

Crushed it: Elucidation of systemic vasculitis caused by injected hydromorphone tablets via skin biopsy



Robin Rolader, BS,^a Brian Bishop, MD, MPH,^b Zachary W. Eyre, MD, MBA,^b and Justin T. Cheeley, MD, FAAD^{b,c}
Atlanta, Georgia

Key words: antineutrophil cytoplasmic antibodies; autoimmune markers; crushed tablets; hydromorphone; inflammation; medium-vessel vasculitis; microcrystalline cellulose; mixed-vessel vasculitis; opioid; self-injection; small-vessel vasculitis.

INTRODUCTION

Intravenous administration of crushed oral medications has been associated with significant pulmonary complications that are often challenging to diagnose.¹⁻⁶ We report a case of surreptitious intravenous injection of crushed hydromorphone tablets that presented as a small- and medium-vessel vasculitis with associated renal failure and elevated autoimmune markers.

CASE REPORT

A 40-year-old white woman with a medical history of Crohn's disease, total proctocolectomy, primary sclerosing cholangitis, and recently diagnosed Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis with crescentic glomerulonephritis was transferred from an outside hospital for further management of acute renal failure and worsening cutaneous vasculitis.

The patient's initial diagnosis was suspected ANCA-associated vasculitis made at an outside hospital after laboratory investigation found a positive cytoplasmic ANCA (c-ANCA) in the setting of biopsy-supported crescentic glomerulonephritis. She was started on oral glucocorticoids and cyclophosphamide infusions for immunosuppressive therapy with improvement in her symptoms. The patient was subsequently lost to follow-up and presented to the emergency room 1 month later with complaints of worsening fevers, rash, lower extremity edema,

Abbreviations used:

ANCA: antineutrophil cytoplasmic antibody
c-ANCA: cytoplasmic antineutrophil cytoplasmic antibody

pain, pruritus, and decreased urine output. She further reported intermittent epistaxis and the development of multiple tender nodules on her thighs, wrists, and left breast (Fig 1).

On examination, the patient had multiple deep-seated, tender, racemose purpuric plaques and nodules affecting the fatty areas of the body including the bilateral breasts and proximal thighs (Fig 2). She also had innumerable palpable petechial papules coalescing into purpuric thin plaques on all 4 extremities.

The patient had progressively worsening renal failure and started on empiric prednisone, 60 mg orally daily, because of a subjective history of drug-induced pancreatitis from intravenous steroids in the past. A full workup into the etiopathology of her multisystem disease was undertaken, with assistance by the rheumatology, nephrology, and dermatology departments.

Repeat autoimmune workup was significant for a positive antinuclear antibody (1:320 speckled), positive rheumatoid factor (>300), marked polyclonal gammopathy on serum protein electrophoresis, and

From Emory University School of Medicine^a and the Departments of Dermatology^b and Medicine,^c Emory University.

Funding sources: None.

Conflicts of interest: None disclosed.

This case was presented as a poster at the 42nd Annual Southeastern Consortium for Dermatology in November 2018 in Charleston, South Carolina.

Correspondence to: Justin T. Cheeley, MD, FAAD, Assistant Professor, Dermatology and Internal Medicine, Emory University School of Medicine, 1525 Clifton Rd. NE,

Dermatology Office Suite 100, Office 122, Atlanta, GA 30322.

E-mail: jcheele@emory.edu.

JAAD Case Reports 2019;5:906-8.

2352-5126

© 2019 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jidcr.2019.08.016>



Fig 1. Mixed vessel vasculitis caused by intravenous injection of crushed hydromorphone tablets. Multiple angulated hyperpigmented plaques and nodules are present on the thighs as well as bright red papules and linear plaques.

minimally decreased C3 and C4. Serum ANCA, cryoglobulins, anticyclic citrullinated peptide antibody, anti-dsDNA, and extractable nuclear antigens were negative. Interestingly, at the outside hospital, she had very low c-ANCA titers (1:80) with negative anti-proteinase 3 and anti-myeloperoxidase antibodies. The outside hospital renal biopsy found focal necrotizing and crescentic glomerulonephritis with mesangial staining of IgM, C3, and C1q as well as subendothelial electron-dense deposits on immunofluorescence, consistent with immune complex deposition.

Initial differential diagnoses favored mixed small- and medium-sized vessel vasculitis such as microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, but also included classically medium vessel vasculitis such as polyarteritis nodosa.

A skin biopsy was performed down to the muscle to evaluate for a suspected medium vessel vasculitis. Initial histology found evidence of vasculitis and granuloma formation in the deeper sections of the biopsy surrounding larger vessels (Fig 3). However, those findings were adjacent to necrotic tissue, which could produce similar findings on histology. Further inspection with polarized light microscopy found extensive amounts of polarizable foreign material throughout the dermis and within the vessels, consistent with injection of foreign material (Fig 4).

After explaining the biopsy findings to the patient, she admitted to self-injecting crushed hydromorphone tablets into a peripheral intravenous line during a previous outside hospitalization, the method of which she learned from an online forum. She did so in response to the tremendous amount of emotional and physical pain she was feeling at the



Fig 2. Mixed vessel vasculitis caused by intravenous injection of crushed hydromorphone tablets. Purpuric and hemorrhagic nodule on the left anterior thigh.

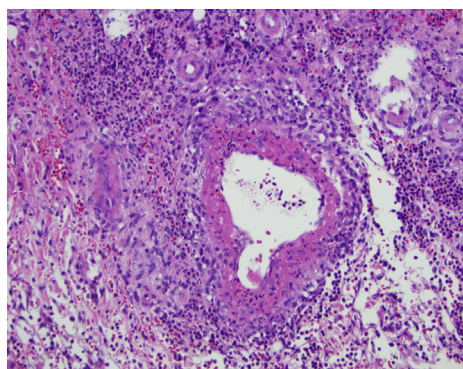


Fig 3. Mixed vessel vasculitis caused by intravenous injection of crushed hydromorphone tablets. Fibrinoid necrosis and leukocytoclasia of multiple small- and medium-sized vessels. (Original magnification: $\times 20$.)

time; she denied any suicidal intent with this action. She also denied any subsequent use after the one-time injection.

DISCUSSION

Unless the patient is willing to admit what substance has been injected intravenously, microanalytic techniques may need to be used to elucidate the material, although the clinical availability of these assays is limited. In our case, the patient admitted to injecting crushed white hydromorphone tablets only after being presented with the biopsy results.

Review of hydromorphone tablet formulations found only 1 white preparation that matched her prescriptions on the Prescription Drug Monitoring Program. Review of excipients of this formulation on the National Library of Medicine DailyMed website (<https://dailymed.nlm.nih.gov/dailymed>) found microcrystalline cellulose to be the suspected polarizable substance in our specimen, as this substance has been reported in the literature as causing granulomatous vasculitis of the pulmonary

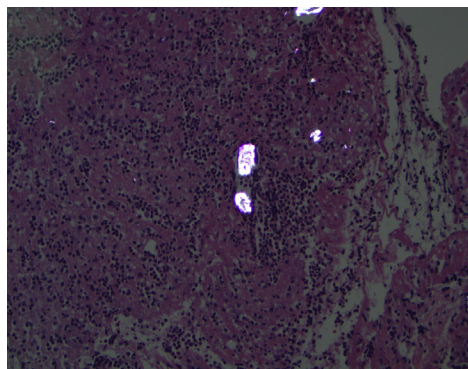


Fig 4. Mixed vessel vasculitis caused by intravenous injection of crushed hydromorphone tablets. Polarizable material is seen within multiple vessels on light microscopy. (Original magnification: $\times 20$.)

vasculature.¹ Cutaneous manifestations from self-injection with a polarizable substance have typically been found at or near the injection site. To our knowledge, our case is the first known of a systemic mixed small- and medium-vessel cutaneous vasculitis attributable to self-injection of a polarizable substance.⁷

Between 50% and 60% of cases of cutaneous necrotizing vasculitis are idiopathic or primary.^{8,9} Although our patient had c-ANCA-positive acute necrotizing glomerulonephritis, it was likely caused by the systemic manifestations of microcrystalline cellulose-induced necrotizing vasculitis causing a robust immunologic response and not from a concomitant ANCA-associated vasculitis. Although not confirmed, her prior diagnoses of crescentic glomerulonephritis, primary sclerosing cholangitis, and Crohn's disease may have been a result of longstanding intravenous hydromorphone tablet abuse.

The increase of the opioid crisis has brought about increased regulations and decreased prescriptions for opioids in the United States.¹⁰ There is a national shortage of intravenous hydromorphone that may cause already addicted patients to seek other means of narcotic administration, including injection of crushed hydromorphone tablets intravenously. In patients who present with necrotizing vasculitis and unusual serologies, a thorough drug use history is warranted, and skin biopsy with polarized light microscopy may elucidate pathomechanisms of a multisystem process.

REFERENCES

- O'Donnell AE, Selig J, Aravamuthan M, Richardson MS. Pulmonary complications associated with illicit drug use. An update. *Chest*. 1995;108(2):460-463.
- Nguyen VT, Chan ES, Chou S-HS, et al. Pulmonary effects of i.v. injection of crushed oral tablets: "excipient lung disease." *AJR Am J Roentgenol*. 2014;203(5):W506-W515.
- Brown D. Pulmonary granulomatosis from intravenous use of oral medication. *Chest*. 1981;79(6):718.
- Milroy CM, Parai JL. The histopathology of drugs of abuse. *Histopathology*. 2011;59(4):579-593.
- Farber HW, Falls R, Glauser FL. Transient pulmonary hypertension from the intravenous injection of crushed, suspended pentazocine tablets. *Chest*. 1981;80(2):178-182.
- Dettmeyer RB, Verhoff MA, Brückel B, Walter D. Widespread pulmonary granulomatosis following long time intravenous drug abuse—a case report. *Forensic Sci Int*. 2010;197(1-3):e27-e30.
- Bouquie R, Wainstein L, Pilet P, et al. Crushed and injected buprenorphine tablets: characteristics of princeps and generic solutions. *PLoS ONE*. 2014;9(12):e113991.
- Russell JP, Gibson LE. Primary cutaneous small vessel vasculitis: approach to diagnosis and treatment. *Int J Dermatol*. 2006;45(1):3-13.
- Carlson JA, Ng BT, Chen K-R. Cutaneous vasculitis update: diagnostic criteria, classification, epidemiology, etiology, pathogenesis, evaluation and prognosis. *Am J Dermatopathol*. 2005;27(6):504-528.
- Weiner SG, Malek SK, Price CN. The Opioid Crisis and Its Consequences. *Transplantation*. 2017;101(4):678-681.