Case Report

Late Onset of Rivaroxaban-Associated Anti-Neutrophil Cytoplasmic Antibody–Associated Vasculitis

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Abstract

Although anti-thyroid drugs (ATDs) are the most common cause of drug-associated anti-neutrophil cytoplasmic antibody (ANCA) vasculitis (AAV), many other classes of drugs can lead to drug-associated AAV. We present a unique case of rivaroxaban-associated AAV. A 76-year-old female with a past medical history of atrial fibrillation on rivaroxaban presented with fatigue, bilateral lower extremity purpura, and hemoptysis to an outside hospital. Investigations revealed a positive cytoplasmic-ANCA (c-ANCA) titer of 1:320 and a positive anti-myeloperoxidase (anti-MPO), and negative perinuclear-ANCA (p-ANCA) and anti-proteinase 3 (anti-PR3). In addition, chest imaging demonstrated bilateral ground-glass opacities which raised suspicion for diffuse alveolar hemorrhage (DAH). A lung biopsy revealed acute and ongoing DAH with focally active capillaritis and characteristic pathological findings, which strongly suggested that was likely secondary to rivaroxaban. Rivaroxaban was discontinued, and the patient received pulses of intravenous glucocorticosteroids and rituximab. Her symptoms improved. She continued immunosuppressive therapy with rituximab for 2 years. She presented to our hospital for a second opinion regarding the discontinuation of rituximab, and we decided to discontinue rituximab. After discontinuation, the patient remained stable after 1.5 years of follow-up and did not have any relapses. This is a unique case of rivaroxaban-associated AAV. Clinicians should consider drug-associated AAV in all patients who present with an atypical clinical presentation and/or pathological findings of AAV. Given the broad and rapidly increasing use of novel anticoagulants, it is important to raise awareness of this potential complication. Prompt discontinuation of the drug and initiation of immunosuppressant treatment in severe cases may be lifesaving.

Keywords

rivaroxaban, vasculitis, ANCA, drug-associated anti-neutrophil cytoplasmic antibody–associated vasculitis

Background

The clinical presentation of primary and drug-associated anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is very similar. It is important to consider drug-associated AAV in the differential diagnosis of AAV.[1] Although anti-thyroid medications have the strongest association with medication-associated AAV, many other medications have been associated with AAV.[2] We present a unique case of possible rivaroxaban-associated AAV. Treatment of drug-associated AAV consists of discontinuation of the offending medication and often includes immunosuppressive therapy.[1] The duration of immunosuppressive therapy in patients with drug-associated AAV is generally shorter than in patients with primary AAV because once the offending agent is removed, the disease usually does not relapse. The present case supports this concept because this patient did not have any relapsing symptoms even after discontinuation of the immunosuppressive therapy.

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Case Presentation

A 76-year-old woman with a past medical history of hypertension, hypothyroidism, and atrial fibrillation who had been on rivaroxaban for 2 years, presented to the Emergency Department of an outside hospital with fatigue, bilateral lower extremity purpura, and a 24-hour history of hemoptysis. She denied any symptoms of sinusitis, hematuria, or palpitations. She denied recreational drug use. The patient's other medications were levothyroxine and losartan. On physical exam, she was noted to have non-blanching, non-tender macules on her bilateral shins and non-tender swelling of the metacarpophalangeal joints of the right hand. Her relevant family history included a sister with systemic lupus erythematosus and 2 daughters with Hashimoto's thyroiditis.

Laboratory testing after transfer to University of Arizona for higher level of care showed a hemoglobin of 8.7 (after tranfusion of 2 units of blood at the outside hospital Emergency Department), white blood cell count of 8.7 (without any evidence of eosinophilia), and platelet count of 224. There was a positive cytoplasmic-ANCA (c-ANCA) titer of 1:320 and a positive anti-myeloperoxidase (anti-MPO) antibody, but perinuclear-ANCA (p-ANCA) and anti-proteinase 3 (anti-PR3) were negative. Kidney function testing was normal with a blood urea nitrogen (BUN) of 17 and creatinine of 0.9. The urinalysis showed a low specific gravity, but it was otherwise normal, without any proteinuria or hematuria. Other immunological testing showed a negative anti-nuclear antibody, negative rheumatoid factor, negative cyclic citrullinated peptide IgG antibody, and negative glomerular basement membrane IgG. An erythrocyte sedimentation rate and C-reactive protein level were not obtained on admission. Computed tomographic (CT) imaging of the chest showed bilateral ground-glass opacities suspicious for diffuse alveolar hemorrhage (DAH) (Figure 1). The patient underwent bronchoscopy, and serial aliquots confirmed DAH. The patient underwent a surgical lung biopsy with sampling of the right middle and lower lobes. The pathological examination revealed acute and ongoing DAH, characterized by the combined presence of acute fibrinous lung injury, fresh blood in alveolar spaces, and focally active capillaritis, occurring in a background of alveolar hemosiderosis from one or more prior episodes of DAH in the past, with an accumulation of innumerable hemosiderin-laden macrophages in alveolar spaces and iron encrustation of elastic connective tissue fibers (Figure 2). There was no evidence of granulomas. Scattered foamy macrophages were also present in the alveolar spaces and were accompanied by vacuolated pneumocytes, findings that are non-specific but frequently associated with adverse drug reactions. The final read by the pathologist was "acute and organizing DAH with features suspicious for focally active capillaritis, most suggestive of a drug-associated AAV, possibly associated with rivaroxaban."

The combination of positive ANCA, DAH, purpuric lesions in lower extremities, and the lung pathological findings suggestive of drug-associated AAV supported the diagnosis of medication-associated AAV. As DAH has been previously reported with rivaroxaban and several other Factor Xa inhibitors, and the patient was not receiving any other agents associated with DAH or AAV, we hypothesized that rivaroxaban was most likely the cause of AAV manifested by DAH, joint swelling, and purpuric lesions in this patient.

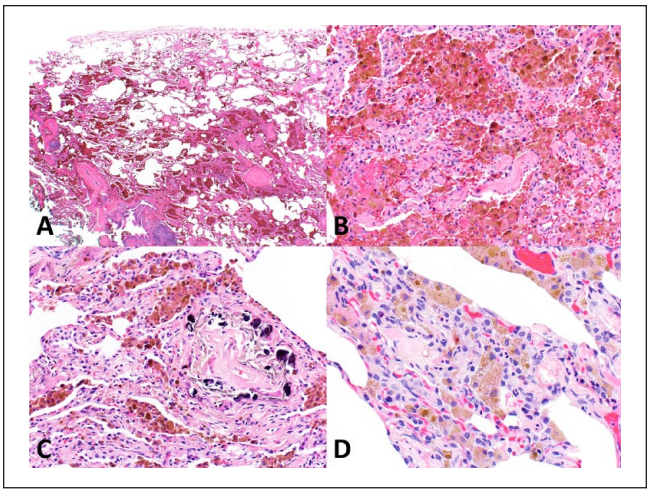

Figure 1. Representative photomicrographs of patient's surgical lung biopsies. (A) At scanning magnification, areas of alveolar filling are readily apparent. (B, C) At higher magnification, alveolar spaces are filled with fresh blood, fibrin, and innumerable pigmented macrophages laden with hemosiderin, diagnostic of acute and ongoing diffuse alveolar hemorrhage, and (C) some areas also show iron encrustation of elastic fibers with an associated histiocytic inflammatory reaction and Schaumann body formation, indicative of alveolar hemosiderosis from prior bouts of hemorrhage. (D) In some areas, focally active capillaritis is present with scattered interstitial neutrophils. Though subtle, vacuolated pneumocytes and scattered foamy macrophages can also be seen. Hematoxylin and eosin (all images); original magnifications 20x, 200x, 200x, and 400x, respectively.

Rivaroxaban was discontinued, and the patient was transitioned to dabigatran. She received intravenous methylprednisolone 1000 mg per day for 3 days. She also initially received 4 doses of weekly rituximab 375 mg/m^2, and her symptoms improved with steroids and rituximab. At the 1-month follow-up, the anti-MPO antibody was still positive, and the anti-PR3 antibody was negative. At the 6-month follow-up, her anti-MPO antibody and anti-PR3 antibody were negative. She was progressively tapered off steroids over a 10-month period. In addition, she received 2 doses of rituximab 500 mg at the 6-month follow-up, followed by 500 mg every 6 months for another 2 doses. The patient received treatment with rituximab for approximately 2 years.

Approximately 2.5 years after her episode of DAH, the patient wanted to discuss the discontinuation of rituximab, and she presented to Mayo Clinic Arizona for a second

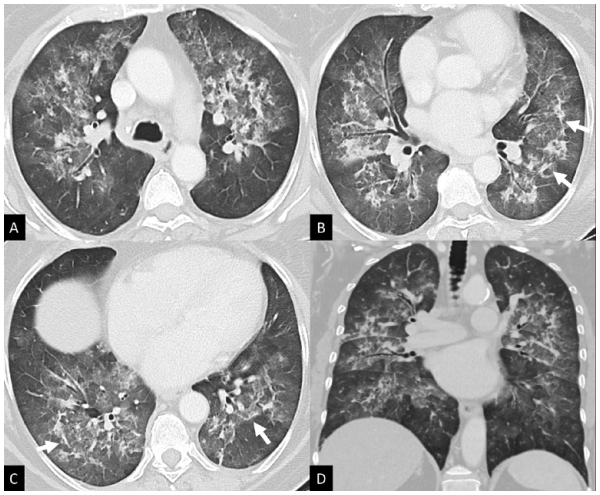

Figure 2. Contrast-enhanced CT images with lung windowing in axial plane through the upper, mid, and lower lungs (A-C) and coronal plane (D) demonstrate a central distribution of airspace disease sparing the peripheral subpleural lung with predominant ground-glass opacities in a centrilobular and peri-bronchovascular distribution. There is mild bronchial wall thickening and airway distention in certain regions such as the right middle lobe (B), in addition to areas of developing distortion as evidenced by the linear nature of portions of the airspace disease (arrows, B and C). While the imaging findings are not specific for one disease process, based on imaging alone, differential diagnostic possibilities would include pulmonary hemorrhage, inhalational exposure (such as vaping), infectious bronchiolitis, and organizing pneumonia as a manifestation of acute lung injury. The distortion and mild bronchial dilatation are in keeping with organizing areas of lung injury suggesting some component of subacute or chronic repetitive disease.

opinion. She was concerned about the increased risk of severe infections, especially in the setting of the COVID pandemic. At that time, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), C3, C4, liver function, and kidney function were normal. Anti-MPO antibody, anti-PR3 antibody, antinuclear antibody (ANA), and anti-phospholipid antibodies were negative. Immunofluorescent ANCA testing was not performed. Because the patient had not had any relapses in 2.5 years, had discontinued the likely offending medication, and had been on immunosuppressant treatment for 2 years, we decided to stop rituximab. The patient has been followed for approximately 1.5 years after the last dose of rituximab, and she has not had any flares.

Discussion and Conclusions

Rivaroxaban is a relatively new oral anticoagulant that inhibits Factor Xa. Diffuse alveolar damage and DAH have been reported in association with rivaroxaban and may be fatal. There are only a few cases reported in the literature.[3] Patients usually present with cough, dyspnea, and hemoptysis and have lung infiltrates or diffuse ground-glass opacities. Although our patient could have just had rivaroxaban-associated DAH, the purpuric lower extremity lesions, the joint swelling, the positive ANCA test, and the biopsy were concerning for drug reaction, and made drug-associated AAV the most likely diagnosis. Another differential to consider was primary AAV with DAH that was exacerbated by rivaroxaban, but the pathology was suggestive of drug-associated AAV, which makes primary AAV with DAH less likely.

Primary systemic AAV and drug-associated AAV can be difficult to differentiate as they have similar clinical manifestations. Primary AAVs are characterized by positive ANCA and inflammation of the small blood vessels, and they include 3 subtypes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Microscopic polyangiitis and EGPA are typically associated with positive p-ANCA and positive anti-MPO antibodies, and GPA is typically associated with a positive c-ANCA and PR3 antibody.[4]

Over the years, many cases of drug-associated vasculitides have been reported, and many of these cases have been associated with positive ANCA. Over 1000 cases of propylthiouracil (PTU)-associated AAV have been reported.[5] Other medications that are strongly associated with drug-associated AAV include other anti-thyroid medications like benzyl-thiouracil, hydralazine, anti-tumor necrosis factor-alpha (TNF-α) agents, sulfasalazine, D-penicillamine, and minocycline.[2] Although these are the most common medications associated with AAV, there have been many other case reports linking many additional classes of medications to drug-associated AAV.[6-18]

As mentioned, most of the data about drug-associated AAV come from anti-thyroid drug (ATD)–associated AAV (ATD-AAV). However, the clinical manifestations and severity of drug-associated AAV vary from drug to drug. Compared with primary AAV, ATD-AAV is more likely to affect younger and female patients. Bonaci-Nikolic et al showed that approximately 52% of patients with primary AAV were female, and approximately 94% of patients with ATD-AAV were female. In addition, the mean age of diagnosis for primary AAV was 52 years, whereas the mean age of diagnosis for ATD-AAV was 31 years.[19] Patients with ATD-AAV were less likely to have systemic symptoms, such as fevers and weight loss. Approximately 25% of patients with ATD-AAV have fevers, and 31% have at least a 2-kg weight loss. In comparison, 86% of patients with primary AAV have fevers, and 84% have weight loss.[19] Anti-thyroid drug–associated AAV is more likely to involve the skin and is less likely to involve other organs including the kidney, lungs, gastrointestinal tract (GI) tract, and nervous system. One study with 16 patients with ATD-AAV showed that 10 patients (62.5%) had skin involvement, 3 patients had renal involvement (19%), 3 patients had lung involvement (19%), 1 patient (6%) had nervous system involvement, and no patients had GI or ear, nose, and throat (ENT) involvement. In comparison, among

patients with primary AAV, 14% had skin involvement, 75% had renal involvement, 50% had lung involvement, 46% had nervous system involvement, 12% had GI tract involvement, and 27% had ENT involvement.[19] In addition, ATD-AAV was associated with milder disease and better prognosis.[2] Therefore, the clinical presentation of drug-associated AAV is very variable, and it ranges from arthralgias to isolated skin involvement, to severe single-organ or multi-organ involvement.[1]

In terms of laboratory testing, most of the patients with drug-associated vasculitis have positive p-ANCA and anti-MPO antibodies. Few patients have positive c-ANCA or anti-PR3.[19-21] Furthermore, some patients with drug-associated AAV have antibodies against multiple ANCA-specific antigens or immunofluorescence patterns. One study demonstrated that among patients with PTU-associated AAV, 89% of patients were positive for p-ANCA only, 8% of patients were positive for both c-ANCA and p-ANCA, and 3% of patients were positive for c-ANCA only.[20] The pathogenesis of drug-associated AAV is most likely multifactorial and still not completely understood. Many medications require the formation of a complex to induce the production of antibodies that drive the immune response. The translocation of ANCA antigens to the cell surface induces the formation of ANCA, which binds the ANCA antigens on the cell membrane and perpetuates the activation by cross-linking PR3 or MPO and Fcγ receptors. In patients with primary AAV, the ANCA usually recognize only 1 antigen, either MPO or PR3, but in drug-associated AAV, antibodies against multiple ANCA antigens may develop.[22]

There are no diagnostic or classification criteria for drug-associated AAV. The 2012 International Chapel Hill Consensus Conference (CHCC) proposed a nomenclature system for the main types and subtypes of vasculitides but did not specify diagnostic criteria for clinical care or classification criteria for clinical studies. According to the CHCC, drug-associated AAV is one of the vasculitides associated with probable etiology.[4] The diagnosis of drug-associated AAV is largely presumptive and is typically based on the temporal relationship between the clinical manifestations and initiation of the offending drug. Symptoms should begin after the initiation of the offending medication and should improve after discontinuation of the offending medication. In addition, serum ANCA should be positive, and other similar diseases—especially infections, malignancies, and other autoimmune rheumatic diseases—should be ruled out.[2] Some authors have suggested that long-standing therapy with the offending drug might be a risk factor for developing clinically evident vasculitis, as it would allow for more extensive immune system activation, and this could have been the case in our patient who developed AAV after 2 years of treatment with rivaroxaban.[22]

We presented a unique case of that is likely rivaroxaban-associated AAV. This patient's clinical presentation and positive ANCA were consistent with AAV. The 2 main considerations were anti-MPO positive MPA that exclusively manifested as DAH, joint swelling, and purpuric lesions in lower extremities, vs drug-associated AAV secondary to rivaroxaban. Throughout her disease course, the patient had skin, joint, and pulmonary involvement. She did not have symptoms or findings suggestive of sinus, renal, or heart involvement. Although she had atrial fibrillation, it is a very frequent arrhythmia in the elderly population, and we think that it was most likely pre-existent and unrelated to the AAV. Although skin involvement is more common in drug-associated vasculitis, pulmonary involvement is more common in primary AAV. Some investigators have suggested that more severe specific organ involvement develops in patients with non-specific systemic symptoms when the causal drug is not withdrawn soon. Intra-alveolar hemorrhage is the most common pulmonary manifestation of drug-associated AAV.[22] The discordant laboratory results of positive c-ANCA with negative anti-PR3 and negative p-ANCA with positive anti-MPO antibodies were more consistent with drug-associated AAV. Patients with drug-associated vasculitis are more likely to have several and sometimes discordant circulating autoantibodies.[20] In addition, although the DAH could be secondary to an idiopathic autoimmune disorder, the histologic presence of foamy macrophages and vacuolated pneumocytes was suggestive of a drug-associated reaction.[23] The responses of alveolar macrophages to inhaled toxins results in an increase in the number of vacuolated or foamy macrophages in animal models.[24] Typical pathological findings of chemical-induced pneumonitis consist on lipid-laden pulmonary alveolar macrophages with vacuolization and vacuolated pneumocytes.[25] In addition, drug-induced pneumotoxicity has been known to be associated with alveolar macrophages and type II pneumocytes, with the most evidence coming from amiodarone-associated penumotoxicity.[26,27] Finally, after discontinuation of rivaroxaban and following treatment with immunosuppression, the patient did not have any relapses. The patient's discordant laboratory results, pathological features suggestive of drug-associated vasculitis, and clinical stability without relapses after rivaroxaban was discontinued were all consistent with drug-associated AAV secondary to rivaroxaban.

All cases of drug-associated AAV should be treated with the rapid withdrawal of the causal agent. In addition, patients with severe or life-threatening disease may require additional immunosuppression for treatment and prevention of relapse.[1,2] The duration of the immunosuppressive treatment after withdrawing the offending agent is unclear. In general, the treatment is shorter than in the case of primary AAV, and the risk of relapse after complete remission and withdrawal of immunosuppression is low.[28] However, the ideal duration of the immunosuppressive treatment in patients with severe drug-associated AAV is not known. In this case, the patient was treated with immunosuppression for 2 years, and after

1.5 years of additional follow-up, she has not had any relapses to date.

To our knowledge, this is the first extended report of a case in the literature of possible rivaroxaban-associated AAV. Given the broad and increasing use of novel anticoagulant agents, we think that it is important to raise awareness of this potential complication because prompt discontinuation of the drug, and immunosuppressant treatment in severe life-threatening cases, may be lifesaving.

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal and written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Prior Presentation of Abstract Statement

This case was previously presented at the American Thoracic Society Internation Conference in 2020 (https://doi.org/10.1164/ajrccm-conference.2020.201.1_MeetingAbstracts.A4953?force_isolation=true).

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