Hydralazine-induced vasculitis presenting with ocular manifestations

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Abstract

Purpose: The objective of the study is to report a case of ocular manifestations in a patient with hydralazine-induced vasculitis.  
Observations: An 88-year-old female was admitted for lower gastrointestinal bleeding. Nine days after admission, she developed bilateral conjunctival chemosis and injection, which rapidly progressed into grouped blistering eruptions of the periorbital skin, face, and neck. After extensive testing and evaluation, her constellation of findings was diagnosed as hydralazine-induced vasculitis. Treatment with intravenous steroids and discontinuation of hydralazine resulted in improvement of the cutaneous and ocular manifestations. Herein we describe the clinical course of an adult patient with symptoms and signs consistent with hydralazine-induced vasculitis to highlight that ophthalmological manifestations can be the first symptoms in patients with life-threatening dermatological conditions.  
Conclusions and Importance: To our knowledge, this report is the first case of hydralazine-induced vasculitis initially presenting with ocular manifestations.

1. Introduction

Drug-induced vasculitis (DIV) is a multifactorial, environmentally triggered condition that has possible genetic and epigenetic components. 1 It is characterized as an inflammatory vasculitis in which a particular drug is identified as the cause when other mechanisms of vasculitis have been ruled out. Hydralazine is the most frequent anti-hypertensive treatment associated with vasculitis, and its cutaneous manifestations include lower extremity palpable purpuric and maculopapular lesions, as well as hemorrhagic blisters on the lower legs, arms, trunk, nasal septum, and uvula. 2 – 4 There have not been any reports in the current literature describing hydralazine-induced vasculitis presenting initially with only ocular manifestations. We present a case of hydralazine-induced vasculitis that first presented with bilateral conjunctival injection and chemosis.

2. Case report

An 88-year-old woman was first admitted to our medical intensive care unit for a lower gastrointestinal bleed after a seven-day stay in an outside intensive care unit. Her medical history included multiple transfusions for bleeding per rectum, chronic anemia, diabetes mellitus, hypertension, coronary artery disease, and renal cell carcinoma. Six months prior to this, she was treated for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Physical examination on admission was unremarkable except for rhonchi upon auscultation. The patient’s family reported baseline dementia, and she exhibited variable delirium throughout her hospital course.

She was on multiple long-term medications for her cardiovascular and diabetic conditions, including amiodipine, aspirin, furosemide, lisinopril-hydrochlorothiazide, metformin, metoprolol, simvastatin, and hydralazine (50 milligrams (mg) three times daily). She had previously taken hydralazine 100 mg three times per day for periods of a few weeks in the preceding five years. She was continued on hydralazine for hypertension on the second day of admission, seven days prior to the appearance of the ocular manifestations.

Nine days after admission, she developed nonspecific bilateral chemosis and injection, with no other physical findings. She had been resting in supine positioning and had not been intubated. The hydralazine was incidentally switched that day for ease of dosing to another...
which was followed by a slow steroid taper. Possible development of scarring and symblepharon. Concurrently, presentation of conjunctival injection and chemosis, due to concern for improvement upon discontinuation of hydralazine and administration of dexamethasone. Topical tobramycin and dexamethasone ointment was started on IV dexamethasone 10 mg daily for angioedema protocol. Chemosis and injection as well as the discontinuation of hydralazine, she was started on IV dexamethasone 10 mg daily for angioedema protocol. One week later, the patient was switched to pulse 250 mg methylprednisolone daily. Topical tobramycin and dexamethasone ointment was administered three times daily to both eyes starting six days after initial presentation of conjunctival injection and chemosis, due to concern for possible development of scarring and symblepharon. Concurrently, bacitracin and erythromycin ointments were applied to the periorbital skin lesions. The patient exhibited increased alertness and improvement of facial lesions after receiving pulse steroid therapy for three days, which was followed by a slow steroid taper.

Extensive laboratory and bacteriology investigations were pursued and notably positive for anti-nuclear antibodies (ANA) with speckled nuclear antibody pattern, ribosomal P antibody, cold agglutinin, rheumatoid factor, perinuclear antineutrophil cytoplasmic antibody (p-ANCA), myeloperoxidase (MPO) antibody, anti-histone antibody, HSV-1 immunoglobulin (Ig) G, and low complement component 3 (C3). Given her diagnosis of renal cell carcinoma, paraneoplastic phenomenon was also included in the working differential. Skin punch biopsy showed dense, neutrophil-rich dermatitis with abundant basophilic inflammatory debris and did not suggest an immune-mediated vesiculobulbar disorder. Based on the history, physical exam, and laboratory and pathology results, the cutaneous findings were suspected of being drug-induced ANCA-associated vasculitis secondary to hydralazine, despite lacking findings such as arthralgias or systemic signs and symptoms. Hydralazine-induced ANCA vasculitis was confirmed given the patient’s improvement upon discontinuation of hydralazine and administration of high dose steroids, as well as the positive vasculitis serologic workup.

The patient’s cutaneous lesions and mental status demonstrated improvement upon discontinuation of hydralazine and administration of IV steroids. Her conjunctival injection and chemosis were also noted to slightly improve on tobramycin and dexamethasone ointment, while no cicatricial findings such as symblepharon were ever observed. However, the patient had an acute deterioration of her general condition in the setting of continued lower GI bleeding. On the 32nd day of admission, she developed cardiac arrest requiring cardiopulmonary resuscitation, which was not successful.

3. Discussion

Here we describe a case of hydralazine-induced vasculitis in which the presenting physical findings were limited to ophthalmic findings comprising chemosis and injection, with subsequent rapid progression to periorbital and diffuse dermatological findings. While fluid distribution may have contributed to the patient’s conjunctival chemosis, hydralazine-induced vasculitis was found to be responsible for the ophthalmic and cutaneous findings. In our review of the current literature, no cases of drug-induced vasculitis have been reported with initial findings solely consisting of ophthalmic manifestations.

A prior case similar to our patient was a 71-year-old woman who presented with two days of odynophagia, muscle weakness, shortness of breath, conjunctival injection, ulcerations of the lips and tongue, tense hemorrhage vesicles, vesiculopustular lesions on the elbows, palms, fingers, lower legs, and toes. Her condition was attributed to hydralazine-induced ANCA-positive vasculitis, presenting two years after initiation of hydralazine. Another report of drug-induced vasculitis presented first with bilateral episceritis, followed by lung infiltrates, fevers, fatigue, arthralgias, and myalgias, and was later diagnosed with propylthiouracil-induced ANCA-associated vasculitis. Two cases of hydralazine-induced lupus with eye disease were reported, in which patients had bilateral retinal vasculitis, with additional episcleritis in one patient. The patients exhibited prominent polyarthralgia, weight loss, positive ANA with negative DNA binding, and normal complement levels. Following discontinuation of hydralazine, both patients experienced a timely recovery with no changes in ocular disease.

Vasculitic reactions make up 10–20% of drug-induced cutaneous reactions, and among all vasculitides, drug-induced vasculitis is the most common. DIV frequently presents as a cutaneous vasculitis with associated myalgias and arthralgias but may also present with renal and pulmonary manifestations. Cutaneous manifestations of DIV are most commonly palpable purpura, and less frequently ulceration, blisters, erythematous macules, erythema nodosum, and subcutaneous involvement. Laboratory findings typically include anemia, thrombocytopenia, leukocytosis, and eosinophilia. Serology findings may be remarkable for ANA, ANCA, antiphospholipid antibodies, double stranded DNA antibodies (anti-dsDNA), low C3 and C4 complement levels, histone antibodies, and B2 glycoprotein-1 antibodies.

Hydralazine is a low-cost direct-acting vasodilator that has been in use since the 1950’s for treating essential hypertension, and the first reported case of DIV associated with hydralazine was described in 1953. According to the current literature, hydralazine-induced vasculitis has an incidence of 5–8% and common symptoms include arthralgia, myalgia, fever, rash, pleuritis, and leukopenia. Serology findings of hydralazine-induced vasculitis also include detectable ANA, ANCA, and anti-histone antibodies.

Cases of drug-induced vasculitis typically present with ANCA antibodies directed against one or multiple neutrophil cytoplasmic antigens. ANCA serologic testing is performed by indirect immunofluorescence which characterizes the perinuclear (p-ANCA) or cytoplasmic (c-ANCA) staining pattern. The antibody specificity of ANCA against myeloperoxidase (MPO-ANCA) and proteinase 3 (PR3-ANCA) or other antigens is determined via enzyme-linked immunosorbent assays (ELISA). Most cases of p-ANCAs are directed against myeloperoxidase MPO, while a majority of c-ANCAs recognize PR3. However, p-ANCAs directed against MPO and c-ANCAs directed against PR3 are also observed. Furthermore, both p-ANCA and c-ANCA antibodies may be directed towards antigens besides MPO and PR3. In DIV, MPO-ANCA is more common than PR3-ANCA.

While cases of idiopathic vasculitis typically have elevated levels of only one type of ANCA, patients with DIV often produce ANCA directed against multiple antigens. ANCA directed against human leukocyte elastase, and lactoferrin are strongly associated with DIV. Hydralazine-induced vasculitis is also characterized by high MPO-ANCA titers and “atypical” ANCs that do not follow perinuclear or...
cytoplasmic staining patterns. In a study looking at patients with hydralazine-induced vasculitis and high MPO-ANCA titers, 9 of 10 patients had ANCs targeting human leukocyte elastase, and 7 of 10 had ANCs targeting lactoferin. Moreover, DIV is strongly suggested if a combination of multiple ANCA antibody types, antinuclear antibodies, histone antibodies, and B2 glycoprotein-1 antibodies are present. Hydralazine-induced vasculitis presents with a constellation of lab findings, rather than with an isolated elevation in one type of ANCA; no serologic test is pathognomonic but a combination may suggest hydralazine-induced vasculitis.

In 2002, Holder et al. conducted an extensive review of drug-induced vasculitis, which reported 25 cases associated with hydralazine. Presenting symptoms of hydralazine-induced vasculitis included arthralgias and myalgias, and manifestations can also include hoarseness and retinal vascular inflammation, which develop between six months to thirteen years after initiation of hydralazine treatment. The cases were characterized by positive ANA, p-ANCA, and anti-dsDNA antibodies. Scant deposits of IgG, IgM, and C3, classic in ANCA-positive pauci-immune glomerulonephritis, were found on renal biopsy. Cutaneous lesions revealed deposits of IgM, fibrin, and C3 under direct immunofluorescence. Vasculitic lesions resolved in ten days to eight months after discontinuing hydralazine and with the addition of prednisone in several cases.

In a study by Yogokawa et al., 68 cases of hydralazine-induced vasculitis, 100% of patients tested for MPO-ANCA had positive results. Of those tested for ANA, 96% were positive, and 91% had a homogeneous pattern. Anti-dsDNA antibodies were positive in 26% of those tested, and 44% of tested cases exhibited hypocomplementemia. Overall, 76% of the patients required immunosuppressive therapies.

Longer duration of therapy and higher daily and cumulative doses are risk factors for developing hydralazine-induced vasculitis. Discontinuation of hydralazine as initial treatment has been shown to be adequate treatment in some cases, but often more aggressive treatment is necessary, consisting of immunosuppression such as steroids, cyclophosphamide, rituximab, and plasmapheresis. Our patient developed conjunctival injection and chemosis, as well as cutaneous manifestations of vasculitis after five years of intermittent hydralazine use, and the condition improved with discontinuation of the suspected offending drug and administration of IV steroids.

The clinical manifestations of hydralazine-induced vasculitis have substantial overlap with hydralazine-induced lupus, and care should be taken to not conflate the two. Hydralazine-induced vasculitis is less common and often more severe than hydralazine-induced lupus. Yoko-gawa et al. differentiated hydralazine-induced vasculitis from hydralazine-induced lupus based on the presence of vasculitic symptoms such as rapidly progressive glomerulonephritis, ANCA-positive glomerulonephritis, pulmonary damage, necrotizing cutaneous vasculitis, or retinal vasculitis. Hypocomplementemia, leuкоopenia, and neutrophilic symptoms, when present also suggest hydralazine-induced vasculitis as they are rare in hydralazine-induced lupus. Retinal abnormalities were not present in our patient, but her cutaneous vasculitis points the diagnosis toward hydralazine-induced vasculitis rather than lupus. Additionally, our patient did exhibit neuropsychiatric symptoms that improved with discontinuation of hydralazine and steroid treatment. To our knowledge, this is the first reported case in the literature of hydralazine-induced vasculitis presenting initially with only ophthalmic findings.

4. Conclusion

This is the first reported case of hydralazine-induced vasculitis presenting with isolated ophthalmic manifestations. The patient developed nonspecific bilateral chemosis and injection after five years of intermittent hydralazine use. Her ocular and other manifestations of hydralazine-induced vasculitis improved after discontinuation of hydralazine and administration of IV steroids and ophthalmic tobramycin and dexamethasone ointment. The findings of chemosis and conjunctival injection in many cases may be attributed to non-life-threatening etiologies, and it can be easy to dismiss such findings on exam; however, we should always remain vigilant and have a high level of suspicion for serious conditions, especially when caring for those with an extensive medical history. In addition to a thorough physical exam, a careful review of the patient’s past medical history and current medications should be performed.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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