



ROADMAP TO VASCULITIS

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ABSTRACT

Vasculitis is characterized by vessel wall injury caused by an immunologically initiated inflammatory reaction. Vessel wall injury leads to vascular stenosis, aneurysm, bleeding, thrombosis, embolism, vasospasms and ischemia. The vasculitis is clinically important when the patient has general inflammatory and multifocal symptoms, which progress in episodes and can be explained by these vascular lesions. The clinical manifestations of these depend on the size, localization and number of blood vessels involved. This forms the basis of the current vasculitis classification. It is important to recognize the secondary vasculitides, as their treatment is mainly based on elimination of the triggering factor. In primary vasculitides, immunosuppression alone is the basis of treatment in almost all cases, whereas the management of pseudovasculitis is dependent on its aetiology. In primary care, basic evaluation should be done: patient history, physical examination, basic laboratory tests and other non-invasive tests to verify suspected surrogate findings. After this, patients should be urgently referred to a specialized centre, where the required histological and radiological tests are performed for diagnosis and immunosuppressive and other necessary treatment is initiated.

Keywords: Vasculitis; Classification; Diagnosis; Treatment.

RESUMO

As vasculites são caracterizadas por lesão da parede vascular causada por uma reacção inflamatória mediada imunologicamente. Esta lesão causa estenose, aneurismas, hemorragias, trombozes, embolias, vasoespasmos e isquémia. A vasculite é clinicamente importante quando o doente tem inflamação sistémica e sintomas multifocais, que progridem por crises e que são explicáveis por estas lesões vasculares. As manifestações clínicas dependem do tamanho, localização e número de vasos envolvidos. É esta a base da actual classificação das vasculites. É importante reconhecer as vasculites secundárias, porque o seu tratamento é baseado na eliminação do factor precipitante. Nas vasculites primárias a imunossupressão é a base do tratamento em quase todos os casos, ao passo que o tratamento das pseudovasculites está dependente da etiologia. Nos cuidados primários deve ser feita uma avaliação básica: história clínica, exame objectivo, testes laboratoriais gerais e outros exames não invasivos orientados pela sintomatologia do doente. Após esta fase, estes doentes devem ser referenciados urgentemente a centros especializados onde os exames radiológicos e histológicos fundamentais para o diagnóstico serão realizados e a imunossupressão ou outras eventuais medidas terapêuticas serão iniciadas.

Palavras-Chave: Vasculites; Classificação; Diagnóstico; Terapêutica.

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Vasculitis typically damages the blood vessel wall via an immunologically initiated inflammatory reaction. Damage in the vessel wall can lead to aneurysm and bleeding or, alternatively, obstruction of the vascular lumen, thrombosis/embolism, vasospasm and ischemia. The clinical manifestations depend on what and what size and type of blood vessel or vessels are affected. This is also used as the basis in the classification of primary vasculitis¹⁻³. In examination of vasculitis patients, it is essential to determine fast and accurately the severity of the vasculitic changes and map the affected organs. In the treatment of the patient with serious vasculitis, the clinician has to rapidly determine diagnosis, because delay of aggressive treatment endangers treatment results.

On clinical grounds, vasculitis has to be suspected, when the patient suffers from an illness leading to general symptoms, inflammatory and multifocal disease with unpredictable development of manifestations, which can be explained on the basis of blood vessel damage⁴. When suspicion of vasculitis has been raised, it is necessary to try to identify any triggering or perpetuating factors and to exclude pseudovasculitis. From the point of view of management, it is important to consider the possibility of secondary vasculitis and pseudovasculitis. In secondary vasculitis the management is based on the elimination of the triggering or perpetuating factor and in pseudovasculitis on the aetiology, whereas the management of primary vasculitis is

usually based on immunosuppression. Mixed and empirical treatments are sometimes necessary.

In general practice patient history, physical examination, basic laboratory tests and eventually non-invasive diagnostic procedures to identify surrogate changes should be done. A patient can develop “unstable vasculitic plaques” (pro-thrombotic inflammation, which forms initiation sites for thrombi) in blood vessels of vital organs. A patient who is suspected to suffer from vasculitis should be urgently referred to a specialized institution for further diagnostic work up and management. This enables invasive diagnostic procedures such as biopsies and invasive radiology and initiation of appropriate immunosuppressive or other initial treatment.

STOP Sign

Since vasculitis is a rare disease, the most difficult and important step in tackling vasculitis is to stop and consider the possibility of it. Typically, vasculitis presents as a suddenly developed and jerk-wise, progressive multiple organ damage in a severely ill patient, the symptoms of whom can be best explained by immune-inflammatory damage of the blood vessel wall (Table I).

First Road Sign: Triggering Factors

Typically, vasculitis is associated with immunological reactivity such as an immune response leading to antigen specific reaction in form of production of antibodies or T cell receptor mediated activation of T lymphocytes to produce cytokines. Vasculitis is not an inherited disease, although a susceptibility to react in a harmful way to antigenic stimuli and to develop severe disease would be inheritable, e.g. in form of complement or immunoglobulin subclass deficiencies. Family history does not usually provide much help in definition of

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Table I. Typical general and organ and tissue specific changes caused by vasculitis

General symptoms	Fever, loss of weight, loss of appetite, fatigue
Skin	Palpable purpura, vasculitic urticaria, subcutaneous nodules, vasculitic ulcers and necrosis, livedo reticularis
Mucosal membranes	Oral and genital aphthae, nose bleeding, crusts and obstructive changes in nasal mucosa
Musculoskeletal changes	Arthralgia, myalgia, arthritis, myositis
Nervous system	Headache, mononeuritis multiplex, polyneuropathy, cranial nerve palsies, spinal cord lesions, hemiparesis
Ears	Serous middle-ear infections, conductive hearing loss
Eyes	Sugillation, scleritis, uveitis, keratitis, proptosis, paralysis of the ocular muscles and diplopia, amaurosis fugax, bleeding and exudates in fundus of the eyes, loss of vision
Cardiovascular	Systolic bruits, pulse and pressure differences, pericarditic pain and friction rub, arrhythmias and heart failure in particular in young patients lacking usual risk factors
Airways and lungs	Sinusitis, saddle nose, obstructions of trachea, hemoptysis, changing lung infiltrates
Abdomen	Abdominal pain, melena, perforations, pancreatitis
Kidneys	Glomerulonephritis, nephropathy, secondary hypertension

the type of disease. In vasculitis the triggering and the perpetuating factors are of central importance.

From the point of view of the practising physician, it is important to try to identify triggering factors. Usually vasculitis of unknown cause (in which no triggering or perpetuating factor is known) is

separated from secondary vasculitic disease (in which some triggering or perpetuating factors can be found) (Table II). Triggering factors comprise bacterial, viral, fungal and parasitic infections, drugs, vaccinations, nutrients and various connective tissue diseases, malignancies and other disea-

Table II. Triggering and/or perpetuating factors in secondary vasculitis

Infections	<ul style="list-style-type: none"> • Hepatitis C • Hepatitis B • HIV • Parvovirus B19 • Septicaemia in meningococcal infections • Septicaemia in streptococcal infections • Septicaemia in gonococcal infections
Drugs, vaccinations and food items	<ul style="list-style-type: none"> • Allopurinol, phenytoin, cefaclor, isotretinoin, methotrexate, NSAIDs, antibiotics, diuretics • Pneumococcal, influenza or hepatitis B-vaccinations • Food items and additives
Connective tissue diseases and inflammatory bowel diseases	<ul style="list-style-type: none"> • Rheumatoid arthritis • Systemic lupus erythematosus • Sjögren's syndrome • Dermato-polymyositis • Crohn's disease • Ulcerative colitis
Tumours and carcinomas	<ul style="list-style-type: none"> • Lymphoproliferative diseases • Myeloproliferative diseases • Lung cancer

ses associated with the presence of antigens or allergens⁵. Infections as triggering factors form a special case. Secondary vasculitis and infection always need to be excluded before a specific primary vasculitis is diagnosed.

Management of secondary vasculitis is based on the elimination or minimization of the triggering stimulus e.g. by the use of antibiotics, antiviral medication, interferon, change of the medication, use of anti-inflammatory immunosuppressive drug or surgery, radiation and chemotherapy. Smoking should be stopped. In clinical praxis this treatment aiming to elimination or diminution of the triggering and perpetuating factors is often combined with a simultaneous anti-inflammatory and immunosuppressive treatment of the vasculitic complications.

With time, the distinction between primary and secondary vasculitis has become less clear, becau-

se even primary vasculitic disease can often nowadays be connected with triggering stimuli, for example, hepatitis B virus surface antigen (HBsAg) with polyarteritis nodosa, *Staphylococcus aureus* with Wegener's granulomatosis, A-group streptococci and mycoplasmae with Henoch-Schönlein purpura, hepatitis C-virus with essential cryoglobulinaemia and various drugs with cutaneous leucocytoclastic vasculitis. On the other hand, in secondary vasculitis with a clear-cut triggering or perpetuating stimulus it may be necessary to treat the vasculitic changes *per se*.

The Second Road Sign: The Primary Vasculitis

Because the triggering stimulus according to definition is not known in primary vasculitis, current classification of primary vasculitis is instead based

Table III. Classification of the typical primary and atypical vasculitis diseases has been based on the size of the vessel affected. Classification also takes histological changes and typical clinical manifestations in consideration. Some vasculitic diseases also affect veins (phlebitis). Behçet'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.

Takayasu arteritis (giant cell arteritis)	Large arteries ¹
Temporal arteritis (giant cell arteritis)	Large- and middle-sized arteries ²
Behçet's disease	Arteries and veins of all sizes ³
Polyarteritis nodosa	Middle- and small-sized arteries ⁴
Kawasaki disease	Middle- and small-sized arteries ⁵
Thromboangiitis obliterans (Bürger's disease)	Middle- and small-sized arteries, small veins ⁶
Wegener's granulomatosis	Small arteries ⁷
Microscopic polyangiitis	Small arteries ⁷
Churg-Strauss syndrome	Small arteries ⁷
Primary angiitis of the central nervous system	Small arteries ⁸
Henoch-Schönlein purpura	Small blood vessels ⁹
Essential cryoglobulinaemic vasculitis	Small blood vessels ⁹
Leucocytoclastic vasculitis of the skin¹⁰	Small blood vessels ⁹
Lobular panniculitis	Small arteries ¹¹
Septal panniculitis	Small veins ¹¹

¹ Thoracic and abdominal aorta and their branches as well as the pulmonary arteries

² Blood vessels affected have lamina elastica interna

³ In particular small veins are affected, can also be regarded as a secondary vasculitis

⁴ Disease can also lead to nephropathy, but not to glomerulonephritis

⁵ Mucocutaneous lymph node syndrome

⁶ Panarteritis and panphlebitis, can also be regarded as pseudovasculitis or secondary vasculitis

⁷ Small arteries, small veins, capillaries and arterioles usually associated with ANCA (ANCA-vasculitis)

⁸ Primary (and isolated) angiitis of the central nervous system or PACNS; in particular small arteries

⁹ Small arteries, capillaries and small veins, leading to palpable leucocytoclastic purpura

¹⁰ Was earlier known as hypersensitivity vasculitis

¹¹ A heterogeneous group of conditions

on the size of the affected blood vessels, the localization of these vasculitic lesions and their histopathology^{1,2} (Table III). In autoantibody negative vasculitis, vascular wall damage can be mediated by cell-mediated immune reactions. Nowadays, anti-neutrophilic cytoplasmic autoantibodies (ANCA) are an important new classification criterion⁶. Association with hepatitis or the presence of immune complexes can modify the management approach taken. As no triggering or perpetuating factor is known in primary vasculitides, there is no test-tube test either, which could be used to demonstrate a specific disease-associated autoantibody or T-lymphocyte reactivity enabling a specific and unanimous diagnosis. In large blood vessel disease vascular luminal stenosis and occlusions occur upon thickening of the blood vessel wall, whereas in the disease of middle-sized arteries, focal necrotizing aneurysmatic lesions can develop upon weakening of the blood vessel wall. In the diseases of small arteries, blood vessel wall does usually not contain immunoglobulin precipitations, but the immunological basis of the disease is evident as the patient has circulating ANCA. 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. Immune complexes or cryoglobulins, which precipitate in the blood vessel wall, are found in the small vessel disease, affecting arterioles, capillaries and in particular venules. The typical clinical manifestation developing on this basis is a palpable purpura.

Takayasu arteritis

Takayasu panarteritis (Table IV) damages aorta and its large branches as well as pulmonary arteries in young women leading to blood vessel stenosis and occlusion⁸. Also thrombosis and aneurysms can develop. Takayasu panarteritis is probably based on a cell-mediated autoimmune response against the smooth muscle cells in the vessel wall media. A febrile and generally sick patient develops aortic arch syndrome. Pulses disappear or become weak ("pulseless disease"), systolic bruits can be heard above large blood vessels and blood pressure measurement can demonstrate more than 10 mmHg difference between the arms. Stenosis of the coronary arteries, brachiocephalic trunk, left carotid artery and subclavian artery and

Table IV. Takayasu arteritis is characterized by at least three of these 1990 ACR criteria⁷

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

mesenteric and renal arteries lead to angina pectoris, claudication of the upper extremity, fainting, visual disturbances, and stroke, postprandial angina, and renovascular hypertension associated with kidney failure. Aneurysmatic dilation of aorta can lead to secondary aortic valve insufficiency and involvement of the pulmonary arteries can lead to pulmonary hypertension.

Takayasu arteritis is a typical granulomatous giant cell arteritis, the diagnosis of which can be rarely confirmed by histology *ante mortem*, as it is difficult to obtain biopsies of the target lesions. Diagnosis is usually reached by the use of computed tomography, magnetic resonance imaging and angiographies, showing stenosis and poststenotic vessel dilations⁹⁻¹¹. The most important differential diagnoses are atherosclerosis, fibromuscular dysplasia, sarcoidosis, biochemical disturbances of the connective tissue and thrombotic tendencies.

Temporal or giant cell arteritis

A panarteritis can occur in the superficial temporal arteries (Table V), but also in other extracranial, large and middle-sized arteries, leading to thickening of the vascular wall and stenosis and occlusion of lumen¹³⁻¹⁵. Inflammation of the vertebral arteries can lead to transient ischemic attack (TIA), stroke and vertigo. Inflammation of the subclavian, carotid and brachial arteries can lead to aortic arch syndrome, claudication of the upper extremities and asymmetric pulses or pulselessness. The disease is also known as giant cell arteritis as it can affect also arteries other than temporal arteries. Temporal arteritis is a relatively common primary vasculitis. Its incidence in patients over 50 years of age is estimated at up to 200/million/year. Temporal arteritis and polymyalgia rheumatica follow the rule of 50: both the patient and the erythrocyte sedimentation rate (ESR) are usually over 50. Tempo-

Table V. Temporal arteritis or giant cell arteritis is characterized by at least 3 of these 1990 ACR criteria¹²

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

ral arteritis is not associated with any typical autoantibody marker. It has been considered a manifestation of cell-mediated immune reaction and granulomatous foreign body reaction against lamina elastica interna damaged by atherosclerosis and by the pulse pressure¹⁶. Therefore, intracranial blood vessels, which lack lamina elastica interna, are spared. Arteritis leads to a new headache and tenderness on palpation or weak and asymmetric pulses in the temporal arteries. Masticatory claudication can occur. A much feared complication is a sudden and painless loss of vision, which can be preceded by amaurosis fugax and can affect the whole visual field or parts of it. Diplopia can develop. Giant cell arteritis leads to prominent general symptoms, such as fever, loss of weight and polymyalgia rheumatica and even synovitis. Some other vasculitides, such as polyarteritis nodosa and Wegener's granulomatosis as well as amyloidosis can affect superficial temporal arteries and may mimic the symptoms of giant cell arteritis.

Treatment is initiated with prednisolone, 40-60 mg/day, which has to be, due to the risk for blindness, commenced immediately when the diagnosis is suspected¹⁷. If the patient develops ocular symptoms, treatment is initiated with methylprednisolone pulses given intravenously. Musculoskeletal symptoms usually disappear rapidly upon initiation of prednisolone treatment, and this provides support to the working diagnosis at the initial stages. A small dose of acetosalicylic acid protects against thrombotic complications of the vasculitic lesions. Diagnosis has to be confirmed as soon as possible from temporal artery biopsies, which demonstrate destruction of lamina elastica interna, inflammatory cells in adventitia and giant cell granulomas. False negative biopsies also occur, so the decision to treat is at the end the clinician's responsibility. Because these inflammatory changes are patchy, it is generally recommended that

about 2-3 cm piece of temporal artery be taken to avoid false negative findings. When involvement of the large vessels is suspected, angiography is recommended. In spite of the excellent subjective treatment response on short term, blood vessel wall inflammation can gradually in long-term, usually over decades, lead to aortic aneurysms and aortic valve insufficiency.

Polyarteritis nodosa

Polyarteritis nodosa (Table VI) is a relatively rare disease leading typically to nodular arterial aneurysms¹³. The classical polyarteritis nodosa affects middle-sized arteries. Unlike microscopic polyangiitis (microscopic polyarteritis), polyarteritis nodosa does not affect capillaries or venules. Eventually immune complex mediated disease of the middle-sized arteries leads to ischemia and infarction of the target organs, which can lead to angina pectoris, myocardial infarction, melena or gastrointestinal perforation, hypertension, kidney failure and mononeuritis multiplex. Livedo reticularis refers to mottled, reticular skin changes of proportions of the extremities or torso caused by involvement of cutaneous blood vessels. Purpura, upper respiratory tract pathology, pulmonary changes and glomerulonephritis are not typical for polyarteritis nodosa. If the patient has these types of changes, she might suffer from small vessel or small artery vasculitis.

There is no serological autoantibody test for polyarteritis nodosa, but the patient can have he-

Table VI. Polyarteritis nodosa is characterized by at least 3 of these 10 1990 ACR criteria¹⁸

1. Disease associated weight loss ≥ 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 mm Hg
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

patitis-C or human immunodeficiency virus antibodies or she can be a carrier of hepatitis-B virus (HBsAg), which apparently all act as some type of triggering and underlying factors. Thrombocytopenia and leukocytopenia are not typical for primary polyarteritis nodosa and these changes suggest some other associated disease, e.g. hairy cell leukaemia. If electromyography demonstrates abnormal conduction in the sural nerve or some other peripheral nerve, a nerve biopsy can demonstrate necrotizing arteritis or ischemic neuropathy. If the symptoms suggest ischemic muscle disease, muscle biopsy is indicated and can be diagnostic. If no good target for biopsy can be found, it is possible to use angiography to demonstrate microaneurysms of the middle-sized arteries.

Kawasaki disease

Kawasaki disease (Table VII) usually follows the rule of five: the patient is less than five years of age and has had fever for at least five days²⁰. In Kawasaki disease fever is associated with mucocutaneous lymph node syndrome and often also diar-

Table VII. Kawasaki disease can be diagnosed if in addition to high fever a child has at least four of the following¹⁹:

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 edema of palms and soles developing to peeling of skin from fingertips

rhoea. 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 in the subsequent subacute (days 11-20) and convalescent (days 21-60) phases. The disease is possibly caused by an abnormal immune response against some as yet unrecognized virus or bacterium. Febrile upper respiratory tract symptoms are accompanied with those enumerated in the fact box above. Laboratory tests disclose signs of acute inflammation. Myocarditis can lead to arrhythmias. These patients must be urgently referred to a specialist for further diagnostic work up and management.

Echocardiography should always be performed. After the acute phase, thrombocytosis and aneurysms develop. In the hospital, anti-inflammatory treatment is provided but the basic treatment comprises intravenous immunoglobulins (2 g/kg, up to 70 g) in one dose (20). Prednisolone can increase the risk for aneurysms by weakening the blood vessel wall and by promoting thromboses of the vasculitic plaques. It seems to be unnecessary to follow the old praxis to order high- (80–100 mg/kg per day as were used in North America) or medium-dose (30–50 mg/kg per day as were used in Japan) acetosalicylic acid in these children. Low dose acetosalicylic acid is used in thrombocytosis as a prophylaxis. Prompt diagnosis is critical, since the early administration of intravenous immunoglobulins and aspirin reduces the rate of coronary abnormalities to less than 5 % of patients.

Bürger's disease

Bürger's disease is also known as thromboangiitis obliterans. 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 small and middle sized peripheral arteries (arteritis) and small veins (migrating superficial phlebitis and venous thrombosis), different from atherosclerosis (21). This disease and its progression are associated with smoking. Bürger's disease rises somehow as a vasculitic hypersensitivity reaction against some component of cigarettes. It usually manifests in patients under 45 years of age, leading to 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. Elderly men with hyperlipidaemia, diabetes and hypertension with intermittent leg pain during walking are much more likely to suffer from plain atherosclerosis. To demonstrate involvement of such small peripheral arteries, patients can be 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.

There are no disease specific and diagnostically useful autoantibodies in this disease. Angiography of the extremities discloses non-atherosclerotic occlusions, which, in long lasting disease, are often surrounded by corkscrew like collaterals. Smoking must be stopped. Calcium channel blockers and prostacyclin analogues can be used to avoid amputations.

Wegener's granulomatosis

Wegener's granulomatosis (Table VIII), Churg-Strauss syndrome and microscopic polyangiitis are the three ANCA vasculitides, defined by the presence of ANCA²³⁻²⁵. Wegener's granulomatosis affects mainly small arteries and is characterized by c-ANCA (cytoplasmic-ANCA) with proteinase-3 specificity (Table IX). In Wegener's granulomatosis the upper airways are affected in over 90 % of the patients. Lungs are affected by necrotizing granulomatosis and kidneys by glomerulonephritis.

Wegener's granulomatosis can be limited to upper airways, lungs or kidneys, but this limited form of the disease can transform into a more widespread disease. The upper airways, sinuses, nose and middle ear should be examined. Patients have changes in the upper airways, such as sinusitis, crusts on nasal mucosa, nose bleeds and saddle nose, middle ear inflammations and conductive hearing loss or obstruction of the trachea. Lung disease can lead to cough, haemoptysis and dyspnoea and can progress to alveolar bleeding. In glomerulonephritis, which presents with hematuria, proteinuria, and cylindruria, renal failure can develop very rapidly. Other disease manifestations include purpura, infarctions of nail beds and ocular disease, such as conjunctival bleeding, scleritis, uveitis, proptosis and ocular muscle paralysis cau-

Table VIII. Wegener's granulomatosis is characterized by at least 2 of the 1990 ACR criteria²²

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

Table IX. Use of cytoplasmic anti-neutrophil-antibodies in the diagnosis of vasculitis

- Immunofluorescence (IF) for c-ANCA and p-ANCA (this refers to cytoplasmic or perinuclear staining respectively) is a good screening method.
- Positive ANCA has to be confirmed using ELISA for the demonstration of potential proteinase-3 (PR3) and myeloperoxidase-(MPO) autoantibodies.
- 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, only in clinically typical c-ANCA/PR3-positive disease.
- p-ANCA/MPO is usually seen in microscopic polyangiitis and Churg-Strauss syndrome.
- p-ANCA without positive PR3- or MPO-ELISA result is a nonspecific finding, typical for many infections and autoimmune diseases.
- Negative ANCA does not exclude vasculitis.
- Continuously high ANCA is associated with increased risk of relapse.
- Selection of IF- or ELISA-assay in the follow up is done based on findings at the time of diagnosis.

sed by retrobulbar inflammation. Patients can also develop melena, myocardial ischemia, sensory neuropathy or mononeuritis multiplex. Wegener's granulomatosis is characterized by c-ANCA with antiproteinase-3 specificity.

Diagnosis should be confirmed radiologically and histologically. Computed tomography can demonstrate changes in sinuses and lungs even in cases where regular x-ray images appear normal. Biopsies may contain so much necrotic tissue, that demonstration of vasculitis can be difficult. Biopsies are taken from nasal mucosa, upper airways or kidneys. The best samples from the diagnostic point of view are obtained by open lung biopsy, which demonstrates vasculitis, necrotizing inflammation and giant cell granulomas. Granulomatous inflammations caused by microbes should be excluded. Renal biopsy determines the type and severity of the renal involvement. Non-specific focal and necrotizing glomerulonephritic changes without immune complexes are typical findings.

Churg-Strauss syndrome

Churg-Strauss syndrome (Table X) is one of the

Table X. Churg-Strauss syndrome is characterized by at least 4 of the 1990 ACR criteria²⁶

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

three vasculitides, which can be defined by the presence of ANCA²⁷. It affects mainly small arteries and is characterized by p-ANCA with myeloperoxidase specificity. These patients always have atopy and asthma, which can become milder upon development of vasculitic changes. Patients suffer from chronic respiratory tract symptoms and have lung infiltrates. Glomerulonephritis is rarer and usually milder than in Wegener's granulomatosis, even though the kidney biopsy can demonstrate similar changes. Mononeuritis multiplex and coronary artery lesions can develop. Churg-Strauss syndrome should always be suspected on clinical grounds, when the patient has peripheral eosinophilia. Blood test demonstrates p-ANCA (perinuclear ANCA) due to myeloperoxidase antibodies. Diagnosis can be confirmed by demonstration of granulomatous and necrotizing vasculitis with eosinophilic infiltrates.

Microscopic polyangiitis

Microscopic polyangiitis (microscopic polyarteritis) (Table XI) is one of the three ANCA vasculitides²⁹. It affects small blood vessels (venules, capillaries, arterioles and small arteries). Microscopic polyangiitis is a better name than microscopic polyarteritis because some patients have no evidence of arterial involvement. Usually patients

Table XI. Microscopic polyangiitis (MPA) is characterized by three changes²⁸

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

have p-ANCA with myeloperoxidase specificity or less often c-ANCA with proteinase-3 specificity. These features clearly differentiate it from polyarteritis nodosa, which affects middle-sized arteries and lacks ANCA. After exclusion of hepatitis B, C and HIV, in a patient with no or only mild upper airway involvement, who has alveolar bleeding and glomerulonephritis, the diagnosis of microscopic polyangiitis should be suspected. However, this form of vasculitis would have earlier been diagnosed as polyarteritis nodosa. To recapitulate, microscopic polyangiitis differs from polyarteritis nodosa as microscopic polyangiitis often affects lung tissue, also affects veins and rarely leads to difficult hypertension, is usually ANCA positive, almost always requires cyclophosphamide treatment, and recurs more often after remission. Overlap syndromes between microscopic polyangiitis and polyarteritis nodosa are also known.

Microscopic polyangiitis can also be clearly differentiated from immune complex-mediated leukocytoclastic vasculitides of small blood vessels since the focal necrotizing glomerulonephritis is not associated with immune complex deposition. Giant cells do not occur in this vasculitis.

Primary angiitis of the central nervous system

Some patients with neurological changes without any clear-cut reasons disclose vasculitis of small arteries of the central nervous system in angiography or histology in the absence of systemic vasculitic changes^{30,31}. This condition is then known as primary angiitis of the central nervous system (PACNS). Patients with such symptoms should be studied for an eventual 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. Clinically this leads to neurological symptoms, such as headaches, mental changes and focal or systemic neurological defects. These can at the beginning be reminiscent of transient ischemic attacks. Benign disease is usually acute in onset and monophasic, whereas granulomatous disease evolves slowly, is chronic and tends to remit. Diagnostic work up usually begins with magnetic resonance imaging of the brain, which is usually abnormal, and by examination of the cerebrospinal fluid, which usually demonstrates inflammatory changes in the

granulomatous disease. Diagnosis of the benign form of the disease is based on angiography, and of granulomatous disease on biopsy and associated inflammatory changes in the cerebrospinal fluid. ESR and CRP are usually within reference limits and the ANCA test is negative.

Treatment is based on prednisolone used in combination with cyclophosphamide in granulomatous disease, and with calcium channel blockers in the benign disease. PACNS has not yet found its final place in the official classification of vasculitis.

Henoch-Schönlein purpura

Henoch-Schönlein purpura (Table XII), cryoglobulinaemias and leukocytoclastic vasculitis of the skin are characterized by immune complex deposition in the walls of the small vessels leading to leukocytoclasia, rupture of the vascular wall, and palpable purpura³³. Leukocytoclastic vasculitis can also occur in severe systemic ANCA-associated vasculitides that must be excluded. Henoch-Schönlein purpura occurs usually in children as an IgA-dominated febrile hypersensitivity reaction in response to an upper respiratory tract infection. Small artery disease leads to arthralgias, arthritis, microscopic haematuria and abdominal pain. Hypotension, melena and hematemesis can develop. CRP and ESR increase. Anaemia, leukocytopenia or thrombocytopenia can occur.

Patients presenting with general symptoms and abdominal pain should be sent to hospital for follow up. Diagnosis is confirmed by skin biopsy, which demonstrates leukocytoclastic vasculitis and IgA and C3 deposits in the vessel wall. These can also be found in renal biopsies. Meningococcal sepsis should be considered in differential diagnosis, as it can also lead to petechiae and joint symptoms.

Table XII. Henoch-Schönlein purpura is characterized by at least 2 of these 1990 ACR criteria³²

1. Palpable purpura (hemorrhagic 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 form of bloody diarrhea
4. Leukocytoclastic vasculitis on biopsy

Cryoglobulinaemia

Cryoglobulinaemia (Table XIII) refers to cold precipitating immune complexes or aggregates of monoclonal antibody leading to complement consumption, leukocytoclastic immune complex vasculitis of small blood vessels and palpable purpura³⁵. Simple type I cryoglobulinaemia is caused by lymphoproliferative diseases in which the neoplastic clone produces monoclonal cryoglobulin. Mixed type II and III cryoglobulinaemias are associated with rheumatoid factor, which in type II diseases is monoclonal and in type III diseases polyclonal. These forms are more common in adults, who suffer from lymphoproliferative disorders, chronic infections (in type II particularly hepatitis C) or other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE) or Sjögren's syndrome. Cryoglobulinaemia is called essential if the patient does not have any underlying infectious, immunological or neoplastic disorders. Cryoglobulins accumulate in the wall of small blood vessels, where they fix complement and lead to leukocytoclastic vasculitis and clinically to palpable purpura, but also to cold urticaria, glomerulonephritis, arthralgias, abdominal pain, neuropathy, Raynaud's phenomenon, ulcerations and necrosis.

Potential association with the lymphoproliferative diseases, infections or autoimmune diseases should be looked for. Cryoglobulins, the hallmark of this condition, are always found in blood and should be analyzed for their composition. Hypo-

Table XIII. Mixed cryoglobulinaemia can be diagnosed if all 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 or histopathological criteria³⁴

Major criteria

Clinical: palpable purpura
Serological: cryoglobulins and hypocomplementemia
Histopathological: leukocytoclastic vasculitis

Minor criteria

Clinical: chronic hepatitis, membranoproliferative glomerulonephritis, peripheral neuropathy or skin ulcers
Serological: rheumatoid factor, hepatitis C, hepatitis B positivity
Histopathological: clonal B-cell infiltrates in the liver and/or bone marrow

complementemia is common. Skin biopsies demonstrate leucocytoclastic vasculitis and cryoglobulin deposits, which are also found in glomeruli.

Leukocytoclastic 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 leucocytoclastic vasculitis and palpable purpura. Thus, these patients do not suffer from abdominal pain and do not have any blood in their stools, do not have hematuria or proteinuria and have no arthralgias. Patients of all ages can develop vasculitis of small vessels restricted to the skin²⁴. Drugs and infections can lead to leukocytoclastic vasculitis, which can also occur as a secondary manifestation of, for example, rheumatoid arthritis and SLE. Systemic involvement must be excluded and eventual triggering factors looked for.

Goodpasture's syndrome

Goodpasture's syndrome is a rare but clinically important syndrome, the classical syndrome triad consisting of pulmonary haemorrhages, glomerulonephritis and anti-basement membrane antibodies³⁶. It is characterized by pathogenic autoantibodies usually called anti-glomerular basement membrane autoantibodies, but these antibodies actually react with the noncollagenous 1 (NC1) domain of the α_3 chain of basement membrane type IV collagen. They lead to rapidly progressive and eventually fatal inflammation in alveolar (alveolar bleeding) and glomerular (glomerulonephritis) basement membranes, where the corresponding autoantigen is relatively exposed to antibody binding. Locally formed antigen-antibody complexes fix complement, which leads to basement membrane damage. Serum samples contain anti-glomerular basement membrane antibodies and renal and lung biopsies disclose linear deposits of (auto)antibodies in these basement membranes. Rapid diagnosis is essential as prednisolone and cyclophosphamide are necessary to suppress anti-glomerular basement membrane autoantibody production, combined with plasmapheresis to remove the pathogenic autoantibodies.

Panniculitis

Panniculitis is inflammation of fat tissue, which is

divided into lobules by septa. It leads to red subcutaneous nodules occasionally associated with vasculitis of small or even middle-sized blood vessels³⁷. If 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 involvement of both arteries and veins can coexist, and which can be triggered by a delayed hypersensitivity reaction. These patients have often 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 panniculitis is caused by cutaneous polyarteritis nodosa which leads to nodules, ulcerations and livedo reticularis in the legs, but also to myalgias and arthralgias or even involvement of middle-sized arteries. Classification of panniculitis is not straight-forward, because in many cases a triggering stimulus can not be identified.

The biopsy taken for diagnosis should be deep enough to extend to subcutaneous fat. Management is based on the elimination of the triggering factor, if any, and symptomatic treatment. Cutaneous polyarteritis nodosa is treated with prednisolone and occasionally even with cyclophosphamide.

The Third Road Sign: Pseudovasculitis

In addition to vascular wall inflammation and damage caused by immunological-inflammatory vasculitis, a large number of conditions has been described which on some other basis lead to stenosis, occlusion, thromboembolism, vasospasm, infection or inflammation, all of which can lead to a wrong road³⁸ (Table XIV). These conditions are named pseudovasculitis and they are characterized by disturbances in the vascular circulation in the absence of vasculitic changes in the blood vessel wall. In spite of this, 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. As a matter of fact, the road sign to secondary vasculitis and to pseudovasculitis should be checked before the one pointing to primary vasculitis is followed. It is always important to look for

Table XIV. Pseudovasculitis can be classified as blood vessel damaging, obstructing, thromboembolic or vasospastic conditions and other pseudovasculitis.

Pathogenetic mechanism	Clinical changes/diagnosis
Diseases of the blood vessel wall	<ul style="list-style-type: none"> • Atherosclerosis • Bürger's disease • Fibromuscular dysplasia • Amyloidosis • Scurvy • Calciphylaxis • Moyamoya disease
Infections	<ul style="list-style-type: none"> • Syphilis • Lyme disease (Borreliosis) • Miliary tuberculosis • Chronic viral hepatitis • Meningoencephalitis • Sepsis
Coagulation disorders	<ul style="list-style-type: none"> • Antiphospholipid antibody syndrome • Thrombotic thrombocytopenic purpura • Hemolytic-uremic syndrome • Disseminated intravascular coagulation • Coagulation disorders associated with the use of heparin or warfarin (also thrombocytopenia caused by heparin, i.e. HIT)
Embolization	<ul style="list-style-type: none"> • Infective endocarditis • Myxoma • Cholesterol embolism • Non-bacterial thrombotic endocarditis • Use of intravenous narcotics
Drugs and Narcotics (vasospasms)	<ul style="list-style-type: none"> • Phenyl prophanol amines • Amphetamines • Cocaine
Hormones (vasospasms)	<ul style="list-style-type: none"> • Pheochromocytoma
Miscellaneous	<ul style="list-style-type: none"> • Neoplasms • Hypereosinophilic syndrome • Intravascular lymphoma • Hyperviscosity syndrome • Connective tissue diseases

triggering factors and to exclude pseudovasculitis. Management of pseudovasculitides is very different from that of primary systemic vasculitides, which emphasizes the importance of differential diagnosis. 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 is a common disease of large

and middle-sized arteries, in which atherosclerotic plaques cause stenosis of the arteries and may lead to their occlusion as a result of plaque rupture and thromboembolic disease. Ischemic pain and skin alterations in severe cases resemble those caused by vasculitides. Atherosclerosis is one of the most common differential diagnostic alternatives for vasculitis. Also, atherosclerotic plaques contain inflammatory cells. However, patients with atherosclerosis do not usually develop prominent acute phase responses although slightly elevated CRP and fibrinogen are risk factors.

Infections do predispose to atherosclerotic plaque rupture, which can lead to medical calamities like myocardial infarction or stroke and to differential diagnostic problems. Usually atherosclerotic changes are stable so that a certain degree of physical exercise always and consistently leads to ischemic pain, such as angina pectoris or intermittent claudication. Atherosclerosis as such is slowly progressive and the patients typically have a long history spanning back for even a few decades.

Antiphospholipid antibody syndrome (slightly modified criteria)

Antiphospholipid antibody syndrome (Table XV) is characterized by arterial and venous thrombosis, thrombocytopenia and recurrent abortions as well as cardiolipin antibodies, β_2 -glycoprotein I antibodies and/or positive lupus anticoagulant⁴⁰. Antiphospholipid antibody associated clinical symptoms form a wide spectrum and can include stroke, livedo reticularis and varicose ulcers, which can be similar to those seen in systemic vasculitides. Antiphospholipid antibody syndrome associated Libman-Sacks endocarditis can be a source of peripheral emboli. The so called catastrophic antiphospholipid syndrome is caused by occlusion of the microvasculature and can manifest itself as a progressive renal and multi-organ failure. SLE patients can have antiphospholipid antibodies and, therefore, non-inflammatory vascular occlusions and secondary immune complex vasculitis. Antiphospholipid antibody syndrome can be aggravated by e.g. estrogens and glucocorticoids.

Infective endocarditis

Infective endocarditis is caused by inflammation of the endocardium and heart valves, which contain aggregated platelets, fibrin, microbes and inflammatory cells in form of vegetations. Heart valve pathology, such as bicuspid aortic valve or mitral valve insufficiency, as well as immunocompromising states predispose to endocarditis. Patient history can reveal an iatrogenic or accidental trauma, but often the source of bacteraemia remains unclear. The clinical symptoms and findings, such as petechiae, hematuria, arthralgias and arthritis can resemble a systemic connective tissue disease or a vasculitis. Infective endocarditis can lead to pseudovasculitis as a result of microembolisms, which can also be caused by secondary vasculitis associated with immune complex formation. Even fungal endocarditis has to be considered as a cau-

se of large vessel stenosis resembling vasculitis. Typically, auscultation reveals heart murmurs, which shift 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 and blood cultures can be used to disclose bacteraemia. Acute phase reaction, hypergammaglobulinemia and rheumatoid factor can be found by laboratory tests in both endocarditis and vasculitis.

Table XV. 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 met³⁹:

Clinical criteria

1. Vascular thrombosis
One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
 - One or more unexplained deaths of a morphologically normal foetus at or beyond the 10th week of gestation, with normal foetal morphology documented by ultrasound or by direct examination of the foetus, or
 - One or more premature births of a morphologically normal neonate at or before the 34th week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency, or
 - Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation in the absence of maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes.

Laboratory criteria (on at least two occasions, at least 6 weeks apart, measured from a blood test using methods fulfilling international standards)

- Anticardiolipin antibody of IgG and/or IgM isotype, present in medium or high titer
- Lupus anticoagulant
- Beta-2 glycoprotein I antibodies

Myxoma of the heart

Myxoma of the heart is a benign intracardial tumour, which can occur at all ages, more commonly in women than in men⁴¹. Myxoma can lead to cardiac and extra-cardiac symptoms, such as embolization to peripheral tissues and lungs, arthritis, petechiae and Raynaud's phenomenon. Haematuria and proteinuria occur. Embolic manifestations can simulate vasculitis as they develop suddenly and lead to severe ischemic changes. Approximately half of these patients have fever and lose weight depending on the production of pro-inflammatory cytokines in myxomatous tissue. Anaemia, leukocytosis, thrombocytosis and increased ESR are common laboratory findings, which are in part caused by interleukin-6 production 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 or magnetic resonance imaging. Resection of myxoma is usually a curative treatment.

Cholesterol embolism

Occasionally the atherosclerotic plaque ulcerates as a result of endovascular procedures (mechanical manipulation), anticoagulation (exposing the plaque surface below the thrombus mass) or spontaneously, leading to cholesterol crystal embolization⁴². Small, needle-like cholesterol crystals are disseminated into various tissues, usually kidneys. The typical patient is an elderly man suffering from advanced atherosclerosis, who has recently undergone an invasive vascular procedure, for example an angiography. In some cases the condition has been reported after warfarin or thrombolytic treatment. Also, spontaneous cholesterol embolizations can occur. The manifestations greatly resemble those caused by vasculitis, for example eczema, petechiae, ulcerations and livedo reticularis are common. As the cholesterol emboli are so small, the peripheral pulses of the larger blood vessels remain easily palpable in spite of the colour of the toes in a typical 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.

Laboratory tests usually demonstrate increased ESR, leukocytosis and often eosinophilia. Thrombocytopenia and hypocomplementemia can also occur. Rheumatoid factor, antinuclear antibodies and even ANCA, usually non-proteinase-3, non-myeloperoxidase type, can be found. Diagnosis is histopathological and is based on the demonstration of cholesterol crystals, which leave slits in the damaged tissue as they are dissolved away during regular tissue sample processing. There is no specific medical treatment for cholesterol embolism and the mortality of the reported cases has been relatively high. If a patient using warfarin is diagnosed suffering from cholesterol embolisms, warfarin may have to be stopped. Without surgical treatment, cholesterol embolism is a recurrent process with a high mortality rate.

The First Milestone: Patient History and Physical Examination

Careful patient history and physical examination have been emphasized as central in establishing the diagnosis. The more complicated the situation seems to be, the more important these are so that invasive (=potentially dangerous and expensive) examinations can be correctly targeted.

In vasculitis of aorta and large arteries, transient ischemic attack and vision disturbances in young women or new headache and polymyalgia rheumatica in elderly patients are important clues. Non-symmetrical pulse and difference in the blood pressure in the upper extremities or tenderness of the temporal arteries and pulse difference between the right and the left side are useful findings. When middle-sized arteries are affected in polyarteritis nodosa, this often leads to a serious generalized disease, in which multiple organ lesions and mononeuritis multiplex lead the thoughts to the possibility of vasculitis. Kawasaki disease is typically a disease of small children and manifests in form of mucocutaneous lymph node syndrome, which can lead to formation of coronary artery aneurysms and in which immunomodulatory treatment is different from the usual regime. When the small arteries are diseased in Wegener's granulomatosis, upper respiratory tract, pulmonary and renal changes develop; in microscopic polyangiitis severe renal disease and palpable purpura; and in Churg-Strauss syndrome a patient with atopy and asthma develops eosinophilia and pulmonary in-

filtrates. In diseases of the very smallest blood vessels, in particular immune complex mediated vasculitis, palpable purpura is the cardinal finding, but it can also occur in vasculitis of small-size arteries. Henoch-Schönlein purpura usually develops in a child after an upper respiratory tract infection and also leads to arthralgia, haematuria and melena, but in the somewhat similar cryoglobulinaemic vasculitis melena is usually absent. Inflammation of the superficial and deep veins can lead to thrombophlebitis and phlebothrombosis. Hydrostatic pressure increases and leads to local peripheral oedema. The most feared complication in this condition is pulmonary embolism.

The Second Milestone: Laboratory Tests and Surrogate Markers

Inflammation leads to cytokine production and acute phase reaction, which lead to general symptoms like fever, fatigue, anorexia, weight loss, night sweats and myalgias and arthralgias associated with typical laboratory findings (Table XVI).

Already relatively few, but well directed laboratory tests can be helpful in the diagnosis of vasculitis. In almost all primary vasculitic diseases the ESR and CRP are increased. Complete blood count with white cell differential is one of those basic laboratory tests to be ordered in suspected vasculitis cases. Primary vasculitis is usually associated with normocytic anaemia, leukocytosis and

thrombocytosis. In contrast, thrombocytopenia is not usually seen in primary vasculitis, but is rather suggestive of SLE, infiltration of malignant diseases into the bone marrow, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation or antiphospholipid antibody syndrome. Leukocytopenia is not typical for vasculitis, but can be suggestive of SLE, sepsis or some other severe or viral infections, aleukaemic leukaemia, myelodysplasia or various drugs. Eosinophilia is part of the Churg-Strauss syndrome, but it can also be seen in Wegener's granulomatosis and in rheumatoid vasculitis. Chemical screening of the urinary sample and/or urine cytology are pathological in glomerulonephritis.

Autoantibody tests are to a large extent performed in the referral hospital. All tests are not necessary in the evaluation of all patients suspected of having vasculitis, but the selection of the tests is dependent on the clinical symptoms. Antinuclear antibodies and anti-DNA antibodies are recommended when SLE is suspected or has to be excluded. Glomerular basement membrane antibodies are important when the cause for alveolar bleeding and glomerulonephritis is sought. Antiphospholipid antibodies are important when unclear arterial or venous thrombosis or thrombocytopenia are evaluated and are also necessary when catastrophic antiphospholipid antibody syndrome is suspected. Serum complement components C3 and C4 decrease upon consumption in leukocytoclastic, immune complex-mediated vasculitides and are sometimes useful in the follow-up of glomerulonephritis. Complement concentrations are low in cryoglobulinaemia and they can be decreased in endocarditis, but are usually normal in polyarteritis nodosa, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and Henoch-Schönlein purpura and can increase in infections as they are acute phase reactants. Serological tests for the demonstration of hepatitis B and C can be recommended if the patient suffers from polyarteritis nodosa, cryoglobulinaemia, polyarthritis or cutaneous vasculitis.

ANCA, which has proteinase-3 or myeloperoxidase specificity, are seen in a large proportion of patients, who have generalized small artery vasculitis. c-ANCA and proteinase 3 antibodies are strongly suggestive of Wegener's granulomatosis⁴³. p-ANCA with myeloperoxidase specificity rather imply microscopic polyangiitis or Churg-Strauss syndrome. ANCA are seen in many other diseases

Table XVI. Laboratory tests and findings in basic health care when vasculitic diseases are suspected

- Erythrocyte sedimentation rate and C-reactive protein are increased
- Complete blood count with white cell differential demonstrates anaemia, leucocytosis, eosinophilia and thrombocytosis
- X-ray of the sinuses demonstrates shadowing or fluid levels
- Chest X-ray demonstrates pulmonary infiltrates
- Urinary sample demonstrates haematuria
- ANCA suggest small artery vasculitis
- Tests are ordered based on the clinical picture and they can also be used to demonstrate the triggering or perpetuating factor in secondary vasculitis and to exclude pseudovasculitis

such as infections, vasculitic reactions caused by drugs and in many inflammatory diseases other than vasculitides. The reactivity is then usually against something else than proteinase-3 or myeloperoxidase. Therefore, the vasculitis diagnosis can never be based solely on demonstration of ANCA positivity.

Immunological events induce vasculitic inflammation. This can be directly observed in biopsies taken from symptomatic organs or tissues. Histopathological diagnosis forms the basis of exact diagnosis, but because such procedures are invasive, attempts have been made to develop surrogate changes for histopathology (Table XVII).

General practitioners can easily take skin biopsies to confirm leukocytoclastic vasculitis, but as palpable purpura is also clinically easily recognizable, such patients should be sent without biopsy to a specialist, if elimination of the triggering stimulus has not corrected the situation and suspicion of vasculitis has been confirmed or still remains after the basic tests, except in trivial and mild cases, often restricted to the skin. Patients with unstable angina pectoris are urgently referred to hospital and the same principle should naturally apply if progressive and unpredictable vasculitic changes develop in potentially dangerous sites since these are "unstable vasculitic plaques" and can lead to severe vital organ damage and failure of heart, kidneys, brain, and lungs. In the diagnosis and treatment of vasculitis an early diagnosis is important, also because the use of anti-platelet drugs or anti-coagulants is difficult in vasculitis, which is asso-

ciated with bleeding tendency. In fact, such drugs may be contraindicated in spite of a prothrombotic inflammatory condition associated with unstable vasculitic plaques.

The Third Milestone: Tests in Specialized Centers

Histopathology

When the patient has been referred to a specialized centre after the basic work up on the primary health care level including patient history, physical examination and basic laboratory tests, biopsies of symptomatic organs are performed. Recognition of targets for biopsies is based on clinical findings, laboratory tests and other objective examinations, as blind biopsies easily lead to false negative results. If several organs are affected by the disease, choice of the site of the biopsy is determined by the potential risks and the likeliness to obtain a disease specific diagnosis. The biopsy sample has to be large enough since vasculitis does not affect the blood vessels and tissues in a uniform and predictable way, but in a haphazard manner. Biopsies can demonstrate immunoglobulin and complement depositions, T-lymphocytes, macrophages, granulomas and necrosis. For example, in giant cell arteritis giant cells and granulomas are seen, in necrotizing polyarteritis nodosa the neutrophilic granulocyte is the main cell and in Churg-Strauss syndrome associated with atopy and asthma the eosinophil is the main cell. In small vessel

Table XVII. Surrogate markers in the diagnosis of vasculitis

Target Organ	Surrogate Parameter
Glomerulonephritis	• Proteinuria, haematuria and blood cell casts
Arteritis	• Angiographic or ultrasound demonstration of aneurysms or stenosis in arteries if also clinical sign of vasculitis are present
Granulomatous inflammation of the upper respiratory tract	• Bloody nasal secretions and/or inflammation in the upper respiratory tract, which last for longer than one month • Chronic sinusitis, otitis and/or mastoiditis (X-ray examination, computerized tomography or magnetic resonance imaging) • Sudden hearing loss without trauma • Destruction of the skull bones and/or cartilage
Granulomatous inflammation of the lower respiratory tract	• Radiological demonstration of inflammation in lower respiratory tract (shadowing or cavitations), which last longer than one month
Inflammation of the capillary blood vessels in lung tissue	• Radiologically diffuse infiltrates, which last at least one month.

leukocytoclastic vasculitis the dominating cell is a neutrophil associated with nuclear dust. Tissues affected by vasculitis may demonstrate ischemic lesions and necrosis without apparent vasculitic changes. Sometimes it can be difficult to differentiate vasculitis, for example, from infections or angiocentric lymphoma. The phenotypic examination of the cells and other special techniques can be helpful.

Angiographies

Lesions in the vascular wall can lead to stenosis, occlusion, vasospasm, thrombosis, embolism, ischemia, aneurysm or bleeding. Angiography and Doppler ultrasound examination can demonstrate stenosis, occlusions, vasospasms, aneurysms, thrombosis and bleedings. X-rays, computed tomography and magnetic resonance imaging are suitable for the demonstration of bleedings, lesions, complications and assessment of the extent of the disease.

Angiographies are useful when lesions in the aorta and its main branches are suspected or if the patient has aneurysms. It can also be useful in the diagnosis and follow-up of vasculitis of the central nervous system and of Kawasaki disease and arteritis of the coronary arteries. Magnetic resonance angiography (MRA) is useful for the evaluation of the size of the lumen of the large blood vessels and the thickness of their wall. Angiography of the abdominal arteries is used when arteritis of the middle-sized arteries is suspected and histological diagnosis has not been obtained. Polyarteritis nodosa and other middle-sized artery diseases can lead to microaneurysms and stenosis, which can be visualized using angiography. Polyarteritis nodosa has microaneurysms in 60-90 % of cases. Aneurysms are more likely to develop with time and are not always found in the early stages of the disease. Microaneurysms of internal organs are not diagnostic of polyarteritis nodosa, as they can also be found in other diseases affecting middle-sized or slightly smaller arteries, for example Wegener's granulomatosis and Churg-Strauss syndrome, as well as in non-vasculitic conditions, such as myxoma of the heart atria and in infectious endocarditis. Angiography has no place in the diagnosis of small vessel vasculitis.

Empiric treatment with glucocorticoids

Empiric treatment with glucocorticoids is sometimes necessary as a part of the diagnostic work-up,

but even though patients would benefit from such medications, this is not enough for diagnosing vasculitis. A complete diagnostic work up should always be performed if at all possible.

Management of Vasculitis

In the hospital, the activity and extent of vasculitis is examined. In this workout, structured instruments such as The Birmingham Vasculitis Activity Score (BVAS)⁴⁴ and The Vasculitis Damage Index (VDI)⁴⁵ are useful. They enable clinicians to identify an active disease, including the level of its activity, and to separate it from irreversible but already stable damage. This can be of great importance in justifying the use of immunosuppressive treatment. Some new tests like measurement of von Willebrand factor or procalcitonin can be helpful in this respect. In many centres vasculitis patients are enrolled into international controlled clinical trials on the treatment of vasculitis.

If and when the triggering and perpetuating factor can not be identified, the management of primary vasculitis is based on immunosuppression⁴⁶ (Table XVIII). Immunosuppression is also used in the management of the secondary vasculitis with poor response to treatment targeted at the elimination of the suspected triggering factor⁴⁷. Treatment is tailor-made, but some general management strategies have been created.

In arteritis of the large vessels treatment is initiated with prednisolone alone in high immunosuppressive doses¹⁶. In Takayasu arteritis azathioprine or weekly methotrexate can add to the efficacy and enable tapering of the glucocorticoids⁴⁸. In temporal arteritis occasionally azathioprine or methotrexate is added to the glucocorticoid treatment as a glucocorticoid sparing agent.

Treatment of vasculitis of the middle and small sized arteries is based on prednisolone combined with cyclophosphamide, either *per os* (more effective) or intravenously (safer)^{46,49}. The dose of the immunosuppressants is adjusted so that blood leukocytes remain over $3.0-3.5 \times 10^9/l$ and neutrophils over $1.0-1.5 \times 10^9/l$. To avoid irritation and eventual development of cancer of the urinary bladder, fluid intake should be at least three litres per day and can be combined with prophylactic treatment with mesna. In Kawasaki disease in children, glucocorticoids should not be used as the vasculitic plaques of the coronary arteries in chil-

Table XVIII. Anti-inflammatory, immunosuppressive and other systemic treatments of vasculitic diseases.

Takayasu arteritis	Glucocorticoid ¹
Temporal arteritis	Glucocorticoid ¹
Behçet's disease	Glucocorticoid ¹ , cyclophosphamide ² , chlorambucil, azathioprine, cyclosporine, colchicine, thalidomide ³
Polyarteritis nodosa	Glucocorticoid ¹ , cyclophosphamide ²
Kawasaki disease	Intravenous immunoglobulins
Bürger's disease	Smoking cessation, intravenous prostacyclin analogues
Wegener's granulomatosis	Glucocorticoid ¹ , cyclophosphamide ² , (azathioprine) ⁴ , (plasmapheresis) ⁵
Microscopic polyangiitis	Glucocorticoid ¹ , cyclophosphamide ² , (azathioprine) ⁴ , (plasmapheresis) ⁵
Churg-Strauss syndrome	Glucocorticoid ¹ , cyclophosphamide ² , (azathioprine) ⁴
Primary angiitis of the central nervous system	Glucocorticoid ¹ , cyclophosphamide ² or calcium channel blockers ⁶
Henoch-Schönlein purpura	NSAID ⁷ , glucocorticoid ⁸ , (cytotoxic drugs) ⁸
Leucocytoclastic vasculitis of the skin	NSAID ⁷ , dapsone, (glucocorticoid) ⁸ , (cytotoxic drugs) ⁸
Essential cryoglobulinaemic vasculitis	NSAID ⁷ , dapsone, (glucocorticoid) ⁸ , (cytotoxic drugs) ⁸ , (plasmapheresis) ⁵
Panniculitis	Elimination or treatment of the causative factor; anti-inflammatory drugs, cold wrappings, (glucocorticoid) ⁸ , (cytotoxic drugs) ⁸

¹ An immunosuppressive prednisolone dose is 1 mg/kg/day

² Cyclophosphamide dose is 2-4 mg/kg/day per os or 0.5-1.0 g/m² intravenously every 2-4 weeks

³ In the treatment of arthritis and mucosal or skin changes, cyclosporine also in the treatment of uveitis

⁴ Immuno-suppressant drugs are used during the maintenance phase in this and other vasculitic diseases as glucocorticoid sparing drugs

⁵ In crisis situations

⁶ Cyclophosphamide can be combined with glucocorticoids in a severe granulomatous form of the condition and calcium blockers in the milder, benign forms.

⁷ As a symptomatic drug, anti-inflammatory drug (non-steroidal anti-inflammatory drug, NSAID)

⁸ In severe and recurrent cases

dren with thrombocytosis may be further weakened as result of the catabolic effects of glucocorticoids which can lead to ruptures and bleeding. Instead, intravenous immunoglobulins are the treatment of choice for Kawasaki disease²⁰. In the treatment of Behçet's disease, cyclosporine in particular, but also dapsone and colchicine have a place. When patients are treated with cyclophosphamide, it is often substituted with either methotrexate or azathioprine after 3-12 months of use to avoid long-term adverse events⁵⁰. In vasculitic crisis methylprednisolone can be given in 0.5-1.0 g/day dose on three successive days, and plasmapheresis or immunoadsorption should also be considered to facilitate removal of immunoglobulins and immune complexes with exchange of plasma or immunoglobulin binding protein A. In the treatment of vasculitis of arterioles, capillaries and venules, in other words of small vessel vasculitis, follow up and symptomatic treatment (in palpable purpura) or antihistamines (in urticaria) may suffice. The sulfonamide dapsone has some non-

-antimicrobial effects on neutrophils, which can be useful in leucocytoclastic vasculitis. Tacrolimus, mycophenolate mofetil and the so called biological drugs and combination treatments are still seeking their place in the management of vasculitis.

Triggering factors have also been identified in so called primary vasculitic diseases. Lamivudine or interferon- α can be used together with plasmapheresis in the treatment of hepatitis B-associated polyarteritis nodosa. Ribavirin and interferon- α can be used in hepatitis C-associated cryoglobulinaemic vasculitis. Combination of trimethoprim and sulfamethoxazol is used in Wegener's granulomatosis to maintain remission and nasal mupirocin for the eradication of *Staphylococcus aureus* and penicillin in the treatment of *Streptococcus* infections associated with polyarteritis nodosa in children. Henoch-Schönlein purpura develops with approximately three weeks latency and usually the triggering infection has already healed during that time. So called banal infections should be

rapidly and effectively diagnosed and treated in vasculitis patients on immunosuppressive drugs. The initiation treatment in vasculitis often also includes empiric treatment with antimicrobial drugs. Patients with vasculitis should be more actively and aggressively treated for their infectious diseases than other patients, as an infection can destabilize their condition and lead to an activation of their vasculitis. In fact this attitude can act as some type of secondary prophylaxis in such a setting.

Vasculitis is associated with increased risk for thrombosis. Low dose acetylsalicylic acid (ASA) has been used in combination with high-dose prednisolone. However, inflammation in the vascular wall predisposes to thrombosis. In addition, prednisolone inhibits anti-thrombotic prostacyclin synthesis in the endothelial cells, but does not affect platelets, which lack nuclei and thus continue to effectively produce prothrombotic thromboxane. Mini-ASA has been reported to be useful in prophylaxis against visual loss and apoplexy in temporal arteritis. Instead, venous thrombosis is usually associated with activation of the coagulation cascade. If vasculitis patients do not have any obvious bleedings or high blood pressure, low molecular weight heparin can be considered for thrombosis prophylaxis in bedridden patients. Under such circumstances its effect should preferably be followed by using factor Xa activity measurements. This approach is still experimental. Thrombophlebitis may be cured by removal of intravenous cannulae, and non-medical thrombosis prophylaxis should be particularly effective in vasculitis patients. If a vasculitis patient develops thrombosis, its medical treatment must be tailor-made individually.

Conclusion

General practitioners have an important task in screening and finding rare, but severe and often life threatening vasculitis patients from their large patient flow. Careful patient history and physical examination are the cornerstones of success. Targeted basic laboratory tests and imaging studies help to differentiate secondary and pseudovasculitis from primary vasculitis. Patients who are suspected to have clinically significant vasculitis should then be urgently referred to specialized centres for invasive histological and radiological diagnosis confirmation, initiation of immunosuppressive treat-

ment, and follow-up.

Vasculitis case report 1

A 77 year-old economist consulted a rheumatologist about muscle pain that prevented him from playing tennis. For three months he had suffered from aching shoulder and pelvic regions. The problems started after a weekend in London, where he visited a theatre play and thought that he had caught a common cold. Two weeks after the trip to London he visited his dentist complaining of lower jaw pains. Two teeth cavities were treated, but there was no relief of his jaw pain. Antibiotics (phenoxymethylpenicillin 1 million units $\times 3$) were initiated and were switched to cephalexin (500 mg $\times 3$) as the dentist suspected a root canal infection. This diagnosis was made because the serum C-reactive protein (CRP) concentration was 49 mg/l, but it was 66 mg/l two weeks after dental therapy that did not result in pain relief. At follow-up CRP was 55 mg/l and the patient was put on ibuprofen (600 mg $\times 3$). The proximal polymyalgic and lower jaw complaints persisted, altogether preventing the economist from playing tennis, and resulting in a weight loss of 6 kg in two months.

The rheumatologist suspected giant cell arteritis as the ESR was 88 mm/h and CRP 78 mg/l. The patient was referred to a rheumatologic in-ward facility for a temporal artery biopsy. Oral prednisolone (40 mg) was immediately initiated. One week later, the patient won his tennis game over his opponent who had been mostly beating him during his disease. Biopsy showed a low-grade panarteritis without multinuclear giant cells. After one month on the initial prednisolone dose, the drug was tapered by 5 mg/week until a dose of 5 mg/day was reached. Eleven months after initiation of therapy he remains on this dose.

Vasculitis case report 2

A 40 year-old male was diagnosed with Wegener's granulomatosis at the age of 20. When diagnosed he suffered from arthritis and lung manifestations as well as from recurring sinusitis. The diagnosis was based on biopsy from a nasal granuloma. Because of generalized symptoms he was treated with high-dose prednisolone (1 mg/kg/day) in combination with oral cyclophosphamide (2 mg/kg/day) for one year. After the first year, cyclophosphamide was changed to oral azathioprine (2 mg/kg/day) in combination with low-dose prednisolone (5-10 mg/day). This combination therapy was con-

tinued for two years. His symptoms disappeared and therapy was discontinued for ten years. Two years before the current episode, proteinuria (3-4 g/day) was discovered when reason for his ankle oedemas were sought for. A renal biopsy revealed an inactive necrotizing glomerulonephritis as a manifestation of Wegener's granulomatosis. At this stage c-ANCA and proteinase-3 antibodies (14 U) were positive. Serum creatinine was 200 µmol/l but as the glomerulonephritis appeared inactive, no immunosuppressive therapy was initiated. Instead, oral losartan was started (100 mg/day) in order to control proteinuria and it was used in combination with furosemide. The patient did not complain of any respiratory symptoms at this stage.

Almost two years later the patient developed a fever of 38°C without respiratory or urinary tract symptoms. He was found to have a small perianal abscess that was treated with oral cephalosporin. This, however, was not considered to be able to explain the deteriorated clinical situation. Laboratory tests revealed an elevated serum creatinine of 370 µmol/l and an increased urinary protein excretion of 9 g/day. Proteinase-3 antibodies were now 104 U/l suggesting activation of his Wegener's granulomatosis. This led to an initiation of prednisolone 80 mg/day. Azathioprine was also re-started (2 mg/kg) together with low-dose aspirin due to a prothrombotic situation caused by a combination of proteinuria and high-dose corticosteroids. This treatment regimen lowered serum creatinine to 260 µmol/l and was continued with a plan to taper it 5 mg weekly until 5 mg/day dose is reached. If the situation deteriorates a bridging therapy consisting of intravenous immunoglobulin infusions is considered as a more aggressive immunosuppressive therapy.

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