Diffuse Alveolar Hemorrhage in Acute Myeloid Leukemia
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Summary: Diffuse alveolar hemorrhage is a potentially fatal pulmonary disease syndrome that affects individuals with hematological and nonhematological malignancies. The range of inciting factors is wide for this syndrome and includes thrombocytopenia, underlying infection, coagulopathy, and the frequent use of anticoagulants, given the high incidence of venous thrombosis in this population. Dyspnea, fever, and cough are commonly presenting symptoms. However, clinical manifestations can be variable. Obvious bleeding (hemoptysis) is not always present and can pose a potential diagnostic challenge. Without prompt treatment, hypoxia that rapidly progresses to respiratory failure can occur. Diagnosis is primarily based on radiological and bronchoscopic findings. This syndrome is especially common in patients with hematological malignancies, given an even greater propensity for thrombocytopenia as a result of bone marrow suppression as well as the often prolonged immunosuppression in this patient population. The syndrome also has an increased incidence in individuals with hematological malignancies who have received a bone marrow transplant. We present a case series of 5 patients with acute myeloid leukemia presenting with diffuse alveolar hemorrhage at our institution. A comparison of clinical manifestations, radiographic findings, treatment course, and outcomes are described. A review of the literature and general overview of the diagnostic evaluation, differential diagnoses, pathophysiology, and treatment of this syndrome are discussed.

Introduction
Diffuse alveolar hemorrhage (DAH) is a potentially fatal pulmonary disease that affects individuals with cancer and hematological/nonhematological malignancies. Clinicians caring for patients with acute myeloid leukemia (AML) must maintain a high index of suspicion for DAH, because these patients are immunocompromised by their underlying disease process and subsequently at increased risk because they typically receive treatment with immunosuppressive agents and stem cell transplantation. Here we present a case series of 5 patients with AML who developed DAH. We also review the clinical presentation, diagnostic evaluation, differential diagnosis, and therapeutic management of this potentially life-threatening clinical syndrome.

Case Series
Table 1 summarizes the clinical characteristics for the 5 patients. The median patient age was 57 years (range, 51–70 years). Three (60%) patients were women. No congruity was observed on the AML subtype diagnosed by pathology. Two (40%) patients had received allogeneic hematopoietic stem cell transplantation (HSCT) with matched unrelated donors in the year prior to developing DAH, whereas the other 3 patients were receiving induction chemotherapy (7 days standard-dose cytarabine plus 3 days of daunorubicin). The 2 patients who received HSCT had prior pulmonary function tests available, with results revealing decreased diffusing lung capacity for carbon monoxide of below 80%. Three patients had a history of a prior or underlying pulmonary disorder, including 1 patient with a history of left lower lobe resection, 1 patient with a history of chronic obstructive pulmonary disease, and 2 patients with a history of cryptogenic organizing pneumonia. One patient had a history of an unknown autoimmune disorder affecting his ear.

Each patient’s clinical presentation was different. One patient presented with fever at the time of diagnosis of DAH (by bronchoscopy). Four patients developed hypoxia with increasing oxygen requirements and dyspnea. Three patients complained of cough, and 2 patients presented with bleeding at other sites in the form of epistaxis. One patient had hemoptysis and that patient was neither hypoxic nor dyspneic at the time. All patients were thrombocytopenic and anemic.

On radiological imaging, all 5 patients had bilateral, ground-glass pulmonary opacities on computed tomography (CT). In 3 patients, the findings of bronchoalveo-
lar lavage (BAL) on bronchoscopy confirmed the diagnosis of DAH by retrieving progressively bloody effluent on BAL. DAH was suspected in 1 patient by her clinical syndrome and pinkish effluent on BAL, and 1 patient had suspected DAH based on documentation of bloody secretions noted from bronchoscopy performed at a different institution. Although none of the cultures taken during bronchoscopy in the 5 patients revealed an underlying infectious process, all patients were being empirically given broad-spectrum antibiotics.

All 5 patients were treated with high-dose steroids and 1 patient also received aminocaproic acid and factor VII. Three patients died due to hypoxic respiratory failure within 30 days of confirming the DAH diagnosis by bronchoscopy. The other 2 patients did not require intubation and were weaned off supplemental oxygen and discharged home in stable condition.

Discussion

DAH is a clinical syndrome defined by a disturbance of the alveolar-capillary basement membrane that causes bleeding into the pulmonary alveoli. It is a final, common pathway for a variety of underlying issues affecting the lungs, including autoimmune vasculitides, drug

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Malignancy</th>
<th>Oncological Therapy at DAH Diagnosis</th>
<th>Pulmonary Disease History</th>
<th>Exposure to Anticoagulants</th>
<th>Symptoms</th>
<th>Bleeding at Other Sites</th>
<th>Available Vitals on Presentation</th>
<th>WBC, 10⁹/µL</th>
<th>Hemoglobin, g/dL</th>
<th>Platelet Count, 10⁹/µL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>63</td>
<td>AML (FAB, M5a)</td>
<td>7 + 3 induction COP</td>
<td>LLL resection Unknown autoimmune disorder</td>
<td>No</td>
<td>Cough Dyspnea Fever Hypoxia</td>
<td>Epistaxis BP: 124/78 mm Hg HR: 102 beats/minute RR: 20 breaths/minute Temp: 98.8 °F</td>
<td>3.74</td>
<td>7.4</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>51</td>
<td>AML (FAB, M1 in relapse)</td>
<td>MUD Allogenic HSCT COP COPD Rhinovirus</td>
<td>Prophylactic dalteparin (5000 U)</td>
<td>Cough Fever Hemoptysis</td>
<td>Epistaxis BP: 121/80 mm Hg HR: 109 beats/minute RR: 20 breaths/minute O₂ saturation: 96% on room air Temp: 98.7 °F</td>
<td>0.02</td>
<td>8.1</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>70</td>
<td>ALL (WHO, therapy-related myeloid neoplasms)</td>
<td>Reinduction MEC</td>
<td>Nodular pneumonia Suspected sleep apnea</td>
<td>No</td>
<td>Dyspnea Hypoxia</td>
<td>No BP: 99/51 mm Hg HR: 76 beats/minute RR: 17 breaths/minute Temp: 97.7 °F</td>
<td>0.03</td>
<td>7.4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>57</td>
<td>AML (WHO, with myelodysplasia-related changes)</td>
<td>MUD Allogenic HSCT</td>
<td>None</td>
<td>No</td>
<td>Dyspnea Hypoxia Left chest wall pain</td>
<td>No BP: 127/71 mm Hg HR: 78 beats/minute RR: 30 breaths/minute O₂ saturation: 97% on room air Temp: 97.8 °F</td>
<td>0.30</td>
<td>9.8</td>
<td>15</td>
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<tr>
<td>5</td>
<td>F</td>
<td>56</td>
<td>AML (FAB, M4)</td>
<td>7 + 3 induction None</td>
<td>No</td>
<td>Cough Dyspnea Hypoxia</td>
<td>No BP: 139/88 mm Hg HR: 109 beats/minute RR: 22 breaths/minute O₂ saturation: 95% on room air Temp: 99.3 °F</td>
<td>95.10</td>
<td>7.1</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. — Select Clinical Characteristics of Study Patients

continued on the next page
toxicities, infections, organ transplantation, and radiotherapy.\textsuperscript{1,2} Among patients with leukemia, DAH is one of the most common, noninfectious complications related to thrombocytopenia.\textsuperscript{2} In particular, DAH has been associated with patients following HSCT, with a reported incidence of 3% to 20% in patients following HSCT and a mortality rate that ranges from 50% to 80%.\textsuperscript{3} Early recognition and management is crucial given the potential for rapid progression and the high rate of mortality.

DAH can be divided into 3 characteristic patterns on histological examination, thus reflecting different pathophysiological mechanisms. The most common presentation described is associated with pulmonary vasculitis or capillaritis and involves neutrophilic infiltration and destruction of the pulmonary interstitium.\textsuperscript{2,7} This pattern of DAH is often caused by systemic autoimmune vasculitides. Another characteristic pattern involves extravasation of red blood cells into the alveoli without signs of vasculitis or inflammation, and it may be seen with infections and a variety of drugs, including anticoagulants.\textsuperscript{2,7} Diffuse alveolar damage with edema of the alveolar septa without signs of lung inflammation or direct extravasation of red blood cells characterizes a third pattern of DAH, with hyaline membranes forming along the alveolar spaces.\textsuperscript{7} Infections, transplantation, including HSCT, and radiotherapy have all been associated with this pattern of DAH.\textsuperscript{7}

**Clinical Presentation**

In accordance with the patients in our case series, the clinical signs and symptoms of DAH may vary. The onset of symptoms is typically acute and nonspecific; fever, cough, dyspnea, and chest pain are among the most commonly presenting symptoms.\textsuperscript{1}

Although hemoptysis may occur in up to two-thirds of individuals with DAH, our case series demonstrates that hemoptysis is often absent.\textsuperscript{1} A decrease in hematocrit level should alert the clinician to possible DAH. Another report has underscored the absence of hemoptysis in patients with DAH, so hemoptysis...
sis alone is not a reliable indicator for diagnosing DAH. However, bleeding from other sites may support clinical suspicion for DAH. Our patients exhibited epistaxis, but other signs or symptoms of coagulopathy such as purpura may be present. Acute respiratory failure with hypoxia and an increasing oxygen requirement is also often seen as a presenting symptom. Findings on a pulmonary examination are typically nonspecific and may reveal tachypnea, crackles, or bronchial breath sounds.

Although the underlying pathophysiology that leads to DAH following HSCT is not well understood, patients who have received stem cell transplants are often at greatest risk for DAH within the first 30 days following transplantation. DAH occurs in approximately 5% of allogenic and autologous recipients and has a mortality rate that ranges from 50% to 100%. Other risk factors for DAH following HSCT include advanced age, myeloablative chemotherapy prior to transplantation, radiotherapy, and severe acute graft-vs-host disease. Our 2 patients who received stem cell transplants did not have DAH in the early post-transplant period, but it is worth noting that patients with leukemia remain at risk given their underlying immunosuppression and hematological disorder.

**Diagnostic Evaluation**

Abnormal blood cell counts, including those resulting in anemia and leukocytosis, and elevated inflammatory markers are typical in the setting of DAH. However, in patients with AML, these laboratory abnormalities are often ubiquitous and, thus, are limited in offering diagnostic clues. Furthermore, prior research in patients receiving HSCTs has found that the initial degree of thrombocytopenia does not correlate with the development of DAH. Findings on pulmonary function tests in the setting of DAH are typically characterized by an increased diffusing lung capacity for carbon monoxide and decreased levels of exhaled nitric oxide. The patients in our case series had normal findings on pulmonary function testing, but these tests were performed prior to the onset of clinical symptoms of DAH. With the rapid progression and severity of DAH, patients are often unable to complete pulmonary function testing at the time of symptoms and diagnosis.

Findings on chest radiography may appear normal or may show nonspecific, diffuse opacities reflective of diffuse lung disease (Fig 1). CT of the chest will characteristically show diffuse or patchy, bilateral ground-glass opacities, as were seen in all 5 of our case patients (Fig 2). These opacities are often more centrally located and at the bases; they typically spare the periphery. In addition, interlobular septal thickening may develop. Findings on CT are likely to rapidly progress in conjunction with disease progression. Although DAH is a clinical syndrome drawing together clinical symptoms, laboratory abnormalities, and find-

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**Fig 1.** — Posteroanterior radiograph of the chest demonstrates bilateral, multifocal opacities.

**Fig 2A–B.** — (A) Axial CT of the chest demonstrates bilateral, multifocal ground-glass opacities with a geographical distribution compatible with alveolar hemorrhage. (B) These opacities were acutely increased from findings on CT obtained 5 days prior. CT = computed tomography.
Pulmonary infections, acute eosinophilic ectasis, tumor, or infection should be distinguished from DAH.1 Pulmonary hemorrhage caused by bronchiectasis, tumor, or infection should be distinguished from DAH.2 Table 2 lists the infectious causes of DAH.9-20

Although it is essential to maintain a high index of suspicion for DAH, clinicians must also consider a broad differential of alternative diagnoses. In addition, consideration should be given to the potential etiologies instigating DAH. Patients with leukemia may develop DAH related to thrombocytopenia or another coagulopathy triggered by the malignancy. These patients also often require treatment with anticoagulants given their propensity for venous thrombosis. Other treatments can place patients at risk for developing DAH through bone marrow suppression. Use of cytarabine and all-transretinoic acid are among several immunosuppressive agents associated with DAH.2

When considering alternative diagnoses to DAH, localized pulmonary hemorrhage caused by bronchiectasis, tumor, or infection should be distinguished from DAH.1 Pulmonary infections, acute eosinophilic pneumonia, aspiration pneumonitis, and acute respiratory distress syndrome can all present with similar clinical and radiographic findings. Diffuse leukemic infiltration of the lungs may be a manifestation of malignancy and can be confused with DAH.5 Viral pneumonias, *Pneumocystis jiroveci* infection, *Mycoplasma pneumoniae* infection, and toxoplasmosis, among other atypical infections, can often present with diffuse pulmonary infiltrates comparable with CT findings for DAH.2 Table 2 lists the infectious causes of DAH.9-20

It is important that clinicians remember that DAH can disguise itself in areas of infection as well as infarction.2 As reflected in our case series, it seems reasonable to consider empirical antibiotic coverage while establishing a diagnosis. Furthermore, pulmonary edema and prior injury from radiotherapy can complicate or obscure the diagnosis and should be worked-up and treated if necessary.2

In patients who have received HSCT, idiopathic pneumonia syndrome and engraftment syndrome should also be considered in the differential diagnosis.2 Engraftment syndrome is usually characterized by noninfectious fever following HSCT, skin rash or erythroderma, and increased capillary permeability leading to pulmonary edema with similar radiological appearances to DAH.2 Engraftment syndrome occurs in 30% to 40% of patients following bone marrow transplant, and it is thought to be related to cytokine production during engraftment.2,8 Idiopathic pneumonia syndrome has been described in patients following HSCT, typically within the first 6 months after transplantation.2,8 This syndrome is associated with symptoms and signs of pneumonia and widespread alveolar injury despite the absence of infection, cardiac dysfunction, renal failure, or iatrogenic fluid.2,8 Indeed, this expansive definition encompasses a variety of disorders, and DAH following HSCT and engraftment syndrome have both been considered subset classifications of idiopathic pneumonia syndrome.8

## Treatment

Standard treatment strategies for DAH are typically directed toward the underlying etiology. Supportive-care measures, including hemodynamic support and invasive or noninvasive oxygen supplementation, the discontinuation of any offending agents, and reversal of coagulopathy are basic first-line therapies. In cases of DAH with an etiology suspected to be attributable to autoimmune vasculitides, immunosuppressive therapies and plasmapheresis have been used. Systemic high-dose steroids are typically recommended for noninfectious cases of DAH to combat the inflammation precipitated by the underlying disease process.9 However, research has not shown significant differences in rates of mortality between patients with DAH receiving low-, medium-, or high-dose steroids.9

Use of platelet transfusions to treat thrombocytopenia in the setting of hemorrhage is widely accepted, but further research is necessary for the use of other treatments such as aminocaproic acid and activated factor VII. Although initial study results have suggested a benefit to using aminocaproic acid in addition to steroids to treat DAH in patients who had received allogeneic HSCT, subsequent research has showed no benefit.9 Prior case reports and research have shown that use of factor VII can control bleeding in the set-

| Table 2. — Infectious Causes of Diffuse Alveolar Hemorrhage |
|---|---|
| **Category** | **Agent/Disease** |
| Bacterial | *Legionella*<sup>9</sup> |
| | *Leptospira*<sup>10</sup> |
| | *Mycobacterium tuberculosis*<sup>11</sup> |
| | *Mycoplasma pneumoniae*<sup>12</sup> |
| | *Stenotrophomonas maltophilia*<sup>6</sup> |
| Fungal | Invasive aspergillosis<sup>13</sup> |
| | *Mucormycosis*<sup>19</sup> |
| Parasitic | *Strongyloides stercoralis*<sup>10</sup> |
| Viral | *Cytomegalovirus*<sup>14</sup> |
| | *Dengue*<sup>14</sup> |
| | *Influenza H1N1*<sup>16</sup> |
| | *Hantavirus*<sup>17</sup> |
ting of DAH, but the cost can be restrictive in patients whose underlying disease remains grim.10 Use of factor VII must also be weighed against the risk of thrombosis, and clinicians should use it with caution or avoid it altogether in patients who have had recent surgery or have a history of thrombosis, liver disease, myocardial infarction, or stroke.10 The patients in our case series all received high-dose steroids in accordance with current recommendations; 1 patient received aminocaproic acid and factor VII without success.

Conclusions

Early recognition and prompt diagnosis of diffuse alveolar hemorrhage (DAH) in patients with acute myeloid leukemia can be a challenging but decisive step toward decreasing the high mortality rate associated with this life-threatening syndrome. Our case series highlights the combination of clinical signs and diagnostic evidence that can help distinguish DAH from alternative diagnoses. Further research may help elucidate the underlying pathophysiological mechanisms of DAH, particularly following hematopoietic stem cell transplantation, and unlock prospects for improved diagnosis and treatment.

References