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Mini-Symposium: Pulmonary Complications of Paediatric Systemic Disorders

Pulmonary Complications of Systemic Vasculitides

Brian P. O'Sullivan *

Department of Pediatrics, University of Mass. Memorial Health Care; Worcester, MA 01655

EDUCATIONAL AIMS

The reader will be able to:

1 Recognise the different forms of small vessel vasculitis that affect the lung.
2 Know the difference between PR-3 ANCA (cANCA) and MPO ANCA (pANCA) diseases.
3 Understand treatment options and rationale for these diseases.

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SUMMARY

The pulmonary vasculitides are a heterogeneous group of diseases that often occur as a component of systemic vasculitic diseases. Most frequently, pulmonary vasculitis is observed in vasculitic syndromes that preferentially affect small vessels. Pulmonary involvement may develop because the lung has an extensive vascular and microvascular network. Sensitising antigens can easily reach the lung, and there are large numbers of vasoactive and activated immune cells in the lung. A diagnosis often can be made on the basis of clinical presentation and serologic studies, but biopsy of skin, nose, kidney, or lung may be necessary to ascertain the precise syndrome.

INTRODUCTION

Simply defined, vasculitis is inflammation of the walls of blood vessels. There is a distinction between pulmonary vasculitis and pulmonary capillaritis. Pulmonary vasculitis refers to inflammation of the lung vessels of any size, whereas pulmonary capillaritis is confined to the microcirculation of the lung (alveolar capillaries, arterioles, and venules). However, both may be seen in systemic vasculitides and the connective tissue diseases. The clinical and pathological features are variable and depend on the site and type of blood vessel involved. The affected vessels may be arteries, veins, or capillaries; large, medium-sized, or small arteries may be compromised; the infiltrate may be neutrophils, lymphocytes, eosinophils, or plasma cells; the inflammation may be necrotising or granulomatous; there may or may not be immune-complex deposition, or anti-neutrophil antibodies. All of these determine the specific type of vasculitis. This review focuses on small-vessel vasculitis as a cause for pulmonary disease as this is seen more frequently in children, in this rare group of conditions.

CLASSIFICATION

Small-vessel vasculitides often present with pulmonary and/or renal manifestations. These include Henoch-Schönlein purpura (HSP), Wegener granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), Goodpasture syndrome (GPS), and many others. Small-vessel vasculitides are associated with a greater degree of necrotising injury. There is a significant overlap regarding which vessels are involved in some of these diseases, notably WG and MPA.[1,2] Large-vessel vasculitides, such as giant cell arteritis and Takayasu's arteritis rarely affect the lungs, because the intra-pulmonary arteries are medium-sized or smaller. Medium-sized vessel vasculitides such as polyarteritis nodosa and Kawasaki disease do not commonly manifest with pulmonary problems,[3] although case reports of lung disease in these conditions have been published.[4–6] The newly adopted classification for common childhood vasculitides comes from the consensus criteria endorsed by the European League Against Rheumatism and the Pediatric Rheumatology European Society (Table 1).[1]

AETIOLOGY

The pathogenesis of vascular inflammation is unknown in most cases. Vasculitis probably results from the combination of multiple

* Tel.: +508 856 4155; fax: +508 856 2609.
E-mail address: osullivb@ummhc.org.

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Table 1
New Classification of Childhood Vasculitis[1]

I. Predominantly large-vessel vasculitis
A. Takayasu arteritis
II. Predominantly medium-sized vessel vasculitis
A. Kawasaki disease
B. Childhood polyarteritis nodosa
C. Cutaneous polyarteritis
III. Predominantly small-vessels vasculitis
A. Granulomatous
1. Wegener granulomatosis
2. Churg-Strauss syndrome
B. Non-Granulomatous
1. Henoch-Schönlein purpura
2. Microscopic polyangiitis
3. Isolated cutaneous leukocytoclastic vasculitis
4. Hypocomplementemic urticarial vasculitis
5. Goodpasture's syndrome
IV. Other vasculitides
A. Behçet disease
B. Vasculitis secondary to infection (including Hepatitis B-associated polyarteritis nodosa), malignancies, and drugs (including hypersensitivity vasculitis)
C. Vasculitis associated with connective tissue diseases
D. Isolated vasculitis of the CNS
E. Cogan syndrome
F. Unclassified

Adapted from Reference 1 with permission.

risk factors including genetic predisposition, environmental factors (infection and inhalation of particulate matter), and chance. Figure 1 shows the distribution of vasculitis type in various sized vessels.

Goodpasture syndrome (GPS) is the classic example of IgA-related complex deposition.[7] A subset of small-vessel vasculitides has minimal immune-complex deposition in their walls; these so-called pauci-immune vasculitides include WG, MPA, CSS, and renal-limited vasculitis. The precise cause of tissue injury in WG and MPA is uncertain, but these forms of vasculitis are strongly associated with antineutrophil cytoplasmic autoantibodies (ANCA).[7]

CLINICAL PRESENTATION AND DIAGNOSIS

Pulmonary vasculitis is often accompanied by systemic manifestations including malaise, fever, weight loss, joint pain, kidney disease, and rash.[2] Pulmonary haemorrhage originating from the small, medium, and large pulmonary vessels is most commonly due to systemic vasculitis, which can also involve the microcirculation. Diffuse alveolar haemorrhage (DAH) is a clinico-pathologic syndrome describing the accumulation of intraalveolar red blood cells originating from the alveolar capillaries. All causes of DAH result from injury to the alveolar microcirculation. Pulmonary haemorrhage may be massive and life threatening and usually manifests as anaemia, haemoptysis, patchy, focal, or diffuse radiographic pulmonary infiltrates and, if severe, with hypoxaemic respiratory failure. Glomerulonephritis may also be severe with little prodrome.

Serologic testing is critically important in the diagnosis of small-vessel vasculitis syndromes. GPS is diagnosed by finding the presence of anti-glomerular basement membrane antibodies; whereas, WG and MPA and other vasculitides generally are associated with the presence of ANCA (Table 2). The initial designations used for ANCA, **c**-ANCA for (**c**ytoplasmic staining) and **p**-ANCA for (**p**erinuclear staining) have been replaced by terms based on the specific antigens against which ANCA is directed. The target for **c**-ANCA is proteinase-3 **(PR3**) and for **p**-ANCA is most frequently myeloperoxidase (**MPO**) (although some other antigens have been reported).[7,8]

A combination of indirect immunoflourescence (IIF) and enzyme-linked immunosorbent assay (ELISA) tests for ANCA should be obtained if the diagnosis of an ANCA-associated vasculitis is suspected. A positive ANCA by IIF alone is not specific for systemic vasculitis; a positive IIF test can be seen in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis, and other diseases.[9] It is important to also obtain the ELISA test, which differentiates PR3-ANCA from MPO-ANCA. Levels of PR3 antigen expression may be genetically determined, making some people more prone to ANCA-associated diseases than others.[10]

Flexible bronchoscopy may be useful if uncertainty exists regarding pulmonary haemorrhage versus infection as the cause of the clinical manifestations and radiologic abnormalities. Lung

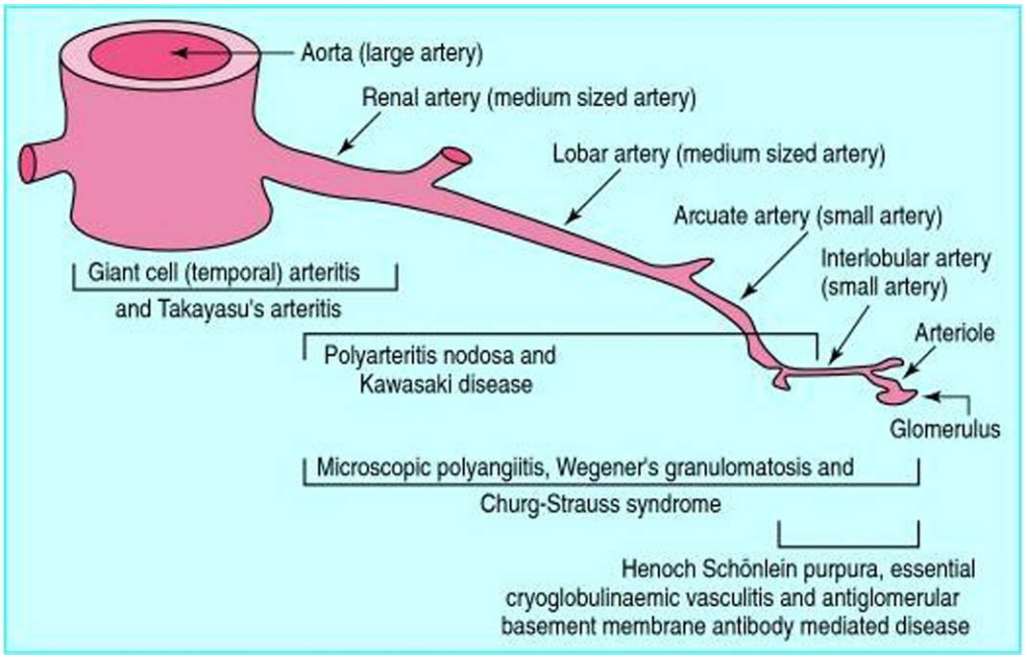

Figure 1. Spectrum of systemic vasculitides organised according to predominant size of vessels affected. Reprinted from reference 2 with permission.