

Alveolar Hemorrhage in Vasculitis: Primary and Secondary

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ABSTRACT

Diffuse alveolar hemorrhage (DAH) in primary and secondary vasculitis occurs when capillaritis is present. The diagnosis of DAH is considered in patients who develop progressive dyspnea with alveolar opacities on chest imaging (with density ranging from ground glass to consolidation) that cannot be explained otherwise. Hemoptysis, a valuable sign, is often absent. A decline of blood hemoglobin level over a few days without hemolysis or any hemorrhage elsewhere should be an alert for DAH. Bronchoalveolar lavage, retrieving bright red fluid, is the best diagnostic clue. Lung biopsy is not recommended. A search for anti-neutrophil cytoplasmic autoantibodies (ANCA) is mandatory. Once DAH is diagnosed and hemodynamic as well as infectious causes have been excluded, ANCA-associated vasculitis is taken into account (mainly microscopic polyangiitis or Wegener granulomatosis, and, exceptionally, Churg-Strauss syndrome). Drug-induced DAH, especially antithyroid drugs such as propylthiouracil may be coupled with ANCA. Isolated DAH with capillaritis with or without ANCA is rare. DAH in systemic lupus erythematosus is either associated or not with capillaritis. Treatment of DAH should target the underlying disorder. In the primary vasculitides, corticosteroids and immunosuppressants, especially cyclophosphamide, are the mainstay of therapy, but plasma exchange, particularly in severe DAH, is the rule, although evidence of its effectiveness is awaited.

KEYWORDS: Alveolar hemorrhage, vasculitis, drug-induced lung disease, connective tissue disease

Diffuse alveolar hemorrhage (DAH) is characterized within alveoli by the presence of red blood cells deriving from alveolar capillaries and venules. It differs from alveolar filling, with blood emanating from localized bleeding, usually of bronchial origin, especially in patients with impaired hemostasis (e.g., receiving excess anticoagulation). Although DAH may be part of diffuse alveolar injury of any origin, it may arise from the inflammation of capillaries associated with neutrophils (capillaritis).¹⁻³ Capillaritis may be

present in every type of DAH with vasculitis but also in disorders that are not classified as vasculitis, such as anti-basement membrane antibody (ABMA) disease, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA).³ Other mechanisms may intervene in the development of DAH (e.g., immune processes, such as ABMA disease in Goodpasture syndrome). Idiopathic hemosiderosis is defined by the absence of any detectable etiology, with DAH often recurring for years.

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Capillaritis leads to the injury of epithelial-endothelial cells and basement membranes with further flooding of the alveolar lumen by erythrocytes. Erythrophagocytosis and leukocytoclasia are common. Intra-alveolar hemosiderin-laden macrophages (siderophages) are conspicuous in the days following acute DAH and in chronic DAH.

When severe, diffuse DAH results in respiratory failure secondary to impaired oxygen uptake from alveoli filled with erythrocytes.

DIAGNOSIS OF DIFFUSE ALVEOLAR HEMORRHAGE

Clinical Manifestations and Signs

The clinical manifestations of DAH are often not specific (dyspnea, cough), and hemoptysis, which is characteristic, is not always present. They may develop insidiously or acutely over a few days.

Anemia, either acute or lasting for several weeks, is a common feature in DAH. Decreased hemoglobin or hematocrit levels over a few days without exteriorized bleeding are a major argument for DAH, especially if associated with increasing pulmonary alveolar opacities.

Fiberoptic Bronchoscopy and Bronchoalveolar Lavage

At fiberoptic bronchoscopy, blood is frequently seen originating diffusely from the distal airways, in the absence of any localized cause of bleeding. The diagnosis of DAH, whatever its cause, relies mainly on bronchoalveolar lavage (BAL), which is often increasingly hemorrhagic with serial lavage and the eventual bright red blood return of saline instilled within the distal airspaces. If saline return is frankly hemorrhagic from the start it does not clear with serial lavage. In mild DAH, the fluid is rose colored.

Whereas intact erythrocytes in alveolar macrophages are viewed as evidence of recent alveolar hemorrhage, occult and chronic alveolar hemorrhage derives from increased alveolar macrophage hemosiderin content (siderophages).

The Golde score is measured by counting Prussian blue-stained macrophages, with each cell graded from 0 to 4 (calculating a mean score of 100 cells), resulting in scores ranging from 0 to 400.⁴ Scores > 100, a value obtained by correlation with the histological diagnosis of DAH, are indicative of DAH.⁵ The Golde score, which is time consuming, correlates well with the more simple counting of siderophage percentages.⁶ Siderophage percentages $\geq 67\%$ are related to DAH with Golde score greater than 100. Percentages of siderophages $\geq 20\%$ at BAL are considered to establish the diagnosis of DAH.⁶ However, siderophages in excess of

20% may be found in various disorders, especially in immunocompromised patients.⁶

One must especially remember that alveolar siderophages are present in cardiac left ventricular failure with chronic pulmonary edema (siderophages were even called cardiac cells at the beginning of the 20th century).⁷ Therefore, we consider that the diagnostic value of siderophages in BAL is limited for the diagnosis of DAH.⁸

Microbiological investigations of BAL fluid should be systematic because DAH may accompany lung damage of infectious origin (eg, bacterial or *Pneumocystis jiroveci* infection). Cytological examination may exclude pulmonary hemorrhage from neoplastic metastatic disease.

Surgical Lung Biopsy

Lung biopsy is the diagnostic gold standard for DAH in vasculitis, showing both alveolar hemorrhage with erythrocytes filling the alveolar spaces and capillaritis (neutrophilic inflammation, with possible fibrinoid necrosis), and no pathological features suggestive of any other etiology. Capillaritis must be searched for attentively because "the ease with which one recognizes a vasculitis histopathologically is inversely related to the size of the blood vessel."² Capillaritis may be especially overshadowed by massive intraalveolar hemorrhage.⁹

Surgical (video-assisted) lung biopsy has become less necessary after anti-neutrophil cytoplasmic autoantibodies (ANCA) proved to be a major diagnostic tool.¹⁰ Currently, it has only limited indications and should not be undertaken in patients with severe respiratory failure. It is considered when BAL and biological investigations fail to define the etiology of DAH and when no extrapulmonary assessment provides an etiological clue. The main contribution of biopsy is to reveal the presence of vasculitis (capillaritis), as already described, or to exclude vasculitis with treatment consequences.

Exceptionally, linear alveolar labeling with ABMA may identify lung-limited Goodpasture syndrome in patients without circulating ABMA and/or characteristic immunohistochemistry features at renal biopsy. Immune complexes deposits may be found, especially in lupus, where DAH may¹¹ or may not¹² be associated with capillaritis.

Capillaritis may be seen on transbronchial lung biopsy,¹³ but the yield of this procedure is not known.

Imaging

Chest x-ray and high-resolution computed tomographic (HRCT) features in DAH are not specific.¹⁴⁻¹⁶ They consist of alveolar opacities ranging from ground glass to intense consolidation on air bronchogram (Figs. 1, 2, and 3). The opacities are bilateral, patchy or diffuse, with predominance in the perihilar areas and in the mid and

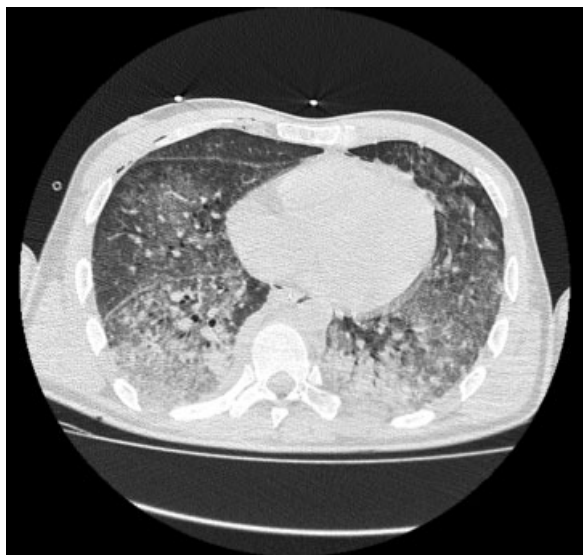


Figure 1 High-resolution computed tomography of the chest in a patient with diffuse alveolar hemorrhage and Wegener granulomatosis, demonstrating bilateral consolidation with air bronchogram and ground-glass opacity.

lower zones of the lungs. Some interlobular septal thickening may be present but should raise the possibility of left ventricular failure (e.g., cardiomyopathy related to vasculitis). Pleural effusion is not a feature of DAH. When bilateral pleural effusion is apparent, heart failure (or renal failure) must be suspected.

The evolution of opacities is often very rapid, with extension and increased density in uncontrolled DAH as well as rapid clearing (within 48 hours) and no sequelae as DAH regresses.



Figure 2 High-resolution computed tomography of the chest in a patient with diffuse alveolar hemorrhage and Wegener granulomatosis, demonstrating a diffuse pattern with ground-glass opacity and bilateral posterior consolidation.

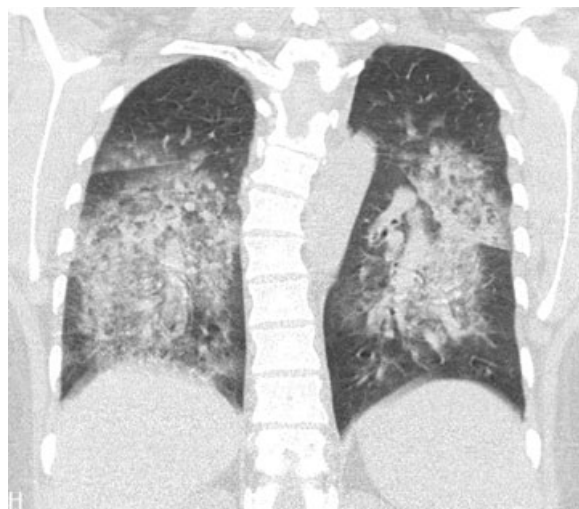


Figure 3 High-resolution computed tomography of the chest in a patient with diffuse alveolar hemorrhage and microscopic polyangiitis, demonstrating bilateral consolidation and ground-glass opacity with central distribution.

Evaluation of Gas Exchange

Increased carbon monoxide diffusion (uptake by intra-alveolar hemoglobin of erythrocytes) in recent (48 to 72 hours) DAH has served as a diagnostic tool but is not reliable and currently stands abandoned.

PaO₂ measurement and follow-up are warranted for referral, if necessary, to intensive care unit and ventilatory support. Serial hematocrit or hemoglobin measurement provides information on DAH control or progression.

ETIOLOGICAL DIAGNOSIS OF DIFFUSE ALVEOLAR HEMORRHAGE

Several conditions either associated with vasculitis (Table 1) or not (Table 2) should be considered in DAH. Systematic evaluation of hemostasis, drug intake, and epidemiological context (e.g., professional and geographical risk for leptospirosis) is necessary.

Previous systemic manifestations of disorders, such as vasculitis or connective tissue disease, may give an obvious etiological orientation.

The search for ANCA, with antiproteinase 3 (PR3-ANCA) or anti-myeloperoxidase (MPO-ANCA) specificity, ABMA, and antinuclear antibodies should be undertaken as soon as DAH is suspected, with results required within the shortest possible delay. In a series of 65 hospitalized patients diagnosed with ANCA-related vasculitis and pulmonary complications, all underwent lung biopsy showing that capillaritis was the most common pathological finding (60%). The majority of patients had pulmonary infiltrates on chest radiograph (58%) and ground-glass opacities on chest computed

Table 1 Diffuse Alveolar Hemorrhage with Pulmonary Capillaritis

PRIMARY CAPILLARITIS	SECONDARY CAPILLARITIS
ANCA-associated vasculitis*	Drug-induced DAH [†]
–Microscopic polyangiitis	Connective tissue disease
–Wegener granulomatosis	–Systemic lupus erythematosus [†]
–Churg-Strauss syndrome	–Scleroderma
–Isolated pulmonary capillaritis	–Polymyositis
Other	–Rheumatoid arthritis
–Henoch-Schönlein purpura	–Mixed connective tissue disease
	–Primary antiphospholipid syndrome
	Others
	–Goodpasture syndrome [†]
	–IgA nephropathy
	–Acute lung transplant rejection
	–Cryoglobulinemia

ANCA, anti-neutrophil cytoplasmic antibody; DAH, diffuse alveolar hemorrhage; IgA, immunoglobulin A.

*ANCA-associated vasculitis denotes a condition where ANCAs are present in a proportion of patients but may be absent in a given patient.

[†]Conditions where DAH often or usually occurs without capillaritis.

tomography (40%).¹⁷ ANCAs associated with DAH were more commonly MPO-ANCAs than PR3-ANCAs in a series of 88 patients with evidence of lung hemorrhage and nephritis, of whom 55 had ANCAs (with ABMA in seven), including 29 with MPO-ANCAs and 19 with PR3-ANCAs.¹⁸

In a series of 58 cases of pulmonary capillaritis proved by biopsy specimen, the majority (47%) consisted of isolated pulmonary capillaritis, microscopic polyangiitis (MPA), and Wegener granulomatosis (WG), followed by connective tissue disease (24%), especially SLE (14%).¹⁹

Table 2 Other Causes of Diffuse Alveolar Hemorrhage

HEMODYNAMIC CONDITIONS*
Left ventricle dysfunction (systolic and/or diastolic)
Valvular heart disease (especially mitral stenosis)
Atrial tumors
COAGULATION DISORDERS
Iatrogenic vitamin K deficiency
Thrombolytic drugs
Thrombocytopenia (of any cause)
DIFFUSE ALVEOLAR DAMAGE (OF ANY CAUSE)
INFECTION [†]
OTHERS [‡]
Lymphangioleiomyomatosis (sporadic or associated with tuberous sclerosis)
Pulmonary hypertension in veno-occlusive disease/pulmonary capillary hemangiomas
IDIOPATHIC HEMOSIDEROSIS

*Characterized by increased pulmonary capillary pressure.

[†]Especially leptospirosis, which may further present as pulmonary-renal syndrome.

[‡]Conditions where some chronic diffuse alveolar hemorrhage (DAH) is present but only exceptionally with clinically significant DAH.

Systematic renal investigation is mandatory because pulmonary-renal syndrome with DAH and rapidly progressive glomerulonephritis are usual manifestations of small vessel vasculitis (more rarely of Goodpasture syndrome).

Vasculitis was the etiology in 25 (26%) in a series of 97 patients with DAH. The following most common cause (22 patients) was increased pulmonary capillary pressure (which must thus systematically be considered in any patient with DAH or suspected DAH).²⁰

In 76 patients from the same group,²¹ including 32 with DAH deemed to be due to vasculitis, four parameters independently associated with immune-related DAH were identified: onset of respiratory symptoms ≥ 11 days, fatigue and/or weight loss during the month prior to presentation, arthralgia or arthritis, and proteinuria ≥ 1 g/L.

Vasculitis was causative in seven out of a series of 89 patients with severe respiratory failure due to DAH, with ANCA disease in five.²²

DRUG-INDUCED VASCULITIS WITH DIFFUSE ALVEOLAR HEMORRHAGE

As iatrogenic DAH requires immediate withdrawal of an incriminated drug, it should be taken into account first. Several drugs may evoke vasculitis with ANCA and/or capillaritis on lung biopsy. An exhaustive list of drugs that may cause DAH is available on www.pneumotox.com.

The prevalence of drug-associated, ANCA-positive vasculitis was assessed in 30 patients who had anti-MPO titers more than 12 times the median in a series of 250 patients with MPO-ANCAs.²³ Ten (33%) had been exposed to hydralazine and three (10%) to propylthiouracil (PTU). Five other patients (17%) had been subjected

to other drugs (penicillamine, allopurinol, sulfasalazine). Antibodies to elastase and/or lactoferrin were present in 9/10 patients treated with hydralazine. Interestingly, both MPO-ANCAs and PR3-ANCAs were found in some patients.²⁴ The coexistence of MPO-ANCAs with antielastase and/or antilactoferrin antibodies is characteristic of vasculitis associated with hydralazine or PTU exposure, an observation reported previously.²⁵

The prevalence of ANCAs in patients administered PTU ranges from 4.1 to 64%.²⁶ In a series of 46 patients with ANCAs, 10.3% continued to show ANCA positivity 2 years after withdrawal of PTU treatment.²⁶ Anti-MPO antibodies in patients with PTU-induced vasculitis might recognize restricted epitopes of the MPO molecule.²⁷

Overt systemic vasculitis with severe DAH and acute capillaritis at lung biopsy as well as anti-MPO-ANCAs were reported in an 18-year-old female receiving methimazole for hyperthyroidism.²⁸ She had previously received PTU on and off for 2 years. Both methimazole and PTU contain a thionamide group, and sensitization to one drug may precede vasculitis induced by the other drug. In a patient with a history of agranulocytosis with methimazole in previous years, vasculitis developed on PTU exposure.²⁴

Drugs associated with DAH and vasculitis (i.e., with capillaritis at lung biopsy and/or ANCAs and/or crescentic necrotizing glomerulonephritis, resulting in pulmonary-renal syndrome) comprise hydralazine,^{23,29} PTU,³⁰⁻³⁷ carbimazole,^{28,38} methimazole,³⁹ penicillamine,^{23,40} allopurinol,²³ and all-trans-retinoic acid.⁴¹

Only reports of established DAH with capillaritis on lung biopsy and/or the presence of ANCAs have been described here. In other cases of drug-induced DAH, lung biopsy did not show capillaritis. Because lung biopsy is not always done in cases of suspected drug-induced DAH, it is likely that some of these drugs may occasionally induce DAH with capillaritis. In most of these cases, improvement followed discontinuation of the drug.

PRIMARY VASCULITIDES

Microscopic Polyangiitis

MPA is a nongranulomatous and noneosinophilic small vessel vasculitis associated with ANCAs (especially MPO-ANCAs). Renal involvement with necrotizing glomerulonephritis is present in almost all patients. The characteristic pulmonary manifestation is alveolar hemorrhage resulting from capillaritis.

The prevalence of DAH in MPA varies from ~10 to 30%, depending on the diagnostic criteria of DAH and the medical specialty in published series (internal medicine, nephrology, pulmonology).⁴²⁻⁴⁶ In addition, DAH is not always clearly individualized in studies of

series where only "pulmonary involvement" is mentioned.^{47,48} Several studies suffer from a rather poor definition of DAH. For example, in a retrospective analysis by the European Vasculitis Study Group, including 387 patients with ANCA-associated vasculitis, DAH diagnosis was defined only by hemoptysis and/or pulmonary infiltrates.⁴⁹ With this rather loose definition, the prevalence of DAH was 24% at presentation. The validity of this prevalence is clearly questionable.

In a series of 85 patients with MPA,⁴³ DAH was observed in 10 patients (and part of pulmonary-renal syndrome in eight), with hemoptysis preceding the other manifestations of vasculitis by several weeks or months. "Frank pulmonary hemorrhage" was reported in 10 out of 34 patients with MPA (29%),⁴² of whom four required ventilation (three died from hypoxia within 2 weeks without responding to treatment). In a series of 107 ANCA-positive patients with necrotizing and crescentic glomerulonephritis, 69 presented evidence of MPA, with "pulmonary involvement" in 36%.⁴⁸ The relative risk of death was 8.65 times greater in patients with pulmonary hemorrhage. The relative risk of pulmonary hemorrhage was no different by ANCA pattern.

MPA characteristically presents as pulmonary-renal syndrome but may occur with predominant or exclusive involvement of either the kidney or the lung.⁵⁰ From a practical point of view, minor involvement of either organ should be carefully followed up (to avoid the development of silent glomerulonephritis with further chronic renal failure or massive alveolar hemorrhage with respiratory failure, respectively). One must also be aware of possible DAH developing in patients with renal failure once on hemodialysis and off immunosuppressants. In a study of 198 patients with ANCA-associated vasculitis,⁵¹ 66 progressed to end-stage renal disease, of whom five (with initial pulmonary and renal involvement) incurred severe pulmonary hemorrhage during follow-up. All five patients had MPO-ANCAs and were diagnosed as MPA. DAH could be controlled in four patients; however, one died of respiratory failure because of late referral.

The onset of DAH in MPA is rapidly progressive in the majority of patients, although it may follow a more insidious course with small occasional hemoptysis and fleeting ground-glass alveolar opacities on chest x-ray. Symptoms may precede the diagnosis of DAH by more than 52 weeks in about one fourth of patients.⁵²

In our series of MPA with DAH, anemia was severe with a mean hemoglobin level of 81 g/L.⁵² Renal involvement was present in 28/29 patients with a mean creatinine level of 407 $\mu\text{mol/L}$ and creatinine > 500 $\mu\text{mol/L}$ in six patients. In addition to corticosteroids and cyclophosphamide, plasmapheresis was used in seven patients with severe renal and/or respiratory failure. Three patients required mechanical ventilation, and eight were dialysed during the first week. Death from

massive or fulminant DAH occurred in two patients uncontrolled in the first 6 weeks of treatment, and in two patients from relapse several years after the first episode. Most patients with initial creatinine level > 250 $\mu\text{mol/L}$ eventually required dialysis. Seven patients had persistent alterations on pulmonary function tests. The overall mortality rate was 31% with death related to vasculitis (five patients) or side-effects of treatment.⁴ Deaths were more frequent in aged or mechanically ventilated patients.

In this series,⁵² the ear, nose, and throat (ENT) were involved in 31% of cases, consisting of epistaxis, sore throat, mouth ulcers, and hearing loss. Nasal ulceration was apparent in a patient with DAH and rapidly progressive renal failure.⁵³ Although her condition suggested WG, biopsies of the nasal septum showed small vessel leukocytoclastic angiitis, lung biopsy disclosed DAH with capillaritis, and renal biopsy revealed crescentic glomerulonephritis. ENT manifestations in MPA are distinct from those of WG (nasal perforation and saddle nose deformation are especially not present in MPA); however, one must emphasize that ENT involvement associated with DAH may occur in MPA.

Progressive obstructive airway disease has been occasionally reported in nonsmokers with systemic MPA and pulmonary capillaritis.^{54,55}

Wegener Granulomatosis

Whereas DAH is a characteristic feature of MPA, its prevalence in ANCA-associated, granulomatous, necrotizing, systemic vasculitis (Wegener granulomatosis) is more difficult to assess. Hemoptysis was observed in 12% of patients initially, in 30% during the course of WG,⁵⁶ and in 39% in our series.⁵⁷ However, hemoptysis in WG may result from causes other than DAH, especially bronchial involvement and parenchymal lesions with necrosis. The prevalence of DAH according to firm diagnostic criteria was thus only 8% in our series of pulmonary WG.⁵⁷ Pulmonary infiltrates with hemoptysis were reported in 12 out of a series of 155 patients with WG.⁵⁸

Focal capillaritis with hemorrhage was present in 7/20 lung biopsies from patients with WG containing otherwise typical granulomatous inflammation and vasculitis.⁹

DAH and diffuse alveolar infiltrates at chest x-ray were noted in a patient with previous purulent sinusitis and serous otitis media.⁹ Pulmonary biopsy in this patient showed extensive alveolar filling with erythrocytes and associated necrotizing capillaritis without granulomas. He was treated with cyclophosphamide but died a few days later. At autopsy, DAH was still apparent, and capillaritis could no longer be identified, whereas poorly circumscribed 3 to 4 cm nodules with central necrosis were found to consist of necrotizing

granulomas and multinucleated, giant cells, with further necrotizing granulomatous vasculitis in medium-sized pulmonary arteries and veins.

Other cases of granulomatous vasculitis associated with DAH have been discerned.⁵⁹⁻⁶³ DAH developed in two children with WG.^{64,65}

Conversely, capillaritis was seen in a series of all 36 patients with ANCA and DAH, but granulomatous inflammation was not present in any case, including eight with WG.⁶⁶

MPA with late emergence of WG has been reported.^{67,68} In 6/64 (9%) patients with initial MPA (including one patient with DAH), WG was later diagnosed (at a mean time of 42 months) by characteristic findings in the lungs, nasal mucosa, soft palate, and bronchi (at the time of developing WG, two patients had DAH, including relapse in one, with eventual death from diffuse pulmonary hemorrhage and refractory respiratory failure).⁶⁸

From the foregoing, it is clear that phenotypic (clinical-pathological-imaging) modulation may vary from granulomatous to small vessel (capillary) disease.

Isolated Diffuse Alveolar Hemorrhage with Capillaritis

Isolated pauci-immune capillaritis is small vessel vasculitis confined to the lungs without features of associated systemic disease.⁶⁹

Isolated DAH ANCA-negative, biopsy-proven pauci-immune capillaritis has been reported in a series of eight patients (with upper respiratory tract symptoms prior to DAH onset in seven). The outcome was favorable with corticosteroids and cyclophosphamide.^{70,71}

Isolated DAH with capillaritis has been observed in MPO-ANCA-positive patients⁷² and cytoplasmic (C)-ANCA-positive patients.⁷³ Negative pressure following upper airway obstruction has been suspected to contribute to DAH with perinuclear (P)-ANCA-associated capillaritis.⁷⁴

Churg-Strauss Syndrome

Initially described by the eponym authors as widespread, necrotizing vasculitis in an autopsy series, Churg-Strauss syndrome (CSS) is increasingly considered as a dual condition with distinct phenotypes.⁷⁵ The most common phenotype is that of eosinophilic asthma with further eosinophilic tissular disease (including eosinophilic pneumonia and myocarditis) with ANCA not present in the majority of patients. The other phenotype is characterized by further vasculitis and ANCA (MPO-ANCA) in most cases. Alveolar hemorrhage seems to be more common in the latter vasculitic phenotype. Alveolar hemorrhage in CSS is preferentially associated with other manifestations of small vessel

vasculitis of the skin and kidneys. The kidneys are involved in less than one quarter of patients with CSS, contrasting with the higher prevalence of necrotizing glomerulonephritis in WG and MPA. Alveolar hemorrhage is usually not mentioned in pathology papers on CSS.^{76,77}

The rarity of DAH in CSS is due to several reasons, the first being the true relative rarity of small vessel–necrotizing vasculitis in CSS. Another reason is that mild-to-moderate alveolar hemorrhage may be overlooked because it is confused with more common pulmonary alveolar infiltrates related to eosinophilic pneumonia in CSS. Furthermore, both DAH and eosinophilic pneumonia may clear rapidly with corticosteroids. BAL is not systematically undertaken in CSS patients with pulmonary infiltrates and peripheral elevated eosinophilia because the finding of alveolar eosinophilia may not alter clinical management of the patient. Thus mild alveolar hemorrhage may be missed in some patients. One must be aware that in patients with severe CSS cardiomyopathy, pulmonary edema may also be confused with DAH of vasculitic origin.

Descriptions of DAH in CSS are usually limited or scarce. In an Italian series of 93 patients with CSS,⁷⁸ pulmonary hemorrhage (with criteria not precisely defined) was reported in seven out of 35 ANCA-positive patients (20%) and none out of 58 ANCA-negative patients (0%, $p < 0.001$). In this series, renal involvement was apparent in 51% of ANCA-positive patients and in 12% of ANCA-negative patients ($p < 0.001$). In a further series investigated by the same group,⁷⁹ about one quarter of patients with CSS had renal abnormalities. All 11 patients with necrotizing crescentic glomerulonephritis were ANCA-positive, with one long-term dialysis-treated patient with PR3-ANCA eventually dying of DAH.

Comparison of HLA-DRB4-positive and HLA-DRB4-negative patients disclosed a trend toward higher prevalence of “vasculitis symptoms” that identified the ANCA-positive subset of CSS (i.e., purpura, alveolar hemorrhage, and mononeuritis multiplex) in HLA-DRB4-positive patients.⁸⁰

In a French series of 112 patients with CSS,⁸¹ moderate DAH was observed in 3/43 ANCA-positive patients and in 5/69 ANCA-negative patients (diagnosis of DAH was assessed by BAL in only three of these eight patients). The prevalence of DAH was not mentioned in a U.S. series of 91 patients.⁸² It was present in only one out of 32 patients in a Spanish series,⁸³ and one out of 19 patients in an Italian series.⁸⁴

Severe alveolar hemorrhage in CSS has only exceptionally been reported.^{85–88} In two patients with severe DAH⁸⁵ hemoptysis was severe, and PaO₂ was 5.3 kPa on air in one of them. The pulmonary manifestations were associated with severe systemic vasculitis. Widespread cutaneous vasculitis and severe

mononeuritis were found in one patient, whereas no overt systemic involvement was noted in the other patient. Rather surprisingly, the kidneys were not affected in the former, and renal function was only mildly abnormal in the latter. Both patients improved with corticosteroids and immunosuppressants (with further plasma exchanges in the patient with systemic vasculitis).

Henoch-Schönlein Purpura

Henoch-Schönlein purpura is systemic vasculitis characterized by palpable purpura, gastrointestinal manifestations, and glomerulonephritis. It is small vessel vasculitis manifesting immune deposits with immunoglobulin A (IgA). It occurs especially in children from 4 to 7 years old but may affect adults. DAH has been reported in children^{89,90} and adults.^{91–94}

IgA lining the alveolar septal vessels throughout the hemorrhagic area has been observed (together with IgA deposition in glomerular capillaries in crescentic glomerulonephritis).⁹³

DIFFUSE ALVEOLAR HEMORRHAGE IN CONNECTIVE TISSUE DISEASE

Systemic Lupus Erythematosus and Primary Antiphospholipid Syndrome

DAH, often concurrent with lupus nephritis, is an uncommon manifestation of SLE occurring in less than 5% of patients.^{95–97} However, DAH has been reported as the first manifestation of SLE in up to 20% of patients.⁹⁷ The prognosis of DAH, which was very poor in the past, has markedly improved, with a good prognosis in recent years.⁹⁸

Two types of DAH may occur in SLE. The most common finding at lung biopsy is “bland” alveolar hemorrhage⁹⁷ with inflammatory features but no vasculitis. Vasculitis of the small vessels with capillaritis, which is considered as less frequent, has nevertheless been reported in up to 80% at biopsy or postmortem examination.⁹⁷ Immune complex deposits have been observed in patients with both bland DAH and nephritis pathogenetically similar to lupus microangiopathy of the kidneys.^{11,12}

It is likely that capillaritis may be overlooked in some cases if not specifically searched while vasculitis of arterioles and venules was present.^{99,100}

The current treatment of DAH in SLE is similar to that of vasculitis, with corticosteroids, cyclophosphamide, and further plasma exchange in patients with severe DAH.¹⁰¹

DAH in SLE may further be enhanced by antiphospholipid syndrome, thrombocytopenia, and infection. In primary antiphospholipid syndrome, DAH is

associated with microvascular thrombosis with or without capillaritis.^{102,103}

Other Connective Tissue Diseases

DAH in scleroderma is a rare complication that may manifest as pulmonary-renal syndrome with small vessel vasculitis.^{104–106} DAH may be linked with the presence of P-ANCAs,¹⁰⁷ especially MPO-ANCAs.^{108,109} DAH was reported in a patient with long-standing, diffuse, cutaneous, systemic sclerosis, MPO-ANCAs, and features consistent with combined pulmonary-fibrosis and emphysema syndrome.¹¹⁰

DAH with capillaritis was noted in a patient with mixed connective tissue disease with anti-ribonucleoprotein antibodies,¹⁹ and in two patients as a primary manifestation of polymyositis (with anti-Jo-1 antibodies in one patient).¹¹¹

DAH with capillaritis was observed in three patients with RA¹⁹ with no other features of systemic rheumatoid vasculitis.¹¹²

OTHER CAUSES OF DIFFUSE ALVEOLAR HEMORRHAGE WITH CAPILLARITIS

ABMAs characterize Goodpasture syndrome, an immune nonvasculitic disorder leading to pulmonary-renal syndrome with DAH and renal glomerular disease. The coexistence or successive development of Goodpasture syndrome and ANCA-associated vasculitis has been reported in some patients. This was illustrated in a patient with DAH who showed linear deposition of IgG along glomerular basement membranes (a characteristic feature of Goodpasture syndrome) in two sequential biopsies and ABMAs in the serum. The concomitant presence of P-ANCAs was not deemed to be of significance at that time. The patient improved with prednisone and plasmapheresis. He further had spontaneously resolving hemoptysis. The patient's pulmonary symptoms later relapsed, and he eventually developed crescentic pauci-immune glomerulonephritis with MPO-ANCAs. Such a case suggests that an initial, mild, vasculitic insult to the kidneys may result in secondary ABMA nephritis.¹¹³

Although linear deposition of IgG along alveolar capillary basement membranes is the hallmark of pulmonary Goodpasture syndrome with DAH,¹¹⁴ pulmonary capillaritis may be associated.^{115–118} ANCAs have been detected in up to one third of patients diagnosed to have anti-glomerular basement membrane disease, with alveolar hemorrhage present in about one half of patients with ABMA disease and ANCA, or ABMA disease alone. Seven patients, including one with both DAH-ANCAs and DAH-ABMAs, were among a series of 13 patients with ABMAs.¹⁸

Pulmonary capillaritis, reported in a patient with IgA nephropathy with DAH,¹¹⁹ has been proposed as a possible histological form of acute pulmonary allograft rejection.^{120–122}

DAH with capillaritis has been observed in hepatitis C virus-related cryoglobulinemia (monoclonal IgM kappa-rheumatoid factor-polyclonal IgG).¹²³ DAH was noted in multiorgan-affecting, cytomegalovirus-associated cryoglobulinemic vasculitis.¹²⁴

MANAGEMENT OF DIFFUSE ALVEOLAR HEMORRHAGE

DAH in primary vasculitis may develop slowly and progressively, either isolated or as part of systemic vasculitis. However, it may be severe right away or worsen rapidly or progressively. In a series of 38 patients with small vessel vasculitis admitted to an intensive care unit,¹²⁵ 19 (50%) had WG, 16 (42%) had MPA, and one had CSS. DAH was the reason for admission in most cases (37%). In an analysis of 32 patients (24 WG and eight MPA) with first-line induction-refractory disease in the WEGENT trial, DAH was present in 13, including five with massive DAH. DAH was independently associated with induction-refractory disease and, further, with higher mortality.¹²⁶

The treatment of DAH in primary vasculitis relies on corticosteroids and immunosuppressants, especially cyclophosphamide. Furthermore, plasma exchange is largely used in ANCA-associated vasculitis with DAH, although there is currently no definitive evidence of a benefit with this procedure.^{127,128} High-dose factor VIIa temporarily halted refractory, life-threatening bleeding in DAH in a patient with MPA.¹²⁹

DAH in secondary vasculitis relies on etiologic management first. In drug-induced vasculitis, stopping the drug is mandatory. In connective tissue diseases, especially SLE, treatment relies on corticosteroids and immunosuppressants (corticosteroids could nevertheless be deleterious in systemic sclerosis) and possible plasma exchange.

Mechanical ventilation may be necessary in patients with respiratory failure and hypoxemia.

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