SKIN

BRIEF ARTICLE

A Case of Hydroxyurea-Associated Cutaneous Only Polyarteritis Nodosa

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ABSTRACT

Hydroxyurea is a common antineoplastic agent used to treat several cancers and myeloproliferative conditions, such as chronic myelogenous leukemia and polycythemia vera. Long-term use has been associated with several adverse cutaneous reactions, including skin ulcers, xerosis, and hyperpigmentation. We report a patient who presented with tender, indurated, erythematous nodules in his legs and thighs who had been taking hydroxyurea for 8 years to treat polycythemia vera. Biopsy revealed medium-sized arteries with intramural neutrophils, eosinophils, and edema. Histopathology and clinical features were highly suggestive of cutaneous polyarteritis nodosa (CPAN). Discontinuation of hydroxyurea resulted in full resolution of his lesions.

INTRODUCTION

Vasculitis refers to a group of autoimmune disorders that are characterized by inflammation of blood vessels, and can occur as a primary disease or secondary to other etiologies.[1] Vasculitis can affect vessels of various types, sizes, and locations, and these features help classify the disease.[1] Polyarteritis nodosa (PAN) is a form of vasculitis that affects medium-sized arteries.[2] In its classic form, PAN is a systemic disease that affects several organs; the skin, heart, liver, gastrointestinal tract, kidneys, and central nervous system are most commonly affected.[2] PAN can be idiopathic or secondary to other disease processes, such as streptococci, mycobacteriae, viral agents such as hepatitis B and C, HIV, parvovirus B19, or even some medications.[2]

Cutaneous polyarteritis nodosa (CPAN) is a variant of PAN that affects only the small and medium-sized arteries of the dermis and subcutis and is restricted to localized regions, typically the extremities.[1, 3] The diagnosis is made in the presence of clinical features including tender cutaneous nodules and livedo reticularis, and only after exclusion of other organ system involvement.[3] Herein, we present a rare case of hydroxyurea-related CPAN.

CASE REPORT

A 72-year-old man presented with a one-year history of recurrent, tender, livedo-like bruising on his right dorsal thigh, which progressed to his left thigh. His medical history was significant for polycythemia vera (PV), atrial fibrillation, long-standing hypertension-related chronic kidney disease

stage III, well-controlled type 2 diabetes, dyslipidemia, obstructive sleep apnea, and untreated prostate cancer (under observation). His medications included atorvastatin, amlodipine, metoprolol, propafenone, ranitidine, ropinirole, sertraline, warfarin, and vitamin D. His PV was initially treated with hydroxyurea 500 mg/day and phlebotomy for 8 years. A monitoring bone marrow biopsy in 2017 revealed a JAK2 mutation (V617F).

Initial punch biopsies from his right thigh showed deep dermal periarterial fibrosis and arterial thrombosis with early organization. The underlying subcutis displayed non-inflammatory foci of vascular proliferation, suggesting small, resolving arterial thromboses.

Four months later, he reported new tender nodules of both anterior thighs (**Figure 1)**. Doppler ultrasound of both legs were normal.

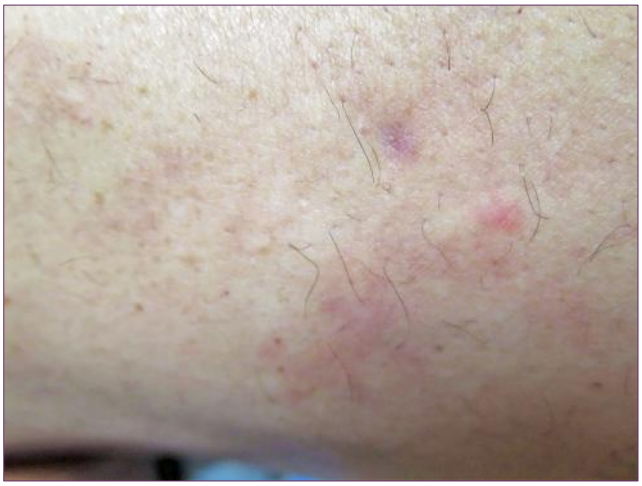

Figure 1.

Three months later, he had additional tender nodules on his left leg, and a new rash on his back, buttocks, and posterior legs. There were also indurated, red nodules on his left flank and left lateral distal thigh, and tender reticulate erythema of his left dorsal foot. A second set of punch biopsies showed medium-sized arteries with intramural edema, surrounded by neutrophils and some eosinophils (**Figure 2A and 2B**). Two medium-sized arteries displayed intraluminal thrombi, with similar involvement of thinner-walled vessels.

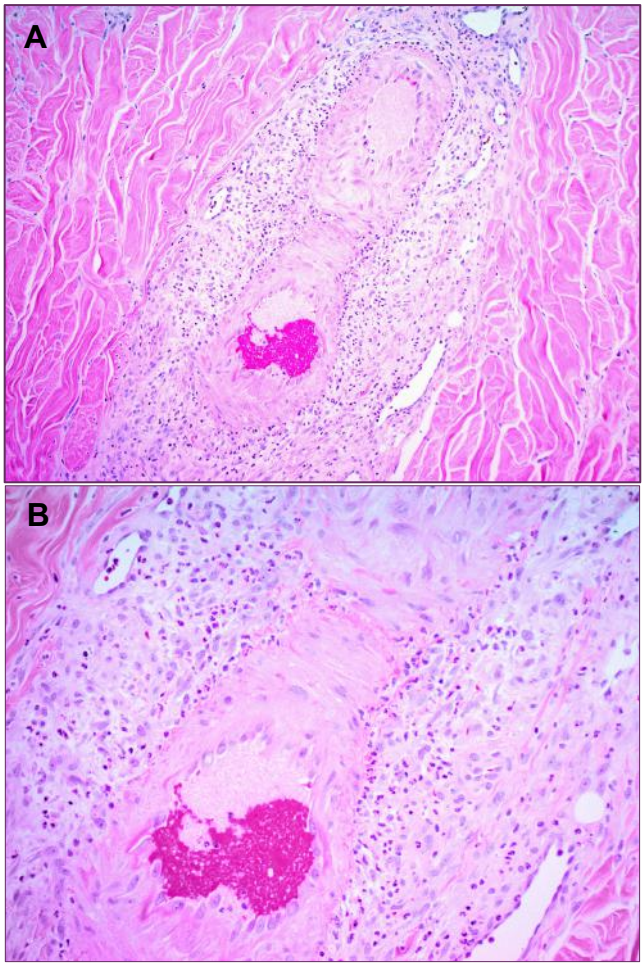

Figure 2. A) H&E, 100x **B)** H&E 200x

Complete blood count showed a leukocytosis of 25,600, but no anemia or platelet abnormalities. CRP, ESR, and C3, C4, and CH50 levels were normal. Anti-neutrophil cytoplasmic (ANCA) antibodies, anti-histone antibody, ANA panel, lupus anticoagulant, anti-phospholipid panel, anti-cyclic citrullinated peptide antibody, hepatitis B, hepatitis C, HIV, cryoglobulins, cryofibrinogen, and quantitative immunoglobulin G, A, and M were all negative/normal. CMP was normal except for

a low estimated glomerular filtration rate (eGFR) of 40 mL/min. Multiple urinalyses were normal. Abdominal MRI showed foci of renal artery vascular narrowing but were not felt by the radiologist to be vasculitic. Chest CT without contrast was non-contributory.

The integration of the history, histopathology, imaging, and laboratory findings favored the diagnosis of CPAN. Despite starting colchicine, he developed new lesions on his left thigh, left buttock, and flank over the next several months. Concomitantly, his eGFR declined to 23 mL/min.

Given that the vasculitis was limited to the skin and had not improved, colchicine was discontinued. Since a bone marrow biopsy in 2017 showed a JAK2 mutation, his PV treatment was changed to the JAK kinase inhibitor, ruxolitinib. Within 11 weeks, the nodules began to resolve. A few weeks later, only non-tender, reticulate pigmentation remained. Ruxolitinib controlled his PV. His eGFR stabilized at 40 ml/min, likely due to discontinuation of the colchicine. The nephrologist did not believe his chronic kidney disease was related to CPAN renal involvement. Over the next six months, the skin changes completely resolved.

Based on the rapid resolution of the tender cutaneous nodules after discontinuing hydroxyurea, we conclude that the CPAN resulted from hydroxyurea use.

DISCUSSION

Hydroxyurea is used to treat solid tumors and myeloproliferative diseases, such as chronic myelogenous leukemia and PV.[4] It is an antimetabolite that inhibits ribonucleotide reductase, an enzyme required for DNA synthesis. While generally well-tolerated, there have been reports of adverse cutaneous reactions after prolonged use in roughly 5% of patients.[4] These include skin eruptions, skin ulcers, xerosis, diffuse hyperpigmentation, alopecia, nail dystrophy, dermatomyositis-like syndrome, and an increased risk of squamous and basal cell carcinoma.[4] One of the most serious complications is painful ulcers of the lower legs that can be severe and even life-threatening.[5]

Leg ulcers with hydroxyurea use have occasionally been associated with leukocytoclastic vasculitis, with at least one report of medium vessel vasculitis and panniculitis.[4-6] Cessation of hydroxyurea was necessary for resolution of nearly all of the reported cases, with or without documented vasculitis.

Vasculitis is commonly drug-induced and often results in cutaneously-limited vasculitis.[7] Although the pathogenesis is not clear, the similar clinical profiles of drug-induced vasculitis suggest a common mechanism, such as formation of immune complexes.[7] Many medications are implicated in drug-induced vasculitis, including antimicrobials, antithyroid drugs, and tumor necrosis factor inhibitors.[7] In particular, there have been several cases of minocycline-induced cutaneous and systemic PAN-like vasculitis and one case of empagliflozin-induced CPAN.[8, 9]

While the mechanism of most hydroxyurea-induced skin damage is not well characterized, it is thought that the inhibition of DNA synthesis results in damage of the basal layer of the epidermis.[10] This, combined with trauma, may cause poorly-healing ulcers. Other proposed mechanisms include platelet dysregulation and macrocytosis, leading to disrupted microcirculation and microthrombi formation.[10]

CONCLUSION

Hydroxyurea is a commonly prescribed antimetabolite used to treat many oncologic and hematologic diseases and has been associated with various adverse cutaneous reactions. We report a unique case of hydroxyurea-induced vasculitis best classified as CPAN. This case contributes to our understanding of the range of adverse cutaneous effects of the medication and can aid in the clinical management of patients taking long-term hydroxyurea.

List of Abbreviations and Acronyms:

ANCA	Antineutrophil Cytoplasmic Antibodies
CMP	Complete Metabolic Panel
CPAN	Cutaneous Polyarteritis Nodosa
CRP	C-Reactive Protein
eGFR	Estimated Glomerular Filtration Rate
ESR	Erythrocyte Sedimentation Rate
HIV	Human Immunodeficiency Virus
JAK2	Janus Kinase 2
PAN	Polyarteritis Nodosa
PV	Polycythemia Vera

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