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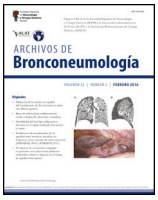

Editorial

Pulmonary Vasculitis: An Update☆

Actualización en vasculitis pulmonar

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Vasculitis is a general term for a heterogeneous group of diseases characterized by inflammation and destruction of blood vessel walls. These diseases are rare: primary vasculitis occurs at an annual incidence of 20–100 cases per million and a prevalence of 150–450 cases per million.[1] The affected organ and vessel size influence the clinical and radiological findings, and these are the criteria used in the Chapel-Hill classification of 2012.[2] Small-vessel antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is the type that most frequently affects the lung.

Vasculitis is difficult to diagnose because the forms of presentation vary and signs and symptoms overlap with other more common entities. Vasculitis should be suspected in the following clinical scenarios: (1) diffuse alveolar hemorrhage (DAH) (triad of diffuse alveolar infiltrates, hemoptysis [not always necessary], and decreased hematocrit, sometimes with increased diffusion capacity >30%); (2) rapidly progressive glomerulonephritis (active urine sediment [erythrocyte cylinders, hematuria with dysmorphic RBCs and proteinuria >500 mg/dL], elevated serum urea and creatinine, hypertension, and edema); (3) lung–kidney syndrome (patients with DAH and glomerulonephritis); (4) ulceration/deformity of the upper airway soft tissue; (5) cavitary or nodular pulmonary lesions on image testing; (6) palpable purpura (suggesting cutaneous vasculitis); (7) peripheral nervous system manifestation, such as mononeuritis; and (8) systemic disease (simultaneous presence of signs and symptoms suggesting multiorgan involvement or different organs affected over time).

In DAH, the most common laboratory test abnormalities include anemia, leukocytosis, elevated urea, and creatinine (in the case of glomerulonephritis or lung-kidney syndrome), and positive ANCAs (IgG antibodies against cytoplasmic antigens in neutrophils and monocytes [c-ANCA, specific anti-proteinase-3 antibodies, and p-ANCA, anti-myeloperoxidase antibodies]). ANCAs promote neutrophil migration, vessel wall degranulation, and the release of proteases and other toxic metabolites responsible for vascular damage,[3] so they play a significant role in the pathophysiology of AAV (granulomatosis and microscopic polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis), and are important for establishing a diagnosis. A finding of cryoglobulins and anti-basal membrane antibodies can also help establish the final diagnosis.

In DAH, high-resolution computed tomography generally reveals bilateral consolidations or bilateral diffuse ground glass opacities; in more advanced stages, septal thickening (crazy-paving pattern) can also be visualized, and if DAHs are recurrent, they can lead to pulmonary fibrosis.[4] Bronchoalveolar lavage can confirm the diagnosis of DAH, if at least 20% of the alveolar macrophages in the sample are hemosiderin-laden. The yield of transbronchial biopsy is usually <10%, but the yield of lung biopsy obtained by video-assisted thoracoscopy for the diagnosis of small-vessels vasculitis is generally high.[5] The final diagnosis is established on the basis of specific patterns of clinical, laboratory, radiological, and histopathological abnormalities.

Treatment of vasculitis consists of aggressive immunosuppression, and complications are common and severe. For this reason, evaluation of disease severity according to the proposal of the European League Against Rheumatism (EULAR)[6] is recommended. Treatment is often split into an initial "induction of remission" phase, in which a more intensive immunosuppressive therapy is used to control the active disease, followed by a "maintenance" phase, with less aggressive treatment to minimize side effects, while maintaining disease remission. For decades, treatment consisted of high-dose cyclophosphamide and glucocorticoids, which induced remission in 75% of patients within 3 months and in up to 90% within 6 months, although relapses and adverse effects were common.[7] New biological treatments seek to limit exposure to cyclophosphamide. Thus, B-cell-targeted therapy to eliminate ANCAs appears to selectively reduce the production of antibodies while preserving other immune cells. Rituximab is an anti-CD20 monoclonal antibody expressed on the surface of B-cells. Two clinical trials (rituximab vs oral cyclophosphamide in AAV[8] and rituximab vs intravenous cyclophosphamide in ANCA-associated renal vasculitis[9]) showed that rituximab was not inferior to cyclophosphamide, although the evidence strongly suggested superiority in c-ANCA-positive patients with recurrent or severe disease. No reduction in adverse events was achieved in either trial. Patients treated with rituximab who have low $CD5^+$ B-cell

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percentages relapse significantly earlier than those who maintain normal levels, so these cells are thought to be an indicator of disease activity and can be used to guide maintenance treatment in remission.[10] The EULAR currently recommends the use of either rituximab or cyclophosphamide combined with glucocorticoids as induction therapy.[6] Tocilizumab, an interleukin-6 alpha receptor antagonist, can reduce the doses of glucocorticoids required in giant cell arteritis.[11] Infliximab, an inhibitor of tumor necrosis factor-alfa that is overexpressed in vasculitis, has shown clinical improvement, reduction of inflammatory markers, and regression of pulmonary artery aneurysms in patients with Behçet's disease[12] and may, like adalimumab, be a useful glucocorticoid-sparing agent in large-vessel vasculitis.[13] Finally, plasmapheresis is another strategy for the elimination of ANCAs and circulating inflammatory markers that has proven utility in AAV patients with severe renal deterioration or DAH.[14,15]

In summary, for an optimal outcome, pulmonary vasculitis must be diagnosed and treated rapidly. Diagnosis requires a high level of suspicion and clinical experience in the management of these entities. Therapeutic strategies are more personalized nowadays and are designed according to the features of the disease. Cyclophosphamide exposure can be minimized with the use of rituximab, and infliximab and adalimumab are effective corticosteroid-sparing agents. Continuous advances in the understanding of the mechanisms involved in the etiology of these diseases will lead in the future to the development of more effective treatments.

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