CASE REPORT

Rheumatoid arthritis causing diffuse alveolar haemorrhage: a novel therapeutic approach

Afaf Osman,¹ Panagis Galiatsatos,^{2,3} Sonali Bose,³ Sonye Danoff³

¹Department of Internal Medicine, Johns Hopkins Medicine, Baltimore, Maryland, USA

²Department of Critical Care Medical, National Institutes of Health, Bethesda, Maryland, USA

³Division of Pulmonary and Critical Care, Johns Hopkins Medicine, Baltimore, Maryland, USA

Correspondence to
Dr Panagis Galiatsatos,
panagis.galiatsatos@nih.gov

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SUMMARY

Pulmonary vascular involvement due to rheumatoid arthritis, presenting as diffuse alveolar haemorrhage (DAH), is a rare phenomenon, especially if there are no signs of systemic vasculitides. Furthermore, how to proceed with the management of these patients is challenging, as in the case of our patient, who had recurrent DAH. We present a case of a patient with known rheumatoid arthritis who had recurrence of DAH that spanned over several years, often presenting with life-threatening respiratory failure. While her DAH presentation improved with high-dose glucocorticoids, to resolve her recurrence, we opted to initiate treatment with rituximab, with a short course of azathioprine. After the second round of rituximab, the patient continues to do well without any further DAH-related complications. We also summarise prior cases of such patients to highlight variable treatment options.

BACKGROUND

Rheumatoid arthritis (RA) is a systemic autoimmune disease that is estimated to affect 1.3–1.5 million adults in the USA, often leading to significant morbidity and mortality.^{1–3} The disease mainly involves small joints causing joint pain, destruction and deformation. Extra-articular manifestations of RA, including associated lung disease, occur through the inflammatory response associated with the disease. Interstitial lung disease (ILD) is the most common form of pulmonary involvement in RA, occurring in 10%–20% of patients with RA.⁴ ILD encompasses a variety of diffuse parenchymal processes, including usual interstitial pneumonia and non-specific interstitial pneumonia.⁴ RA can also cause small airway disease, due to its affect on the non-cartilaginous airways with an internal diameter less than 2 mm.⁵ Rarely, pulmonary vascular involvement due to RA, presenting as diffuse alveolar haemorrhage (DAH), may occur and has been described in a few case reports.

DAH is a clinicopathological entity characterised by pulmonary haemorrhage originating from the alveolar microcirculation.⁶ The usual clinical presentation of DAH includes haemoptysis, diffuse alveolar infiltrates on imaging and potential progression to hypoxaemic respiratory failure. There are three main histological patterns associated with DAH: diffuse alveolar damage, bland pulmonary haemorrhage and capillaritis.⁷ Of these, capillaritis represents destruction of pulmonary microcirculation by processes such as vasculitides,

especially those associated with connective tissue diseases (CTD). The most common CTD causing DAH is systemic lupus erythematosus (SLE), where DAH is estimated to occur in 3.7% of hospitalised patients with SLE.⁷ DAH may occur in other CTD, such as RA, but it is a rare phenomenon, especially if there are no signs of vasculitides.⁶

In this report, we present a case of a patient with DAH associated with RA without signs of vasculitides. The clinical course proved challenging, necessitating a unique immunosuppressive regimen. Furthermore, we review prior cases of DAH associated with RA and provide potential treatment options for aggressive DAH associated with RA.

CASE PRESENTATION

A 36-year-old woman from Kuwait had a medical history of seropositive RA diagnosed at age 16 years. Her RA manifested as joint pain predominantly in her hands and wrists. She was treated with several therapies throughout the course of her disease: hydroxychloroquine, sulfasalazine and glucocorticoids. No active RA musculoskeletal issues for several years. Furthermore, she is a never smoker, housewife, with no family history of autoimmune or pulmonary disease.

In 2015 while in Kuwait, she developed acute respiratory distress 2 days after an uncomplicated caesarean section delivery (pregnancy went to term), requiring mechanical ventilation due to respiratory failure. She was treated with glucocorticoids and antibiotics. She survived her critical care course and recovered without a clear aetiology of her respiratory failure. Five months later, she developed respiratory failure, again necessitating mechanical ventilation. The aetiologies of both of her respiratory failure episodes were unclear. However, some non-specific findings and events were noted during these intensive care unit admissions. First, multiple chest CT images showed diffuse alveolar and ground-glass infiltrates. Second, she required several units of red blood cells due to an acute drop in haematocrit in both cases. After surviving both respiratory failure episodes, she had ongoing pulmonary symptoms: supplemental oxygen needs, dyspnoea on exertion and coughing, and occasional haemoptysis. She was started on hydrocortisone without much improvement in her pulmonary symptoms. Due to concern for another life-threatening respiratory failure episode in the setting of persistent pulmonary symptoms without an obvious diagnosis or treatment plan, the patient sought a second opinion abroad.

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Figure 1 A representative cut of a chest CT performed with intravenous contrast demonstrating bilateral ground-glass opacities, nodules and bronchial thickening.

At the time of her presentation to the pulmonary clinic, her main symptoms included dyspnoea on exertion, cough and haemoptysis. Her RA-associated joint symptoms were well controlled, and she denied joint swelling and pain. Chest CT imaging showed diffuse ground-glass opacities and bronchial wall thickening ([figure 1](#)). A bronchoscopy was performed as a result of these findings. Serial aliquots of bronchoalveolar lavage (BAL) showed sanguineous return suggesting the presence of DAH. Analysis of the fluid showed 15 960 red blood cells/mm³. Cytology from the lavage showed abundant pulmonary alveolar macrophages with haemosiderin deposition. Infectious work up was unrevealing. Given her bronchoscopy findings, laboratory data from her BAL and clinical picture, she was given a diagnosis of DAH. Additional connective tissue markers were sent to evaluate the aetiology of her DAH: anti-neutrophil cytoplasmic antibody (ANCA), anti-double-stranded DNA, antinuclear antibody, anti-Ro, anti-La, anti-glomerular basement membrane (GBM), antiphospholipid, anti-Smith and anti-RNP antibodies, which were all negative. A thorough review of all of her medications was performed. Given these results, she was diagnosed with DAH associated with RA. She received pulse dose glucocorticoids and had an acute improvement in regards to her pulmonary symptoms. Furthermore, given she had two life-threatening respiratory episodes (with a high likelihood that it was due to DAH associated with RA), as well as presenting to our clinic with active symptoms, it was decided to increase her immunosuppressive regimen and add an additional agent to her high-dose glucocorticoids. Thus, our patient began treatment with rituximab, receiving one dose shortly after her diagnosis.

One month after her initial clinic visit, she returned to the emergency room with increasing dyspnoea and hypoxaemia. A dry chest CT demonstrated significantly increased perihilar consolidations and ground-glass opacities ([figure 2](#)) compared with her chest CT from her first admission ([figure 1](#)). A repeat bronchoscopy was pursued with BAL demonstrating increasingly sanguineous return and red blood cells too numerous to count on the cell analysis. Infectious workup was repeated and was unrevealing. She was diagnosed with DAH and was treated with a repeat pulse dose of glucocorticoids. However, since she relapsed on both glucocorticoids and after only one round of rituximab, azathioprine was added in order to serve as a bridge until her next round of rituximab. The patient's symptoms of

Figure 2 A representative cut of a chest CT demonstrating worsening of the bilateral ground glass opacities, nodules and bronchial thickening occurring 1 month after the CT scan on [figure 1](#).

hypoxaemia and dyspnoea resolved, and she was discharged home.

Azathioprine was discontinued as an outpatient once she received her second dose of rituximab. At a follow-up clinic visit 3 months later, her dyspnoea and haemoptysis had fully resolved, and she did not require supplemental oxygen.

INVESTIGATIONS

Two bronchoscopies were performed. Serial aliquots of BAL from both bronchoscopies showed sanguineous return suggesting the presence of DAH.

Additional connective tissue markers were sent to evaluate the aetiology of her DAH: ANCA, anti-double-stranded DNA, antinuclear antibody, anti-Ro, anti-La, anti-GBM, antiphospholipid, anti-Smith and anti-RNP antibodies, which were all negative. A thorough review of all of her medications was performed. Given these results, she was diagnosed with DAH associated with RA.

DIFFERENTIAL DIAGNOSIS

DAH was the pulmonary diagnosis, but what it was caused by was thoroughly investigated. Causes of DAH included other autoimmune processes, infections, malignancies and medications.

TREATMENT

Given her recurrence of her disease, a novel therapeutic approach was sought. Her acute management was handled well with high-dose glucocorticoids (1 mg/kg). To treat her recurrence, we initiated rituximab as an outpatient. Furthermore, until she received two doses of rituximab, with her first and second dose separated by 6 weeks, she was put on a short course of azathioprine.

OUTCOME AND FOLLOW-UP

Azathioprine was discontinued as an outpatient once she received her second dose of rituximab. At a follow-up clinic visit 3 months after her second round of rituximab, her dyspnoea and haemoptysis had fully resolved, and she did not require supplemental oxygen.

Table 1 Patient characteristics from case reports of patients with DAH thought to be due to RA without vasculitis overlap

Age (years)	Sex	RA symptoms	Time between RA diagnosis and DAH diagnosis (years)	Treatment
56*	Male	Synovitis Subcutaneous nodules	40	Glucocorticoids Cyclophosphamide
64*	Male	Synovitis Ulnar deviation	20	Glucocorticoids
25*	Female	Synovitis	2	Glucocorticoids Cyclophosphamide
45†	Female	Synovitis	—‡	Glucocorticoids
36§	Female	Synovitis Ulnar deviation	20 years	Glucocorticoids Rituximab Azathioprine
33¶	Male	Synovitis	21 years	Glucocorticoids IVIg Cyclophosphamide

*Patients from Schwarz et al⁸.†Patient from Vaishnav et al¹⁵.

‡DAH was presenting symptom.

§Our patient.

¶Patient from Watanabe et al¹⁶ (though note patient had juvenile idiopathic arthritis).

DAH, diffuse alveolar haemorrhage; IVIg, intravenous immunoglobulins; RA, rheumatoid arthritis.

DISCUSSION

DAH is a rare complication of RA. The underlying pathology for DAH associated with RA is thought to be pulmonary capillaritis, as has been demonstrated by lung biopsies in three prior cases.⁸ Furthermore, immune complex deposition was noted in some of the lung biopsies of these cases.⁸ Thus, DAH associated with RA is most likely a manifestation of an autoimmune phenomenon directed against the lung microcirculation. DAH may be seen in RA due to other aetiologies. For example, with some RA-specific therapies, such as leflunomide and etanercept, DAH has been found to be a side effect of these medications, although the mechanism of drug-induced DAH cases is unclear.^{9–10} Our patient's clinical history, bronchoscopy and BAL results and response to therapy assure of the diagnosis of DAH associated with RA.

While systemic vasculitis can be associated with capillaritis of the lungs, pulmonary capillaritis can also exist without involvement of other organ systems. DAH associated with RA patient without serological and clinical markers of vasculitis has been reported in only four prior cases (literature review limited to English publications only), summarised in table 1.^{8–11} Schwarz et al⁸ described three cases with a known diagnosis of RA who were found to have DAH and capillaritis on lung biopsy. None of these three patients had an associated systemic vasculitis or ANCA positivity. In the fourth case report, DAH was the initial presenting symptom of RA in a patient not previously known to have RA.¹¹ Our presentation is the fifth case with DAH associated with RA without systemic vasculitis. Note that there have been reports of DAH associated with RA and evidence of vasculitis. Three cases discuss DAH associated with RA and clinical manifestations of systemic vasculitis coexisting with RA,^{12–13} while two other cases identify DAH associated with RA and with positive ANCA serological testing.^{14–15} Finally, there is a reported case of a patient with juvenile idiopathic arthritis who developed DAH with negative serology (rheumatoid factor and

antinuclear factor),¹⁶ who we have included in our summary of cases in table 1.

Our patient's clinical course was challenging and unique given her observed recurrence of DAH as well as speculation that her prior episodes of respiratory failure were also related to DAH. Her DAH relapsed while on standard immunosuppression necessitating escalation of her immunosuppressive regimen. The use of glucocorticoids along with azathioprine and rituximab has not been previously described and, to our knowledge, was not trialled in prior DAH cases associated with RA. The strategy of glucocorticoids and rituximab was previously described in cases of DAH associated with SLE.⁷ Thus far, no clinical trials on the treatment of DAH associated with RA exist, likely due to the rarity of the condition.

In conclusion, our case demonstrates the importance of considering DAH associated with rheumatoid arthritis in a patient who presents with acute hypoxaemic respiratory failure. To date, this is the fifth published description of DAH associated with RA along with negative serologies for vasculitides and negative vasculitis findings. While the cornerstone of management for DAH has been glucocorticoids, our patient demonstrated that DAH associated with RA may necessitate additional immunosuppressive agents. In cases of relapsed or refractory DAH, escalation of immunosuppression with additional agents should be considered. Rituximab in particular may be an ideal choice for patients with RA-related DAH; however, additional agents may be needed as immunosuppressive bridging until a sufficient amount of rituximab has been given. In our patient's case, glucocorticoids and rituximab were used for long-term management and proved to be effective in controlling her DAH symptoms after her second round. DAH associated with RA remains a rare and clinically challenging condition, especially if it does not respond to traditional immunosuppressive therapy, as demonstrated by our reported case.

Learning points

- ▶ Diffuse alveolar haemorrhage due to rheumatoid arthritis is a rare phenomenon that has a high rate of recurrence.
- ▶ Management in the acute setting for diffuse alveolar haemorrhage relies on high-dose glucocorticoids and supportive therapy.
- ▶ To prevent recurrence, additional immunosuppressive agents should be sought, as in our case with rituximab and a short course of azathioprine.

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Competing interests None declared.

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