A Deadly Complication of Systemic Lupus Erythematosus

Diffuse alveolar hemorrhage (DAH), often a catastrophic event resulting in acute respiratory failure, occurs in the setting of the collagen vascular diseases, in particular systemic lupus erythematosus (SLE). There are a number of other systemic conditions that may result in this complication, including any of the systemic vasculitides, ant basement membrane antibody disease, medications that result in vasculitis, antiphospholipid syndrome, various coagulopathies, thrombocytopenia from any cause, and less frequently, severe viral infections¹.

In this issue of *The Journal* Martinez-Martinez, *et al* describe 50 subjects with SLE, both adults and juveniles, who experienced 57 episodes of DAH². This represents the largest collection of patients with this SLE complication. There were no differences in outcomes between juveniles (< 18 yrs) and adults. In the adult group 90% were women and the mean age for the entire cohort was 23 years. Overall mortality was 42%, and not unexpectedly, the sicker patients, i.e., those requiring mechanical ventilation and those with infections, renal dysfunction, hypocomplementemia, and thrombocytopenia, had the worst outcomes. Because this was a retrospective analysis, there was no standardization of treatment before or during the DAH episode. The results reported in this study correspond to prior studies, i.e., survival depending on disease severity and the presence of infection^{3,4,5}. It is unclear, however, whether the infections resulted from the SLE treatment prior to the DAH episode or occurred following treatment for this complication. It is unlikely, however, that diffuse pneumonia alone accounts for DAH in SLE. It is known, however, that in several cases of influenza and severe acute respiratory syndrome not associated with SLE, DAH can occur⁶.

There are several lung histology findings underlying diagnosis of DAH in SLE. The first and likely most frequent is pulmonary capillaritis. This represents a small vessel vasculitis of the lung involving capillaries, arterioles, and venules. This histologic picture is similar to what occurs in

DAH that complicates antineutrophil cytoplasmic antibody positive and negative systemic vasculitides⁷. The second is organizing diffuse alveolar damage. This is the lung injury pattern that underlies the acute respiratory distress syndrome, idiopathic acute interstitial pneumonia (the Hamman Rich syndrome) and likely what was previously referred to as acute lupus pneumonitis⁸. The last is bland pulmonary hemorrhage, in which there are no inflammatory changes in the lung but rather blood and hemosiderin-laden macrophages filling the alveolar spaces. This same picture occurs in idiopathic pulmonary hemosiderosis and with DAH of the coagulopathies¹. In all 3 histologic pictures there is injury to the shared basement membrane between alveolar capillaries and epithelium, with leakage of blood into the alveolar spaces. It is estimated that 2% of patients with SLE will develop DAH, and this complication accounts for up to 4% of all pulmonary hospital admissions in SLE³. Most admissions for SLE pulmonary-associated complications are due to bacterial and viral pneumonias and thromboembolic disease.

The article by Martinez-Martinez, *et al* confirms the high mortality of DAH in SLE, which is most often due to respiratory failure. It also confirms the association of DAH with lupus nephritis. As expected, the most common demographic affected are younger women. They also noted that only 57% of these patients reported hemoptysis. This is not unusual, as up to 33% of subjects with DAH from all causes fail to report this symptom⁷. Pulmonologists always consider the possibility of DAH from any etiology in any patient who presents with more or less diffuse pulmonary infiltrates and a falling hemoglobin level. In such patients, bronchoalveolar lavage (BAL) is performed. If BAL demonstrates increasing red blood cell counts in sequential lavages, the diagnosis of DAH is established but not the etiology or the underlying pathology. BAL was not routinely performed, and in some cases premorbid serum hemoglobin levels were unknown in the Martinez-Martinez series.

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This brings us to an important point: In the Martinez-Martinez, *et al* article, 35% of the episodes of DAH represented the initial manifestation of SLE. This supports all prior series of this complication in SLE^{3,4,5}. Another important issue that should be noted: Once a DAH episode occurs in SLE, reoccurrences are sometimes a continuing problem. Unfortunately, neither the literature nor the current study reports any tested treatment protocol. Because pulmonary capillaritis underlies DAH, similarly to what occurs in the systemic vasculitides, high-dose intravenous glucocorticoids, cyclophosphamide, rituximab, and plasmapheresis are the usual treatments initiated^{9,10,11}. Other case reports describe the effective use of intravenous immunoglobulin. In uncontrolled DAH with severe respiratory failure, extracorporeal membrane oxygenation and activated factor VIII to control hemorrhage have been successful in several reports^{12,13}.

Fortunately, DAH in SLE, although often fatal, represents an uncommon complication. BAL establishes the DAH diagnosis, and the lavagete can also be evaluated for infectious agents. Early recognition and prompt treatment likely offer the best chance for improved survival.

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