Vasculitis and Rheumatology

20

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20.1 Learning Objectives

By the end of this chapter, you should be able to:

- Discuss pathologic mechanisms underlying vasculitis.
- Review classification and nomenclature of vasculitis.
- Compose a diagnostic approach to a patient with vasculitis.
- Describe major forms of vasculitis.

Vasculitis is a clinicopathologic process characterized by inflammation and damage of blood vessels by leucocytes which leads to bleeding. Compromise of vascular lumen results in ischemia and necrosis of the tissues supplied by the involved vessels. Vasculitis can be a primary disease process, or it may be secondary to another underlying disease [1].

20.1.1 Pathologic Mechanisms Underlying Vasculitis

The exact mechanisms are unclear. However, three different models have been advanced [2]:

1. Pathogenic immune-complex formation and/or deposition
   (IgA vasculitis, hepatitis C-associated vasculitis, hepatitis B-associated vasculitis)
2. Production of antineutrophil cytoplasmic antibodies (ANCA)
   (Microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis)
3. Pathogenic T lymphocytic responses and granuloma formation
   (Giant cell arteritis, Takayasu's arteritis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis)

The end result of these immunopathologic pathways is endothelial cell activation, with subsequent vessel obstruction and ischemia of dependent tissue. This may cause hemorrhage in the surrounding tissues and, in some cases, weakening of the vessel wall, which leads to the formation of aneurysms. For almost all forms of vasculitis, the triggering event initiating and driving this inflammatory response is unknown.

20.1.2 Classification of Vasculitis

Vasculitis is classified based on the predominant size of vessels affected. Types of vessels are

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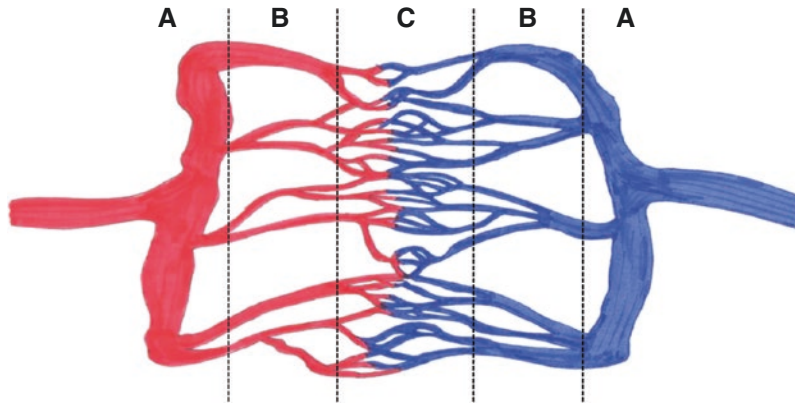

Fig. 20.1 Types of vessels that are defined by the 2012 Chapel Hill Consensus Conference nomenclature system. (**a**) Large vessels represents the aorta, its major branches and their corresponding veins. (**b**) Medium vessels are the visceral arteries, veins and their main branches. (**c**) Small vessels consist of interparenchymal arteries, arterioles, capillaries, venules and veins

defined in the (CHCC) 2012 [3, 4]. This is illustrated in Fig. 20.1.

20.1.3 The 2012 Chapel Hill Consensus Conference (CHCC) on Nomenclature of Vasculitis

The CHCC is a nomenclature system. It is neither a classification system nor a diagnostic system. It specifies the name that should be used for a specifically defined disease process. The following names are adopted by the CHCC 2012 on the nomenclature of vasculitides [4], and their definitions are presented in Table 20.1.

Large Vessel Vasculitis (LVV):
1. Takayasu's arthritis (TA).
2. Giant cell arthritis (GCA).

Medium Vessel Vasculitis (MVV):
1. Polyarteritis nodosa (PAN).
2. Kawasaki disease (KD).

Small Vessel Vasculitis (SVV):
1. Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis:
   (a) Granulomatosis with polyangiitis (GPA).
   (b) Microscopic polyangiitis (MPA).
   (c) Eosinophilic granulomatosis with polyangiitis (EGPA).
2. Immune-complex-associated vasculitis:
   (a) Anti-glomerular basement membrane (Anti-GBM) disease.
   (b) Cryoglobulinemic vasculitis (CV).
   (c) IgA vasculitis (IgAV).
   (d) Hypocomplementemic urticarial vasculitis (HUV) (Anti-C1q).

Variable Vessel Vasculitis (VVV):
1. Behcet's disease (BD).
2. Cogan's syndrome (CS).

Single Organ Vasculitis (SOV):
1. Cutaneous leukocytoclastic angiitis.
2. Cutaneous arteritis.
3. Primary central nervous system vasculitis.
4. Isolated aortitis.

Vasculitis Associated with Systemic Disease:
1. Lupus vasculitis.
2. Rheumatoid vasculitis.
3. Sarcoid vasculitis.

Vasculitis Associated with Probable Etiology:
1. Hepatitis C-associated cryoglobulinemic vasculitis.
2. Hepatitis B-associated vasculitis.
3. Syphilis-associated vasculitis.
4. Drug-associated immune-complex vasculitis.
5. Drug-associated ANCA-associated vasculitis.
6. Cancer-associated vasculitis.

Table 20.1 Definitions adopted by the 2012 CHCC on the nomenclature of vasculitides [4]

CHCC2012 name	CHCC2012 definition
Large vessel vasculitis (LVV)	"Vasculitis affecting large arteries more often than other vasculitides. Large arteries are the aorta and its major branches. Any size artery may be affected. Page no. 6"
Takayasu arteritis (TAK)	"Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. Onset usually inpatients younger than 50 years. Page no. 6"
Giant cell arteritis (GCA)	"Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involves the temporal artery. Onset usually in patients older than 50 years and often associated with polymyalgia rheumatica. Page no. 6"
Medium vessel vasculitis (MVV)	"Vasculitis predominantly affecting medium arteries defined as the main visceral arteries and their branches. Any size artery may be affected. Inflammatory aneurysms and stenoses are common. Page no. 6"
Polyarteritis nodosa (pan)	"Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with antineutrophil cytoplasmic antibodies (ANCAs). Page no. 6"
Kawasaki disease (KD)	"Arteritis associated with the mucocutaneous lymph node syndrome and predominantly affecting medium and small arteries. Coronary arteries are often involved. Aorta and large arteries may be involved. Usually occurs in infants and young children. Page no. 6"
Small vessel vasculitis (SVV)	"Vasculitis predominantly affecting small vessels, defined as small intraparenchymal arteries, arterioles, capillaries, and venules. Medium arteries and veins may be affected. Page no. 6"
ANCA-associated vasculitis (AAV)	"Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries), associated with myeloperoxidase (MPO)ANCA or proteinase 3 (PR3) ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, e.g., MPO-ANCA, PR3-ANCA, ANCA negative. Page no. 6"
Microscopic polyangiitis (MPA)	"Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent. Page no. 6"
Granulomatosis with polyangiitis (GPA)	"Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries and veins). Necrotizing glomerulonephritis is common. Page no. 6"
Eosinophilic granulomatosis with polyangiitis (EGPA)	"Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present. Page no. 6"
Immune complex vasculitis	"Vasculitis with moderate to marked vessel wall deposits of immunoglobulin and/or complement components predominantly affecting small vessels (i.e., capillaries, venules, arterioles, and small arteries). Glomerulonephritis is frequent. Page no. 6"
Anti-glomerular basement membrane disease (anti-GBM)	"Vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with GBM deposition of anti-GBM autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents. Page no. 6"
Cryoglobulinemic vasculitis (CV)	"Vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with serum cryoglobulins. Skin, glomeruli, and peripheral nerves are often involved. Page no. 6"
IgA vasculitis (IgAV)	"Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract, and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur. Page no. 6"

(continued)

Table 20.1 (continued)

CHCC2012 name	CHCC2012 definition
Hypocomplementemic Urticarial vasculitis (HUV) (anti-C1q vasculitis)	"Vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels (i.e., capillaries, venules, or arterioles), and associated with anti-C1qantibodies. Glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common. Page no. 6"
Variable vessel vasculitis (VVV)	"Vasculitis with no predominant type of vessel involved that can affect vessels of any size (small, medium, and large) and type (arteries, veins, and capillaries). Page no. 6"
Behcet's disease (BD)	"Vasculitis occurring in patients with Behcet's disease that can affect arteries or veins. Behcet's disease is characterized by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, and/or central nervous system inflammatory lesions. Small vessel vasculitis, thromboangiitis, thrombosis, arteritis, and arterial aneurysms may occur. Page no. 6"
Cogan's syndrome (CS)	"Vasculitis occurring in patients with Cogan's syndrome. Cogan's syndrome characterized by ocular inflammatory lesions, including interstitial keratitis, uveitis, and episcleritis, and inner ear disease, including sensorineural hearing loss and vestibular dysfunction. Vasculitic manifestations may include arteritis (affecting small, medium, or large arteries), aortitis, aortic aneurysms, and aortic and mitral valvulitis. Page no. 6"
Single-organ vasculitis (SOV)	"Vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a systemic vasculitis. The involved organ and vessel type should be included in the name (e.g., cutaneous small vessel vasculitis, testicular arteritis, central nervous system vasculitis). Vasculitis distribution may be unifocal or multifocal (diffuse) within an organ. Some patients originally diagnosed as having SOV will develop additional disease manifestations that warrant redefining the case as one of the systemic vasculitides (e.g., cutaneous arteritis later becoming systemic polyarteritis nodosa, etc.). Page no. 7"
Vasculitis associated with systemic disease	"Vasculitis that is associated with and maybe secondary to (caused by) a systemic disease. The name (diagnosis) should have a prefix term specifying the systemic disease (e.g., rheumatoid vasculitis, lupus vasculitis, etc.). Page no. 7"
Vasculitis associated with probable etiology	"Vasculitis that is associated with a probable specific etiology. The name (diagnosis) should have a prefix term specifying the association (e.g., hydralazine-associated microscopic polyangiitis, hepatitis B virus–associated vasculitis, hepatitis C virus-associated cryoglobulinemic vasculitis, etc.). Page no. 7"

20.1.4 How to Approach a Patient with Vasculitis?

20.1.4.1 A Case Scenario

A lady comes to the clinic with a rash over her legs. She is aged 32 years and for the last 6 months has been unwell, with intermittent fevers, loss of appetite, and fatigue. Recent blood tests show elevated erythrocyte sedimentation rate (ESR; 83 mm/h) and C-reactive protein (CRP; 46 mg/dL). Today she has palpable purpura on her lower legs. Urinalysis is positive for blood and protein.

What are the clinical clues to vasculitis?
What investigations will assist with a precise diagnosis?
How should the condition be treated and monitored?

Tables 20.2, 20.3 and 20.4 summarize history, physical examination findings (Fig. 20.3), and work-up of a patient presenting with suspected vasculitis. Figure 20.2 summarizes history taking from a patient presenting with suspected vasculitis. This includes review of systems, past medical history, and medication history. Figures 20.4, 20.5 and 20.6 show different mucocutaneous finding that can be present in a patient with vasculitis.

20.1.5 Major Forms of Vasculitis

20.1.5.1 Takayasu's Arteritis (TA)

TA primarily affects the aorta and its primary branches [5]. It is an uncommon form of vasculitis. Up to 90% of the cases are women of reproductive age, and it is more prevalent in Asia [6].

Table 20.2 What to ask a patient presenting with suspected vasculitis?

Non-specific systemic symptoms	Fever, weight loss, malaise, loss of appetite, and fatigue
Skin	Rash, palpable purpura, nodules, ulcers, and cutaneous or nailfold infarctions
Ocular symptoms	Pain, redness, diplopia, and visual loss
Neurological	Numbness, weakness, pain consistent with mononeuritis multiplex, transient ischemic attacks, and symptoms suggestive of stroke
Cardiac	Chest pain and dyspnea
Pulmonary	Chest pain, dyspnea, cough, and hemoptysis
Gastrointestinal	Abdominal pain and upper or lower gastrointestinal bleeding
Musculoskeletal	Arthralgias and arthritis
Renal	Hematuria
Past medical history	Systemic rheumatic diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, scleroderma, dermatomyositis) Malignancies (lymphoma, leukemia) Hematological conditions (thrombotic thrombocytopenic purpura) Bronchial asthma, hyperactive airways Infections (HIV, viral hepatitis B or C)
Medication history	Hydralazine, propylthiouracil, thiazide, allopurinol, penicillin, gold, phenytoin, and sulfonamide

Table 20.3 What to look for when physically examining a patient with suspected vasculitis?

Skin	Palpable purpura, nodules, papules, ulcers, and digital ischemia
Pulse and blood pressure	Unequal pulses and high blood pressure (especially diastolic)
Face	Pallor, conjunctivitis, septal nasal perforation, and saddle nose deformity
Oral cavity and neck	Strawberry gums, oral ulcers, and cervical lymphadenopathy
Cardiac	Cardiac bruits
Pulmonary	Bilateral crepitations
Gastrointestinal	Abdominal tenderness
Musculoskeletal	Arthritis and migratory polyarthritis

Table 20.4 What are the laboratory tests that help ascertain the type of vasculitis?

CBC	Anemia, leukocytosis, leukopenia, thrombocytosis, and thrombocytopenia
Renal profile	Hyperkalemia and elevated creatinine
Hepatic profile	Abnormal if there is an underlying hepatitis
ANCA, RF, ANA, and cryoglobulins	Screening
Complements C3 and C4	Hypocomplementemia
Hepatitis and HIV serology	Rule out hepatitis B or C and HIV infection
Urinalysis	Active sediment or red blood cell casts
Inflammatory markers	Elevated ESR and/or CRP
Chest X-ray	Pulmonary involvement (nodules, infiltrates, cavities, etc.)
2D echocardiogram	Cardiac involvement
CT angiography/ MRA	Aneurysms, vascular irregularities, stenosis, and post-stenotic dilatation
Tissue biopsy	Identify the histopathology

The inflammation is characterized by thickening of the arterial wall. This can lead to narrowing, occlusion, or dilatation of the arteries [7].

The pathogenesis of TA is not clear. Presence of mononuclear cells is thought to cause active inflammation that leads to granuloma formation [8]. Aneurysms are formed due to laminal destruction. Arterial plaques were also found in patients with TA [9].

Systemic symptoms are manifested early in TA [10]. As the disease progresses, vascular involvement becomes evident. Subclavian artery stenosis proximal to the origin of the vertebral artery can lead to the so-called subclavian steal syndrome [11]. Ischemic ulcerations and gangrene may develop as results of vascular occlusion.

The differential diagnosis of TA includes fibromuscular dysplasia, excess ergotamine intake, Ehlers-Danlos syndrome, and GCA.

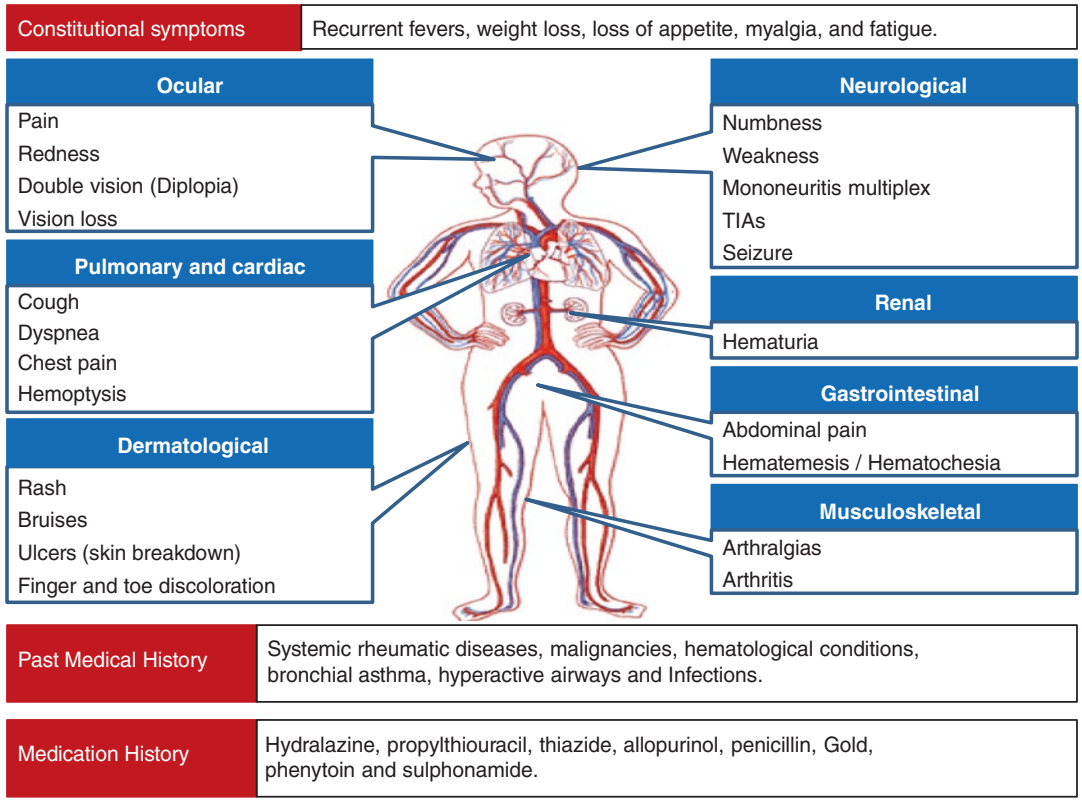

Fig. 20.2 History taking from a patient presenting with suspected vasculitis. This includes review of systems, past medical history and medication history

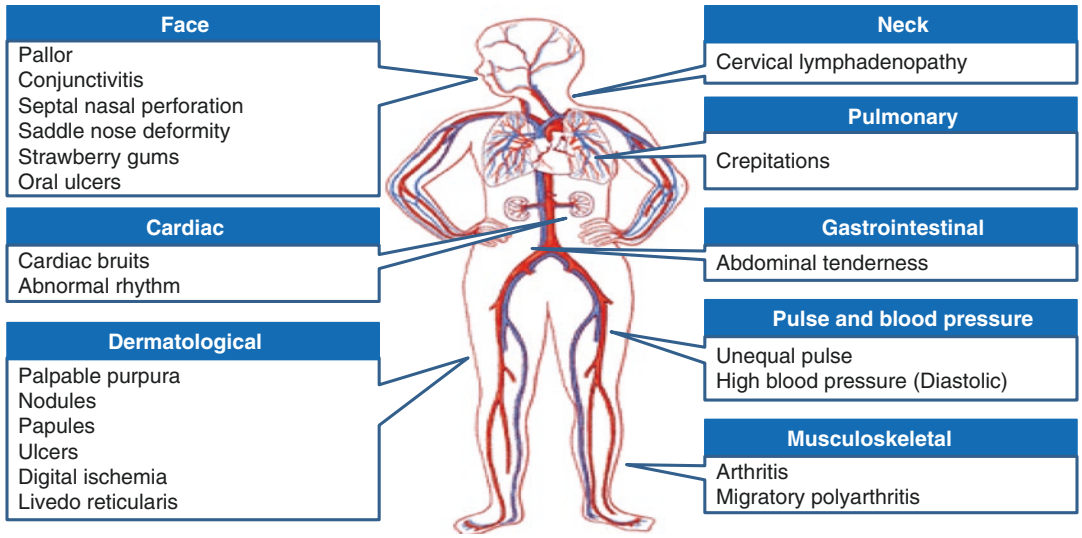

Fig. 20.3 Physical signs that should be checked for in a patient presenting with suspected vasculitis

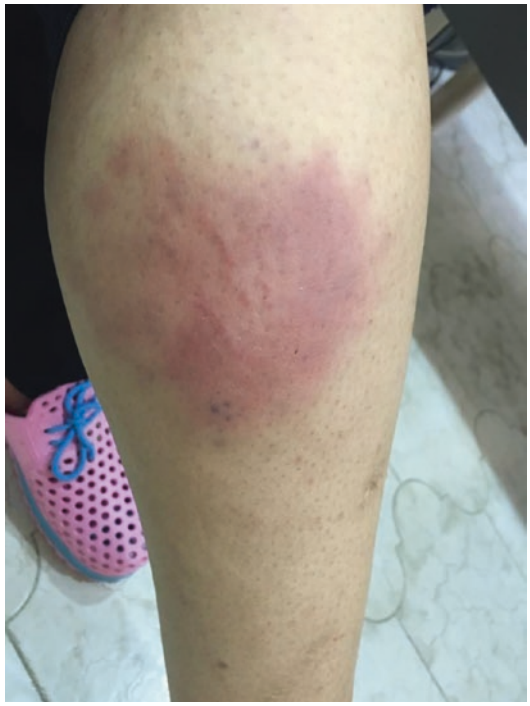

Fig. 20.4 Erythema nodosum in polyarteritis nodosa. Courtesy of Prof. Hani Almoallim

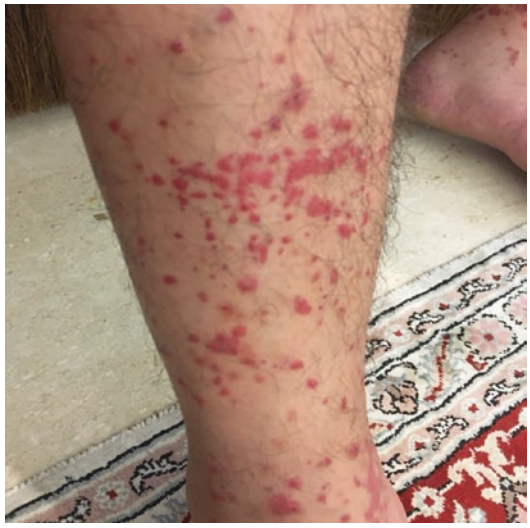

Fig. 20.5 Leukocytoclastic vasculitis with palpable purpura in a patient with immune-complex-associated small vessel vasculitis. Courtesy of Prof. Hani Almoallim

Glucocorticoids are the mainstay treatment. They reduce both systemic symptoms and disease progression [12]. Azathioprine, mycophenolate, methotrexate, tocilizumab, or leflunomide can be used in glucocorticoid-resistant cases, while cyclophosphamide is for those who have continued disease activity despite those medications [13, 14]. Percutaneous transluminal angioplasty or bypass grafts may be considered in late cases when irreversible arterial stenosis has occurred and when significant ischemic symptoms develop [15].

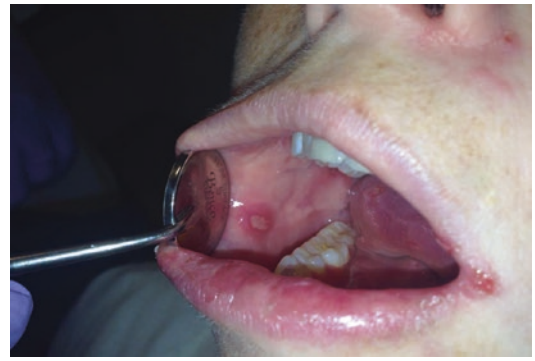

Fig. 20.6 Oral ulcer in a patient with Behcet's disease. Courtesy of Dr. Lujain Homeida

Table 20.5 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, American College of Rheumatology (ACR) 1990 classification criteria, and treatment of TA.

20.1.5.2 Giant Cell Arteritis (GCA)

GCA is a vasculitis of large-sized vessels. Up to 90% of cases are above the age of 60 [16]. It affects the aorta and its major branches, mainly the carotid and vertebral arteries [17].

The pathogenesis of GCA is poorly understood. It is thought that an initial trigger (e.g., viral infection or other factor) activates monocytes in a susceptible host. These monocytes cause systemic symptoms. Release of inflammatory mediators and tissue injury may lead to fibrosis, scarring, and narrowing or occlusion of the arteries [18].

Symptoms of GCA start gradually but may manifest acutely in some patients. An efficient history should include questions about systemic symptoms, such as fever, fatigue, and weight loss; headache; jaw claudication, which is the most specific symptom of GCA; visual symptoms; and symptoms of polymyalgia rheumatica [19–21].

Table 20.5 Takayasu's arteritis (pulseless disease)

CHCC 2012 definition	Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. Onset usually in patients younger than 50 years [4]
Epidemiology	Most common in Asia and in young women of reproductive age
Clinical manifestation	Phase 1: Inflammatory period (fever, arthralgias, weight loss) Phase 2: Vessel pain and tenderness, unequal pulses in extremities, bruits, limb claudication, hypertension, aortic aneurysm, and insufficiency Phase 3: Vessel fibrosis
Diagnostic studies	Elevated ESR (75%) and CRP Angiography and MRI/MRA: Stenosis, occlusion, irregularity, and aneurysms Biopsy: Pan arteritis, cellular infiltrates with granulomas, and giant cells
ACR 1990 Classification criteria	1. Age less than 40 at disease onset. 2. Claudication of extremities. 3. Decrease in brachial artery pulse. 4. Systolic BP difference by more than 10 mmHg between both arms. 5. Bruit over subclavian artery or aorta. 6. Arteriographic narrowing or occlusion. Presence of 3 out of 6 is 90.5% sensitive (se) and 97.8% specific (Sp) [3]
Treatment	Steroids: 40–60 mg/day initially, then slow tapering based on clinical and radiological response. Methotrexate, leflunomide, azathioprine, or tocilizumab for resistant cases. May consider antiplatelet therapy or surgical/endovascular revascularization

Table 20.6 Giant cell arteritis

CHCC 2012 definition	Arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries. Often involves the temporal artery. Onset usually in patients older than 50 years and often associated with polymyalgia rheumatica [4]
Epidemiology	90% are above 60 years, rare below 50 years, female/male ratio is 2:1
Clinical manifestation	Constitutional symptoms, headache, tender and pulseless temporal arteries, optic neuritis, diplopia, amaurosis fugax, blindness, jaw claudication, Raynaud's phenomenon, and thoracic aortic aneurysm
Diagnostic studies	Elevated ESR and CRP. Anemia Angiography, MRI/MRA: If aortic aneurysm is suspected Bilateral temporal artery biopsy: Vasculitis and granulomas
ACR 1990 Classification criteria	1. Age more than 50 at disease onset. 2. New headache. 3. Temporal artery tenderness or decreased pulse. 4. ESR more than 50 mm/h. 5. Biopsy: Vasculitis and granulomas. Presence of 3 out of 5 is 93.5% Se and 91.2% Sp [3]
Polymyalgia rheumatica	Seen in 50% of patients with GCA, 15% of patients with PMR develop GCA. Bilateral aching and morning stiffness for more than 30 min for more than 1 month, involving two of the following areas: Neck or torso, shoulders or proximal arms, hips or proximal thighs, and night time pain. Age at onset is usually more than 40
Treatment	Steroids: 40 to 60 mg/day and 10 to 20 mg/day for polymyalgia rheumatica. Taper down treatment based on clinical response. Monitor ESR and CRP Methotrexate and tocilizumab can be added as steroid-sparing agents

Temporal artery biopsy is the gold standard modality for the diagnosis of GCA. However, if the clinical suspicion is high or vision is threatened, high-dose glucocorticoid therapy should be started immediately. Appropriate measures to prevent glucocorticoid-induced osteoporosis should be taken [22]. Methotrexate is moderately effective as a glucocorticoid-sparing agent. Tocilizumab was recently granted a breakthrough designation status by the US Food and Drug Association for GCA based on positive results from a phase 3 clinical trial [23].

Table 20.6 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic

studies, ACR 1990 classification criteria, and treatment of GCA.

20.1.5.3 Polyarteritis Nodosa (PAN)

PAN is a systemic necrotizing arteritis of the medium-sized muscular arteries, with occasional involvement of small muscular arteries. It is not associated with the presence of ANCA. It is more common in men in the sixth decade of life [24].

PAN is mostly idiopathic, although hepatitis B virus infection, hepatitis C virus infection, and hairy cell leukemia are important in the pathogenesis of some cases. The pathogenesis is poorly understood. It is characterized by segmental transmural inflammation of muscular arteries which leads to fibrinoid necrosis and disruption of the elastic lamina. Unlike other forms of systemic vasculitis, it does not involve veins [25].

Like most types of vasculitis, patients with PAN present with systemic symptoms (fatigue, weight loss, weakness, fever, arthralgias) and signs of multisystem involvement (skin lesions, hypertension, renal insufficiency, neurologic dysfunction, and abdominal pain). PAN has a striking tendency to spare the lungs.

The differential diagnosis of PAN is broad, including infectious diseases that affect the vasculature or that are complicated by systemic vasculitis; noninfectious disorders, particularly those that can cause widespread arterial embolism, thrombosis, or vasospasm; and other systemic vasculitides.

Treatment of PAN depends on the severity of the disease. Mild disease can be treated with prednisolone at a dose of 1 mg/kg per day (maximum 60 to 80 mg/day) for approximately 4 weeks and then to be tapered based on clinical improvement [26]. Moderate to severe disease is treated with methotrexate, azathioprine, mycophenolate, or cyclophosphamide [26].

Table 20.7 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of PAN.

Table 20.7 Polyarteritis nodosa

CHCC 2012 definition	Necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules and not associated with antineutrophil cytoplasmic antibodies (ANCAs) [4]
Epidemiology	More common in men. Average age at onset is 50. Strongly associated with HBV
Clinical manifestation	Constitutional symptoms, myalgias, arthralgias, arthritis, active urinary sediment, hypertension, renal impairment, peripheral neuropathy, mononeuritis multiplex, abdominal pain, GI bleeding, testicular pain, livedo reticularis, purpura, coronary arteritis, pericarditis, and Raynaud's phenomenon
Diagnostic studies	Elevated ESR and CRP. Leukocytosis. HbsAg is positive in about 30% ANCA is negative Angiography or CTA: Microaneurysms and focal vessel narrowing Biopsy of sural nerve, skin, or affected organ: Vasculitis, necrosis, and no granulomas
ACR 1990 Classification criteria	1. More than 4 kilograms of weight loss. 2. Livedo reticularis. 3. Testicular pain or tenderness. 4. Myalgias, weakness, and leg tenderness. 5. Mono or polyneuropathy. 6. Diastolic BP more than 90 mmHg. 7. Elevated BUN more than 40 mg/dL or Cr more than 1.5 mg/dL. 8. HBV. 9. Arteriographic abnormality. 10. Vasculitis on biopsy. Presence of 3 out of 10 is 82% Se and 87% Sp [3]
Treatment	Steroids: 40–60 mg/day initially and then slow tapering based on clinical and radiological response. Steroid-sparing agents for resistant cases. Antiviral therapy for HBV-related disease

20.1.5.4 Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)

These are types of vasculitis that affect small vessels. They occur mostly in older adults, and both genders are equally affected. Both types are associated with ANCA and have similar features on renal histology (crescentic, pauci-immune glomerulonephritis) [27].

An initiating event (e.g., infection or drug) causes tissue injury and immune response [28]. This leads to production of ANCA. Up to 80% of the antigens observed in granulomatosis with polyangiitis are proteinase 3 (PR3) (c-ANCA), while myeloperoxidase (MPO) (p-ANCA) is observed in 10% of patients. About 70% of microscopic polyangiitis patients have positive ANCA which is mostly p-ANCA.

Patients typically present with constitutional symptoms that may last for weeks to months without evidence of specific organ involvement. Both types affect multiple systems including pulmonary, renal, ocular, neurologic, and hematologic [29].

The distinction of these types of small vessel vasculitis from other systemic rheumatic diseases is challenging. Differential diagnosis includes diseases with similar general clinical features like EGPA, similar lung and/or renal signs like anti-GBM disease, and/or positive ANCA serologies like renal-limited vasculitis.

Therapy has two components: induction of remission with initial immunosuppressive therapy and maintenance immunosuppressive therapy for a variable period to prevent relapse. Choice of drug regimen in induction of remission depends on the severity of the disease. Mild disease can be treated by a combination therapy with glucocorticoids and methotrexate, while cyclophosphamide or rituximab [30] is required to treat severe disease. Plasma exchange is added in case of glomerulonephritis or pulmonary hemorrhage [31, 32].

Tables 20.8 and 20.9 summarize CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of GPA and MPA.

Table 20.8 Granulomatosis with polyangiitis

CHCC 2012 definition	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract and necrotizing vasculitis affecting predominantly small to medium vessels (e.g., capillaries, venules, arterioles, arteries, and veins). Necrotizing glomerulonephritis is common [4]
Epidemiology	Can occur at any age, but mostly in young and middle-aged adults
Clinical manifestation	Pulmonary: Sinusitis, rhinitis, nasal mucosal ulceration, saddle nose deformity, pleurisy, pulmonary infiltrates, nodules, hemorrhage, and hemoptysis Renal: Hematuria and glomerulonephritis Ocular: Episcleritis, uveitis, proptosis, corneal ulcers Neurological: Cranial and peripheral neuropathies and mononeuritis multiplex Hematological: Increase incidence of DVT/PE
Diagnostic studies	90% have positive ANCA (80 to 95% c-ANCA, remainder p-ANCA) CXR or CT chest: Nodules, infiltrates, cavities. CT sinus: Sinusitis Elevated BUN and creatinine, hematuria, proteinuria, and sediment with RBC casts Biopsy: Necrotizing granulomatous inflammation
ACR 1990 Classification criteria	1. Nasal or oral inflammation: Oral ulcers, purulent or bloody nasal discharge. 2. CXR showing nodules, fixed infiltrates or cavities. 3. Microscopic hematuria or urinary red cell casts. 4. Granulomatous inflammation on biopsy. Presence of 2 out of 4 is 88% Se and 92% Sp [3]
Treatment	Induction: Cyclophosphamide PO (2 mg/kg/day for 3 to 6 months or pulse 15 mg/kg/day every 2 to 3 weeks) or IV rituximab 375 mg/m^2 per week for 4 weeks and prednisolone 1 to 2 mg/kg/day taper over 6 to 18 months. If rapidly progressive glomerulonephritis, add plasma exchange Maintenance: Methotrexate or azathioprine for 2 years. Bactrim may prevent respiratory infections

Table 20.9 Microscopic polyangiitis

CHCC 2012 definition	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent [4]
Epidemiology	Not associated with HBV
Clinical manifestation	Similar to granulomatosis with polyangiitis but renal involvement is more common than pulmonary involvement
Diagnostic studies	70% have positive ANCA (almost all p-ANCA) CXR or CT chest: Nodules, infiltrates, cavities Elevated BUN and creatinine, hematuria, proteinuria, sediment with RBC casts, and dysmorphic RBCs Biopsy: Pauci-immune inflammation
ACR 1990 Classification criteria	None
Treatment	Induction: Cyclophosphamide PO (2 mg/kg/day for 3 to 6 months or pulse 15 mg/kg/day every 2 to 3 weeks) or IV rituximab 375 mg/m^2 per week for 4 weeks and prednisolone 1 to 2 mg/kg/day taper over 6 to 18 months. If rapidly progressive glomerulonephritis, add plasma exchange Maintenance: Methotrexate or azathioprine for 2 years. Bactrim may prevent respiratory infections

20.1.5.5 Eosinophilic Granulomatosis with Polyangiitis (EGPA)

EGPA is a multisystem disease characterized by allergic rhinitis, asthma, and prominent peripheral blood eosinophilia [33].

In this disease, ANCA is detected in about 50% of patients. The etiology of EGPA is unknown. However, genetic factors such as HLA-DRB4 are thought to play a role. Presence of ANCA produces an immune response, which then leads to eosinophilic infiltration and necrotizing granuloma [34].

Clinical features of EGPA develop in several phases: the prodromal phase which is characterized by presence of asthma and allergic rhinitis; the eosinophilic phase with eosinophilic infiltration of multiple organs; and the vasculitis phase that may be heralded by nonspecific constitutional symptoms [35].

Differential diagnosis includes aspirin-exacerbated respiratory disease, the eosinophilic pneumonias, allergic bronchopulmonary aspergillosis, the hyper-eosinophilic syndrome, and other ANCA-associated vasculitides.

Treatment of EGPA consists of induction of remission and maintenance of remission. For mild disease, induction can be achieved with high-dose glucocorticoids. Cyclophosphamide is added to glucocorticoids in severe disease. For maintenance of remission, azathioprine or methotrexate can be used [36].

Table 20.10 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of EGPA.

20.1.5.6 IgA Vasculitis (IgAV)

IgA vasculitis, also previously called Henoch-Schönlein Purpura, is the most common systemic.

vasculitis of childhood. Up to 10% of IgA vasculitis occur in adults.

It is a self-limited disease and is characterized by the presence of the following: palpable purpura without thrombocytopenia and coagulopathy, arthralgias and/or arthritis, abdominal pain, and renal disease [37].

The underlying cause of IgA vasculitis is unknown. It is thought that IgA vasculitis represents an immune-mediated vasculitis that may be triggered by a variety of antigens, including various infections or immunizations [38].

Treatment of IgA vasculitis is supportive and should be directed toward adequate oral hydration, bed rest, and symptomatic relief of joint and abdominal pain. Nonsteroidal anti-inflammatory drugs can be used to alleviate joint or abdominal pain. Glucocorticoids are used for more severe cases [39].

Table 20.10 Eosinophilic granulomatosis with polyangiitis

CHCC 2012 definition	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present [4]
Epidemiology	Rare condition, can present at any age. Associated with HLA-DRB4
Clinical manifestation	Asthma and allergic rhinitis Eosinophilic infiltrative disease or pneumonia Systemic small vessel vasculitis with granuloma Neuropathy, glomerulonephritis Cardiac involvement: Coronary arteritis, myocarditis, and vascular insufficiency Dermatological: Palpable purpura, petechiae, and subcutaneous nodules
Diagnostic studies	50% have positive ANCA (c-ANCA or p-ANCA). Eosinophilia CXR: Shifting pulmonary infiltrates Elevated BUN and creatinine, hematuria, proteinuria, and sediment with RBC casts Biopsy: Microgranulomas with eosinophilic infiltrates
ACR 1990 Classification criteria	1. Asthma. 2. Eosinophilia more than 10%. 3. Mono- or polyneuropathy. 4. Migratory or transitory pulmonary infiltrates. 5. Paranasal sinus abnormality. 6. Extravascular eosinophils on biopsy. Presence of 4 out of 6 is 85% Se and 99.7% Sp [3]
Treatment	Induction: High-dose corticosteroids. Cyclophosphamide can be used if necessary Maintenance: Azathioprine or methotrexate

Table 20.11 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of IgA vasculitis.

20.1.5.7 Cutaneous Leukocytoclastic Angiitis

Cutaneous leukocytoclastic angiitis, also previously called hypersensitivity vasculitis, is a form of single-organ vasculitis that involves cutaneous vessels of any size with no evidence of systemic vasculitis [4].

Table 20.11 IgA vasculitis

CHCC 2012 definition	Vasculitis, with IgA1-dominant immune deposits, affecting small vessels (predominantly capillaries, venules, or arterioles). Often involves skin and gastrointestinal tract and frequently causes arthritis. Glomerulonephritis indistinguishable from IgA nephropathy may occur [4]
Epidemiology	Males are affected more than females. Begins after an infection or drug exposure
Clinical manifestation	Palpable purpura on extensor surfaces and buttocks Polyarthralgias, abdominal pain, GI bleeding, microscopic hematuria and fever
Diagnostic studies	Normal platelet count Skin biopsy: Leukocytoclastic vasculitis with IgA and C3 deposition in vessel wall Renal biopsy: Mesangial IgA deposition
ACR 1990 Classification criteria	1. Palpable purpura. 2. Age less than 20 at disease onset. 3. Bowel angina. 4. Skin biopsy: Leukocytoclastic vasculitis with IgA and C3 deposition in vessel wall. Presence of 2 out of 4 is 87% Se and 88% Sp [3]
Treatment	Supportive, steroids, and disease-modifying antirheumatic drugs for renal involvement or severe disease

It is the most common type of vasculitis. It may be idiopathic, but it may be directly caused by drugs, infections, tumor antigens, and serum sickness.

It is difficult to distinguish cutaneous leukocytoclastic angiitis from other forms of vasculitis, particularly when confined to the skin. Many types of systemic vasculitis may present initially with cutaneous involvement, so careful evaluation is required.

Treatment of the underlying cause or withdrawal of the offending agent lead to resolution within a period of days to a few weeks. Glucocorticoids are preserved for progressive disease [40].

Table 20.12 Cutaneous leukocytoclastic angiitis

CHCC 2012 definition	A form of single-organ vasculitis, involves arteries or veins of any size in the skin that has no features indicating that it is a limited expression of systemic vasculitis [4]
Epidemiology	Most common type of vasculitis. Caused by drugs (e.g., penicillin, cephalosporins, phenytoin, allopurinol, aspirin, amphetamine, thiazide, chemicals and immunizations), by infections (e.g., streptococcal throat infection, bacterial endocarditis, and TB), tumor antigens, and serum sickness
Clinical manifestation	Palpable purpura, ulceration, transient arthralgias, fever, peripheral neuropathy
Diagnostic studies	Elevated ESR and eosinophils. Low complements Skin biopsy: Leukocytoclastic vasculitis with neutrophils. No IgA deposition
ACR 1990 Classification criteria	1. Age more than 16. 2. Medication taken at disease onset. 3. Palpable purpura. 4. Maculopapular rash. 5. Skin biopsy: Leukocytoclastic vasculitis with neutrophils. Presence of 3 out of 5 is 71% Se and 84% Sp [3]
Treatment	Withdrawal of the offending agent and rapid prednisolone taper

Table 20.12 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of cutaneous leukocytoclastic angiitis.

20.1.5.8 Behcet's Disease (BD)

It is a type of vasculitis that can affect blood vessels of all sizes. It is characterized by recurrent oral aphthae and any of several systemic manifestations including genital aphthae, ocular disease, skin lesions, gastrointestinal involvement, neurologic disease, vascular disease, or arthritis. It is more common along the ancient silk road, which extends from Eastern Asia to the Mediterranean. It typically affects adults between the age of 20 and 40 with a similar prevalence between both genders [41].

The underlying cause of BD is unknown. It is thought that the immune response is triggered by exposure to an agent (e.g., infection, chemicals). It is also found to be associated with HLA-B51 [42]. Both cellular and humoral immunity responses are activated [43]. Endothelial dysfunction leads to inflammation and thrombus formation in BD [43].

Ocular, vascular, and neurological manifestations account for the greatest morbidity and mor-

Table 20.13 Behcet's disease

CHCC 2012 definition	Vasculitis occurring in patients with Behcet's disease that can affect arteries or veins. Behcet's disease is characterized by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, and/or central nervous system inflammatory lesions. Small vessel vasculitis, thromboangiitis, thrombosis, arteritis, and arterial aneurysms may occur [4]
Epidemiology	Associated with HLA-B51. Highest prevalence in Turkey and other Asian countries
Classification criteria	1. Recurrent oral aphthous ulceration (at least 3 times a year). 2. Recurrent genital ulceration. 3. Eye lesion (uveitis, scleritis, optic neuritis). 4. Skin lesions (pustules, papules, erythema nodosum). 5. Positive pathergy test (skin prick with a sterile needle will produce a pustule). Presence of first criteria plus two or more of the others is 91% se and 96% Sp
Other clinical manifestation	Arthritis, focal neurological deficit, venous thrombosis, arterial stenosis, or aneurysm
Diagnostic studies	Ulcer biopsy Slit lamp and fundoscopic eye examination
Treatment	Mucocutaneous Mild: Colchicine, topical steroids, and dapsone Severe: Oral steroids, azathioprine, methotrexate, cyclosporine, and anti-TNF Arthritis: NSAIDs, colchicine, steroids, and anti-TNF Ocular: Steroids, azathioprine, infliximab, cyclosporine, and cyclophosphamide Vascular: High-dose steroids and cyclophosphamide. Then azathioprine for maintenance. Anticoagulation for venous thrombosis Neurological: Steroids, methotrexate, azathioprine, cyclophosphamide, and adalimumab. Anticoagulation for dural sinus thrombosis

tality in BD. Cutaneous and articular involvement are also common [44].

Treatment of BD depends on the severity of the disease. Mild disease can be treated with colchicine and oral glucocorticoids. Severe disease requires addition of immunosuppressive therapy such as cyclophosphamide, TNF-alpha blockers, and azathioprine [45].

Table 20.13 summarizes CHCC12 definition, epidemiology, clinical manifestation, diagnostic studies, ACR 1990 classification criteria, and treatment of BD.

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