CASE REPORT

We present a case of a 34-year-old female without prior comorbidities. The patient developed lower limb rashes, which were maculopapular and purpura, along with small and large joint pains and redness of eyes. A computed tomography (CT) chest had shown axial predominant bilateral ground opacity with dense consolidation in the interstitial lung. The patient was diagnosed with diffuse alveolar hemorrhage (DAH) presenting along with thrombosis and the related management.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis predominantly includes granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis, and microscopic polyangiitis. It has associations with both thrombosis and diffuse alveolar hemorrhage (DAH). The management of DAH includes plasmapheresis which further increases risk for thrombosis, thus treating patients of DAH with anticoagulation can be a dubious decision. Lacunae in knowledge remain regarding managing the anticoagulation in patients having both venous thrombosis with pulmonary hemorrhage. We present a case report and a systematic review of DAH presenting along with thrombosis and the related management.

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KEY WORDS: Antineutrophil cytoplasmic antibody-associated vasculitis, diffuse alveolar haemorrhage, granulomatosis with polyangiitis, thrombosis

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bilateral lower lobes [Figure 1]. Autoimmune workup was suggestive of diffusely cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA) positivity. Bronchoscopy was done which revealed hemosiderin-laden macrophages with the negative infective profile. However, renal functions, ocular, ENT, and other systemic evaluations were normal. Thus, a diagnosis of granulomatosis with polyangiitis (GPA) was made and the patient started on immunosuppression with pulse cyclophosphamide (6 cycles) along with oral steroids. After remission, azathioprine was started and steroids were tapered over the next 6 months [Figure 2]. CT chest after 1 year of onset of treatment showed significant clinico-radiological resolution. The patient discontinued treatment after 13 months.

After an asymptomatic period of 10 months, there was a recurrence of joint pains and skin lesions along with exertional breathlessness. The patient was also found to be pregnant during this admission. The patient had a spontaneous abortion two days after admission. CT chest revealed increase in opacities [Figure 3]. A repeat bronchoscopy was suggestive of hemosiderin-laden macrophages, thereby confirming a relapse of DAH due to GPA. The patient was retreated with steroid pulse followed by oral steroids in tapering doses. In view of DAH, the patient was started on plasmapheresis; however, after 2 cycles, she complained of right lower limb pain and swelling. Doppler was suggestive of deep-vein thrombosis. As the patient had stabilized without any evidence of hemoptysis or drop in hemoglobin along with a risk of pulmonary embolism, anticoagulation was initiated with low-molecular-weight heparin (LMWH). For the maintenance of immunosuppression, rituximab was started.

**REVIEW OF LITERATURE**

The decision to start anticoagulation in a patient with DAH is a challenging situation. Hence, we performed a literature review for case studies addressing this question. We searched for articles in Embase and PubMed.
with search term being (“ANCA-associated vasculitis” OR “wegener’s” OR “GPA” OR “granulomatosis with polyangiitis”) AND (“pulmonary hemorrhage” OR “diffuse alveolar hemorrhage” OR “DAH” OR “diffuse pulmonary hemorrhage”) AND (“venous thromboembolism” OR “DVT”) OR “deep-vein thrombosis”). We found a total of 43 articles of which 8 articles were finally selected.

The systematic review methodology is summarized in [Figure 4]. The details of the finally selected studies for review are summarized in Tables 1 and 2.

**DISCUSSION**

In our review, we found 12 patients, of which seven were PR3-ANCA-positive while five were myeloperoxidase (MPO)-ANCA-positive. All patients survived after the relevant treatment. Deep vein thrombosis (DVT) was associated in 10 patients while pulmonary embolism was seen in 10 patients and a coexisting pulmonary embolism with DVT was seen in seven patients. Simultaneous occurrence of DAH and thromboembolism was seen in six patients (46%) while thromboembolism preceded DAH in four patients (30%) while DAH preceded in three patients (23%). All patients received immunosuppression, the most common agent used has been steroid pulse therapy, given in 12 patients (92.3%), while cyclophosphamide was used in eight patients (61.5%), rituximab and MMF were used in two patients each (15.3%), and plasmapheresis was used in another seven patients (53.8%). Anticoagulation was used in 12 patients (92.3%), the most commonly used agent was LMWH in seven patients while warfarin was used in five patients, UFH (Unfractionated Heparin) in three patients, and rivaroxaban was used in one patient. Inferior vena cava filter was also used in five patients. All of these patients survived.

Along with DAH, our patient had skin, joint involvement, and mild proteinuria. To the best of our knowledge, this is the only case of pregnant GPA patients having both DAH and thrombosis, and has been successfully treated for the same. One of the common causes of DAH is GPA; however, thromboembolism is a frequent accompaniment

| Table 1: Diffuse alveolar haemorrhage with thrombosis in positive proteinase 3 antineutrophil cytoplasmic antibody |
|---|---|---|---|---|
| **Author** | **Age/Sex** | **Organ systems involved** | **Chronology of DAH and venous thromboembolism** | **Immunosuppression** | **Anticoagulation measures** |
| Dreyer and Fan, 2009 | 31/male | Lung, kidney, ENT | DVT and PE followed by DAH | Steroids, cyclophosphamide and plasmapheresis | UFH, warfarin and IVC filter |
| Hughes et al., 2010 | 79/female | Lung, kidney, ENT, joint pains, UGI bleed | DAH followed by PE | Steroids and cyclophosphamide | UFH |
| De Sousa et al., 2012 | 48/female | Lung, kidney, ENT | Simultaneous PE and DAH | Steroids, MMF and plasmapheresis | IVC filter |
| | 19/female | Lung, kidney, ENT | Simultaneous DAH and PE and upper limb DVT | Steroids and cyclophosphamide | UFH |
| | 45/male | Lung, kidney, ENT | DAH before PE and lower limb DVT | Steroids and cyclophosphamide | - |
| Shovman et al., 2013 | 58/male | Lung, kidney, lupus anticoagulant positive | Simultaneous lower limb DVT | Steroids, cyclophosphamide and plasmapheresis | - |
| Moreno-Gonzalez et al., 2014 | 42/male | Lung, kidney | DVT, PE followed by DAH | Initially on anticoagulation (LMWH followed by warfarin), stopped after DAH. Steroids, cyclophosphamide and plasmapheresis | LMWH |
| Our study | 34/female | Joint pains, skin, kidney, lung | DAH followed by DVT | Steroid, plasmapheresis and rituximab | LMWH |

DAH: Diffuse alveolar hemorrhage, DVT: Deep vein thrombosis, PE: Pulmonary embolism, LMWH: Low molecular weight heparin, UFI: Unfractionated heparin, ENT: Ear, nose, and throat, IVC: Inferior vena cava, UGI: Upper gastrointestinal, MMF: Mycophenolate mofetil

| Table 2: Diffuse alveolar hemorrhage with thrombosis in myeloperoxidase antineutrophil cytoplasmic antibody |
|---|---|---|---|---|---|
| **Author** | **Age/Sex** | **Organ systems involved** | **Chronology of DAH and venous thromboembolism** | **Immunosuppression** | **Anticoagulation measures** |
| Tseng et al., 2015 | 14/female | Lung, kidney, skin | DAH 5 days after lower limb DVT | Steroids, MMF, cyclophosphamide and plasmapheresis | LMWH |
| Yun et al., 2014 | 60/female | Lung, skin | Simultaneous DAH and PE and lower limb DVT | Rituximab | Warfarin |
| De Sousa et al., 2012 | 61/male | Lung, kidney, ENT | PE diagnosed 2 weeks before DAH | Steroids, plasmapheresis and rituximab | LMWH and IVC filter |
| | 58/female | Lung and polymyositis and pulmonary fibrosis (anti-synthetase syndrome) | Simultaneous DAH, DVT and PE | Steroids and cyclophosphamide | LMWH with IVC filter |
| Naito et al., 2018 | 41/female | Lung, skin | Simultaneous lower limb DVT, pulmonary embolism and DAH | Steroids | LMWH and rivaroxaban |

DAH: Diffuse alveolar hemorrhage, DVT: Deep vein thrombosis, PE: Pulmonary embolism, LMWH: Low molecular weight heparin, ENT: Ear, nose, and throat, IVC: Inferior vena cava, MMF: Mycophenolate mofetil
CONCLUSION

Thromboembolism is a common entity in patients with ANCA-associated vasculitis. However, simultaneous presentation of DAH and thrombosis is rare. Clinicians need to be watchful for this condition. Prompt initiation of immunosuppression is life-saving in patients of vasculitis, however, in patients presenting with simultaneous DAH and thromboembolism, it is worthwhile to note that simultaneous anticoagulation seems a safe option for treatment, which is not associated with adverse clinical outcomes, although we need additional data to support this.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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