A Review of Clinical and Imaging Features of Diffuse Pulmonary Hemorrhage

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Cardiothoracic Imaging · Review

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OBJECTIVE. The purpose of this article is to review the clinical and imaging features of diffuse pulmonary hemorrhage.

CONCLUSION. Diffuse pulmonary hemorrhage is a life-threatening syndrome associated with a wide variety of underlying pathologic categories. Nonspecific clinical and imaging features pose challenges to promptly diagnosing this condition. Chest radiography commonly shows alveolar opacification, and CT reveals the extent of disease. Integration of clinical, radiologic, laboratory, and pathologic findings facilitates timely diagnosis and etiologic identification.

Diffuse pulmonary hemorrhage (DPH) is an uncommon clinicopathologic syndrome characterized by diffuse disruption of the alveolar-capillary basement membrane that results in intraalveolar hemorrhage. DPH is a medical emergency requiring expedient diagnosis and treatment. The clinical features of DPH include hemoptysis, anemia, and hypoxemic respiratory failure. Histopathologic examination reveals intraalveolar accumulation of RBCs and fibrin with evidence of hemophagocytosis. Three general patterns of underlying alveolar histopathology are commonly described: diffuse alveolar hemorrhage without evidence of alveolar destruction (known as bland pulmonary hemorrhage), diffuse alveolar hemorrhage with capillaritis, and diffuse alveolar damage without capillaritis. Causes with immunologic mechanisms of injury are commonly associated with capillaritis [1], including Goodpasture syndrome, antineutrophil cytoplasmic autoantibody (ANCA)–associated vasculitides, collagen vascular disease, and isolated pauciimmune pulmonary capillaritis. Conditions causing nonimmunologic injury are less common and include a wide spectrum of diverse causes, including idiopathic pulmonary hemosiderosis, anticoagulation and antiplatelet therapy, coagulation disorders, pulmonary venoocclusive disease, and conditions associated with acute respiratory distress syndrome.

The varied causes and nonspecific presentation of DPH can pose significant challenges to the clinician. Hemorrhage originating in the bronchial circulation, large pulmonary vessels, or localized pulmonary abnormalities may mimic DPH. Proper diagnosis requires integration of patient history, laboratory testing, imaging findings, endoscopic evaluation, and sometimes histologic examination.

Diagnosis

The most common presenting signs and symptoms of DPH include dyspnea and diffuse bilateral alveolar opacities. Hemoptysis is common but is absent in up to 33% of patients [2] and may be absent even when hemorrhage is significant enough to cause anemia [3]. A low or decreasing hemoglobin level may provide a clue to the presence of hemorrhage when frank hemoptysis is absent. Chest radiography and chest CT are of limited value in distinguishing hemorrhage from infection or other causes of diffuse alveolar opacification. Bronchoalveolar lavage is often required to identify or confirm alveolar hemorrhage and exclude infection, but it has limited utility in establishing an underlying cause. Increasing blood return in serial lavage aliquots is highly suggestive of alveolar hemorrhage [4] and helps distinguish alveolar from endobronchial disease. Lung biopsy and histopathologic examination are not commonly warranted, but they may be required when the diagnosis or cause remains uncertain. Figure 1 is a flow diagram of imaging-related diagnostic decisions regarding hemoptysis.

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A detailed history, physical examination, and laboratory testing are vital to identifying the underlying cause of DPH. The history and physical examination may suggest specific associated injuries, diseases, or exposures. General laboratory studies commonly include microbiologic studies to exclude infection and urinalysis and renal function testing to evaluate for a pulmonary-renal syndrome. Serologic and drug screening tests may suggest the presence of a particular underlying disorder.

Radiologic evaluation with chest radiography and chest CT is helpful for the evaluation of patients with DPH, although the findings are often nonspecific, and adjudicating a cause based primarily on imaging usually is not possible. The most common chest radiographic finding is diffuse bilateral alveolar opacification that sometimes has a central and lower lung distribution [5], similar to radiographic findings seen in other diseases that are characterized by alveolar filling. The periphery and apices are commonly spared [6]. Chest CT confirms radiographic findings and more accurately defines the extent of pulmonary disease [7]. Findings on chest radiography and CT studies may be negative in up to 50% of cases [8], and a focal or unilateral opacification distribution does not exclude hemorrhage [7, 9]. Integration of imaging findings with clinical, endoscopic, and pathologic findings facilitates prompt diagnosis and management.

Causes
Goodpasture Syndrome

Goodpasture syndrome is a form of anti–glomerular basement membrane (anti-GBM) disease characterized by alveolar hemorrhage and glomerulonephritis. Anti-GBM diseases are mediated by anti-GBM antibodies directed at the α_3-chain of type IV collagen in GBMs, alveolar basement membranes, or both. Anti-GBM disease is a rare disorder that affects 0.5 per one million individuals per year, most commonly young White men between 20 and 30 years of age. The pathogenesis of anti-GBM diseases remains undetermined, although exposure to cigarette smoke, infection, or toxins may be associated with antibody development when underlying genetic susceptibilities are present [10, 11]. Rapidly progressive glomerulonephritis is the most common presenting complaint [12]. Concomitant alveolar hemorrhage is present in approximately 50% of patients and is a defining feature of Goodpasture syndrome. Prominent systemic symptoms are uncommon [13] and may suggest concurrent vasculitis.

Common presenting complaints include hemoptysis (90%), dyspnea (65%), and cough (55%). Symptoms of renal disease are less common and often are nonspecific. Patients may complain of fatigue and edema. Hypertension and decreased urine output may be acutely seen in severe disease. Laboratory findings are consistent with rapidly progressive glomerulonephritis, including a rapid increase in blood urea nitrogen and creatinine levels, increased inflammatory markers, nonselective glomerular proteinuria, pyuria, and microhematuria. Iron deficiency anemia is typical (occurring in 93% of patients). The diagnosis of Goodpasture syndrome requires showing anti-GBM antibodies in the serum or kidney. Serologic tests for anti-GBM antibodies are highly sensitive (> 95%) and include indirect immunofluorescence testing or direct enzyme-linked immunosorbent assay, which are highly sensitive (> 95%) and specific (> 97%) [14]. If the serologic test findings for patients with suspected anti-GBM disease are negative, kidney bi-opsy with immunofluorescence staining is performed. The presence of linear IgG deposits along glomerular membranes confirms the diagnosis. Some clinicians favor biopsy for all patients with suspected anti-GBM disease [12], because tissue analysis can more reliably establish or exclude the diagnosis, provide information regarding disease activity, and guide therapy [15, 16]. Lung biopsy is rarely performed because of the risk of complications and high false-negative rates [17]. Standard treatment includes immunosuppression with high-dose corticosteroids and cyclophosphamide. Urgent plasma exchange, dialysis, assisted ventilation, or a combination of these efforts may be required for patients with severe disease. Short-term prognosis is good, with a 90% recovery rate after prompt immunosuppressive therapy [17]. Long-term prognosis is related to the degree of renal impairment.

Chest imaging studies are not required to establish the diagnosis of anti-GBM disease, but they are usually performed for patients who present with dyspnea or hemoptysis. Imaging findings are similar to those of hemorrhage caused by other diseases. The most commonly described chest radiographic findings are coalescent airspace opacities seen at presentation that evolve to a more reticular pattern over several days. Chest CT commonly reveals ground-glass or airspace opacities that progress to a crazy-paving pattern (Fig. 2). Lower lung involvement is more common than upper lung manifestations [18], and hilar lymphadenopathy may also be seen. Apical involvement [19] and pleural effusions [8] are uncommon and suggest a different underlying condition. Consolidation begins to resolve in 2–3 days with residual irregular opacification or septal thickening [6, 20]. Complete radiographic resolution is common in 2–3 weeks.

Antineutrophil Cytoplasmic Autoantibody–Associated Vasculitides

The most common immunologically mediated causes of DPH are ANCA-associated vasculitides, including granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). These diseases are among the small-vessel vasculitides associated with ANCAs that are collectively classified as ANCA-associated vasculitides. The annual incidences of GPA and MPA are similar, with estimates varying from two to 12 cases per million individuals per year [21]. Observation of a granulomatous change on pathologic tissue examination is the defining factor distinguishing between GPA and MPA, but no broadly accepted diagnostic criteria exist to differentiate between these diseases [22]. Glomerulonephritis and pulmonary hemorrhage are frequent in both GPA and MPA, but significant upper airway disease is common in GPA only. Diffuse pulmonary hemorrhage is rarely seen in eosinophilic granulomatosis with polyangiitis. Although the prognosis of untreated ANCA-associated vasculitides is poor, remission is achieved in 90% of patients treated with corticosteroids and cyclophosphamide [23].

Chest radiography and CT may show airspace consolidation during the acute phase of these diseases, often with air bronchograms (Figs. 3–5). Lung apices and costophrenic angles are commonly spared [6] (Fig. 6). Most patients with GPA have lung disease develop that is related to their underlying disease. The most common imaging manifestation of GPA is multiple bilateral nodules or irregular masses with no zonal predominance [24]. Approximately 50% of lung nodules seen in GPA are cavitary, typically with thick and irregular walls [19]. Bronchial wall thickening

is seen in 70% of patients [25]. Sinus disease is also characteristic of GPA. These imaging findings are not commonly seen in other causes of pulmonary hemorrhage, and they suggest that GPA is the cause of hemorrhage. Less common nonspecific findings include patchy airspace or ground-glass opacities with a peribronchovascular distribution, pleural effusions, and thoracic lymphadenopathy [25].

Collagen Vascular Diseases

Collagen vascular diseases are occasionally associated with pulmonary hemorrhage. Most often, the hemorrhage is immune mediated. The most common collagen vascular disease manifesting with pulmonary hemorrhage is systemic lupus erythematosus (SLE) [6]. Although DPH in the setting of SLE is most often a late complication of known SLE disease [26], in a minority of patients it may be a presenting or early manifestation of SLE [27–29]. Infection is far more likely in patients with SLE who present with pulmonary symptoms, and it must be aggressively excluded before immunosuppressive therapy is provided [29]. Although DPH is an uncommon manifestation of SLE, with a prevalence of 2.0–5.4%, mortality rates of 50–90% have been reported among patients with DPH associated with SLE [30, 31]. Immunosuppressive treatment strategies have been proven ineffective in treating alveolar hemorrhage associated with SLE [32, 33]. Successful treatment with rituximab [34] and recombinant activated factor VIIa [33] have been described in case reports.

Common chest imaging findings are nonspecific bilateral consolidation [35, 36] (Fig. 7). Unilateral and focal lobar opacities uncommon but have been reported [29, 37]. Pleural effusions may be present in up to one-third of patients [2]. Pleural effusion is uncommon in most cases of DPH [8] and is suggestive of SLE. Signs of pulmonary fibrosis are not commonly seen on chest radiography, but they are detected by use of high-resolution CT in approximately 30% of patients [19] (Fig. 8). Radiographic findings related to the underlying disease include decreased lung volumes, pulmonary edema, and musculoskeletal findings related to renal disease or prolonged corticosteroid use [38, 39].

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis (IPH) is a rare disease that primarily affects children and adolescents and is characterized by episodic alveolar hemorrhage leading to pulmonary fibrosis. Developmental [40] and immune-mediated [41] abnormalities have been hypothesized as the underlying defects manifesting as IPH, but no consistent structural or immunologic abnormality has been seen among patients with IPH [42], and IPH remains a diagnosis of exclusion. IPH most commonly presents between the ages of 1 and 7 years with no sex predominance; however, a 2:1 predominance among men versus women in seen among adults who present with IPH [43]. An annual incidence of 0.24 cases per million children has been reported in Sweden [44].

Clinical manifestations of acute hemorrhage secondary to IPH are indistinct; however, mild, chronic disease may manifest as anemia, chronic cough, dyspnea on exertion, and failure to thrive [45, 46]. Chronic or recurrent disease may manifest as digital clubbing, jaundice, and splenomegaly, progressing to cor pulmonale and heart failure [47]. Patients are often treated with long-term immunosuppressive therapy, but limited evidence exists regarding the effectiveness of these measures in preventing disease recurrence or progression. Prognosis is variable but usually poor. Mean survival of 2.5–5 years was reported in some early studies [43, 48–50], but a 5-year survival rate of 86% was reported in a later cohort from 1999 [51]. Patients with protracted courses may have periods of remission, but they almost invariably have severe restrictive pulmonary disease, cor pulmonale, and heart failure develop. Heart failure developing secondary to pulmonary hypertension may be an almost invariably fatal outcome [42].

Chest radiographic findings include nonspecific opacities that sometimes have a central and lower lung distribution. Lung apices and costophrenic angles are typically spared unless disease is extensive [52] (Fig. 9). Lymphadenopathy and pleural effusions are uncommon [53]. Isolated findings consistent with diffuse hemorrhage without associated findings and negative serologic test results are characteristic of IPH. Diffuse reticulonodular opacities are commonly seen in the setting of recurrent or chronic hemorrhage due to organization and pulmonary fibrosis.

Hematopoietic Stem Cell Transplant

Alveolar hemorrhage complicates the course of approximately 5% of both autologous and allogeneic bone marrow transplants [54–56]. Older age, intensive chemotherapy, total body irradiation, and thoracic irradiation are associated with a higher risk of hemorrhagic pulmonary complications [57, 58]. This complication is most often seen within 2 weeks after transplant [56]. Systemic glucocorticoids are often administered despite limited efficacy data [59, 60]. Mechanical ventilation is almost always required. The mortality rate is approximately 80%, with death most often resulting from sepsis or multiple organ failure [55].

Diffuse bilateral interstitial opacities, alveolar opacities, or both types of opacities are seen on chest radiography. Findings may be more prominent centrally and in the middle or lower lung [9]. CT shows nonspecific ground-glass opacities, consolidative opacities, or both types of opacities [55].

A variety of other conditions are less commonly associated with DPH. These conditions include diffuse alveolar damage, often in the setting of acute respiratory distress syndrome, coagulopathies or excess anticoagulation [61, 62], rheumatoid arthritis [63], Behçet disease [64], Henoch–Schönlein purpura [65], eosinophilic granulomatosis with polyangiitis [66], polymyositis [67], isolated pauciimmune pulmonary capillaritis [68], and lung transplant complications (Fig. 10). In addition, many drug and chemical exposures have been associated with DPH, including cocaine, amiodarone, nitrofurantoin, and penicillamine, propylthiouracil.

Of importance, DPH should be differentiated from hemorrhage originating in the bronchial circulation, large pulmonary vessels, or localized pulmonary disease [7]. Massive hemoptysis is rarely caused by alveolar hemorrhage [69] and suggests an arterial pathology. Bronchial circulation hemorrhage causes up to 90% of cases of massive hemoptysis [70]. The most common causes include active mycobacterial infection or sequalae of prior tuberculous disease, bronchiectasis, lung cancer, and necrotizing pneumonia [71]. Iatrogenic injury should also be considered in patients with a history of pulmonary intervention such as biopsy, ablative therapy, or stent placement. Rarely, pulmonary artery catheterization can be complicated by rupture and hemorrhage [72] (Fig. 11). Hemoptysis is considered idiopathic in 7–34% of cases [73].

TABLE I: Clinical and Imaging Features Suggestive of Specific Conditions

Condition	Suggestive Features
Granulomatosis with polyangiitis	Multiple bilateral pulmonary nodules or masses
	Cavitated pulmonary opacities
	Bronchial wall thickening
	Sinus disease
Systemic lupus erythematosus	Pleural effusion
	Elevated hemidiaphragm
	Systemic manifestations
Chronic pulmonary venous hypertension and mitral valve disease	Left atrial enlargement
	Valve pathology
	Kerley B lines
Goodpasture syndrome	Glomerulonephritis
Idiopathic pulmonary hemosiderosis	Hemorrhage without associated findings
	Negative serology testing

Because the presentation and features of DPH are often non-specific, clinicians should be mindful of the clinical and imaging features that suggest specific causes (Table 1). Multiple bilateral nodules or irregular masses, cavitated masses, and bronchial wall thickening suggest GPA. Pleural effusion, decreased lung volumes, and elevated hemidiaphragm suggest SLE. Left atrial enlargement and valve disease suggest chronic pulmonary venous hypertension. Suggestive clinical findings include glomerulonephritis in GPA and Goodpasture syndrome and systemic manifestations in SLE and vasculitides. Idiopathic pulmonary hemosiderosis may be considered when finding are isolated to hemorrhage without associated clinical and imaging features and negative serologic test results.

Conclusion

A high index of suspicion is essential for the timely diagnosis and management of diffuse pulmonary hemorrhage. A careful, focused review of the general medical history, the history of the present illness, symptoms, and imaging findings are the most essential factors in the diagnosis of pulmonary hemorrhage. Bronchoalveolar lavage is often used to identify or confirm the diagnosis. Uncovering the cause of hemorrhage requires integration of clinical assessment, chest radiography and CT findings, and the results of serologic studies. Biopsy of the kidney or other extrapulmonary organs may be required for diagnosis. The radiologist who encounters diffuse pulmonary hemorrhage may consider Goodpasture syndrome, ANCA-associated vasculitides, collagen vascular disorders, idiopathic pulmonary hemosiderosis, and miscellaneous conditions.

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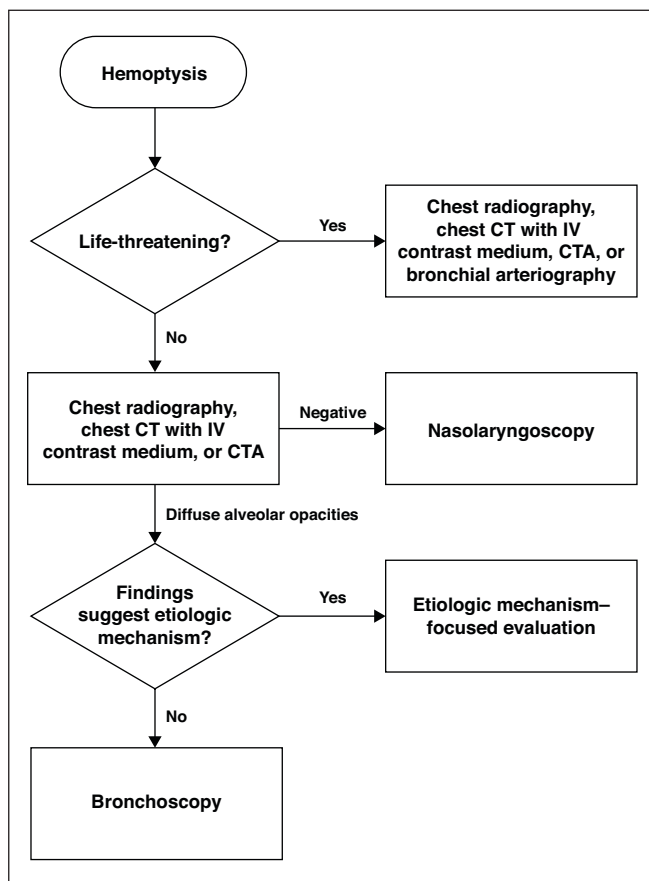
Fig. 1—Flowchart of imaging-related diagnostic considerations for patients presenting with hemoptysis.
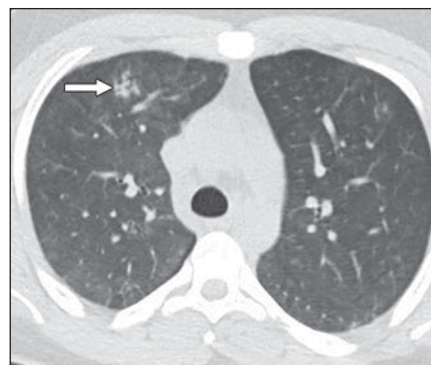
Fig. 2—20-year-old man with renal failure, hemoptysis, and hemoglobin level of 5.3 g/dL. Axial chest CT image obtained at presentation shows diffuse nonspecific ground-glass opacities with areas of confluence (*arrow*) and multiple subcentimeter nodular opacities bilaterally.
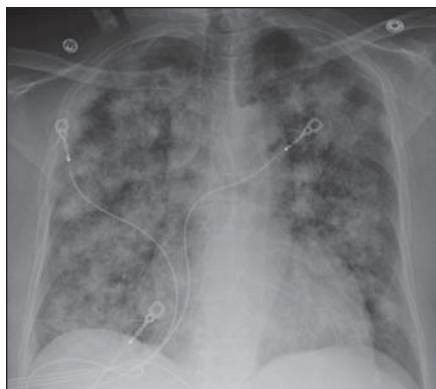
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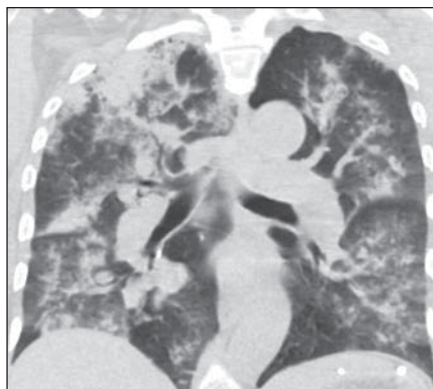
B

Fig. 3—61-year-old woman with antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis who presented with dyspnea and hypoxemia.
A, Chest radiograph obtained at presentation shows multiple bilateral dense nodular and patchy consolidative pulmonary opacities, which are suggestive of diffuse airspace disease.
**B**, Coronal reformat CT image shows corresponding diffuse nodular and ill-defined consolidative opacities.
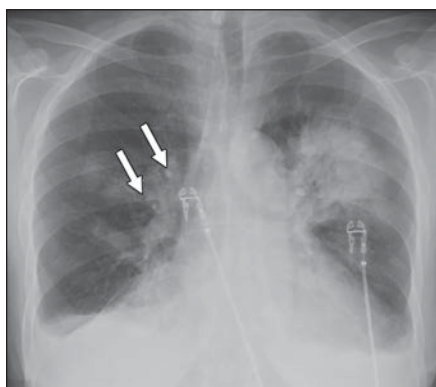
A
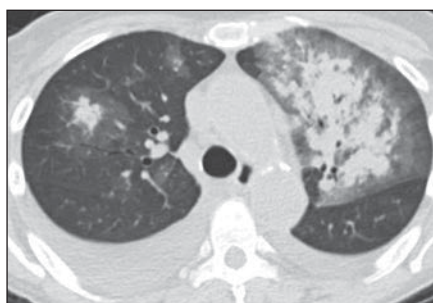
B

Fig. 4—72-year-old woman with granulomatosis with polyangiitis who presented with dyspnea.
A, Chest radiograph obtained at presentation shows dense focal pulmonary opacity in left midlung with air bronchograms. Milder areas of opacification are present as well. Thickening and dilatation of proximal segmental bronchi (*arrows*) are seen in right lung.
B, Chest CT image shows consolidative opacity in left upper lobe with perilesional ground-glass opacification. Smaller lesions of similar description are present in anterior segment of right upper lobe.
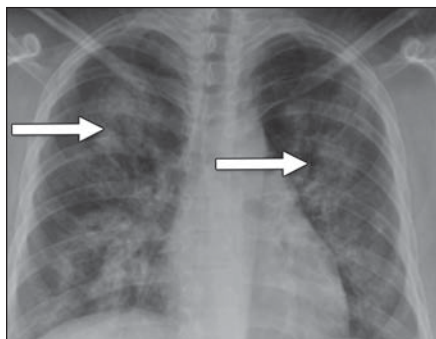

A

B

C

D
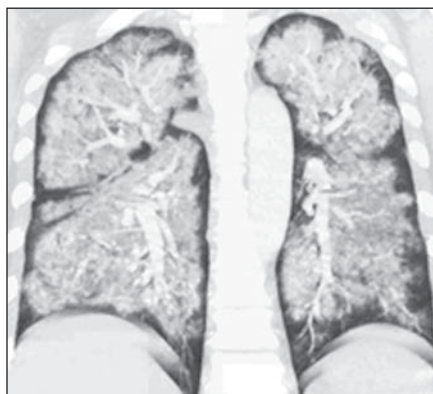
E

Fig. 5—37-year-old woman with shortness of breath. (Courtesy of Berkowitz E, Emory University, Atlanta, GA)
A, Posteroanterior chest radiograph obtained at presentation shows diffuse bilateral air-space opacities with air bronchograms (*arrows*).
B, Axial CT image obtained at presentation shows diffuse, bilateral consolidative opacities with associated air bronchograms (*arrows*).
C, Chest radiograph obtained on day 3 after clinical deterioration shows extensive bilateral confluent airspace disease with relative sparing of apices, periphery, and subpleural space.
D and **E**, Axial (**D**) and coronal (**E**) reformat CT images obtained on day 3 show severe diffuse airspace disease bilaterally. Patient subsequently was given diagnosis of diffuse pulmonary hemorrhage secondary to granulomatosis with polyangiitis.
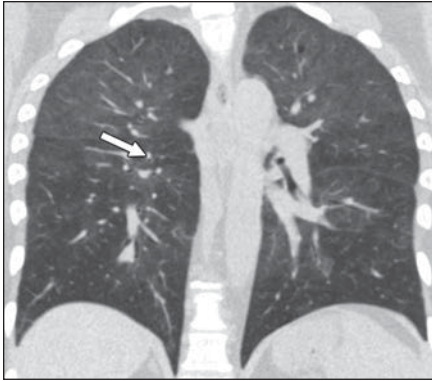
Fig. 6—34-year-old woman with recent history of alveolar hemorrhage who had positive findings of antineutrophilic cytoplasmic antibody and presented with dyspnea. Coronal CT reformat image of posterior lung shows diffuse ground-glass opacities bilaterally with upper lobe predominance and associated mild bronchial wall thickening (*arrow*). Relative peripheral and subpleural sparing is seen.

A

B

C
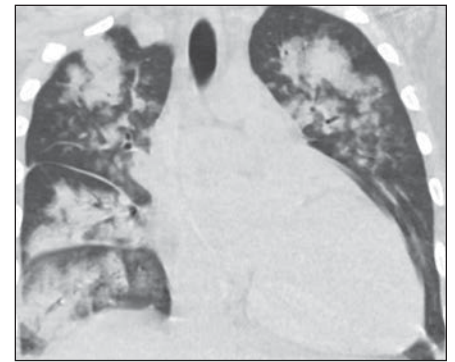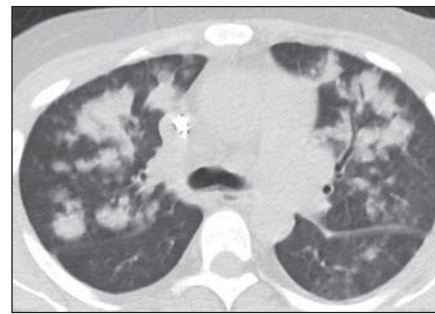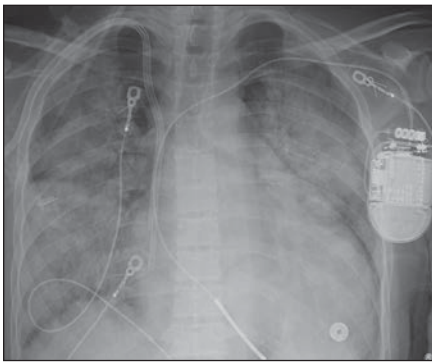
Fig. 7—33-year-old woman with history of congestive heart failure and systemic lupus erythematosus who presented with chest pain. She was hypoxic, tachypneic, and producing pink sputum.
A, Anteroposterior chest radiograph obtained at presentation shows diffuse patchy opacities bilaterally and trace right pleural effusion.
B and **C**, Axial (**B**) and coronal (**C**) reformat CT images show multifocal patchy centrilobular consolidative opacities in bilateral upper lobes and right middle and lower lobes, consistent with acute hemorrhage or infection.
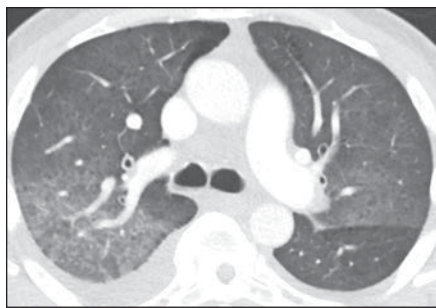

A

B
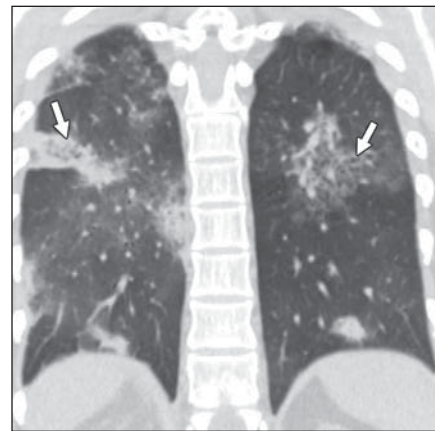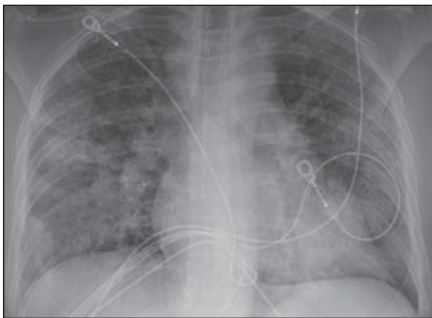
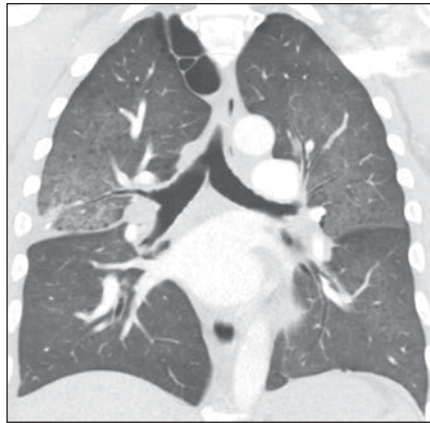**Fig. 8**—26-year-old woman with hemoptysis and skin rash.
A, Chest radiograph obtained at presentation shows bilateral diffuse pulmonary opacities.
B, Coronal reformat CT image shows consolidative, ground-glass, and reticular (*arrows*) opacities. Reticulation suggests evolving, organizing subacute hemorrhage.

Fig. 9—51-year-old man with weight loss, chronic hemoptysis, and negative antineutrophilic cytoplasmic antibody findings. Biopsy showed hemosiderosis. (Courtesy of Goyal N, Northwell Health, Manhasset, NY)
A and **B**, Axial (**A**) and coronal (**B**) reformat CT images show bilateral diffuse ground-glass opacification with septal thickening. No cause was uncovered, and idiopathic pulmonary hemosiderosis was diagnosed.
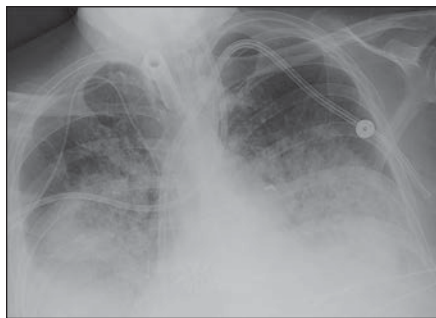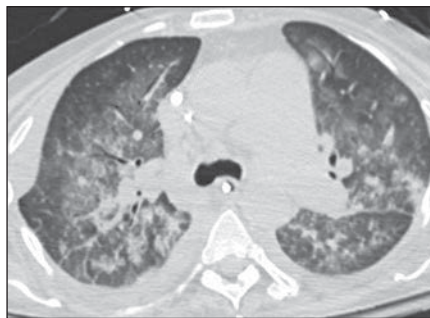
Fig. 10—62-year-old woman who had pulmonary hemorrhage 1 month after undergoing bilateral lung transplant secondary to combined pulmonary fibrosis and emphysema.
A, Initial anteroposterior chest radiograph shows bilateral air-space opacities with lower lung distribution.
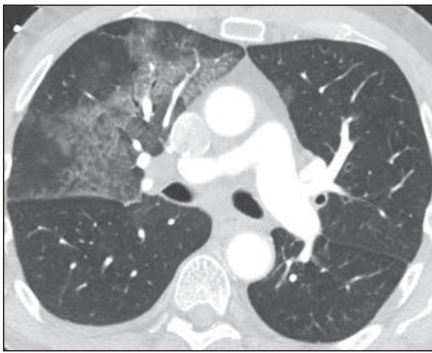**B**, Axial CT image shows corresponding diffuse ill-defined ground-glass opacities bilaterally.

Fig. 11—60-year-old man with pulmonary hemorrhage secondary to iatrogenic bronchial artery injury during pulmonary vein isolation for atrial fibrillation.
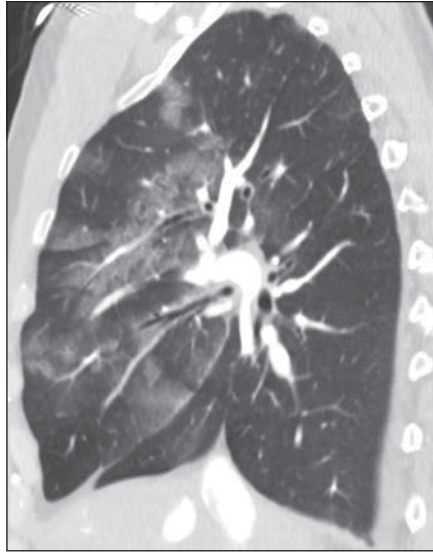**A**, Initial posteroanterior chest radiograph shows asymmetric ill-defined hazy opacity in peripheral middle to upper right lung.
B, Lateral chest radiograph shows opacity located anteriorly and primarily in upper lobe.

(Fig. 11 continues on next page)

C

D

Fig. 11 (continued)—60-year-old man with pulmonary hemorrhage secondary to iatrogenic bronchial artery injury during pulmonary vein isolation for atrial fibrillation.
C and **D**, Axial (**C**) and sagittal (**D**) reformat CT images through right lung show ground-glass opacification throughout right upper lobe and, to lesser extent, right middle lobe.