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Invited Review

Clinical Findings, Pathogenesis, and Treatment in Non-Infectious Peripheral Ulcerative Keratitis

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Abstract

Peripheral ulcerative keratitis (PUK) is a group of diseases that manifest with ulceration and/or thinning in the peripheral cornea. Although this group of diseases can occur as a result of infection, most cases are of immunological origin and are associated with autoimmune diseases (AID). The most common form of AID associated with PUK is rheumatoid arthritis (RA). However, PUK may also be seen with other AIDs, such as systemic lupus erythematosus and Wegener's granulomatosis. There are immunological differences between the peripheral and central cornea that may explain the localization of PUK in the peripheral cornea. For example, the proximity to limbal blood vessels and conjunctival lymphatics is different. Both humoral and cellular immunity play a role in the development of PUK. Although the number of CD8+ T cells did not vary significantly in RA patients, the number of CD4+ T cells was significantly greater. As PUK is very serious, early diagnosis and treatment are very important. Local and systemic corticosteroids, immunosuppressants, biological agents, bandage contact lenses, tissue adhesives, and in some cases, surgical treatment can be applied. Adjacent conjunctival excision, patch lamellar grafts, and keratoplasty are options in surgical treatment. It is very important not to forget the possibility of disease progression despite surgery, and the treatment of underlying disease is crucial. Keratoplasty in PUK cases may not be successful as a result of several factors, such as dry eye and the underlying immunological disease..

Keywords: Peripheral ulcerative keratitis, rheumatoid arthritis, systemic lupus erythematosus.

Introduction

Peripheral ulcerative keratitis (PUK) includes a group of inflammatory corneal diseases characterized by ulceration and/or thinning in the peripheral cornea, cell infiltration, various degrees of vaso-occlusive disease, and injection of adjacent vessels. This group of diseases can be caused by infection; however, most cases are of immunological origin and more than half are associated with autoimmune diseases (AID). The peripheral corneal localization of these diseases is explained by the immunological differences between the peripheral and central parts of the cornea. To summarize, the peripheral cornea is closer to the conjunctiva than the central cornea, and the conjunctiva has mediators that can produce an autoimmune reaction (1). The peripheral cornea, limbal blood vessels, and the conjunctiva are also closer to the lymphatic circulation (2). Conjunctival and limbal Langerhans cell density have been found to be similar in studies. Langerhans cell density decreases from the peripheral cornea to the central cornea. Langerhans cells are dendritic cells carrying human leukocyte antigen-D related (HLA-DR). These cells are thought to play a role in the formation of PUK through the release of inflammatory mediators. There are immunoglobulins (Igs) in the cornea. These Igs pass through the limbal blood vessels into the cornea. While the IgG and IgA concentrations are not different in the peripheral and central cornea, the IgM concentration is

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greater in the peripheral cornea. IgM is the first antibody produced by B cells and has the strongest antibacterial effect among immunoglobulins. As a result of these properties, IgM is thought to be a factor that protects the peripheral cornea against pathogens. The complement component 1 (C1), which activates the classical complement pathway, is more dense in the peripheral cornea than in the central cornea (1, 3).

AIDs are inflammatory diseases that damage not just 1 kind of tissue or organ in the body, but which may damage many organs or systems. The major AID that is the most common cause of PUK is rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) is the second most common cause of PUK. Although the cause of these diseases is not fully understood, it has been established that these diseases cause serious complications in many organs, systems, and tissues, including the eye. The ocular surface is one of the most affected tissues, and the first finding of these diseases may be ocular surface involvement (4). Tauber et al. (5) found that underlying collagen vascular disease was present in 32 (53%) of 61 cases diagnosed as PUK, and in 8 cases (25%) they reported that the diagnosis of collagen vascular disease was made after the diagnosis of PUK.

Approximately 34% to 42% of PUK cases develop due to RA. PUK may also be associated with other AIDs, such as Wegener granulomatosis (WG), polyarteritis nodosa, ulcerative colitis, sarcoidosis, and Sweet's syndrome (6). Although it is very rare, PUK has also been reported in cases of Behçet's disease (7). PUK occurs in Behçet's disease during the exacerbation period with unilateral and sectoral involvement (6). PUK cases have also occasionally been reported in diseases such as pyoderma gangrenosum and autoimmune hepatitis (8, 9).

Ocular findings in AIDs include dry eye syndrome, episcleritis, scleritis, uveitis, retinal vasculitis, and PUK. The most common finding in these diseases is dry eye syndrome and the most severe finding is the development of PUK, which is very rare (10, 11). Spontaneous or traumatic corneal perforation and visual loss may occur in PUK cases. There are also cases in which perforation develops in a very short time. A multidisciplinary approach is needed for AID-related PUK cases. Clinical findings of PUK include ocular irritation, redness, pain, photophobia, and decreased vision due to developing astigmatism and corneal opacity (11, 12). In these cases, conjunctival, episcleral, and scleral inflammation is usually seen. Adjacent scleritis is often present in WG (13). Ocular infections, palpebral malformation, lagophthalmia, and neurotrophic factors can also cause PUK (2). In the differential diagnosis, Acanthamoeba keratitis, phlyctenulosis, marginal keratitis, vernal keratoconjunctivitis, immune corneal rings, corneal degeneration, and corneal diseases such as Mooren's ulcer should be excluded (5, 14-17). Although it has been reported that there is an important link between infectious PUK and tuberculosis in previous publications, staphylococci have been reported to be more frequent in infectious PUK in recent publications (18). Syphilis is a venereal disease that should definitely come to mind in the differential diagnosis of PUK cases. Mooren's ulcer is a painful, chronic unilateral or bilateral peripheral corneal ulceration, usually located in the interpalpebral space and thought to be associated with ocular autoimmunity. Scleritis does not accompany these ulcers and the pain can be very severe. In these cases, iritis and secondary glaucoma may develop. It may spread circumferentially and then centrally, as corneal thickness rapidly diminishes. It should be considered in the differential diagnosis of PUK (17).

Studies have indicated that both humoral and cellular immunity play a role in AIDs (20, 21). The following is the latest information on the pathogenesis and treatment of the diseases that are the most common causes of PUK.

Rheumatoid Arthritis

A) Clinical findings and pathogenesis

RA is a chronic polyarthritis that involves the peripheral small joints. It is 3 times more common in females than in males, and occurs in approximately 3% of the general population. Extra-articular findings are seen in this disease at a rate of some 25%. In 1 study, more than 1 ocular finding was found in 20% of RA patients who had ocular findings. In these cases, a disease that affects the level of vision, such as cataract or dry eye, is present (22). Normally, the immune system is not responsive to autologous antigens. Depending on some factors, such as genetic and environmental factors, synoviocytes are thought to be converted to autoantigens in RA. Autoantigens stimulate T and B cells, causing damage to joints, the ocular surface, and other organs and tissues (20, 21, 23). Although RA can cause many complications in the body, the most serious complication is PUK. Foster et al. (24) reported a 10-year mortality rate of approximately 50% in patients with RA with PUK/necrotizing scleritis. T cells cause continuous antibody formation and the accumulation of immunocomplexes at the corneal border (21, 25). Proinflammatory cytokines secreted by T cells stimulate the inflammatory cells to accumulate in the corneal stroma. Due to the release of proteolytic and collagenolytic enzymes in the cornea, a crescent-shaped area is formed in the cornea. Then an epithelial defect and progressive stromal melting is seen in this crescent-shaped area (26). Other factors that play a role in the development of PUK include antigen-presenting host cells (APHC) and chemokines (27). Antigen presentation to T cells is restricted to major histocompatibility complex (MHC) class II (28). HLA-DR is an MHC class II cell

surface receptor found in APHCs. HLA-DR, which presents antigen to T cells, plays a role not only in RA initiation, but also in the entire disease process (29). T cells can be divided into 2 groups according to their receptors: gamma-delta and alpha-beta. The alpha-beta T cells are further classified into 2 groups: CD4+ T cells and CD8+ T cells, according to their surface receptors. CD4+ T cells were found to be significantly more prevalent in RA patients (30-32) CD4+ T cells are transformed into 3 different T-helper (Th) cell subtypes when stimulated by different cytokines and factors. These 3 groups are Th1, Th2, and Th17 cells. Th1 cells secrete tumor necrosis factor (TNF)-γ, Th2 cells secrete interleukin (IL) 4, IL-5, and IL-13; Th17 cells secrete IL-17 (28). The balance between Th1 and Th2 cells is associated with the onset, progression, and healing processes of the disease. Chemokines help T cells migrate to joints and other areas and T cells secrete proinflammatory cytokines that affect and activate macrophages, monocytes, and other cells in these areas (28, 31). T-cell subtypes (Th1, Th2, Th17) activated in these regions secrete lymphokines and help in the pathogenesis of RA through B cell proliferation and autoantibody construction (32). IL-17 levels are also high in serum and active peripheral blood mononuclear cells other than synovial tissue and synovial fluid (33, 34). It has been demonstrated that the level of IL-17 in tears was higher in cases with ocular surface changes. IL-17 enhances B cell proliferation and leads to the conversion of B cells into plasma cells (35). IL-17 itself, along with other proinflammatory cytokines (such as IL-6, TNF-alpha, IL-1, and IL-8) triggers destructive enzymes such as metalloproteinase (MMP)-9 (35-37). Other T cell subgroups, such as Th17, gamma-delta T cells and natural killer T cells, cause the release of some chemokines, cytokines, and MMPs (22).

Under normal conditions, B cells have a natural tolerance to their own body antigens. In RA, this tolerance doesn't exist. First, rheumatoid factor (RF), an autoantibody that binds to the Fc portion of human IgG, has been shown to be associated with RA. Then anti-citrullinated protein antibodies were discovered. Anti-cyclic citrullinated peptide antibodies (anti-CCP antibodies) have been shown to be more sensitive than RF in RA. Anti-CCP antibodies are the markers specific to systemic involvement in RA and appear to be associated with more intense and severe ocular findings when compared with RF (22, 38). Autoantibodies that occur in RA have been shown to bind to their own antigens to form immune complexes that activate B cells and inflammatory cells (39, 40).

Besides producing autoantibodies, B cells secrete cytokines that stimulate pathological T cell responses (41). B cells in the peripheral blood are an important source of some cytokines in RA, such as TNF and IL6. IL-6 has been shown to regulate the balance between Th17/regulatory T cells (42). Moreover, B cells regulate the Th1/Th2 cell balance (43).

Corneal epithelial cells in the area of a corneal ulcer or the abnormal production of HLA class II antigens in keratocytes and vasculitis in the adjacent conjunctiva are thought to be responsible for the pathogenesis of PUK in RA (44, 45). The limbic vascular structure causes the accumulation of immunocomplexes and the activation of the classic complement system in the periphery of the cornea. Immunocyte accumulation in the peripheral cornea causes angiogenesis in the periphery of the cornea resulting in a vicious cycle (46). While the cycle continues, inflammatory cells, especially neutrophils and macrophages, reach the cornea through the veins and produce collagenase and other proteases that cause corneal damage. The release of proinflammatory cytokines, such as IL-1, induces the release of MMP 1 and 2 in stromal keratocytes (2). In the presence of corneal epithelial damage, circulating autoantibodies attack specific corneal proteins and initiate PUK development (47).

MMPs are proteolytic enzymes and the main source of these enzymes is local fibroblasts, mononuclear cells and granulocytes, epithelial cells, and keratocytes in RA (48, 49). The imbalance between MMPs and their inhibitory factors (MMPIF) results in disease progression (50, 51). MMPIFs are dense in the intact cornea and inhibit MMP activity (49).

MMP-1 has been shown to play a major role in dissolving type I collagen in the cornea (52) MMP-1 correlates with corneal perforation in patients with PUK. MMP-2 and MMP-9 are enzymes required to hydrolyze type IV collagen, which is a major component of basal membranes (49). These enzymes are thought to limit tissue repair and to facilitate the passage of inflammatory cells and their proteolytic enzymes to the corneal stroma by bypassing the corneal basement membrane (53).

B) Treatment

Bandage contact lenses, patching with amniotic membrane, resection of conjunctiva adjacent to PUK, topical steroids, antibiotics, and topical immunosuppressives are the topical treatment options in PUK with unilateral AID (54). Topical use of corticosteroids reduce systemic side effects and improve the lesion significantly, but epithelial healing may be delayed and new collagen production may be inhibited. Although the immunosuppressive effects of these drugs are strong, it should be remembered that they increase the risk of perforation because they inhibit the production of new collagen. For this reason, the decision to start the use of topical corticosteroids in AID-related PUK cases should be made carefully (55).

Cyclosporin (cyclosporin A) is the most commonly used topical immunosuppressant. Cyclosporin A is an agent that

acts on T lymphocytes (56). The topical application of cyclosporin prevents nephrotoxicity on a large scale (57).

Collagenase inhibitors or collagenase synthetase inhibitors inhibit corneal stromal melting by inhibiting collagenase. Topical 1% medroxyprogesterone and topical 20% acetylcysteine have recently been used clinically. Oral tetracycline provides additional benefit because it reduces protease activity (58). When applied in patch or graft fashion, the amniotic membrane can reduce inflammation and accelerate corneal epithelization. This can be achieved by reducing inflammation and activating suppressor T cell functions using substances such as fas-ligand and human leukocyte antigen-G (59-60). When corneal perforation develops, cyanoacrylate glue, conjunctival resection in the inflamed area, conjunctival flap, lamellar patch graft, or penetrating keratoplasty (PK) may be required (61-65). A corneal adhesive may delay the need for immediate keratoplasty. After the application of a tissue adhesive to perforations smaller than 2.0 mm, a bandage contact lens application is preferred. Tissue adhesives have been shown to prevent the loss of stroma by removing acute inflammatory cells from the affected cornea (61). Conjunctival flaps may be effective in non-progressive perforations and accelerate healing; however, conjunctival flaps may not be effective in the event of ongoing perforation or leakage under the flap in active keratitis. Tectonic lamellar keratoplasty or PK is usually used to provide anatomical integrity of the eyeball in cases of corneal necrosis, thinning, and perforation (62). In the presence of high graft rejection, lamellar patch graft is a good choice when compared to PK. PK is necessary in some cases, depending on the location and size of the perforation (≥3 mm diameter) (63). However, as a result of dry eye and corneal hypoesthesia due to an underlying AID, PK results may not be not successful in PUK cases (64). Maneo et al. (65) reported that despite the cytotoxic agents administered in PUK cases, the risk of recurrence of surgery was significantly higher than in other cases of PK. The keratolytic processes leading to corneal melting continue to occur after transplantation.

Systemic treatment is required for patients with PUK and RA. According to scientific study results, systemic corticosteroid administration is successful in the acute phase when PUK and RA are seen together. However, systemic corticosteroid therapy is not sufficient in most cases. Although there are many corticosteroid options for systemic administration, prednisolone is superior to other steroids and clinically preferred because of moderate-intensity glucocorticoid effects, poor effect on electrolyte metabolism, and reasonable half-life (66). Usually, the initial dose is 1 mg/kg/day. A maximum dose of 60 mg is administered daily. The dose is reduced according to the clinical response. Pulse methylprednisolone (1g/day) can be given for 3 days in severe vision-threatening cases and then oral treatment can be applied. Common side effects of corticosteroids include osteoporosis, impaired blood pressure and glucose regulation, gastrointestinal bleeding, and elecrolide imbalance that limit the use of these drugs (21).

Less mortality and ocular morbidity were seen in a study examining immunosuppressive medications (cyclophosphamide [CTX], methotrexate [MT]), azathioprine) in patients with PUK and RA (10). If treatment with oral corticosteroids fails to respond or if side effects occur, MTX (7.5-25mg/week) and azathioprine (1.0-2.5 mg/kg/day) are the most appropriate options for treatment (67). MTX causes fewer side effects because it acts only on actively producing cells (68). If side effects occur with MTX and azathioprine, the alternative is oral mycophenolate mofetil (1.0 g, twice a day) (66). Furthermore, there have been reports that leflunomide is successful in controlling inflammation in RA (69). However, in some patients, even high doses of systemic corticosteroids and immunosuppressive agents do not control this disease, and therefore, new agents are being studied (70).

As mentioned earlier, TNF-alpha, IL-1, IL-6 have important roles in the pathogenesis of RA-associated PUK. Treatment targeting these agents is termed biological therapy, and it has been accepted in recent years that biological therapy may be the second or even the first treatment option in PUK cases with RA. Etanercept, infliximab, adalimumab, golimubab, certolizumab pegol proinflammatory cytokine inhibits TNF-alpha.71 Etanercept is the first TNF inhibitor used and binds to soluble TNF to prevent TNF from binding to its own receptor. This drug is administered subcutaneously with a dosage of 50 mg once a week or 25 mg twice a week. Etanersept and MTX have an additive effect when used together (72). Infliximab is another TNF-alpha targeting agent and is administered intravenously by infusion. This agent is both soluble and a transmembrane TNF-alpha binding chimeric mouse/human IgG1 monoclonal antibody. It is also more effective than etanercept because it binds to transmembrane TNF-alpha (73). The infliximab dosage for RA is initially 3 mg/kg in the 2nd and 6th weeks and then every 8 weeks for 18 months. This agent has been shown to stop keratolysis in 77.2% of cases, but due to a severe side effect profile, it should be used in serious cases where other treatment has not been not effective (70). Before starting infliximab, tuberculosis must be absolutely excluded (74). It has been reported that infliximab increases the risk of thrombosis, and it can cause diseases such as venous occlusion and pulmonary embolism (75). Antano et al. treated a patient with RA who had PUK while being treated with prednisolone, MTX, and diclofenac. They first increased the dose of systemic treatment, then applied a cyanocrylate adhesive

and bandage contact lenses after bilateral perforation developed. In follow-up, as the systemic treatment was gradually reduced, bilateral perforation developed once again and they applied an amniotic membrane after a tissue adhesive. Bilateral tectonic keratoplasty was performed, given the recurrence of perforation. Systemic treatment doses were once again increased. This time, treatment with 5 mg/kg infliximab was initiated on the postoperative first day and after 18 months, the results were successful in both eyes. In this case, phacoemulsification surgery with intraocular lens implantation in the posterior chamber was performed 9 months after keratoplasty and the initiation of infliximab treatment. There was no problem during or after surgery (76). Adalimumab is a humanized recombinant IgG1 monoclonal antibody that targets TNF-alpha. The subcutaneous delivery ofadalimumab is a significant advantage compared with infliximab, which is delivered by infusion (54). Golimumab is also a biological agent. Initially, it is applied every 4 weeks and then every 8 weeks. Golimumab is used in cases of RA-associated PUK in which MTX alone or with other anti-TNF drugs can not stop PUK progression (77). Another inhibitor of TNF is certolizumab pegol (66). Rituximab is a monoclonal antibody targeting the molecule CD20 on B cells. This agent not only inhibits antigen delivery, but also antibody/cytokine production, and contributes to the depletion of circulating B cells. It is an appropriate option in cases where at least 2 biological agents, at least 1 of which is an anti-TNF agent, are ineffective (78).

Other agents include anakinra (recombinant human IL-1 receptor antagonist), tosilizumab (humanized anti-human IL-6 receptor antibody of the IgG1 subset), and abatacept (T cell blocking protein Fc fragment of CTLA-4 extracellular domain). Secukinumab and ixekizumab are 2 human monoclonal antibodies that directly block IL-17 (79, 80).

Systemic lupus erythematosus

A) Clinic and pathogenesis

SLE is most often seen in young women. The joints (arthritis), skin (facial rash, discoid lupus, alopecia, photosensitivity, and Raynaud's phenomenon), kidneys (proteinuria), lungs (pleurisy), blood (anemia, leukopenia and thrombocytopenia), nervous system (psychosis and convulsion), cardiovascular system (pericarditis), and ocular tissues can be involved in SLE (81). Disruption of B cell tolerance leads to the production of antinuclear antibodies (ANAs). The immunocomplexes formed in this case are called CRP (affecting apoptotic cell clearance). Apoptotic cell cleansing is thus impaired in SLE. More nuclear antigens arise from uncleared apoptotic cells and cause intense binding of ANAs. Tissue damage is also seen in the uninvolved area of the immune complexes because of the secretion of C3a and C5a by the activation of an intravascular complement system, the activation of inflammatory cells, and damage to endothelial cells (81). Immune complexes accumulate in the basement membranes of peripheral corneal endothelial cells in SLE and the reactions contribute to melting in the cornea (83). There is an increase in proinflammatory Th17 cells while there is a decrease in anti-inflammatory Treg cells in patients with SLE (82). PUK pathogenesis associated with SLE is similar to PUK pathogenesis in patients with RA in some stages, such as Th17, immune complex and MMP production (84).

B) Treatment

As in RA, the treatment of SLE requires medical and surgical treatment. IL-2 is responsible for most of the effects of AIDs. It is a growth, survival, and transformation factor for active T cells, as well as a driving force in the exchange of effector cytolytic T cells and in activation-induced cell death. Therefore, inhibition of IL-2 is important for SLE treatment and is being investigated (85). Biological agents are widely used in the treatment of SLE. However, only rituximab and belimumab are used in clinical practice and they both target B cells. Belimumab is known to target the B cell survival factor (86).

Wegener granulomatosis

A) Clinic and pathogenesis

WG is a life-threatening systemic granulomatous vasculitis. The small vessels, upper and lower respiratory tracts, and kidneys are usually involved in this disease. Ocular findings in WG are similar to those in RA and SLE. The frequency of ocular involvement in WG ranges from 29% to 58%. PUK and necrotizing scleritis can be the first signs of disease. PUK may be bilateral, and PUK is always accompanied by scleral inflammation (87). Watkins et al. (88) reported a PUK ratio of 16.1% in their WG case series.

Autoantibodies and inflammatory cells are responsible for WG. They reach the cornea through the limbal vessels (89, 90). PUK pathogenesis in WG is explained through pathological B and T lymphocytes, and possibly antineutrophil cytoplasmic antibodies (ANCA) (91). The antineutrophil cytoplasmic antibody test in cases of PUK coexisting with WG is a specific and sensitive indicator (92). ANCA binds to receptors in neutrophils and monocytes stimulated by cytokines. The resulting complex releases the lytic enzymes and proinflammatory cytokines such as IL-8. Moreover, the combination of ANCA and neutrophils causes adhesion and cytotoxicity in cultured endothelial cells. In addition, IL-17-expressing Th17 cells have been shown to be critical mediators of PUK associated with WG. IL-1, IL-6, IL-17, IL-23, TNF-gamma, and other cytokines have similar effects in the pathogenesis of RA and WG (89).

B) Treatment

Systemic immunosuppressive therapy should definitely be applied in WG patients. Other therapies provide a benefit only if they are given in addition to immunosuppressive treatment (91). Conjunctival excision combined with cryotherapy in addition to immunosuppressive treatment can be effective in these cases. All inflammatory cells and agents that cause necrotic tissue and inflammation are removed from the environment (90). PUK associated with WG is severe and perforation is common. Therefore, surgical treatment is usually required in addition to systemic immunosuppressive treatment (92).

In addition to oral corticosteroids, oral or intravenous CTX is the appropriate treatment choice for these patients. Hoffman et al. (93) reported successful results in the treatment of PUK associated with WG with 2 mg/kg CTX and 1 mg prednisone per day. Although azathioprine is a safer immunosuppressant than CTX, it has not demonstrated adequate efficacy in these cases compared with RA cases. MTX or azathioprine can be used to provide remission in severe cases (94). Metzler et al. (95) reported that leflunomide was more effective than MTX during attacks. Active ANCA-associated vasculitis responds well to rituximab while limited WG generally responds well to MTX (91).

Differential Diagnosis

After excluding all possible causes, including infectious causes, in patients with PUK findings, a detailed personal and family history in terms of AID must be investigated. Treatment choices vary according to the underlying AID (50). A study revealed that the mean time between the onset of RA and the development of ocular findings was 2.1 years, while the time required to develop eye symptoms was 5.4 years. In the same study, the mean time until the development of severe ocular findings such as PUK and sclerosing keratitis was reported to be 10.5 years (22). PUK is usually seen in patients with RA of long duration. However, cases with PUK detected without arthritis have also been reported (38). In cases of WG and other systemic vasculitis, corneal perforation due to PUK and PUK may occur early. Visual loss can develop even within a few days (21). Since PUK findings are similar in cases of AIDs, we distinguish PUK cases with underlying systemic diseases (such as RA, SLE, and WG).

Results

Non-infectious PUK is associated with AIDs, but the pathogenesis is still unclear. The most common disease associated with PUK is RA. PUK requires early diagnosis and treatment because it is a serious and severe disease. The pathogenesis must be understood very well in order to provide the appropriate treatment. Both humoral and cellular immunity play a role in the pathogenesis. Corticosteroids and immunosuppressives are generally used topically and systemically in treatment. Recently, biological agents have also been introduced. Surgical treatment options are also available in these cases. A multidisciplinary approach is needed.

Disclosures

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