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Review Article

Treatment of Pyoderma Gangrenosum with Topical Cromoglycate: A Forgotten Treatment Option? Presentation of Own Case and Review of Literature

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ABSTRACT

A challenging case of a patient with pyoderma gangrenosum dating back to 1990s is presented. After multiple and prolonged treatment attempts for 1.5 years, extensive ulcers started to heal rather fast within weeks with topical 2% cromolycate solution, which is more commonly used as an eye allergy drug. By the literature, the use of topical cromolycate has not been published for treatment of Pyoderma Gangrenosum after 2000.

Keywords: Pyoderma gangrenosum; Cromoglycate; Treatment

Introduction

Pyoderma gangrenosum (PG) is a rare ulcerative neutrophilic dermatosis with features of vasculitis-like appearance. The etiology is unknown and histology not specific for PG. The pathogenesis is complex, and dysregulation of innate and adaptive immunity are involved[1]. The incidence is thought to be about 6,3 per 1,000,000 with the median age at presentation of 59 years. The sex incidence is from equal, to females being predominant up to 76 % of cases[2]. PG is often associated with a systemic disease, such as ulcerative colitis, Crohn's disease, chronic active hepatitis, rheumatoid arthritis, monoclonal gammopathy/myeloma, hematological malignancies, sarcoidosis, or a malignant or other proliferative disease[3], and syndromes such as PAPA, PASH, PAPASH and SAPHO[1]. Infections caused by streptococci, staphylococci or gram-negative bacteria have also been suspected as the causative agents.

The treatment of pyoderma gangrenosum is aimed at the established underlying disease. Often, however, it cannot be diagnosed, and then the treatment is aimed at soothing the wound process with different means. For example, bacterial pyoderma, deep fungal infections, syphilitic gumma, necrotizing vasculitis and treatment-related ulcerations must be ruled out[4]. The clinical pictures of bacterial pyoderma and necrotizing vasculitis overlap with pyoderma gangrenosum.

Treatments

Since the effectiveness of local treatments is usually insufficient, systemic corticosteroid medication at doses of 40–120 mg/day is the first-line treatment[4,5]. Intravenous pulse therapy methylprednisolone 1,000 mg/day for 1–5 days[6] has been given to reduce the side effects of steroids. Other treatments have included plasmapheresis, tetracyclines, vancomycin, metzocillin, dapsone, salazosulfapyridine, azathioprine, alkylating agents (cyclophosphamide, melphalan, chlorambucil, clofazimine), which have had varying degrees of efficacy[4,5,7]. Cyclosporine[4,8,9] and tacrolimus (a macrolide antibiotic, which has an immunosuppressive effect similar to cyclosporine) have been shown in a small data set[4]. Individual patients have been treated with thalidomide and hyperbaric oxygen therapy[4]. GM-CSF

(granulocyte macrophage-colony stimulating factor) has been reported to be beneficial[10].

A recent review with proposed algorithm for treatment of PG has been presented for treatment of PG nowadays: systemic corticosteroids, cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, systemic tacrolimus, dapsone, colchicine, thalidomide, i.v.-immunoglobulin, granulocyte-macrophage adsorption apheresis, and the most recent biologics such as inhibitors for TNF-alfa, IL-1-beta, IL-1alfa, IL-17, IL-23, C5a, IL-6, CD3, CD20, integrin, PDE4, and JAKs[1].

Topical Treatments

Local topical treatments are aimed at alleviating pain and preventing secondary infection. In mild forms of the disease, the effect of topical antimicrobial treatments may be sufficient when they are continued with a topical or intradermal corticosteroid (triamcinolone) or topical 5-aminosalicylic acid. Individual cases have also been described treated with systemic cyclosporine and topical mechlorethamine (topical nitrogen mustard)[4,5].

A recent description of topical treatments is presented for PG in a review: corticosteroids, calcineurin inhibitors, miscellaneous basic wound care treatments, topical timolol and phenytoin[1].

Topical Cromoglycate

A total of 17 patients treated with cromoglycate have been described in the literature from 1980 until 1998, and treatment response was achieved in 15 cases[11-17]. Of the two patients who did not respond to treatment, one had monoclonal gammopathy[18] and the other had recurrent idiopathic PG for 14 years, in which cyclosporine was effective[19]. In the study of five patients, only one was given topical cromoglycate as the only treatment; four received oral steroids (prednisone 60 mg/day) at the same time and two of them also received 5-aminosalicylate (2g/day)[16]. The response to 4% cromoglycate appeared in 3 days and the wounds healed in about 3 months[17].

Local cromoglycate under occlusion with clobetasol dipropionate lead to only partial healing but adding oral cyclosporin and triamcinolone injections led to progressive complete healing after 7 months[20]. Thus, the contribution of topical cromoglycate to overall healing cannot be determined.

A wide range of oral and topical treatments (including corticosteroids and cromoglycate) were shown ineffective in the treatment of PG of a 68-year-old woman but oral mycophenolate mofetil in combination with oral cyclosporine showed an effect with thrombocytic growth factors followed 8 weeks later by split thickness skin grafts[21].

A study described a series of 7 patients with peristomal PG. A 72-year-old female with Crohn's disease got an effect by use of topical clobetasol propionate and cromoglycate with intravenous infliximab. However, cromoglycate was ineffective for a 64-year-old male with bladder cancer[22].

Cromoglycate can be used only locally, because the absorption of cromoglycate through the mucous membrane of the gastrointestinal tract is poor; in rat and rabbit experiments, absorption has been found to be only about 0.1–2.5%[23]. Absorption of 4% cromoglycate emulsion cream through the skin is also very low at about 0.01–2.75%[24]. The mechanism of action of cromoglycate has been shown to be based on the stabilization of the cell membrane of the mast cell by indirectly inhibiting the function of calcium channels, as a result of which the release of neurotransmitters and the inflammatory reaction of the mast cells are inhibited[25]. The mechanism of action of cromolycate in pyoderma gangrenosum is unclear. However, in several studies, cromoglycate has been found to have direct effects on neutrophils and other inflammatory cells at very low concentrations, even at 10 nM[25-27].

Case Presentation

The patient was a 64-year-old woman who developed difficult-to-treat ulcers on her lower legs in the spring of 1993. For years, she had hypercholesterolemia, supraventricular arrhythmias, hypertension and coronary artery disease, and left ventricular hypertrophy. In 1984, due to aortic enlargement and aortic valve leakage, she underwent reconstruction and an aortic valve prosthesis installation, and coronary artery bypass surgery was performed at the same time. In 1985, a diagnosis of polymyalgia rheumatica was made. The treatment was oral steroid medication, which had a quick response and the SR returned to normal. The patient had been diagnosed with mild kidney failure related to polycystic kidneys, and she also had many cysts in the liver. The medication was verapamil, indapamide, lovastatin, potassium chloride, warfarin and prednisolone (5 mg/day).

The patient came to the dermatology clinic for examinations and treatments in October 1993. On admission, several 1–3 cm-sized infected ulcers in the leg area were found, with vasculitis-like redness at the edges, and purple, livedo reticularis and darker blue-red macular patches around the wounds. Since then, these ulcerated, multiplied and began to expand and merge into larger wounds **(Figure 1)**.

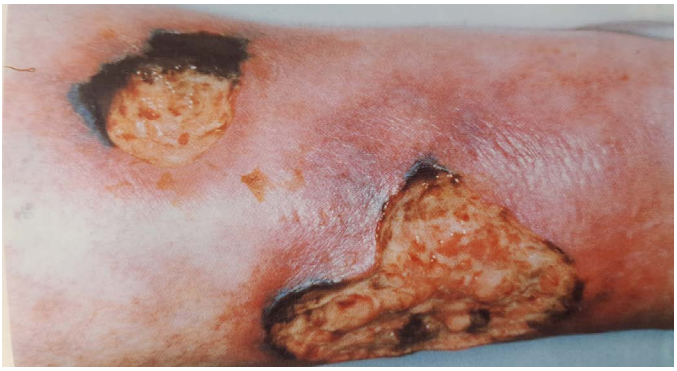

Figure 1: After 6 months of disease (left leg lateral aspect).

Extensive investigations did not reveal a clear underlying immunological disorder. The pathological-anatomical diagnosis of the wound edge specimen was ulceration. The reddened livedo reticularis area showed a microscopic examination of chronic dermatitis; no specific findings were found in the immunofluorescence study. Complete blood count, SR, CRP, thyrotropin, IgE, AST, creatine kinase, aldolase, complement C3 and C4, and circulating immune complexes were determined repeatedly with normal results. The result of the Waaler-Rose test was also repeatedly normal. Cryoglobulins, hepatitis B and C antibodies, herpes simplex, borrelia, nuclear and ANC antibodies were not detected. Serum creatinine concentration was 150–160 µmol/l. Fungal cultures from test pieces at the edge of leg wounds were negative. Electrophoretic fractionation of serum proteins did not reveal paraproteinemia, but hypoalbuminemia and hypogammaglobulinemia were found, which was consistent with renal failure and proteinuria of renal origin. X-rays of the lungs and computed tomography of the abdomen showed no signs of cancer. No indications of hematological abnormalities were found in the bone marrow aspiration sample.

From the entry stage, Staphylococcus aureus, Proteus mirabilis, Enterococcus faecalis, Acinetobacter and candida were detected in the wounds. Later, in bacterial cultures, various bacteria were also found, such as Citrobacter freundii, Xanthomonas maltophilia, Klebsiella pneumoniae, Enterobacter cloacae, E. coli, usually with combinations of 2–3 different bacteria and candida.

The patient had osteoporosis and a mild moon-like face, and therefore prednisolone in small doses (15 mg/day) and azathioprine (100 mg/day) were started to treat the wounds. Cephalexin was chosen as the antibiotic and Intrasite-gel and Iodosorb-cream were used as local treatment. Despite these treatments, however, the condition progressed; the sizes of the wounds increased, the new ulcers had a vasculitis-like feature, and the edges of the wounds had a bluish tint. The prednisolone dose was increased to 40 mg/day and the azathioprine dose to 150 mg/day, and cephalexin, sulfadiazine-trimethoprim, bacampicillin and ciprofloxacin were used as antibiotics according to bacterial culture results. In addition, GM-CSF was tried as a local treatment for a short time. Potassium permanganate baths twice a week and 0.1 % silver nitrate baths twice a day were given as drying and antimicrobial local treatment.

As additional etiology exclusion, temporarily, warfarin was also changed to phenindione, but later it was returned back to warfarin because the change had no effect on the wounds; warfarin-induced ulcers were ruled out with this drug change.

Due to the lack of treatment response, azathioprine was replaced by cyclophosphamide at doses of 100 mg/day and the prednisolone dose was kept at 35 mg/day. Due to osteoporosis, calcium supplements (1,000 mg/day) and calcitonin nasal sprays were started. After a week of using cyclophosphamide, a significant leukopenia (1.6 x10^9/L) occurred, and this medication was stopped. In the studies of increased back pain, osteoporotic collapse fractures of the vertebral bodies of the spine at levels L3-L4 were found. After this, plasmapheresis was performed on 5 consecutive days, but it had no clear effect on PG. Next, cyclosporine medication was started at doses of 3 mg/kg/day, but the dose was reduced by half about a month later due to an increase in the serum creatinine concentration to 350 µmol/L, and increase in blood pressure and swelling, which were caused by hypokalemia and hypomagnesemia from the furosemide used. The steroid dose was gradually reduced over the course of months to 15 mg/day, when the redness at the edges of the wounds had decreased and the increase in size had stopped. After a stable period, the situation began to deteriorate rapidly less than 3 months after the start of cyclosporine medication. This medication was discontinued and replaced with dapsone at doses of 100 mg/day, but after a week of use the dose was reduced by 50 % due to an increase in the methemoglobin value. The prednisolone dose was further slowly reduced to 7.5 mg/day. The situation remained somewhat stable for a few weeks, but then the wounds started to get worse again quickly. The steroid dose was not increased due to concurrent herpes zoster infection **(Figure 2)**.

At this stage, in October 1994, local treatment with 2% cromoglycate (Lecrolyn, single-dose pipettes without preservatives) was started. The medicine was given once a day (a pipette per wound area of about 4 cm) and at the same time the wound areas were covered with Duoderm sheets. In this case, the dose of dapsone had been 50 mg/day for about 1.5 months, and this medication was continued at the same time as the cromolycate treatment with prednisolone dose at 7.5 mg/day. The pain in the lower legs had been constant, and because of them, ketoprofen (200 mg/day) and dextropropoxyphene (130 mg/day) had been given, and later buprenorphine (0.4-0.8 mg/day) had been given instead. The pain caused by the wounds that had been growing for months was clearly alleviated and the redness reduced in 2-3 days, and then the wounds started to shrink in 3.5 weeks noticeably after growing for about 1.5 years **(Figure 3)**. At the same time, the dose of dapsone was quickly reduced to 100 mg/week and the use of buprenorphine for painkillers was stopped. The use of ketoprofen also decreased. After rapid initial progress, wound reduction slowed, and eventually final wound closure after approximately 14 months, and dapsone was stopped and prednisolone dose was further reduced to 5 mg/day.

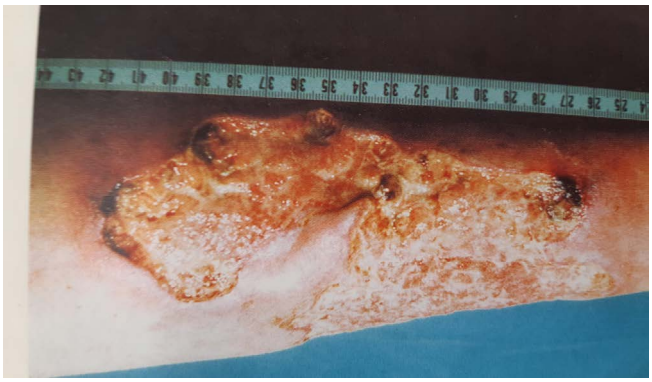

Figure 2: At 1.5 years of disease and at the time topical treatment with cromoglycate was initiated.

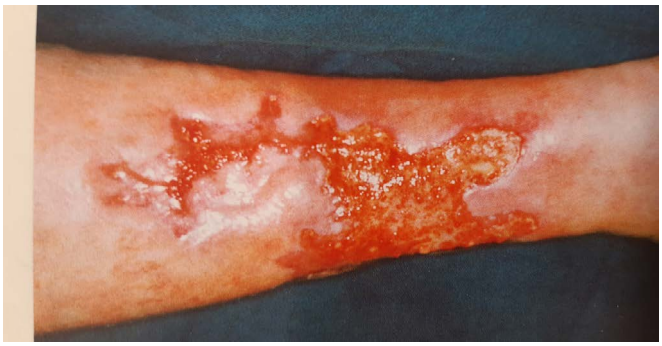

Figure 3: After 3.5 weeks with topical cromoglycate treatment.

The patient used continuous oral antibiotic therapy for more than two years. In the follow-up at 2 years, the wounds have remained closed **(Figure 4)**.

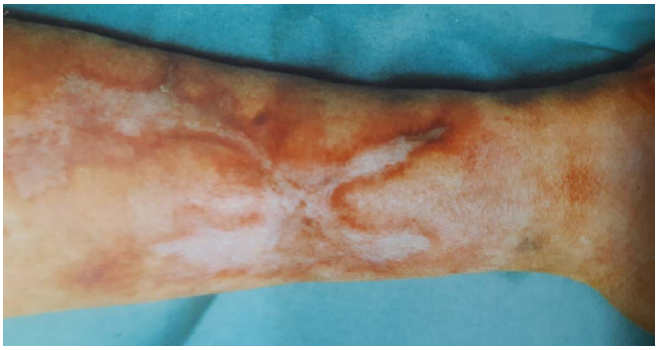

Figure 4: After 2-year follow up, wounds healed fully 10 months earlier. The patient's legs were saved from amputation.

Discussion

The patient developed difficult-to-treat painful and constantly growing ulcers in the lower legs. Based on the examinations

and the clinical picture, the diagnosis was PG. After several drug treatment trials that were ineffective or failed due to side effects, we decided to proceed on local cromolycate treatment, with which a clear response was achieved in just 2-3 days. This treatment was started in a situation where treatments known to be effective were no longer available, and thus the patient, who had been active until then, was threatened with amputation of both lower limbs.

The literature describes a response to cromolycate in 3 days and a wound healing in 5 weeks in a patient who apparently had hepatitis C-based liver cirrhosis and portal hypertension. However, the ulcers of the patient in question were clearly more superficial[16] than in our own patient. Other patients in the study[16] also received high doses of prednisone (110 mg/day) and two additional doses of 5-aminosalicylic acid (2 g/day). In these patients, wound healing times were 5-8 weeks. In another patient case, a response was also obtained in 3 days, and the final healing of the ulcers took about 3 months[17].

The ulcers on our patient's legs were very painful, deep, and extensive. Based on the discussion and consideration with her, a conservative treatment line was chosen. It took a little over a year to achieve a complete healing. High-dose steroid treatment would obviously have been beneficial, but soon after the prednisolone dose was increased to 40 mg/day, the patient developed osteoporotic collapse fractures of the spinal vertebrae, which calcitonin and calcium supplementation could not prevent. Giant-dose steroid pulse therapy may be associated with electrolyte disturbances, which this patient already had due to treatment for kidney disease and associated hypertension. At a dose tolerated by the patient, cyclosporine remained ineffective, and renal toxicity began to emerge at a dose of 3 mg/kg/day, at which level the efficacy of cyclosporine is insufficient[9]. Cyclophosphamide treatment caused severe leukopenia after only one week and it had to be discontinued. There was no response to plasmapheresis treatment. Dapsone at a dose of 100 mg/day was associated with methemoglobinemia, which was corrected with a dose of 50 mg/day.

Dapsone had been used for about 1.5 months when the condition of the wounds worsened, and local cromolycate treatment was then started. This resulted in a very quick response within a few days, which we attribute primarily to the effect of cromolycate, although a synergistic effect with dapsone and prednisolon is also possible. At that time, the dose of prednisolone was small (7.5 mg/day), but due to the simultaneous herpes zoster infection, the steroid dose was not increased.

Prednisolone inhibits the responses of both antibody and cell-mediated immunity and, in large doses, can cause the infection to spread. The results from use of steroid to prevent post-shingles pain have been variable, and according to the Textbook of Dermatology[28], one study had a favorable response in immunologically normal herpes zoster patients. Instead, in PG, the cause has been considered a process directly affecting the immunological system, the nature of which is admittedly not known in more details. Thus, in the case of this patient, it was decided to remain on low-dose steroid therapy for the duration of the zoster infection. The importance of herpes zoster in the exacerbation of PG is not known.

For local treatment, cromolycate was given once a day until the wounds healed. Treatment given 4 times a day might have been more effective[17], but there were no practical possibilities for this. The concentrations of topically used cromolycate described in the literature have been 1-4%. Cromoglycate was used until the wounds closed. The etiology of PG is unknown, although underlying diseases often affect the immune system. A bacterial etiology has been suggested. Of the bacteria grown in wounds, especially Staphylococcus aureus and Enterococcus are quite pathogenic, Proteus and klebsiella are less pathogenic. The patient was given antibiotic treatment for a total of 2 years. The purpose of this was to prevent the worsening of the situation caused by secondary bacterial infection, and, as prevention of erysipelas, as cromolycate has no antimicrobial effect.

Numerous different local and systemic treatments have been presented in the literature, and the response to them has been varied. Thus, this skin disease may have several etiological factors and mechanisms. The use of cromoglycate has been minimal, but in the described cases – including ours - a positive response has been found in 16 out of 18 patients.

Later, there was not found the use of cromoglycate in PG-wounds by search from PubMed after 2000. In this context, it should be emphasized that there have likely been a few treated patients, and it is possible that only the cases with a positive result will be published. Also, even positive outcomes may not have been presented.

In our clinic since 1999, only a few PG patients have been treated by topical cromoglycate combined with various oral and topical treatments with variable outcome, and the role a cromoglycate cannot be solely determined unlike in this our patient for whom practically all possible treatments were given at the time in the 1990s, so we considered the trial of cromoglycate treatment, which gave a clear fast response, to be ethically acceptable, even though this form of treatment was not mentioned as a treatment option for this disease at the time and not in the recent reviews[1,2].

The later treatment options by biologics during the last decades targeted on various interleukins that are more often used in the treatment of psoriasis might have also a good effect[1,2]. Cromoglycate is cheap and has a few side effects and can be combined with systemic or topical treatments. This option should be considered already in the early stages of PG treatment, alone or combined with other treatments.

The treatment of our patient was very challenging with the treatment options available in the 1990s, with drawbacks and side effects of used medications. In the end, the wounds healed and have remained closed during the follow-up period of 2 years. The patient had felt well and moved actively on her own feet.

Conflicts of interest: Author declares none.

This case is based on our previous article in 1999 in Finnish language with updated review of literature since then, focused mainly on the use of cromoglycate in the treatment of Pyoderma Gangrenosum: Harvima RJ, Hollmeń A, Mattila R, Harvima IT, Kaminska R, Laukkanen A, Räsänen L, Horsmanheimo M. (Local treatment of pyoderma gangrenosum with cromoglycate solution). Duodecim 1999; 115: 2085-2090. PMID: 11941802. Figures reprinted with permission from Aikakauslehti Duodecim.

References

1. Maronese CA, Pimentel MA, Li MM, Genovese G, Ortega-Loayza AG, Marzano AV. Pyoderma gangrenosum: An updated literature review on established and emerging pharmacological treatments. Am J Clin Dermatol 2022;23:615-634.
2. George C, Deroide F, Rustin M. Pyoderma gangrenosum - A guide to diagnosis and management. Clin Med (Lond) 2019;19:224-228.
3. Schwaegerle SM, Bergfeld WF, Senitzer D, Tidrick RT. Pyoderma gangrenosum: A review. J Am Acad Dermatol 1988;18:559-568.
4. Chow RK, Ho VC. Treatment of pyoderma gangrenosum. J Am Acad Dermatol 1996;34:1047-1060.
5. Powell FC, Su WP, Perry HO. Pyoderma gangrenosum: Classification and management. J Am Acad Dermatol 1996;34:395-409.
6. Johnson RB, Lazarus GS. Pulse therapy: Therapeutic efficacy in the treatment of pyoderma gangrenosum. Arch Dermatol 1982;118:76-84.
7. Berger TG, Elias PM, Wintroub BU. Pyoderma gangrenosum. In: Manual of therapy for skin diseases. New York: Churchill-Livingstone 1990;256-258.
8. Elgart G, Stover P, Larson K, et al. Treatment of pyoderma gangrenosum with cyclosporine: results in seven patients. J Am Acad Dermatol 1991;24(1):83-86.
9. Soria C, Allegue F, Martin M, Ledo A. Treatment of pyoderma gangrenosum with cyclosporin A. Clin Exp Dermatol 1991;16(5):392-394.
10. Bulvik S, Jacobs P. Pyoderma gangrenosum in myelodysplasia responding to granulocyte macrophage-colony stimulating factor (GM-CSF). BJD 1997;136(4):637-638.
11. DeCock KM, Thorne MG. The treatment of pyoderma gangrenosum with sodium cromoglycolate. BJD 1980;102(2):231-233.
12. Saffouri-Hom BM, Mertesdorf JM, Cardiner JE. Treatment of pyoderma gangrenosum with disodium cromoglycate. Dig Dis Sci 1984;29(2):183-185.
13. Massone L, Borghi S, Pestarino A, Gambini C. Topical disodium cromoglycate in the management of pyoderma gangrenosum. Cutis 1985;42(2):459-462.
14. Smith KC, Su WP, Leiferman KM. Cromolyn sodium in 2 % aqueous solution under an occlusive hydrocolloid dressing may be effective adjunctive treatment in the management of pyoderma gangrenosum. J Am Acad Dermatol 1987;17(3):509-510.
15. Anderson LL, Samlaska CP, Cardone JS, Holtzmuller KC. Treatment of pyoderma gangrenosum with 4 % Cromolyn. Arch Dermatol 1994;130:1117-1120.
16. Tamir A, Landau M, Brenner S. Topical treatment with 1 % sodium cromoglycate in pyoderma gangrenosum. Dermatology 1996;192(3):252-254.
17. Langenbach N, Goetz A, Hohenleutner U, Landthaler M. Effectiveness of 4 % disodium cromoglycate in the treatment of disseminated pyoderma gangrenosum. Acta Derm Venereol 1997;76(6):501-502.
18. Powell FC, Schroeter AL, Su WP, Perry HO. Pyoderma gangrenosum and monoclonal gammopathy. Arch Dermatol 1983;119(6):468-472.
19. Curley RK, MacFarlane AW, Vickers CFH. Pyoderma gangrenosum treated with cyclosporin A. Br J Dermatol 1985;113(5):601-604.
20. Duffill MB. Cyclosporine, azathioprine and local therapy for pyoderma gangrenosum. Australas J Dermatol 1994;35(1):15-18.
21. Michel S, Hohenleutner U, Mohr V, Landthaler M. (Therapy-resistant pyoderma gangrenosum - treatment with mycophenolate mofetil and cyclosporine A). Hautarzt 1999;50(6):428-431.
22. Hughes AP Jackson JM, Callen JP. Clinical Features and Treatment of Peristomal Pyoderma Gangrenosum. JAMA 2000;284(12):1546-1548.
23. Yoshimi A, Hashizume H, Kitagawa M, Nishimura K, Kakeya N. Characteristics of 1,3-bis-(2-ethoxycarbonylchromon-5-yloxy)-2-((S)-lysyloxy)propane dihydrochloride (N-556), a prodrug for the oral delivery of disodium cromoglycate, in absorption and excretion in rats and rabbits. J Pharmacobiodyn 1992;15(12):581-686.
24. Ariyanayagam M, Barlow TJ, Graham P, Hall-Smith SP, Harris JM. Topical sodium cromoglicate in the management of atopic eczema - A controlled trial. Br J Dermatol 1985;112(3):343-348.
25. Kay AB, Walsh GM, Moqbel R, et al. Disodium cromoglycate inhibits activation of human inflammatory cells in vitro. J Allergy Clin Immunol 1987;80(1):1-8.
26. Patalano F, Ruggieri F. Sodium cromoglycate: a review. Eur Respir J 1989;556S-560S.
27. Papageorgiou N, Carroll M, Durham SR, Lee TH, Walsh GM, Kay AB. Complement receptor enhancement as evidence of neutrophil activation after exercise-induced asthma. Lancet 1983;2(8361):1220-1223.
28. Sterling JC, Kurtz JB. Varicella zoster. In: Champion RH, Burton JL, Burns DA, Breathnach SM, Toim. Rook/Wilkinson/Ebling. Textbook of dermatology 6th edition. Oxford: Blackwell 1998;1015-1022.