REVIEW ARTICLE

Diffuse Alveolar Hemorrhage

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Diffuse alveolar hemorrhage is a clinical syndrome that can be life threatening if not diagnosed and treated in time. In most cases it occurs largely as a result of small-vessel vasculitis of the lungs. The many different forms can be classified into 3 large groups: *a)* pauciimmune disease, which generally involves pulmonary capillaritis and is associated with the presence of antineutrophil cytoplasmic antibodies; *b)* syndromes caused by immune deposits, which can be detected by immunofluorescence; and *c)* a large miscellaneous group that includes drug reactions, infections, and idiopathic disease. Diagnosis is based on a combination of signs, symptoms, serology, and histology. Biopsy with video-assisted thoracoscopy should be recommended in patients with diffuse alveolar hemorrhage without known cause and with no prior diagnosis of systemic disease, in whom serology studies do not reveal conclusive data, and in general in those patients for whom there is a high level of suspicion of diffuse alveolar hemorrhage. In all such cases, the fresh biopsy material should be sent to the pathology laboratory for preparation of frozen sections to be used for immunofluorescence.

Key words: *Diffuse alveolar hemorrhage. Diagnosis. Lung biopsy.*

Hemorragias alveolares difusas pulmonares

Las hemorragias alveolares difusas son cuadros clínicos que pueden ser catastróficos si no se diagnostican y tratan a tiempo. Suelen estar causadas en gran parte por vasculitis de vasos pequeños pulmonares. Existen 3 grandes grupos: *a)* las pauciinmunitarias, generalmente asociadas a capilaritis y anticuerpos citoplásmicos antineutrófilos; *b)* las producidas por depósitos inmunológicos, que pueden detectarse mediante inmunofluorescencia, y *c)* un gran grupo misceláneo, que incluye toxicidad por fármacos, infecciones y causas idiopáticas. El diagnóstico se basa en la integración de signos, síntomas, estudios serológicos y morfológicos. Se debe recomendar la realización de una biopsia por videotoracoscopia en los pacientes con hemorragia alveolar difusa de causa inexplicada, sin un diagnóstico previo de enfermedad sistémica, en la que los estudios serológicos no proporcionan datos concluyentes, y en general en aquellos pacientes con un elevado índice de sospecha de que estén desarrollando una hemorragia alveolar difusa. En todos estos casos, la biopsia debe remitirse en fresco a los servicios de anatomía patológica para permitir la congelación de un fragmento tisular, que será utilizado para el estudio por inmunofluorescencia.

Palabras clave: *Hemorragia alveolar difusa. Diagnóstico. Biopsia pulmonar.*

Introduction

Alveolar hemorrhage represents a group of signs and symptoms defined as a syndrome in its own right; it is generally associated with serious clinical states and deserves to be considered in detail.[1] However, diagnosis is often difficult. Although some patients have a prior diagnosis of vasculitis or collagenosis and associated renal disease, along with the classic clinical findings of bilateral alveolar infiltrates, hemoptysis, reduction of hemoglobin levels and/or hematocrit, and carbon monoxide diffusing capacity of more than 30%, it is relatively common for alveolar hemorrhage with necrotizing capillaritis to be the form of onset of a systemic disease, for the classic signs to be absent, or for the syndrome to be restricted to the lungs. In these difficult-to-diagnose cases, an exhaustive search should be performed for signs of systemic disease (sinusitis, cutaneous leukocytoclastic vasculitis, iridocyclitis, synovitis, and glomerulonephritis) and lung biopsy may yield important information.

Inflammatory disease of the blood vessels has always presented diagnostic and therapeutic difficulties. Rokitansky and Virchow took the initial steps in the diagnosis and recognition of the vasculitides with their description of polyarteritis nodosa in the 19th century. Nevertheless, it is generally accepted that Kussmaul and Maier were the first to describe the disease in 1866. Those authors drew attention to the occurrence of nodular arterial aneurysms accompanied by inflammation of the adventitia

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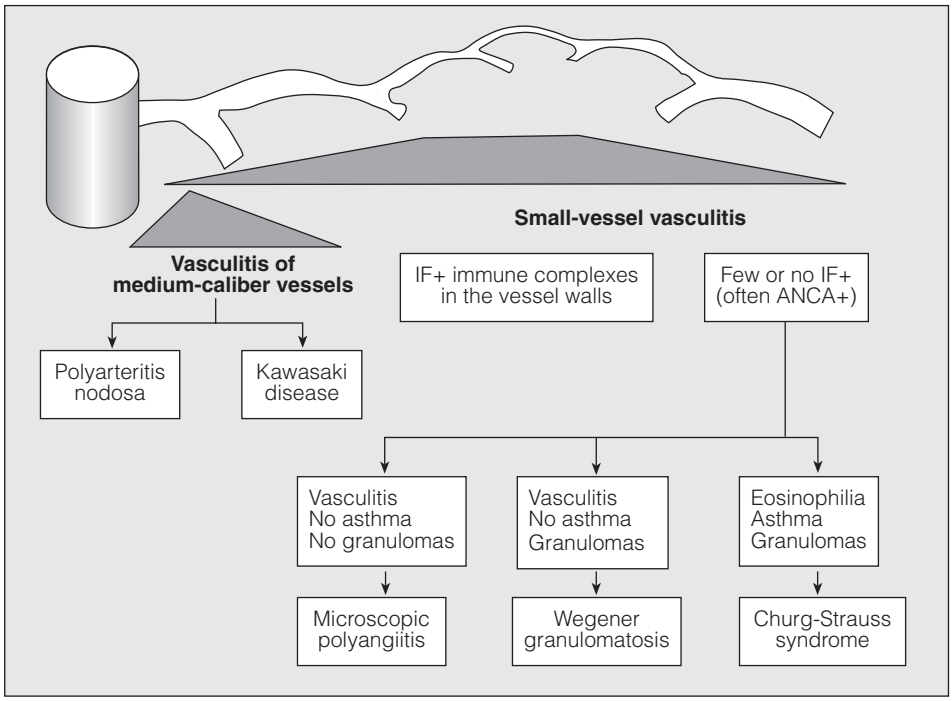

Figure 1. Classification of vasculitis. ANCA indicates antineutrophil cytoplasmic antibodies; IF, immunofluorescence. (Adapted from Jenette et al[2])

that they referred to as *periarteritis nodosa*. In 1903, Ferrari recovered the original term, polyarteritis nodosa, on observing the multifocal and transmural nature of the process.

In 1910, Goodpasture described a patient with pulmonary hemorrhage and glomerulonephritis with extracapillary proliferation (the so-called glomerular crescents). His observations remained in obscurity until 1958, when Stanton and Tange described a group of patients with similar characteristics, for which they coined the term Goodpasture syndrome, defined as pulmonary hemorrhage associated with nephritis. However, the pathogenesis was not elucidated until 1964, when it was found that some of those patients had linear deposits of immunoglobulin (Ig) G that could be detected by immunofluorescence in the basement membrane of the renal glomeruli. Since then, the presence of pulmonary hemorrhage was associated to some extent with renal disease and systemic inflammatory disease of the blood vessels, the so-called vasculitides.

In 1937, Wegener observed another type of pulmonary-renal syndrome in various patients. The syndrome involved granulomatous vasculitis of the upper airways and pulmonary parenchyma, along with necrotizing glomerulonephritis with crescent formation. Godman and Churg subsequently named this syndrome Wegener granulomatosis. The disease shared characteristics with polyarteritis nodosa, but differed in terms of the presence of granulomas, the affected organs, and the occasional occurrence of alveolar hemorrhage as an initial presentation.

In the 1970s, the combination of pulmonary hemorrhage and glomerulonephritis with crescent formation in the absence of other signs of arteritis was classified as a single, specific entity mediated by antibodies against the glomerular basement membrane (GBM). Cases of pulmonary hemorrhage with nephritis and arteritis but without anti-GBM antibodies were categorized as Wegener granulomatosis or polyarteritis nodosa in an overly simplistic classification. The situation was complicated by the description of cases of pulmonary hemorrhage and nephritis without deposits of anti-GBM antibodies but associated with deposits of immunocomplexes (systemic lupus erythematosus, mixed cryoglobulinemia, and Henoch-Schönlein purpura), leading to a widening of the spectrum of diseases and pathophysiologic mechanisms that could generate vascular inflammation and/or pulmonary hemorrhage. Currently, the 1994 Chapel-Hill consensus classification[2] is used for the systemic vasculitides (Figures 1 and 2).

In pulmonary disease, the clinicopathologic presentation of diffuse alveolar hemorrhage is cause for great concern as a result of its seriousness and heterogeneity. There are many causes of pulmonary hemorrhage, not just in association with vasculitis, and this has necessitated a classification centered primarily on diagnostic and therapeutic usefulness.

Causes of Diffuse Alveolar Hemorrhage

From a diagnostic and therapeutic perspective it can be useful to divide cases of alveolar hemorrhage into 2 large groups: those associated with inflammation of the network of small pulmonary capillaries (capillaritis) and those not associated with capillaritis[3,4] (Table 1).

Therefore, if histologic appearance is taken as a guide for differential diagnosis, it is necessary to undertake a careful microscopic examination of the tissue. This is of particular importance since partial treatment of the patient prior to biopsy could result in vasculitis appearing

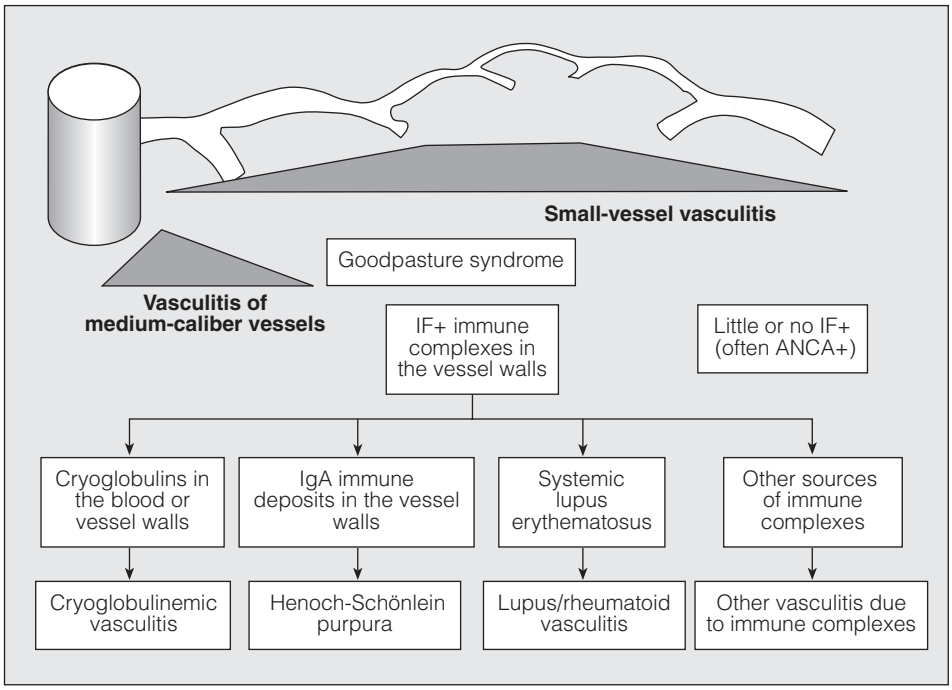

Figure 2. Classification of vasculitis (continued from Figure 1). ANCA indicates antineutrophil cytoplasmic antibodies; IF, immunofluorescence; IgA, immunoglobulin A. (Adapted from Jenette et al[2])

histologically as alveolar hemorrhage without capillaritis. Consequently, efforts should be made to obtain biopsy samples before the patient receives any treatment, although, given the serious nature of the disease and the urgency of the clinical situation the pathologist should be informed of all treatments administered to the patient prior to biopsy.

Within each of the groups mentioned (hemorrhage with or without capillaritis) the causes of alveolar hemorrhage can vary greatly, but a number of variables can be analyzed in an effort to reach a diagnosis.[5] The inclusion of a clinical history (essential in all diseases, but even more so in these patients), laboratory analyses (antineutrophil cytoplasmic antibodies [ANCA] and other markers), and biopsy findings, both histologic and based on immunofluorescence[6] (Table 2), are the elements that facilitate diagnosis.

TABLE 1
Alveolar Hemorrhage With or Without Associated Pulmonary Capillaritis

With Pulmonary Capillaritis	Without Pulmonary Capillaritis
Wegener granulomatosis	Idiopathic pulmonary hemosiderosis
Microscopic polyangiitis	Systemic lupus erythematosus
Isolated pulmonary capillaritis	Goodpasture syndrome[a]
Connective tissue disease	Diffuse alveolar damage
Antiphospholipid syndrome	Penicillamine
Mixed cryoglobulinemia	Trimethyl anhydride
Behçet syndrome	Mitral stenosis
Henoch-Schönlein purpura	Abnormal coagulation
Pauciimmune glomerulonephritis	Veno-occlusive disease
Glomerulonephritis with immune complex deposits	Hemangiomatosis
Drug-induced	Lymphangioleiomatosis/ tuberous sclerosis
Acute transplant rejection	

[a]Can display focal capillaritis.

Antineutrophil Cytoplasmic Antibodies

ANCA, which were described by Davis in 1982, are specific for proteins found in the granules of polymorphonuclear leukocytes and in the peroxidase-positive lysosomes of monocytes. They are markers that display a good specificity for Wegener granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome. Various forms of ANCA have been described, although 2 are more important from a diagnostic point of view: anti-proteinase-3 and anti-myeloperoxidase.

There are 2 methods used to detect ANCA in clinical practice: indirect immunofluorescence and specific enzyme-linked immunosorbent assay. In indirect immunofluorescence, polymorphonuclear leukocytes are centrifuged onto slides, fixed with ethanol, and incubated with patient serum. Following washes, the cells are incubated with a fluorescently labeled anti-human-immunoglobulin antibody. If the test is positive, 3 patterns of immunofluorescence are recognized:

1. ANCA with a cytoplasmic distribution (c-ANCA), characterized by granular cytoplasmic staining that is accentuated between the lobules and respects the nucleus. In 1989, the antigen recognized by c-ANCA was identified as a serum serine protease of 29 kDa (neutrophilic proteinase 3), present in the azurophilic granules found in polymorphonuclear leucocytes and monocytes. The correlation between c-ANCA and antibodies against proteinase 3 is good if the immunofluorescence is interpreted by someone with experience.

TABLE 2
Histologic and Immunofluorescence Data That Facilitate Diagnosis

Mechanism	Immunofluorescence Pattern	Terminology
Anti-GBM antibodies	Linear	Goodpasture syndromea
Immune complexes	Granular	Systemic lupus erythematosusa and other connective tissue diseases[a] Henoch-Schönlein purpura. Immunoglobulin A nephropathy. Idiopathic necrotizing glomerulonephritis with immune complexes
ANCA	Negative or pauciimmune	Wegener granulomatosisa Microscopic polyangiitis[a]. Churg-Strauss syndrome[a]. Idiopathic necrotizing glomerulonephritis without immune complexes
Unknown	Negative or pauciimmune	Idiopathic pulmonary hemorrhage[a]

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; GBM, glomerular basement membrane. [a]The most common at pulmonary sites

2. ANCA with a perinuclear pattern (p-ANCA), labeling the nucleus or perinuclear area. This pattern is an artifact of the redistribution of cytoplasmic antigens to the nucleus during ethanol fixation, since the granules rupture and the positively charged basic proteins migrate towards the nucleus, which is negatively charged. This second type of ANCA, which recognizes myeloperoxidase, was described by Falk and Jenette in 1988. However, the correlation between p-ANCA and myeloperoxidase is not as clear, even when judged by someone with experience in interpreting this staining.

3. Finally, there is an atypical ANCA staining pattern (snowstorm) that is not associated with a specific antigen, although in some patients a reaction is seen against lactoferrin, lysozyme, β-glucuronidase, or cathepsin G.

The highest rate of positivity for ANCA is observed in patients who are not in treatment and who have active disease. Both the titer and the rate of positivity are reduced with immunosuppressant therapy and entry of the disease into a quiescent phase.

Pulmonary Biopsy and Immunofluorescence

There are 3 main aims of lung biopsy in cases of suspected pulmonary hemorrhage. Firstly, histologic methods should be used to confirm the presence of alveolar hemorrhage and rule out small-vessel inflammation (capillaritis). Secondly, the presence of factors other than vasculitis that could account for hemorrhage should be ruled out. Thirdly, it should provide information regarding the possible immune deposits, detected by immunofluorescence.[7] The question of a possible increase in surgical morbidity and mortality in these patients as a result of biopsy is highly debatable, since there is no evidence of such an increase.[4]

Immunofluorescence studies of the lung tissue require fresh tissue, since although peroxidase-conjugated antibodies against immunoglobulins are available for use with formalin-fixed, paraffin-embedded tissue, they tend not to yield good results. It is therefore necessary to freeze a piece of lung parenchyma to perform immunofluorescence against IgA, IgG, IgM, and complement fractions C3, C4, and C1q, as well as fibrinogen and albumin. It should be noted that interpreting the results of these techniques is much more complicated in lung than in renal tissue, due to the large amounts of elastic fibers in the lung, the level of autofluorescence, and the presence of other lesions such as hemorrhage, inflammation, or exudates that can lead to interpretation errors.

Integration of serology findings along with histology and immunofluorescence allows the condition to be divided into those cases that are associated with capillaritis and those that are not, and into pauciimmune conditions (with little or no immune deposits) and those associated with immune deposits.

Recently, the value of transbronchial biopsy for the diagnosis of diffuse interstitial disease has begun to be reconsidered. Although it is true that video-assisted thoracoscopy is the best solution because it allows a complete histologic and immunologic study to be performed, transbronchial biopsy can be useful and generate data that support or rule out certain diseases,[8,9] thereby extending the differential diagnosis and offering treatment options in certain cases.

Pauciimmune Conditions

Pauciimmune conditions include ANCA-associated syndromes (Wegener granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, necrotizing glomerulonephritis with crescent formation and with or without pulmonary hemorrhage) and mixed forms.[10] They occur most often in men aged 50 to 60 years. Histologically they are characterized by capillaritis or small-vessel vasculitis. However, the presence of capillaritis in lung biopsy tissue is not entirely specific, and this phenomenon can be observed in patients with vasculitic syndromes without alveolar hemorrhage.[11] The 2 characteristics that most reliably indicate capillaritis are accumulation of polymorphonuclear leukocytes in the interstitium, beyond the numbers that could be explained by the presence of those cells in the alveolar space, and the presence of cell debris from those cells (karyorrhexis)[12] (Figure 3). By definition, immunofluorescence should not reveal immune deposits in the pulmonary capillaries.

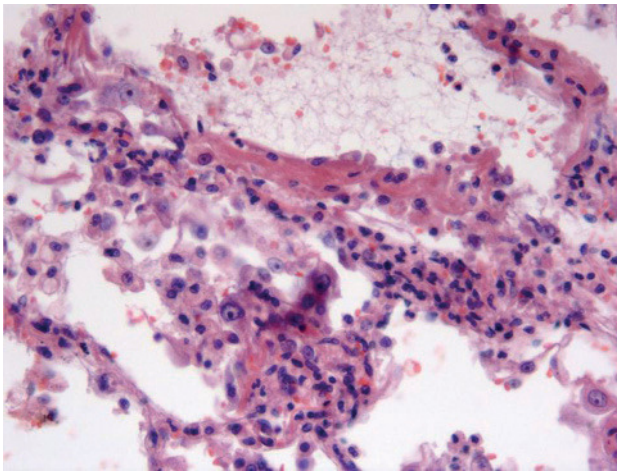

Figure 3. Pulmonary capillaritis: enlarged interstitium with increased cellularity. Note the polymorphonuclear leukocytes, with the difference in proportion of intersitial and alveolar leukocytes. Bloody material in the alveolar space. (Hematoxylin-eosin, ×100.)

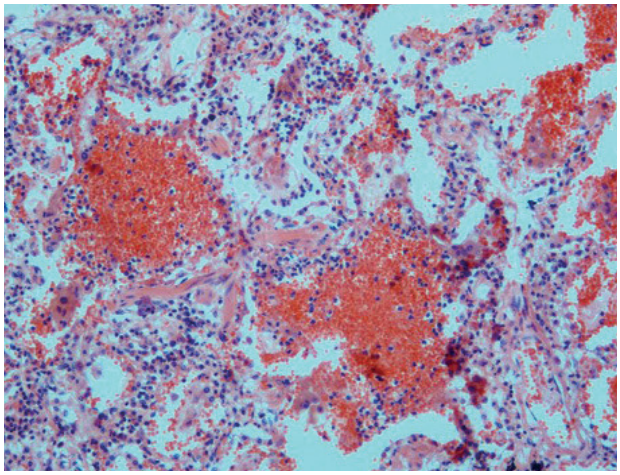

Figure 4. Microscopic polyangiitis: image showing capillaritis and alveolar hemorrhage with a butterfly appearance. (Hematoxylin-eosin, ×40.)

Capillaritis is a reflection of vascular damage and ANCA are generally implicated in the pathogenesis. However, as with any diagnostic test, the sensitivity does not reach 100%, since not all cases of the disease described here are positive for ANCA (Table 3). Neither does the specificity reach 100%, since there are hematogenous infections, particularly in immunodepressed patients, in which ANCA are sometimes present in peripheral blood, as occurs in patients with inflammatory bowel disease and other autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis.[11] A single positive result for ANCA should therefore not be used in isolation as diagnostic of Wegener granulomatosis or microscopic polyangiitis in a patient who does not clearly meet the criteria.[13]

The aim of this review is not to describe in detail all histologic aspects of these diseases but rather to highlight that all can include diffuse alveolar hemorrhage as a presenting sign.

Wegener Granulomatosis

Wegener granulomatosis is defined as a granulomatous inflammation that affects the respiratory apparatus in association with vasculitis affecting the medium and small blood vessels. The classic presentation is well known. However, diffuse alveolar hemorrhage secondary to small-vessel vasculitis may represent an initial and unique manifestation of Wegener granulomatosis.[14] Approximately 40 cases with these characteristics have been reported.[4] The patients usually have severe renal disease, and the association with renal insufficiency can be of diagnostic use. Early death is considerably more common in patients who initially present with alveolar hemorrhage, both due to the seriousness of the condition and to secondary infections caused by the aggressive immunosuppressant treatment used.

TABLE 3
Antibody Findings in Pauciimmune Disease

	Microscopic Polyangiitis	Wegener Granulomatosis	Churg-Strauss Syndrome
Proteinase-3-ANCA (c-ANCA)	40%	75%	10%
Myeloperoxidase-ANCA (p-ANCA)	50%	20%	60%
Negative	10%	5%	30%

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; c-ANCA, ANCA with a cytoplasmic distribution; p-ANCA, ANCA with a perinuclear distribution.

Microscopic Polyangiitis

According to the Chapel-Hill classification, microscopic polyangiitis is a necrotizing vasculitis with few or no immune deposits and affects the small vessels. This definition includes cases that were previously classified as hypersensitivity vasculitis or polyarteritis nodosa. The most common pulmonary lesion is capillaritis with alveolar hemorrhage, with or without necrotizing arteritis (Figure 4).

The differential characteristics in relation to classic polyarteritis nodosa, in addition to the caliber of the affected vessels, are that microscopic polyangiitis is almost never associated with prior hepatitis B or C infection, that pulmonary disease is rare in the classic variant but occurs in 10% to 30% of patients with the microscopic form, and that rapidly progressive glomerulonephritis, which occurs in 80% to 100% of cases of microscopic polyangiitis, does not occur in polyarteritis nodosa.

Lung involvement increases the likelihood of early death in microscopic polyangiitis. In fact, up to 25% of patients die during the first episode of alveolar hemorrhage.[4] Among those who survive the first episode, subsequent recurrence of hemorrhage leads to obstructive disease (thought to be emphysema but this is not clearly demonstrated) and pulmonary fibrosis. Furthermore, in the areas where there

has been necrotizing vascular inflammation, vascular sclerosis develops with disruption of elastic fibers.

Churg-Strauss Syndrome

Churg-Strauss syndrome is defined as a granulomatous inflammation rich in eosinophils that affects the respiratory apparatus along with necrotizing vasculitis involving the medium and small vessels, associated with asthma and eosinophilia. Biopsy may or may not be consistent with the clinical diagnosis. Thus, the pathologist does not confirm or rule out a diagnosis of Churg-Strauss syndrome but rather acts as a guide based on histologic criteria.[15] The presence of alveolar hemorrhage is much less common than in other small-vessel vasculitides.[11]

Isolated Pulmonary Capillaritis

Isolated pulmonary capillaritis is a syndrome of diffuse alveolar hemorrhage that can appear in patients with or without p-ANCA. The few patients described who did not have ANCA did not develop clinical or serologic evidence of systemic disease after extensive follow-up.[4,16] All the patients displayed disease limited to the lungs and it has been suggested that this is a pulmonary equivalent of idiopathic pauciimmune glomerulonephritis. These cases are difficult to distinguish from microscopic polyangiitis, and their nature and existence continue to be debated.

Presentations Associated With Immune Deposits

Anti-GBM Disease (Without ANCA)

Anti-GBM antibodies are directed against epitopes in the NC1 domain of the α_3 chain of type IV collagen (Goodpasture antigen).

The characteristic diagnosis is made by lung biopsy and immunofluorescence, leading to detection of a linear distribution of IgG in the pulmonary capillary basement membrane, similar to that seen in the renal biopsy, where a linear IgG deposit is observed in the renal glomerulus. However, this finding is not entirely specific since IgG can form nonspecific linear deposits. The key in these cases is provided by albumin staining, which if it displays a similar pattern to that of IgG would correspond to a pattern that is not characteristic of disease caused by anti-GBM antibodies.

In some isolated cases there may also be positivity for ANCA. The disease is rare (0.5 cases per million individuals per year) and tends to affect men around 40 years of age, usually smokers.

Histologically it appears as alveolar hemorrhage without arteritis, though focal capillaritis may be present. The alveolar network of reticulin and elastin fibers is preserved. The IgG deposit in the alveolar basement membrane can sometimes be demonstrated by immunofluorescence, but is usually not extensive.[17]

Not all patients with disease due to anti-GBM antibodies develop pulmonary lesions, suggesting that there may be underlying factors involved other than the antibodies, such as smoking or inflammatory cytokines.[18]

Diseases Associated With Other Immune Deposits

Collagen diseases are another relatively common cause of pulmonary hemorrhage.[19] These diseases are difficult to diagnose due to their nonspecific presentation. It is often necessary to carry out various imaging studies and assess serology for various antibodies along with histology findings from biopsy material. As a result, it is necessary to be familiar with the variety of disease of this type that can present with alveolar hemorrhage in order to facilitate a rapid differential diagnosis.

Diffuse alveolar hemorrhage is a complication in 4% of cases of systemic lupus erythematosus, according to Hughson et al.[20] Those authors reported it as a presenting symptom of the disease in 23% of cases, and as the most common cause of death, with mortality reaching 50% in cases in which this phenomenon is present. They also described that when alveolar hemorrhage appears after diagnosis of lupus, it does so after a mean delay of 30 months, and it is noteworthy that hemoptysis is only described as an initial symptom in 42% to 66% of cases. However, lupus nephritis almost always occurs as an accompanying sign, they point out. The main differential diagnosis is with infection, which is the most common cause of pulmonary parenchymal disease in these patients.

The histologic lesions that accompany pulmonary hemorrhage in patients with systemic lupus erythematosus can affect all types of vessels. They include thrombogenic vasculopathy with limited inflammation, lymphocytic vasculitis, neutrophilic vascular reactions, and systemic vasculitis similar to microscopic polyangiitis. The mechanism of thrombosis includes the presence of antibodies against endothelial cells, circulating immunocomplexes deposited in the endothelium, and other factors affecting coagulation such as lupus anticoagulant.[21]

Deposits of IgG and complement fractions in the alveolar walls have a granular appearance (Figure 5). If the deposits only contain IgA, a diagnosis of alveolar hemorrhage as a manifestation of Henoch-Schönlein purpura or IgA nephropathy should be considered.[4,22] This association occurs in less than 5% of cases.[2] However, this may be because too few cases have been studied by biopsy and immunofluorescence, since, as in any disease caused by immune complexes, the complexes are circulating and therefore can be deposited in the lung, as shown in cases in which other interstitial diseases such as bronchiolitis have been diagnosed.[23]

Rheumatoid arthritis is a chronic inflammatory disease with manifestations in tissues outside the joints, including the lungs. In patients with extra-articular disease, rheumatoid factor is usually present. Vasculitis is rare (<10% of patients)[10] and can affect all types of blood vessels, leading to thrombotic phenomena. Inflammatory infiltrates are of varying density and can be lymphoid, granulomatous, or neutrophilic and be accompanied by pulmonary hemorrhage.[24]

Alveolar hemorrhage has also been described, although very rarely, in patients with polymyositis, mixed connective tissue disease, and scleroderma.[25,26]

The catastrophic variant of antiphospholipid syndrome (Figure 6) is one of the most severe conditions associated

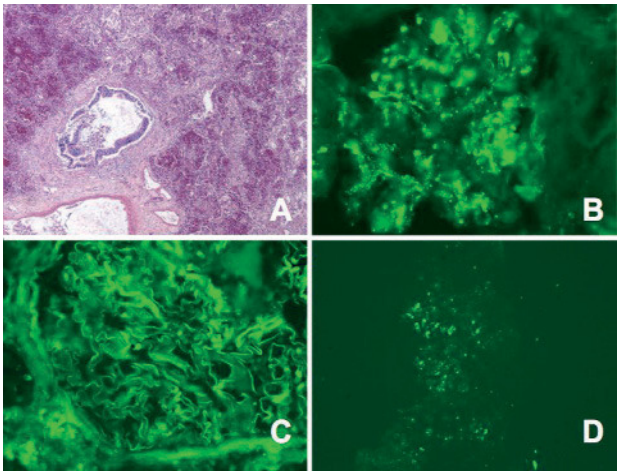

Figure 5. Alveolar hemorrhage without capillaritis in a case of systemic lupus erythematosus. (Panel A: Hematoxylin-eosin, ×10.) B, and C show immunofluorescence images revealing a double granular deposit in the renal glomerulus (B, anti-immunoglobulin G antibody; C, anti-C3; original magnification, ×100). Panel D shows a granular deposit in the pulmonary capillaries (anti-C3 antibody; original magnification, ×340).

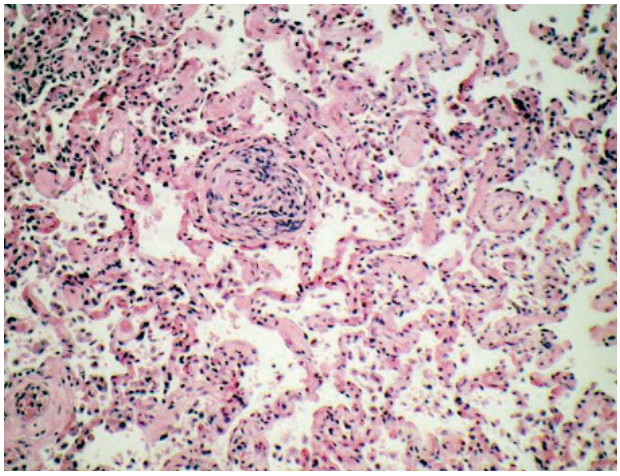

Figure 6. Catastrophic antiphospholipid syndrome: massive vascular thrombosis. (Hematoxylin-eosin, ×40.)

with immune disease that causes alveolar hemorrhage. It mainly affects women (66%), is not always associated with a classic antiphospholipid syndrome, and can appear in association with systemic lupus erythematosus, pseudolupus syndrome, or rheumatoid arthritis. It can present in childhood and a series of precipitating factors has been described (infections, drugs, major surgery, etc). The clinical presentation involves microangiopathy with multiorgan failure, thrombocytopenia, hemolytic anemia, disseminated intravascular coagulation, and presence of schistocytes in peripheral blood.

Laboratory workup can reveal lupus anticoagulant, anti-cardiolipin antibodies, antibodies against double-stranded DNA, antinuclear antibodies, anti-Ro/SS-A, anti-ribonucleoprotein antibodies, and anti-LA/SS-B. It manifests as thrombotic phenomena throughout the vasculature. It is extremely serious, with 50% mortality despite anticoagulation therapy and treatment with corticosteroids, plasmapheresis, or intravenous immunoglobulin.[27,28]

Miscellaneous Causes of Pulmonary Hemorrhage

Other causes of diffuse alveolar hemorrhage include diffuse alveolar damage, veno-occlusive disease, the noninflammatory lung disease that can occur in mitral stenosis, complications associated with anticoagulation and thrombolytic therapy[29,30] (in those cases with normal histology), use of all-trans retinoic acid in promyelocytic leukemia,[31] coagulopathies, toxicity caused by drugs such as gemtuzumab,[32] infliximab,[33] sirolimus,[34] everolimus, penicillamine,[35] rituximab,[36] vasculitis caused by infectious agents, noninfectious complications following bone-marrow transplant,[37] and idiopathic pulmonary hemosiderosis.

It is necessary to obtain an exhaustive clinical history that includes use of crack cocaine,[38] which causes hemorrhage as a result of diffuse alveolar damage, and propylthiouracil or diphenylhydantoin, which cause hypersensitivity vasculitis.[39]

Cases attributable to cocaine toxicity are associated with extensive symptoms of diffuse alveolar damage with organizing phenomena and an abundance of alveolar macrophages loaded with iron pigment to a greater extent than is usually seen in cases of hemorrhage due to other causes. If this condition is suspected, transbronchial biopsy can be extremely useful to demonstrate a pattern of hemorrhage without capillaritis.

In cases of toxicity caused by drugs such as penicillamine, in addition to alveolar hemorrhage, other patterns of lesions common to cases of toxicity are observed, such as bronchiolitis, lymphoid hyperplasia, or areas of organizing pneumonia, almost always without vasculitis. The role of penicillamine in the development of pulmonary lesions has been a subject of debate, since most cases have been described in patients treated for rheumatoid arthritis, and sometimes the lesions caused by the drug and by the disease itself are similar. However, other patients with the same type of disease, such as those with Wilson disease, have hemorrhage, bronchiolitis obliterans, and lymphoid hyperplasia, revealing the role of the drug in the production of toxicity.

There are other much less common causes of diffuse alveolar hemorrhage that should nevertheless be taken into consideration, such as umbilical cord blood transplant for rare diseases, a procedure which, as with progenitor-cell transplants, will become increasingly common.[40]

Diffuse alveolar hemorrhage also occurs relatively frequently in the context of hematopoietic stem-cell transplant.[41] It is characterized by rapid onset of symptoms comprising dyspnea, cough, and hypoxemia, with or without fever. Frank hemoptysis is rare. Hemorrhage can be associated with 3 situations. Firstly, alveolar hemorrhage can appear at an early stage usually following autologous transplant. It occurs in 7% to 14% of cases and appears to be associated with the presence of graft versus host

disease.[42] This situation has been associated with a mortality of 75% despite treatment.[42] Secondly, and again occurring in an early phase, respiratory distress syndrome can develop following autologous transplant and have characteristics of diffuse alveolar damage and hemorrhage that responds well to corticosteroid therapy. The third situation associated with alveolar hemorrhage is delayed pulmonary toxicity syndrome, which occurs months after transplant, responds poorly to treatment,[42] and could be associated with the conditioning regimen used prior to transplant.

The appearance of pulmonary hemorrhage secondary to septic vasculitis is a known complication of bacterial, viral, and fungal agents. In fact, hemorrhagic pneumonia in immunocompromised patients often occurs as a result of infection, and the most common causative agents are fungi belonging to angioinvasive *Aspergillus* species[43] and a particular form of fungus known as *Scedosporium prolificans*, which is important in patients with hematologic disease.[44] The best known cause of pulmonary hemorrhage as a result of bacterial agents is that occurring due to leptospirosis.[45] Viral agents such as cytomegalovirus or hepatitis B and C viruses can cause hemorrhagic complications, both directly (cytomegalovirus) or via indirect mechanisms (mixed cryoglobulinemia and hepatitis B and C).[46,47]

This area would appear to merit further consideration, since most cases of vasculitis in humans are thought to be idiopathic or autoimmune, whereas in the animal world the infectious agents responsible for vasculitis are well known. The use of molecular techniques to identify pathogens—both viral and bacterial—in the lesioned tissue itself will probably yield valuable information regarding pathogenesis and treatment in these patients.[48]

The last cause of diffuse alveolar hemorrhage is idiopathic pulmonary hemosiderosis. The disease usually presents in children aged less than 16 years and is sometimes associated with celiac disease and increased titers of IgA. From a histologic point of view, it manifests without vasculitis or renal disease. The classic lesion is nonspecific, nongranulomatous inflammation that is histologically indistinguishable from Goodpasture syndrome, with no immune complex deposits. Given the lack of clinical and histologic specificity, diagnosis involves a process of exclusion.[49] Cases have been reported in which corticosteroids and immunosuppressants may be effective.

In summary, diffuse alveolar hemorrhage is a serious condition that can be catastrophic if not diagnosed and treated in time. The key to diagnosis is a good clinical history and integration of serology and histology findings.

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