Case Report

Combined diffuse alveolar hemorrhage and venous thrombosis in a patient with granulomatosis with polyangiitis: Case report and systematic review of literature

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ABSTRACT

Antineutrophil cytoplasmic antibody-associated vasculitis has associations with both thrombosis and diffuse alveolar hemorrhage (DAH). Management of patients having coexistence of both thrombotic and hemorrhagic manifestations is challenging. Thrombotic conditions require anticoagulation, which can theoretically increase the risk of bleeding and thereby worsen DAH. In this review, we highlight the management of a patient of granulomatosis with polyangiitis with DAH who developed deep vein thrombosis. A systematic review of the literature was also performed summarizing and discussing the issues pertaining to the management of such patients.

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

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Submitted: 16-Sep-2020 **Accepted:** 24-Jun-2021 **Published:** 28-Dec-2021

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[1] 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.

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_761_20

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

How to cite this article: Madan M, Iyer H, Tiwari P, Mohan A, Madan K, Hadda V, *et al*. Combined diffuse alveolar hemorrhage and venous thrombosis in a patient with granulomatosis with polyangiitis: Case report and systematic review of literature. Lung India 2022;39:70-3.

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.

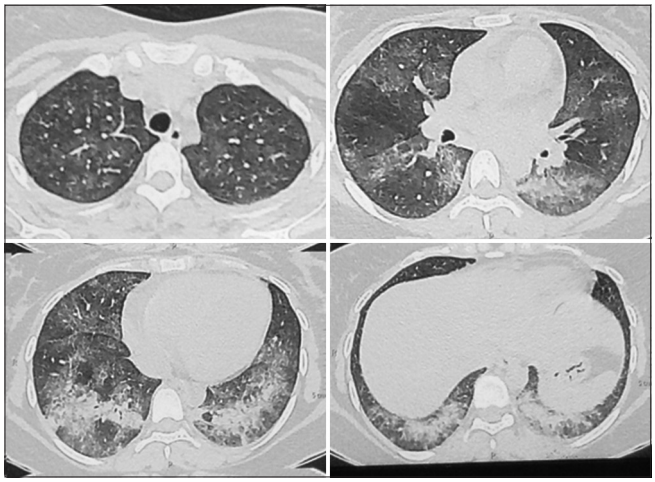

Figure 1: Computed tomography chest showing bilateral consolidation and ground glassing with axial and basal predominance

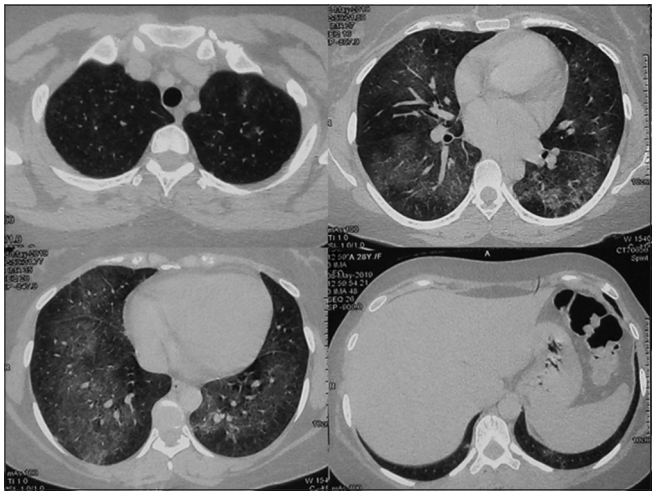

Figure 3: Computed tomography chest showing relapse with increase in areas of ground glass

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

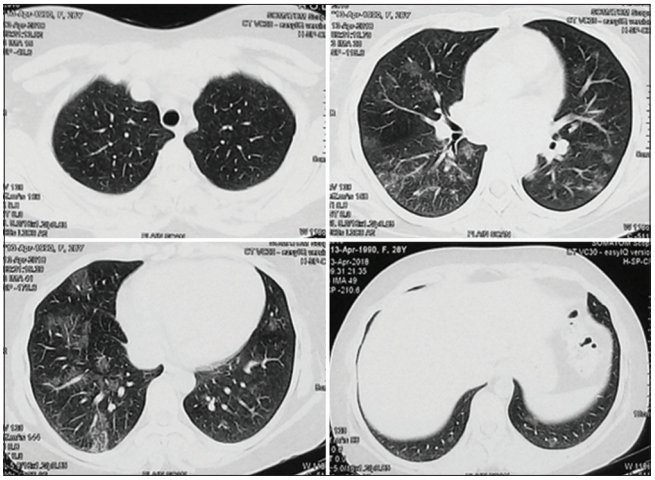

Figure 2: Computed tomography chest showing resolution in the opacities

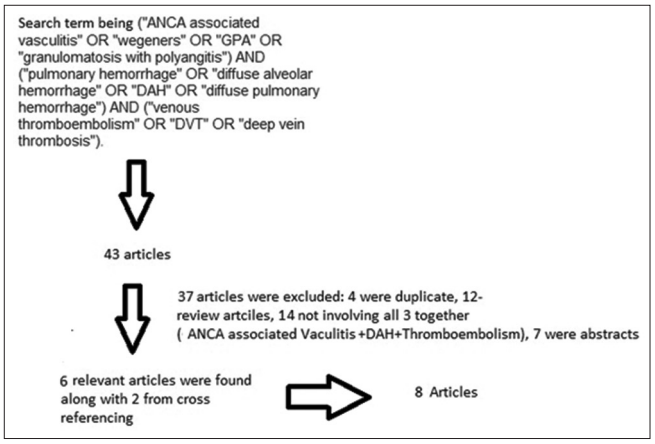

Figure 4: Methodology of systematic review of literature regarding combined pulmonary hemorrhage and thrombosis in ANCA associated vasculitis

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[2]	31/male	Lung, kidney, ENT	DVT and PE followed by DAH	Steroids, cyclophospshphamide and plasmapheresis	UFH, warfarin and IVC filter
Hughes *et al*., 2010[3]	79/female	Lung, kidney, ENT, joint pains, UGI bleed	DAH followed by PE	Steroids and cyclophosphamide	UFH and warfarin
De Sousa *et al*., 2012[4]	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	LMWH and IVC filter
Shovman *et al*., 2013[5]	58/male	Lung, kidney, lupus anticoagulant positive	Simultaneous lower limb DVT and DAH	Steroids, cyclophosphamide and plasmapheresis	Warfarin
Moreno-Gonzalez *et al*., 2014[6]	42/male	Lung, kidney	DVT, PE followed by DAH	Initially on anticoagulation (LMWH followed by warfarin), stopped after DAH. Steroids, cyclophosphamide and plasmapheresis	-
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, UFH: 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[7]	14/female	Lung, kidney, skin	DAH 5 days after lower limb DVT	Steroids, MMF, cyclophospshphamide and plasmapheresis	LMWH
Yun *et al*., 2014[8]	60/female	Lung, skin	Simultaneous DAH, upper limb DVT and PE	Rituximab	Warfarin
De Sousa *et al*., 2012[4]	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[9]	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

with reported odds being as high as 18 in comparison with 0.3/100 person-years in the general population. Its incidence is higher in active disease (overall incidence of 1.8/100 person-years versus 6.7/100 person-years in active disease) as compared to those in remission.[10] There may be multiple other factors which may have contributed to thrombosis in our patients such as plasmapheresis which is associated with both arterial[11] and venous thrombosis,[12] along with the state of pregnancy which can predispose to DVT and the presence of a catheter in the lower limb which was used for plasmapheresis. Prolonged immobilization is an important factor in hospitalized patients which can lead to DVT; hence, it is necessary in such group of patients to administer prophylactic anticoagulation. However, in the case of underlying DAH, the choice of administration of anticoagulation is a tough one. The factors which could have guided us in taking this decision are stable hemoglobin and no radiological worsening, which would have implied no ongoing hemorrhage. In view of the risk factors described above, which the patient was predisposed to, prophylactic anticoagulation could have helped in avoiding a DVT. Rather than a retrospection, we need a prospective study to answer the question as to when to initiate anticoagulation in a patient of GPA with DAH.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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