



Case Report

# Isotretinoin induced small vessel vasculitis: a life-threatening pulmonary-renal syndrome—a case report

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**Abstract:** Oral isotretinoin is a synthetic analog of vitamin - A, reserved for cases with severe resistant acne. We hereby report a case of drug-induced vasculitis (DV) from isotretinoin exposure leading to life-threatening pulmonary-renal syndrome requiring immunosuppression and plasmapheresis. A previously healthy 21-year-old female receiving oral isotretinoin presented with a 10-day history of worsening myalgias, arthralgias, and abdominal pain. Soon after admission she progressed to severe pulmonary-renal syndrome requiring intubation and renal replacement therapy. Urinalysis revealed >50 dysmorphic RBC with casts and renal ultrasound was unremarkable. Serological testing was only positive for antineutrophil cytoplasmic antibodies (ANCA) at 1:80 with Anti- proteinase 3 (PR3) at 830 AU/mL and Anti-histone Ab at 2.9. As clinical presentation and serology are highly suggestive of ANCA associated DV, plasmapheresis, and rituximab were also initiated along with the continuation of steroids. She clinically improved but remained dialysis dependent and received a live donor renal transplant. The temporal relationship of symptom onset and drug initiation with no other possible identifiable etiologies—DV in our case was attributed to isotretinoin exposure. Though considered safe, oral Isotretinoin in rare instances can cause the life-threatening pulmonary-renal syndrome. Given its widespread use, it is prudent that prescribers should educate patients regarding the possible symptoms of vasculitis and to seek immediate medical attention when warranted. Physicians should also be vigilant of this complication and should act swiftly to avoid uneventful outcomes.

**Keywords:** Vasculitis; drug-induced vasculitis; pulmonary-renal syndrome; isotretinoin; antineutrophil cytoplasmic antibodies (ANCA)

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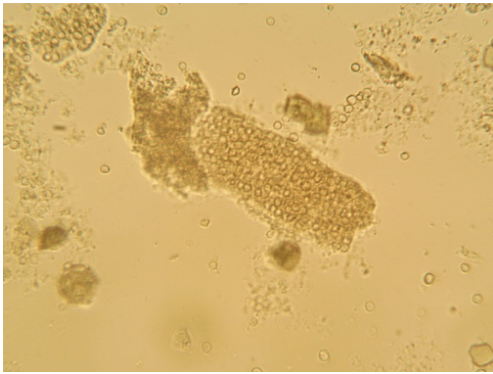
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## Introduction

Vasculitis is defined as the inflammation of blood vessels, which can result in loss of blood vessel integrity leading to downstream tissue ischemia and necrosis (1). Diagnosis of drug-induced vasculitis (DV) is largely based on the temporal relation of drug administration and symptom onset after the exclusion of other possible etiologies along with the resolution of symptoms after the offending drug was withdrawn. Most commonly reported drugs to include but not limited to anti-thyroid drugs, hydralazine,

allopurinol, sulfasalazine, levamisole, D-penicillamine, and minocycline (2). Oral isotretinoin is a synthetic analog of vitamin A, reserved for cases with severe resistant recalcitrant nodular acne (3). Since its approval by the Federal Drug Administration (FDA) in 1982, the use of oral isotretinoin has been steadily increasing every year with an estimated 1–2 million annual prescriptions (4). Though considered to be relatively safe in non-pregnant adults, case reports of DV vasculitis with isotretinoin use have been reported (5-7). Symptoms are usually mild, resolve with the discontinuation of the isotretinoin



**Figure 1** Urine microscopy with red blood cell casts.



**Figure 2** Chest X-ray with diffuse bilateral airspace disease.

without any associated mortality or morbidity with very few cases requiring immunosuppression (7). We hereby report a case of Isotretinoin induced antineutrophilic cytoplasmic antibody (ANCA) associated vasculitis (AAV) leading to life-threatening pulmonary-renal syndrome requiring immunosuppression and plasmapheresis. Renal function did not recover, she remained dialysis dependent and eventually underwent live donor renal transplant. We present the following article in accordance with the CARE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-4212>).

### Case presentation

A 21-year-old female presented with a 10-day history of worsening myalgias, arthralgias, right lower quadrant abdominal pain, and decreasing urine output. She was initiated on oral Isotretinoin 30 mg twice daily 2 months before this presentation. Physical examination was unremarkable except for nodular acne and bilateral flank

tenderness. No skin rash was noticed. Laboratory work was significant for creatinine of 7.6 mg/dL, blood urea nitrogen of 65 mg/dL, potassium of 6.7 mmol/L. Serum aspartate transaminase, alanine transaminase, bilirubin and lactate levels were within normal limits. Urinalysis revealed greater than 50 dysmorphic red blood cells (RBC) with casts (*Figure 1*), 16 to 30 white blood cells with Wrights stain positive for eosinophils, urine protein at 100 mg/dL and negative for nitrites and leucocyte esterase. Abdominal and renal ultrasound were unremarkable. Soon after the presentation, she developed hemoptysis with rapidly worsening bilateral infiltrates and deteriorating respiratory status requiring intubation (*Figure 2*). Emergent renal replacement therapy was also initiated secondary to worsening acute kidney injury, refractory hyperkalemia, and metabolic acidosis. Methylprednisone 1-gram IV daily was initiated as concerned for immune-mediated vasculitis and pulmonary-renal syndrome. Kidney biopsy or bronchoscopy was not attempted in our case secondary to clinical instability. Extensive serological testing resulted positive only for ANCA IgG at 1:80 with ANCA- proteinase 3 (PR3) at 830 AU/mL and Anti histone Ab IgG at 2.9. C-reactive protein was elevated at 63 mg/dL. ANCA-MPO, Anti-GBM IgG, Anti ds-DNA Ab, Anti Smith Ab, Anti RNP, Lupus anticoagulant, Beta 2 glycoprotein, and Anti-cardiolipin Ab resulted negative. Serum complement levels, creatinine kinase, and aldolase levels were normal. HIV ELISA and serology for hepatitis A, B, and C were negative. Direct Coombs test was negative and peripheral smear was unremarkable. Viral respiratory panel and peritonsillar Streptococcus culture and group A streptococcus antigen tests and oral HSV PCR were negative. Blood, sputum, and urine cultures were also negative. Urine streptococcal and legionella antigen testing resulted negative. Echocardiogram was unremarkable and serum beta-natriuretic peptide level was normal. As presentation and laboratory evidence were highly suggestive of the pulmonary-renal syndrome from ANCA mediated DV along with high severity of illness-rituximab and plasmapheresis were also initiated along with continuing steroids. She in total received 7 cycles of plasmapheresis and was continued on weekly rituximab and daily 60 mg prednisone. CRP, and ANCA-PR-3 levels normalized on follow up visits. However, the patient remained dialysis dependent with no signs of renal recovery at the time of discharge, 4 weeks after initial presentation. Respiratory status returned to baseline on discharge. Subsequent renal biopsy 10 weeks after initial presentation showed chronic changes with globally sclerotic

glomeruli, severe interstitial fibrosis, and tubular atrophy. No significant immunofluorescent glomerular staining was noted. She successfully received a live donor transplant. Given the temporal relationship between isotretinoin and symptom onset, positive serological work up along with no other identified etiologies—severe pulmonary-renal syndrome in our case was attributed to isotretinoin induced ANCA mediated vasculitis.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient

## Discussion

Drug-induced vasculitis as the name suggests is a type of systemic vasculitis secondary to drug exposure. ANCA associated vasculitis (AAV) is postulated as a possible mechanism in cases of DV. ANCA's were first described in 1982 in a case of pauci-immune glomerulonephritis (8). Antibodies against antigens, myeloperoxidase (MPO-ANCA), and proteinase 3 (PR3-ANCA) are the two most clinically relevant ANCA's with cytoplasmic (P-ANCA) and peri-nuclear (C-ANCA) representing their immunofluorescence patterns respectively (9). Majority of the drug-induced vasculitis cases are P-ANCA positive with high serum MPO-ANCA Ab titers (10). PR3-ANCA positive DV though uncommon was also reported with propylthiouracil and adulterated cocaine (11,12). Our case was positive for C-ANCA with high PR3-ANCA titers at 830 AU/mL and negative for MPO-ANCA. Anti-histone antibodies were also positive at 2.9 in our case. Along with cases of drug-induced lupus, the presence of anti-histone antibodies is a well-documented phenomenon in cases of DV and should not delay in diagnosis (13). DV and drug-induced lupus have been postulated as a continuum of drug-induced autoimmune disorders especially with hydralazine (14). Review by Yokogawa *et al.*, concluded overlapping clinicopathologic features of hydralazine induced lupus and vasculitis, with vasculitis cases tend to have a more severe clinical course requiring aggressive treatment (15). We postulate that the presence of anti-histone and PR3-ANCA in our case and rapid clinical deterioration represents a similar continuum of drug-induced lupus and DV.

With no precise criteria exist, DV is always a diagnosis of exclusion. Diagnosis is based on temporal relation to drug

administration and symptom onset in the absence of other possible etiologies along with the resolution of symptoms after withdrawing the offending drug. Reported symptoms of Isotretinoin induced vasculitis are usually mild and fever, myalgias, arthralgias, epistaxis, morbilliform skin eruptions and glomerulonephritis (3,5-7). Symptoms in our case were consistent with previously reported cases and were in chronological relation to the drug initiation. Isotretinoin and its metabolite oxo-isotretinoin reach steady-state concentration after 10 days with oxo-isotretinoin levels 4–5 times higher than the drug itself. After discontinuation, terminal states half-life's of the drug and the metabolite were reported around 20 and 29 hours respectively (16). This means the drug and its metabolite stay at detectable concentrations for at least 5–7 days. This pharmacokinetic profile might explain the continued worsening of symptoms despite drug discontinuation seen in our case. Our case does not report any history of autoimmune disorders and is not receiving any other over the contour or prescription medications except for isotretinoin. Extensive serological testing resulted positive only for ANCA with ANCA-proteinase 3 (PR3) and Anti histone Ab. Our case developed hemoptysis and chest X-ray showed rapidly progressive bilateral infiltrates with no alternative explanation other than alveolar hemorrhage. Despite the lack of evidence from renal biopsy and bronchoalveolar lavage to confirm renal vasculitis and diffuse alveolar hemorrhage—the above-mentioned findings, active urine sediment along with observed hemoptysis and compatible chest X-ray findings is consistent with the diagnosis of severe vasculitis leading to the pulmonary-renal syndrome. As such clinical presentation along with extensive negative autoimmune and infectious workup did not point towards an alternative diagnosis in our case.

Treatment of DV includes stopping the offending drug along with immunosuppression if needed based on the severity of the presentation and progression of the disease (7). Our case presented with severe pulmonary-renal syndrome requiring high dose induction therapy along with plasmapheresis. Induction immunosuppressive therapy regimen includes high dose steroids along with either cyclophosphamide or rituximab. Side effects of cyclophosphamide include infertility, pancytopenia, hemorrhagic cystitis, and bladder cancer (17). Rituximab was shown to non-inferior to cyclophosphamide for induction and remission in cases of ANCA vasculitis (18). Given the childbearing age and favorable side effect profile, we opted rituximab for induction therapy in

our case followed by maintenance therapy with steroids and rituximab. Owing to rapidly deteriorating renal function needing renal replacement therapy and alveolar hemorrhage leading to hypoxic respiratory failure requiring mechanical ventilation, our case also received 7 cycles of plasma exchange therapy (19). Literature published months after our clinical encounter reported no beneficial effects of plasm exchange in preventing end-stage renal disease or mortality in cases of ANCA mediated vasculitis (20). Despite our aggressive therapy, renal recovery was not achieved in our case, and renal transplant was performed eventually.

## Conclusions

Diagnosis of DV was difficult in our case owing to clinical challenges in performing a renal biopsy, bronchoalveolar lavage and drug re-challenge to prove the causality. However clinical presentation, serological analysis points strongly towards drug-induced vasculitis leading to pulmonary-renal syndrome than any other alternative etiology. Though rare, DV secondary to isotretinoin is life-threatening and lead to significant morbidity if survived. Our case showed no evidence of renal recovery and eventually underwent renal transplantation. Given the widespread use of isotretinoin for acne, it is prudent that prescribers should educate patients regarding the possible symptoms of vasculitis and to seek immediate medical attention when warranted. Physicians should also be vigilant of this complication and should act swiftly to avoid uneventful outcomes.

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## Footnote

*Reporting Checklist:* The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-4212>

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-4212>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

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