

## Roadmap to vasculitis: a rheumatological treasure hunt

### Part II. Classification, features of individual vasculitides and differential diagnosis against pseudovasculitis

YT Konttinen<sup>1,2,3</sup>, T Pettersson<sup>1</sup>, M Matucci-Cerinic<sup>4</sup>, J Dadoniene<sup>5</sup>, P Poduval<sup>1</sup>

#### ABSTRACT

Since the triggering factors causing primary vasculitides are by definition not (yet) known, we have to classify them to clinical syndromes based on the size, site, type and effect of the blood vessel involvement. ACR classification criteria and Chapel Hill nomenclature are useful tools to familiarize with the primary vasculitides, although a lot of criticism has been voiced in the literature indicating that they only represent the best available consensus. The present text takes advantage of the recent developments such as introduction of the anti-neutrophilic cytoplasmic auto (ANCA) antibodies, and divides the vasculitides to those affecting typically the large, medium and small arteries or only small blood vessels. In addition, some vasculitides, which are still difficult to place to the vasculitis map, like B rger's disease, Goodpasture's syndrome, primary angiitis of the central nervous system (PACNS) and panniculitis, are dealt with. As it is a long and winding road, attention has to be paid to the clinical details to follow the road sign to "pseudovasculitis", when that is the right way to go. They represent a bunch of non-vasculitic conditions, which lead to structural or vasospastic impairment of the blood flow, bleeding or thromboembolism and hyperviscosity. These imitators have to some extent, similar clinical symptoms and signs as well as laboratory and radiological findings to those found in true systemic vasculitides. This also emphasizes the importance of internal medicine as the intellectual (albeit not necessarily organizational) home of rheumatology and rheumatologists as we deal with conditions like atherosclerosis, antiphospholipid antibody syndrome, infectious endocarditis, myxoma of the heart and cholesterol embolism.

**Keywords:** Classification, differential diagnosis, pseudovasculitis, vasculitis.

#### INTRODUCTION

In the first part of this four-part review, vasculitides were defined as the inflammation of the vessel wall leading to its weakening, and obstruction of the vascular lumen causing tissue damage and oedema. The importance of patient history, physical status and eventual identification of the insulting antigen/trigger raising a vasculitic immune response in the blood vessel wall were emphasized. At the vasculitic stop sign, also road signs to primary vasculitides and pseudovasculitides are standing erect. This part will deal

with classification, features of individual vasculitides and differential diagnosis against pseudovasculitis.

#### THE SECOND ROAD SIGN: PRIMARY VASCULITIS

Since the triggers in primary vasculitis are not known, they are instead classified based on the size, site, type and effect of the blood vessel involvement (Table 1).<sup>1,2</sup> Anti-neutrophilic

<sup>1</sup>Department of Medicine/Inv rtes Medicine, Helsinki University Central Hospital, Helsinki, <sup>2</sup>ORTON Orthopaedic Hospital of the Invalid Foundation, Helsinki, <sup>3</sup>COXA Hospital for Joint Replacement, Tampere, Finland, <sup>4</sup>Department of Medicine, University of Florence, Florence, Italy, <sup>5</sup>Institute of Experimental & Clinical Medicine, Vilnius University, Vilnius, Lithuania.  
Correspondence: Dr. YT Konttinen, email: yrjo.konttinen@helsinki.fi

**Table 1** Classification of the typical primary and atypical vasculitis diseases is based on the type, size and sites of the vessels affected

Takayasu arteritis (giant cell arteritis)	Large arteries <sup>a</sup>
Temporal arteritis (giant cell arteritis)	Large arteries <sup>b</sup>
Polyarteritis nodosa	Middle- and small-sized arteries <sup>c</sup>
Kawasaki disease	Middle- and small-sized arteries <sup>d</sup>
Wegener's granulomatosis	Small arteries <sup>e</sup>
Microscopic polyangiitis	Small arteries <sup>e</sup>
Churg–Strauss syndrome	Small arteries <sup>e</sup>
Primary angiitis of the central nervous system	Small arteries <sup>f</sup>
Henoch–Schönlein purpura	Small blood vessels <sup>g</sup>
Essential cryoglobulinaemic vasculitis	Small blood vessels <sup>g</sup>
Leucocytoclastic vasculitis of the skin	Small blood vessels <sup>g,h</sup>
Miscellaneous vasculitic syndromes	Arteries and veins of all sizes <sup>i</sup>
Behcet's disease	
Thromboangiitis obliterans (Bürger's disease)	Middle- and small-sized arteries, small veins <sup>j</sup>
Lobular panniculitis	Small arteries <sup>k</sup>
Septal panniculitis	Small veins <sup>k</sup>

This blood vessel- and symptom-based classification scheme into vasculitic syndromes also takes histological changes and clinical manifestations in consideration. Some vasculitic diseases also affect veins (phlebitis). Behcet's disease, thromboangiitis obliterans, primary angiitis of the central nervous system, panniculitis and Goodpasture's syndrome have not yet found their final place on the map of vasculitic diseases.

<sup>a</sup>Thoracic and abdominal aorta and their branches, pulmonary arteries.

<sup>b</sup>All blood vessels affected have lamina elastica interna.

<sup>c</sup>Can lead to nephropathy, but not to glomerulonephritis.

<sup>d</sup>Mucocutaneous lymph node syndrome.

<sup>e</sup>Small arteries, small veins, capillaries and arterioles, usually associated with ANCA (ANCA-vasculitis).

<sup>f</sup>Primary (and isolated) angiitis of the central nervous system or PACNS; in particular small arteries.

<sup>g</sup>Small arteries and arterioles, capillaries and small veins, leading to palpable leucocytoclastic purpura.

<sup>h</sup>Was earlier known as hypersensitivity vasculitis.

<sup>i</sup>In particular small veins are affected.

<sup>j</sup>Panarteritis and panphlebitis, can also be regarded as pseudovasculitis or secondary vasculitis.

<sup>k</sup>A heterogeneous group of conditions.

cytoplasmic autoantibodies (ANCA) form an important new classification criterion.<sup>3</sup> ANCA vasculitides comprise Wegener's granulomatosis, microscopic polyangiitis and Churg–Strauss syndrome. ANCA can also be found in many secondary vasculitic diseases, but then they usually possess specificity other than proteinase-3 or myeloperoxidase. In

the present article, primary vasculitides will be overviewed with the help of fact boxes.

### Takayasu arteritis ("pulseless disease")

Takayasu arteritis is characterized by at least three of the following 1990 ACR criteria:

1. Age at disease onset  $\leq 40$  years.
2. Claudication of extremities.
3. Decreased brachial artery pulse.
4. Blood pressure difference  $>10$  mmHg between left and right arm.
5. Bruit over subclavian arteries or aorta.
6. Arteriographic abnormality.

According to the Chapel Hill nomenclature, Takayasu's arteritis is a granulomatous inflammation of the aorta and its major branches, which usually occurs in patients younger than 50 years of age.

Takayasu arteritis and temporal arteritis are both diseases of aorta and of large arteries, which classically leads to aortic arch syndrome ("pulseless disease"), although atypical coarctation may be more common and dilated and mixed types also occur. Takayasu panarteritis damages the aorta and its large branches as well as pulmonary arteries in young women leading to blood vessel stenosis and occlusion or eventually even to thrombosis and aneurysms<sup>4</sup> because of a cell-mediated autoimmune response against the smooth muscle cells of tunica media. The most important differential diagnoses are atherosclerosis, fibromuscular dysplasia, syphilitic aortitis, temporal arteritis, sarcoidosis, biochemical disturbances of the connective tissue and thrombotic tendencies.

### Temporal or giant cell arteritis

Temporal arteritis or giant cell arteritis is characterized by at least three of the following 1990 ACR criteria:

1. Age at disease onset  $\geq 50$  years.
2. New headache.
3. Temporal artery abnormality (tender, pulse changes).
4. Erythrocyte sedimentation rate  $\geq 50$  mm/hour.
5. Abnormal artery biopsy.

According to the Chapel Hill nomenclature, temporal arteritis is a granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery, which often involves the temporal artery and usually occurs in patients older than 50 years of age and is often associated with polymyalgia rheumatica.

Temporal arteritis<sup>5-7</sup> may represent a cell-mediated immune and granulomatous foreign body reaction against lamina elastica interna damaged by atherosclerosis and by the pulse pressure.<sup>8,9</sup> The intracranial blood vessels, which lack lamina elastica interna, are spared. This panarteritis occurs, apart from the superficial temporal arteries, also in the other extracranial, middle and large size arteries and aorta. The risk to develop thoracic and abdominal aortic aneurysms was reported to be higher by 17.3 and 2.4 times respectively.<sup>10</sup> Stenosis of large arteries have been described in 13% of temporal arteritis patients.<sup>11</sup> The incidence of temporal arteritis in patients over 50 years of age is estimated as 200/million/year. Polyarteritis nodosa, Wegener's granulomatosis and amyloidosis can affect the superficial temporal arteries and mimic giant cell arteritis.

### Polyarteritis nodosa

Polyarteritis nodosa is characterized by at least three of the following 10 1990 ACR criteria:

1. Disease associated weight loss  $\geq 4$  kg.
2. Livedo reticularis.
3. Testicular pain or tenderness.
4. Diffuse myalgias (excluding shoulder and hip girdle), weakness or leg tenderness.
5. Mononeuropathy (may be multiple) or polyneuropathy.
6. Diastolic blood pressure  $>90$  mmHg.
7. Elevated creatinine or blood urea nitrogen.
8. Hepatitis B virus surface antigen or antibody.
9. Arteriographic abnormality (aneurysms or occlusions of the visceral arteries).
10. Biopsy of small or medium-sized artery containing neutrophils.

According to the Chapel Hill nomenclature polyarteritis nodosa is a systemic necrotizing vasculitis characterized by inflammation and necrosis of small and medium-sized arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules.

The classical polyarteritis nodosa and Kawasaki disease most typically affect the middle-size arteries. Chapel Hill nomenclature excludes conditions, where also the small blood vessels are involved, although the histology is similar in microscopic polyangiitis to that seen in polyarteritis nodosa. Thus, polyarteritis nodosa is a rare necrotizing arteritis leading typically to nodular arterial aneurysms (microaneurysms) of the affected vessels.<sup>5</sup> Polyarteritis nodosa patients can be carriers of hepatitis B virus (HBsAg) or have hepatitis C or human immunodeficiency virus antibodies. It can also be

associated with an underlying autoimmune disease, such as rheumatoid arthritis. Eventually an immune complex-mediated disease of the middle-sized arteries leads to ischemia and infarction of the target organs.

### Kawasaki disease (mucocutaneous lymph node syndrome)

Kawasaki disease can be diagnosed if in addition to high fever a child has at least four of the following:

1. Conjunctivitis (bilateral, bulbar, non-suppurative).
2. Red cracked lips, strawberry tongue, diffuse oropharyngeal erythema.
3. Lymphadenopathy (cervical lymph nodes  $>1.5$  cm).
4. Polymorphous rash, not vesicles or crusts.
5. Erythema and oedema of palms and soles developing to peeling of skin from fingertips.

Chapel Hill nomenclature defines Kawasaki disease as an arteritis involving large, medium-sized, small arteries and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved, aorta and veins may be involved and it occurs usually in children.

Kawasaki disease is probably caused by an abnormal immune response against some unrecognized virus or bacterium causing a febrile upper respiratory tract infection.<sup>12</sup> It can damage middle-sized arteries in its acute phase (days 1–10), which can lead to the development of coronary artery aneurysms and ruptures or thromboembolic complications in the subsequent subacute (days 11–20) and convalescent (days 21–60) phases.

Prompt diagnosis is critical, since the early administration of intravenous immunoglobulins and mini-aspirin reduces the rate of coronary manifestations to  $<5\%$ .

### Wegener's granulomatosis

Wegener's granulomatosis is characterized by at least two of the following 1990 ACR criteria:

1. Nasal or oral inflammation leading to purulent or bloody nasal discharge or oral ulcers.
2. Abnormal chest radiograph showing nodules, fixed infiltrates or cavities.
3. Microhaematuria or red cell casts in urine sediment.
4. Granulomatous inflammation in the arterial wall or peri- or extra-vascular tissue around arteries or arterioles.

Wegener's granulomatosis, Churg–Strauss syndrome and microscopic polyangiitis are the three ANCA vasculitides

**Table 2** Use of cytoplasmic anti-neutrophil-antibodies in the diagnosis of vasculitis

- Immunofluorescence (IF) for c-ANCA and p-ANCA is a good screening test. Positive result should preferably be confirmed using ELISA for PR3 and MPO autoantibodies
- p-ANCA without positive PR3- or MPO-ELISA result is a non-specific finding, typically seen in many infections and autoimmune diseases
- Negative ANCA does not exclude vasculitis
- c-ANCA/PR3 are usually seen in Wegener's granulomatosis, but also in microscopic polyangiitis and Churg–Strauss syndrome
- Wegener's granulomatosis can be diagnosed without histology, but only in clinically typical c-ANCA/PR3-positive disease
- p-ANCA/MPO is usually seen in microscopic polyangiitis and Churg–Strauss syndrome
- Persistently elevated ANCA is associated with increased risk of relapse
- Selection of IF- or ELISA in the follow-up is done based on findings at the time of diagnosis

that affect mainly small arteries (Table 2).<sup>14–16</sup> It has been described that cytoplasmic protein-3 and myeloperoxidase can be translocated to the surface of the neutrophils by, e.g. *S. aureus*, lipopolysaccharide or tumour necrosis factor- $\alpha$ . At this new location they are accessible to circulating proteinase-3 and myeloperoxidase specific ANCA. This antigen–antibody binding seems to lead to neutrophil activation and pauci-immune endothelial damage. Thus, ANCA is useful in the diagnosis of AAV, but may also be pathogenic. This has already received some therapeutic consequences, such as anti-CD20 treatment (B cell depletion) and plasma exchange (antibody and immune complex removal).

According to the Chapel Hill nomenclature Wegener's granulomatosis is a granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, e.g. capillaries, venules, arterioles and arteries, in which a necrotizing glomerulonephritis is common. Although Wegener's granulomatosis affects mainly the small arteries, it can also affect small blood vessels and is characterized by c-ANCA (cytoplasmic-ANCA) with proteinase-3 specificity. Wegener's granulomatosis is often associated with nasal *S. aureus*. In Wegener's granulomatosis the upper airways are affected in over 90% of the patients.

Wegener's granulomatosis can be limited (to the upper airways, lungs or kidneys), but later transform to a systemic disease. The upper airways are involved at presentation in some 70–75% of cases and will be affected in over 90% of cases at some time during the course of the disease. Involvement of the lower airways is less common at presentation (45–50%), whereas renal involvement is often asymptomatic and more rare at the time of presentation (20%). Although Wegener's granulomatosis does not affect large or medium-sized veins, the risk for deep venous thrombosis is clearly increased in these patients, its incidence being 7.0/100 person-years (95% CI 4.0–11.4).<sup>17</sup> Diagnosis of Wegener's granulomatosis should be confirmed both radiologically and histologically.

### Churg–Strauss syndrome

Churg–Strauss syndrome is characterized by at least four of the following 1990 ACR criteria:

1. Asthma.
2. Eosinophilia >10%.
3. Pulmonary infiltrates, non-fixed.
4. Paranasal sinus abnormality.
5. Extravascular eosinophils.
6. Mono- or polyneuropathy.

According to the Chapel Hill nomenclature Churg–Strauss syndrome is an eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and blood eosinophilia. Churg–Strauss syndrome affects mainly small arteries and is characterized by perinuclear p-ANCA with myeloperoxidase specificity.<sup>18</sup> These patients practically always have atopy and asthma, which can become milder upon development of vasculitic changes. Apart from nasal and pulmonary changes, nerves, skin, gastrointestinal tract, kidney and heart can be affected and Churg–Strauss syndrome should be suspected when such a patient has peripheral eosinophilia.

### Microscopic polyangiitis

Microscopic polyangiitis (MPA) is characterized by the following three changes:

1. Presence of rapidly progressive glomerulonephritis and/or alveolar haemorrhages.
2. Histological demonstration of small-sized vessel vasculitis or segmental pauci-immune necrotizing glomerulonephritis.
3. Symptoms suggesting small-vessel involvement.

According to the Chapel Hill nomenclature, MPA is a necrotizing vasculitis with few or no immune deposits affecting small vessels, i.e. arterioles, capillaries, or venules. Necrotizing arteritis of small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common and pulmonary capillaritis often occurs.

MPA is a better name for this condition than MPA as some patients have no evidence of arterial involvement. These patients most often have p-ANCA with myeloperoxidase specificity or less often have c-ANCA with proteinase-3 specificity.<sup>19</sup> In contrast, polyarteritis nodosa lacks ANCA and affects middle-sized arteries. MPA is differentiated from immune complex-mediated leucocytoclastic vasculitides, since the focal necrotizing glomerulonephritis in MPA is not associated with immune complex deposition, i.e. it is pauci-immune. Giant cells and granulomas do not occur in this vasculitis.

### Primary angiitis of the central nervous system (PACNS)

Neurological changes as a result of vasculitis of small arteries of the central nervous system and in the absence of systemic vasculitic changes occur in primary angiitis of the central nervous system (PACNS), which has not yet been placed in the official vasculitis map.<sup>20,21</sup> In spite of its name (primary), the patient may have an underlying myeloproliferative disease, HIV-infection or vasospastic tendency. This condition can be classified as benign (BACNS), granulomatous (GACNS) and atypical.

The vasculitic lesion of the wall of the artery leads to thrombosis, ischemia and necrosis and, thus, to headaches, mental changes and focal or systemic neurological defects. These can, in the beginning, be reminiscent of transient ischemic attacks. Benign disease is usually acute on onset and monophasic, whereas granulomatous disease evolves slowly, is chronic and tends to remit.

### Henoch–Schönlein purpura

Henoch–Schönlein purpura is characterized by at least two of the following 1990 ACR criteria:

1. Palpable purpura (haemorrhagic skin lesions not related to thrombocytopenia).
2. Age  $\leq 20$  years at disease onset.
3. Bowel angina worsening after meals or bowel ischemia usually in the form of bloody diarrhoea.
4. Leucocytoclastic vasculitis on biopsy.

Henoch–Schönlein purpura, cryoglobulinaemias and leucocytoclastic vasculitis of the skin are characterized by the immune complex deposition in the walls of the small vessels leading to leucocytoclasia, rupture of the vascular wall, and palpable purpura.<sup>22</sup>

According to the Chapel Hill nomenclature Henoch–Schönlein is a vasculitis, with IgA-dominant immune deposits, affecting small vessels (i.e. capillaries, venules, or arterioles), which typically involves skin, gut, and glomeruli, and which is associated with arthralgia or arthritis.

Leucocytoclastic vasculitis can also occur in severe systemic ANCA-associated vasculitides that must be excluded. Henoch–Schönlein purpura usually occurs in children as an IgA-dominated febrile response to an upper respiratory tract infection together with arthralgias/arthritis, glomerulonephritis and gastrointestinal changes. Henoch–Schönlein purpura shares many features with IgA nephropathy, to which it is related. Both glomerulonephritides are characterized by an abnormal O-glycosylation of the hinge region of serum IgA<sub>1</sub>, which favours pathological aggregation, mesangial deposition and initiation of glomerular inflammatory processes.

Patients with general symptoms and abdominal pain should be sent to the hospital for follow-up. Meningococcal sepsis and other septicemias should be considered in differential diagnosis, as they can also lead to petechiae and joint symptoms.<sup>23</sup>

### Cryoglobulinaemia

Mixed cryoglobulinaemia can be diagnosed if all the following three major criteria are fulfilled. One major criterion is enough if it occurs together with at least two minor clinical criteria and two minor serological/histopathological criteria.

#### Major criteria

Clinical: Palpable purpura.

Serological: Cryoglobulins and hypocomplementemia.

Histopathological: Leucocytoclastic vasculitis.

#### Minor criteria

Clinical: Chronic hepatitis, membranoproliferative glomerulonephritis, peripheral neuropathy, skin ulcers.

Serological: Rheumatoid factor+, hepatitis C+, hepatitis B+.

Histopathological: Clonal B-cell infiltrates in the liver and/or bone marrow.

According to the Chapel Hill nomenclature “essential” cryoglobulinemia is a vasculitis, with cryoglobulin immune deposits, affecting small vessels (i.e. capillaries, venules, or arterioles) and associated with cryoglobulins in serum, in which skin and glomeruli are often involved.

Cryoglobulinaemia refers to cold precipitating immune complexes or aggregates of monoclonal antibody, which usually consume the complement.<sup>24</sup> However, simple type I cryoglobulinaemia is caused by lymphoproliferative diseases (lymphoma, Waldenström’s macroglobulinemia, multiple myeloma) in which the neoplastic clone produces monoclonal cryoglobulin. As these monoclonal cryoglobulins do not usually fix the complement, these conditions can remain clinically asymptomatic if they do not cause a hyperviscosity syndrome. Mixed cryoglobulins also contain rheumatoid factor, in type II disease monoclonal and in type III disease polyclonal. They fix the complement and cause small vessel vasculitis. These usually occur in adults, who suffer from lymphoproliferative disorders, chronic infections or autoimmune diseases. Cryoglobulinaemia should actually only be called essential if the patient does not have any underlying neoplastic, infectious or immunological disorders. Chronic hepatitis, glomerulonephritis, neuropathy, skin ulcers, cold urticaria, Raynaud’s phenomenon, arthralgias and abdominal pain can also occur.

### **Leucocytoclastic vasculitis of the skin (previously hypersensitivity vasculitis)**

The most benign form of the immune complex-mediated small vessel vasculitis family is the one without any manifestations from the gastrointestinal tract, kidneys or joints, solely restricted to the skin in the form of palpable purpura and leucocytoclastic vasculitis. Chapel Hill defines it as an isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis. Patients of all ages can develop vasculitis of small vessels restricted to the skin. Drugs and infections can lead to leucocytoclastic vasculitis, which can also occur as a secondary manifestation of autoimmune diseases like rheumatoid arthritis and SLE, which apparently provide endogenous antigens to drive the vasculitic process. Systemic involvement must be excluded and triggering factors looked for.

## **MISCELLANEOUS VASCULITIC SYNDROMES**

### **Behçet’s disease**

According to the international classification criteria<sup>25</sup> it is possible to classify a condition as Behçet’s disease, if

there is no other explanation and if just one major criterion and at least two of the four minor criteria can be reliably documented.

### *Major criterion*

Recurrent oral ulceration in form of minor, major or herpeticiform aphthae, which recur  $\geq 3$  times during one year.

### *Minor criteria*

1. Recurrent genital aphthous ulceration or scarring.
2. Eye lesions, either anterior uveitis, posterior uveitis, and cells in vitreous upon slit-lamp examination or retinal vasculitis observed by the ophthalmologist.
3. Skin lesions, either erythema nodosum-like lesions, pseudofolliculitis, and papulopustular lesions or acne-like nodules.
4. Positive pathergy test, which refers to an erythematous  $\geq 2$  mm large papule at the site for 20–22 gauge sterile needle prick 2 days after oblique penetration of avascular skin to a depth of 5 mm.

In a review article published in this issue of the *Indian Journal of Rheumatology* “Behçet’s disease: global perspective” Davatchi refers to 14 different sets of diagnostic criteria, which had been proposed until 2004 and compares some of the key diagnostic criteria sets in a compact table format. There is also a citation to the new Revised International Criteria for Behçet’s Disease, which were created in 2006 and contain six items (oral aphthosis one point, skin manifestations one point, vascular lesions/arterial and venous thrombosis or aneurysms one point, pathergy test one point, genital aphthosis two points and ocular lesions two points). Behçet’s disease is diagnosed when three or more points are scored. This table format is probably more practical for clinical work than the classification tree, which is also available.<sup>26</sup>

The controversy that exists about the “universality” of the above-mentioned classification criteria is not because the clinical syndrome differs in different geographical areas like Middle East, the Mediterranean Basin and Far East. Apart from the classification criteria, these patients often display arthritis, central nervous system lesions and vasculitic lesions, which usually involve small veins, but may also involve any part of the vascular tree, including the great vessels. Cardiovascular, gastrointestinal, renal, pulmonary changes can also occur. In many studies, e.g. from Lebanon, male dominance has been described,<sup>27</sup> whereas the other studies, e.g. from Korea have described a female dominance.<sup>28</sup> Studies on the influence of gender might be biased as the severe manifestation of the disease tends to occur more often in males.

### Bürger's disease (thromboangiitis obliterans)

This disease and its progression are associated with smoking. Bürger's disease arises somehow as a vasculitic hypersensitivity reaction against some component of the cigarette. Placement of this vasculitis onto the vasculitis map is difficult, because it could be also classified as a secondary vasculitis or a pseudovasculitis. It is a segmental, inflammatory and thrombotic arteritis of the small and middle-sized peripheral arteries (arteritis) and small veins (migrating superficial phlebitis and venous thrombosis) and thus different from atherosclerosis.<sup>13</sup> Patients under 45 years of age develop claudication and resting pain in the distal parts of the extremities, ischemic ulcerations, necrosis and Raynaud's phenomenon. In contrast to atherosclerosis, these lesions also occur in the upper extremities and more distally, even in small size arteries. Typical atherosclerosis occurs in elderly men with dyslipidaemia, diabetes and hypertension with intermittent leg pain during walking.

To demonstrate the involvement of small peripheral arteries in Bürger's disease, the patient is asked to raise a hand and make a fist. Both radial and ulnar arteries are then simultaneously compressed and the patient is asked to open the fist. By releasing one artery at a time (Allen's test) it can be demonstrated whether the distal part of this artery can conduct blood to the palm. If the released artery is distally occluded, the palm will remain pale and will not turn red because the blood is not able to flow beyond the occlusion.

### Goodpasture's syndrome

The classical triad of Goodpasture's syndrome consists of pulmonary haemorrhages, glomerulonephritis and anti-basement

membrane antibodies.<sup>29</sup> Locally formed antigen-antibody complexes fix the complement and damage basement membrane.

### Panniculitis

Panniculitis refers to the inflammation of fat tissue, clinically to red subcutaneous nodules.<sup>30</sup> If small arteries are involved, the entire fat lobule is affected (lobular panniculitis), but if only veins are involved the inflammation is confined to the septum (septal panniculitis). The most common form of panniculitis is erythema nodosum in which the involvement of both arteries and veins can coexist. These patients often have had streptococcus or yersinia infection, have used sulfonamides or birth control pills, or suffer from Crohn's disease, tuberculosis or sarcoidosis. The most common vasculitic lobular panniculitis is caused by cutaneous polyarteritis nodosa, which can lead to nodules, ulcerations and livedo reticularis in the legs.

### THE THIRD ROAD SIGN: PSEUDOVASCULITIS

A large number of non-vasculitic conditions (pseudovasculitis) have been described, which lead to stenosis, occlusion, vasospasm, thromboembolism, vessel wall weakening, dilatation, dissection or hyperviscosity of the blood, all of which can lead to a wrong road (Table 3).<sup>31</sup> Their clinical symptoms and signs, laboratory and radiological findings can be very similar to those found in systemic vasculitides. Pseudovasculitides are not rare and should always be kept in mind when systemic vasculitis is suspected. The road

**Table 3** Pseudovasculitis results from non-vasculitic blood vessel damage, obstruction, thromboembolism, vasospasm or other pathology

<i>Pathogenetic mechanism</i>	<i>Clinical diagnosis</i>
Diseases of the blood vessel wall	Atherosclerosis, Bürger's disease, fibromuscular dysplasia, amyloidosis, scurvy, calciphylaxis, Moyamoya disease
Infections	Syphilis, Lyme disease, miliary tuberculosis, chronic viral hepatitis meningoencephalitis, sepsis
Coagulation disorders	Antiphospholipid antibody syndrome, TTP/HUS, DIC, coagulation disorders, heparin-induced thrombocytopenia or HIT
Embolisation	Infective endocarditis, myxoma, cholesterol embolism, non-bacterial thrombotic endocarditis
Drugs and narcotics (vasospasm)	Phenylpropanolamines, amphetamines, cocaine
Hormones (vasospasm)	Pheochromocytoma
Miscellaneous	Neoplasms, hypereosinophilic syndrome, intravascular lymphoma, hyperviscosity syndrome, connective tissue diseases

sign to pseudovasculitis and secondary vasculitis should be checked before the one pointing towards primary vasculitis is followed. Different specific and even curative treatments are often available for pseudovasculitis. On the other hand, treatment for vasculitis in a patient with pseudovasculitis can result in irreparable damage.

## Atherosclerosis

Atherosclerosis causes stenosis of large and middle-sized arteries. Ischemic pain and skin alterations in severe cases resemble those caused by vasculitides. Atherosclerotic plaques contain inflammatory cells, but the acute phase reactants are almost normal although slightly elevated CRP and fibrinogen are risk factors. On the other hand, infections predispose to atherosclerotic plaque rupture, which can lead to medical calamities like myocardial infarction or stroke. In stable plaques, a certain degree of physical exercise consistently leads to ischemic pain, such as angina pectoris or intermittent claudication. Atherosclerosis is slowly progressive and the patients typically have a long history spanning back to even decades.

## Antiphospholipid antibody syndrome (slightly modified criteria)

A condition can be classified as a definite antiphospholipid antibody syndrome if at least one of the following clinical and one of the laboratory criteria are met:

### Clinical criteria

#### 1. Vascular thrombosis:

At least one clinical episode of arterial, venous, or small vessel thrombosis, in any tissue or organ, confirmed by imaging, doppler or histopathology, with the exception of superficial venous thrombosis. For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

#### 2. Pregnancy morbidity:

Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

One or more unexplained deaths of a normal foetus at or beyond the 10th week of gestation, documented by ultrasound or by direct examination of the foetus.

At least one premature birth of a morphologically normal neonate at or before the 34th week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency.

*Laboratory criteria* (on two or more occasions, at least 6 weeks apart, detected following the international standards)

1. Anticardiolipin antibody of IgG and/or IgM isotype in serum, present in medium or high titre.
2. Lupus anticoagulant present in plasma.
3. Beta-2 glycoprotein I antibodies in serum.

Antiphospholipid antibody syndrome is characterized by arterial and venous thrombosis, thrombocytopenia, recurrent abortions and anti-phospholipid antibodies.<sup>32</sup> It can cause stroke, livedo reticularis and ulcers, which can be similar to those seen in systemic vasculitides. Libman-Sacks endocarditis can be a source of peripheral emboli. Catastrophic antiphospholipid syndrome is caused by the occlusion of the microvasculature leading to progressive renal and multi-organ failure. SLE patients can have antiphospholipid antibodies and, therefore, both non-inflammatory vascular occlusions and secondary immune complex vasculitis. Antiphospholipid antibody syndrome can be aggravated by estrogens used for oral contraception or hormone replacement therapy and by smoking.

## Infectious endocarditis

Infectious endocarditis is caused by the infectious inflammation of the endocardium and heart valves, which collect aggregated platelets, fibrin, microbes and inflammatory cells in the form of vegetations. Often the source of bacteraemia remains unclear. Heart valve pathology (e.g. bicuspid aortic valve, mitral valve insufficiency) and immunocompromising states predispose to endocarditis. Clinical findings, such as petechiae, haematuria, arthralgias and arthritis resemble those associated with a systemic connective tissue disease or vasculitis. Although infectious endocarditis can lead to pseudovasculitis because of microembolisms, it can also cause secondary vasculitis associated with immune complex formation. Auscultation reveals heart murmurs, which vary in character as the vegetations change as they grow or embolize. Transthoracic or transesophageal echocardiography can be used to visualize vegetations and underlying or endocarditis-associated valve pathology. Repeated blood cultures should be taken before antibiotic treatment and at fever peaks to disclose bacteraemia and obtain samples for identification and sensitivity testing of the causative microbe. Acute phase reaction, hypergammaglobulinemia

and rheumatoid factor can be found in both endocarditis and vasculitis.

### *Myxoma of the heart*

Myxoma of the heart is *per se* a benign intracardial tumour, which can occur at all ages, more commonly in women than in men.<sup>33</sup> Myxoma can lead to cardiac and extracardiac symptoms, such as lung emboli, arthritis, petechiae, Raynaud's phenomenon, haematuria and proteinuria. Embolic manifestations can simulate vasculitis as they develop suddenly and lead to severe ischemic end organ and tissue changes. Approximately half of these patients have fever and lose weight. These changes and anaemia, leucocytosis, thrombocytosis, hypersedimentation and high CRP values are in part caused by interleukin-6 produced by the myxomatous cells.

Biopsies and the embolic lesions demonstrate myxomatous cells, but not vasculitic changes. Transthoracic and transesophageal echocardiographies are useful, although differential diagnosis between myxoma and intracardial thrombosis can be difficult. Diagnosis of myxoma is confirmed with computed tomography (CT) or magnetic resonance imaging (MRI). Resection of myxoma is usually a curative treatment.

### **Cholesterol embolism ("blue toe syndrome")**

Occasionally the atherosclerotic plaque ulcerates because of endovascular procedures (mechanical manipulation), anticoagulation (exposing the plaque surface below the "protective" thrombus mass) or spontaneously, leading to cholesterol crystal embolization.<sup>34</sup> Small, needle-like cholesterol crystals are disseminated into various tissues, usually kidneys. The typical patient, an elderly man suffering from advanced atherosclerosis, has recently undergone an invasive vascular procedure, e.g. an angiography. The manifestations greatly resemble those caused by vasculitis, e.g. petechiae and ulcerations are common. As the cholesterol emboli are so small, the peripheral pulses of the larger blood vessels remain easily palpable even in the blue or purple toe syndrome. The most serious manifestations of cholesterol embolism are amaurosis fugax and permanent blindness, myocardial infarction, bowel infarction, peripheral neuropathy and progressive renal failure.

Diagnosis is histopathological and is based on the demonstration of cholesterol crystals (or actually their voids), which leave slits in the damaged tissue as they are dissolved away during the regular tissue sample processing. There is no specific medical treatment, but if the patient uses warfarin,

it may have to be stopped. Without surgical treatment, i.e. removal of the atheroembolic source material, cholesterol embolism is a recurrent process with a high mortality rate.

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## Cocaine abuse: an important mimic of vasculitis

A 43-year-old woman with a history of cocaine abuse presented with decreased mental responsiveness and cyanosis of the extremities several hours after repeated use of “crack” cocaine. She developed bilateral hand compartment syndrome requiring emergency fasciotomy and gangrene of both hands and legs despite anticoagulant and antithrombotic therapy. Digital and above-knee amputations were performed. There was no evidence of an autoimmune disorder

or vasculitis on laboratory evaluation and tissue histology. Peripheral vasospasm may have been the mechanism of toxicity in this case, and the use of intravenous vasodilators should be considered as potential additional therapy.

*Source:* Dhawan SS, Wang BW. Four-extremity gangrene associated with crack cocaine abuse. *Ann Emerg Med* 2007; 49: 186–9.