Diffuse Alveolar Hemorrhage in Autoimmune Diseases

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Diffuse alveolar hemorrhage may develop in autoimmune diseases, coagulation disorders, infections, or following exposure to inhaled toxins. Most cases are caused by capillaritis. Among the autoimmune diseases, DAH is reported in antiphospholipid syndrome, Behcet's syndrome, Goodpasture's syndrome, Henoch-Shoenlein syndrome, Wegener's granulomatosis, microscopic polyarteritis, and systemic lupus erythematosus [1,2]. In this issue of *IMAJ*, Bar Dayan et al. [3] report the fifth known case in the literature of a patient with ulcerative colitis who developed DAH.

The clinical manifestations of DAH include dyspnea, hemoptysis, anemia, with a rapid drop in hemoglobin of >1 g/dl, fever, hypoxia, and diffuse crackles on lung examination. There may be extrathoracic evidence of systemic vasculitis. The pathognomonic clinical triad consists of the 3 Hs – hemoptysis, hypoxia, and a drop in the hemoglobin level. In the case described here, the patient presented with all of these manifestations. However, hemoptysis has been reported in only 60% of cases. Laboratory tests include antinuclear factor, anti-dsDNA, C3, C4, erythrocyte sedimentation rate, anticardiolipin antibody, antineutrophil cytoplasmic antibodies, and anti-glomerular basement membrane [1,2].

The reported patient had a low C4. Interestingly, anti-lactoferrin antibodies, a subtype of ANCA, were also detected. These antibodies are infrequently related to vasculitis, but are described in patients with inflammatory bowel disease. The pathologic role of the anti-lactoferrin ANCA antibodies is yet to be elucidated [4].

Radiologic findings are diverse. They include bilateral alveolar-interstitial infiltrates – perihilar or basilar, that spare the apices and periphery – unilateral densities and pleural effusions; but they may also be normal [1,2].

If the patient's general and respiratory status permits, valuable information can be gained from measuring the diffusing capacity for carbon monoxide. The DLCO in DAH increases >130% predicted or increases 30% above baseline. In contrast, DLCO decreases in pneumonitis [1,2].

Further recommended ancillary tests should include bronchoalveolar lavage, to be performed within the first 48 hours of admission. The diagnostic findings are: polymorphonuclear cells 30–91%, macrophages and monocytes 1–45%, and lymphocytes 0–8%. Hemosiderin-laden or pigment-laden macrophages are found in virtually 100% of cases. In many cases, a transbronchial or thoracoscopic lung biopsy is warranted [1].

The histologic picture consists of interstitial erythrocytes and/or hemosiderin, fibrinoid necrosis of capillary walls, inter-alveolar septal capillary occlusion by fibrin thrombi, and neutrophils and nuclear dust in the interstitium, in the fibrin, and in the adjacent alveolar spaces. Fibrin clots are attached to inter-alveolar septa. There may be immune complex deposition. These histologic findings are compatible with vasculitis [2].

There is limited yet compelling evidence that the deposition of immune complexes in or along the microvascular endothelium plays a major role in the pathogenesis of most vasculitic syndromes, including the pulmonary microvascular injury seen in pulmonary capillaritis. Cellular damage results from immune complex activation. Immune complexes are difficult to demonstrate in DAH [5]. Possibly, at the time of biopsy, the immune complexes may already be cleared.

Santos-Ocampo et al. [6] described their experience with DAH in seven SLE patients. DAH is an uncommon complication of SLE, occurs in 1.5–3.7% of hospital admissions, and is the presenting manifestation in 11% of patients. The mean duration of SLE was 4.5 years. Patients with lupus nephritis were at increased risk. Recurrent DAH occurred in four patients. Six patients were receiving treatment for SLE at the time of DAH. Hemoptysis occurred in 54% of cases. Initial treatment included empiric antibiotics, high dose corticosteroids orally or intravenously, with or without cyclophosphamide. Plasmapharesis was added in five episodes. Mechanical ventilation was required in four cases. There was a 100% survival rate. However, in three other case series, the survival rate was 50–75%.

In patients with Wegener's granulomatosis, DAH is uncommon. However, when it does develop, it is often the initial presentation of the disease. Furthermore, these patients tend to have a fulminant course. Even with corticosteroid and cyclophosphamide treatment, the mortality rate may reach 66%, whereas 75% have complete remission with the more common presentation of Wegener's granulomatosis [7].

Pulmonary capillaritis is also reported in microscopic polyangiitis. In a retrospective study of 29 patients with MPA and alveolar

DAH = diffuse alveolar hemorrhage
ANCA = antineutrophil cytoplasmic antibodies
DLCO = diffusing capacity for carbon monoxide

SLE = systemic lupus erythematosus
MPA = microscopic polyangiitis

hemorrhage, pulmonary manifestations were investigated at presentation and the short and long-term outcomes were assessed. MPA was diagnosed when alveolar hemorrhage was associated with focal segmental necrotizing glomerulonephritis at kidney biopsy, or with pathologically proven small vessel vasculitis. The onset was rapidly progressive, but in 28% of patients the symptoms preceded the diagnosis by more than 1 year. The most constant systemic finding associated with alveolar hemorrhage was glomerulonephritis in 97% of patients. Lung opacities were bilateral in 26 (90%), most frequently involving the lower part of the lungs. Bronchoalveolar lavage, performed in 27 patients, was hemorrhagic in 25 (93%) and contained numerous siderophages in others. ANCA, present in 27 of the 29 patients, exhibited a pattern that was perinuclear (in 14), cytoplasmic (in 11), or mixed (in one). Patients were treated with corticosteroids (100%), cyclophosphamide (79%), plasmapheresis (24%), dialysis (28%), and mechanical ventilation (10%). The overall mortality rate was 31%. Deaths were related to vasculitis or the side effects of treatment. The 5 year survival rate was 68%. The recovery of respiratory function among survivors was considered clinically complete in 69% of the patients, However, 24% had persistent alterations on pulmonary function tests. Of the 11 patients who had relapses, 2 died from alveolar hemorrhage [8].

Pulmonary involvement in Behcet's syndrome is rare, often presents with hemoptysis, and consists of a necrotizing vasculitis that involves all sizes of pulmonary arteries, veins, and capillaries. In a patient with pulmonary capillaritis and glomerulonephritis, biopsy specimens revealed staining for immunoglobulin G, C3 and C4. Circulating immune complexes were also identified [2]. DAH is a rare complication of the antiphospholipid syndrome, with only two cases described in the literature. One of these patients had brochiolitis obliterans and the other had microvascular thrombi [9]. Most cases of DAH associated with penicillamine, hydralazine, or propylthiouracil treatment appear to be the result of ANCA-associated vasculitis [10].

Perhaps, in multisystem autoimmune diseases and systemic vasculitides, other organs are already afflicted, usually the kidneys, increasing the morbidity and mortality rates. In addition, some autoimmune diseases including SLE may have multiple causes for pulmonary involvement, sometimes resulting in a later diagnosis or necessitating a biopsy for accurate diagnosis. Possibly, in organ-specific diseases, like ulcerative colitis, the survival rate may be better. In such a disease, a prompt diagnosis is clear-cut.

DAH is a medical emergency and treatment should be initiated promptly. Prognosis depends on early diagnosis and aggressive therapy. The therapeutic modalities include: mechanical ventilation, intravenous methylprednisolone 240–1,000 mg/day for 3 days (a repeated pulse can be administered after 1 week if necessary), cyclophosphamide 2–5 mg/kg/day (IV or orally), plasmapharesis (3–4 sessions) for persistent disease, and empiric intravenous antibiotic therapy for 1–5 days until cultures are negative. Since most diseases that result in pulmonary capillaritis are treated with immunosuppression, infection must be treated aggressively. Patients with systemic inflammatory disorders who are treated with corticosteroids, alone or in combination with cyclophosphamide, are at risk to develop *Pneumocystis carinii* pneumonia, leading to significant morbidity and mortality. Prophylaxis should be considered in this patient population [2,6].

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