Review Article

Diffuse Pulmonary Hemorrhage: Clinical, Pathologic, and Imaging Features

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Diffuse pulmonary hemorrhage (DPH) is a syndrome characterized by the presence of widespread hemorrhage from the pulmonary microvasculature leading to hemoptysis, iron deficiency anemia, and a chest radiograph showing bilateral air-space consolidation. Diagnostic imaging consists primarily of chest radiography, but CT and MR imaging may be helpful in selected cases. There are many causes of DPH, and the differential diagnosis and diagnostic approach depend on whether the patient is immunocompetent or immunocompromised. This review summarizes the clinical, pathologic, and imaging features of DPH and the treatment of its more common causes.

Diffuse pulmonary hemorrhage (DPH) is a syndrome with a few defining clinical and radiologic features [1–3]. The classic clinical presentation consists of hemoptysis and dyspnea in the setting of iron deficiency anemia and a chest radiograph showing bilateral air-space consolidation with apical sparing. However, each of these features is nonspecific and may be absent or variable. For example, hemoptysis may not be present even with pulmonary hemorrhage severe enough to cause anemia [1]. The radiograph may show atypical findings with focal or asymmetric bilateral areas of consolidation [4]. For these reasons, DPH is often a challenging clinical problem.

DPH must be distinguished from localized pulmonary hemorrhage with diffuse aspiration of blood. Localized pulmonary hemorrhage is most commonly due to chronic bronchitis, bronchiectasis, tumors, or localized infections, and thus is distinguished from DPH by clinical, bronchoscopic, and radiologic findings. In patients with focal pulmonary hemorrhage and hemoptysis, the chest radiograph demonstrates a localized abnormality in approximately 60% of cases [5, 6]. The most common findings include lobar consolidation, atelectasis, a mass, and cavitation [5, 6]. In the remaining 40% of cases, the radiograph is normal or demonstrates nonlocalizing abnormalities. CT is helpful and indicated in patients with hemoptysis in whom a focal abnormality is suspected [5, 6], but it plays a limited role in the assessment of patients with DPH [7]. Although MR has been used to confirm lung hemorrhage [8, 9], it is probably of limited use in most clinical settings. Histologically, the unifying features of DPH are the presence of recent hemorrhage in alveolar spaces and hemosiderin-laden macrophages in alveolar spaces and interstitium. The finding of large numbers of hemosiderin-laden macrophages in bronchoalveolar lavage fluid is presumptive evidence of DPH.

The treatment and prognosis of DPH depend on the underlying cause. Table 1 illustrates the etiologic classification scheme of DPH that we have found most useful. The aim of this review is to summarize the clinical features, pathogenesis, radiologic manifestations, and treatment of the more common causes of DPH.

DPH in Immunocompetent Patients

Antiglomerular Basement Membrane Disease

In 1919, Goodpasture [10] reported a patient with repeated hemoptysis 6 weeks after an attack of influenza. Autopsy

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TABLE 1: Classification of Diffuse Pulmonary Hemorrhage

Immunocompetent Host	Immunocompromised Host
Antiglomerular basement membrane disease (Goodpasture's syndrome)	Idiopathic diseases Diseases associated with infection Tumors
Collagen vascular diseases of probable immune etiology and autoimmune diseases	
Systemic lupus erythematosus	
Wegener's granulomatosis	
Other	
Diseases not apparently immunologically mediated	
Idiopathic pulmonary hemosiderosis	
Blood dyscrasias	
Drug reactions	
Tumors	

showed diffuse pulmonary hemorrhage and glomerulonephritis. In 1958, the eponym "Goodpasture's syndrome" was first used to describe the combination of DPH and glomerulonephritis [11]. Subsequently, many patients with this syndrome were found to have antibodies against their glomerular basement membrane, and the condition was renamed antiglomerular basement membrane disease (AGBMD). AGBMD is defined by a triad of DPH, glomerulonephritis, and circulating antiglomerular basement membrane antibodies.

AGBMD typically occurs in young adult men. Most patients have pulmonary signs and symptoms, although the majority of patients also have laboratory evidence of renal disease at the time of presentation, including microscopic hematuria, proteinuria, and elevated serum creatinine levels. The clinical presentation of AGBMD usually consists of dry cough, hemoptysis, and progressive dyspnea, weakness, and anemia. The hemoptysis is usually mild and seldom massive.

The radiographic appearance of AGBMD is that of diffuse air-space consolidation [4, 12]. The consolidation is usually bilateral and symmetric and often has a perihilar predominance with a tendency to spare the lung apices [4, 12] (Fig. 1). However, the consolidation may also be asymmetric or unilateral. The consolidation usually resolves within 2–3 days, being replaced by irregular linear opacities and interlobular septal thickening [12, 13]. Patients with DPH due to AGBMD may have normal findings on a chest radiograph despite the presence of extensive pulmonary hemorrhage. Bowley et al. [4] reported that the findings on the chest radiograph were normal in seven (18%) out of 39 cases. Pleural effusions can be seen but are usually due to fluid overload or infection.

The diagnosis of AGBMD is established by detecting antiglomerular basement membrane antibodies. A radioimmunoassay can detect these antibodies in the serum in more than 90% of cases [1]. Alternatively, demonstration by immunofluorescence of linear deposition of immunoglobulin G on glomerular basement membranes in renal biopsy specimens can establish the diagnosis [1, 3]. Lung biopsy is seldom performed in cases of suspected AGBMD. Linear deposition of immunoglobulin is found along alveolar basement membranes, but the distribution is patchy, and autofluorescence of lung tissue makes interpretation of lung biopsies more difficult than interpretation of renal biopsies.

The histologic findings by hematoxylin and eosin staining in both renal and lung biopsy material are nonspecific [14]. Renal biopsy classically shows necrotizing proliferative glomerulonephritis with crescent formation, although biopsies may show normal or nearly normal tissue in patients with minimal renal dysfunction [15]. Open lung biopsy specimens usually show intraalveolar hemorrhage and hemosiderin deposition (Fig. 2), although occasional cases also have a neutrophilic vasculitis of the alveolar capillaries [16, 17].

Treatment consists of high-dose corticosteroids and plasmapheresis to remove the antiglomerular basement membrane antibody. AGBMD has a fulminant course if untreated, but remissions in renal and pulmonary disease can occur if treatment is instituted early [14].

Collagen Vascular and Autoimmune Disease

DPH may occur in association with many collagen vascular diseases. This complication is most commonly seen in patients with systemic lupus erythematosus (SLE) and Wegener's granulomatosis and less commonly in patients with mixed connective tissue disease, systemic necrotizing vasculitis, and rheumatoid arthritis [16, 18, 19].

Most patients with DPH in association with SLE have an established diagnosis of multisystem SLE before the episodes of DPH occur, although in rare cases DPH may be the first manifestation of SLE [1, 2, 20–22]. DPH in SLE is characterized by rapidly progressive respiratory failure, usually with hemoptysis. The hemoptysis may be massive, particularly in children.

The chest radiograph in cases of DPH associated with SLE usually shows bilateral areas of air-space consolidation. MR imaging may be useful in distinguishing DPH from other pleuropulmonary complications of SLE. Hsu et al. [9] described the MR findings in a 12-year-old girl with SLE complicated by DPH. The T1-weighted images showed diffuse intermediate parenchymal signal intensity. The T2-weighted images showed markedly decreased signal intensity due to the paramagnetic effects of ferric iron in the hemorrhage. Hsu et al. [9] postulated that in the proper clinical setting, the presence of shortening of the T2-weighted signal on MR imaging may allow confident diagnosis of DPH. Although the findings in this single case report are encouraging, further studies are required to determine the role of MR imaging in the diagnosis of DPH.

The most common histologic lesion underlying the development of DPH in patients with SLE is neutrophilic alveolar capillaritis (Fig. 3). Neutrophils are distributed primarily along alveolar walls, but in areas in which capillary thrombosis and necrosis have occurred, neutrophils and RBCs are found in alveolar spaces. Lung biopsy may demonstrate immune complexes by immunofluorescence in occasional cases of SLE-associated DPH [22]. These histologic and immunofluo-

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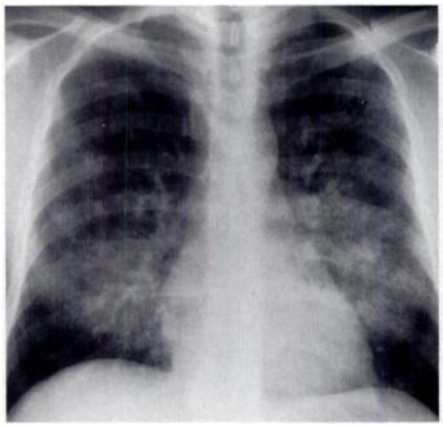

Fig. 1.—27-year-old man with diffuse pulmonary hemorrhage due to antiglomerular basement membrane disease. Chest radiograph shows bilateral air-space consolidation with perihilar predominance. Lung apices and costophrenic angles are relatively spared.

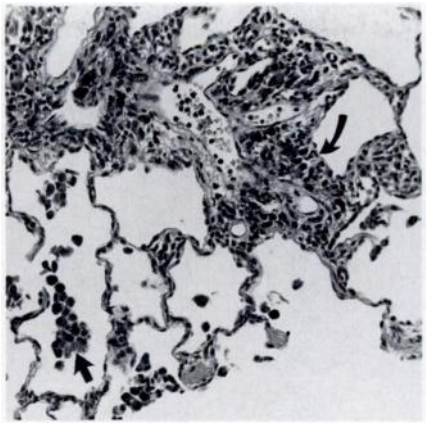

Fig. 2.—Photomicrograph shows classic findings of diffuse pulmonary hemorrhage in lung biopsy material, characterized by intraalveolar (*straight arrow*) and interstitial (*curved arrow*) hemosiderin deposition. No acute hemorrhage is present in this particular field.

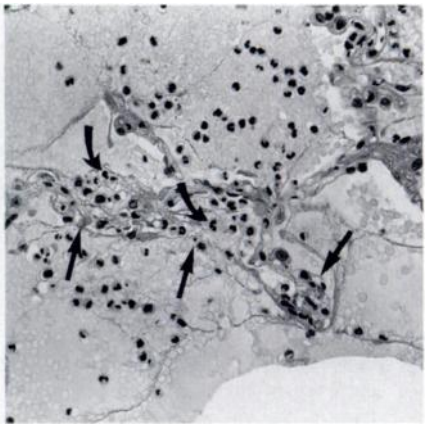

Fig. 3.—Acute capillaritis associated with diffuse pulmonary hemorrhage. Photomicrograph shows alveolar wall expansion due to neutrophils and fibrin (*straight arrows*). Note scattered neutrophils (*curved arrows*) and innumerable RBCs in alveolar spaces.

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rescent findings are not specific, and the diagnosis of SLE must be established by the detection of serum antinuclear antibodies. The prognosis is relatively good with immunosuppressive therapy.

Wegener's granulomatosis most commonly affects patients between 30 and 60 years of age. Most patients have rhinitis, sinusitis, and cough. Hemoptysis is common and may be massive. Renal manifestations, including hematuria, proteinuria, and renal failure, eventually develop in most patients with Wegener's granulomatosis, but they are not common at presentation [16, 23–25]. The most common radiographic findings of Wegener's granulomatosis are multiple pulmonary nodules that frequently cavitate [26]. Less common manifestations include solitary pulmonary nodules, focal infiltrates, bilateral air-space consolidation, atelectasis, and pleural effusions [26]. Bilateral air-space consolidation in patients with Wegener's granulomatosis is usually a manifestation of DPH. In a series of 77 patients with Wegener's granulomatosis reported by Cordier et al. [23], 6 (8%) presented with DPH. The radiographic findings of DPH associated with Wegener's granulomatosis consist of bilateral air-space consolidation. Papiris et al. [27] described the CT findings in two patients with DPH associated with Wegener's granulomatosis. The predominant finding in both patients was the presence of diffuse consolidation. Additionally, nodules in a peribronchovascular distribution were shown by CT. CT may show areas of ground-glass attenuation in patients with normal findings on chest radiographs (Fig. 4).

The primary histologic finding in DPH due to Wegener's granulomatosis is neutrophilic capillaritis similar to that described for SLE (Fig. 3). In most of these cases, additional histologic features diagnostic of Wegener's granulomatosis, such as granulomatous inflammation and necrotizing vasculitis of larger vessels, will be found in an open lung biopsy specimen. In cases lacking these more specific histologic features, the definitive diagnosis of Wegener's granulomatosis requires demonstration of serum antineutrophil cytoplasmic antibody or diagnostic histologic findings in another site [14, 28, 29]. The prognosis in patients with DPH due to Wegener's granulomatosis is relatively good with immunosuppressive therapy.

DPH Not Apparently Immunologically Mediated

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis (IPH) is a disorder of unknown origin characterized by the syndrome of DPH without glomerulonephritis or consistent serologic abnormalities. IPH most commonly occurs in children less than 10 years old but may also be seen in patients in their late teens and twenties. Although it is equally common in boys and girls, in adults IPH occurs more commonly in men [30, 31]. IPH is occasionally associated with celiac disease [32] or immunoglobulin A gammopathy [33].

Patients with IPH usually have hemoptysis, although this may not be obvious in the early episodes of DPH [31]. There is often recurrent hemoptysis, but the hemoptysis is usually not massive. Dyspnea, cough, fever, cyanosis, and anemia are common. The course of IPH is usually chronic, with recurrences and spontaneous remissions occurring over many years.

The typical radiographic findings are areas of air-space consolidation or ground-glass opacities (Fig. 5). There is usually a perihilar and lower lung zone predominance [30]. Although the lung apices and costophrenic angles are typically spared, the costophrenic angles may occasionally be the regions most extensively involved [30]. The areas of consolidation usually clear within 3 days of presentation and are replaced by a reticular pattern. The reticular opacities will initially resolve, but may progress to fibrosis after multiple recurrences. Lymphadenopathy and pleural effusions are

infrequent findings. The radiographic manifestations of IPH in children and adults are identical [30, 34].

Cheah et al. [7] recently described the CT findings of four patients with IPH, two of whom also had celiac disease. The predominant findings in the subacute phase were diffuse nodules and patchy areas of ground-glass attenuation. Two of these patients were also scanned during an exacerbation, and CT showed diffuse, homogeneous areas of ground-glass attenuation.

The MR imaging findings of a 2.5-year-old boy with IPH were described by Rubin et al. [8]. The T1-weighted images showed diffusely increased parenchymal signal intensity. The T2-weighted images showed markedly reduced signal intensity attributable to the paramagnetic properties of hemosiderin. In this case, the presumptive noninvasive diagnosis allowed initiation of therapy before the diagnosis was confirmed with open lung biopsy.

Pathologically, the appearance of IPH is similar to that of AGBMD. Alveolar hemorrhage, hemosiderin-laden macrophages, and free hemosiderin are typically present, with a variable degree of interstitial fibrosis. Immune complexes are not seen. Foci of neutrophilic capillaritis in IPH have been described in rare cases [16], but in general no type of vasculitis is seen in IPH.

The long-term prognosis of IPH is poor, with pulmonary fibrosis developing in most patients within 5 years of presentation [34]. Corticosteroid and immunosuppressive therapy can be used, but the efficacy of treatment has been difficult to assess because of the occurrence of spontaneous remissions. In some of the cases of IPH associated with celiac disease, both diseases improved when the patients were placed on a gluten-free diet [7, 32].

Other Nonimmunologically Mediated Causes

Despite the widespread use of anticoagulants such as warfarin, DPH has only rarely been described as a complication of anticoagulant therapy [35, 36]. Radiographic findings are similar to those for other causes of DPH and include perihilar and basilar air-space consolidation. Rapid clearing of areas of consolidation occurs after cessation or reduction of anticoagulant therapy [35]. CT scans show air-space consolidation or areas of ground-glass attenuation (Fig. 6). A group of rodenticides acts identically to warfarin for a longer duration. DPH after intentional ingestion of rat poison has recently been described [37]. DPH occurs in approximately 14% of patients with disseminated intravascular coagulation and is frequently the cause of death [38]. DPH may also be a complication of thrombotic thrombocytopenic purpura [39].

DPH is a rare manifestation of penicillamine toxicity that may occur in patients receiving high doses [1]. Inhalation of trimellitic anhydride or related acid anhydrides, which are used in the manufacture of plastics and paints, has been reported to cause DPH [1, 40, 41]. Reactions to these drugs are thought to be immunologically mediated [2]. DPH is an infrequently reported complication after lymphography [42, 43], when it is thought to be due to direct pulmonary capillary damage by embolized Ethiodol. DPH has also been reported as a direct toxic or hypersensitivity reaction to cocaine [44].

Angiosarcoma, both primary and metastatic to the lung, has also been described as causing DPH [45–47].

DPH in Immunocompromised Patients

Some degree of DPH is common among immunocompromised patients, particularly in patients with leukemia [48, 49], in patients within the first month after bone marrow transplantation [50] (Fig. 7), and in cardiac transplant patients [51].

Thrombocytopenia and/or coagulopathies are almost always present. However, a coexisting abnormality seems to be necessary for the development of DPH. Most commonly, coexisting fungal, bacterial, or viral pneumonia is found. In a minority of cases, no associated pathogens are demonstra-

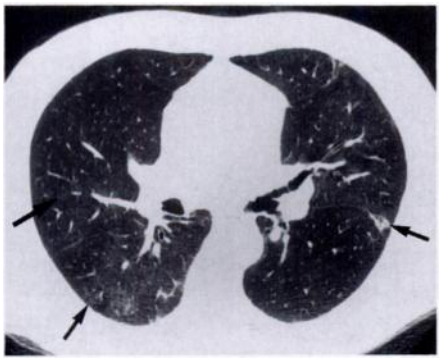

Fig. 4.—61-year-old man with Wegener's granulomatosis and diffuse pulmonary hemorrhage. Chest radiograph (*not shown*) showed no definite abnormality. CT scan with 1-mm collimation at level of lingular bronchus shows bilateral areas of ground-glass attenuation (*arrows*).

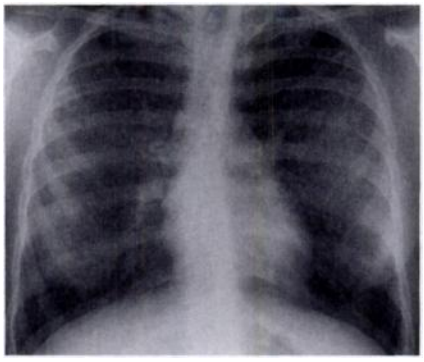

Fig. 5.—19-year-old woman with idiopathic pulmonary hemosiderosis. Chest radiograph shows diffuse bilateral ground-glass opacities.

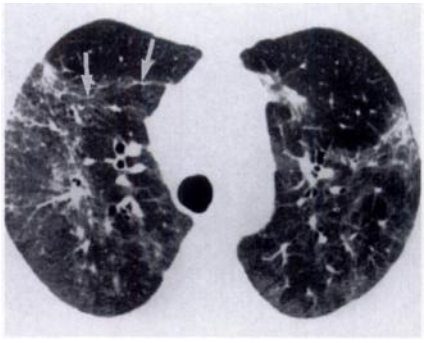

Fig. 6.—76-year-old woman with diffuse pulmonary hemorrhage related to anticoagulation. CT scan with 1-mm collimation through upper lobes shows bilateral areas of ground-glass attenuation. Note interlobular septal thickening (*arrows*) and occasional irregular lines.

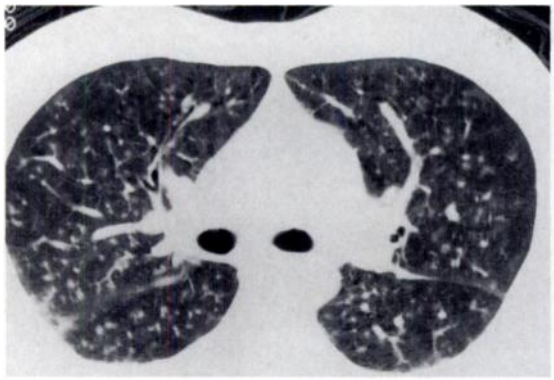

Fig. 7.—40-year-old man with diffuse pulmonary hemorrhage after bone marrow transplantation. No associated infection was identified. CT scan with 1.5-mm collimation shows small nodules and areas of ground-glass attenuation bilaterally.

ble [48, 52–54], and in these cases of idiopathic DPH, it is postulated that damage induced by radiation or chemotherapy has predisposed the patient to DPH [55].

Pathologically, DPH in the immunocompromised host tends to be more recent with more acute hemorrhage and less hemosiderosis than in the immunocompetent population. In patients without underlying infection, associated diffuse alveolar damage (adult respiratory distress syndrome) is very common.

The earliest radiographic manifestation of DPH in immunocompromised patients is the presence of bilateral fine reticular opacities [52, 56]. There is typically a mid and lower lung zone predominance. The radiographic findings can rapidly progress to diffuse bilateral air-space consolidation. In addition to these common but not specific findings of DPH, radiologic changes suggestive of infection may be found. Although clearing can occur with treatment of the underlying causes, DPH in an immunocompromised patient is often terminal [50, 52].

Although angioinvasive aspergillosis usually causes focal pulmonary hemorrhage, it may also be associated with DPH. Pathologically, angioinvasive aspergillosis is characterized by vascular invasion and thrombosis leading to hemorrhagic infarction. Radiographic findings consist of subsegmental, segmental, or lobar consolidation. Nodules may also be present. CT allows early recognition of angioinvasive pulmonary aspergillosis by the presence of nodules with a surrounding halo of ground-glass attenuation (CT halo sign) [57]. The halo of ground-glass attenuation has been shown pathologically to represent hemorrhagic necrosis. Although the halo sign is most commonly seen in patients with angioinvasive pulmonary aspergillosis, it may also be seen with candidiasis, cytomegalovirus, and herpes simplex virus pneumonia [58]. The CT halo sign may also be seen with noninfectious etiologies of focal pulmonary hemorrhage such as Wegener's granulomatosis, Kaposi's sarcoma, and angiosarcoma metastases [58].

Candida pneumonia is characterized pathologically by multiple small abscesses that may be associated with DPH. The chest radiograph shows patchy air-space consolidation [59] or a diffuse miliary pattern [60]. The most common CT finding in patients with *Candida* pneumonia is the presence of 3- to 10-mm-diameter nodules with surrounding halos of ground-glass attenuation [61].

Cytomegalovirus pneumonia is most commonly seen in solid organ and bone marrow transplant recipients. The radiographic findings consist of diffuse reticulation or air-space consolidation. The most common pattern on CT scans in patients with cytomegalovirus pneumonia is multiple small nodules with associated ground-glass attenuation [61].

In patients who are immunocompromised because of HIV infection, hemoptysis and DPH may be found as a complications of Kaposi's sarcoma [62]. Bronchoscopy characteristically shows erythematous plaques on the bronchial mucosa; many physicians recommend that these plaques not be sampled by biopsy because of the risk of bleeding [62]. The radiologic features of Kaposi's sarcoma include bilateral poorly defined nodular opacities and interstitial and air-space infiltrates [62, 63]. On CT scans, the nodules and areas of consolidation are most marked in the perihilar regions and have a peribronchial and perivascular distribution [63–65]. The nodules have irregular margins and often have a halo of ground-glass attenuation, presumably due to hemorrhage [58, 65].

Conclusion

DPH is characterized by anemia and diffuse air-space consolidation. Although hemoptysis is commonly seen, dyspnea and cough are more common at presentation. The characteristic radiologic findings include bilateral air-space consolidation with sparing of the lung apices. The differential diagnosis depends on the patient's immune status. The most common causes in the immunocompetent patient are AGBMD, collagen vascular disease, and IPH. In immunocompromised patients, DPH is almost always associated with an underlying infection or lung injury. The common feature histologically is the presence of recent hemorrhage and/or hemosiderin, but this is not specific, and precise diagnosis requires additional clinical, serologic, or pathologic information.

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