Pulmonary Manifestations of Vasculitis

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Introduction

The term "pulmonary vasculitis" has been used in different ways. Primarily, it refers simply to inflammation of the walls of vessels of any size in the lower respiratory tract. The term is, however, also used for the systemic vasculitis syndromes that commonly or predominantly present with involvement of the respiratory tract, such as the vasculitis syndromes associated with antineutrophil cytoplasmic antibodies (ANCA). Pulmonary vasculitis is usually associated with a systemic disorder caused by a variety of immunologic mechanisms. In the context of a vasculitis syndrome, the lungs and lower airways can be affected by three major pathologic processes: (1) inflammatory cell infiltration and necrosis of the pulmonary parenchyma; (2) inflammation of the tracheobronchial tree often leading to stenoses; and (3) pulmonary capillaritis causing diffuse alveolar hemorrhage (DAH). Beyond capillaritis, inflammation of vessels of different sizes in the lung, including pulmonary arteries, veins, and bronchial arteries, are comparably rare manifestations of some unique vasculitis syndromes. Clinicians should also remember that not all respiratory symptoms occurring in patients with vasculitis are caused by inflammation of pulmonary vessels or the underlying vasculitis syndrome, infection being the most important alternative diagnosis. This chapter reviews the pulmonary manifestations of the various vasculitis syndromes using the recently revised Chapel Hill Consensus definitions and nomenclature [1].

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Pulmonary Manifestations of Small Vessel Vasculitis

ANCA-Associated Vasculitis

Microscopic polyangiitis (MPA), granulomatosis with polyangiitis (Wegener's; GPA), and eosinophilic granulomatosis with polyangiitis (Churg–Strauss; EGPA) are the three primary systemic small vessel vasculitis syndromes with prominent respiratory tract involvement [1]. In contrast to the other forms of vasculitis with predilections for larger vessels, most patients with active MPA and GPA as well as the majority of patients with active EGPA have ANCA. MPA and GPA will be discussed together as the same diagnostic and therapeutic principles apply. EGPA will be covered separately.

Microscopic Polyangiitis and Granulomatosis with Polyangiitis

MPA is defined as necrotizing vasculitis with few or no immune deposits, affecting small vessels

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including capillaries, venules, or arterioles (polyangiitis). Necrotizing arteritis involving small- and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common; pulmonary capillaritis resulting in alveolar hemorrhage occurs frequently [1]. GPA is characterized by necrotizing granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels. The most commonly affected vessels are capillaries, venules, arterioles, and arteries, but the wall of the aorta can also be affected by necrotizing granulomatous inflammation [1]. For these reasons the term "polyangiitis" is used for these syndromes [1]. It is the necrotizing granulomatous inflammation that sets GPA apart from MPA. The diagnosis of GPA depends on the presence of clinical, pathologic, or radiographic evidence or surrogates of granulomatous inflammation. The vasculitis of MPA is indistinguishable from that of GPA, and there may be substantial overlap between the syndromes. For these reasons, the therapeutic approach to patients with GPA and MPA is governed by the same principles, and most clinical studies and therapeutic trials have combined both diseases.

The following paragraphs will focus on respiratory manifestations of MPA and GPA other than pulmonary capillaritis. Other organ manifestations will be covered briefly as they pertain to general treatment decisions. The pulmonary capillaritis of MPA and GPA will be discussed in more detail in the section on DAH.

The pathognomonic histopathologic features of GPA include neutrophilic microabscesses, fibrinoid necrosis, palisading histiocytes, and giant cells forming a granulomatous inflammation pattern that is often referred to as "geographic necrosis" [2]. Focal vasculitis, thrombosis, and fibrous obliteration of vascular lumina may be seen in areas affected by this type of inflammation which affects predominantly the upper respiratory tract and lungs, but may involve any organ. Atypical and rare histopathologic features of GPA include organizing pneumonia, bronchocentric inflammation, and occasionally a marked number of eosinophils in the inflammatory infiltrates [3]. Tracheobronchial inflammation, often representing unique treatment challenges, is another feature of GPA not shared with MPA [4, 5].

The etiology of MPA and GPA remains unknown. A multifactorial genetic predisposition for the development of ANCA-associated vasculitis seems to be required [6, 7]. Environmental triggers such as exposure to silica and more commonly infections appear to be linked to the onset of the disease as well as to relapses by initiating and perpetuating an inflammatory environment that leads to the production of ANCA, which in turn appear instrumental for the development of capillaritis [8].

Greater than 90 % of patients with GPA are Caucasian. The clinical presentation of GPA varies from subacute nonspecific respiratory illness to rapidly progressive alveolar hemorrhage syndrome. The majority of disease manifestations of GPA affecting the upper and lower respiratory tract are caused by the necrotizing granulomatous inflammation. Ear, nose, and throat symptoms affect more than 85 % of patients [9]. These may include rhinorrhea, purulent or bloody nasal discharge, nasal mucosal drying and crust formation, epistaxis, and serous otitis media. Deep facial pain from paranasal sinus involvement, nasal septal perforation, and ulceration of the vomer are important signs. *Staphylococcus aureus* is frequently detected in the nose and sinuses and has been linked to relapses of the disease [10]. Aphthous lesions of the nasal and oral mucosa and inflammation and destruction of the nasal cartilage lead to a "saddle-nose deformity." Ulcerated lesions of the larynx and trachea are present in 30 % of untreated cases [4]. These may cause hemoptysis.

The diagnostic evaluation of patients suspected of having GPA or MPA should include screening for all possible organ manifestations and treatment toxicities and then be adjusted based on patient-specific symptoms. Measurement of nonspecific markers of inflammation including erythrocyte sedimentation rate and C-reactive protein, complete blood count, serum chemistry panel, urine analysis, and microscopy and testing for ANCA and chest imaging constitutes the core of diagnostic screening. Pulmonary function testing should be performed if the patient has any respiratory symptoms or chest roentgenographic abnormalities.

Respiratory symptoms such as cough, hemoptysis, dyspnea, stridor, or chest wall pain are

usually associated with roentgenographic abnormalities, but roentgenographic abnormalities may be asymptomatic [11]. Lung nodules or mass lesions which may or may not cavitate, can be singular, but are usually multiple and bilateral. They can range in size from a few millimeters to several centimeters. Alveolar infiltrates should prompt consideration of DAH even in the absence of hemoptysis (see discussion later in this chapter). Unusual manifestations include lymphadenopathy, lobar consolidation, and large pleural effusions. Tracheobronchial lesions are common, may be asymptomatic, and only detectable by bronchoscopy. When airway stenoses occur, symptoms that can be mistaken for asthma include stridor or localized wheezes. Pulmonary function testing including inspiratory and expiratory flow-volume loops may provide important clues to the presence of airway narrowing. Bronchoscopic inspection of the tracheobronchial tree is recommended for patients with unexplained respiratory symptoms, abnormalities on pulmonary function test results, or radiographic abnormalities [5, 12].

MPA with MPO-ANCA can occasionally be associated with lung fibrosis, predominantly of the usual interstitial pneumonia (UIP) and sometimes of the nonspecific interstitial pneumonitis (NSIP) variety [13]. The causal relationship between the interstitial lung disease and MPA remains unclear. In most instances the lung fibrosis precedes the development of vasculitis or is detected at the time of first vasculitis disease manifestations. In such patients the MPA disease manifestations respond to immunosuppressive therapy as expected, whereas the lung fibrosis generally does not.

Treatment of MPA and GPA follows several general principles. First is the distinction of disease categories based on disease severity. Second is the separation of treatment phases into a remission induction phase, followed by a remission maintenance phase. Third is the distinction between symptoms caused by damage from the disease itself or treatment and those attributable to active inflammation. Lastly, all therapeutic interventions need to be paired with adjunctive measures aimed at minimizing treatment toxicities, or designed to repair damage.

To stratify remission induction therapy, patients' disease activity is categorized as "limited or non-severe disease" or "severe disease." "Severe disease" is either life-threatening or threatening an affected organ with irreversible loss of function. This includes alveolar hemorrhage, glomerulonephritis, eye involvement (except mere episcleritis), and nervous system involvement including sensorineural hearing loss. "Limited or non-severe disease" includes essentially all patients with disease activity that does not qualify as "severe" by our definitions. The term "limited disease" used in the United States comprises what European investigators have referred to as "early-systemic disease" as well as "localized disease." Even though this separation is not based on well-defined biological distinctions, most disease manifestations leading to the categorization as "severe disease" are caused by capillaritis. In contrast, most symptoms leading to the classification as "limited or non-severe" disease are the result of necrotizing granulomatous inflammation. Patients with limited GPA have a more protracted disease course, a greater likelihood of experiencing a disease relapse following a period of remission, and a higher prevalence of destructive upper respiratory tract disorders (e.g., saddle-nose deformity).

Therapy for MPA and GPA follows similar principles and is based on randomized controlled trial results. Methotrexate (MTX) given once a week at a dose of up to 25 mg in combination with daily oral prednisone is considered the standard of care for patients with non-severe GPA [14]. For remission induction in severe GPA and MPA, CYC at a dose of 2 mg/kg/day in combination with prednisone has been the standard of care until recently [9, 15]. Rituximab (RTX) has now been proven to be an effective and safe alternative for CYC, and for patients presenting with a severe disease relapse RTX was shown to be superior to CYC [16, 17].

Once remission has been induced and the prednisone taper is well under way, CYC should be switched to either azathioprine (AZA, preferred in patients with renal involvement and any degree of renal insufficiency) or MTX [18]. MTX and AZA are equivalent for remission maintenance, whereas another randomized controlled

trial showed that mycophenolate mofetil (MMF) is not as effective as AZA for remission maintenance [19]. Thus, the use of MMF for remission maintenance can only be supported for patients who have failed MTX and AZA, or who have contraindications for both agents. The Wegener's Granulomatosis Etanercept trial (WGET), in which MTX was used for remission maintenance, confirmed that long-term remission remains an elusive goal for many patients, as remission was maintained in less than half of the patients [20]. The RTX in ANCA-associated Vasculitis (RAVE) trial showed that a single 4-week infusion series of RTX was as effective as 18 months of conventional cytotoxic therapy with CYC followed by AZA, even though patients in the RTX treatment arm of that trial received no further therapy following the original infusion therapy [17]. Several recent studies including the RAVE trial have shown that PR3-ANCA (versus MPO-ANCA), the diagnosis of GPA (versus MPA), and relapsing disease (versus new diagnosis) represent risk factors for subsequent relapses even when patients are maintained on AZA for maintenance therapy [17, 21, 22].

Large airway involvement in GPA may call for specialized management beyond standard immunosuppression [5]. Subglottic stenosis is often addressed with dilation procedures paired with local injection of long-acting glucocorticoids with or without mitomycin C [23]. Stenosis of the large airways may require bronchoscopic interventions, including dilation by rigid bronchoscope, YAG-laser treatment, and the placement of silicone airway stents, or balloon dilations which can be performed with the flexible bronchoscope [5]. Tracheobronchial infections, like nose or sinus infections, are thought to play a role in the pathogenesis of the disease by promoting relapses. For this reason, it is advisable to provide antimicrobial therapy based on culture and susceptibility results from bronchial washings. The application of topical glucocorticoids may spare patients with tracheobronchial involvement from ongoing oral glucocorticoid therapy. Lastly, pneumocystis *jerovecii* pneumonia is a well recognized and potentially fatal complication of immunosuppressive therapy for GPA that can easily be prevented [24]. Pneumocystis pneumonia prophylaxis is recommended for all patients with GPA receiving any kind of immunosuppression including being B-cell depleted after RTX therapy [25].

Eosinophilic Granulomatosis with Polyangiitis (Churg–Strauss)

The Chapel Hill Consensus defines EGPA as "eosinophil-rich and granulomatous inflammation involving the respiratory, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia" [1]. EGPA is included among the ANCA-associated vasculitides, but only 40–70 % of patients with active EGPA have detectable ANCA prior to treatment. If ANCA is detectable it is usually of the P-ANCA/MPO-ANCA type [26, 27]. EGPA is primarily distinguished from GPA and MPA by a high prevalence of asthma and peripheral blood and tissue eosinophilia. Three distinct disease phases which may not always follow in sequence have been described for the disease [28]. A *prodromal allergic phase* with asthma may last for a number of years. The *eosinophilic phase* with prominent peripheral and tissue eosinophilia may also last a number of years, and the manifestations may remit and recur over this time period. The differential diagnosis for patients in this phase of the disease includes parasitic infection and chronic eosinophilic pneumonia. The *vasculitic phase* consisting of systemic vasculitis may be life-threatening. This is usually the last phase and may be masked or prevented by glucocorticoid therapy used for the management of earlier phases. Asthma usually predates the vasculitic phase by a mean of 7 years (range 0–61). "Formes frustes" of EGPA have also been described with eosinophilic vasculitis and/or eosinophilic granulomas in isolated organs without evidence of systemic disease [29].

Pulmonary parenchymal involvement in the form of transient alveolar-type infiltrates occurs in 38 % of patients. These have a predominantly peripheral distribution and are indistinguishable from infiltrates seen in chronic eosinophilic

pneumonia [26]. Nodular lesions are rare in EGPA. In contrast to GPA and MPA, alveolar hemorrhage is exceedingly rare (<5 % of cases). Renal involvement in EGPA is less prominent than in GPA or MPA and does not generally lead to renal failure [30]. In contrast, peripheral nerve involvement, typically in the form of mononeuritis multiplex, is more frequent [26, 27, 31]. Skin, heart, central nervous system, and abdominal viscera may also be involved.

The classic histopathologic picture consists of necrotizing vasculitis, eosinophilic tissue infiltration, and extravascular granulomas. However, not all features are found in every case, and they are not pathognomonic of the condition. Particularly the finding of a "Churg–Strauss granuloma" on skin biopsy should not be confused with the diagnosis of EGPA. This type of necrotizing extravascular granuloma may be seen in EGPA as well as in other systemic autoimmune diseases including GPA and rheumatoid arthritis. Recent studies suggest that a more vasculitic disease phenotype is associated with the presence of ANCA, but this was not confirmed by all studies. There remains substantial overlap of organ manifestations between patients with EGPA who are ANCA positive and those who are ANCA negative [26, 27, 31].

Several case studies and limited population-based incidence estimates have indicated that leukotriene receptor blocking agents may lead to unmasking of vasculitic symptoms in asthmatics, by allowing dose reductions or discontinuation of oral glucocorticoid therapy. There is currently no evidence suggesting that these agents directly cause the disease or need to be avoided in EGPA.

The overall mortality of EGPA is lower than that of GPA or MPA and not significantly different from the normal population [26]. Most reported deaths are secondary to cardiac involvement [31].

Systemic glucocorticoids remain the mainstay of therapy. There are no randomized controlled trials that provide clear guidance. Treatment approaches following the principles applied to the management of ANCA-associated vasculitis have been adopted for EGPA. Accordingly, CYC should be added to glucocorticoids for remission induction in all patients with disease manifestations that threaten the patient's life or the function of a vital organ, i.e., particularly those with central- or peripheral nerve involvement, glomerulonephritis, heart involvement, or alveolar hemorrhage [32]. MTX, AZA, and MMF have all been used as glucocorticoid-sparing agents in less severe disease and for remission maintenance. Refractory disease, and disease dominated by difficult-to-control eosinophilic inflammation, has been reported to respond to interferon-alpha therapy, and more recently anti-interleukin-5 therapy [33, 34]. RTX has also been used successfully in EGPA, particularly ANCA-positive patients with renal disease, but the data are still scarce, and it cannot be recommended to use RTX instead of CYC for patients with severe EGPA [35].

IgA Vasculitis (Henoch–Schönlein)

IgA vasculitis is an immune-complex-mediated disease characterized by IgA1-dominant immune deposits affecting predominantly capillaries, venules, and arterioles leading to acute purpura, arthritis, colicky abdominal pain, and nephritis. Proliferative and necrotizing glomerulonephritis is usually mild. Immunofluorescence microscopy shows large deposits of IgA in the skin and kidney. IgA vasculitis is more common in children (mean age of patients, 17 years), but adults can also be affected. The triad of purpura, arthritis, and abdominal pain is present in approximately 80 % of patients. Joint involvement affecting the large joints is typically monoarticular and transient causing pain that is out of proportion to the objective evidence of synovitis. Peritonitis and melena are common.

Pulmonary manifestations of IgA vasculitis are rare. Only 36 cases have been reported to date, and capillaritis has been documented histopathologically only in a minority of them. As in the skin and glomeruli, IgA deposits along the pulmonary capillary walls are pathognomonic for the disease. Half of the patients with IgA vasculitis associated DAH required mechanical ventilation and almost a third of the reported patients died [36].

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis is characterized by circulating cryoglobulins and their deposits in small vessels including capillaries, venules, and arterioles. Half of all cases are linked to *Hepatitis C Virus* infection [37]. Compared to skin, peripheral nerve, and renal involvement, capillaritis of the lung leading to DAH is rare (3 %), but associated with a high mortality (80 %) [37]. RTX is now the preferred immunosuppressive agent for cryoglobulinemic vasculitis [38].

Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis)

Another rare small vessel vasculitis is hypocomplementemic urticarial vasculitis (HUV). HUV is characterized by urticaria, hypocomplementemia, anti-C1q antibodies, and vasculitis of small vessels [1]. Signs and symptoms consist of fever, arthralgias, arthritis, angioedema, uveitis, episcleritis, abdominal pain, glomerulonephritis, and seizures occurring at variable frequencies and combinations. The reported pulmonary complications of HUV are not directly caused by vasculitis. Obstructive pulmonary disease, often severe, occurs in up to 66 % patients [39]. Its immunologic etiology remains unclear, and cannot always be related to smoking.

Pulmonary Manifestations of Medium-Sized Vessel Vasculitis

Classic Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is not associated with ANCA and does not affect capillaries. Therefore, it does not cause glomerulonephritis or alveolar hemorrhage. However, case reports of classic PAN affecting the bronchial or bronchiolar arteries have been reported as the cause of occasional lung hemorrhage. Most cases of classic PAN diagnosed today are associated with viral infections, specifically hepatitis B and C. Consequently, antiviral therapy plays a prominent role in the management of such cases in addition to immunosuppression [40]. In contrast to MPA, classic PAN rarely relapses.

Pulmonary Manifestations of Large Vessel Vasculitis

Giant Cell Arteritis

Giant cell arteritis (GCA) represents a generalized inflammatory disorder involving large- and medium-sized arteries. GCA is the most common form of vasculitis in elderly patients of the Northern hemisphere. Granulomatous inflammation of vessel walls can be found in 60 % of temporal artery biopsy specimens, and the aorta may also be affected possibly leading to thoracic aortic aneurysms in the elderly.

Respiratory symptoms have been reported in up to 25 % of patients, but are usually mild and of little consequence. However, respiratory symptoms can sometimes be the initial presentation of GCA. Therefore, GCA should be considered in elderly patients presenting with new onset of cough, hoarseness, or throat pain without other identifiable cause [41]. An elevated sedimentation rate may lead to the correct diagnosis, and cough, hoarseness, and throat pain usually resolve promptly with glucocorticoid therapy. Pleural effusion or multinodular pulmonary lesions associated with GCA have also been reported on rare occasions raising questions about a possible overlap with GPA since the latter may also involve the temporal arteries. Therapy of GCA continues to be based on the use of glucocorticoids without proven alternative. The glucocorticoid-sparing role of MTX for GCA remains controversial.

Takayasu's Arteritis

Takayasu's arteritis (TA) is a large vessel vasculitis affecting predominantly the aorta and its major branches in young patients most commonly affecting women [1]. It is not limited to patients of Asian descent. Constitutional symptoms, low

grade fever, and arthralgias are often early disease manifestations. More characteristic features of this chronically relapsing disease include variable pulses of the extremities and claudication of affected vascular territories. Renovascular hypertension, pulmonary hypertension, and ischemia of affected organs can be disabling.

The pulmonary manifestations are caused by a unique arteriopathy affecting the large- and medium-sized pulmonary vessels. Pulmonary artery stenoses and occlusion as well as pulmonary hypertension can occur in up to half of all patients as a result of progressive defects in the outer media of the arteries and ingrowth of granulation tissue-like capillaries associated with thickened intima and subendothelial smooth muscle proliferation. The inflammatory infiltrate of the vessel wall consists of lymphocytes, plasma cells, and giant cells. The involvement of pulmonary arteries which is often asymptomatic can be detectable by conventional angiography, perfusion scan, magnetic resonance angiography, or PET scanning [42]. Chest roentgenograms are usually normal, but computed tomography may show areas of low attenuation as a result of regional hypoperfusion, subpleural reticulolinear changes, and pleural thickening. Fistulas can form between pulmonary artery branches and bronchial arteries. Nonspecific inflammatory interstitial lung disease has also been reported.

Therapy for TA relies on immunosuppression with glucocorticoids and MTX [43]. Unfortunately, many patients relapse when the glucocorticoid dose is reduced below 15 mg daily. Antitumor necrosis factor-alpha agents may also be useful. Vascular bypass procedures may restore perfusion to areas affected by severe arterial stenoses, but the results are only temporary [44].

Behçet's Disease

Behçet's disease (BD) is a rare chronically relapsing systemic inflammatory disorder characterized by aphthous oral ulcers and at least two or more of the following: aphthous genital ulcers, uveitis, cutaneous nodules or pustules, or meningoencephalitis [1]. The reported prevalence varies widely between different ethnic groups, for instance 1:16,000 in Japan but 1:200,000 in the United States. The disease is associated with the major histocompatibility complex antigen HLA-B51. The mean age of patients at the onset of BD is 35 years, and men are predominantly affected. Respiratory manifestations of BD consist of cough, hemoptysis, chest pain, and dyspnea [45]. The vasculitis of BD is immune-complex mediated, and may affect vessels of all sizes. Secondary thrombosis with major venous occlusion can occur. Anticoagulation may not be effective for prevention of thrombosis, but aspirin 80 mg/day has been advocated. Destruction of the elastic lamina of pulmonary arteries causing aneurysm formation, secondary erosion of bronchi, and arterial-bronchial fistulae may result in massive hemoptysis, which can be fatal. Computed tomography or magnetic resonance angiography is recommended for detection of pulmonary artery aneurysms. Recurrent pneumonia, organizing pneumonia, and bronchial obstruction resulting from mucosal inflammation have also been described.

Therapy of the underlying disease consists of immunosuppression. Prednisone alone may not be sufficient to control the vasculitis. The addition of other drugs, such as colchicine, chlorambucil, MTX, cyclosporin, or AZA, is recommended. The use of biologic agents, in particular anti-TNF agents and RTX, has also been reported recently. The addition of AZA or CYC to glucocorticoids may result in resolution of pulmonary aneurysms. Anticoagulation should be avoided once pulmonary artery aneurysms have been identified, but coil embolization of identified aneurysms may prevent fatal hemorrhage. The prognosis of pulmonary involvement overall remains poor. About one third of patients die within 2 years of developing pulmonary involvement, most from fatal pulmonary hemorrhage.

Secondary Vasculitis

Infectious processes, particularly infections with *Aspergillus* and *Mucor* species, invade vascular structures and produce secondary vasculitis. Certain

drugs and chemicals can induce a systemic vasculitis picture that mimics MPA. Other uncommon secondary vasculitic entities include benign lymphocytic angiitis and granulomatosis, bronchocentric granulomatosis, and necrotizing sarcoid angiitis.

Clinical Approach to DAH

Diffuse hemorrhage into the alveolar spaces is often referred to as *DAH syndrome*. The clinical course of DAH is unpredictable and, therefore, should always be considered potentially life-threatening. Patients usually seek care because of nonspecific symptoms, including dyspnea, cough, and possibly fever. Diffuse alveolar filling defects on chest roentgenogram are usually found, and anemia and hypoxemia may be prominent at the time of presentation. Hemoptysis is common, but DAH should be considered in the differential diagnostic evaluation of any patient with alveolar infiltrates on chest roentgenogram even in the absence of hemoptysis. DAH can result from a variety of underlying or associated conditions that cause a disruption of the alveolar-capillary basement membrane integrity including immunological inflammatory conditions causing immune-complex deposition or capillaritis (e.g., anti-GBM disease (Goodpasture's), systemic lupus erythematosus (SLE), ANCA-associated vasculitis), direct chemical/toxic injury (e.g., from toxic or chemical inhalation, abciximab use, all-trans-retinoic acid, trimellitic anhydride, or smoked crack cocaine), physical trauma (e.g., pulmonary contusion), and increased vascular pressure within the capillaries (e.g., mitral stenosis or severe left ventricular failure) (Table 10.1). Pulmonary alveolar hemorrhage can also be associated with thrombocytopenia (<50,000 cells/μL), other abnormal coagulation variables, renal failure (creatinine concentration, ≥2.5 mg/dL), and occasionally with a history of heavy smoking. Only the vasculitis syndromes giving rise to DAH will be discussed here.

Bronchoalveolar lavage (BAL) is the best diagnostic modality to confirm the presence of DAH. Progressively more bloody return indicates alveolar origin of active bleeding. A positive iron stain in more than 20 % of all alveolar macrophages recovered by BAL is indicative of DAH, even in the absence of ongoing active bleeding. In patients with an established diagnosis of vasculitis, BAL should be performed in any patient with new alveolar infiltrates to differentiate infection, DAH, and other inflammatory infiltrates such as eosinophilic pneumonia. Once DAH is established the additional diagnostic approach is aimed at the rapid identification of the underlying cause and at prompt implementation of appropriate therapy.

History and physical examination can provide important first clues about the specific etiology of DAH. Exposure to inhalational toxins including trimellitic anhydride or pyromellitic dianhydrate, drug abuse such as crack cocaine abuse, and smoking should be identified. The past medical history may reveal comorbidities that can cause DAH, including mitral stenosis, coagulation disorders, recent bone marrow or hematopoietic stem cell transplantation, preexisting autoimmune disorders, and therapeutic drugs. The initial physical exam findings may also point towards a specific systemic autoimmune disease as cause of the DAH.

Table 10.1 Causes of diffuse alveolar hemorrhage

Immune-mediated capillaritis and vasculitis
Pauci-immune small vessel vasculitides
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegener's)
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)
Idiopathic pauci-immune pulmonary capillaritis
Drug-induced ANCA-associated vasculitis
Immune-complex-mediated disease
Systemic lupus erythematosus (rarely other collagen vascular diseases)
Antiphospholipid syndrome
IgA vasculitis (Henoch–Schönlein)
Cryoglobulinemic vasculitis
Anti-glomerular basement membrane disease
Drug-induced immune-complex-mediated vasculitis
Immune mediated without capillaritis
Anti-glomerular basement membrane disease
Celiac disease (Lane-Hamilton syndrome)
Idiopathic pulmonary hemosiderosis
Nonimmune mediated
Mitral valve disease
Coagulopathy (anticoagulation, thrombocytopenia, renal failure)[a]
Diffuse alveolar damage
Chest trauma (pulmonary contusion)
Other rare causes

[a]Usually requires "second hit" such as pulmonary inflammation or inhalational injury

Laboratory testing performed during an evaluation of DAH should assess the acuity, progression, or stability of the disease process, uncover potential other organ involvement, and help to identify a specific underlying cause. Thus, initial laboratory testing should consist of a complete blood count, metabolic panel, urine analysis, and microscopy, and determine the current coagulation status (APTT, INR). Baseline markers of inflammation (erythrocyte sedimentation rate and C-reactive protein) are helpful to monitor subsequent responses to therapy. Specific autoantibody testing for a potential underlying systemic disease process should also be initiated promptly, including testing for ANCA, anti-GBM antibodies, antinuclear antibodies, anti-double-stranded DNA antibodies, and antiphospholipid antibodies, as well as determination of cryoglobulins, complement, and creatinine kinase levels.

A lung biopsy is not always necessary to obtain a specific diagnosis for a DAH syndrome. Factors deserving careful consideration before performing a biopsy include the risks of the biopsy procedure, the likelihood of obtaining a diagnostic piece of tissue, the likelihood of the biopsy findings to alter the therapeutic approach, and the risks associated with the chosen therapy. Most lung biopsies obtained from patients with DAH will show either pulmonary capillaritis or a "bland histology" in which the pulmonary architecture is well preserved and inflammatory changes are minimal. The histopathologic diagnosis of pulmonary capillaritis requires the findings of alveolar wall infiltration with inflammatory cells centered on capillary walls and small veins and fibrinoid necrosis of alveolar and vessel walls. The inflammatory cells are usually neutrophils, but can be eosinophils or monocytes. Leukocytoclasis, a phenomenon describing pyknotic cells and nuclear fragments from neutrophils associated with cell apoptosis, is also an important feature of capillaritis. Capillaritis usually causes and may culminate in the destruction of the underlying lung architecture. Capillaritis needs to be distinguished from the predominant intra-alveolar neutrophilic infiltration associated with active infections and from mere neutrophil margination related to surgical trauma.

Most of the syndromes associated with pulmonary capillaritis leading to DAH have been discussed in the previous sections of this chapter. The subsequent paragraphs will describe a few unique syndromes or conditions that may also be associated with DAH and variable degrees of capillaritis.

ANCA-Associated Vasculitis and DAH

MPA and GPA combined represent the most common causes of pulmonary capillaritis. Alveolar hemorrhage caused by capillaritis in the setting of MPA or GPA may be subtle or rapidly progressive. Its course is unpredictable and this condition should always be considered life-threatening or severe disease regardless of how well maintained oxygenation may be at the time of presentation. The presence of renal disease, the requirement of mechanical ventilation, and advanced age have all been identified as factors portending a worse prognosis [46–48]. Early implementation of definitive therapy is crucial, and the application of 1–3 daily doses of 1 g of methyl-prednisolone intravenously is considered standard prior to implementation of additional standard therapy for severe disease. The RAVE trial had shown that patients with severe GPA or MPA with DAH achieve the same outcomes as all other patients with severe GPA or MPA [16]. However, patients requiring mechanical ventilation because of their DAH were excluded from participation in the trial.

For some patients with GPA and MPA the combination of glucocorticoids and CYC or RTX may not be sufficient to induce a remission quickly. Plasma exchange (PLEX) has been advocated for early consideration in patients who present with DAH as well as for those presenting with rapidly progressive glomerulonephritis and renal failure. The MEPEX (Methyl-prednisolone versus Plasma Exchange) trial compared three pulses of intravenous methyl-prednisolone to 2 weeks of PLEX (7×60 mL/kg) in addition to standard therapy for severe disease (oral prednisone and CYC) in 156 patients who presented with a serum creatinine level of 5.5 mg/dL or greater [49]. Even though this trial showed

significantly better patient and renal survival at 6 months, there was no long-term advantage of PLEX and there were too few patients with DAH to allow a subset analysis. Only one single-center cohort study focusing on MPA with DAH in 20 patients admitted to an intensive care unit described 100 % survival of these patients when PLEX was added to standard immunosuppressive therapy [50]. The role of PLEX in severe AAV is currently undergoing further investigation. If DAH is uncontrolled despite aggressive immunosuppressive therapy and PLEX, the endobronchial application of recombinant-activated factor VII may be considered as salvage therapy. In patients who survive DAH caused by MPA or GPA, lung function usually recovers well.

Idiopathic Pauci-Immune Pulmonary Capillaritis

This rare condition is by definition not a systemic form of vasculitis [51]. This isolated pulmonary capillaritis of unknown etiology is histopathologically indistinguishable from the pauci-immune capillaritis seen in ANCA-associated vasculitis. No specific autoantibodies have been identified in these patients. This disorder represents a diagnosis of exclusion, and these patients are best treated with an immunosuppressive regimen that follows the guidelines for severe MPA.

Anti-glomerular Basement Membrane Antibody Disease (Goodpasture Syndrome)

Anti-glomerular basement membrane antibody disease (anti-GBM disease) or Goodpasture syndrome is a rare autoimmune disease caused by autoantibodies directed against the NC1-domain of the alpha-3 chain of basement membrane collagen type IV. This epitope is only accessible for autoantibodies in the basement membranes of kidneys and lungs. DAH occurs in about half of patients with anti-GBM disease and requires an additional inhalational injury, particularly smoking, to render the antigen accessible for the autoantibodies and for the development of the pulmonary disease manifestation. Anti-GBM disease rarely causes isolated alveolar hemorrhage in the absence of renal disease. Even though patients usually have serum anti-GBM autoantibodies, the diagnosis of anti-GBM disease cannot be established without histopathologic documentation of linear immunoglobulin G deposits along the basement membranes in lung or kidney. Whether anti-GBM disease represents a true vasculitis is a matter of definition. As the glomerulus is a capillary structure, its inflammation by definition represents a form of capillaritis. This is the main reason for the inclusion of anti-GBM disease in the nomenclature and definitions of the Chapel Hill classification. Yet, the prominent histopathologic finding in the lung of patients with anti-GBM disease is the "bland histopathology," whereas capillaritis represents a secondary histopathologic feature that has also been described in some patients [52]. Early implementation of immunosuppressive therapy in conjunction with PLEX is the key to a favorable outcome in patients with anti-GBM disease [53]. Lung function usually recovers fully from anti-GBM disease, but chronic renal failure is common and defines the overall outcome of the disease.

SLE and Other Collagen Vascular Disorders

DAH as a result of immune-complex-mediated pulmonary capillaritis is a rare but usually severe complication of SLE. The onset of DAH in patients with SLE is usually abrupt, but hardly ever the first sign of the disease. The disease presentation is usually rapidly progressive with pulmonary infiltrates and fever, mimicking infection, and hemoptysis may be absent. Consequently, the differentiation of DAH from infection in SLE usually requires a diagnostic BAL. Mechanical ventilation, infection, and CYC therapy were reported as negative prognostic factors in one report. The reported mortality of DAH in SLE varies between 0 and 90 % [54–56]. Treatment consists of glucocorticoids and CYC. The use of PLEX has been suggested, but its benefit remains unproven.

Respiratory complications are very common in most other types of collagen vascular or connective tissue disorders. Yet, pulmonary capillaritis

presenting as DAH is rare. Isolated cases have been reported with polymyositis, rheumatoid arthritis, and mixed connective tissue disease. Consequently, serologic testing performed as part of an evaluation of DAH should include studies aimed at the identification of these potential underlying disease entities.

Antiphospholipid Syndrome

DAH resulting from capillaritis can also be a rare complication of primary antiphospholipid syndrome (APS). Other respiratory complications include pulmonary embolism and infarction, pulmonary microthrombosis, and pulmonary arterial thrombosis with secondary pulmonary hypertension, all resulting from the hypercoagulability characterizing this disorder. However, primary pulmonary hypertension as well as adult respiratory distress syndrome can also occur.

The clinical presentation of DAH in primary APS is nonspecific and consists of cough, dyspnea, fever, and bilateral pulmonary infiltrates. As DAH can also occur in the context of adult respiratory distress syndrome, and hemoptysis is absent in over half of the reported patients with APS and DAH, BAL should be performed early to establish the diagnosis. Tissue necrosis from microthrombosis as well as pulmonary capillaritis has been implicated as causes of DAH in APS. The capillaritis of APS is immune-complex mediated. The coexistence of thrombosis and capillaritis with DAH represents a therapeutic dilemma, as anticoagulation may need to be interrupted to control the hemorrhage, and patients often require placement of an inferior vena cava filter. The largest single-center report comprising 17 patients and review of 24 cases published in the literature indicates a high mortality of about 40 % despite aggressive immunosuppressive therapy [57]. Glucocorticoid therapy alone is usually ineffective, as is monotherapy with agents like AZA or MMF. PLEX in addition to immunosuppressive therapy is often considered, but its efficacy remains questionable in patients with APS and DAH. Best results were obtained with cyclophosphamide or RTX, sometimes in combination.

Case Vignette: 20-Year-Old Young Man with Granulomatosis with Polyangiitis (GPA, Wegener's)

Five months prior to presentation at the emergency room of a tertiary care center, this young man had developed maxillary sinusitis, unresponsive to broad spectrum antibiotics. This lingered until he experienced significant worsening of sinusitis symptoms 3 months later. At that time he also developed epistaxis prompting an evaluation by an allergist. A couple of weeks later he developed acute left-sided hearing loss, night sweats, and migratory large joint arthralgias. By this time he had already lost 10 lb of weight due to malaise and lack of appetite. Four months after the onset of first symptoms he was hospitalized at a local rural hospital, where he was found to have dry cough, bilateral episcleritis, lower extremity palpable purpura, and nodular lesions on chest roentgenogram. A rheumatology evaluation at the local hospital led to testing for ANCA, and a nasal biopsy was obtained. Renal function and urinary sediment were normal. The ANCA test was positive for C-ANCA and PR3-ANCA, and the nasal biopsy reportedly showed "granulomas." The patient was treated for 3 days with intravenous methylprednisolone and dismissed on oral prednisone 40 mg twice daily to be tapered to 30 mg daily over the course of the next 3 weeks. He was scheduled for initiation of RTX infusions 375 mg/m^2 as an outpatient. Scheduling difficulties led to a delay in initiation of the infusions. Three weeks later, while on prednisone 30 mg daily he had noted significant worsening of symptoms consisting of cough and malaise.

At this time he presented to the emergency room of a tertiary referral center with cough, malaise, and bilateral alveolar infiltrates on chest roentgenogram (Fig. 10.1a). He denied hemoptysis. The patient's room air oxygenation was 93 %, respiratory rate 20 per minute, temperature

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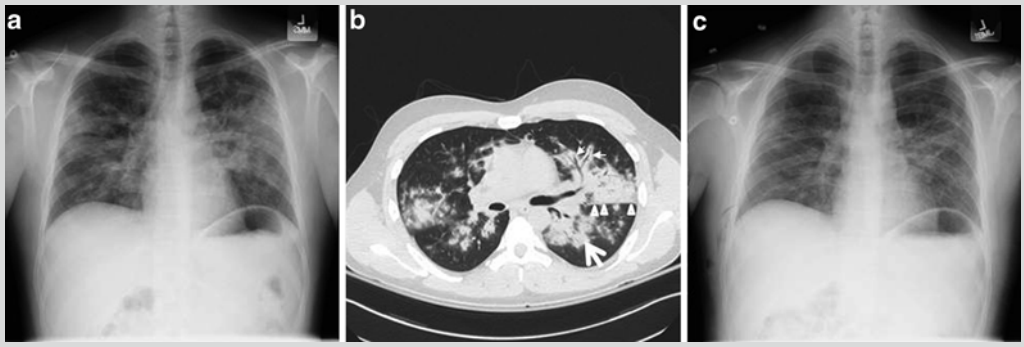

Fig. 10.1 (**a**) Chest roentgenogram of 20-year-old man with recently diagnosed granulomatosis with polyangiitis (GPA) presenting with diffuse alveolar hemorrhage. (**b**) Computed tomography of the chest obtained 1 day later shows diffuse alveolar infiltrates respecting the lobar plains (*white triangles*), nodular lesions distinguishing GPA from MPA (*thick white arrow*), and prominent peribronchial inflammation (*thin white arrows*) frequently seen in GPA. (**c**) Follow-up chest roentgenogram obtained 14 days later shows resolution of diffuse alveolar infiltrates caused by hemorrhage, but nodular lesions and peribronchial inflammation are still detectable on this imaging study

36.6 °C, pulse 78 beats per minute, blood pressure 114/64. Physical examination of eyes, ears, nose, heart, and lungs was unremarkable. Hemoglobin was 11.0 g/dL, white blood count 23.3×10^9/L, platelet count 405×10^9/L, and lymphocyte and CD4 count are normal. An electrolyte panel and urinalysis and microscopy were normal. The patient's only medications consisted of prednisone and trimethoprim-sulfamethoxazole for pneumocystis pneumonia prophylaxis. The patient was dismissed from the emergency room for further outpatient evaluation by rheumatology the next day. A CT scan of the chest is obtained (Fig. 10.1b) and after consultation with a pulmonologist a bronchoscopy with BAL is performed. This shows progressively bloody return indicative of alveolar hemorrhage. Over the next several hours the patient's respiratory status worsens, hemoglobin drops to 8.8 g/dL, and patient is admitted to the medical intensive care unit and requires mechanical ventilation. His course is complicated by the development of bilateral pneumothoraces requiring bilateral chest tube placement. Methyl-prednisolone is given at a dose of 1 g/day for 3 days, and one dose of RTX, 375 mg/m^2, is given, followed 48 h later by eight daily sessions of PLEX. Ten days after admission to the intensive care unit he is transferred to the general ward where the second chest tube is removed (Fig. 10.1c). Following completion of PLEX, he receives completion of the RTX course (the remaining three once weekly doses). Following recovery he completes the taper of the prednisone dose to complete discontinuation before month 6. He has not relapsed over the course of the last 3 years. However, he has been retreated once with RTX without glucocorticoids following reconstitution of B-cells and recurrence of PR3-ANCA positivity.

This case offers the following teaching and discussion points:

- The development of symptoms and disease manifestations is quite typical in this patient. Despite this, the diagnosis of GPA is often delayed.
- Glucocorticoids alone can only temporize and do not control this systemic disease process very well at doses below 60 mg daily without prompt implementation of definitive therapy.
- Even though the combination of ENT disease with pulmonary nodules could be

(continued)

interpreted as "non-severe" disease allowing the choice of MTX in combination with glucocorticoids as first remission induction regimen, the severe constitutional symptoms (night sweats and weight loss) and the presence of palpable purpura suggest a rapidly progressive disease process with developing features of capillaritis. The provided information does not allow the distinction between conductive or sensorineural hearing loss, and we don't know whether the eye inflammation was merely episcleritis or early scleritis. Sensorineural hearing loss and scleritis are clearly severe disease manifestations. The classification as severe disease for treatment purposes made at the outside hospital is certainly appropriate. For a newly diagnosed patient with severe GPA, cyclophosphamide or RTX is equally effective. However, in this young man who wanted to preserve his fertility, RTX is the preferred choice for that reason.

- Without prompt implementation of definitive therapy, the disease progresses, and in this case DAH developed.
- DAH presents without hemoptysis in a large proportion of patients, and the absence of hemoptysis should not dissuade from suspecting it, particularly in a patient with preexisting diagnosis of GPA. Infection is the alternative explanation for the chest roentgenographic changes at the time of presentation to the emergency room.
- DAH of any degree of severity should be considered as potentially life-threatening, and patients should be closely monitored until a definitive diagnosis is established, definitive therapy has been initiated, and control of disease activity has been ascertained.
- Bronchoscopy with BAL for the evaluation of suspected DAH should be conducted in a safe setting, where worsening of the respiratory status that can be associated with the procedure can be treated with the necessary supportive measures.
- Once disease activity is controlled and the pulmonary bleeding stops, alveolar hemorrhagic infiltrates clear fast, unless diffuse alveolar damage with ARDS develops.
- Survivors of DAH usually experience complete recovery of lung function.
- The role of PLEX in this patient's course remains unclear. There is currently no data from a randomized controlled trial that applies to patients with DAH caused by ANCA-associated vasculitis.

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