

Review

Clinical review: Vasculitis on the intensive care unit – part 1: diagnosis

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Abstract

The first part of this review addresses the diagnosis and differential diagnosis of the primary vasculitides Wegener's granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome and polyarteritis nodosa. Prompt diagnosis and treatment of these conditions ensures an optimal prognosis. The development of assays for antineutrophil cytoplasmic antibodies has aided the diagnosis of Wegener's granulomatosis and microscopic polyangiitis. However, even in cases where there is high clinical likelihood that these conditions are present, up to 20% may be antibody negative, whereas alternative diagnoses may be antibody positive. The final diagnosis rests on a balance of clinical, laboratory, radiological and histological features. The exclusion of alternative diagnoses is important in assuring appropriate therapy. Particular attention is paid to the more fulminant presentations of these conditions and the role of the critical care physician in their diagnosis and management.

Keywords antineutrophil cytoplasmic antibody, critical care, Churg–Strauss syndrome, diagnosis, microscopic polyangiitis, polyarteritis nodosa, vasculitis, Wegener's granulomatosis

Introduction

Systemic necrotizing vasculitis represents a major challenge in critical care units. The prognosis of a fulminating vasculitic illness is poor. For example, patients admitted to the intensive care unit (ICU) with suspected pulmonary vasculitis have a mortality of 25–50% [1]. Early and accurate diagnosis and aggressive treatment are essential to improving outcome while avoiding unnecessary immunosuppressive therapy. The first presentation to the ICU may be with respiratory failure and nonspecific changes on the chest radiograph rather than the more classical renal failure. In a series of 26 patients admitted to the ICU with systemic necrotizing vasculitis, the initial diagnosis of vasculitis was made in the ICU in 42% of cases [2]. It is therefore essential that vasculitis is included in the differential diagnosis of unexplained pulmonary or renal failure.

The clinical manifestations of the vasculitides are diverse, and this is reflected in the manner of their presentation to the ICU. Typically, this involves the lungs or kidneys, or both, although the heart, central nervous system and gastrointestinal tract can also all be involved. The most common conditions are Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg–Strauss syndrome (CSS) and polyarteritis nodosa (PAN). We explore the diagnosis of these entities in the setting of the ICU and discuss their treatment, with an emphasis on the role of the ICU. Detailed discussion of more benign manifestations and the prolonged clinical course and treatment can be found elsewhere [3–8].

Diagnosis

The conditions discussed here are uncommon. The prevalences of WG, MPA, CSS and PAN have been quoted as

ANCA = antineutrophil cytoplasmic antibody; cANCA = cytoplasmic antineutrophil cytoplasmic antibody; CSS = Churg–Strauss syndrome; ICU = intensive care unit; MPA = microscopic polyangiitis; MPO = myeloperoxidase; NPV = negative predictive value; PAN = polyarteritis nodosa; pANCA = perinuclear antineutrophil cytoplasmic antibody; PPV = positive predictive value; PR = proteinase; WG = Wegener's granulomatosis.

Table 1

Presenting features	Disease			
	WG	MPA	CSS	PAN
Constitutional upset	++	++	++	++
Sinusitis	+++	+	+++	+
Asthma	-	-	+++	-
SOB/cough	+++	+	++	+
Rash	+	+	++	+
Abdominal pain	+	+	+	++
Hypertension	+	+	+	++
Proteinuria/haematuria	+++	+++	++	-
Cardiac failure/pericarditis	+	+	++	+
Mononeuritis (multiplex)	+	+	++	++

CSS, Churg–Strauss syndrome; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa; SOB, shortness of breath; WG, Wegener's granulomatosis.

23, 25, 10, and 30 cases per million adult population, respectively [9]. Other, more common diseases may share their key clinical features, and therefore the clinician must have a high index of suspicion in order to diagnose these conditions.

Although specific vasculitides do have their 'classical' symptoms, such as the temporal headache of giant cell arteritis, the vasculitides liable to present in the ICU are less definable. Despite this, clues in the clinical picture may aid diagnosis (Table 1). Although the vasculitides may mimic an infective process, in retrospect it may be apparent that the clinical course is atypical, often with an extended, generalized, nonspecific, prodromal illness in which repeated courses of antibiotics have failed to produce the expected improvement [10]. Careful enquiry may reveal multiorgan involvement that had previously been overlooked. Table 2 gives the approximate frequencies of organ involvement in the vasculitides considered in this review.

Attention to the past medical history may highlight associated conditions, such as hepatitis (associated with PAN) as well as, of course, a past history of vasculitis. It is worth noting that asthma associated with CSS can precede the vasculitic phase by up to 10 years.

The general examination may reveal subtle evidence of the vasculitic process: nail-fold infarcts and splinter haemorrhages, retinal haemorrhages and Roth spots (which are not just seen in bacterial endocarditis), scleritis and episcleritis, palpable purpura and other less classical rashes, absent pulses or bruits (indications of large vessel involvement), and oral ulceration.

Pointers to a possible vasculitis may be found in the bedside and 'routine' laboratory investigations. The temperature chart will typically show a persistent low-grade pyrexia, while new onset hypertension may be a marker of undiagnosed renal involvement, particularly in PAN. Urinalysis must be performed. Is the patient being treated for urinary sepsis on the basis of blood and protein on the urine dipstick in the absence of leucocytes and/or nitrites? Could this be evidence of glomerulonephritis instead? Unexplained hypoxia may indicate subclinical pulmonary haemorrhage, often identified in retrospect once the diagnosis is apparent.

Normocytic anaemia, neutrophil leucocytosis, and a raised erythrocyte sedimentation rate and capsular reactive protein are typical findings, but they add little in determining the specific diagnosis. The urea and creatinine can vary enormously, and premorbid values are particularly important in interpreting these findings. Blood and protein identified on the bedside urinalysis should prompt urine microscopy. The chest radiograph can range from normal to showing evidence of florid pulmonary haemorrhage or multiple cavitating lesions. However, it more commonly shows a non-discriminatory patchy alveolar infiltration.

The American College of Rheumatology produced classification criteria for WG, CSS and PAN in patients with a confirmed vasculitis [11–15]. These are not diagnostic criteria. These classification criteria have sensitivities and specificities for distinguishing vasculitides between 80% and 90% [13–15]. They are intended to classify confirmed vasculitides (principally for research purposes) and are not intended to differentiate vasculitic from nonvasculitic disorders [12]. Furthermore, they do not recognize the diagnosis of MPA; patients with this disorder are classified as having WG. Their positive predictive value (PPV) for diagnosing WG or PAN in patients only suspected of having a vasculitis may be as low as 17–25%, making them unsuitable diagnostic criteria [16].

Antineutrophil cytoplasmic antibody-associated small vessel vasculitides

Wegener's granulomatosis/microscopic polyangiitis

WG and MPA are often grouped together as the antineutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitides. However, up to 10% of these cases will be ANCA negative [17]. They can affect many organ systems, and clinically are differentiated by their predilection for the pulmonary system (Table 2). No single test is capable of diagnosing or distinguishing between these conditions. Therefore, a combination of clinical, serological and histopathological factors must be considered to provide a final diagnosis.

Clinical features

WG is a granulomatous vasculitis that, in contrast to CSS, does not cause asthma, although the two may coexist because of the prevalence of asthma in the population. Nasal,

Table 2

Approximate frequencies (%) of major organ involvement				
Organ system	WG	MPA	CSS	PAN
Skin	50	40	60	50
Renal	80	90	60–80	30
Pulmonary	90	50	40 ^a	Rare
Ear, nose and throat	90	35	50	Uncommon
Musculoskeletal	60	60	50	50–60
Neurological	30	30	70	60–70 ^b
GI tract	50	50	50	30
Cardiac	10		20–40	20–30

^aEvidence of pulmonary vasculitis; excludes asthma. ^bPredominantly mononeuritis multiplex. CSS, Churg–Strauss syndrome; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa; WG, Wegener's granulomatosis. Data compiled from [3,18,20,26,28].

oropharyngeal, or pulmonary involvement is essentially universal at diagnosis. Ear, nose and throat disease includes epistaxis, nasal and oral ulceration and necrosis, sinus pain and hearing loss. Pulmonary involvement includes haemorrhage, pleural effusions and large airway inflammation and stenosis. Pulmonary haemorrhage may be extensive before haemoptysis or other overt clinical signs become apparent. Renal involvement ranges from a subclinical glomerulonephritis (blood and protein on the urine bedside test) to rapidly progressive glomerulonephritis, and it is nearly universal [18]. A respiratory limited form of the diseases has been touted, but over 80% of these cases go on to develop renal disease, and so the distinction is of little use [19]. The presence of renal disease is arbitrarily used to define generalized.

MPA is a nongranulomatous vasculitis that has less of a predilection for the lungs, although pulmonary involvement is still seen in up to 40% of cases [20]. Renal involvement is again common.

Cardiac involvement can occur in both, manifesting as myocarditis, coronary arteritis, valvulitis, endocarditis, conduction disturbances and pericarditis. Acute pericardial inflammation may lead to life threatening tamponade [21]. The musculoskeletal, neurological and cutaneous systems are also frequently affected, in WG more than in MPA.

Antineutrophil cytoplasmic antibodies

Particularly important in both the diagnosis and pathogenesis of the small vessel vasculitides is the ANCA. Indirect immunofluorescence identifies two clinically important patterns of staining: cytoplasmic ANCA (cANCA) and perinuclear ANCA (pANCA). In WG and MPA, these are directed against specific constituents of neutrophil granules, namely the antigens proteinase (PR)-3 and myeloperoxidase (MPO),

Table 3

Approximate sensitivity and specificity of antineutrophil cytoplasmic antibody in detecting primary vasculitides		
	Sensitivity (%)	Specificity (%)
WG		
cANCA	64	95
PR-3	66	87
PR-3 + ANCA	55	99
MPA		
pANCA	58	81
MPO	58	91
MPO + ANCA	49	99
WG or MPA		
PR-3 + cANCA or MPO + pANCA	67–73	99

cANCA, cytoplasmic antineutrophil cytoplasmic antibody; MPA, microscopic polyangiitis; MPO, myeloperoxidase; pANCA, perinuclear antineutrophil cytoplasmic antibody; PR, proteinase; WG, Wegener's granulomatosis. Data from Hagen and coworkers [22].

respectively. In practice this is demonstrated by an enzyme-linked immunosorbent assay. Binding of ANCAs to these molecules on activated neutrophils is felt to be an important mechanism of tissue injury in vasculitis. The sensitivities and specificities of these assays are shown in Table 3.

There is some crossover of cANCAs and pANCAs between WG and MPA. pANCAs directed against MPO are found in up to 24% of WG cases, whereas up to 27% of MPA cases will be cANCA positive [22]. Pragmatically, because distinguishing WG from MPA does not change therapy in the ICU, it is only necessary to identify the presence of a small vessel vasculitis and not to classify it. By using testing with both indirect immunofluorescence and enzyme-linked immunosorbent assay for the combination of cANCA and PR-3 or pANCA and MPO, the sensitivity for diagnosing the presence of either WG or MPA can be increased to approximately 73%, while the specificity remains at approximately 99% [22]. However, the presence or absence of ANCAs cannot be used in isolation to diagnose or exclude WG or MPA. Other conditions may also produce a positive ANCA (up to 50% of CSS patients will give a positive result for PR-3 or MPO [22]), and other antigens can produce a similar staining pattern (especially the pANCA). Furthermore, the PPV and negative predictive value (NPV) of any diagnostic test depend on the prevalence of the disease in the population being investigated. ANCA has the highest PPV and the lowest NPV in patients who have the most classical clinical presentation, but neither value ever reaches 100%; a negative result, while decreasing the likelihood of the diagnosis, never excludes it. For example, when

attempting to diagnosis renal vasculitis in the context of significant renal impairment and other clinical features consistent with WG or MPA, the presence or absence of pANCA–MPO or cANCA–PR-3 combinations have a PPV of 92–98% and a NPV of 80–93% [23]. Therefore, a negative ANCA still leaves a likelihood of up to a 20% that such a patient has a small vessel vasculitis.

Imaging

Radiological techniques can be used to help confirm the involvement of multiple organs in the disease process, but there are few features that are specific to WG or MPA alone. Granulomata, pulmonary infiltrates, or haemorrhage can be identified on chest radiography or, with more sensitivity, on high-resolution computed tomography. However, there are many other conditions (e.g. tuberculosis, sarcoidosis and malignancy) that can mimic these changes. Their presence adds to the overall picture but should not be interpreted in isolation. A computed tomography scan of the sinuses may be more helpful, especially in WG, in which a mucosal thickening, bony destruction and infiltration to the orbits can all suggest WG [24].

Histology

Where possible, biopsy of an affected organ is desirable. Skin biopsy shows a leucocytoclastic vasculitis, which confirms the presence of a vasculitic process, but it is also seen in many conditions other than MPA and WG. Nasopharyngeal biopsy is useful if lesions are present and may provide diagnostic information for WG if granulomatous disease is identified. However, relatively small amounts of tissue are often obtained and only one-third of biopsies show features distinguishable as active vasculitis.

When no easily accessible lesions are present, then a decision on the next most appropriate site for biopsy must be made based on the clinical picture. Renal biopsy shows a segmental necrotizing crescentic glomerulonephritis, with no immunoglobulin deposition (so called 'pauci-immune'). This contrasts with other causes of crescentic glomerulonephritis, such as bacterial endocarditis or the collagen vascular diseases, which have immunoglobulin deposited in the glomerulus. Although diagnostic of a primary small vessel vasculitis, this histological picture rarely distinguishes WG from MPA because granulomas are seen infrequently. Lung biopsy reveals a granulomatous inflammation and vasculitis. Open or thoroscopic biopsy has a far higher diagnostic yield (up to 90% if specific lesions can be identified) than transbronchial biopsy, which provides diagnostic material in only 10% of cases.

Churg–Strauss syndrome

The hallmarks of CSS are asthma (95%), allergic rhinitis (55–70%), a peripheral blood eosinophilia ($>1.5 \times 10^9/l$ or $>10\%$ of total white cell count) and evidence of a systemic vasculitis affecting two or more extrapulmonary organs.

Particularly important is cardiac involvement (acute pericarditis, constrictive pericarditis, heart failure and myocardial infarction), which accounts for up to 50% of deaths attributable to CSS [7,25].

Clinical features

Characteristically, the asthma precedes the vasculitic phase of the illness by up to 2–3 decades, although the two can appear simultaneously. Often this is problematic enough to warrant long-term steroids, which can have the effect of masking the development of future systemic features. As well as asthma, allergic rhinitis and skin lesions (tender subcutaneous nodules on the extensor surfaces, palpable purpura, haemorrhagic lesions or a maculopapular rash) are exceedingly common (Table 2).

Renal disease is more common than originally appreciated, with up to 84% of patients in one series of 19 patients exhibiting some degree of renal involvement, ranging from subclinical proteinuria to renal failure [26]. However, renal failure requiring replacement therapy is still relatively rare (around 10% of cases).

Other investigations

There is no diagnostic laboratory test. A marked peripheral eosinophilia is the most common finding, but it is not specific. Furthermore, this can fluctuate rapidly, particularly in response to treatment, and can therefore easily be missed if steroids are started for the asthma before investigations are performed. IgE levels are also typically elevated, and there are circulating immune complexes. pANCA is positive against MPO, as in MPA, in around 50% of cases [7].

Imaging

Chest radiographic features can be very diverse, ranging from transient patchy opacities to the widespread shadowing of pulmonary haemorrhage. High-resolution computed tomography is more useful, and the findings of enlargement of the peripheral pulmonary arteries and alterations in their configuration may help to support the diagnosis.

Histology

Open or thoroscopic lung biopsy is again more useful than transbronchial biopsy. Alternatively, sural nerve biopsy, in patients with evidence of a polyneuritis, may be helpful. Renal biopsy typically shows the nondiagnostic features of a focal segmental glomerulonephritis, and extravascular eosinophilic granulomas are rarely seen [26]. As such, renal biopsy adds little to the diagnosis that could not have been predicted from urine microscopy and analysis.

Polyarteritis nodosa

PAN is a necrotizing vasculitis of the medium and small muscular vessels, which may affect any organ system. Historically it has often been considered part of a spectrum of disease involving MPA and CSS. However, it is now clear

that these are discrete conditions. In a subgroup of patients with PAN the disease process seems related to active hepatitis B infection. Clinically, this is indistinguishable from idiopathic PAN; however, the treatment strategies are quite different [27]. For this reason, testing for hepatitis B should be conducted early in the disease course.

Clinical features

The characteristic features of PAN can be appreciated from the consequences of infarction and ischaemia in critical organs because of the involvement of small and medium sized arteries. This commonly presents as a syndrome of multiorgan failure/compromise, on the background of constitutional upset (e.g. fever, malaise, weight loss). This may involve the nervous system, skin, kidneys and gastrointestinal tract, although any organ can be affected (Table 2). Pulmonary involvement is documented, but this is far less common than in the other vasculitides. Cardiac involvement occurs in only about 10–30% of cases [28] but can produce significant compromise.

Nerve involvement typically takes the form of mononeuritis multiplex, with both sensory and motor components. This can be present in up to 65% of cases [28] and, in the absence of diabetes, is highly suggestive of PAN. Central nervous system involvement is increasingly recognized. Most commonly, this takes the form of stroke (either ischaemic or haemorrhagic) or cranial nerve palsies, due to necrosis and narrowing of medium sized intracranial vessels.

Renal involvement is clinically significant in up to 50% of cases [28], but it is even more commonly found at autopsy. Narrowing of renal vessels leads to multiple areas of renal infarction, glomerular ischaemia and hypertension. A true glomerulonephritis is not typically found, and so the urine is frequently normal (unlike in WG, MPA and CSS).

Gastrointestinal tract involvement is heralded by abdominal pain, which may worsen after meals (abdominal angina). The spectrum then continues to include haemorrhage, infarction and perforation.

Imaging

In most vasculitides imaging techniques are of little value in diagnosis, but this is not the case for PAN. Angiography of either the gastrointestinal tract or kidneys characteristically shows multiple aneurysms and irregular constriction of the large vessels and occlusion of the penetrating vessels. This is often considered diagnostic in the correct clinical setting, making it possible to avoid the need to obtain a tissue diagnosis from a potentially very sick patient.

Histology

A tissue biopsy is still the 'gold standard' diagnostic test, and affected areas will show the classical necrotic inflammation of the medium sized arteries, which is diagnostic of PAN.

Table 4

Common differential diagnoses

Differential diagnosis	Examples
Infection	Overwhelming sepsis (e.g. meningococcal sepsis) Atypical pneumonia <i>Legionella</i> infection Lyme's disease Leptospirosis Tuberculosis Bacterial endocarditis Mycotic aneurysms Haemolytic-uraemic syndrome
Collagen vascular disease	Systemic lupus erythematosus Rheumatoid arthritis Antiphospholipid syndrome Sjögren's syndrome Cryoglobulinaemia
Malignancy	Lymphoma/leukaemia Paraneoplastic syndromes
Other	Sarcoid Thrombotic thrombocytopenic purpura Cholesterol emboli

Differential diagnosis

Excluding alternative diagnoses is as important as positively identifying a vasculitis. Exactly what this involves will depend to a large degree on the clinical picture and the potential mimics are legion. However, the principal alternative diagnoses include infection, immune-mediated conditions such as thrombotic thrombocytopenic purpura and cryoglobulinaemia, malignancy and the collagen vascular diseases (Table 4).

Infection

Distinguishing infection from vasculitis is of paramount importance. Close liaison with microbiology is essential. Persistently negative microbiological assays, in the context of an inflammatory illness, increase the possibility that a vasculitis is present. Bacterial endocarditis, if suspected, requires multiple blood cultures at different times. Complement levels can be helpful, tending to be low in immune complex diseases (including cryoglobulinaemia) but normal or elevated in primary systemic vasculitis. The blood film is helpful in identifying microangiopathic haemolysis associated with disseminated intravascular coagulation, haemolytic-uraemic syndrome and thrombocytopenic thrombotic purpura, all of which may mimic vasculitis. Consideration must also be given to the patient being treated

in the ICU. Unfortunately, nosocomial infections are likely to occur. Surveillance should always be borne in mind.

Collagen vascular disease

The collagen vascular diseases often require serological differentiation from primary vasculitis. Antinuclear, double-stranded DNA, antiphospholipid antibodies, rheumatoid factor and extractable nuclear antigen antibodies should be tested for. Again, complement levels may be low. Cryoglobulinaemia, sometimes associated with rheumatoid arthritis (and hepatitis C), requires careful investigation if suspected.

Malignancy

Malignancy can mimic vasculitis either through bone marrow suppression or paramalignant processes. These paramalignant syndromes do not tend to produce florid organ failure, and so they are unlikely to be the cause of a patient's admission to critical care.

Conclusion

The vasculitides remain an important diagnostic challenge to the critical care physician. Their presentation remains diverse and closely resembles other, more common conditions. They require prompt diagnosis if significant permanent organ damage is to be avoided, but no single reliable test exists to readily and reliably confirm or exclude their presence. Furthermore, in those cases in which the disease is severe enough to warrant admission to ICU, approximately 50% may be undiagnosed.

The final diagnosis requires a high index of suspicion, careful compilation of all the clinical, laboratory, radiological and histological evidence available, and exclusion of important alternative diagnoses.

The second part of this review will consider treatment of these conditions, giving emphasis to the role of the ICU, before going on to discuss their prognosis.

Competing interests

The author(s) declare that they have no competing interests.

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