies in the blood serum are measured.[11] Additionally, a histological examination of biopsy specimens acquired from blistering lesions on the surface will reveal acantholysis above the basal cell layer.[14]

Differential Diagnosis:

It is important to distinguish acute paronchia as assign of pemphigus vulgaris exacerbation from other similar clinical presentations, such as bacterial or candidal paronychia , genetic paronychia, or trauma. Paronychia presenting with pemphigus vulgaris with have a characteristic pathologic feature: suprabasal acantholysis without sponiosis or exocytosis. In addition, ballooning degeneration, reticular degeneration, and multinucleated giant cells in the epidermis are absent, which may be present in the above- mentioned alternative diagnosis.[15] Bacterial and fungal cultures should be performed. ELISA may be utilized to detect circulating autoantibodies to BP180 as well as to monitor disease activity through the measurement of antibody titers.[16]

TREATMENT OF PEMPHIGUS VULGARIS (PV):

There is currently no cure for PV, although the symptoms respond well to high doses of steroid medication. Using a high dose of steroids over a long period of time can cause serious effects. So when the symptoms have cleared, low doses are used in combination with other medicine. This is known as steroid sparing therapy, and it prevents some of the dangerous side effects associated with long term steroids use.

Treatment for pemphigus vulgaris (PV) usually involves taking a combination of two types of medication – steroid medication (oral corticosteroids) and immune-suppressants.

Both of these types of medication can prevent the immune system from damaging healthy tissue. It can take a while to determine the best dose of these medications. There is often a fine balance to successfully controlling symptoms while limiting unpleasant side effects, so it may take some months until this balance can be achieved. The aim of treatment is:

- To heal the blisters and prevent new ones from forming. It usually takes up to eight weeks for the blisters to heal and two to three weeks to prevent new ones from forming.
- To reduce the medication gradually to the lowest possible dose that will still control symptoms.

Oral corticosteroids:

Oral steroids are a basic option for the management of PV in any phase of the disease, and since their introduction have contributed to improve patient survival. [17, 18] The benefits afforded by oral steroid use with or without the Lever scheme are great. At conventional doses, these drugs reduce blister outbreaks within 2-3 weeks with complete disease remission in up to 29 % of cases.[19] Prednisone dosing via the oral route is arbitrary, since different management schemes have been developed, and no general consensus has been reached over the best treatment option for PV. The drug dose is empirically adjusted to the severity of the disease, though in most cases a dose of 0.5-1 mg/kg body weight is prescribed, reaching 2 mg/kg/day as required. Steroid dose reduction should be carried out gradually. In our practice we apply weekly 5-mg reductions to 20 mg, followed by weekly 2.5 mg reductions in an attempt to completely obviate the need for such medication while ensuring control of the disease.[20]

Methylprednisolone or dexamethasone pulses:

Steroid pulses have been widely applied to ampullar diseases, and fundamentally to PV, to avoid the complications and side effects of chronic daily oral steroid dosing. [21] The term "pulse" refers to discontinuous intravenous infusion of supratherapeutic drug doses in a short period of time Pulse therapy is recommended as an adjuvant to the initial management plan for patients with more severe. PV involvement Methylprednisolone (and dexamethasone) is the most commonly intravenous glucocorticoid.[22] The dose corresponding to each pulse has not been standardized, but ranges from 10-20 mg/kg in the case of methylprednisolone, and 2-5 mg/kg in the case of dexamethasone with a three-hour infusion in 500 ml of 5 % glucose solution. The mechanism of action of the glucocorticoid pulses comprises the inhibition of acantholysis induced by IgG in PV, as a result of which the spread of keratinocyte deterioration is reduced. The maximum effect is recorded 3-5 days after administration in agreement with the observation of animal studies.[23]The utilization of these megadoses has revolutionized the treatment of PV, for although such therapy is not the first choice management option, it almost always improves patient prognosis when prescribed on an opportune basis.

The treatment options for PV include substances known as adjuvant drugs, which are agents that support the effect of steroids administered fundamentally via the oral route. Some of these adjuvants act as "steroid sparing agents". The principal representatives are azathioprine and cyclophosphamide.

Azathioprine:

Azathioprine is one of the most common adjuvants to PV therapy, and has been shown to be effective in application to many diseases apart from PV, such as bullous pemphigoid and atopic dermatitis [24].While its utility is increasingly acknowledged, the principal side effect of azathioprine (potentially severe myelosuppression) has led to the recommendation of thiopurine methyltransferase testing as a predictor of azathioprine-mediated myelosuppression . The administration of azathioprine as adjuvant therapy in PV increases percentage disease remission up to 45 %. While the drug can be administered as sole therapy, its use in monotherapy (and even more as initial treatment) is not advised, due to the frequency of side effects involved.[25] Azathioprine offers better results when administered at a dose of 1-3 mg/kg for 6 weeks. After this period of treatment, bone marrow function must be carefully monitored.[25]

Oral cyclophosphamide:

The use of oral cyclophosphamide as steroid-sparing adjuvant therapy in PV has been documented in many reviews published in the literature. The use of oral cyclophosphamide in monotherapy entails many side

effects such as hematuria, overinfection and bladder carcinoma, and remission takes too long to achieve (8 months). In this period of time, the aforementioned side effects very often appear. Consequently, oral cyclophosphamide is not recommended as monotherapy or as a first treatment option.[26]

Methotrexate:

While the utility of methotrexate as monotherapy for PV has always been the subject of discussion, it is most widely accepted as an adjuvant. In effect, the combination of high doses of methotrexate (up to 125 mg a week are advised) with prednisone 0.5-1 mg/kg/day appears to bring the disease under control within 6 months. Despite evidence of the effectiveness of methotrexate as an adjuvant to therapy in patients with PV, in practice it is difficult to use because of its side effects (mainly at hepatic level). These effects are more likely when such high doses of the drug are used. [27]

Thus, methotrexate as adjuvant is reserved for those cases of PV in which it is not possible to use some other adjuvant substance such as azathioprine or cyclophosphamide.[27]

Dapsone Dapsone is one of the most useful agents in application to many diseases, including leprosy. There have been isolated reports on the utility of dapsone in application to PV. In this context, the drug has been postulated to control the levels of antibodies in PV, though the results of an experimental study suggest that dapsone exerts no effects upon serum antibody levels in PV.[28] Despite this, case studies have been made involving the use of this drug. It has not been shown to be of use in monotherapy, but can be used as an adjuvant. In any case, the data available to date are not conclusive.[29]

Rituximab Rituximab is a new type of medication that works by targeting what are known as B cells. These are a type of white blood cell that the immune system uses to attack healthy skin tissue in cases of PV. Research published in 2011 concluded that rituximab is an effective alternative to conventional treatment in cases where it is ineffective or causes serious side effects. Rituximab is administered directly into your vein over the course of a few hours. It is still unclear what the most effective method of prescribing rituximab is. Some doctors have tried using it once a week over the course of four weeks. It is common to experience flu-like symptoms when you are being treated with rituximab. Possible symptoms include:

- headache
- fever or chills
- fatigue
- muscle pain

Complications of pemphigus vulgaris:

Secondary infections are a common complication of Pemphigus Vulgaris (PV).
The blister caused by PV is vulnerable to infection and this is made worse as most of the medications used to treat PV weaken the Immune system.
Symptoms of an infected blister include:

- the blister or surrounding skin becomes more painful and hot
- the blister is filled with yellow or green pus
- there are red streaks leading away from the blister

It's important not to ignore an infected blister as it could potentially lead to secondary impetigo (a contagious bacterial infection of the skin) if it splits open (rupture). This could lead to further complications such as cellulitis (a bacterial infection of the deeper layers of the skin) or sepsis (a life threatening infection of the blood).
An infected blister can be treated with antibiotics:

Long-term uses of corticosteroid:

If you are required to take steroid medication (corticosteroids) on a long-term basis (more than three months) the side effects include:

- further weight gain
- thinning skin that can bruise easily
- muscle weakness
- a combination of fatty deposits that develop in the face (moon face), stretch marks across the body and acne – Cushing syndrome
- weakening of the bones
- the onset of diabetes or worsening of existing diabetes
- Blood pressure (High)
- eye condition where fluid gathers inside the eye (Glaucoma)
- eye condition where cloudy patches develop at the front of the eye(Cataract)
- delayed wound healing
- increased risk of infection

CONCLUSION:

In summary, pemphigus vulgaris and bullous pemphigoid are autoimmune blistering disorders, that require the integration of clinical, histopathologic and immunopathologic findings for diagnosis. Communication between the clinician and the dermtopathologist/ immundermatologist is essential for prompt and accurate diagnosis, allowing for the immediate initiation of immunosuppressive therapy in order to significantly reduce morbidity and mortality. While many treatments

have been developed for pemphigus vulgaris (PV), none have been shown to offer absolute efficacy in controlling the disease. The management of choice is steroid therapy via the oral or intravenous route, which offers an adequate response and favorably modifies the prognosis.

The drugs described above are only part of the repertoire currently available for the management of PV. The more salient options have been described, in view of their ease of use and accessibility. Though it is the not too distant future we hope also to be able to introduce photodynamic therapy and specific plasmapheresis, among other therapeutic options.

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