Diffuse Alveolar Hemorrhage as a Manifestation of Childhood-Onset Systemic Lupus Erythematosus

Saimun Singla, DO, a Debra L. Canter, MS, a, b Timothy J. Vece, MD, b, c Eyal Muscal, MD, MS, a, b Marietta DeGuzman, MD a, b

BACKGROUND: Diffuse alveolar hemorrhage (DAH) is a devastating clinical syndrome characterized by a falling hematocrit, respiratory insufficiency, and radiographic evidence of pulmonary infiltrates. Literature regarding management of DAH in childhood-onset SLE (cSLE) is limited.

METHODS: We reviewed the presentation, management, and outcome of DAH in a pediatric tertiary medical center with one of the largest cSLE cohorts in North America. During a 10 year period 7 of 410 children with cSLE had DAH.

RESULTS: The majority of cSLE patients with DAH were male (71%) and Hispanic (57%). The median age at the time of DAH diagnosis was 14 years (range 3 -15 years). DAH was the presenting manifestation of cSLE in 29% of children; 71% presented with DAH within 3 months of their diagnosis. All patients had cough, 86% had dyspnea, and 29% had hemoptysis. All patients had anemia and 71% had thrombocytopenia. Eighty-six percent had hematuria/proteinuria, and a positive anti-double stranded DNA antibody. Chest imaging showed diffuse ground glass opacities in all events. All patients developed respiratory insufficiency (29% supplemental oxygenation and 71% mechanical ventilation). Transfusions were required in 57% of cases. All patients received corticosteroids and additional immunomodulation to achieve disease control. Eighty-six percent of our DAH/cSLE cohort survived their initial event (median follow-up 2.5 years). No survivor required supplemental oxygen or had a DAH recurrence.

CONCLUSIONS: SLE should be in the hospitalist’s differential diagnosis for any child with respiratory insufficiency, cytopenias, and/or urinary abnormalities. Once cSLE is identified, initiation of aggressive immune suppression with multiple agents may enhance outcomes.
Diffuse alveolar hemorrhage (DAH) is a rare and potentially devastating clinical syndrome characterized by falling hematocrit, hypoxemic respiratory insufficiency, and radiographic evidence of pulmonary infiltrates. The incidence of DAH is only 1% to 5% in adult systemic lupus erythematosus (SLE) patients, yet the mortality rate typically exceeds 50%, with recurrences reported even after survival of the initial bleed. Literature regarding management of DAH in childhood-onset SLE (cSLE) patients is limited. Additionally, there are a paucity of cSLE-related DAH case series with long-term follow-up. We reviewed the frequency, presentation, management, and outcome of DAH in a pediatric SLE population at a pediatric tertiary medical center with one of the largest cSLE cohorts in North America. Given that cSLE is rarely encountered by most pediatric providers, our findings will improve the ability of pediatric hospitalists to recognize and implement early and effective care for cSLE patients with DAH.

METHODS
We performed a 10-year retrospective review of all cSLE patients presenting with DAH at a pediatric tertiary care center that serves as a regional and international referral institution. We searched electronic medical records for a coded diagnosis of cSLE as well as DAH or pulmonary hemorrhage from January 2000 to August 2010. The charts of cSLE patients during that time period were reviewed to (1) confirm that patients met 4 of 11 American College of Rheumatology criteria for SLE (verified by a Pediatric Rheumatologist) and (2) identify hypoxia, dyspnea, cough, anemia, infiltrates on chest radiograph, hemosiderin-laden macrophages on bronchoalveolar lavage, and/or histologic evidence of DAH. Patients with drug-induced lupus or mixed connective tissue disease were excluded. We identified 410 cSLE patients during the review period. Seven patients met inclusion criteria for our series. Chart review was performed by two reviewers. Patient demographics, clinical and laboratory manifestations at time of DAH, treatments, and outcomes were recorded. This study was approved by the Baylor College of Medicine Institutional Review Board. Descriptive statistics were generated using Stata 13.0 (Stata Corp., College Station, TX).

RESULTS
Patient Demographics and Clinical Presentation
The majority of cSLE patients with DAH were male (71%) and Hispanic (57%). This is in comparison with 17% male and 37% Hispanic patients in the total cSLE cohort included in the review period. Median age at the time of DAH diagnosis was 14 years (range 3–15 years). In 29%, DAH was the presenting manifestation of cSLE. Seventy-one percent presented with DAH within 3 months of initial SLE diagnosis. All patients had cough, and 86% had dyspnea at the time of DAH presentation. Hemoptysis was present in 29%. All patients had anemia, 71% had thrombocytopenia, 86% had hematuria and proteinuria, 57% had class IV lupus nephritis based on renal biopsies, and 86% tested positive for anti–double-stranded DNA (anti-dsDNA) at the time of DAH presentation. Chest x-rays for all 7 patients revealed findings consistent with DAH, including diffuse ground-glass opacities (Fig 1A). Chest computerized tomography (CT) in 5 patients demonstrated ground-glass opacities and septal thickening (Fig 1B). Bronchoalveolar lavage obtained in 3 patients showed hemosiderin-laden macrophages without evidence of infection. Lung biopsy specimens in 2 patients demonstrated hemosiderin-laden macrophages, multifocal capillaritis with immunoglobulin and complement deposition, and neutrophilic infiltration in the pulmonary capillaries.

Clinical Management
All patients developed respiratory insufficiency, with 29% requiring...
TABLE 1  Treatments and outcomes of DAH in 7 cSLE patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Immunosuppressive Therapies</th>
<th>Other Therapies</th>
<th>Oxygen Requirement</th>
<th>Length of Follow-up, y</th>
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<tr>
<td>1</td>
<td>IVMP, AZA</td>
<td></td>
<td>NC</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>IVMP, CYC</td>
<td></td>
<td>MV</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>PRED, CYC, RTX</td>
<td></td>
<td>MV</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>IVMP, MTX, RTX, IVIG</td>
<td>PLEX</td>
<td>MV</td>
<td>2.5</td>
</tr>
<tr>
<td>5</td>
<td>IVMP, CYC</td>
<td></td>
<td>NC</td>
<td>2.75</td>
</tr>
<tr>
<td>6</td>
<td>IVMP, CYC, RTX</td>
<td></td>
<td>MV</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>7</td>
<td>IVMP, CYC, IVIG</td>
<td>PLEX</td>
<td>MV*</td>
<td>Died 22 d after admission</td>
</tr>
</tbody>
</table>

AZA, azathioprine; CYC, cyclophosphamide; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MTX, methotrexate; PLEX, plasma exchange; PRED, prednisone; RTX, rituximab.

* Required oscillatory support.

supplemental oxygenation and 71% requiring mechanical ventilation. Fifty-seven percent required transfusions to maintain adequate hemoglobin levels. All patients received corticosteroids and ≥1 additional immunomodulator to achieve disease control (Table 1).

Outcomes

Eighty-six percent of the DAH/cSLE cohort survived their initial event. The median length of follow-up was 2.5 years after initial admission (range 0.5–2.8 years). None of the DAH survivors required supplemental oxygen after discharge or had a recurrence of DAH, flare-up of underlying disease, or significant complications (such as infection) after therapy for DAH.

DISCUSSION

The catastrophic nature of DAH has been reported in adult SLE cohorts, but there is a paucity of literature on this manifestation in the pediatric population (Table 2). Management of DAH in cSLE patients is largely empirical and based on case reports and small series that often predate the use of multiple immunomodulators. To our knowledge, this study is one of the largest series on DAH exclusively in children with lupus and provides pediatric hospitalists with guidance regarding initial presentation of DAH and potential for favorable outcomes with early recognition and use of multimodal therapy.

The frequency of DAH during a 10-year period approximated that of the adult SLE literature. However, compared with adult DAH SLE cohorts, we report a higher percentage of male patients. This is also in contrast to the higher frequency of DAH seen in female cSLE patients from a Brazilian study. Another notable difference between adult studies was that a majority of our cSLE patients presented with DAH within 3 months of their initial diagnosis, signifying ongoing, underlying disease activity.

Only 2 patients presented with overt hemoptysis. This is opposed to other reports in the adult SLE and cSLE literature in which hemoptysis is a prominent feature of DAH, making the diagnosis much more recognizable. Unlike adults, hemoptysis is not a prominent symptom in children with pulmonary hemorrhage and is present in ~25% of pediatric patients. Fullmer et al stated that this could be a function of the size and anatomy of the pediatric airway or of the decreased ability of children to expectorate. This element underscores the importance of clinical vigilance for DAH in both previously healthy patients and severely ill lupus patients who develop acute respiratory distress without hemoptysis. The pattern of hemorrhage on imaging should be a consideration in evaluating any patient presenting with pulmonary hemorrhage. In our series, all patients had chest imaging consistent with a diffuse pattern of intra-alveolar bleed, as demonstrated by ground-glass opacities and septal thickening. This is supported by Susarla and Fan, who found that children with DAH typically have bilateral mixed airspace and interstitial infiltrates on chest films and CT. Our findings of diffuse alveolar infiltrates on chest imaging was also observed in a study by Araujo et al, who compared the presentation of adult and pediatric SLE-related DAH cases.

Extrapulmonary organ involvement in a DAH patient should make the hospitalist concerned about cSLE. These manifestations include cytopenias, renal involvement, and positive anti-dsDNA antibodies. Hematologic abnormalities such as anemia and/or thrombocytopenia were present in the majority of our cohort. In addition to blood loss, these derangements, often secondary to immune-mediated mechanisms in lupus, were more likely a feature of underlying cSLE disease activity rather than a causative factor for DAH. Our findings are concordant with Araujo et al and Martinez-Martinez et al, whose studies both noted frequent occurrence of thrombocytopenia and DAH in cSLE patients. Although the degree of anemia would not help differentiate isolated conditions from underlying lupus.
DAH from that of DAH complicating cSLE, laboratory results such as cytopenias and/or positive markers of hemolysis should raise suspicion for lupus. A peripheral smear and direct Coombs test to detect autoimmune hemolytic anemia may provide clues to cSLE in a patient with DAH.

Six of our patients had hematuria and proteinuria at DAH presentation, indicative of glomerulonephritis. The concurrent presentation of renal and pulmonary disease approximates findings in other adult and pediatric DAH cohorts and is related to similar immune-mediated microvascular injury patterns in both organs. Renal involvement in addition to DAH can indicate an underlying systemic disorder such as lupus or antineutrophil cytoplasmic antibody-associated small vessel vasculitides. Urinalysis to evaluate for hematuria and proteinuria could help identify concomitant extrapulmonary organ involvement. If renal involvement is present, serum anti-dsDNA antibody should be obtained, as it is highly diagnostic for SLE and has been implicated in the pathogenesis of lupus nephritis.

Outcomes at our center were favorable, with 14% mortality. This is in direct contrast to reported fatalities of 69% and 33% in cSLE patients from studies by Araujo et al5 and Martinez-Martinez et al, respectively. Our series suggests that a DAH presentation of cSLE may not be catastrophic despite dramatic respiratory failure and reportedly high mortality rates. We believe this difference was a result of our early diagnosis and use of aggressive, multimodal immunosuppressive therapies. Paramount to maximizing patient outcomes is a multidisciplinary approach with hospitalists, intensivists, rheumatologists, and pulmonologists. We recognize that this cooperation can be unique to tertiary care centers but should be optimized as much as possible in all settings.

Given the similarity in pathogenesis of microvascular injury, our therapy plan often included the use of cyclophosphamide or rituximab, approximating the treatment of antineutrophil cytoplasmic antibody-associated small vessel vasculitides, which can also present with DAH.6,7 In our series, plasma exchange and intravenous immunoglobulin were used in the patients with life-threatening disease, often with a combination of hemodynamic compromise, mechanical ventilation, inability to maintain adequate hemoglobin without blood products, and worsening organ dysfunction despite ongoing immunosuppressive therapy. The 5 cSLE patients with DAH who had adequate follow-up did not appear to have significant adverse outcomes. We believe this is noteworthy given that DAH can lead to organized pneumonia, collagen deposition, and pulmonary fibrosis, which in time can cause changes in pulmonary function with either restrictive or obstructive deficits.13

We recognize that the nature of this review makes us unable to determine whether our results are representative of the general cSLE population presenting with DAH. However, our single-center experience provides a basis for further investigations, including well-designed comparative trials that may warrant pooling of data from other institutions in North America, given the rarity of this disease entity.

CONCLUSIONS
Recognizing and treating DAH in children is challenging, especially without overt symptoms of pulmonary hemorrhage such as hemoptysis. Although DAH is not included in the American College of Rheumatology classification criteria for diagnosis of systemic lupus, cSLE should be in the hospitalist’s differential diagnosis for any patient with respiratory insufficiency, anemia, and extrapulmonary involvement such as cytopenias and hematuria/proteinuria. Once the disease is identified, our series supports initiation of aggressive immune suppression with multiple agents to maximize patient outcomes.

REFERENCES


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