

REVIEW ARTICLE

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Mucous membrane pemphigoid: A wide-ranging assessment of various cases and corresponding methods of diagnosis and treatment

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Abstract

Mucous Membrane Pemphigoid (MMP) is as an infrequent yet tenacious autoimmune blistering disease involving the mucosae of the oral cavity, as well as the conjunctiva, genitals, nasal cavity, pharynx and occasionally the skin. It is seen most commonly in older adults, although cases have been reported throughout early childhood. This review article will provide a thorough explanation of MMP by discussing common misdiagnosis scenarios, presenting rare case reports, and exploring recent treatment options in hopes of spreading awareness for furthering research on diagnosis techniques. The purpose this article is to bring light to the dental community, medical professionals and autoimmune disease researchers, the importance of an early and authentic diagnosis and corresponding methods of recent treatments.

Keywords: Pemphigoid, oral, misdiagnosis, autoimmune blistering, MMP

Introduction

Mucous Membrane Pemphigoid (MMP), is reputed as a persistent, heterogenous group of autoimmune blistering disease primarily involving mucous membranes, however, it can be detected on skin periodically [1,2]. The specific immune deposits that are most commonly found in MMP, include immunoglobulins IgG, and IgA, and complement C3 [3]. These immune deposits exist in the basement membrane of stratified squamous epithelium, as the term “pemphigoid” is a result of these unique characterizations [4]. Before today’s term, MMP, was called by a more derivative based name, Cicatricial Pemphigoid. The root cicatrix, which is used to form the word Cicatricial, comes from Latin origins meaning “to scar”. The presence of scars related to CP, were diagnosed with the inclusion of scar tissue as a baseline identifier in commonalities and contrasts in the variety of cases [5]. Today, MMP is most commonly located in the oral mucosa, but can also be found in the conjunctiva, hypopharyngeal mucosae, inner nostril lining, sinus cavity, esophagus, larynx, and genital mucous membranes [6]. When the lesions are constricted only in the oral region, then the term oral pemphigoid (OP) can be used. When MMP is found in the ocular mucosa, it will then be termed as ocular cicatricial pemphigoid (OCP) [7]. Additionally, if the bullous vesicles are found only in the skin, this condition will be called Bullous Pemphigoid (BP) [8].

Although MMP is not classified as damaging as the pemphigus family, due to its unique characterization, patients can still experience detrimental effects or discomfort that can last months to even years [4]. Without taking the right precautions, or an early diagnosis, patients are at risk for irreversible scarring, strictures, and/or blindness. There are evidences of cases that could have severe consequences involving the diagnosis of patients whom have cancer with a link to protein laminin 332. This protein can be found in the hemidesmosome, the junction responsible for the adhesion of cells of the epithelium and the basement membrane [9]. Due to these findings it has been recorded, about 30 percent of patients with anti-laminin have a cancer present and develop MMP shortly thereafter. The most common manifestation of MMP is desquamative gingivitis, which is an erratic or fragmentary sloughing that involves ulcers and abrasions [10]. There are also cases reported in which specific vaccines can result in MMP [2]. While these cases are rare, it is imperative that they are made aware to medical professionals. Collecting information from experiments in larger group of patients with MMP, trying different techniques and researching what unknown components can be present in MMP, could be a vast step forward in the prevention of harmful effects [11].

This review will provide an extensive explanation of MMP by discussing common misdiagnosis scenarios, presenting rare case reports, and exploring recent treatment options in hopes of spreading awareness for furthering research on diagnosis techniques and a better understanding of this autoimmune disease. Although the cause of MMP is still unknown, continuing further

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research and collecting data could be very beneficial to many individuals in the present and the future. The purpose of this paper is to bring light to the dental community, medical professionals and autoimmune disease researchers, the importance of an early and authentic diagnosis and discussing corresponding methods on recent discoveries on rare cases and advancements.

Prevalence, Clinical Presentations, and Severity Levels

MMP is known to be a rare disease. Exact occurrences of this disease are relatively unknown, with estimates ranging in from only one in 12,000 up to one in 40,000 [12]. Although this percentage may seem low, when applied to the world population, the number of cases is rather astounding. Those who are diagnosed with this autoimmune disease may have to live in excruciating pain through the term of their recovery, depending on the location and the severity of their distinct condition and symptoms [6]. Approximately, 85 percent of the time MMP is found, the autoimmune disease is located strictly in the oral mucosa; 64 percent of the time, it is found in the conjunctiva. Locations such as skin, pharynx, external genitals, and nasal mucosa are far less prevalent, ranging from 15 to 24 percent [9]. The least frequently affected locations are larynx, anus, and esophagus, ranging from only 4 to 8 percent [1]. A probable reason, which would explain why the oral mucosa is more often affected than the other parts of the body, could be primarily due to its accessible location including the gingiva in combination with continuous saliva. Despite, there being no known scientific reason for the prevalence of this mucosa to be the most affected area compared to the other membranous locations, the probable reason stated above may provide researchers with future insight to identifying specific causes. As far as the clinical presentation, erythema is present 95 percent of the time. Erosion will be present 90 percent of the time and 70 percent of the time, blistering will occur [13]. The blistering that commonly occurs eventually will rupture and as a result will cause pseudo-membrane emergence. Patients with blistering have been charted to complain about the symptoms of bleeding, dysphagia, pain, and sloughing of the mucosal surface, which may appear a creamy white color [14].

The female to male ratio for MMP is 2:1, possibly since females have a thinner lamina lucida than males, although the scientific reasoning is currently unknown. This ratio is most prevalent in older individuals ranging from 50-80 years old [10]. The elderly population might be more at risk since we tend to become more sensitive to environmental factors as our immune system debilitates, as we get older. Albeit rarely seen, MMP should also be taken into consideration in children due to the fact there has been 20 cases reported and presumably many others that have gone unknown [15]. The reason is why MMP appears in children is unknown as in adults, but it could be due to periodontitis, or desquamative gingivitis caused by poor oral hygiene, highly acidic substances, or hard foods, which is often seen in cases with children affected at a youthful age [16]. It is imperative to upkeep with a regular maintenance on oral hygiene to prevent gingival or periodontal disease.

A clinical sign of MMP that has been noted on numerous occasions is the appearance of gingival desquamation, a reddish and easily crumbled gingiva with the tear of the epithelium [17]. Patients who are showing symptoms of desquamative gingivitis, should be tested for MMP to ensure that the lab and biopsy results support

a non-diagnosis. This is because 90 percent of patients diagnosed with MMP often show signs of gingival involvement. However, this alone should not be a finite diagnosis without the additional biopsy results, as there is a diverse amount of autoimmune diseases that share this characteristic as well [5].

Patients with MMP are categorized with either a 'low-risk' or a 'high-risk' status depending on the severity of their condition. The high-risk group is a collaboration of patients recorded with the involvement of the ocular, esophageal, genital, nasopharyngeal, and laryngeal mucosa locations. While the occurrences of hypopharyngeal presentation might be acute, when present, can cause significant complications, which involve blindness, stenosis of the pharynx, larynx, and nasal cavity [18]. An example of a high-risk patient is someone who has been previously diagnosed with cicatricial pemphigoid five years prior to treatment with hypopharyngeal involvement. Although this type of involvement is rare, it could result in serious side effects, such as, difficulty of swallowing and dense scarring [6]. Without the correct diagnosis and treatment, this condition could potentially lead to death. In contrast, the low-risk patients predominantly involve the oral mucosa and the skin [19]. An example of a low-risk patient, is someone who will have only oral mucosal involvement and subsequently, the treatment will be conventional. Using drugs such as dapsone, low dose prednisone, and topical glucocorticoids, in contrast to a high-risk patient, which are treated with systemic corticosteroids, IVIG, taper dapsone, or surgery as, needed [20].

Immunohistochemistry and Related Malignancy of Anti-Laminin 332

Knowing the precise antibodies, antigens, proteins, and cells involved is a crucial aspect in understanding MMP. The foremost way to detect a biopsy specimen is done by direct immunofluorescence (DIF). This method shows the detachment of the lamina propria of the mucosa layer from the epithelial basement membrane. In contrast to DIF, indirect immunofluorescence (IIF), utilizes a salt-split skin method, which shows the immunoglobulin attachments along the basement membrane zone (BMZ) [13]. These methods are the key to correctly diagnosing MMP. The techniques must be performed in the most accurate manner to prevent a possible misdiagnosis. Both DIF and IIF use specific autoantibodies or antigens as markers when conducting the immunofluorescence testing. The involved autoantibodies most commonly seen in MMP are predominantly immunoglobulin G, followed by immunoglobulin A, and C3, a complement test that confirms an abnormality in the complement system of a patient. These immune deposits bind to the basement membrane zone (BMZ) of the epithelium and can create a sub-epidermal detachment [4]. Studies have shown that the autoantibodies IgG and IgA, target antigen BP180 in more than 75% of the patients [14]. In addition to BP180, other recognized target antigens include BP230 kDa, and the $\alpha 6 \beta 4$ integrin. Having this knowledge could facilitate the process of immunofluorescence testing and lead to an affirmative diagnosis. The major proteins that exist in the hemidesmosome are the transmembrane proteins, cytoplasmic adapter proteins and cytoskeletal filaments. These proteins along with the laminin 332 protein is what will attach to the basal layer and will aid to form the adhesion complex found specifically in blistering autoimmune diseases [21]. The hemidesmosome is then used to observe the

detachment of the epithelium from the connective tissue. As a result, reforming the hemidesmosome is critical in proper healing procedures [22].

MMP is a disease characterized by type II hypersensitivity, which is the type that includes the Ag-Ab complex and results in the activation of the complement system with the predominant involvement of B-lymphocytes. Autoantibodies target mainly bullous pemphigoid antigens, BPA180, and less commonly BP230, laminin 332, and type VII collagens. When this phenomenon takes place, the splitting of sub-epithelial occurs and causes tissue damage by a complement pathway or an Fc-mediated pathway. If enough tissue is present for testing, this can be seen in an IIF. IIF provides enough of a substantial exposure of these antigens to be able to correctly diagnose MMP [23]. Shortly after the split, a chronic inflammatory reaction occurs and causes an infiltration of white blood cells including lymphocytes, eosinophils, and neutrophils into the mucosa, more specifically the lamina propria, a layer of loose connective tissue [14]. This infiltration can cause the disruption of the protein connections and components of the hemidesmosomes resulting in MMP. The main cause behind this is still unknown, but the more research that is performed, the easier it will be to identify and eradicate.

There have been a few cases where the association of HLA-DQ β 1*0301 allele have been led to the enhancement of developing MMP. Upon serologic testing, it was found that two half-sisters had circulating antibodies to the β 4-integrin. The sisters shared the same mother and developed MMP at the same age. While one had a more severe case of MMP that extended into her larynx causing her to suffer for over 6 years, the other had flaccid blisters and responded well to treatment. Both sisters shared the HLA-DQ β 1*0301 allele in common, therefore there are theories that this allele is linked to MMP. This recurred in a set of twins who also both carried this allele, however, in this case, only one sister developed a diagnosis for a proven ocular pemphigoid, while the other sister has not yet been reported to develop any form of MMP [24]. With these provided facts and incidences, there should be further research done around this allele to check for a direct correlation, especially in those who share the same DNA.

Anti-laminin 332, which has also been previously called by other names such as epiligrin, nicein, kalinin, and laminin 5, has been linked to malignancies in multiple disorders [25]. The list of disorders includes malignancies such as solid organ malignancy, non-Hodgkin lymphoma, visceral adenocarcinoma, cutaneous T-cell lymphoma, and leukemia. The connection between the autoantibodies and laminin 332, is termed anti-epiligrin cicatricial pemphigoid (AECp). This type of pemphigoid is a distinct subtype of MMP that is far more severe and commonly involves the laryngeal and intranasal surfaces. This subtype of MMP is histologically indistinguishable from MMP, but should be distinctly identified as a subtype in need of awareness due to its linkage with malignancy in adults. As of now, cases with children are unknown, yet should still not be omitted without collecting lab results. Using an immunoblotting technique, a keratinocyte extract shows AECp to be associated mainly targeting against the α 3 or γ 2 subunits, yet there have been cases where it targets against the β 3 subunit although this circumstance is rare [26]. With this knowledge we notice cases of patients whom have acute myeloblastic leukemia,

rheumatoid arthritis, diabetes mellitus and prostate carcinoma to be linked to AECp with showing attachment to the β 3 subunit. The complications that commonly arise from AECp are laryngeal stenosis and symblepharon, which is an adhesion of the palpebral conjunctiva, either partially or completely [2]. If a patient has been already diagnosed with any of these malignancies, they should also be tested for MMP, as blistering can occur and further symptoms of MMP could bring extra pain and suffering or eventually result in death, as already noted in one case [9].

Diagnosis Techniques and Correlating Symptoms

Diagnosing MMP can be strenuous, nevertheless, misdiagnosing, or delayed diagnosing will be a major fallback for patients in critical condition. Especially, in the initial stages, misdiagnosis is common due to the false negative feedback from biopsies and its dissimilarity in clinical presentations [7]. An example is the hemidesmosomal components, which are arduous to detect, as they are only present in low titer. As a result, DIF testing is reputed to be highly sensitive, and repeated testing of immunofluorescence is highly suggested to ensure a correct diagnosis. Experiments have been done in groups of patients for this range of sensitivity and the initial results yielded in false-negative responses. The second time around, the tests often showed positive results. Therefore, a formula was created to calculate the sensitivity values. This formula is $\text{sensitivity} = \frac{\text{true-positive}}{(\text{true-positives} + \text{false-negatives})}$ [27,28]. It is imperative to be aware of the sensitivity probabilities for diagnosis as this could result in a patient going home untreated properly.

Symptoms to look for when diagnosing MMP are as follows: bleeding gums, burning mouth, blisters, ocular dryness, irritation of the conjunctiva, nasal obstruction dysuria, erosions, ulcerations, vesicles, crusts, pseudo-membranes, sexual dysfunction, desquamative gingivitis, symblepharon, and airway obstruction [17]. When these symptoms are present in a patient, dental and medical professionals should test for MMP. The most practical and accurate ways are by using the following techniques; IIF, DIF, ELISA, and immunoblotting. As mentioned beforehand, IIF is used for identification of autoimmune diseases and it is done by introducing antibodies to detect antigens that are present in the disease. After a lot of experiments performed, it is now known, the best method to get antibodies is from using the salt-split skin tool. This tool is far more efficient in diagnosing sub-epidermal autoimmune diseases than any other resource, such as rabbit esophagus or intact skin [8]. While IIF provides you with principal antigen data, DIF is another immunofluorescence tool used when diagnosing MMP and other autoimmune diseases. DIF detects the immunoglobulins present in the perilesional mucosa by showing an immune deposition that is observed as linear at the BMZ and is considered a crucial diagnostic tool. DIF can help tell apart MMP from its subtypes and from similar disorders, such as the pemphigus family or the bullous pemphigoid [18]. A way to detect the proteins present in MMP is by using the western blot or immunoblotting technique. This method uses antibodies to detect the target proteins present in each serum [29]. The fourth method ELISA, is another technique that can provide serum samples with immunopathological data. Even more profoundly it can detect the anti-laminin 332 antibodies, and this is paramount for the earlier mentioned malignancy linkage with anti-laminin 332 [11]. A

combination of all these tools should give a conclusive result and the most accurate diagnosis of MMP.

Utilizing these different techniques such as DIF, IIF, immunoblotting and ELISA, certain autoantibodies have been linked to specific mucosal locations due to experimentation and repetitive outcomes. Further research has shown skin lesions to be more commonly associated with the BP180 antigen in multiple patients, while patients who have the autoimmunity to $\alpha 6\beta 4$ integrin have been associated with the oral (anti- $\alpha 6$ integrin) or ocular involvement (anti- $\beta 4$ integrin). Understanding these linkages could be beneficial in the accuracy of diagnosis and could prevent future misdiagnosis. Another linkage is between DG and periodontitis. As mentioned earlier, desquamative gingivitis is a pronounced sign of MMP, and if an individual with DG has been diagnosed with MMP, it's been recorded that this could lead further to an inflammatory disease called periodontitis [17]. This disease could lead to the destruction of gums and can cause even worse cases of MMP, such as bullous pemphigoid. Periodontitis is a result of poor hygiene, fewer dental check-ups, acidic foods, insufficient number of cleanings and untreated DG [16]. This connection is recently discovered and should be made aware to those patients who have DG, to prevent the combination from being an even more painful and destructive process.

Rare Case Reports

Approximately, 20 cases of children with MMP were reported in the last few years, with ages ranging from 2 years old to 18 years old [15]. An example of a 'high-risk' case involving a 9-year old girl of African American descent, identified as Patient X* by Kahn E. et al. Patient X presented with symptoms including dysphonia, oral erosions, progressive hoarseness, and coughing. When an endoscopy was performed, she showed reflux and gastritis, leading to treatment that did not give her relief. After an in-office laryngoscopy disclosed erosions in the nasal cavity, oral mucosa, and pharyngeal mucosa, she then proceeded to have a direct form of laryngoscopy. Patient X's epiglottis had thickened, and showed an abnormal narrowing of her spinal canal, with her tracheal mucosa being crumbled. DIF, IIF, IB, and ELISA were all used for Patient X and she was later diagnosed with the anti-laminin 332 MMP. Patient X took over a year to be treated and data taken from her case became precedent to make others aware of this possibility [30].

Furthermore, Mostafa M. et al., recorded Patient Y* who is a 6-year-old boy with an oral mucous membrane diagnosis. His symptoms began at age 3, with redness in the gums and continued till he was 5. He proceeded to have trouble during mastication and bleeding of the gums which lead to the peeling of his gingiva. Due to lab testing errors, Patient Y was misdiagnosed with chronic periodontitis and the treatment that were given to him were unsuccessful. Doctors then suspected DG and used the DIF technique, which revealed a clear detachment of the epithelium from the lamina propria. This led to the diagnosis of OMMP and treatment, including mouthwash, was prescribed twice daily to avoid calculus formation. Over the next few weeks Patient Y's bleeding gums and redness of the gingiva had returned. He had to have a follow up for over 4 years with multiple treatment options and had extra oral examination every 6 weeks. He was given topical fluocinonide with occlusive therapy till his condition bettered [31]. This case demonstrates the importance of the authenticity of a

correct diagnosis as well as maintaining a healthy oral hygiene scheme.

A unique case report by Sezin et al., discusses Patient Z* that is diagnosed with MMP after receiving a diphtheria tetanus (DT) vaccination. Generally, vaccinations are done to prevent infectious diseases, yet they can aggravate the immune system to a point where they can induce an autoimmune disease. This circumstance presented itself in the case of Patient Z, a male in his late 20's. A couple of days after his vaccination, Patient Z developed symptoms of tense blisters on the nasal cavity, flaccid blisters on the groin and erosions on the face, with widespread erosion in the oral mucosa. When it comes to post-vaccination, target antigen BP180 and/or BP230 are most commonly found in the data results of lab testing from ELISA or IB. After Patient Z was given the appropriate tests, he was diagnosed with anti-laminin 332 MMP. With proper treatment, his condition led down to DG and with continuous prednisone, he is now in complete remission. Post vaccination is more common to develop the bullous pemphigoid mentioned earlier, but MMP has now also been seen after post vaccination and this is something to be aware of post DT vaccinations. Other vaccines that could result in an autoimmune blistering disease are found to be the anti-influenza vaccine and diphtheria tetanus pertussis vaccines. In the case of Patient Z, it could be possible that he already had pre-existing anti-laminin 332 antibodies that were induced by the vaccination which ultimately caused his reaction [32].

Additionally, Sato H., et al, provided us with a review on Patient A*, also a male in his late 20's who was diagnosed with anti-laminin 332 resulting in microstomia. Shortly after his diagnosis, he started to notice a shrinkage in his mouth size. This is considered a high-risk MMP, as microstomia makes it difficult to eat, swallow and articulate. Patient A had erosions in his mouth starting in 2005, and his mouth had becoming smaller and smaller. His dentist referred him to a clinic in 2009, unfortunately with the process taking a lengthy duration, Patient A had developed a ring-shaped scar contracture, limited to the oral mucosa. When a biopsy was taken, the mucosa of the oral cavity presented bullous erosions with massive infiltrations of white blood cells, including neutrophils, lymphocytes, and eosinophils. A 5-flap Z-plasty was performed to correct his microstomia. Since microstomia is usually a cause of electric burns, tumor excisions or systemic sclerosis, it was not predicted that MMP might have caused the condition of Patient A [25]. He suffered a lengthy recovery but 2 years after his surgery, he was in full remission. With this information we can now correlate MMP with microstomia in the future and run more clinical tests to prevent this from happening to someone else.

Although rare, Tham H., et al, reported at least 16 cases of MMP found in canines. The German Shepherd breed presented to be the most predominant breed in having been diagnosed with MMP, but a diagnosis has also been made in the Sheepdog, Spaniel, Pug, Schnauzer, and Rottweiler breeds. In this report, the canines that were diagnosed had symptoms of lesions on the mucocutaneous junctions, oral cavities, malodor, pain during eating, drooling continuously, and excessive salivation. Age data for canines aren't as distinct as humans, as it can show up in age range starting as young as a year old through senior aged canines. Veterinarians subsequently prescribe glucocorticoids, dapson, azathioprine, niacinamide, colchicine, and tetracycline antibiotics as treatment, much like the human equivalent. To diagnose, one should utilize

DIF, IIF and serological testing [20]. As of now MMP seems to be most common bullous disease to occur in canines and this should be made aware to veterinarians worldwide to prevent further cases from going unnoticed.

Recent Advancements and Treatments

Within the last decade, research on MMP has heightened. There are continuous findings that provide new diagnostic tools or new treatment procedures. There have been new discoveries that involve combined serologic testing to diagnose MMP as well as indirect immunofluorescence (IIF), which has been exceptionally helpful in diagnosing MMP [29]. Of the new tools that have been discovered to assist in diagnosing, one example is reflectance confocal microscopy (RCM). This tool is used to determine the presence of desquamative gingivitis; which is a substantial aid in diagnosing MMP. In a controlled experiment, a group of patients who exhibited DG were compared against a base group of seemingly healthy patients. The RCM tool was used in the above-mentioned experiment as a trial run for a potential treatment options. Upon performing the experiment and using the diode laser, RCM images of desquamative gingivitis can be obtained from the examined lesions. Once complete, a comparison can be done between MMP, Pemphigus Vulgaris and Oral Lichen Planus to properly diagnose the patient with the correct autoimmune disease. In the RCM images, MMP can be described as an area that is dark and located between the lamina propria and epithelium adhesion. In contrast, PV tends to show findings of acantholytic keratinocytes, which is an essential marker for diagnosing this disease. In LP, the findings often show spongiosis and inflammatory cell infiltration [33]. Thus, with this tool, we can tell apart the different cases of DG in similar autoimmune diseases despite a consistent portrayal of near identical symptomatology.

Another powerful treatment option includes the heat shock protein 90 inhibition (Hsp90). This treatment option, due to its anti-cancer activity and inhibition of inflammatory blister formations and cicatricial processes is very beneficial to patients. So far, Hsp90 has been used solely in vitro experimentation, including treatment of cultured fibroblasts from patients who have MMP. Until a more modified model can be developed, it is only expected to be used in vitro experiments and several clinical trials [34].

Treatment of MMP significantly depends on its severity. It can be determined by the severity of inflammation, morbidity of complications; such as scarring at the sites that were primarily afflicted [35]. Patients with low-risk characteristics can be treated initially with topical therapies, while high-risk patients may require extensive systemic therapy beyond the topical treatments. Systemic corticosteroids have been proven to have an effective result in treating MMP, yet they have adverse effects when used long-term. Other types of medications are also utilized, such as immunosuppressants, biologic agents, inflammatory reducing medications, and antibiotics. Examples of immunosuppressant medications given to patients with MMP include azathioprine, cyclophosphamide, cyclosporine, leflunomide, mycophenolate mofetil and methotrexate. Examples of biologic agents that can decrease antibody production include intravenous immunoglobulin (IVIg) and rituximab. To reduce inflammation, one can treat with tumor necrosis factor alpha inhibitors (TNF- α). Other listed medications to treat MMP are dapsone, sulfonamides, and cycline

antibiotics. As for single agents, treatment options are topical corticosteroids and calcineurin inhibitors [10]. It should be noted that, while these treatments are effective in treating MMP, they may have side effects that cause physical discomfort.

Patients who are non-responders (NR) to standard topical therapies will have to try rituximab as a second option (RTX) [36]. As for patients with ocular cicatricial pemphigoid (OCP), topical medications, such as, topical corticosteroids, are only used as a temporary solution. Sequentially, systemic therapy in combination with topical formulations of calcineurin inhibitors, cyclosporine A, and tacrolimus is then prescribed as the next phase in a wholistic treatment plan. It is imperative to treat OCP with urgency to prevent severe consequences of scarring or blindness. There is a new study involving mini-scleral lens in MMP and this method helps in healing corneal epithelium defects. The development of the new mini-scleral lens was a result of patients not responding to conventional therapy. The invention of these mini-scleral lenses could be the next medical innovation in an extensive line of OCP treatments that would prevent countless future patients from incurring corneal epithelium damage [37].

As mentioned previously, prolonged exposures to any of the above listed treatments could have severe side-effects. A recent advancement doctors can utilize to avoid certain side effects is by testing the low-level laser therapy option. This treatment is used to improve tissue color and to lower the chances of side-effects. Side effects could be a result of lipopolysaccharides (LPS), which is a potent inflammatory stimulator. While using LLLT, this method inhibits prostaglandin E2, as well as decreasing the m-RNA levels of cyclooxygenase-2, which are both induced by LPS. LLLT inhibits nitric oxide, which also plays a vital role in inflammation. Another benefit of LLLT is the ability to stimulate tissue repair, and increase the tension resistance of scars, keratinocyte overproduction, and motility. Factors that play significant roles to treating MMP by using LLLT include dose, wavelength, and the energy amount applied. With these facts noted, it is suggested that this technique could be a beneficial way to treat MMP, yet there are no clinical trials proceeding to prove this method [38]. Upon learning about this method, we hope more of LLLT related clinical trials could be approved for experimentation purposes as it is important to avoid severe side effects that the drugs can potentially cause a patient.

If diagnosed promptly and accurately, there are variety of treatments or therapy options that can be given to achieve full remission. One very common form of therapy is serological testing, which is defined as a diagnostic tool that can identify antibodies in a serum precisely. Therefore, this type of testing can tell us what kind of antibodies or antigens are present in a patient's case. This advancement is essential in making diagnosis of MMP more straightforward to health professionals [12].

Concluding Remarks

After a thorough description of MMP, including a few highlighted unique case reports and several forms of treatment options, the explicit nature of MMP should demonstrate the importance of this autoimmune disease. The need for awareness should be stressed upon in both research and practical settings to ensure that the dental and medical communities are up to date on both diagnosis

and treatment procedures.

Initially, background information on MMP shows what makes this autoimmune disease unique compared to other membranous autoimmune diseases. The low-risk and high-risk severity levels found within MMP along with specific clinical presentations have given MMP a greater public platform on which to stand on. Especially due to its prevalence and the fact that this disease can be found worldwide [15]. Secondly, the discussion of autoantibodies, antigens, proteins, and a specific type of allele that is present in this disease shows how we can separate MMP from other similar diseases. The presented importance of proper diagnosis using techniques such as direct immunofluorescence, indirect immunofluorescence, immunoblotting, ELISA, and serological testing. The emphasis on proper procedural testing is important due to the sensitivity of these diagnosing techniques [27]. Since misdiagnosis is very common with MMP, medical professionals often call for the repeating of tests which could provide more accurate results.

Continually, by providing rare case reports, my purpose was to present what is happening worldwide in terms of the progression of MMP. By providing educational summaries on these different case reports, the hope is to incite any future audience to do further research on these specific case studies which have been mentioned. Lastly, the comprehensive diversity of treatment options discussed, including various subtypes, multiple levels of severity and unique genetic anomalies. This has proven that technological advances in medicine have been able to provide innovative treatments, including the diode laser, LLLT, Hsp90, mini-scleral lenses and entropion repairs, in response to the increasing awareness of MMP [34,37,38]. With the combination of multiple medical professions, including dentists, dermatologists, ophthalmologists, and head and neck specialists, a collaboration of physicians could bring awareness and reduce the delay in diagnosing MMP. Ideally, such a coalition of professions could minimize the duration of therapeutic recovery methods while systematically working on severe forms to eliminate the amount of suffering someone must endure while experiencing the symptoms of this possibly excruciatingly painful autoimmune disease.

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