Review Article

Pulmonary Vasculitis: Indian Perspective

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Abstract

Pulmonary vasculitis is an uncommon disease. Patients present with unexplained haemoptysis, pulmonary infiltrates and constitutional symptoms. Pulmonary vasculitis often goes undiagnosed due to lack of awareness and the disease is often mis-diagnosed as tuberculosis in India. Delayed or missed diagnosis leads to disease progression to a catastrophic event like diffuse alveolar haemorrhage which carries a high mortality. The outcome of appropriately treated cases, on the contrary, is good with excellent long-term survival. The present narrative review attempts to provide an overview of pulmonary vasculitis as it is seen in India. **[Indian J Chest Dis Allied Sci 2016;58:107-119]**

Key words. Pulmonary vasculitis, ANCA-associated vasculitis, Wegener's granulomatosis, Churg-Strauss syndrome, Microscopic polyangiitis, Isolated idiopathic pulmonary capillaritis, Rapidly progressive glomerulonephritis.

Introduction

The pulmonary vasculitides are a heterogeneous group of disorders of unknown aetiology characterised by inflammation, intense cellular infiltration and necrosis of small vessel walls. The lung is mostly involved in idiopathic primary small vessel (arterioles, venules and the pulmonary capillaries) vasculitis associated with anti-nuclear cytoplasmic antibodies (ANCA) called ANCA-associated vasculitis (AAV). AAV diseases include granulomatosis with polyangiitis (GPA), earlier called Wegener's granuomatosis; microscopic polyangiitis (MPA); and eosinophilic granulomatosis with polyangiitis (EGPA), earlier called Churg-Strauss syndrome (CSS). These diseases are grouped together because these share common clinical features, pathologic involvement of the small vessels, similar responses to immuno-suppressive treatment, and are commonly but not always ANCA positive.[1] However, medium-vessel vasculitis (i.e., classical polyarteritis nodosa), large-vessel vasculitis (i.e., Takayasu's arteritis), primary immune complex-mediated vasculitis (i.e., Goodpasture's syndrome), and secondary vasculitis (i.e., systemic lupus erythematosus) can all affect the lung.[1] Since the lung is mostly involved in small vessel AAV diseases we will limit our review to this group diseases only.

Epidemiology

Primary pulmonary vasculitis is rare, the incidence being 15-20 cases per million per year with an estimated prevalence of 90-300 cases per million.[2-5] A continental geographical variation in incidence of the disease has been reported. GPA is more common (8-10 cases per million per year) than MPA or EGPA in North Europe.[6-10] The incidence of EGPA is the least worldwide including India[11] and has been estimated to be 1-3 cases per million per year with a prevalence of 10-15 cases per million.[3,6-8] The mortality risk is 2.6 times higher in vasculitis group than general population.[9] The European Vasculitis Study Group (EUVAS) clinical trials reported survival rates over 1, 2 and 5 years as 88%, 85%, and 78%, respectively.[3,10] The poor prognostic markers include advanced age, higher degrees of disease activity, alveolar haemorrhage, cardiac involvement, and proteinase-3 positivity.[1]

Epidemiology of Pulmonary Vasculitis in India

Epidemiological studies addressing the epidemiology of pulmonary vasculitis have not been done in India so far.[11] The primary vasculitic disorders account for <1% of all vasculitic diseases diagnosed in rheumatology clinics in some of the large cities of the country; the lung is involved in 84% to 94% cases.[11] ANCA is a serological diagnostic marker of AAV diseases and is positive in 70% to 80% cases. GPA is most frequently diagnosed in India and MPA and

[Received: December 8, 2015; accepted: January 11, 2016]

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EGPA have been reported in negligible numbers. Pulmonary vasculitis is mis-diagnosed as tuberculosis (TB), at least initially, in 40% to 50% of the cases.[11]

Classification of Pulmonary Vasculitis

The classification of vasculitis has been challenging and has remained controversial.[12] The efforts of American College of Rheumatology (ACR), and Chapel Hill Consensus Conference (CHCC) 1990 and 2012 to classify the disease, has been unsuccessful to provide a perfect classification.[13-15] The current classification criteria are based on clinico-pathologic features rather than aetiology since aetiology remains unknown[12] and the diagnostic tools are relatively insensitive and non-specific. The most accepted classification is based on the predominant size of the vessels involved (large, medium or small) which correlates well with the clinical presentation of various vasculitis.[15] The alternate classification is based on the pathophysiological mechanism of the disorder which classify the disease into pauci-immune and immune complex-mediated disease.[12] Pulmonary vasculitis is classified as primary and secondary to systemic diseases.[14] The lung is most commonly involved in AAVs.[16]

The CHCC classified the idiopathic primary small-vessel vasculitis (SVV) into (i) AAV; and (ii) immune complex SVV (Table 1).[14]

Idiopathic pauci-immune pulmonary capillaritis, idiopathic pauci-immune rapidly progressive glomerulonephritis (RPGN) are considered as organ-specific subsets of MPA and may be ANCA negative.[16]

Aetiopathogenesis

AAV are rare heterogeneous group of diseases which share common histopathological findings, inflammation and necrosis of small vessel walls. The lungs and kidneys are involved in 70% to 80% cases.[17] Multiple factors have been implicated in the causation of vasculitis which include ethnicity, genetic [human leucocyte antigen (HLA) and others], gender, environmental factors [ultraviolet light, silicosis, infections, toxins, drugs, sarcoidosis, tobacco smoking] and surgery but exact trigger for the disease is not known.[11,12] ANCA is the hallmark of the disease which are the autoantibodies directed against proteinase-3 (PR3) and myeloperoxidase (MPO) antigen present in the azeurophillic granules of neutrophils and peroxidise positive lysosomes of monocyte. ANCA activates primed neutrophils and promote migration. The activated neutrophils express either intra-cytoplasmic antigen PR3 or MPO on their cell surfaces to which the circulating ANCA attach and degranulate, releasing the intra-cytoplasmic proteases, reactive oxygen species and other toxic metabolites into the lung interstitium. These toxic materials are causative to fibrinoid necrosis and damage to the vessel wall. The red blood cells (RBCs) and fibrin enter the alveolar space through the damaged basement membrane of the endothelium. This is referred as diffuse alveolar haemorrhage (DAH). Most SVVs of the lungs, regardless of aetiology, progress to DAH.[16] The process is reinforced by alternative pathway of complement.[17] When the interstitium and alveolar capillaries are involved in the process, it is designated as "necrotising pulmonary capillaritis". Isolated necrotising pulmonary capillaritis may occur without the involvement of arterioles and venules, when the activated primed neutrophils accumulate in the lung interstitium and undergo apoptosis releasing the toxic material. Pulmonary capillaritis in the absence of an associated systemic vasculitis is termed as idiopathic pauci-immune pulmonary capillaritis".[16] Besides ANCA, T-cells, macrophages, and other components of the immune system all have been implicated in pathogenesis of the disease.[17] Bacterial products from infection and cytokines (interleukin-1 [IL-1] and transforming growth factor-β [TGF-β]) are known to prime the circulating neutrophils in ANCA negative cases of SSV.[18] ANCA also exerts a direct cytotoxic effects on endothelial cells.[19-21] The injury to endothelial cells increases expression of adhesion molecules which enhance the attachment of primed neutrophils to endothelial surfaces, and thus, perpetuates the injury.[20] Clinically ANCA titers

Table 1. Classification of small-vessel vasculitis (Chapel Hill Consensus Conference 2012[14])

ANCA-associated Vasulitis (AAV)	Immune Complex SVV
(Necrotising vasculitis with few or no immune deposits in the small to medium vessel wall)	(Moderate to marked vessel wall deposits of immunoglobulin and complement components)
• Wegner's granulomatosis	• Anti-glomerular basement membrane disease
• Microscopic polyangiitis	• Cryoglobulinemic vasculitis
• Churg-Strauss syndrome	• IgA vasculitis (Henoch-Schönlein)
	• Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis).

Definitions of abbreviations: IgA=Immunogloublin-A

correlate with disease activity but alone raised ANCA titers is not sensitive or specific for predicting impending relapse.

Histopathological findings in AAV include, intense inflammation of small vessels of the lung, infiltration of activated neutrophils resulting in fibrinoid necrosis, destruction and occlusion of the vessel walls. Other histological features include arteriolar and capillary thrombosis, organising haemorrhages, epithelial Type-2 cell hyperplasia, and accumulation of free parenchymal haemosiderin and haemosiderin-laden macrophages (siderophage) in alveolar spaces.[18]

The physiological impact of the inflammation include hypoxaemia, increased diffusion capacity of lung for carbon monoxide (DLCO) >30% above baseline value due to accumulation of free haemoglobin in alveolar spaces suggestive of DAH. Uncontrolled or untreated, or repeated episodes of DAH ultimately results in pulmonary fibrosis evidenced by an obstructive or a mixed or a restrictive defect on pulmonary function testing (PFT) and evidence of emphysema on computed tomography (CT) of thorax.[22,23]

Clinical Presentation

The signs and symptoms of vasculitis are variable because the disease being multi-systemic. Suggestive clinical manifestations include DAH; tracheal or subglottic stenosis, pulmonary nodules or cavities, destructive or ulcerating upper airway disease, acute glomerulonephritis pulmonary renal syndrome, mononeuritis multiplex, retro-orbital mass, and palpable purpura. All classical manifestations may not be present in one patient at a given time.[1]

Classical features of DAH include diffuse bilateral alveolar infiltrates (although rarely unilateral in alveolar haemorrhage without pulmonary capillaritis), haemoptysis, and a drop in haematocrit and/or haemoglobin levels.[1] Haemoptysis, pulmonary infiltrates and anaemia representing DAH, is the most common presenting feature seen in two-thirds. However, this triad may be absent in up to 33% of patients even in the presence of a significant intra-alveolar haemorrhage.[24] DAH can be caused by use of drugs like cocaine, transretinoic acid, diphenylhydantoin and propylthiouracil. DAH can also present as alveolar haemorrhage without pulmonary capillaritis following anticoagulant use, thrombolytic therapy, in patients with thrombocytopaenia, and in patients with mitral stenosis.[24] Other symptoms include shortness of breath, cough and constitutional symptoms, like low-grade fever, night sweats etc.[24] These constellation of symptoms are shared by infective diseases, mainly TB in areas where it is highly prevalent. Nearly half of the patients develop respiratory failure requiring assisted ventilation.

Subglottic stenosis present with dyspnoea (on exertion or at rest, depending on severity of stenosis), stridor, hoarseness, brassy cough, recurrent pneumonitis due to narrowing of the extra-thoracic airway obstruction, at the level of cricoid cartilage. The flow-volume curve will typically demonstrate extra-thoracic obstruction. Destructive upper airway disease presents with unexplained chronic refractory sinusitis, epistaxis, otitis, ulcerative, or destructive oral soft tissue or bony lesions and saddle-shaped nose deformity.[1] RPGN occurs in 5% of the patient with renal insufficiency evidenced by elevated blood urea nitrogen, serum creatinine and presence of active urinary sediment (i.e., haematuria, especially with dysmorphic RBCs, RBC casts, and proteinuria >500mg/dL).[25] When glomerulonephritis occur in association with DAH it is designated as pulmonary renal syndrome. Vasculitis should be strongly suspected in patients with destructive upper or lower airway disease associated with renal insufficiency. Other clinical presentation of pulmonary vasculitis include palpable purpura,[26] mononeuritis multiplex, evident by sudden onset of abnormalities of one or more central or peripheral nerve distribution like sudden onset of foot or wrist drop with pain, numbness, paresthesia, weakness, or loss of function.[27,28] and radiological appearance include unexplained pulmonary infiltrates mostly bilateral (rarely unilateral), nodular (55%–70%) and cavitary lesions (35%–50%.)[29-30]

Granulomatosis with polyangiitis

GPA is a multi-systemic disease of small and medium vessels involving pulmonary and extra-pulmonary organs, like kidney, skin, eyes, joints, muscles, nervous system, and the heart.[1] GPA is most studied and diagnosed in India constituting 13.6% of all vasculitis.[11] The peak incidence occurs in the fourth to sixth decades with a slight female preponderance.[11] GPA is characterised by the triad of eye involvement, upper and lower respiratory tract disease and renal involvement (glomerulonephritis). Upper airway involvement is more common (85%) and includes sinusitis, epistaxis, nasal septal perforation, "classic" saddle nose deformity, subglottic or bronchial stenosis. Lower respiratory tract disease occurs in 80% cases. Patients with lung parenchymal involvement present with cough, dyspnoea, chest discomfort, haemoptysis, alveolar haemorrhage, and pulmonary lesions in the chest radiograph.[16] Renal involvement occurs in 80% to 90% patients and may be the initial presentation in 40% of the patients.[16,31-33] A complete triad may not be present at the initial

presentation. Constitutional symptoms accompany or precede disease onset and are most often associated with extra-pulmonary symptoms.[16] Pathologically, GPA is characterised by a necrotising vasculitis of the small and medium vessels, granulomatous inflammation, and parenchymal necrosis.[34,35] The disease is c-ANCA/antiPR-3 positive and has 85% to 95% sensitivity and 90% specificity for active systemic disease and 60% to 65% sensitivity for organ-limited disease and 40% sensitivity for diagnosis during remissions.[36-39] Radiological abnormalities are more common than other AVV and include alveolar, mixed, or interstitial infiltrates and nodular or cavitary disease.[29] High-resolution computed tomography (HRCT) in GPA demonstrates non-specific findings of consolidation, necrosis, multiple pulmonary cavities and nodules.[30]

Microscopic polyangiitis

Microscopic polyangiitis has a long prodromal phase with profound constitutional symptoms followed universally by RPGN.[1] Pulmonary involvement is less frequent than GPA and EGPA and occurs in 10% to 30% of patients.[40] DAH is the most common presentation.[41-43] Up to 25% of patients die during the first episode of DAH.[40] Extra-pulmonary involvement is common and involve the joints, skin, peripheral nervous system, and the gastrointestinal tract.[42] Histopathological findings include focal, segmental necrotising vasculitis and a mixed inflammatory infiltrate without granulomas.[1] Recurrent episodes of DAH leads to pulmonary fibrosis and obstructive lung disease as chronic complications.[22,29,30,40] Other pulmonary complications of MPA may include radiographic infiltrates, pulmonary artery aneurysms, fibrotic changes, and airway disease. HRCT demonstrate heterogeneous, bilateral, ground-glass infiltrates suggestive of DAH. The p-ANCA by indirect immunofluorescence (IIF) is positive in 50% to 75% of patients, and c-ANAC (by IIF) positive in 10% to 15% of cases. The MPO-ANCA by enzyme-linked immunosorbent assay (ELISA) is positive in 35% to 65% of the patients with MPA; however, a negative report does not rule out MPA.[1] Idiopathic pauci-immune pulmonary capillaritis and RPGN are considered as organ specific subsets of MPA and may be ANCA negative.[16]

Eosinophilic Granulomatosis with Polyangiitis

Presence of at least four out of six diagnostic criteria published by ACR[44] are 85% sensitive and 99.7% specific for EGPA. These include (i) bronchial asthma; (ii) peripheral eosinophilia >10%; (iii) mono-neuropathy or polyneuropathy; (iv) migratory or transient pulmonary infiltrates; (v) para-nasal sinus abnormalities; and (vi) extra-vascular eosinophils in a blood vessel on a biopsy specimen.[44]

Three progressive clinical phases have been described, namely, a prodromal "allergic/atopic" phase of asthma and rhinosinusitis; an eosinophilic phase in which eosinophil-rich inflammatory infiltrates develop; and a vasculitic phase that presents with manifestations common to AAV, such as palpable purpura or mononeuritis multiplex.[1] Pulmonary haemorrhage and glomerulonephritis are less common than other SVV.[45-48] Upper airway involvement occurs in 70% to 90% of patients, characterised by chronic rhinosinusitis, with or without nasal polyposis[15] but characteristically with the absence of ulceration. Histopathological findings include necrotising granuloma, small-vessel vasculitis with eosinophilic infiltrate.[49,50] Chest radiographs are abnormal in 70% to 90% of patients and show patchy, bilateral, heterogeneous, migratory infiltrates combined with features of airway disease.[51] Extra-pulmonary manifestations include constitutional symptoms, mononeuritis multiplex, cutaneous lesions glomerulonephritis, and cardiac involvement. Mortality and morbidity are often due to cardiac complications, like cardiomyopathy, myocarditis, coronary arteritis, conduction delays, and sudden death occur in 50% deaths due to eosinophlic GPA, gastrointestinal tract complications, acute severe asthma and respiratory failure.[16] Leukotrine inhibitors were earlier implicated in the pathogenesis of eosinophlic GPA[52] but it is presently postulated that unmasking effect of corticosteroids rather than leukotriene inhibitors could be the causative factor.[1]

Idiopathic pauci-immune pulmonary capillaritis

Idiopathic pauci-immune pulmonary capillaritis is a rare disease isolated to small vessel of the lungs. It presents with DAH as its primary clinical manifestation. In a case series 28% were found to have idiopathic pauci-immune pulmonary capillaritis.[22] The disease is considered as a "lung-limited MPA" and generally ANCA negative. The disease has been occasionally reported from India.[53]

Diagnosis

The diagnosis of pulmonary vasculitis is difficult and challenging because the disease is rare, highly variable and overlapping of signs and symptoms with more common diseases (e.g., infection, malignancy, drug toxicity, connective tissue diseases, sarcoidosis, and interstitial lung diseases).[16,40] The diagnosis depends upon integrating the clinical, laboratory, radiographic, and histopathologic data.[40] A good clinical history is always rewarding, because,

at times a symptom considered unimportant by the patient to divulge, or a past illness history or the history of drug intake (illicit or prescribed) current or in the past, may give an important clue to the diagnosis of pulmonary vasculitis. The other diagnostic tools includes laboratory investigations, radiological studies, bronchoscopy and pulmonary function testing.[16] Presence of a combination of unrelated signs and symptoms, like remote or intermittent constitutional symptoms, unusual dermatological leucocytoclastic vasculitis, iridiocyclitis, rashes, arthritis, or chronic sinus disease, DAH, central or peripheral neuropathy or acute glomerulonephritis strongly suggest pulmonary vasculitis.[24]

Laboratory diagnosis

Laboratory tests include complete blood count, renal function, liver function tests, urinalysis, and situation specific special tests like body fluid/tissue culture, serology, ANCA, among others.[1] Raised total leucocyte and platelet counts, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are all non-specific common findings suggestive of infective pathology and disease activity, respectively. Peripheral eosinophilia (>10%) in a setting of DAH and increased serum immunoglobulin E levels suggest possibility of EGPA.[24] Thrombocytopaenia in bland pulmonary haemorrhage may be caused by idiopathic thrombocytopaenic purpura (ITP), thrombotic thrombocytopaenic purpura, disseminated intravascular coagulation (DIC), leukaemia, among others.[54-56] DAH with thrombocytopaenia/thrombophlebitis suggest the possibility of antiphospholipid syndrome and SLE.[22,57,58] Microscopic haematuria (>5 RBC per high power field or RBC casts) and proteinuria (>500μg) in a fresh sample of urine (before the RBC casts degenerate) are common early findings in GPA and MPA.[1] Raised blood urea, serum creatinine, BUN indicate renal impairment and suggest RPGN and the differential diagnosis includes the AAV, idiopathic pauci-immune glomerulonephritis, SLE, Goodpasture's syndrome, post-infectious glomerulonephritis, IgA nephropathy, Henoch-Schönlein purpura, essential cryoglobulinemia, and membranoproliferative glomerulonephritis.[59] RPGN associated with DAH suggest pulmonary renal syndrome. DAH may be a presentation of Goodpasture's syndrome and the need of estimation of anti-glomerular basement membrane (anti-GBM) antibodies.[58] Anti-GBM antibodies may be absent in 5% to 10% cases of Goodpasture's syndrome without renal symptoms and renal/lung biopsy may be required to establish the diagnosis. Cryoglobulinemia and hepatitis B and C infection should be ruled out.[40] DAH may be the initial presentation of various collagen vascular disorders, like SLE, rheumatoid arthritis,[60] polymyositis,[61] scleroderma.[62] So estimation of anti-CCP antibodies, rheumatoid factor and ANA may be required to establish the diagnosis. In ANA-positive patients, additional serological testing may be of relavence for the diagnosis of specific CVD, like anti-dsDNA for SLE, SS-A/SS-B for Sjogren's syndrome, anti-RNP for mixed connective tissue disease (MCTD), and anti-Jo-1 for polymyositis, anti-Sm and anti SCL-70 for scleroderma.[18] Estimation of serum complement (C3 and C4) levels may be required if the differential diagnosis include SLE since low complement levels support the diagnosis of SLE.[1] Sputum examination for RBC, acid-fast bacilli (AFB), Gram's staining, KOH mount for fungal elements helps to rule out bacterial and fungal aetiology. Blood, sputum, tissue culture helps to establish the infection as the cause before planning for immunotherapy. Cytology and tissue biopsy (histopathology), if available, helps to establish the aetiology. Pulmonary aspergillosis must be ruled out in critically ill patients presenting with haemoptysis and pulmonary infiltrates. This is specially in COPD patients with long-term steroid therapy and immunocompromised neutropenic patients before starting immunosuppressive therapy.[63]

Anti-neutrophilic Cytoplasmic Antibody

Indirect immunofluorescence (IIF) test is a good screening tool for identifying ANCA types. Three ANCA types have been described based on the staining patterns: these include the cytoplasmic-ANCA (c-ANCA), perinuclear-ANCA (p-ANCA), and atypical-ANCA (a-ANCA).[40] The c-ANCA and p-ANCA are important in AAV diseases. The c-ANCA is associated with specific autoantibodies directed against proteinase-3 (PR3), which are 85% to 90% sensitive and 90% specific for generalised active Wegener's granulonmatosis in high pre-clinical probability for Wegener's granulonmatosis.[36,64] ANCA may be positive at lower rates (60% and 40%, respectively) in limited disease and during remission negative in 20% patients of respiratory limited Wegener's granulonmatosis without DAH.[65] The p-ANCA, though less specific than c-ANCA, is positive in MPA, EGPA, RPGN and other autoimmune diseases. PR3 or MPO are the intra-cytoplasmic antigens and antibodies against PR3/MPO antigen are measured by ELISA in ANCA positive patients and adds to ANCA sensitivity and specificity.[16] The diagnosis of GPA can often be made with accuracy in this setting even without tissue biopsy.[1] In limited disease or in remission ANCA positivity is lower (60% and 40%, respectively).[65] The sensitivity of p-ANCA/MPO-ANCA for MPA and EGPA is 50% to 75% and 35% to 50%, respectively.[66,67] A positive p-ANCA is only suggestive of MPA and EGPA, but a negative test does not rule

out the disease. Idiopathic pauci-immune pulmonary capillaritis patients are usually ANCA negative.[22]

Radiological diagnosis

The radiological findings include bilateral patchy or diffused alveolar infiltrates or ground-glass opacities representing underlying DAH and nodular, cavitary lesions but lesions may be unilateral in patients presenting without haemoptysis.[1] No single or a combination of radiological findings are specific of vasculitis. The presence of Kerley B lines on chest radiograph in DAH suggest pulmonary veno-occlusive disease, mitral stenosis, or possibly pulmonary oedema due to myocarditis as a complication of systemic vasculitis or collagen vascular disease.[24] Presence of intra-thoracic lymphadenopathy suggest infection or malignancy and vascular filling defect suggests infarction.[1] Absence of these findings strongly suggest vasculitis. High resolution computerised tomography (HRCT) of thorax is highly sensitive but less specific for vaculitis (Figures 1 and 2).

Bronchoscopy

Bronchoscopy allows direct visualisation of tracheobronchial tree for any endobronchial lesion like stenosis/growth, to obtain clinical material for cytology, microbiology and tissue biopsy directly from the site, to rule out infection and malignancy. Increasing amount of blood in sequential aliquots in bronchoalveolar lavage (BAL) or presence of siderophages (haemosiderin laden alveolar macrophages) >25% or RBCs even in the absence of frank haemorrhage in BAL fluid is diagnostic of DAH.[68] Presence of pulmonary eosinophilia in bronchial lavage indicates eosinophilic lung disease or EGPA. At times bronchoscopy may not be possible in a seriously ill patient of suspected DAH. In these cases, estimation of the carbon monoxide transfer coefficient corrected for lung volume (Kco) may show sequential increases over time, which helps to establish the diagnosis of DAH.[19]

Pulmonary function testing

Spirometery may show obstructive or a mixed or a restrictive disorder. Estimation of diffusion capacity for carbon monoxide (DLCO) helps diagnosis where bronchoscopy is not possible and values more than 30% of the base-line value is highly suggestive of alveolar haemorrhage (DAH) or a bland haemorrhage.[68] DLCO may also be elevated in bland pulmonary haemorrhages without pulmonary capillaritis in mitral stenosis, anti-coagulation and thrombolytic therapy, various coagulopathies,

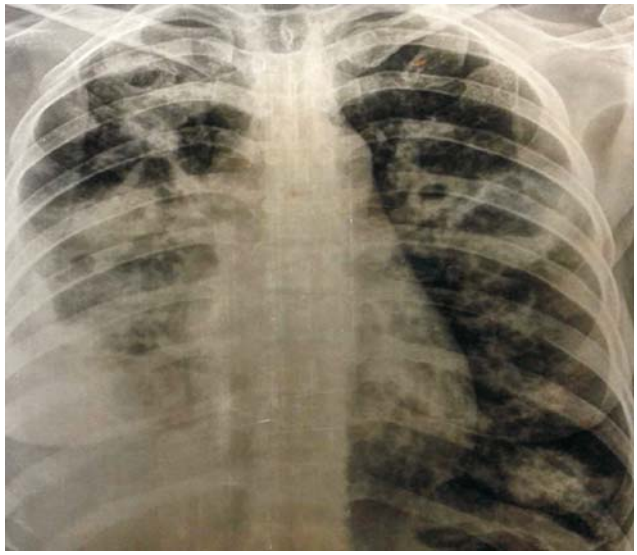

Figure 1. Chest radiograph (postero-anterior view) showing bilateral cavitating nodules.

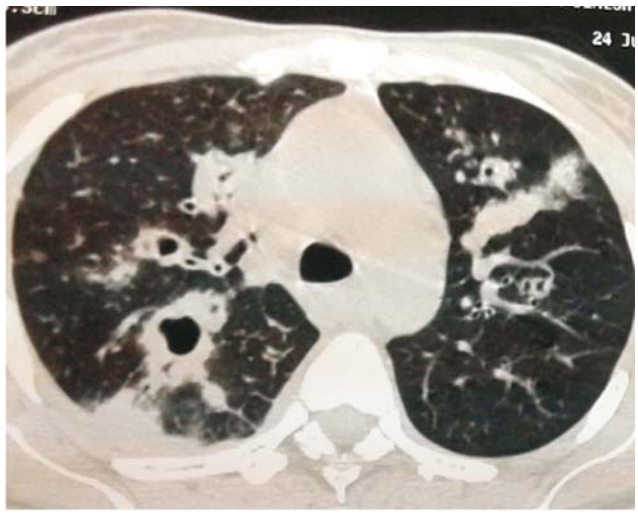

Figure 2. Computed tomograph of thorax of the same patient showing thick-walled cavitating nodules.

idiopathic pulmonary haemosiderosis, and some cases of Goodpasture's syndrome.

Diagnostic biopsy

Biopsy remains the gold standard for the diagnosis.[1] Biopsy from upper airway, sinus or extra-pulmonary sites, like skin, are easy to obtain but yield poor results.[69] Transbronchial lung biopsy is less diagnostic as the tissue from the involved site is seldom obtained.[70] Percutaneous renal biopsy is more invasive than biopsy from other extra-pulmonary sites but yield better results.[69] Surgical lung biopsy or video-assisted thoracoscopy (VATS) biopsy provides accurate diagnosis in the majority of the cases.[1] Samples should be sent for microbiological and histopathological studies in saline as well as in

formalin and frozen sections for immunofluorescence and electronic microscopic studies. Direct immunofluorescence may show specific diagnostic pattern like IgA deposition in Henoch-Schönlein purpura, linear IgG deposition in Goodpasture's syndrome, a granular IgG and complement deposition around the alveolar wall and small vessels of alveoli or glomerular capillaries in SLE.[1] No complement or immunoglobulin deposits are found in AVV diseases GPA, MPA, EGPA, isolated pauci-immune pulmonary capillaritis, or idiopathic pauci-immune glomerulonephritis.[18]

Management of Pulmonary Vasculitis General principles

The general principles of management include early identification of the disease and rapid control of disease with immunosuppression. Supportive therapy includes oxygen therapy, treatment of comorbidities, infection prevention by vaccinations, physical and occupational therapy, maintenance of nutrition, and psychosocial support to minimise the disease associated morbidity and improving quality-of-life.[17] Combined therapy with cyclophosphamide and corticosteroids has lowered 5-year mortality of systemic vasculitis from 50% to 12%.[1] Cyclophosphamide carries substantial risk of adverse effects and complications. To reduce the complications of long-term cyclophophamide use, the pharmacotherapy is divided in two phases: (i) the remission-induction phase with cyclophosphamide; and (ii) maintenance of remission phase with less potent immuno-suppressents azothioprine or methotrexate or mycofolate mofetil for long-term use for sustaining remission.[40] The treatment planning is based on accurate determination of the disease severity.[71]

Determination of disease severity

Many scoring systems are in use for the assessment of disease severity, out of which the EUVAS system developed by Europian Vasculitic Study group is best suited for clinical use and is recommended by most authors.[17,71] The grading based on the number of organ systems involved, the degree of renal disease, and the presence of DAH. EUVAS system categorise the disease severity into limited; early, generalised; active, generalised; severe; and refractory disease (Table 2).[71]

Treatment

The pharmacotherapy of pulmonary vasculitis is largely the same. Cyclophosphamide and corticosteroids, are used regardless of aetiology and type of disease, i.e., isolated organ disease or systemic disease (Table 3).[17]

Remission-induction remission phase

The drug recommendations are based on the extent of disease and organ involvement. For localised disease topical therapy/steroid monotherapy and/or a single moderate potency cytotoxic agent, such as methotrexate, azathioprine, or mycophenolate mofetil is indicated.

For early generalised disease. Both methotrexate or cyclophosphamide with corticosteroid are recommended. The Non-Renal Alternative with Methotrexate (NORAM) trial[72,73] recommended less potent methotrexate for milder disease. The remission onset is early with cyclophosphamide than methotrexate (3.2 *versus* 5.2 months) but at six months, equal relapses in both groups and more relapses in methotrexate group then cyclophosphamide group (74% *versus* 47%) were observed.[72,73] More prolonged use of maintenance therapies appears to have lower relapse rates. Alternative moderate-potency cytotoxic agents include mycophenolate mofetil (MMF) and azathioprine. MMF with corticosteroids in MPA with mild to moderate renal involvement achieved remission in 76% cases and remission was sustained in 70% for 18 months.[74]

For generalised active disease, a daily regimen with oral cyclophosphamide with oral corticosteroids achieves remission in 93% and is the standard regimen for the treatment of GPA.[33] The Daily Oral *versus* Pulse Cyclophosphamide for Renal Vasculitis

Table 2. EUVAS categories of disease severity

Disease Severity	Extent of the Disease and Organ Involvement
Limited	Non-organ-threatening, isolated disease of the upper airway
Early generalised disease	Presence of constitutional symptoms, end-organ involvement, but clearly no immediate threat to organ function
Generalised active disease	Clearly impaired and threatened organ function
Severe disease	Immediate threat of organ failure or death, severe renal insufficiency (creatinine level >5.7mg/dL), alveolar haemorrhage, central nervous system disease, cardiomyopathy, and life-threatening gastrointestinal disease, such as bowel ischaemia or haemorrhage.
Refractory	Failed to respond to conventional therapy

Definitions of abbreviations: EUVAS=European Vasculitis Study Group

Table 3. Immunosuppressents and their recommended doses schedules

Immunosuppressent	Oral Dose	Intravenous (IV) Dose; Pulse Therapy
Cyclophosphamide	2mg/kg per day for 6–12 months and then tapered slowly over months	1g/m^2 body surface area as pulse therapy every 2–4 weeks for severe disease
Methotrexate[73*]	15mg per week escalate to 20–25mg per week by 12 weeks and maintain at this dose till 10 months and then taper and stop by 12 months	—
Azothioprine[81**]	2mg/kg per day (maximum; 200mg per day) reduced to 1.5mg/kg per day after 12 months, 1 mg/kg per day after 18 months, and withdraw after 42 months	—
Mycophenolate mofetil (MMT)[80***]	2000mg per day, reduced to 1500mg per day after 12 months, 1000mg per day after 18 months, and withdraw after 42 months	—
Prednisolone	1mg/kg per day for 6–12 months and then tapered slowly over months	Methylprednisolone 250-1000mg per day for 3–5 days as pulse therapy followed by oral therapy to be tapered over several months

*=Longer duration of treatment reduced relapses.[73]

**=CBC and LFT monitored weekly for one month and thereafter every three months. Recovery if leukopaenia (TWBC <4000/cumm) occur, Stop, till fully recovered and re-instituted in the doses of 25mg per day and monitored for TWBC weekly.[81]

***=CBC weekly for the 1st month, biweekly for the 2nd month, and then monthly for the first year, and then every three months. Drug stopped if leukopaenia occur, until recovery and re-introduced with the dose reduced by 500mg per day. In case of intolerance; reduce initial dose to 1000mg per day and increased by 500mg per day monthly increments to the 2000mg per day target or the highest tolerated dose. For glomerular filtration rate (GFR) <25mL/min/kg, reduce dose to 1000mg per day is recommended.[80]

(CYCLOPS) trial compared pulse intravenous (IV) cyclophosphamide with oral daily cyclophosphamide regimens and observed that both were equally effective in remission induction.[75] The pulse IV cyclophosphamide group received lower cumulative total dose and so had lower incidence of leucopaenia but the risk of relapse was significantly lower in daily oral regimen.[76] The adverse events and the survival rate was equal so either regimens are recommended with equal success as per patient need. The Wegener's Granulomatosis-Entretien (WEGENT) trial suggest that daily regimen was effective in pulse regimen failure patients.[77]

On the basis of the role of ANCA and B-lymphocytes in the pathogenesis of AAV, B-cell depletion therapy with rituximab an anti-CD20 monoclonal antibody, was evaluated as a therapeutic agent in generalised active and severe disease. The Rituximab *versus* Cyclophosphamide for ANCA-Associated Vasculitis (RAVE) trial compared weekly rituximab (375mg/m^2) for four weeks with daily oral cyclophosphamide in the doses of 2mg/kg per day (adjusted for renal function) with corticosteroid common to both the groups. Both the drugs were equally effective in achieving remission at six months and in the treatment of alveolar haemorrhage. The adverse events were similar in both the groups. Rituximab, thereafter, was included as a drug for the induction of remission in AAV.[78] The Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis (RITUXVAS) trial compared rituximab with IV pulse cyclophosphamide (in place of oral cyclophosphamide), for remission induction in generalised active or severe AAV disease with renal involvement, with oral corticosteroid to both the groups. Rituximab group additionally received concomitant pulsed cyclophosphamide with the first and third rituximab infusions. It was observed that remission induction, remission maintenance and the adverse events were similar in both the groups. The hypothesis that rituximab was superior to cyclophosphamide in remission induction could not be sustained. Although in the maintenance phase rituximab group did not require a cytotoxic drug, where azathioprine was required in cyclophosphamide group.[79]

In patients with severe disease, Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis (MEPEX) trial[80] compared high dose methylprednisolone *versus* plasma exchange in combination with corticosteroid and cyclophosphamide. Dialysis-independent survival at three months was significantly better (69%) in plasma exchange group than intravenous corticosteroid group (49%). Based on the trial results plasma exchange with corticosteroids and cyclophosphamide has been recommended for severe disease and alveolar haemorrhage.[80] Rituximab may be used as a potential alternative to cyclophosphamide in severe disease.[79]

Refractory disease by definition is when conventional therapy fails.[71] Investigational agents

like tumour necrosis factor-alpha (TNF-α), a proinflammatory cytokine has been implicated in the pathogenesis of autoimmune diseases including vasculitis. TNF-α inhibitors are used successfully in rheumatoid arthritis. On these grounds anti-TNF-α therapy was hypothesised to be useful in induction of remission and maintenance. Therapy with infliximab, an anti-TNF-α agent was successful in inducing remission in vasculitis in 88% refractory cases but was associated with high infection rate (21%) and relapse rate (20%)[81-85] but TNF-α blocking agent entercept failed in maintenance of remission in Wegener Granulomatosis Etanercept (WGET) Trial.[86] T-cell depletion therapy with anti-thymocyte globulin achieved partial to complete remission but was associated with fatal (alveolar haemorrhage and infection) and non-fatal (serum sickness) complications.[87] Leflunamide is a new immuno-suppressive agent that targets primarily T-cells. A phase II study of the drug found the drug to be relatively well tolerated in GPA when used for remission maintenance, with frequent relapses over the study duration (mean follow-up of 1.75 years).[88] B-cell depletion therapy with rituximab have been used with success.[89] All refractory cases and critically ill patients with other life-threatening manifestations, like CNS and GIT disease are recommended referral to specialised centres.[40]

The-long term use of cyclophosphamide is potentially hazardous, so milder cytotoxic drugs (methotrexate, azathioprin and mycophenolate mofetil) were tried in the maintenance phase with the aim to maintain effective remission with minimum toxicity. The Cyclophosphamide *versus* Azathioprine for Remission in Generalized Vasculitis (CYCAZAREM) study evaluated cyclophosphamide and azathioprine in the maintenance phase soon after the clinical remission was achieved and observed that azathioprine was a good substitute for cyclophosphamide and did not increase the relapse rate.[90] The International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE) trial compared MMT with azathioprine for maintenance phase and found azothioprine superior to MMT as the relapses occurred more in the MMF group.[91] It is conferred that MMT should be reserved for patients who cannot tolerate azathioprine or methotrexate.

All major randomised, controlled trials used high-dose corticosteroid (oral prednisone or equivalent of 1 mg/kg/day) during the induction phase with slowly tapered to "low" maintenance dose (e.g., oral prednisone at 5-10 mg per day) till ultimately stopped as remission is maintained.[16] Low-dose glucocorticoids in the maintenance phase has been found superior to no steroid in maintenance phase. The relapse rate in low-dose steroid group has been reported to be much less (14%) compared to patients who did not receive steroid therapy (43%).[92]

Monitoring of complications and prevention of infection

Vasculitis is a waxing and waning systemic chronic disease and patients suffer one or more relapses most in Wegener's granulomatosis. The differential diagnosis include infection, thromboembolism, drug toxicity and unrelated new disease.[1] A 10% of vasculitic patients treated with cyclophosphamide develop infection,[93] 12% develop cystitis, 8% myelodysplastic syndrome, and 5% solid malignancy.[120] The infection (pneumonia, and sepsis) is the leading cause of death in 13% to 48% cases.[10,95,96] The infection may be caused by atypical organisms or may have atypical clinical presentations or may be a complication of vasculitis through immunosuppression ending up in a vicious cycle of disease flair, immune dysfunction, and infection.[16] Of the patients treated by pulse cyclophosphamide therapy, 20% develop *Pneumocystis jirovecii* pneumonia. Prophylaxis with trimethoprim (T) (160μg)-sulfamethoxazole (S) (800μg) is recommended. The T/P prophylaxis also suppress nasal *Staphylococcus aureus* which is associated with a higher risk of disease relapse in GPA.[97] The other side effects of prolonged cyclophosphamide therapy includes haemorrhagic cystitis which can be prevented and treated by mercaptoethane sulfonate Na (MESNA), bladder cancer in 5% cyclophosphamide treated patients of Wegener's granulomatosis over 10 years and 16% in 15 years.[98] The risk was more in patients with persistent non-glomerular haematuria and use of cumulative dose of cyclophosphamide >100g and longer total duration of treatment >2.7 years.[24] Recurrences of DAH often occur with the tapering of treatment and even after long periods of stability off treatment.[24] Active vasculitis, cardiovascular disease (myocardial infarction, cerebrovascular accident, pulmonary embolus), and malignancy are among the other causes.[99] The venous thromboembolic disease (VTED) is an under-recognised complication of vasculitis and occur equally in new and pre-diagnosed cases of Wegener's granulomatosis. The incidence of VTED is 7% per year.[100] It should be suspected in a known case presenting with new chest or lower extremity symptoms. Regular monitoring of blood pressure, blood sugar and bone density assessment is advisable due to long-term use of corticosteroid therapy.

Other measures in the management include pneumococcal infection and influenza prevention by vaccination, vitamin D prophylaxis and management of proper nutrition and sleep hygine and regular

exercise to optimise musculoskeletal conditioning, physiotherapy, occupational therapy, and rehabilitation as and when required.

The Unanswered Questions

Although the minimal acceptable lower limit of therapy has been defined as 18 months, the optimum duration of therapy,[16] the optimal timing of cyclophosphamide or rituximab administration, potential risks and benefits of intravenous *versus* oral cyclophosphamide, the optimal dose and route of administration of corticosteroids are still to be answered. Whether or not these principles of therapy apply to patients with other life-threatening disease manifestations, i.e., CNS disease or gastrointestinal disease, in critically ill patients, also remains to be addressed.

Both RAVE[78] and RITUXVAS[79] trials used rituximab and low-dose corticosteroids during maintenance phase without immunosuppressive agents. Is this the optimum management? or a disease modifying agent may be required as optimised therapy, needs to be established in future.[16] Presently rituximab relapses are treated by rituximab alone.

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