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Systemic Lupus Erythematosus and Diffuse Alveolar Hemorrhage, etiology and novel treatment strategies

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Abstract,

Diffuse alveolar hemorrhage (DAH) is a severe respiratory complication of Systemic lupus erythematosus (SLE). The illness develops during hours to a few days and is the SLE associated syndrome with highest mortality. Although no specific symptoms have been identified a number of features are associated with DAH, drop in blood hemoglobin being the most prominent. Dyspnea, blood stained sputum, diffuse infiltrates identified by chest imaging, elevated single breath diffusing capacity for monoxide, thrombocytopenia and C3 hypocomplementemia are other commonly reported signs of DAH.

The etiology is not completely understood but many patients develop DAH concomitant with lupus nephritis suggesting immune complex driven pathology. Biopsy studies have identified both cases with capillaritis and with a bland non-inflammatory phenotype. An animal model of DAH has indicated requirement of B lymphocytes and complement receptor mediated apoptotic body phagocytosis by monocytes as part of the pathogenesis.

This review will discuss considerations when diagnosing the condition and currently available therapies. Infections and other causes of hemorrhage have to be excluded as these require different treatment strategies. Methylprednisolone and cyclophosphamide remain the most commonly used therapies. Plasmapheresis and rituximab are other beneficial treatment options. A few studies have also considered intrapulmonary Factor VII therapy, extracorporeal membrane oxygenation and mesenchymal stem cell therapy.

There is an unmet need of better definition of DAHs etiology and pathology for development of improved treatment strategies.

Systemic lupus erythematosus, impacts on the respiratory tract

SLE is an autoimmune disease signified by a range of manifestations including skin rashes, chronic fatigue, arthritis, glomerulonephritis, neurological, cardiovascular involvement, stroke and influences on the lungs. Several of these manifestations can lead to premature death.[1] The disease affects 20-70 individuals per 100,000 of the population, 6-10 times more often women.[1] Disease pathology is driven by a combination of environmental and genetic factors. A feature of SLE is defective phagocytosis and removal of apoptotic cells leading to the accumulation of cell debris of nuclear, cytosolic and membrane origin. Apoptotic debris activates auto-reactive B cells and T cell leading to production of auto-antibodies.[1] Immune complexes (ICs) formed by antibodies (abs), reactive to nuclear and cytosolic antigen, present in the circulation are responsible for several facets of the pathology. ICs can activate the classical pathway of the complement system which can induce inflammation in kidneys and other organs. This persistent auto-antibody (auto-ab) mediated augmentation of the complement system leads to complement depletion and reduced ability of phagocytic removal of dead-cell debris.[1]

Involvement of the respiratory tract occurs in up to 50-70% of the SLE patients and include pleuritis, infiltrating pneumonia, bronchiolitis obliterans, muscular and diaphragmatic involvement and vascular aberrations such as pulmonary hypertension, antiphospholipid syndrome (APS) and diffuse alveolar hemorrhage (DAH).[2, 3] Defect phagocytosis, ICs, complement depletion and auto-antibodies are responsible for these respiratory tract manifestations. ICs inducing inflammation in the alveolar capillaries might be the leading cause for DAH.

Diffuse alveolar hemorrhage (DAH)

DAH was first described in 1904 by Dr William Osler and is one of the most devastating complications of SLE.[4, 5] Patients experiencing DAH present with dyspnea, cough and fever, blood stained sputum and sometimes hemoptysis, symptoms developing rapidly in hours or over a few days. Other autoimmune patient groups are also susceptible for development of DAH. Hence, the disorder is more common in ANCA- vasculitides and also patients with APS can develop DAH.[6] The exact cause for DAH pathology is unknown but the general view is that IC induced pulmonary capillaritis or bland hemorrhage is leading to damage to basement membranes and leakage of erythrocytes into the alveolar space (see pathology section below, and

figure 1).[6] DAH incidence in SLE patients can range from 0.6% to 5.4% which can be compared to 0.5 to 9% of all hospital admissions for the syndrome.[7] However autopsies of SLE patients has identified focal collections of red blood cells or more diffuse involvement in 30% - 66% of cases, suggesting both the presence of unidentified cases and the incidence of subclinical disease.[7, 8] DAH is most common in young women (mean age 27 years) and can occur at an early stage of the disease, at an average 35 months since onset (range 0-276 months).[7, 9] Affected patient may also have recurrent episodes.[4] DAH is a very serious and potentially fatal condition, although with reduced mortality over recent years, reported rates remain between 0 to 92% (estimated average 50%).[2, 6] Factors such as development of acute catastrophic hemoptysis, requirement of mechanical ventilation, infections and thrombocytopenia are associated with increased risk of mortality.[6]

Typical for the condition is a drop in hemoglobin level and diffuse infiltrates visible by chest X-ray (CXR) or high-resolution chest computed tomography (CT, Figure 2).[9] Elevated single breath diffusing capacity for carbon monoxide reflect increased availability of hemoglobin within the alveoli which is measured by Diffusing capacity or transfer factor of the lung for carbon monoxide (DLCO).[10] Some information of risk factors associated with the development of DAH in SLE patients is available. Active disease with a SLE disease activity index (SLEDAI) above 10, serologically high titers of anti-dsDNA, thrombocytopenia, C3 hypocomplementemia, leucopenia, capillaritis and ICs found in biopsies is associated with increased risk of DAH, but none of these factors are disease specific.[6] Hemosiderin laden macrophages found in bronchoalveolar lavage fluid (BALF) often appear only after several days of disease[6] An increased risk for DAH has been reported during active renal disease, especially when manifesting as lupus nephritis. Such an association has been described in up to 80% of cases.[7] Histological analysis of kidney biopsies from such patients often describes class III or IV lupus nephritis.[11]

Infections can be associated with DAH and should be ruled out as a cause during the differential diagnosis. DAH patients with concurrent infections generally show a poor prognosis.[7, 12] Some reports have also indicated that DAH can occur as a side effect of immune suppressive treatment.[13] In our clinical practice we have experienced in four occasions that SLE patients developed DAH after pulse with steroids (unpublished observation). We speculate that this can have occurred either due to the already severe disease level of these patients and/or that

subclinical DAH might have been present. It is not known in these cases whether initiation of steroid therapy could have been a factor for the pathology experienced.

Pathogenesis

Experimental studies have indicated that recruitment of macrophages and neutrophils in the lung occur few days before the onset of alveolar hemorrhage.[14] Associated with the onset of the disease is a drop in complement factors and hemoglobin. Development of DAH pathology has been described both as a consequence of inflammation and capillaritis and due to a non-inflammatory bland alveolar hemorrhage. For the occurrence of both types of hemorrhage, deposition of ICs in the alveolar capillaries seem to be required.[11] A predominant neutrophil interstitial infiltration outside the capillaries, inflammation and necrosis of the alveolar and capillary walls is common during inflammatory capillaritis. One study identified capillaritis in 67% of available biopsy samples.[15] Accumulated neutrophils undergo cytolysis with release of neutrophil extracellular traps (NETs) and cytotoxic proteins leading to loss of integrity of the alveolar-capillary basement membrane.[16] This destruction result in leakage of RBCs into the alveolar space (Figure 1, right).[9] The exact initiation factor for the capillaritis is not known. Antiphospholipid antibodies could be one initiating factor and has been reported in some cases of DAH.[17, 18]

Non-inflammatory bland hemorrhage has also been described and has in some studies been suggested to be a more common cause of DAH.[11] Bland hemorrhage is associated with predominant monocyte infiltration in the alveolar wall.[11] Also this form is associated with deposition of ICs on the arterial wall.[11] A study reported increased apoptosis in the alveolar wall which could explain the hemorrhage process. The origin of the apoptotic cells was unclear but could be alveolar epithelial cells. The apoptosis was accompanied by macrophages, presumable for removal of apoptotic debris and for prevention of inflammation (Figure 1, left).[11] These macrophages had high expression of myeloperoxidase probably as a consequence of phagocytosis of erythrocytes. No neutrophils were found present in the lesions.[11] An alternative suggestion has been proposed to explain the high prevalence of non-inflammatory DAH; Bland hemorrhage might be associated with a widely scattered, difficult to detect, capillaritis, hence, indicating ongoing complement or IC mediated inflammation also in these cases.[11, 19] It is not known if the epithelial cell-derived apoptotic bodies are inefficiently removed due to the

phagocytosis defect that has been reported for SLE.[1] Also a third cause of DAH has been described; diffuse alveolar damage, involving edema of alveolar septa and formation of hyaline membranes.[19]

An animal model of pristane induced lupus with DAH highlighted the importance of B cells mediated ICs for pathology. Also complement was important for disease development but neutrophils were dispensable for pathology in this model. DAH pathology occurred due to complement receptor mediated apoptotic body phagocytosis by monocytes as in bland hemorrhage pathology. The anti-inflammatory cytokine interleukin (IL)-10 was found to dampen the symptoms in this model.[20]

Diagnosis

A careful history and physical examination are required to establish the diagnosis of DAH. A combination of physical examination, radiographic analysis of the lung, blood and BALF analysis will provide evidence for the diagnosis. Upon examination, the rapid onset of dyspnea, hypoxemia, occasionally with hemoptysis could suggest DAH. In addition symptoms such as cough, paleness, thoracic pain, hypotension, and pulmonary crackles might be early manifestations of the condition.[21] It is recommended to perform bronchoscopy immediately and to retrieve consecutive BALF fluids. BALF from patients with DAH is usually hemorrhagic in nature. Equal to of more than 20% hemosiderin laden macrophages in BALF is criterion for DAH but might take 48 to 72 hrs to appear.[9] Accumulation of these cells can occur due to other causes such as infections, acute exacerbations of interstitial pulmonary fibrosis and idiopathic pneumonia syndrome.[22] Collected BALF samples should undergo cultures and analysis for bacterial, fungal, viral, and *Pneumocystis jiroveci* infections.[21] Infections as a cause of the hemorrhage has to be excluded as these are the most common cause of lung disease in SLE.[8] Infections with e.g. cytomegalovirus and *legionella* can lead to bland DAH and diffuse alveolar damage.[19, 23] It should be noted that fungi such as *candida albicans* is present in lungs of healthy individuals.

Blood analysis will provide information whether a drop in hemoglobin levels has occurred (drop by 1.5–2 g/dL), suggestive of alveolar hemorrhage and important for diagnosis. Lab analysis can also provide information of thrombocytopenia and C3 hypocomplementemia, associated with worse SLE and reported during DAH.[24] History of deficit in these two factors is also associated

with increased risk of DAH.[18]

Radiological imaging including CXR and high-resolution chest CT scans provide important information to establish the diagnosis. The radiograph may show atypical findings with focal asymmetric bilateral areas of consolidation (Figure 2) or ground glass opacities.[25] Findings consisting of bilateral patchy infiltrates may however also be found in infectious etiologies and acute respiratory distress syndrome.[19, 25] Ground glass opacities might occur during pulmonary edema, infections, interstitial pulmonary fibrosis or by other causes.[26] Lupus DAH patients CXR scans might also have normal and close to normal appearance. Due to the instability of the patient, procedures to obtaining lung biopsies are risky. Biopsying the lung may be considered in cases where the patient condition is stable and the cause of DAH is unclear.

The combination of dyspnea, drop in hemoglobin, elevated single breath diffusing capacity for carbon monoxide and pulmonary interstitial or alveolar infiltrates will alert for the possibility of DAH. This should particularly be considered for patients with active SLE.[21]

There are a number of conditions with similar presentation that has to be excluded. Clinical signs may be similar to heart failure, infections or acute lupus pneumonitis.[8] I.e. left ventricular failure due to myocarditis or non-bacterial thrombotic endocarditic can cause acute pulmonary syndrome associated with hemoptysis and new pulmonary infiltrates in SLE patients.[27] However, it should be mentioned that diastolic dysfunction, haemodynamic alterations, pulmonary overload and hyperazotaemia can be a consequence of the rapid accumulation of red blood cells within alveoli in lupus DAH.[28] Pulmonary-renal syndrome, associated with SLE or other autoimmune diseases is another cause of DAH-like pathology. Uremia due to lupus nephritis can lead to pneumonitis and diffuse alveolar damage. Localized pulmonary hemorrhage can occur unrelated to SLE due to chronic bronchitis, bronchiectasis, congestive heart failure with acute pulmonary edema, tumors, blunt trauma or drugs.[29]

Management of DAH in SLE

There is a paucity in randomized clinical trials to better treat patients with SLE associated DAH and to management remains individualized across different medical centers.[18] The most frequently used therapies are methylprednisolone, cyclophosphamide and plasmapheresis.[30] One study analyzing 140 patients (172 episodes) found that corticosteroids were most frequently used (98%) followed by cyclophosphamide (54%), plasmapheresis (31%), azathioprine (7%),

intravenous immunoglobulin (IVIG, 5%), mycophenolate (3%), the B cell targeting therapy rituximab (RTX, 6%), and stem cell transplantation (2%).[15]

The usage of methylprednisolone is recommended until cessation of the hemorrhage. Empirical studies have indicated that the survival rate is higher for patients receiving a dose of methylprednisolone above what is conventionally used (4-8g instead of 3g).[31] Also treatment using cyclophosphamide has been shown to improve survival[15]. In another study cyclophosphamide was given to patients that required mechanical ventilation. In this study mortality rate was high (70%) and likely due to the severity of the cases.[7] The combination of methylprednisolone and cyclophosphamide is associated with increased survival rate.[24] Cyclophosphamide treatment is associated with better survival rate than other treatment options such as plasmapheresis [15] (see below). In addition to therapies mentioned, several studies have included antibiotics empirically (see the next section).[13]

Treatment of infections

As immunosuppressive therapy is the preferred treatment for DAH and pulmonary symptoms in SLE often is due to infections, antibiotic therapy is highly recommended until microbial cause of the disease has been excluded.[32] Infections are responsible for 22-25% of SLE patients deaths which has in part been attributed to the therapies used.[33] Hence, untimely usage of immunosuppressants can facilitate microbial growth leading to disease exacerbation.[19, 34] When infection is suspected, broad-spectrum antibiotics should be considered as this might reduce mortality.[2]

Rojas- Serrano et al. performed a study to determine infection rate in 13 SLE patients diagnosed with DAH.[35] Evaluation by bronchoscopy and cultures for bacteria, fungi, and mycobacteria was performed during 14 episodes. The assessment was performed during the first 48 hours of admission and infections were demonstrated in 57% of the cases, including *Pseudomonas aeruginosa, Serratia marcescens, Citrobacter freundii,* and *Aspergillus fumigatus.*[35] Martínez-Martínez et al. evaluated factors associated with infections in patients with DAH and SLE, and found such an association with hypocomplementemia and mechanical ventilation.[12] These findings support initiation of broad spectrum antibiotics early and that patients should undergo continuous surveillance for possible emerging infections. Therapies targeting viral, *P jiroveci* pneumonia, tuberculosis and fungi - should be considered based on findings from the

initial evaluation and from BAL result.[34]

IVIG has been considered in a few cases for patients with active infection. This would be as an adjuvant therapy while waiting for response to antibiotic treatment. In some studies IVIG did not increase survival rate.[15] Such therapy should be considered on an individual case basis, dependent of clinical scenario and disease manifestations.

Plasmapheresis

Plasmapheresis is an efficacious therapy for causes of DAH such as ANCA-associated vasculitis, cryoglobulinemic vasculitis, anti-glomerular basement membrane disease and APS.[21, 36] The therapy is thought to remove pathogenic ICs that are responsible for vascular inflammation.[21] IC's and pathological antibodies are probably responsible for capliaritis in lupus DAH. DAH due to potentially IC independent bland hemorrhage has also been described. One study found IC deposition in lung tissue in five of six of SLE patients with DAH while others have suggested that this deposition is less frequent.[15, 19]

Plasmapheresis as treatment strategy has been chosen for cases where patients responded inadequately to high-doses of corticosteroid and cyclophosphamide therapy.[37] A recent large study analyzed 66 patients with autoimmune diseases subjected to plasmapheresis. Eleven of these were cases of lupus with DAH. Of all patients with DAH treated (total 20) 55% showed improvement.[38] In two other studies plasmapheresis showed similar survival rate as in patients that did not undergo this intervention.[15, 30] The authors reported presence anti-dsDNA antibodies in plasma in 75% of cases suggesting that plasmapheresis could have been a suitable option. The authors speculated that the lack of efficacy could be either because anti-dsDNA is not the cause of DAH or that the antibodies were already bound to the alveolar membrane and could not be removed by the treatment.[15] Another study reported plasmapheresis treatment of 16 of 47 lupus DAH patient with a resulting mortality of 29.2% of the 47 cases. In this study plasmapheresis treatment was associated with death (odds ratio, 7.62). Patients subjected to plasmapheresis did however have more severe disease.[38] Other small studies have described efficacy and increased survival rate when patients were treated with plasmapheresis.[37]

Plasmapheresis is therefore a good treatment option for Lupus DAH patients. There seem to be some variability in treatment response which might be related to the severity of the disease.[38] Further studies to gain knowledge of the underlying etiology for DAH in SLE would be helpful

to identify whether there might be subgroups that are more suitable for this intervention.

Rituximab (RTX)

RTX is a chimeric monoclonal ab that recognizes CD20, a surface receptor on B cells. B cell death is triggered when the ab binds the receptor. RTX is used in treatment of certain autoimmune diseases including cases of SLE.[39] The therapy reduces levels of anti-nuclear abs, ICs and cytokines produced by the B cells. RTX has been described in several case reports to successfully treat DAH. The biologic has been used without addition of cyclophosphamide but never without corticosteroids.[30] RTX treatment was reported to result in superior survival rate comparing to Plasmapheresis.[30] However in one study with three cases treated with RTX, none of the patients survived.[12]

As mentioned before, B cell activation is an important factor in SLE pathology. In some but perhaps not all DAH cases, the disease might be mediated the deposition of ICs in the alveolar capillaries.[19] During acute DAH there might not be sufficient time for the RTX therapy to suppress IC generation. B cells include however different subsets and can present antigens and produce and release inflammatory cytokines which might explain RTX's efficacy for some patients.[30, 40] B cell depletion therapy is a good option, with late action mechanism and must be used in combination with other therapies.

Experimental treatment strategies for DAH

A few approaches have been described for treatment of lupus DAH that are yet to be considered in general practice. These include delivery of rFVIIa by the intrapumonary route, utility of Extracorporeal membrane oxygenation support (ECMO) and Mesenchymal stem cells (MSC) transplantation. Cases reported with these treatment strategies are summarized in Table 1.

Intrapulmonary rFVIIa

Tissue factor is an important regulator of the extrinsic coagulation cascade.[29] The factor is expressed on smooth muscle cells and other cells present on the abluminal side of blood vessels. When damage or leakage occur to the blood vessel, factor VII/VIIa (FVII/VIIa, either prebound or delivered from plasma) activates TF, resulting in conversion and activation of factors of the coagulation cascade, leading to blood clotting. Patients with the bleeding disorder haemophilia

are successfully treated with recombinant FVIIa (rFVIIa) to prevent uncontrolled bleeding.[41] As the lung contains high levels of TF usage of rFVIIa has been considered in individual SLE DAH cases with severe uncontrolled bleeding.[41, 42] The protein has been administered both intravenously and by intrapulmonary delivery using a bronchoscope or a nebulizer. Intrapulmonary delivery was considered as it would increase the chance of rFVIIa to meet TF expressed in the alveolar interstitium and reduce chance of leakage of the factor systemically.[29] Treatment of patients with rFVIIa particularly if administered intravenously, implicates the risk of development of harmful thrombosis which has to be carefully monitored. In small case series this therapy has been successful.[3, 42] Certain patient groups should be excluded such as the ones with liver disease, history of myocardial infarction, stroke or with thrombophilic conditions.[41]

Extracorporeal membrane oxygenation support

During DAH, despite the patient being supported by mechanical ventilation, the rapid accumulation of red blood cells within alveoli can result in refractory hypoxemia. The resulting increase in lung compliance and worsening pulmonary hypertension can potentiate cardiogenic shock from acute right ventricular failure.[28] ECMO might be considered to provide adequate amount of alveolar gas exchange to sustain life for such deteriorating patients. ECMO provide oxygenation of the blood outside the body. Blood can either be led from a common femoral vein to the oxygenator and be returned to the femoral artery (arterial – venous ECMO) or to the right internal jugular vein (venous – venous ECMO), the latter method not providing cardiac support. A complication when using ECMO is that patients should be treated with intravenous heparin to prevent thrombus formation from clotting off the oxygenator which might result in increased alveolar bleeding. However, recent technical advances in the extracorporeal circuit have allowed for the reduction or omission of systemic anticoagulation in this sub-group of patients.[28] During extraordinary circumstances, such as cardiac compromise, ECMO might therefore be considered to maintain life support. ECMO has been used successfully in some DAH cases but in others without increasing the survival rate of the patients.[28, 30] A further evaluation of the safety and efficacy of ECMO for SLE DAH, perhaps in the form of a controlled trial, should be appreciated.

Mesenchymal stem cells transplantation as therapy for DAH

MSCs are multipotent cells able to differentiate into various mesenchymal derived lineages. These cells show low immunogenicity and have the ability to reduce immune responses. Although with some controversy, application of MSCs has been considered for treatment of various conditions including graft-versus-host- and autoimmune diseases.[43] In the aim to reduce inflammation for DAH patients unresponsive to other therapies, umbilical cord derived MSCs as single bolus intravenous infusion (1-2 x 10^6 cells / kg bodyweight) has been used in experimental series. The therapy was given in additions of daily doses of 40mg methyl prednisolone and resulted in good response. Oxygen saturation was improved, and complete resolution of lung infiltrates was seen after 2-3 weeks. Blood hemoglobin did however not return to normal levels until several months after the MSC infusions.[43, 44]

Exactly how MSCs promote DAH resolution is unknown. The cells have been suggested to augment various regulatory immune cells including regulatory T and B cells thereby facilitating an anti-inflammatory environment. It has also been shown that the MSCs have the ability to differentiate into novel alveolar epithelial cells. [43] MSC therapy as a treatment option for DAH in SLE remains at the experimental stage in small case series.

Final words and conclusion

The mortality of DAH in SLE has been reduced over recent years. This is likely due to increasing knowledge of the disorder and the application of novel technologies. However mortality still remains unacceptable high. Patient under suspicion of DAH requires a prompt investigation to exclude unrelated causes with similar presentation. It is for example a delicate balance between initiating early treatment with immunosuppression or treating potential underlying infections with similar pathology.[19] Alveolar hemorrhage caused by infection but treated with immune suppression can lead a worsen status of the patient.

Studies, often in the form of single case studies, are gathering incremental knowledge of this syndrome. Hence, the underlying cause for DAH concomitant to SLE seems to be slightly different from the same pathology in other autoimmune diseases. Plasmapheresis is often efficacious and in cases when not, might be dependent of severity of the disease. It is not clear whether different causes to the pathology exist, as suggested in figure 1, involving different cell types which could explain cases when plasmapheresis is not helpful.[1, 11]. An animal model of SLE DAH has pointed to the importance of IC formation and B cells in the pathology.[20] The

experimental study showed the importance in IL-10 in prevention of DAH. Regulatory B cells are known producers of IL-10 that are decreased in SLE.[45] The fact that RTX can be a viable treatment option is further shining the light on B cells.

For the best chance to gain a better view of the DAH etiology/ies an organized multicenter study, to be able to requite sufficient number of patients, is warranted. Biopsies when possible would give an insight of the relation between capillaritis and bland hemorrhage that has been reported (Figure 1). Also information of immune cells, including B cells, T cells, neutrophils and monocytes/macrophages in blood and biopsies could be assessed in such a study (figure 1).

Evaluation of therapies such as RTX and MSCs should be undertaken in randomized trials.[18] For SLE in general and particularly for SLE DAH there is an unmet need for novel therapies.[46] In DAH, a DNA degrading enzyme, DNase delivered bronchially to remove neutrophil NETs, and for removal of ICs, an humanized effector-null FcγRIIA ab, might be such novel treatment strategies to consider.[16, 47]

For the benefit of the patients, for establishment of improved guidelines, the formation of a committee, containing individuals from diverse specialties such as from rheumatology, intensive care, nephrology, pulmonology, hematology and infectious diseases, would be helpful.

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Table 1: Cases Reported of SLE with DAH treated with recombinant activated clotting factor VII, extracorporeal membrane oxygenation or umbilical cord mesenchymal stem cells transplantation.

	Author	Case	Received Therapy	Outcome
rFVIIa	Esper et al 2014 [3]	37 F	MTP X3, RTX, rFVIIa	Survived
	Alabed 2014 [42]	37 F	MTPX3, CPM, rFVIIa	Survived
	Pathak et al 2015 [41]	2 Cases	Steroids, Plasmapheresis, rFVIIa	Both Survived
ECMO	Wang et al 2018 [30]	3 Cases	MTP, CPM, Plasmapheresis, ECMO	All 3 died
	Pais F et al 2017 [28]	38 F	MTP, Plasmapheresis, ECMO	Survived
	Pacheco Claudio et al 2014 [48]	33 F	MTP, CPM, ECMO	Died
		36 M	MTP, CPM, ECMO	Survived
	Kimura et al 2015 [49]	14 F	MTP, CPM, Plasmapheresis, IVIG, ECMO	Survived
	Patel et al 2014[50]	28 F	MTP, CPM, RTX ECMO	Survived
MSCT	Liang J et al 2012 [43]	19 F	MTP, IVIG, UC-MSCT	Survived
	Shi D eta al. 2012 [44]	4 Cases	Several regimens + UC-MSCT	All 4 improved

Abbreviations: F: female, M: male, rFVIIa: Recombinant activated clotting factor VII, MTP: Methylprednisolone, RTX: Rituximab, CPM: Cyclophosphamide, ECMO: Extracorporeal membrane oxygenation, IVIG: Intravenous immunoglobulin. UC-MSCT: umbilical cord mesenchymal stem cells transplantation.

Figure legends

Figure 1. Diagram suggesting pathologies that are leading to diffuse alveolar hemorrhage. Two reported mechanisms are outlined. **To the left** is shown mechanism of bland hemorrhage, which involves apoptosis of cells associated with the alveoli. The cells undergoing apoptosis might be the epithelial cells. The cells destruction might be driven by ICs or by another mechanism. Apoptosis / band hemorrhage is leading to leakage of red blood cells (RBC) into the alveolar space. Macrophages (MQ), located in the alveolar lumen and monocytes (Mc) located in the alveolar wall, are phagocytosing apoptotic bodies (Ab). **To the right** is shown IC, complement, capillaritis and neutrophil (Ne) mediated DAH. ICs bind endothelial cells inducing an immune response. Tissue infiltrating neutrophils are undergoing necrosis, leading to NET formation and destruction of capillary and alveolar basement membrane. The damage facilitates leakage of blood into the alveolar space. Hemosiderin laden macrophages are present in the alveolar space. B cells (Bc) might be involved both by providing antibodies for IC formation and inflammatory cytokines driving the disease.

Figure 2. Computed tomography image of bilateral alveolar infiltrates suggestive of diffuse alveolar hemorrhage. The patient attended the Royal Hospital, Muscat, Oman. Diffuse, patchy infiltrates are visible in both lungs (arrows). The patient was treated with steroids, IVIG, Plasmapheresis and RTX. The patient survived the episode.

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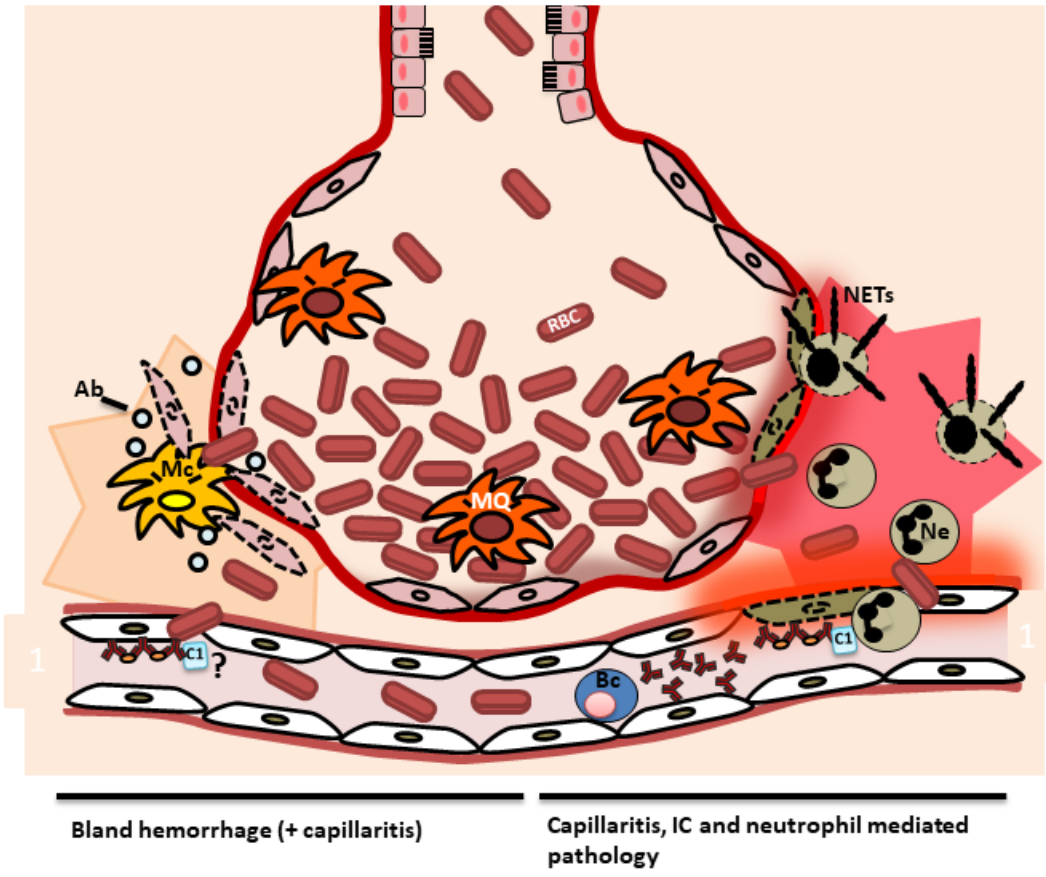

Figure 1. Al-Adhoubi NK, Bystrom J, Lupus and Diffuse Alveolar Hemorrhage, etiology and novel treatment strategies

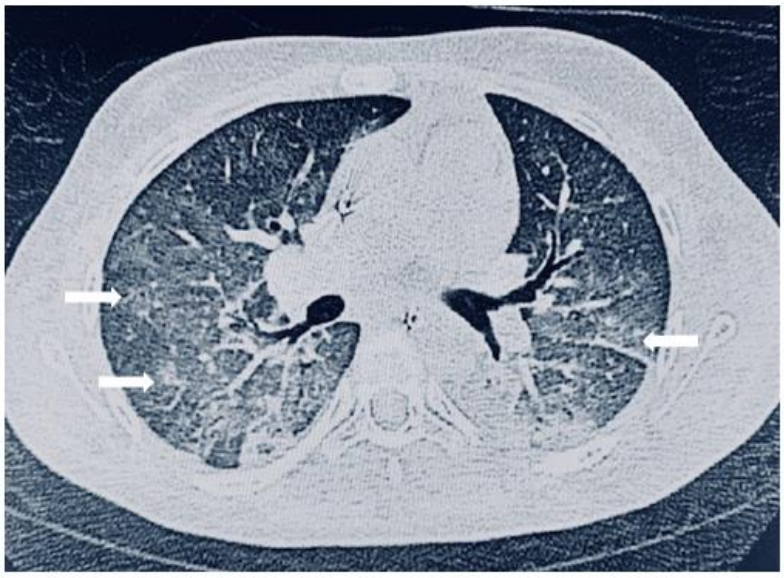

Figure 2. Al-Adhoubi NK, Bystrom J, Lupus and Diffuse Alveolar Hemorrhage, etiology and novel treatment strategies