A 77-Year-Old Woman with Dysphonia and Possible Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Potentially Induced by Hydralazine

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ABSTRACT

BACKGROUND: Hydralazine is the most common antihypertensive that causes drug-induced anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Upper airway involvement including hoarseness is rare in AAV and mostly associated with drug-induced lupus erythematosus (DILE). This case describes a 77-year-old woman on hydralazine who developed bilateral upper extremity pain, periorbital swelling and hoarseness requiring emergent intubation.

CASE REPORT: Bloody secretions in bronchoscopy, joint pain and petechiae clinically suggested vasculitis. Anti-histone, myeloperoxidase (MPO) and anti-proteinase 3 (PR3) antibodies were positive and anti-nuclear antibodies (ANA) and imaging were negative. The patient was treated with high-dose steroids and hydralazine withdrawal. At one-year follow-up on azathioprine as a steroid-sparing agent, dysphonia had resolved.

CONCLUSION: Hoarseness is an atypical feature of hydralazine-induced AAV and may indicate life-threatening upper airway disease. Dual-ANCA and anti-histone positivity, negative ANA status, may potentiate further investigation for dysphonia and AAV while on hydralazine. Early recognition, withdrawal of medication and timely steroids are essential to prevent severe airway complications.

KEYWORDS: Antineutrophil Cytoplasmic Antibody (ANCA); vasculitis; hydralazine; hoarseness

BACKGROUND

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare autoimmune disease characterized by small vessel inflammation leading to organ dysfunction. Although primarily idiopathic, it can be triggered by infections or medications such as hydralazine being the antihypertensive agent most strongly associated with AAV.[1] Although it has been available since the 1950s, the first reported case of hydralazine-induced AAV was in the 1980s.[2] The incidence of hydralazine-induced vasculitis is 5.4% at 100 mg/day and 10.4% at 200 mg/day over three years.[3] Symptoms typically appear within the first five years of use, ranging from six months to 13 years.[4] The risk increases with prolonged use and cumulative dosing, and is higher in slow acetylators, women, and individuals with thyroid disease.[5]

Hydralazine-induced AAV commonly presents with glomerulonephritis (81%), fever, arthralgia (24%), rash (25%), and pulmonary involvement (19%), often as diffuse alveolar hemorrhage.[6] Less frequently, the upper airway (9%), eyes, gastrointestinal tract, and peripheral nerves (3%) may be affected.[6] Laryngeal involvement can present with dyspnea, cough, wheezing, or stridor, typically caused by ulcers, edema, or stenosis.[7] Hoarseness is typically associated with drug-induced lupus erythematosus (DILE), rather than AAV.[8,9] This report describes a 77-year-old woman with ANCA-associated vasculitis and dysphonia while on hydralazine.

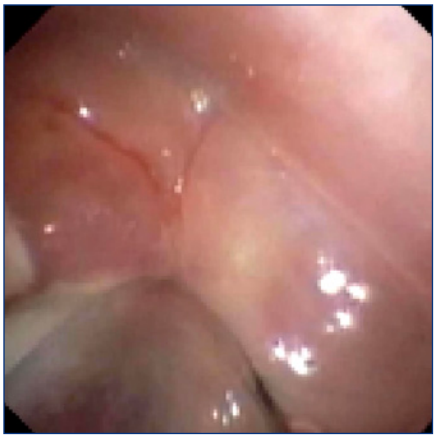
CASE REPORT

A 77-year-old woman with hypertension, gout, chronic thrombocytopenia, left renal artery stenosis, and an atrophic left kidney presented with one month of joint pain, swelling, and myalgia. Initially, she was treated with prednisone (20–40 mg) for suspected polymyalgia rheumatica without improvement. Outpatient work-up revealed elevated myeloperoxidase (MPO) (6 AI, normal <1 AI) and anti-proteinase 3 (PR3) (3.5 AI, normal <1 AI), with negative anti-nuclear antibodies (ANA), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). A recent computed tomography (CT) scan of the neck and chest showed no evidence of vasculitis. She was taking atenolol-chlorthalidone (100/25 mg), amlodipine-valsartan (5/320 mg), and hydralazine (100 mg twice daily), which had been initiated a year prior for resistant hypertension. She had no history of smoking, alcohol, or recreational drug use.

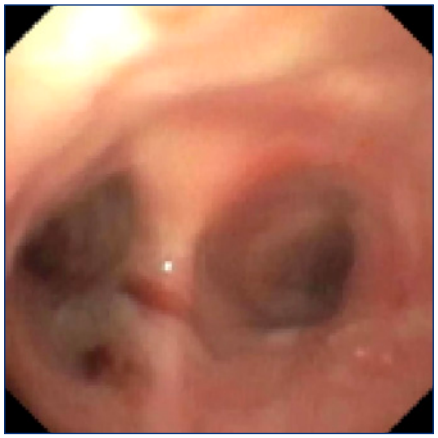
Five days later after the diagnostic work-up, she presented to the emergency room with worsening bilateral wrist and shoulder pain. Within 48 hours, she developed periorbital swelling (right>left), tongue ulcers, sore throat, progressive hoarseness and stridor with suspected laryngeal edema leading to emergency intubation. She was treated with methylprednisolone (60 mg three times daily) for suspected anaphylaxis or angioedema. The CT scan and bronchoscopy findings showed swelling of the aryepiglottic folds significantly

Figure 1. Bronchoscopy findings

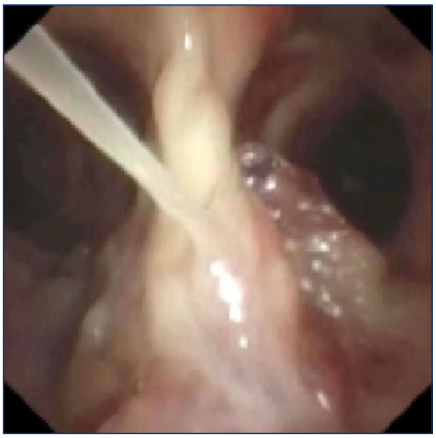
[A] Vestibule with bilateral swelling of Arytenoids



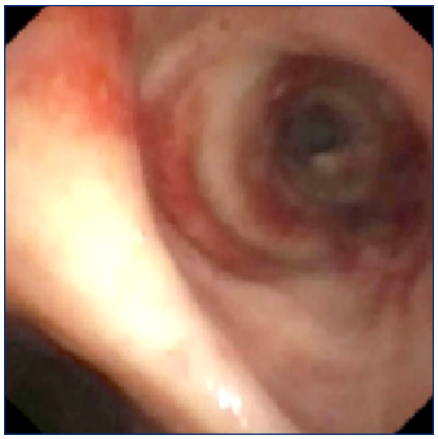
[B] Mucoid and white secretions in carina



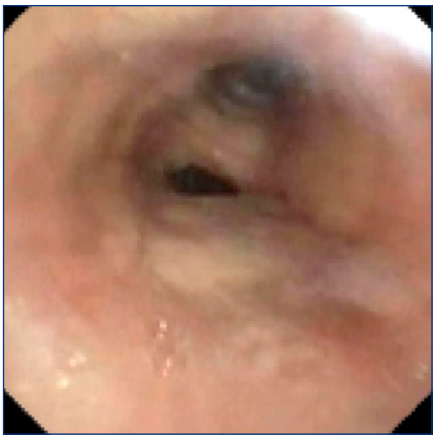
[C] Mucoid and white secretions in carina



[D] Carina after therapeutic suctioning



[E] Edematous left mainstem bronchus



narrowing the airway and bloody secretions, with no orbital mass. She developed a few non-blanching petechial lesions on her knees and hips, prompting hydralazine discontinuation for suspected drug-induced vasculitis. Endotracheal cultures grew *Haemophilus influenzae* necessitating piperacillin-tazobactam for possible tracheitis. Viral swabs for *Herpes simplex* virus were negative. Bradykinin-mediated angioedema was deemed unlikely given borderline complement component (C)1q levels of 4.2 mg/dl (normal 5–8.6), and normal C1 esterase inhibitor levels and function. Repeat bronchoscopy three days after intubation revealed reduced airway swelling, but residual blood clots [**Figures 1A–E**]. Further tests confirmed persistently high MPO (3.5 AI), PR3 (2 AI), anti-histone antibodies (1.8U, negative <1U), elevated CRP (>125 mg/L) and low C3 levels (8 mg/dl). ANA and anti-double stranded DNA (anti-dsDNA) were negative. Due to mucosal friability and bleeding risk, an upper airway biopsy was inadvisable, and a skin biopsy was not performed.

The primary diagnosis of hydralazine-induced AAV was considered likely. The patient was started on prednisone (1mg/kg/d) with a slow taper (5 mg every other week) and hydralazine was permanently discontinued. She was extubated within a week and discharged the following week. At three months, azathioprine (100 mg/day) was started for new lower extremity petechiae. At one year, her hoarseness, presumed secondary to laryngeal edema, had fully resolved, with no further vasculitis manifestations.

DISCUSSION

In summary, this case broadens dysphonia as a potential presentation of hydralazine-induced AAV. The diagnosis was challenging, given the absence of classic systemic findings, such as glomerulonephritis or diffuse pulmonary hemorrhage. Dual ANCA and anti-histone positivity with a negative ANA may raise suspicion for life-threatening airway inflammation in hydralazine-induced AAV, particularly when presenting with hoarseness.

Hydralazine or drug-induced vasculitis primarily affects mucocutaneous tissues, joints, kidneys, and lungs. Skin manifestations include palpable purpura, non-blanching maculopapular eruptions, and hemorrhagic blisters/ulcers affecting the nasal septum, lips, and uvula causing otalgia, odynophagia, and sore throat.[4,10,11] Ocular symptoms include conjunctival injection, episcleritis, and retinal vasculitis. Joint involvement typically presents as arthralgia or arthritis, while peripheral neuropathy may manifest as distal numbness or tingling. Pulmonary involvement often leads to cough, dyspnea and focal or diffuse alveolar hemorrhage, requiring bronchoscopy.[12] Renal manifestations include

necrotizing crescentic or rapidly progressive glomerulonephritis, with extrarenal involvement being rare.[6]

Patients with hydralazine-induced vasculitis often exhibit a mixed serologic profile, displaying characteristics of DILE and AAV.[6] Patients test positive for ANA, ANCA (including MPO, PR3, or dual positivity), dsDNA, and anti-histone antibodies, with low C3 and C4 levels.[6] MPO is the most common (60–100%),[2] with titers up to 12 times higher than the controls.[13] Dual ANCA positivity is 40%, while isolated PR3 positivity is rare (3%). Anti-histone antibodies are present in nearly 100%, with ANA positivity in 90–100% (91% homogenous pattern), while anti-dsDNA is detected in 26%.[2,6,14]

The main step of treatment is immediate discontinuation of the offending medication.[15] Manifestations typically resolve within one to four weeks, though persistence for up to eight months has been reported.[4] Severe cases particularly those with renal involvement, require immunosuppressive therapy in approximately 74% of cases, including high doses of glucocorticoids, rituximab, cyclophosphamide, or mycophenolate. Plasmapheresis or hemodialysis may be necessary in refractory cases.[2]

The only published cases of hydralazine-induced AAV with laryngeal involvement are by Levin[7] and Hawn,[16] neither of which reported hoarseness. Levin described a case with mucocutaneous ulcers, unilateral eyelid edema, dyspnea, and laryngeal edema requiring intubation, which resolved with steroids but was complicated by gastrointestinal bleeding.[7] Unlike our patient, ANA was positive (1:320, diffuse pattern), with MPO (60 U/mL), PR3 (33 U/mL) and anti-histone (4.8 U/mL) positivity while anti-dsDNA was negative. Skin and esophageal biopsies confirmed vasculitis. Hawn reported mucocutaneous blisters, bilateral chemosis and severe laryngeal edema.[16] The patient improved with intravenous steroids after discontinuing hydralazine but later died of gastrointestinal bleeding. The diagnosis was confirmed with a skin biopsy, with serologies positive for ANA (speckled pattern), ribosomal P antibody, cold agglutinin, rheumatoid factor, MPO, PR3, and anti-histone antibodies though titers were not reported. Unlike these cases, our patient survived with a full recovery, emphasizing the importance of early diagnosis and treatment.

Laryngeal manifestations are also more common in primary AAV than drug-induced AAV, mainly in childhood-onset disease. The reported incidence is 16–20% in GPA and 12% in EGPA. GPA typically presents with subglottic stenosis, and hoarseness with a life-threatening risk when airway narrowing reaches 80%.[17] EGPA may present with persistent dysphonia due to vocal cord paralysis from vagus nerve vasculitis or laryngeal polyps/masses, which may be recurrent.[18-20]

In primary AAV, upper airway involvement often accompanied with lower airway and renal disease, with the clinical phenotype influenced by the presence of MPO or PR3 antibodies.[21] Mixed serologic profiles, such as anti-histone, anti-dsDNA, ANA or dual-ANCA positivity are uncommon in primary AAV.[2] First-line therapy includes corticosteroids combined with rituximab or cyclophosphamide as steroid-sparing agent, according to availability, to prevent relapses. Recurrence is atypical for drug-induced AAV once the offending medication is eliminated.[21]

Another important differential diagnosis is DILE, which typically presents with systemic symptoms resembling primary systemic lupus erythematosus such as fever, arthralgia/arthritis, myalgia, rash and serositis.[22] However, these manifestations are usually milder and rarely progress to major life-threatening organ involvement. Serologically, hydralazine-induced lupus is characterized by near-universal positivity for ANA and anti-histone antibodies, while complement levels typically remain within the normal range. ANCA positivity is rare and, when present, is more suggestive of hydralazine-induced vasculitis with renal involvement. Management primarily involves discontinuation of the offending medication, with additional therapies such as NSAIDs, corticosteroids, hydroxychloroquine, or other disease-modifying antirheumatic drugs (DMARDs) as needed, similar to the treatment approach in primary lupus.[22]

The main limitation of our case report is the lack of histopathologic confirmation. As discussed previously, resource constraints and patient-specific factors precluded a tissue biopsy. Without it, the final diagnosis of hydralazine-induced AAV cannot be absolute. However, as we have shown, the patient's atypical constellation of symptoms, relevant medication exposure, mixed serologic findings with dual ANCA positivity, favorable response to withdrawal of the offending medication and treatment with DMARDs not typically used as first-line agents for primary AAV or DILE, as well as the lack of recurrence following cessation, collectively provide strong support for the highly suggestive diagnosis of hydralazine-induced AAV.

CONCLUSION

Hydralazine-induced vasculitis typically presents with a purpuric rash, arthralgia, and pulmonary or kidney involvement, often resolving with medication discontinuation. Severe cases with glomerulonephritis or pulmonary hemorrhage, may require immunosuppression. Laryngeal involvement, particularly hoarseness is rare, but can be life threatening due to airway stenosis. Early recognition is crucial to prevent delayed treatment and complications. Dual-ANCA and anti-histone antibodies may warrant further investigation. This case of dysphonia with uncommon serological findings is a unique presentation of hydralazine-induced AAV, successfully recognized and treated.

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None for all authors

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