

Lowe Lori (Orcid ID: 0000-0002-2359-8426)
Fullen Douglas R (Orcid ID: 0000-0002-2524-4509)

Unusual drug reaction with features of colchicine toxicity in patient on colchicine and allopurinol

Behzad Salari, M.D.¹, Mallory Joseph, M.D.², Milad Eshaq, M.D.², Lori Lowe, M.D.^{1,2}, Douglas R. Fullen, M.D.^{1,2}

¹ Department of Pathology, University of Michigan, Ann Arbor, Michigan

² Department of Dermatology, University of Michigan, Ann Arbor, Michigan

Corresponding author: Douglas R. Fullen, MD, Department of Pathology, Michigan Medicine, NCRC, Bldg. 35, 2800 Plymouth Road, Ann Arbor, MI 48109, USA. Email: dfullen@med.umich.edu.

Presentations: Oral presentation at 58th ASDP Annual meeting, Virtual, USA, 2021.

Disclosures: None

Competing interests: None.

Sponsorships: None.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/cup.14280](https://doi.org/10.1111/cup.14280)

This article is protected by copyright. All rights reserved.

Abstract

A 58-year-old woman was admitted for heart failure and concern for cardiogenic shock. The patient had been recently placed on colchicine and allopurinol, four months and three weeks respectively, prior to admission. Upon admission, she had a cutaneous eruption that had started abruptly several days after allopurinol initiation. It included multiple erythematous papules with scant scale on the forearms and numerous erythematous papules on the legs. Because of the varied morphologic presentation, biopsies from both the thigh and forearm were performed for a suspected drug reaction. The specimen from the thigh demonstrated a superficial dermal band-like lymphocytic infiltrate with dyskeratosis and numerous intraepidermal mitotic figures predominantly in metaphase. In addition, there were neutrophils with leukocytoclasia. The specimen from the forearm showed superficial perivascular lymphocytic inflammation and intraepidermal dyskeratosis with mitotic figures similar to the thigh biopsy specimen but without a dermal neutrophilic infiltrate. An unusual drug eruption with features of colchicine toxicity was favored.

Colchicine toxicity is not a commonly encountered clinical scenario and cutaneous findings have only rarely been described. Herein we report an exceedingly rare case of an unusual drug reaction with “colchicine figures” (i.e. ring-shaped mitotic figures arrested in metaphase) consistent with colchicine toxicity.

Case history

A 58-year-old woman was admitted for heart failure and concern for cardiogenic shock. Her past medical history was significant for Hashimoto thyroiditis, arterial hypertension, long-standing left bundle branch block, aortic stenosis, and mitral regurgitation in the setting of left ventricle dilation. Laboratory evaluation was notable for impaired liver function tests (AST 199 IU/L [reference 8-30 IU/L], ALT 326 IU/L [reference ≤ 35 IU/L], alkaline phosphatase 230 IU/L [reference 40-116 IU/L], and total bilirubin 1.6 mg/dL [reference 0.2-1.2 mg/dL]), and elevated blood urea nitrogen (BUN; 38 mg/dL, reference 8-20 mg/dL), creatinine (Cr; 1.04 mg/dL, reference 0.5-1.0 mg/dL), and negative antinuclear antibody. Uric acid was within normal limits upon admission and on multiple occasions during admission. The patient had been placed on colchicine (1.2 mg/day) by her cardiologist four months prior to admission, as well as allopurinol by her primary care physician for presumed gout three weeks prior to admission. Additionally, she was taking lisinopril, furosemide, spironolactone, metoprolol, aspirin, levothyroxine, and nortriptyline. The patient had been on these other medications for at least a year before her presentation.

The dermatology service was consulted for a cutaneous eruption that was present upon admission and had started abruptly several days after allopurinol initiation. On exam, there were multiple erythematous papules with scant scale on the forearms and numerous erythematous papules on the legs (Figure 1). The dermatology service favored a drug reaction and performed biopsies of both the thigh and forearm because of the varied morphologic presentation.

Both medications were halted, and she was treated with topical steroids, resulting in rapid resolution of the eruption in 4-5 days. It did not recur and within two weeks, all liver function tests improved significantly (AST 34 IU/L, ALT 64 IU/L, alkaline phosphatase 207 IU/L, and total bilirubin 0.8 mg/dL), and BUN and Cr normalized. Four weeks later, she received a heart transplant due to her underlying decompensated heart failure and was not reintroduced to colchicine and allopurinol to date, eight months after initial presentation.

The biopsy specimen from the thigh demonstrated a superficial dermal band-like lymphocytic infiltrate with dyskeratosis and numerous intraepidermal mitotic figures predominantly in metaphase. In addition, there were papillary dermal neutrophils with leukocytoclasia resembling some features of neutrophilic dermatoses such as Sweet syndrome, yet other features typical of Sweet syndrome including a dense neutrophilic infiltrate with leukocytoclasia accentuated around postcapillary venules were absent (Figures 2A and 2B). The biopsy specimen from the forearm showed superficial perivascular lymphocytic inflammation, in addition to dyskeratosis and intraepidermal mitotic figures in the lower half of the epidermis, similar to what was observed in the thigh specimen (Figures 2C and 2D); however, no dermal neutrophilic infiltrate was present. Erythrocyte extravasation was present in the superficial dermis. Eosinophils were absent in both specimens. Based on clinicopathologic correlation, an unusual drug eruption with features of colchicine toxicity was favored. Given the temporal association of the rash with recent initiation of allopurinol therapy, it is possible that this medication also contributed to the cutaneous eruption.

Discussion

Colchicine is a common therapeutic agent used in various clinical conditions such as gout, inflammatory dermatoses, and cardiovascular diseases.^{1,2} Colchicine toxicity, however, is a rarely encountered clinical scenario and cutaneous manifestations are not well described.

Colchicine inhibits tubulin polymerization into microtubules, which in turn disturbs cell functions such as cell division, polarity and motility, phagocytosis, and intracellular movement.³ Its therapeutic window is narrow with widely variable bioavailability between individuals.⁴ It is primarily excreted in bile and through the kidneys.⁵ Therefore, drug interactions and renal function status can cause chronic overdose and intoxication.^{2,6,7}

Clinically, colchicine intoxication has three chronological stages.⁸ The first stage, within 24 hours, is dominated by gastrointestinal symptoms. The second stage, typically within 2-5 days, is characterized by multiorgan dysfunction. If the patient survives, the third phase is a recovery phase manifesting as rebound leukocytosis and reversible alopecia.

While histopathologic findings of colchicine toxicity have been characterized in various organ systems, clinical and dermatopathological findings have rarely been described. Relatively low drug concentration in the skin may be a reason for such observation.⁹ A review of cases of colchicine toxicity from 1968 to 2004 reported a total of 14 documented cutaneous clinical

findings of colchicine toxicity with dermatopathological features described in only three cases and one additional report published later (Table 1).^{10,11}

Alopecia is the most frequently described dermatologic manifestation of colchicine toxicity.^{10,12} However, our patient did not present with or complain of it prior to admission. It can develop after prolonged use or in patients recovering from acute intoxication and typically reverses within two months. Reported cutaneous findings include erythematous cutaneous rash with ulcerative stomatitis,¹³ erythematous eruption (including the present case),¹⁴ toxic epidermal necrolysis (TEN)-like eruption,¹⁰ and violaceous morbilliform rash.¹¹

“Colchicine figures” are an important clue to the diagnosis of colchicine toxicity (Figure 3).¹⁵ They are ring-shaped mitotic figures arrested in metaphase. They have been described in various tissues with rapid turnover, including the epidermis and pilosebaceous units.^{16,17} This finding was a prominent histopathologic feature in both biopsy specimens in our patient.

Including the present patient, there are only five reported cases that included both clinical and histopathological findings of the skin in colchicine toxicity.^{10,11,18,19} Of these, two cases showed either TEN¹⁸ or TEN-like eruption.¹⁰ The former was a 32-year-old HIV-positive male who was started on colchicine for gout while he was also on allopurinol for more than one month. After six days of colchicine, he developed signs of toxicity, including alopecia, erythema, and bullae involving 30% of the skin, and a positive Nikolsky sign. A skin biopsy specimen was interpreted as consistent with TEN. While the clinical picture possibly suggests colchicine toxicity, the

authors attributed the histopathologic findings to allopurinol because of its more common association with TEN.²⁰ Minor skin eruptions have been reported in about 2% of patients on allopurinol. However, it is well known to cause severe skin adverse drug reactions, most notably Stevens-Johnson Syndrome or TEN.²¹

The second case with TEN-like rash¹⁰ was a 48-year-old man with history of gout and alcoholism who was admitted for acute colchicine toxicity. During hospitalization, he received antibiotics and granulocyte colony-stimulating factor (G-CSF) and developed a TEN-like rash including with focal skin sloughing and associated Nikolsky sign. A skin biopsy specimen demonstrated vacuolar interface dermatitis with subepidermal bulla, numerous mitotic figures, and apoptosis of keratinocytes in the lower half of the epidermis. Given the presence of colchicine figures, the authors attributed the findings to colchicine toxicity with TEN-like features.

In another case, a four-year-old girl with familial Mediterranean fever (FMF) developed alopecia, erythematous rash with central bullous areas, and erythema nodosum-like skin lesions following acute colchicine overdose.¹⁹ A skin biopsy specimen showed a dermal neutrophilic infiltrate and the authors concluded that this was a case of colchicine intoxication with features resembling Sweet syndrome. One could speculate, however, that the findings of neutrophilic infiltration also could have been a manifestation of her underlying FMF or due to prior G-CSF administration. Additionally, dermal neutrophilic infiltration with leukocytoclasia has not been reported in other cases of colchicine toxicity. In our patient, however, these findings were evident in the sections from the thigh and absent in the forearm specimen.

Attributing it to either colchicine or allopurinol is difficult due to lack of prior evidence and raises the possibility of a mixed drug reaction.

Most recently,¹¹ a 57-year-old woman with liver transplant who was on numerous medications including allopurinol and colchicine presented with acute colchicine overdose. Skin examination was notable for a diffuse, blanchable, violaceous, morbilliform rash. A biopsy specimen showed a mild interface dermatitis with focal basal vacuolar change, prominent dyskeratosis, and numerous basal mitotic figures in metaphase. Our patient closely mimics these findings. Additionally, they found focal basal vacuolopathy forming small clefts, suggesting early bullous change. The histopathologic differential diagnosis included erythema multiforme and drug eruption due to other medications; however, the prominent metaphase-arrested mitotic figures militated against this.

Dermatologic complications of allopurinol can occur in up to 10–15% of patients including a maculopapular eruption, pruritus, Sweet syndrome, and rarely, Stevens-Johnson syndrome/TEN.²² Generally, the average duration from the administration of a causative agent to the onset of skin lesions is about 5–7 days in most cases.²³⁻²⁵ Our patient presented three weeks after the initiation of allopurinol. Given this time course, her skin eruption was initially presumed to be secondary to allopurinol. While the histopathologic findings confirm colchicine toxicity, allopurinol may also have contributed to the findings.

Summary

We present an exceedingly rare case of an unusual drug reaction with histopathologic evidence of “colchicine figures” typical of colchicine toxicity in separate biopsy specimens occurring shortly after initiation of allopurinol therapy. One can speculate as to whether this is a mixed drug reaction or entirely colchicine toxicity potentially unmasked or triggered by allopurinol. Colchicine toxicity is not a commonly encountered clinical scenario and cutaneous findings have only rarely been described. Mitotic arrest, evidenced in both of our patient’s biopsy specimens, is a known mechanism of action and has been documented histopathologically in colchicine but not allopurinol therapy. Moreover, acute multi-organ injury from decompensated heart failure may have predisposed our patient to drug toxicity. Awareness of colchicine figures is important in establishing the etiologic agent of a drug reaction, especially in patients taking multiple medications, in order to avoid further exposure and worsening colchicine toxicity. As allopurinol may have played a part in exacerbating colchicine toxicity, cessation of this medication may also be warranted.

Figure legends

Figure 1: Patient with A) multiple erythematous papules with scant scale on the forearms, and B) numerous erythematous papules on the legs.

Figure 2: Hematoxylin and eosin stains. A & B) A biopsy specimen from the thigh demonstrates a superficial dermal band-like lymphocytic infiltrate with dyskeratosis and numerous intraepidermal mitotic figures predominantly in metaphase. In addition, there are many neutrophils with leukocytoclasia (A, 40x magnification; B, 200x magnification). C & D) A biopsy specimen from the forearm shows a superficial perivascular lymphocytic inflammation with erythrocyte extravasation, in addition to dyskeratosis and intraepidermal mitotic figures (C, 40x magnification; D, 200x magnification).

Figure 3: Ring-shaped metaphase arrested mitotic figures consistent with “colchicine figures” (Hematoxylin and eosin stain, 400x magnification).

References

1. Imazio M, Nidorf M. Colchicine and the heart. *Eur Heart J*. 2021;42(28):2745-2760.
2. Robinson KP, Chan JJ. Colchicine in dermatology: A review. *Australas J Dermatol*. 2018;59(4):278-285.
3. Panda D, Daijo JE, Jordan MA, Wilson L. Kinetic stabilization of microtubule dynamics at steady state in vitro by substoichiometric concentrations of tubulin-colchicine complex. *Biochemistry*. 1995;34(31):9921-9929.
4. Rochdi M, Sabouraud A, Girre C, Venet R, Scherrmann JM. Pharmacokinetics and absolute bioavailability of colchicine after i.v. and oral administration in healthy human volunteers and elderly subjects. *Eur J Clin Pharmacol*. 1994;46(4):351-354.
5. Niel E, Scherrmann JM. Colchicine today. *Joint Bone Spine*. 2006;73(6):672-678.
6. Kuncl RW, Duncan G, Watson D, Alderson K, Rogawski MA, Peper M. Colchicine myopathy and neuropathy. *N Engl J Med*. 1987;316(25):1562-1568.
7. Hung IF, Wu AK, Cheng VC, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: A retrospective study. *Clin Infect Dis*. 2005;41(3):291-300.
8. Stapczynski JS, Rothstein RJ, Gaye WA, Niemann JT. Colchicine overdose: Report of two cases and review of the literature. *Ann Emerg Med*. 1981;10(7):364-369.
9. Rochdi M, Sabouraud A, Baud FJ, Bismuth C, Scherrmann JM. Toxicokinetics of colchicine in humans: Analysis of tissue, plasma and urine data in ten cases. *Hum Exp Toxicol*. 1992;11(6):510-516.
10. Arroyo MP, Sanders S, Yee H, Schwartz D, Kamino H, Strober BE. Toxic epidermal necrolysis-like reaction secondary to colchicine overdose. *Br J Dermatol*. 2004;150(3):581-588.
11. Mason SE, Smoller BR, Wilkerson AE. Colchicine intoxication diagnosed in a skin biopsy: A case report. *J Cutan Pathol*. 2006;33(4):309-311.
12. Gurkan A, Oguz MM, Boduroglu Cengiz E, Senel S. Dermatologic manifestations of colchicine intoxication. *Pediatr Emerg Care*. 2018;34(7):e131-e133.
13. Bruns BJ. Colchicine toxicity. *Australas Ann Med*. 1968;17(4):341-344.
14. Critchley JA, Critchley LA, Yeung EA, et al. Granulocyte-colony stimulating factor in the treatment of colchicine poisoning. *Hum Exp Toxicol*. 1997;16(4):229-232.
15. Ludford R. The action of toxic substances upon the division of normal and malignant cells in vitro and in vivo. *Arch exp Zellforsch*. 1936;18:411-441.
16. Hoang C, Lavergne A, Bismuth C, Fournier PE, Leclerc JP, Le Charpentier Y. [Visceral histologic lesions of lethal acute colchicine poisoning. Apropos of 12 cases]. *Ann Pathol*. 1982;2(3):229-237.
17. Brown WO, Seed L. Effect of colchicine on human tissues. *Am J Clin Pathol*. 1945;15(5):189-195.
18. Alfandari S, Beuscart C, Delaporte E, Senneville E, Mouton Y. Toxic epidermal necrolysis in a patient suffering from acquired immune deficiency syndrome. *Infection*. 1994;22(5):365.
19. Guven AG, Bahat E, Akman S, Artan R, Erol M. Late diagnosis of severe colchicine intoxication. *Pediatrics*. 2002;109(5):971-973.

20. Roujeau JC, Guillaume JC, Fabre JP, Penso D, Flechet ML, Girre JP. Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981-1985. *Arch Dermatol*. 1990;126(1):37-42.
21. Atzori L, Pinna AL, Mantovani L, et al. Cutaneous adverse drug reactions to allopurinol: 10 year observational survey of the dermatology department--Cagliari University (Italy). *J Eur Acad Dermatol Venereol*. 2012;26(11):1424-1430.
22. Lang PG, Jr. Severe hypersensitivity reactions to allopurinol. *South Med J*. 1979;72(11):1361-1368.
23. Cohen PR, Kurzrock R. Sweet's syndrome revisited: A review of disease concepts. *Int J Dermatol*. 2003;42(10):761-778.
24. Polimeni G, Cardillo R, Garaffo E, et al. Allopurinol-induced Sweet's syndrome. *Int J Immunopathol Pharmacol*. 2016;29(2):329-332.
25. Callen JP. Neutrophilic dermatoses. *Dermatol Clin*. 2002;20(3):409-419.

Unusual drug reaction with features of colchicine toxicity in patient on colchicine and allopurinol

Behzad Salari, M.D.¹, Mallory Joseph, M.D.², Milad Eshaq, M.D.², Lori Lowe, M.D.^{1,2}, Douglas R. Fullen, M.D.^{1,2}

¹ Department of Pathology, University of Michigan, Ann Arbor, Michigan

² Department of Dermatology, University of Michigan, Ann Arbor, Michigan

Corresponding author: Douglas R. Fullen, MD, Department of Pathology, Michigan Medicine, NCRC, Bldg. 35, 2800 Plymouth Road, Ann Arbor, MI 48109, USA. Email: dfullen@med.umich.edu.

Presentations: Oral presentation at 58th ASDP Annual meeting, Virtual, USA, 2021.

Disclosures: None

Competing interests: None.

Sponsorships: None.



Figure1A.tif

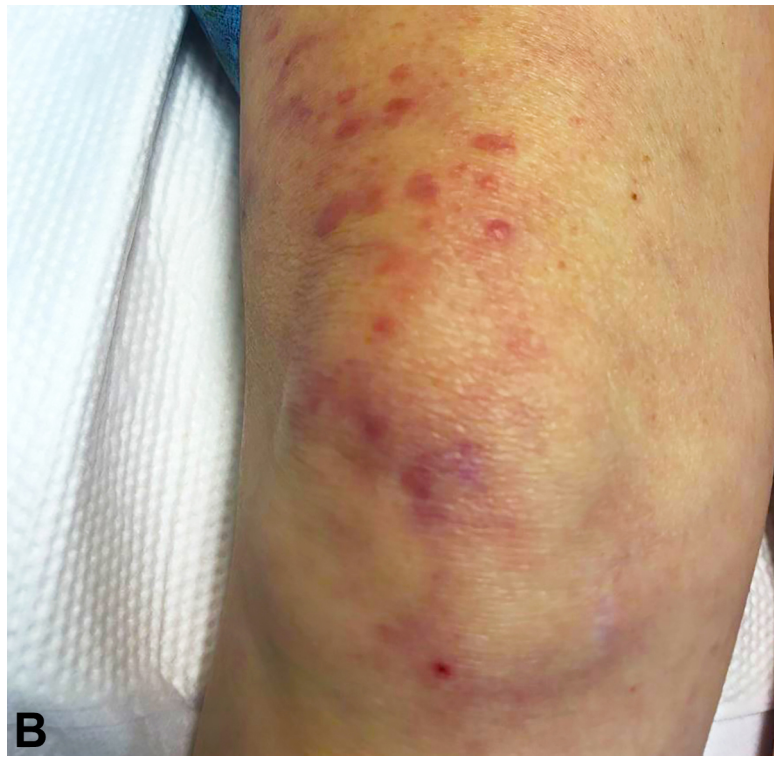
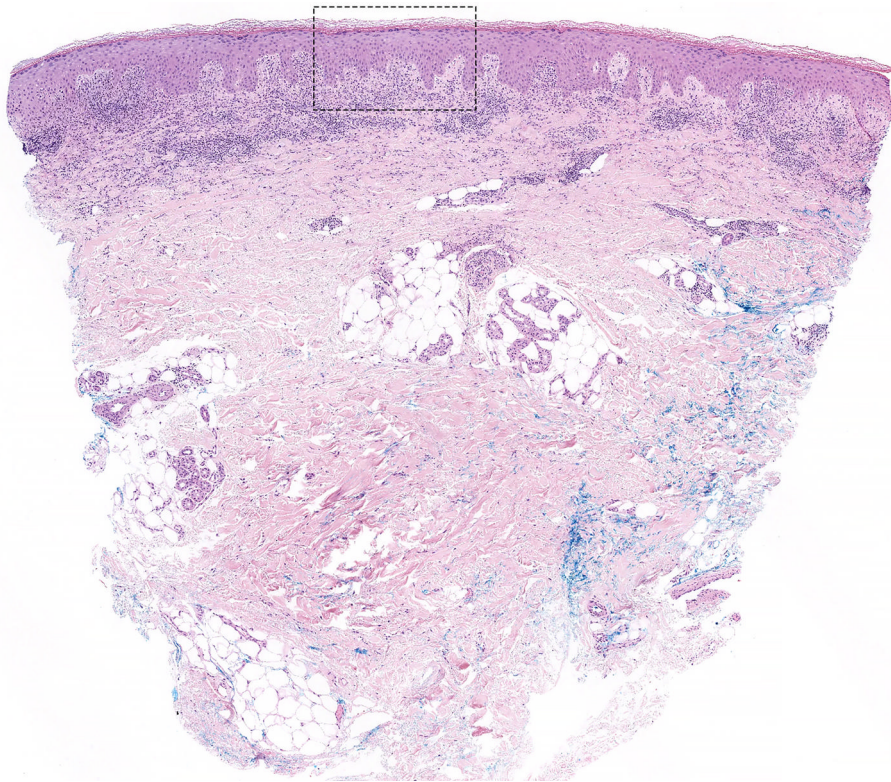


Figure1B.tif

A



40x

Figure2-A.tif

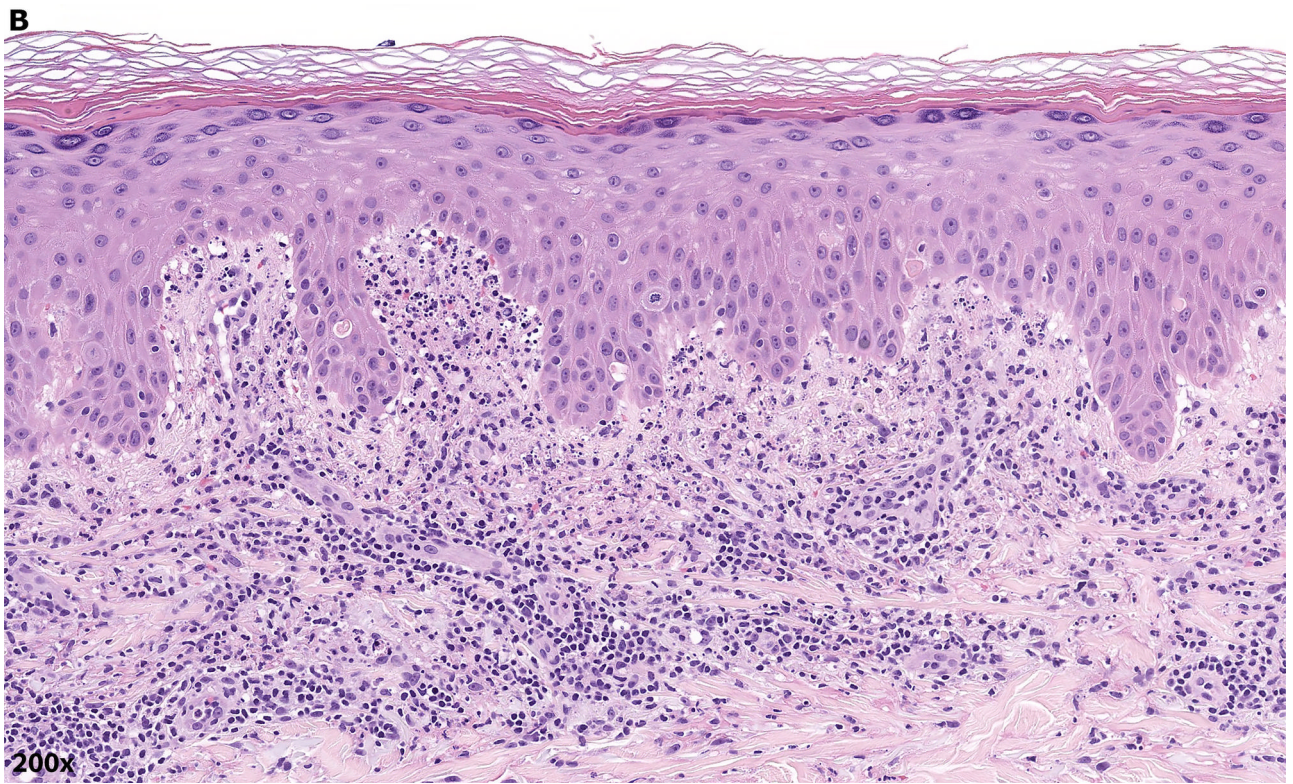
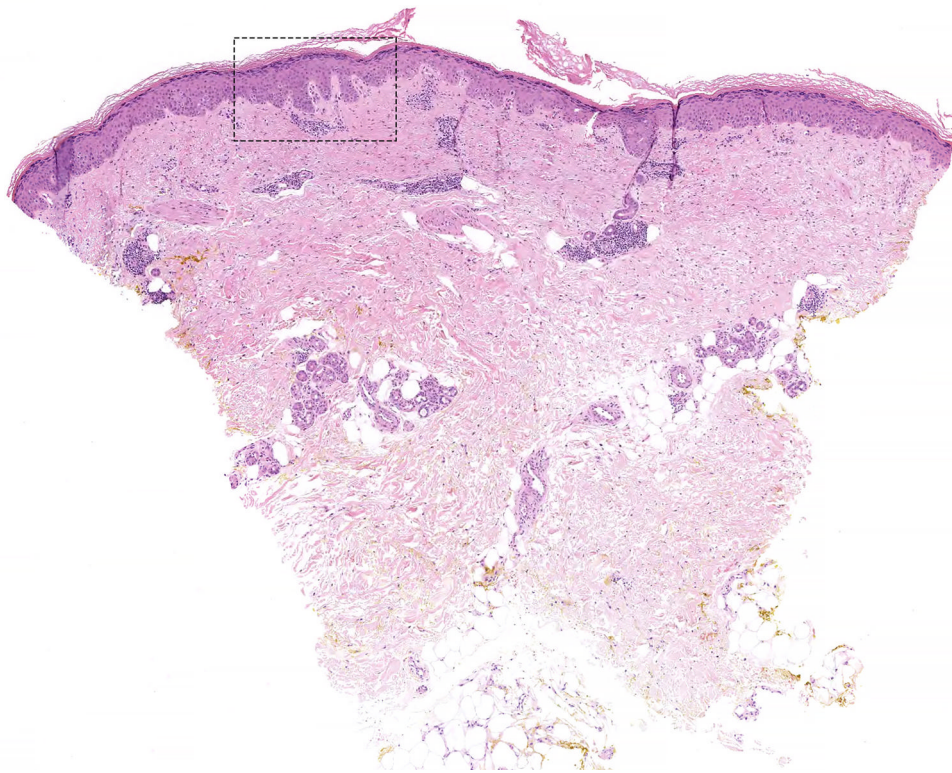


Figure2-B.tif

c



40x

Figure2-C.tif

D

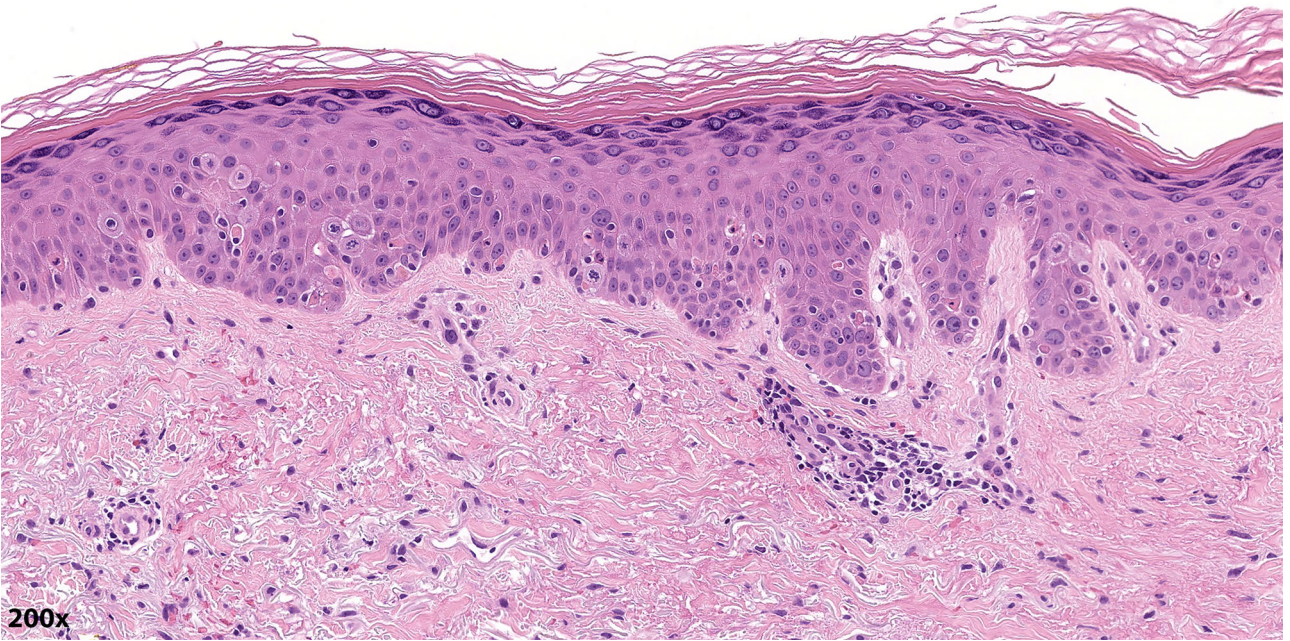


Figure2-D.tif

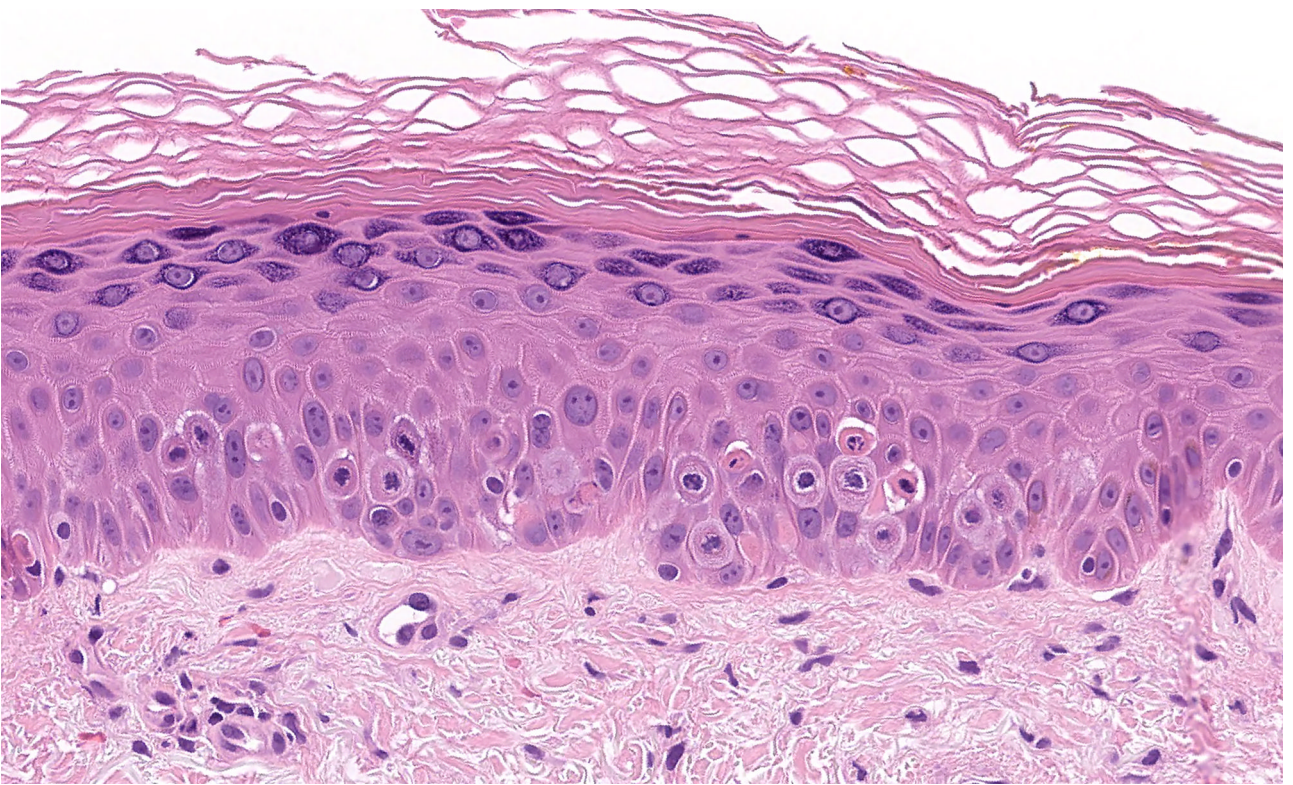


Figure3.tif

Table 1. Clinical and histopathological findings of colchicine toxicity described in four cases from 1968 to 2021.

	Case #1 (Alfandari et al.)¹⁸	Case #2 (Arroyo et al.)¹⁰	Case #3 (Güven et al.)¹⁹	Case #4 (Mason et al.)¹¹
History	<ul style="list-style-type: none"> • 32-year-old HIV-positive man • Was on allopurinol for more than 1 month • Colchicine for gout (6 days) 	<ul style="list-style-type: none"> • 48-year-old man • PMHx: Gout and alcoholism • Acute colchicine intoxication 	<ul style="list-style-type: none"> • Four-year-old girl with FMF • Acute colchicine overdose 	<ul style="list-style-type: none"> • 57-year-old woman • PMHx: Liver transplant • On numerous medications including allopurinol and colchicine • Acute colchicine overdose
Skin exam	<ul style="list-style-type: none"> • Generalized signs of toxicity • Alopecia • Bullae • Positive Nikolsky sign 	<ul style="list-style-type: none"> • TEN-like rash • Coalescing erythematous macules and patches • Focal skin sloughing • Nikolsky sign 	<ul style="list-style-type: none"> • Alopecia • Erythematous rash with central bullous areas • Erythema nodosum-like lesions 	<ul style="list-style-type: none"> • Diffuse, blanchable, violaceous, morbilliform rash
Histopathologic findings	<ul style="list-style-type: none"> • Erythema multiforme <ul style="list-style-type: none"> ○ Necrotic epidermal keratinocytes ○ Mild perivascular lymphocytic infiltrate 	<ul style="list-style-type: none"> • Vacuolar interface dermatitis • Subepidermal bulla • Numerous mitoses • Apoptosis of keratinocytes in the lower half of the epidermis 	<ul style="list-style-type: none"> • Dermal neutrophilic infiltrate with features resembling Sweet syndrome 	<ul style="list-style-type: none"> • Mild interface dermatitis • Focal basal vacuolopathy suggestive of early bullous change • Prominent dyskeratosis • Numerous basal metaphase mitotic figures

PMHx: Past medical history; HIV: Human immunodeficiency virus; TEN: Toxic epidermal necrolysis; FMF: Familial Mediterranean fever.

Cases #2 and #3 received granulocyte colony-stimulating factor (G-CSF) and antibiotics during their hospitalizations.