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Advances in the Management of Pemphigus Vulgaris: A Review Article

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Abstract- Pemphigus Vulgaris (PV) is a debilitating autoimmune disease with a genetic predilection. In most cases, PV affects the oral mucosa, but can also occur in conjunction with skin lesions affecting different areas of the body. Lesions affecting the oral mucosa are characterized by the presence of erosions whereas, skin lesions appear mainly as flaccid bulla in their early stages or as erosions later in the disease course. Pemphigus Vulgarisis characterized by the formation of highly fragile bulla that frequently ruptures, forming denuded, painful, easily bleeding erosions that often become crusted.

Proper diagnosis is considered a significant component of early and efficient management, resulting in less morbidity. The use of corticosteroids in conjunction with immunosuppressant drugs such as azathioprine and mycophenolatein the management of acute attacks has been applied throughout the years (1).

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Advances in the Management of Pemphigus Vulgaris: A Review Article

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Abstract- Pemphigus Vulgaris (PV) is a debilitating autoimmune disease with a genetic predilection. In most cases, PV affects the oral mucosa, but can also occur in conjunction with skin lesions affecting different areas of the body. Lesions affecting the oral mucosa are characterized by the presence of erosions whereas, skin lesions appear mainly as flaccid bulla in their early stages or as erosions later in the disease course. Pemphigus Vulgarisis characterized by the formation of highly fragile bulla that frequently ruptures, forming denuded, painful, easily bleeding erosions that often become crusted.

Proper diagnosis is considered a significant component of early and efficient management, resulting in less morbidity. The use of corticosteroids in conjunction with immunosuppressant drugs such as azathioprine and mycophenolatein the management of acute attacks has been applied throughout the years (1). This practice has exposed patients to the consequential systemic complications associated with prolonged use of these drugs. However, safer and more cost-effective treatments have been introduced. In this review article, we present the clinical, pathophysiologic, diagnostic, and therapeutic aspects of Pemphigus Vulgaris.

Keywords: flaccid bulla, desmosomes, nikolsky sign, asboe-hansen sign, immunofluorescence, corticosteroids, immunosuppressant, anti-cd20 monoclonal antibodies.

I. Purpose

To review Pemphigus Vulgaris in regards to clinical manifestations, diagnosis, and management, presenting the latest therapeutic measures in treating patients with safer and less long-term complications.

II. Methods

In this article, we present the prevalence of Pemphigus Vulgaris and the ethnic considerations taken in the development of the disease. We also discuss different methods of diagnosing Pemphigus Vulgaris and managing patients to yield the best prognostic results. The article publishs data obtained from the Medline/PubMed online database, using the following search terms and key words: "Pemphigus Vulgaris, Corticosteroids, Immunosuppressant and Anti-CD20 monoclonal antibodies".

III. Results

The article identifies clinical and laboratory findings that must be considered in the evaluation of patients with Pemphigus Vulgaris (PV). Early diagnosis and management using Anti-CD20 monoclonal antibodies in PV patients reveal longer-lasting results with less corticosteroids use when compared to immunosuppressant therapy associated with better short and long-term outcomes.

IV. Conclusion

All patients with chronic mucous membranes ulcers with or without skin bulla must undergo a thorough history and physical evaluation, including intra and extra oral examinations. Correctly diagnosing patients with Pemphigus Vulgaris using histopathology and immunofluorescence facilitates early management utilizing optimal therapeutic options with the least possible side effects.

V. Introduction/discussion

Pemphigus Vulgaris (PV) is the most common type of autoimmune bullous disease known as Pemphigus, characterized by chronic relapse that usually occurs within two years following diagnosis (2). Pemphigus Vulgaris is rare, affecting both the skin and mucous membranes. Oral mucosa can be the only site affected in many cases and usually precedes skin involvement (3,4). It occurs most commonly in adults between the ages of 40 and 60 (5), with rare occurrences in children. Pemphigus Vulgaris has a higher propensity for people with Jewish inheritance and those from the Middle East and India (6), with most studies indicating female predisposition (7). It presents clinically as painful blisters or erosions that can result in patient debilitation. Skin epidermal integrity is maintained by the desmosomes present between keratocytes(8). In Pemphigus Vulgaris, IgG antibodies attack cell surface receptors, particularly desmoglein Dsg3 and Dsg1 of the cadherin family (9), destroying the junction between cells resulting in loss of integrity manifested clinically by blisters (10). Developed blisters are highly fragile. They can rupture easily and coalesce together, resulting in large painful ulcers at a high risk of

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infection. Approximately 50% of patients only develop intraoral blisters, with palatal and buccal mucosa being the two most commonly affected sites. Other vulnerable locations include the nose, larynx, pharynx, esophagus, conjunctiva, and genitalia (11,12).

Pemphigus Vulgaris should always be suspected in patients presenting with chronic mucosal ulcers, especially when they are associated with skin bullae. They must also be differentiated from other bullous dermatoses.

Clinical examination of suspected cases is used to detect loss of epidermal cell adhesion. Positive Nikolsky and Asboe-Hansen signs are indicative of PV. Nikolsky sign is considered positive if normal epidermal skin layer adjacent to formed bulla moves laterally upon pressure application (13). Asboe-Hansen sign is tested by applying gentle pressure on intact unruptured bulla resulting in subdermal fluid spreading away from the site of pressure (14). Enzyme-linked immunosorbent assays (ELISA)is used to identify and quantify the autoantibodies, it is also used to titrate the circulating autoantibodies to guide the treating physician in the management decision at the remission phase(15).A correlation between autoantibodies (anti-Dsg1/anti-Dsg3) titer has been associated with the disease activity, showing earlier relapse during remission in patients with high anti-Dsg3 titers(> 20 U/mL) (16). Where lower Dsg-1 titers are found to be associated with longer relapse time (17). However, a biopsy of the lesion with the surrounding skin is indicated to confirm diagnosis. Histopathological examination of the affected tissue will reveal intracellular acantholysis with an intact, unseparated basement membrane (18).This feature differentiates it from bullous pemphigoid, which is considered a less severe entity. Direct immunofluorescence (DIF) testing will reveal IgG and C3 immune deposits bound to cellular desmogleins (DSG), creating a “net-like” pattern that indicates intercellular separation. Indirect immunofluorescence (IIF) of the serum antibodies is a tool to monitor the progression of the diseases and the outcome of the treatment (19).

Different scoring systems have been used in assessing the disease severity and its response to treatment, such as the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and the Pemphigus Disease Area Index (PDAI). The former scoring system measures the changes in pemphigus disease severity, providing both qualitative and quantitative information, and both objective and subjective information for oral involvement, making it superior to other scoring systems (20). The later scoring system (PDAI) consists of three components, including skin, scalp, and mucous membranes, measuring both disease activity and damage level. It has a total possible score ranging from zero to 263, with 250 points representing disease activity, divided as 120 points for skin activity, 10 points for scalp activity and 120 points for mucosal activity, and 13 from damage scores (21). Other less common scoring systems have been applied, including; Pemphigus area and activity score (PAAS), Ikeda index, and Mahajan et al. severity scoring) (22).

The main goal in treating patients with PV is to lower the production of pathogenic autoantibodies. Managing patients in the acute phase of Pemphigus Vulgaris has traditionally been conducted by administering the smallest possible dose of systemic glucocorticoids such as prednisolone (23) to avoid the possible major systemic complications associated with using higher doses. At this stage, patients are also prescribed immunosuppressant drugs such as azathioprine and mycophenolatemofetil (MMF) (24). Tapering the corticosteroids can only be done after the patient has achieved remission; frequent negative Nikolsky’s sign is indicative of remission. After the cessation of corticosteroids, other immunosuppressant drugs can also be tapered while maintaining remission based on the patient’s renal and liver function (25,26). Both Azathioprine and MMF are purine synthesis inhibitors (purine analog) that require close monitoring to reduce their known possible side effects. The most common side effect associated with Azathioprine use is nausea, but other complications, such as bone marrow suppression resulting in pancytopenia, thrombocytopenia, and leukopenia, are also documented (27). MMF is also associated with possible side effects such as nausea, vomiting and gastrointestinal disturbances, and discomfort.

Long-term use of systemic corticosteroids in patients can result in many serious complications, including osteoporosis, causing fractures in up to 50% of patients and osteonecrosis in up to 40% (28). Other complications include hyperglycemia, hypertension, arrhythmias, edema, weight gain, skin thinning and atrophy, cataracts, GI bleeding, impaired wound healing, and neuropsychiatric adverse effects (29).

Anti-CD20 monoclonal antibodies, such as rituximab and ofatumumab, have been introduced to the management of PV, revealing a significant clinical improvement in patients along with reducing the use of concomitant immunosuppressive medication. These medications functions by inhibiting B lymphocytes maturation into autoantibody-producing plasma cells by targeting CD20 antigen on pre-B, immature, and mature B, resulting in antibody-dependent cytotoxicity followed by apoptosis (30), without affecting immunoglobulin synthesis since CD20 is not expressed on stem cells and plasma cells, resulting in the best possible outcome with reduced or complete elimination of corticosteroids use with long lasting results with a single treatment course (31). A randomized, controlled trial comparing the use of rituximab and mycophenolatemofetil in managing PV patients reported superior outcomes with Rituximab therapy producing sustained complete remission at 52 weeks with a higher reduction in

glucocorticoid use (32). Another predictive study of relapse concluded that positively identifying either anti-Dsg1 or anti-Dsg3 antibodies detected with ELISA test following rituximab treatment showed to be associated with disease relapse (33,34). Maho-Vaillant et al. demonstrated that long-lasting Rituximab therapy efficacy is associated with long duration of serum antieDSG-1 and antieDSG-3 IgGþ Abs disappearance following the absence of DSG-specific B cells (35).

Rituximab therapy is associated with multiple side effects, including nausea, vomiting, fever, and headaches, reported to occur mainly during the first infusion. However, other complications have been reported, such as pneumonia and septic arthritis (36). Another rare but serious complication that can result secondary to Rituximab use is the development of viral infection of the brain white matter known as progressive multifocal leukoencephalopathy (PML) (37).

VI. Conclusion

Pemphigus Vulgaris is an autoimmune disease, mainly managed with corticosteroids and immunosuppressants, subjecting patients to multiple serious complications. The introduction of Anti-CD20 monoclonal antibodies treatment revealed significant long-term clinical improvement with single course infusion and a noticeable reduction of the concurrent corticosteroid use in patients with PV. However, future antigen-specific targeted treatments need to be further studied to improve therapeutic outcomes and decrease disease relapse.

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