Available online at http://www.journalijdr.com

IJDR

International Journal of
DEVELOPMENT RESEARCH

ISSN: 2230-9926

International Journal of Development Research
Vol. 07, Issue, 01, pp.11307-11311, January, 2017

Case Study

MANAGEMENT OF A RARE CHRONIC BLISTERING AUTOIMMUNE SKIN DISEASE: PEMPHIGUS VULGARIS

***[1]Preetha. S. Panicker, [1]Dr. Vigneshwaran, L.V. and [2]Sangami Bharathi, M.**

[1]Department of Pharmaceutics, Ahalia School of Pharmacy, Palakkad, Kerala, 678557
[2]Ahalia School of Pharmacy, Palakkad, Kerala, 678557

ARTICLE INFO

Article History:
Received 07th October, 2016
Received in revised form
01st November, 2016
Accepted 19th December, 2016
Published online 30th January, 2017

Key Words:

Pemphigus,
Auto immune,
Keratinocyte,
Desmosomes.

ABSTRACT

Pemphigus vulgaris is an autoimmune, intraepithelial, blistering disease affecting the skin and mucous membrane. The immune system produces anti bodies against specific proteins in the skin and mucous membrane. These anti bodies break the bonds between skin cells. This leads to the formation of a blister. The exact cause is unknown. It is mediated by circulating auto antibodies directed against keratinocyte cell surface. The disease arises most often in middle aged or older people, usually starting with a blister that ruptures easily. The lesions can become quite extensive. As potentially life threatening disease, it has a mortality rate of approximately 5-15%. There are 5 main variant of pemphigus, pemphigus vulgaris, pemphigus foliaceous, pemphigus erythematous, drug induced pemphigus and Para neoplastic pemphigus. Corticosteroids and other immunosuppressive drugs are used to reduce the symptoms of pemphigus. An established alternative to steroids are monoclonal antibody such as rituximab, which are increasingly being used as first line treatment.

INTRODUCTION

Pemphigus vulgaris is a severe auto immune disorder of the skin and mucous membrane that is characterized by the formation of bulla. Oral mucosa plays an important role in the natural history of pemphigus vulgaris. It involves blistering and erosions of the skin and mucous membranes. In approximately 50 -70 percent of patient, the disease starts in the oral cavity and the lesions by several months. Very rarely lesions remain restricted to oral mucosa for prolonged period (Ferri, 2016). In pemphigus patient, an autoimmune process disrupts desmosome function leading to a breakdown of cutaneous and mucosal barriers characteristic in the presence of auto antibodies. (IgA or IgG) against structural components of desmosomes resulting in epithelial cell separation (acantholysis). This process is clinically evident as intraepithelial blister formation, hence the term pemphigus derived from the Greek word Pemphix (bubble or blister). Individual cells of the skin and mucosa, the keratinocytes, are anchored to one another and to the underlying connective tissue by a number of adhesive mechanisms that secure integrity, resist mechanical trauma, prevent microorganism from entering into the body and protect from fluid loss.

****Corresponding author: Preetha. S. Panicker,***
Department of Pharmaceutics, Ahalia School of Pharmacy, Palakkad, Kerala, 678557.

Epithelial cell to cell adhesion above the basal keratinocyte layer is secured by specific adhesion complexes known as desmosomes (Habif, 2016).

Pemphigus Vulgaris

Pemphigus vulgaris is a rare chronic blistering skin disease. It is classified as a type II hypersensitivity reaction, with the formation of antibodies against desmosomes, components of the skin that function to keep certain layers of skin bound to each other.

Pemphigus Foliaceous

Pemphigus foliaceus doesn't cause blisters in the mouth. The blisters first appear on the face and scalp . Blisters then appear on the chest and back. .the blisters are usually itchy and painless.

Pemphigus Vegetans

Pemphigus vegetans causes blisters then appear on the groin, under the arms, and on the feet.

Paraneoplastic Pemphigus

A very rare type of pemphigus that occurs in people with some cancers is called Para neoplastic pemphigus .The blisters and

sores may appear in the mouth, on the lips, and on the skin. This type may also cause scars on the eye lids and eyes. It can also cause lung problems.

Pemphigus Erythematosus

Pemphigus erythematosus, also known as Senear-Usher syndrome, is an overlap syndrome with features of lupus erythematosus (LE) and pemphigus foliaceus. Pemphigus is demonstrated by acantholysis and immunoglobulin deposits in the interkeratinocyte substance (James, 2016).

Epidemiology

Pemphigus affects people across racial and ethnic lines. Men and women are equally affected. Research studies suggest a genetic predisposition to the disease. Although the onset usually occurs in middle-aged and older adults, all forms of the disease may occur in young adults and children. Research has shown that certain ethnic groups (such as the eastern European Jewish community and people of Mediterranean descent) are more susceptible to pemphigus. A particular type of pemphigus occurs more frequently in people who live in the rain forests of Brazil. Peak incidence 30-60 years of age. Mean onset of age is 50 to 60 years (ranges on subtype and can affect persons at all ages) (Grover, 2011).

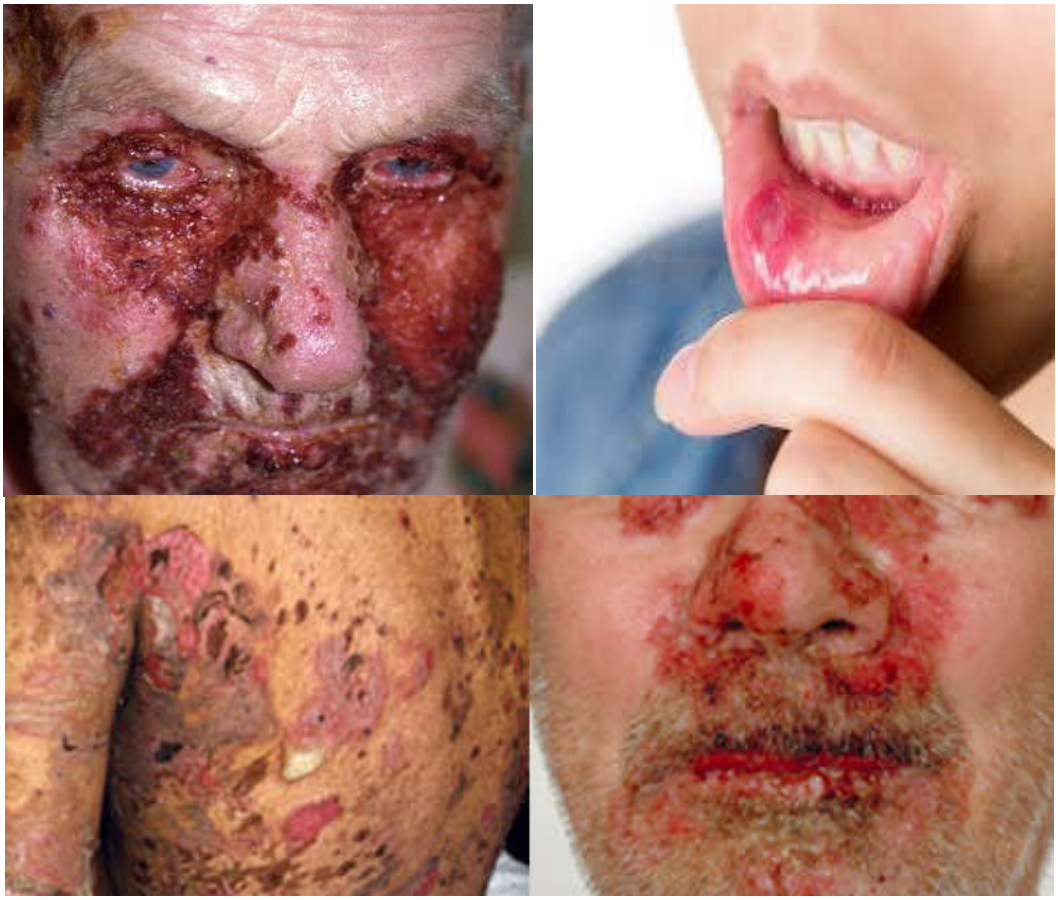

Figure 1. Pemphigus vulgaris affected patients

Genetics

The occurrence of the disease in first-degree relatives, although rare, suggests an inherited susceptibility transferred as a dominant trait. Pemphigus is more common in persons with certain HLA allotypes. HLA DR4 and DR14 (DRB1*0402 and DRB1*0401 more specifically crucial in susceptibility. HLA-DRB1*0402 is associated with the disease in Ashkenazi Jews and DRB1*1401/04 and DQB1*0503 in non-Jewish patients of European or Asian descent. Socioeconomic features: none known as a risk factor or predictor. Pediatric pemphigus is rare, but identical to adult in presentation (Harman, 2013).

Signs and Symptoms

The common signs and symptoms of pemphigus vulgaris include,

- Painful blisters that starts in the mouth or skin areas.
- Skin blisters near the surface of the skin that come and go.
- Oozing,crusting or peeling at the blister sites.

Effect on Mucous membranes: Mucous membranes of the oral cavity are involved in almost all patients with pemphigus vulgaris. Patients may have ill-defined, irregularly shaped, gingival, buccal, or palatine erosions, which are painful and slow to heal. Intact bullae are rare in the mouth. Erosions may be seen on any part of the oral cavity, and they may spread to involve the larynx, with subsequent hoarseness. In juvenile pemphigus vulgaris, stomatitis is the presenting complaint in more than 50% of cases.

Other mucosal surfaces may be involved, including the conjunctiva, esophagus (causes odynophagia and/or dysphagia), labia, vagina, cervix, vulva, penis, urethra, nasal mucosa, and anus.

Effect on Skin: Primary lesion of pemphigus vulgaris is a flaccid blister filled with clear fluid that arises on healthy skin

or on an erythematous base. Blisters are fragile and may rupture, producing painful erosions (the most common skin presentation). Lesions in skin folds readily form vegetating granulations. In some patients, erosions tend to develop excessive granulation tissue and crusting; these individuals display more vegetating lesions.

Effect on Nails: Acute or chronic paronychia, subungual hematomas, and nail dystrophies affecting one or several fingers or toes have been reported with pemphigus vulgaris (Ask Mayo Expert, 2016).

Causes of Pemphigus vulgaris

The immune system produces proteins called antibodies. Antibodies normally attack harmful foreign substances like bacteria and viruses. Pemphigus vulgaris occurs when the immune system mistakenly masks antibodies against proteins in healthy skin and mucous membranes. The antibodies breakdown the bonds between the cells and fluid collect between the layers of the skin. This leads to blisters and erosions on the skin. Certain medication can cause pemphigus vulgaris these drugs include Penicillamine and several ACE inhibitors (http://www.niams.nih.gov/health_info/pemphigus/).

Diagnosis

Blisters occur with a number of conditions, so pemphigus can be difficult to diagnose. Complete examine of skin and mouth has to be done. A Check for skin peeling by making a light rub a patch of normal skin near the blistered area with a cotton swab or finger. In pemphigus, the top layers of the skin are likely to shear off. By skin biopsy a piece of tissue from a blister is removed and examined under a microscope. Blood tests help to detect and identify antibodies in the blood known as desmogleins. These antibodies are often elevated when pemphigus is first diagnosed. The levels of these antibodies usually goes down as symptoms improve. Also undergo endoscopy to check for sore throat (Martin, 2015).

Management

The primary aim of treatment is to decrease blister formation, prevent infections and promote healing of blisters and erosions. Oral corticosteroids are the mainstay of medical treatment for controlling the disease. Since their use, many deaths from pemphigus vulgaris have been prevented (mortality rate dropped from 99% to 5-15%). They are not a cure for the disease but improve the patient's quality of life by reducing disease activity. Unfortunately higher doses of corticosteroids may result in serious side effects and risks. Other immune suppressive drugs are used to minimise steroid use. These include:

- Azathioprine
- Cyclophosphamide
- Dapsone
- Tetracyclines
- Nicotinamide
- Plasmapheresis
- Gold
- Mycophenolate mofetil
- Intravenous immunoglobulin
- The TNFα inhibitor, infliximab
- Anti-CD20 monoclonal antibody (rituximab)

At optimal therapy patients may still continue to experience mild disease activity. Appropriate wound care is particularly important, as this should promote healing of blisters and erosions. Patients should minimize activities that may traumatize the skin and mucous membranes during active phases of the disease. These include activities such as contact sports and eating or drinking food that may irritate or damage the inside of the mouth (spicy, acidic, hard and crunchy foods). There is future hope that future treatment for pemphigus will be more specific with fewer side effects. Investigators have engineered specific chimeric autoantibody receptor T-cells to eliminate Desmoglein-3-specific B cells in mice. The goals of therapy are to bring the disease under control as rapidly as possible, to prevent loss of serum and the development of secondary infection, and to promote re-epithelization (renewal of epithelial tissue).corticosteroids are administered in high doses to control the disease and keep the skin free of blisters. The high dose level is maintained until remission is apparent. In some cases corticosteroids therapy must be maintained for life. High dose corticosteroid therapy has serious effects. Immunosuppresive agents (eg.azathioprine) may be prescribed early in the course of the disease to help control the disease and reduce the corticosteroid dose. The immunosuppressant agent cyclophosphamide may be tried when other medications fail to induce remission. The monoclonal antibody Rituximab is demonstrating promise as an effective therapeutic agent in clinical trials (Bope, 2015).

Complications of pemphigus vulgaris

Secondary infections are the common complications of pemphigus vulgaris. The complications of pemphigus vulgaris can be fatal and severe. They may include, skin infections sepsis or the spread of infection through the blood stream.

Long term corticosteroid use

During steroid medication (corticosteroids) on a long term basic (more than 3 month), 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- this is known as Cushing's syndrome, weakening of the bones (osteoporosis), the onset of diabetes, or worsening of existing diabetes, high blood pressure, glaucoma – an eye condition where fluid gathers inside the eye, cataracts – an eye condition where cloudy patches develop at the front of the eye, delayed wound healing, increases risk of infection, etc…

The open sores of pemphigus make the patient highly vulnerable to infection, which, if it spreads to the bloodstream, can be fatal. Possible complications of pemphigus include infection of the skin, infection that spreads to the bloodstream (sepsis), gum disease and tooth loss, if the patient have blisters in their mouth, medication side effects, such as high blood pressure and infection, death from infection, etc… These side effects should improve if the dosage is reduced. osteoporosis can be a persistent problem, particularly if the patients are over 65. This can make more vulnerable to break a bone. Calcium and vitamin D supplements, which help the bones and can compensate for the effects of prednisolone. The patients may also referred for a type of X-ray called a dual energy X –ray absorptiometry (DEXA) scan.

Do's and Dont's of Pemphigus vulgaris	
• Take medications as prescribed by the doctor. • Inform the doctor of all other medications, including over-the-counter medicines, that the patient is taking. Continue these medications unless the doctor instructs the patient to stop them. • Read the labels of medicines and follow all instructions. Consult the doctor if the patient have any concerns, or if they have new or unexplained symptoms that may result from side effects of the medication. • Eat a well-balanced, nutritious diet. If lesions in the mouth or throat are causing pain with eating or swallowing, follow a liquid or soft diet to ensure adequate nutrition. Avoid protein rich foods, Garlics,etc… • Avoid activities that cause overheating and excessive sweating or moisture. If they perform activities that result in excessive moisture, immediately shower and cleanse the skin lesions. • Maintain good skin hygiene to reduce the risk of secondary bacterial infection. • Keep scheduled follow-up appointments with the doctor. They are essential to monitor the condition, their response to therapy, and to screen for possible side effects of treatment. • Monitor the skin for healing and for evidence of secondary bacterial infection. Signs and symptoms of infection include redness around the skin lesions, purulent discharge (pus), increased pain or swelling of the skin lesions or lymph nodes, and fever. • Frequently wash clothing, towels, and linens when skin lesions are oozing, crusting, or infected. This action reduces the risk of transmission of infection.	• Do not exceed recommended doses of medicines, because higher doses may increase the risk of toxic effects. • Do not use potent topical steroids on the skin of the face or genitals because these areas are most prone to skin injury and atrophy (thinning and wasting of the skin associated with wrinkling, and abnormal, small blood vessels). • Do not abruptly stop steroids or immunosuppressive therapy, because the patient may experience a rebound worsening of the condition. Suddenly stopping steroid medication may result in serious health consequences, including severe weakness, fatigue, and low blood pressure. • Do not drive or perform other potentially hazardous activities when taking medications that can cause drowsiness or sedation (antihistamines or pain medications). • Avoid activities that can increase the risk of infection of skin lesions. • Do not stop the medicine or change the prescribed dose without consulting the doctor[13].

Stomach ulcers can also be a problem for people who take high doses of oral corticosteroids on a long term basis. To protect against stomach ulcers, the patient may be prescribed a type of medication called a proton pump inhibitor (PPI). The patients will also probably have regular checks and tests for conditions such as diabetes, high blood pressure and glaucoma if the patient needs to take oral corticosteroids on a long term basis (Kasperkiewicz, 2012).

Treatment

Specific treatment depends upon the location and severity of the bullous pemphigoid, its impact on the quality of the life, and the response to therapy. Treatment aims to lessen the severity of the condition and to prevent complications. Treatment consists of general measures and medications.

- Maintain good skin hygiene to reduce outbreaks and to decrease the risk of secondary bacterial infection.
- Avoid skin injury, including scratching, which can aggravate bullous pemphigoid and contribute to secondary infections.
- Individuals with bullous pemphigoid can become depressed or experience other psychological conditions and may need psychological counseling (Venugopal, 2011).

The medications include

- Topical steroid creams, lotions, and ointments are effective in mild cases of bullous pemphigoid and as combination therapy for more severe cases. The doctor may recommend placing occlusive dressings over the topical medications to increase their effects. Side effects of topical steroids include skin atrophy, formation of abnormal, small blood vessels, and absorption of medication through the skin into the bloodstream, which can cause toxic effects. To decrease the risk of side effects, do not exceed the recommended dosage prescribed by the doctor.
- Corticosteroid tablets or injections are effective in treating bullous pemphigoid. Side effects are more likely with higher doses and include increased risk of infection, swelling, ulcers, diabetes mellitus, and osteoporosis (thinning of the bones). Do not stop steroid medications without first consulting the doctor because abrupt cessation of these medicines can result in severe weakness, fatigue, and low blood pressure.
- Immunosuppressive medications such as azathioprine and cyclophosphamide are potent suppressors of the patient's immune system and are effective in treating bullous pemphigoid. When these agents are combined with steroids, they allow less steroids to be used, thereby decreasing the risk of side effects. Side effects of these agents include increased susceptibility to infection, and toxicity to the body's organs including the bone marrow (anemia, low values of white blood cells and platelets), liver, and kidneys. The doctor will need to closely monitor the response to therapy and to perform laboratory tests to check for possible toxic effects.

- The doctor may prescribe dapsone to reduce skin eruptions and blistering and to lessen the severity of the condition. The patient will probably need to take this medication for an extended period. The doctor will need to monitor for side effects by checking periodic laboratory tests. Side effects may include breakdown of red blood cells (hemolytic anemia), inflammation of the peripheral nerves (peripheral neuropathy), nausea, vomiting, and abdominal pains.

The doctor may recommend one or more of the following measures to care for the bullous pemphigoid:

- Cleansing baths.
- Local cleansing of skin wounds.
- Wound dressings including topical steroids and use of antibiotic ointments (Heelan, 2014).

Except medications, no specific dietary measures can prevent or treat bullous pemphigoid. In severe cases, lesions in the lining of the mouth or throat cause pain with eating or swallowing. The patients may need to follow a liquid or soft diet to ensure adequate nutrition and will need to aggressively cleanse and monitor the wounds to prevent complications such as infection. Thus the rare blistering type II hypersensitive reaction can be managed.

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