Colchicine in the treatment of refractory aphthous ulcerations: Review of the literature and two case reports

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Abstract. Colchicine has been known and used for over a millennium for its anti-inflammatory properties, being the treatment of choice for gout and familial Mediterranean fever. A tricyclic alkaloid extracted from the herbaceous plant, *Colchicum autumnale*, colchicine blocks multiple inflammatory pathways, and has antimitotic and antifibrotic action. Although there are insufficient data on the beneficial mechanism of action, colchicine is a widely used treatment in dermatology, one of the morbid conditions with more evidence of efficacy being recurrent aphthous stomatitis (RAS), a disorder with incompletely known etiopathogenesis and, consequently, with poorly defined treatment. Colchicine is considered as the first therapeutic line in complex or severe aphthoses, significantly relieving pain, decreasing the number of lesions, increasing the free interval between eruptive episodes, without inducing noticeable side effects. We examined the treatment efficacy of colchicine in two cases of chronic, severe RAS, evolving in different morbid contexts, who did not respond to other therapeutic measures. The two cases presented with recurrent aphthous stomatitis with herpetiform aphthae; one patient with Turner syndrome and one patient with major Sutton ulcers.

Introduction

Colchicine is a traditional natural remedy known for more than a millennium for its anti-inflammatory properties. Biochemically, it is a toxic protoaloalkaloid from the group of tropolon derivatives, that was extracted in 1819 from the bulb of the autumn crocus (*Colchicum autumnale*), and in 1833 was named colchicine by the German pharmacist and chemist Philipp Lorenz Geiger (1-3). The pure crystallized form was obtained by the French pharmacist Alfred Houde (1). The current drug is the same purified natural substance. The mechanism of action is still a research topic today. In the years 1950-1960, the main cellular target of colchicine action, the cytoskeleton, was identified. Microtubules are major constituents of the cytoskeleton with a role in cell dynamics, maintaining cell shape through resistance to compression, intracellular transport and cell division (3-7). Colchicine binds to tubulin heterodimers, constituents of protofilaments in the structure of microtubules, to form dimer-colchicine complexes that attach to the end of microtubules causing alterations in their conformation resulting in altered cell function (3-7). Its therapeutic action is attributed to the inhibition of neutrophil chemotaxis, their adhesion and recruitment in inflammatory lesions as colchicine is more concentrated in leukocytes than in plasma (3,4,7-9). Colchicine also suppresses the production of superoxide by neutrophils and reduces oxidative stress by decreasing the influx of calcium ions (Ca^{2+}) into neutrophils (10,11). Other confirmed effects include modulation of hepatic macrophage secretion of tumor necrosis factor (TNF) α, inhibition of inflammatory cytokine production [interleukin (IL)-1ß, interferon (IFN)γ, IL-8, IL-6], promoting dendritic cell maturation and stimulating the presentation of naive $CD4^+$ lymphocyte antigens, inhibiting vascular endothelial growth factor (VEGF) and endothelial proliferation (3-7,11).

Apart from the anti-inflammatory effect, colchicine also has antifibrotic and cardiovascular protective effects blocking autoinflammatory pathways, including NLRP3 and IL-1 (3,12). Some pathological conditions such as gout or rheumatoid arthritis are associated with high cardiovascular risk due to systemic inflammation. Colchicine is an immune-modulatory agent able to reduce cardiovascular risk for these patients considering inflammation an important component for the development of heart attacks or strokes (13).

After oral administration, colchicine is absorbed in the jejunum and ileum, is metabolized in the liver by the cytochrome P450 (CYP450) enzyme and excreted mainly hepatobiliary and, to a lesser extent, renally (3,4). Drugs inhibiting CYP450 or P-glycoprotein (intracellular transporter molecule important for colchicine absorption and pharmacokinetics), such as erythromycin, clarithromycin, fluconazole, itraconazole, calcium channel blockers (diltiazem, verapamil),

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cyclosporine, tacrolimus or statins enhance the pharmacological effects of colchicine and increase the risk of its toxic effects (11). The official prescribing guidelines for colchicine therefore recommend dose adjustments for patients taking these medications. Colchicine dose reduction is also recommended for patients with severe renal impairment, including patients on hemodialysis, as well as for patients with severe hepatic impairment (14).

Adverse effects are mainly gastrointestinal and are reversible at dose reduction. They consist of abdominal pain, diarrhea, nausea, vomiting and occur in 5-10% of cases (6,7). Increased levels of serum transaminases, myotoxicity and alopecia are rarely encountered (15-18). Rarer acute adverse effects include myopathy, rhabdomyolysis and myelosuppression. A colchicine neuromyopathy may occur with chronic daily use, particularly in patients whose dose has not been appropriately adjusted for renal disease. Symptoms of colchicine toxicity usually resolve within 1 week to several months of discontinuing the drug (6). The classic therapeutic indications of colchicine are gout and familial Mediterranean fever, as well as its complications (amyloidosis).

Since 2009, colchicine has been approved by the Food and Drug Administration for use in rheumatology, immunology, cardiology, oncology, dermatology (17). The use of colchicine has been shown to be beneficial for the treatment of rheumatic diseases, pericarditis, coronary heart disease, atherosclerosis, and has been attempted in various dermatological diseases, orally or topically, with variable efficacy (1,3,5,6). Severe aphthosis is one of the most documented indications for colchicine treatment with beneficial effects of oral colchicine being reported in case studies, case series and less often, in clinical trials (17-25). We present 2 cases of chronic recurrent aphthous stomatitis (RAS), that represented a diagnostic and therapeutic challenge, as consulted in the Dermatology Clinic of the Railways University Hospital in Iasi, Romania.

Case 1

A 23-year-old patient, with Turner syndrome treated with somatotropin and, from the age of 13 with estro-progestins (Zoely), presented with multiple extremely painful oral herpetiform exulcerations, with a tendency to group in plaques with a yellowish-gray fibrinous base, persistent for approximately 10 days (Fig. 1).

Patient interrogation revealed the onset of oral lesions 4 years prior to presentation, with an episodic, recurrent course and difficult healing in 2 to 3 weeks, under various topical treatments with analgesics, borax glycerin and corticosteroids. The clinical context (numerous miliary exulcerations located on the non-keratinized labial and lingual mucosa, extremely painful and recurrent, in a female patient under chronic estrogen-progestative substitution treatment) led to the diagnosis of RAS with herpetiform aphthae.

Hematological and biochemical investigations, including dosing of ferritin, folate, zinc, vitamin B12, revealed normal data. Treatment with colchicine 1 mg/day, after 3 days of testing digestive tolerance with 0.5 mg/day, in combination with topical dexamethasone and hyaluronic acid was initiated. The evolution of the lesions over a follow-up period of 10 months, under maintenance treatment with colchicine 0.5 mg/day, was towards faster healing, on average in 10 days. A greater interval of 2 months between recurrent episodes was also achieved. There were no reported side effects.

Case 2

A non-smoker 67-year-old patient, with no notable personal medical history, except for pulmonary emphysema, presented for consultation for extremely painful, clearly delimited oval ulcerations with a large transverse axis of approximately 2 cm, with intense erythematous halo and yellowish-gray base, localized on the soft palate and buccal mucosa, with recurrent episodes for 8 years (Fig. 2A).

He was repeatedly evaluated over time by several specialists (ENT, infectious disease, gastroenterology, oral medicine, dermatology). Infectious disease (negative anti-HIV1 and 2 antibodies, AgHbs absent), autoimmune bullous dermatosis (negative anti-desmoglein 3 antibodies), and a neoplastic process (repeated biopsies in 2012, 2013, 2015, with nonspecific inflammatory changes) were excluded. The lesions only partially responded to topical treatments with corticosteroids, lidocaine, oral corticosteroids and dapsone (Fig. 2B). Thus, treatment with colchicine 1 mg/day in combination with pentoxifylline 400 mg x 2/day and topical suspension with metronidazole, dexamethasone and nystatin was initiated. The lesions healed significantly in approximately 6 weeks. Treatment with a maintenance dose of colchicine (0.5 mg/day) was continued for the next 4 months, and was well tolerated with no recurrent episodes during this time (Fig. 2C).

Discussion

Efficacious results of colchicine treatment have been reported in several dermatologic conditions, such as chronic urticaria unresponsive to antihistamines, urticarial vasculitis, forms of cutaneous vasculitis (hypocomplementemic urticarial, leukocytoclastic, nodular, necrotic vasculitis, Henoch-Schonlein purpura), palmo-plantar pustular psoriasis (applied as a hydrophilic ointment with colchicine 1%), pyoderma gangrenosum associated or not with inflammatory bowel disease, Sweet syndrome, subcorneal pustulosis, acquired bullous epidermolysis with limited skin lesions, benign mucosal pemphigoid, Behcet's disease, actinic keratosis (applied as a hydrophilic gel with colchicine 1%) or granuloma annulare (3,26-34). Less satisfactory results have been obtained for hidradenitis suppurativa, acne vulgaris, dermatitis herpetiformis, linear IgA dermatosis, scleroderma and psoriasis vulgaris (3,35,36).

Recurrent aphthous stomatitis (RAS) is a recurrent ulcerative stomatitis with an estimated prevalence between 2 and 10%, with an incompletely elucidated etiopathogenesis and, consequently, with poorly defined treatment (37). In developed countries, the incidence in the general population reaches 20%, mainly affecting young adults (38). The pathophysiological substrate consists of an antigenic stimulation of oral mucosal keratinocytes in predisposed individuals, followed by the secretion of proinflammatory cytokines (especially IL-2, TNFα) and the consequent expression of class I major histocompatibility complex antigens (MHC). MHC class I antigen-expressing cells become targets of cytotoxic T lymphocytes (39,40). The inflammatory process, resulting in

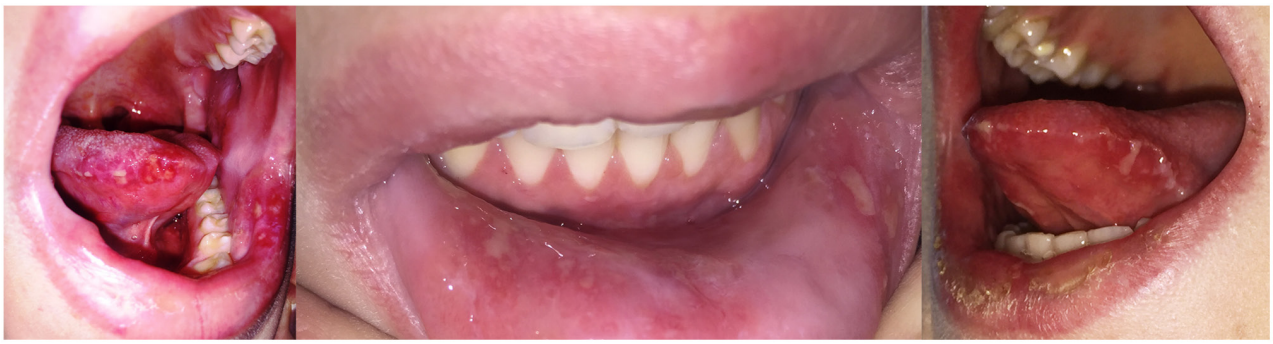

Figure 1. Multiple millimetric exulcerations grouped in erosive patches with micropolicyclic contour on the labial and non-keratinized lingual mucosa.

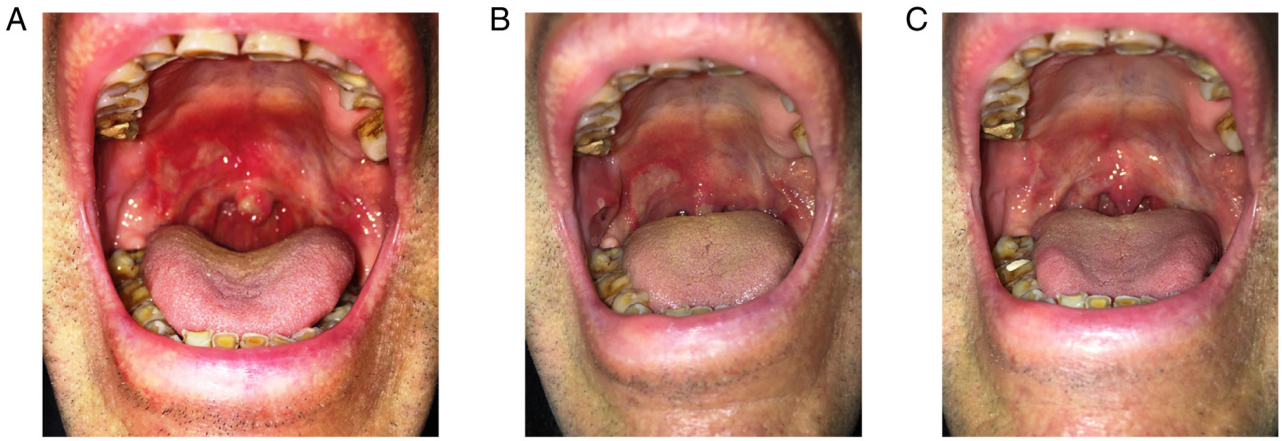

Figure 2. (A) Initial presentation with large ulcers on the soft palate and buccal mucosa. (B) Clinical aspect after treatment with dapsone for 6 weeks. (C) Clinical aspects after treatment with colchicine for 6 weeks (almost complete epithelization of oral ulcers).

variable epithelial necrosis depending on its histopathological site, is the consequence of an aberrant immune response, influenced by an abnormal oral flora (4).

The three modes of clinical expression of the disorder are common aphthae (a few round or oval exulcerations with an average diameter of 2-4 mm, with a gray-yellow base and a characteristic carmine-red areola, with self-limited evolution of approximately 7-10 days), herpetiform aphthae, the rarest (numerous yellowish, millimetric exulcerations, with a tendency to coalesce in erosive patches with micropolycyclicontour, evolving for approximately two weeks) and major aphthae (Sutton's ulcers or periadenitis mucosa necrotica recurrens), the most severe clinical form (crateriform ulcers, with a diameter between 1 and 3 cm, often solitary, accompanied by satellite adenopathy, with difficult healing for 1-2 months with sometimes mutilating scars) (8,39,40). The common clinical features of these ulcerations are intense pain, location on non-keratinized areas of the oral mucosa, self-limiting character and recurrences, either spontaneous or correlated with triggering factors. These factors may be local (e.g. oral trauma, contact hypersensitivity, sodium lauryl sulfate), nutritional deficiencies (iron, vitamin B12, folic acid), medications (angiotensin converting enzyme inhibitors, gold salts, phenobarbital, diclofenac, piroxicam), inflammatory bowel disease (gluten-sensitive enteropathy, Crohn's disease, ulcerative colitis), certain foods (tomatoes, nuts, cocoa, dairy, spices), or a hormonal context with progesterone deficiency in females. RAS is also correlated with a genetic predisposition (3,8,39).

The treatment of RAS is a challenge. In the absence of a clear etiopathogenesis, various topical and systemic therapies have been attempted over time, with the aim to reduce pain, shorten the duration of recurrent episodes, to distance them in time, and in order to improve the quality of life of these patients (40). Severe aphthoses, with very painful lesions accompanied by functional signs (pain when speaking, chewing, swallowing), with frequent recurrences and significant psycho-social impact, raise the issue of systemic therapy. Prednisone, thalidomide, cyclosporine, azathioprine, methotrexate, dapsone, pentoxifylline, and colchicine have been administered. The use of colchicine in the treatment of RAS is well documented. The mechanism by which colchicine positively influences RAS lesions could be essentially explained by inhibiting leukocyte chemotaxis and mobilization, their lysosomal degranulation, by modulating the interaction between leukocytes and vascular endothelium, and by decreasing the production of proinflammatory cytokines, including IL-6 and IL-1ß (19,41). Studies support the effectiveness of colchicine in RAS, both as a monotherapy and in combination with other systemic therapies, as an episode treatment and as a maintenance or prophylactic treatment. The first large retrospective study (1986-2000), on 54 immunocompetent patients with RAS followed on average for 4.7 years, concluded that the administration of colchicine at doses of 1-1.5 mg/day for at

least 3 months had beneficial effects on episode frequency, pain intensity and RAS impact on quality of life in 63% of patients, 37% of whom maintained results for 5 years (41). Very beneficial effects on reducing pain and injury were reported in a series of 20 patients with severe aphthosis, treated with colchicine 0.5 mg three times per day (20). The mean weekly number of aphthae and pain score were assessed in patients treated continuously with colchicine compared to those treated only 2 months after 2 previous months without treatment. This 4-month study highlighted the obvious prophylactic benefit of uninterrupted treatment with colchicine (21). Persistent significant remissions for 3-5 years were also reported in 2 of a series of 3 patients with severe aphthosis treated with colchicine. Administration of colchicine at a dose of 0.5 mg three times per day, 3 consecutive days/week had a similar efficacy to that of prednisolone administered at a dose of 5 mg/day and to combination therapy with levamisole 50 mg/day and prednisolone 5 mg/day in a study on 50 patients with RAS followed for 3 weeks (22). Colchicine can also be used as a prophylactic treatment. Doses with a prophylactic effect of 0.5-1.8 mg/day have been reported in a study on 9 children with PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) and were found to significantly increase the free interval between episodes of oral ulceration (23). Another randomized controlled open label study (18 patients aged 4-11 years) over a period of 6 months, followed the number of active episodes in two groups: One treated for 3 months after 3 months of surveillance and one control. The number of episodes were similar in the first 3 months without treatment in both groups. The number of patients treated during the follow-up 3 months was significantly lower compared to the control and compared to the first 3 months of the study - the authors emphasizing the definite prophylactic role of colchicine. Daily doses of 0.5-1.5 mg of colchicine alone or in combination with dapsone (75-100 mg/day) were also shown to be beneficial in another study of 55 patients with severe aphthosis monitored between 1998 and 2007, 80% of them with a substantial response (24,25).

Considering the clinical context of the disease, with severe episodes, only partially responsive to classic therapies, the two presented cases are part of the group of complex aphthoses. The response was favorable to colchicine, starting with a dose of 1 mg/day until significant remission was obtained, and continuing with a maintenance dose of 0.5 mg/day for several months of follow-up (10 and 4 months, respectively, in our cases), recording only two mild recurrences in the patient with herpetiform aphthae and no recurrence in the patient with Sutton's ulcers. Colchicine was associated with pentoxifylline in our second patient, considering literature reports of its beneficial effects in reducing the severity and frequency of aphthous ulcer episodes. Pentoxifylline inhibits the production of TNFα and reduces the migration of neutrophils, but its specific action in aphthous stomatitis is still unclear (42). There were no side effects in any of our patients during the follow-up period.

In conclusion, inhibition of multiple inflammatory pathways and modulation of the innate immune response are the main attributes of colchicine exploited in the treatment of several dermatoses, including RAS. Case studies, series of patients and clinical trials, although few, provide evidence of the efficacy of colchicine (level of evidence III) in severe aphthosis, refractory to classical therapies with topical or systemic corticosteroids, pentoxifylline, and cyclosporine. There is no consensus on the ideal therapeutic regimen for colchicine in RAS.

Therapeutic doses of 0.5-1.5 mg/day are usually free of noticeable side effects, even after 6-9 months of treatment, provided that drug interactions are avoided and doses are adjusted in patients with hepatic or renal impairment. The choice of treatment with colchicine in severe aphthosis should take into account the severity of the lesions, their chronic nature, the lack of therapeutic efficacy of other medications and the context of the patient morbidity. The mechanism of action underlying the efficacy of colchicine in various dermatoses, as well as the optimal therapeutic regimen, including RAS, require further extensive research.

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Availability of data and materials

The data that support the findings of this study are available from the archives of the Railways University Hospital Iasi, (Iasi, Romania), but restrictions apply to the availability of these data which are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from the Railways University Hospital Iasi.

Author's contributions

TT conceived and supervised the study. MPT, IME and ST analyzed the data. MPT, TT, MM, IME and ST contributed to data acquisition and interpretation and wrote the manuscript. All authors contributed equally to acquisition, analysis and systematization of data, manuscript writing and critical revision of it for important intellectual content. All authors reviewed the results and read and approved the final version of the manuscript.

Ethics approval and consent to participate

The Research Ethics Committee of the Railways University Hospital Iasi (Iasi, Romania) affiliated with 'Grigore T. Popa' University of Medicine and Pharmacy approved the current study.

Patient consent for publication

Informed written consent was obtained from both patients for publication of the case reports.

Competing interests

The authors declare that they have no competing interests.

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