Expert perspectives on pathological findings in vasculitis

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出版情報：Modern Rheumatology. 33 (1), pp.1-11, 2022-05-10. Oxford University Press
バージョン：

Modern Rheumatology, **33**, 2023, 1–11
DOI: https://doi.org/10.1093/mr/roac043
Advance access publication date: 10 May 2022
Review Article

Expert perspectives on pathological findings in vasculitis

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ABSTRACT

Pathological findings are important in the diagnosis of vasculitis. However, due to the rarity of the disease, standard textbooks usually devote only a few pages to this topic, and this makes it difficult for clinicians not specializing in vasculitis to fully understand the pathological findings in vasculitis. To address the paucity of information, we present representative pathological findings in vasculitis classified in the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC2012). The CHCC2012 classifies 26 vasculitides into seven categories: (1) large-vessel vasculitis, (2) medium-vessel vasculitis, (3) small-vessel vasculitis, including antineutrophil cytoplasmic antibody-associated vasculitis and immune complex small-vessel vasculitis, (4) variable-vessel vasculitis, (5) single-organ vasculitis, (6) vasculitis associated with systemic disease, and (7) vasculitis associated with probable aetiology. Moreover, representative pathological findings of vasculitis-related diseases and non-inflammatory vasculopathy not mentioned in the CHCC2012 are also presented. This will be useful for clinicians to refer to typical pathological findings of vasculitis in daily practice.

KEYWORDS: CHCC2012; granulomatous vasculitis; necrotizing vasculitis; leucocytoclastic vasculitis

Introduction

Pathological findings are important in the diagnosis of vasculitis. However, due to the rarity of the disease, standard textbooks usually devote only a few pages to this topic, and this makes it difficult for clinicians not specializing in vasculitis to fully understand the pathological findings in vasculitis. To address this issue, in 2004, the Pathology Group of the Japan Research Committee of the Ministry of Health, Labour and Welfare for Intractable Vasculitis (JPVAS) led the publication of the 'Atlas of Vasculitis' [1], which has come to be considered the gold standard pathological atlas for vasculitis in Japan.

Since its publication, the atlas has not only been very helpful in the routine diagnosis of vasculitis but has also inspired young researchers to become interested in vasculitis. Although the role and importance of the atlas have not changed, the field of vasculitis has had various changes over the years since the atlas was first published. For example, the international classification of vasculitis has been revised, and new disease concepts have been introduced [2]. Therefore, we present here representative pathological findings in vasculitis classified in the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC2012) [2]. The CHCC2012 classifies 26 vasculitides into seven categories: (1) large-vessel vasculitis, (2) medium-vessel vasculitis, (3) small-vessel vasculitis, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and immune complex small-vessel vasculitis, (4) variable-vessel vasculitis,

Received 1 March 2022; Accepted 3 May 2022

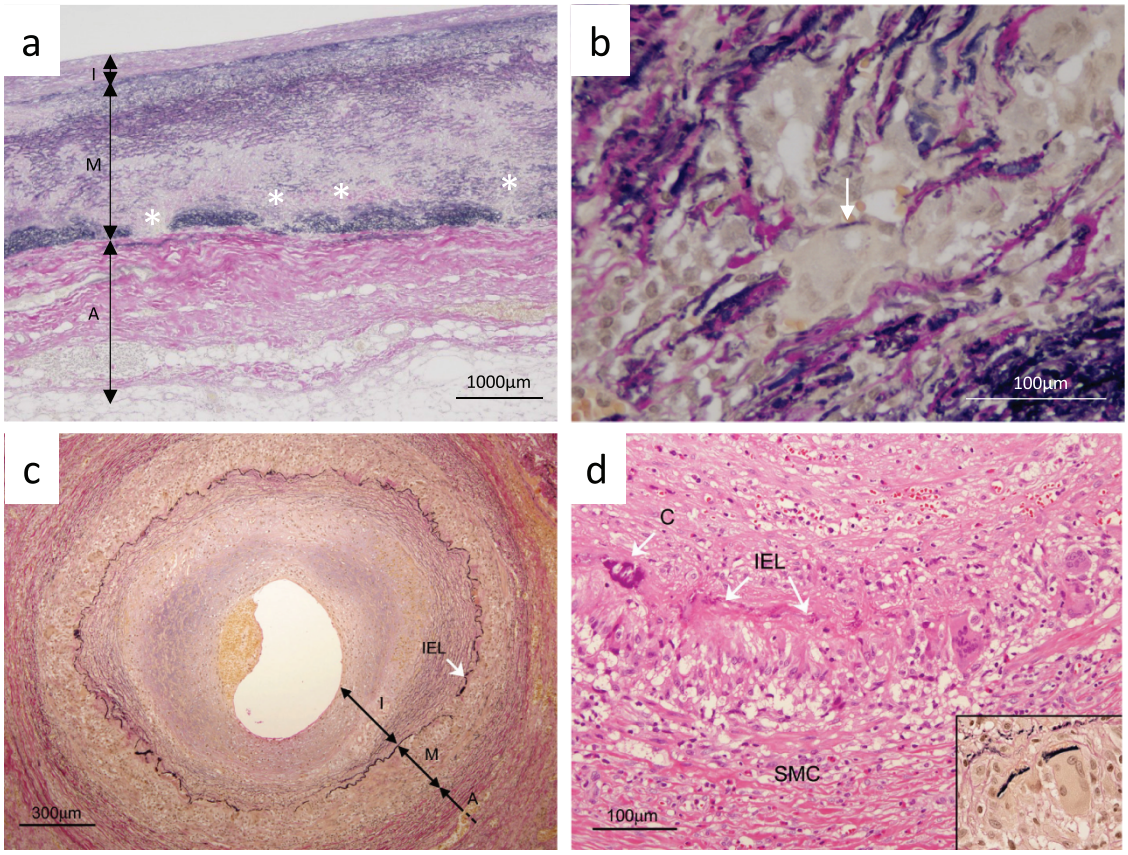

Figure 1. Large-vessel vasculitis.

(a) TAK of the aorta [elastic van Gieson (EVG) staining]. The moth-eaten appearance of elastic fibres is seen on the outer side of the media (asterisk). Intimal and adventitial thicknesses with extensive fibrosis are also seen. I, intima; M, media; A, adventitia. (b) TAK of the aorta (EVG staining). Langhans giant cell phagocytosing the fragmented elastic fibre is seen in the media (arrow). (c) GCA of the temporal artery (EVG staining). A narrowed lumen with significant fibrous thickening of the intima, disruption of the IEL, and fibrosis of the adventitia are present. (d) GCA of the temporal artery (haematoxylin and eosin (HE) staining). Calcification and disruption are observed in the IEL, around which, particularly on the inner side of the media, granulomatous inflammation with histiocytic proliferation is observed. C, calcification. Giant cells of Langhans and foreign body types, some of which are phagocytosing the IEL, are also present (inset: EVG staining).

(5) single-organ vasculitis, (6) vasculitis associated with systemic disease, and (7) vasculitis associated with probable aetiology. Moreover, representative pathological findings of vasculitis-related diseases and non-inflammatory vasculopathy not mentioned in the CHCC2012 are also presented.

Large-vessel vasculitis

Takayasu arteritis

Takayasu arteritis (TAK) predominantly affects the aorta and its major branches in young women [3]. In the early stage of TAK, perivascular infiltration of mononuclear cells around the vasa vasorum is present. Subsequently, the intima progressively thickens, and the adventitia thickens with extensive fibrosis. The moth-eaten appearance, which means an irregular disruption of elastic fibres, is seen on the outer side of the media [4, 5] (Figure 1(a)). Granulomatous panarteritis is a characteristic feature of TAK. Infiltration of Langhans giant cells, which phagocytose fragmented elastic fibres, is sometimes observed in the media (Figure 1(b)).

Giant cell arteritis

Giant cell arteritis (GCA) affects the aorta and its branches, especially the carotid and vertebral arteries [6]. Disruption of the internal elastic lamina (IEL), granulomatous inflammation with giant cells in the media, significant fibrous thickening of the intima, a narrowed lumen, and fibrosis of the adventitia are present (Figure 1(c)). Calcification and disruption are observed in the IEL, around which, particularly on the inner side of the media, granulomatous inflammation with histiocytic proliferation is observed. Many giant cells of Langhans and foreign body types, some of which are phagocytosing the IEL, are also present (Figure 1(d)). In addition, infiltration of lymphocytes and macrophages is seen.

Medium-vessel vasculitis

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a necrotizing vasculitis that affects medium-to-small arteries but not glomeruli [7]. The disease stages were classified by Arkin as (1) degenerative stage, (2) acute inflammatory stage, (3) granulation tissue stage, and (4) healed granulation tissue stage [8]. In the degenerative stage, oedema and fibrinoid degeneration are present in the intima and media. In the acute inflammatory stage, neutrophils and sometimes eosinophils, lymphocytes, and plasma cells infiltrate into the media and adventitia, and fibrinoid necrosis involves all vascular layers, resulting in the disruption and loss of the IEL (Figure 2(a)). After the acute

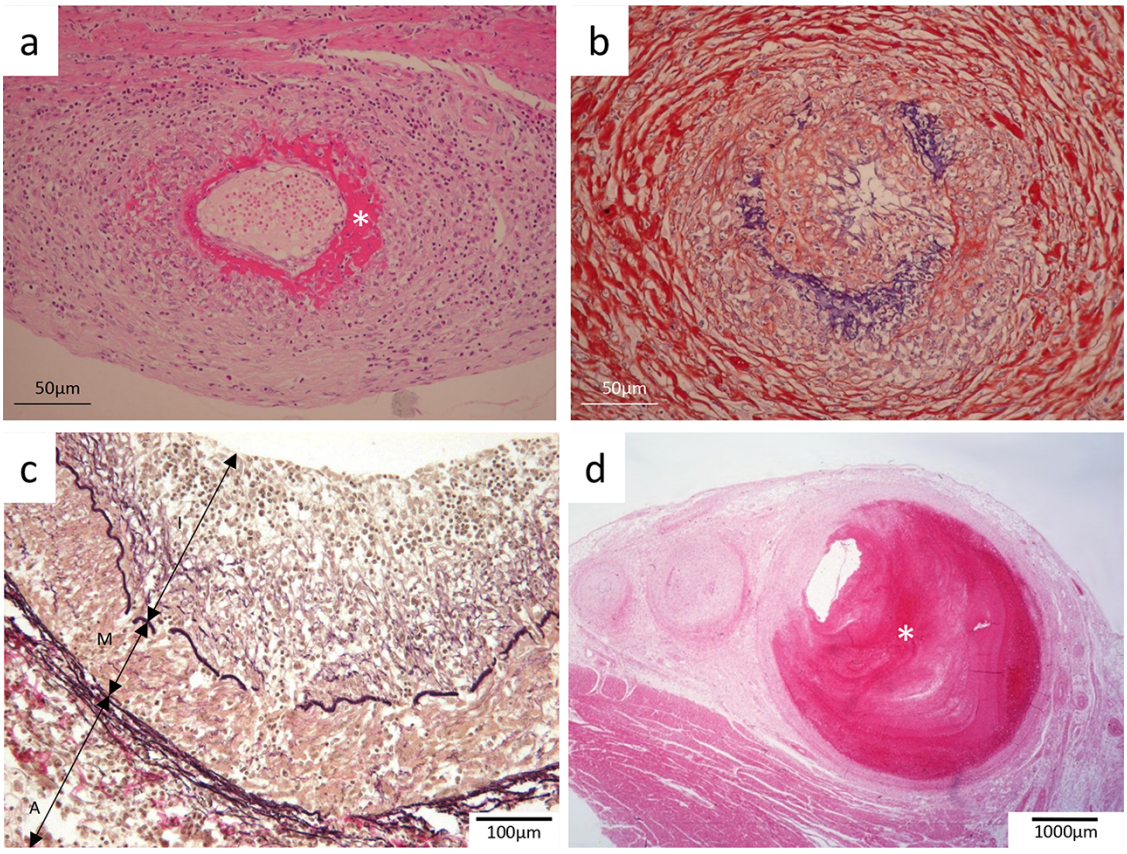

Figure 2. Medium-vessel vasculitis.

(a) Acute inflammatory stage of PAN of the gallbladder [HE staining]. The asterisk indicates fibrinoid necrosis. (b) Granulation tissue stage of PAN of the gallbladder [phosphotungstic acid haematoxylin (PTAH) staining]. The proliferated intima occludes the vascular lumen. Fibrinoid necrosis is observed. (c) Early stage of coronary arteritis in Kawasaki disease (EVG staining). Inflammatory cells invading the arterial wall from the luminal and adventitial sides reach the media while destroying the inner and outer elastic lamina. (d) Thrombotic occlusion of coronary aneurysm (asterisk) in Kawasaki disease (HE staining).

inflammatory stage, the granulation tissue stage begins with the invasion of histiocytes and fibroblasts from the adventitia. In the granulation tissue stage, intimal proliferation occurs, which sometimes occludes the vascular lumen when the progression is severe (Figure 2(b)).

Kawasaki disease

Kawasaki disease, previously known as mucocutaneous lymph node syndrome, usually occurs in infants and children under 4 years old [9]. Inflammation often occurs in medium-sized muscular arteries branching from the aorta, including renal, splenic, mesenteric, and intercostal arteries, in addition to coronary arteries [10]. In the early stage of coronary arteritis, inflammatory cells invading the arterial wall from the luminal and adventitial sides reach the media while destroying the inner and outer elastic lamina (Figure 2(c)). The major infiltrating cells are macrophages, although neutrophils are present in the early stage. Fibrinoid necrosis is rarely seen. Inflammatory cell infiltration peaks at about Day 12 after the onset of Kawasaki disease. Inflammation involving all layers of the arterial wall weakens the artery, which causes the dilation of the artery, resulting in aneurysm formation (Figure 2(d)). Severe inflammatory cell infiltration continues until about Day 25 and then gradually resolves, resulting in fibrosis. Many autopsy cases show thrombus formation in the aneurysm [11, 12].

Small-vessel vasculitis

ANCA-associated vasculitis

ANCA-associated vasculitis is a necrotizing vasculitis associated with ANCA specific for myeloperoxidase (MPO) or proteinase 3 (PR3). This disease predominantly affects small vessels and forms few immune deposits [13].

Microscopic polyangiitis

Microscopic polyangiitis (MPA) leads to rapidly progressive glomerulonephritis with tuft necrosis and crescent formation in the kidneys and pulmonary haemorrhage due to capillaritis in the lungs [14]. A nationwide cohort study in Japan found that the average age of MPA onset is >70 years and that most patients are positive for MPO-ANCA [15].

Glomerulonephritis is the major renal manifestation of MPA. In the affected glomeruli, necrotizing and crescentic glomerulonephritis (NCGN) is seen (Figure 3(a)). There is no significant positive finding in immunofluorescent analysis, suggesting pauci-immune glomerulonephritis. Necrotizing arteritis is often present in interstitial small arteries, including interlobular arteries and arterioles (Figure 3(b)). Necrotic changes and inflammation tend to obscure the structure of arteriolar walls; therefore, special staining and serial sectioning are helpful in the evaluation of MPA. Neutrophil infiltration and erythrocyte extravasation are observed around the capillaries in the medulla. Deposition of fibrin-like

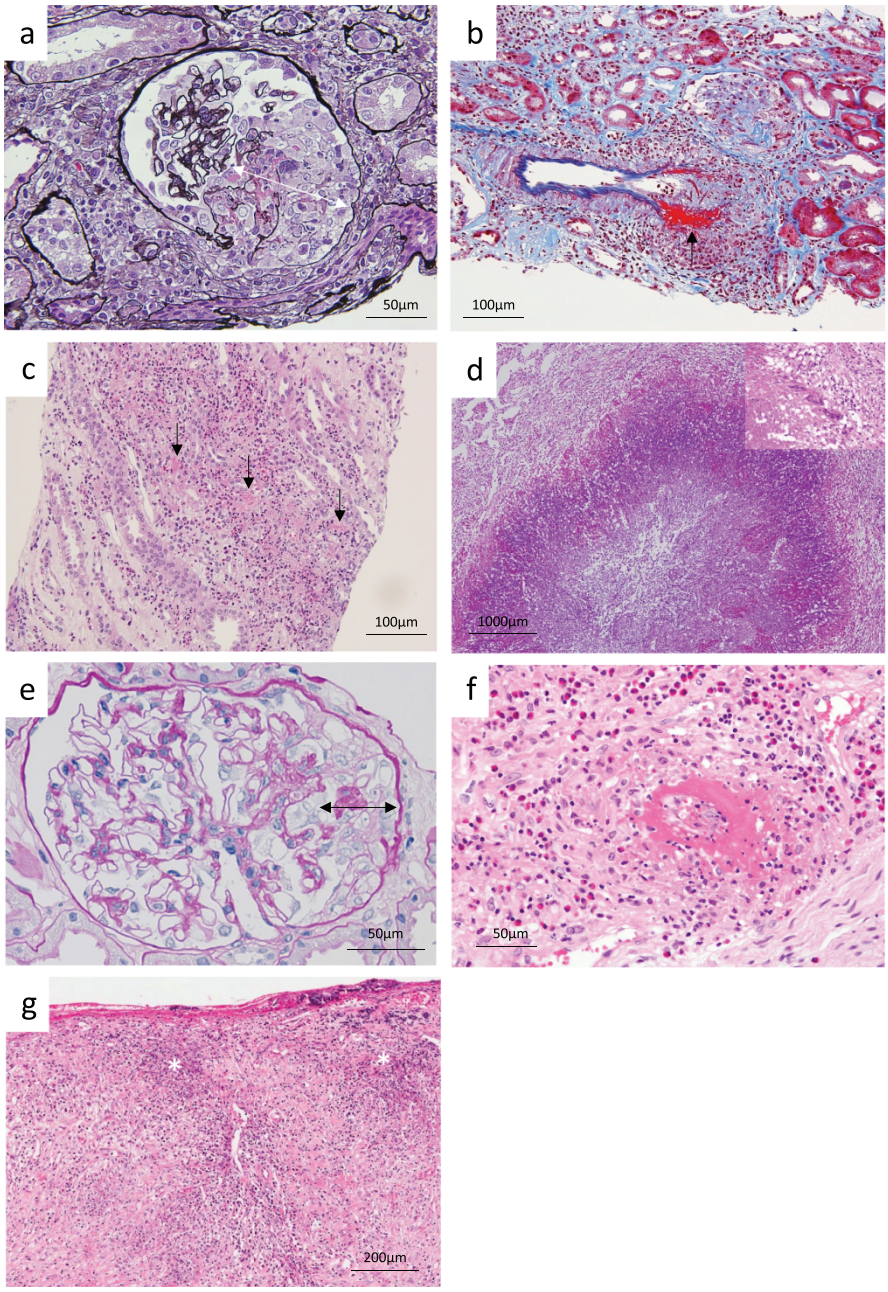

Figure 3. ANCA-associated small-vessel vasculitis.

(a) MPA of the glomerulus [periodic acid methenamine silver–HE staining]. NCGN. The double-headed arrow indicates the formed cellular crescent. (b) MPA of the kidney (elastic Masson staining). Necrotizing arteritis of the interlobular artery (arrow). (c) MPA of the kidney (HE staining). Neutrophil infiltration and erythrocyte extravasation are observed around the capillaries in the medulla. Deposition of fibrin-like eosinophilic substances is seen in some parts of the interstitium (arrows), suggesting medullary angiitis (peritubular capillaritis). (d) GPA of the lung (HE staining). Necrotizing granulomas with infiltration of inflammatory cells, including lymphocytes, histiocytes, and neutrophils. Multinucleated giant cells are found against the background of infiltration of a wide variety of inflammatory cells (inset: high-power field of view). (e) GPA of the glomerulus (PAS staining). NCGN. The double-headed arrow indicates the formed cellular crescent. (f) EGPA of the liver (HE staining). Damaged vascular walls show fibrinoid necrosis with infiltration of many eosinophils. (g) Hypertrophic pachymeningitis in ANCA-associated vasculitis (the dura mater; HE staining). Microabscess-like cell infiltration foci composed of mononuclear cells, neutrophils, and histiocytes are seen (asterisks).

eosinophilic material is seen in some parts of the interstitium, suggesting medullary angiitis (peritubular capillaritis; Figure 3(c)).

Granulomatosis with polyangiitis

Granulomatosis with polyangiitis (GPA) shows necrotizing granulomas in the upper and lower respiratory tracts and necrotizing granulomatous vasculitis in systemic small vessels, with a predilection for patients in their 60s [16]. In Japan, there is an almost equal prevalence of MPO-ANCA and PR3-ANCA in GPA [15]. Necrotizing granulomas are formed in the upper and lower respiratory tracts (Figure 3(d)). Infiltration of inflammatory cells, such as lymphocytes, histiocytes, and neutrophils, is observed around the area of necrosis. A palisade arrangement of epithelioid cells surrounding the necrotic lesion is a characteristic feature of this condition. Multinucleated giant cells are found against the background

of infiltration of a wide variety of inflammatory cells. Small vessels involved in the granuloma sometimes exhibit vasculitic features. NCGN is seen in affected glomeruli (Figure 3(e)). No significant deposition of immunoglobulin or complements is identified in the immunofluorescent analysis, suggesting a pauci-immune type.

Eosinophilic granulomatosis with polyangiitis

Eosinophilic GPA (EGPA) is a systemic necrotizing granulomatous vasculitis associated with allergic symptoms, such as bronchial asthma and eosinophilia, with a peak incidence in patients in their 50s [17]. About half of EGPA patients are positive for MPO-ANCA, but others do not possess ANCA [15]. Necrotizing vasculitis is observed in vessels, ranging from small- and medium-sized muscular arteries to arterioles, capillaries, and venules. Damaged vascular walls show eosinophilic necrosis with infiltration of many eosinophils and deposition of granular components of eosinophils around the necrosis (Figure 3(f)). The presence of extravascular granulomas with eosinophilic infiltration is a characteristic feature of this disease. Although extravascular granulomas are identified in the connective tissue interstitium of the whole body, including the skin and the heart, their frequency is not necessarily high.

Hypertrophic pachymeningitis in ANCA-associated vasculitis

Some patients with ANCA-associated vasculitis develop hypertrophic pachymeningitis [18]. A markedly thickened dura mater is seen with microabscess-like cell infiltration, fibrosis, and erythrocyte leakage. Infiltrating cells are composed of mononuclear cells, neutrophils, and histiocytes (Figure 3(g)). Immunostaining with anti-immunoglobulin G4 (IgG4) antibody shows no significant positive findings.

Immune complex small-vessel vasculitis

Anti-glomerular basement membrane disease

Anti-glomerular basement membrane (anti-GBM) disease is an organ-specific autoimmune disorder characterized by diffuse NCGN and pulmonary haemorrhage with the production of anti-GBM antibody [19]. Renal biopsy specimens often show diffuse global crescent formation (Figure 4(a)), and the clinical course of renal dysfunction is usually rapid and progressive. Many erythrocytes are seen in the renal tubules. Intratubular erythrocytes are often observed in diseases in which basement membranes are broken, such as this anti-GBM disease, resulting in obvious glomerular haematuria. Immunofluorescent analysis typically shows IgG deposition in linear arrays along the glomerular capillary loops (Figure 4(b)). Fragmented positive findings are seen in the remaining basement membrane in the glomerulus, which is almost entirely replaced with crescents.

Cryoglobulinemic vasculitis

In this disease, aggregated cryoglobulins are deposited in small-vessel walls [20]. Renal biopsy specimens demonstrate intraluminal cell proliferation in the glomerulus and periodic acid–Schiff (PAS)-positive hyaline thrombi are seen segmentally in the lumen (Figure 4(c)). Eosinophilic hyaline thrombi that occupy interstitial arterioles are sometimes observed (Figure 4(d)).

IgA vasculitis

IgA vasculitis is a systemic disease that results from the entrapment of circulating IgA-containing immune complexes in the walls of small vessels in the skin, kidneys, and gastrointestinal tract [21]. Biopsy specimens of skin purpura show inflammatory cell infiltration mainly composed of polymorphonuclear leucocytes with karyorrhexis around small vessels, including small arteries, arterioles, and capillaries, representing leucocytoclastic vasculitis. IgA deposition is sometimes observed in the damaged vascular walls under immunofluorescent staining. Multiple necrotizing vasculitis is found in small vessels. Fibrinoid necrosis and the disruption and loss of the elastic layer are observed in the vascular wall. Infiltrating inflammatory cells include neutrophils, eosinophils, and lymphocytes (Figure 4(e)). The focal and segmental proliferation of mesangial and endothelial cells is observed in glomeruli. Diffuse cell proliferation, crescent formation, adhesion of glomerular capillaries to the Bowman's capsule, glomerulosclerosis, and necrosis become apparent with disease progression. Deposition of IgA, C3 and the downstream complement components is observed mainly in mesangial cells under immunofluorescent staining (Figure 4(f)).

Hypocomplementemic urticarial vasculitis

Hypocomplementemic urticarial vasculitis shows urticaria-like erythema that persists longer than urticaria, purpura, and pigmentation [22]. Patients feel a burning sensation with itching. Histopathological findings do not always reveal typical leucocytoclastic vasculitis because urticaria-like rashes cause oedema in the upper dermis. Deposition of immunoglobulins and complements is observed in the vascular wall using direct immunofluorescence of biopsied skin sections, suggesting immune complex-mediated vasculitis (Supplementary Table S1).

Variable-vessel vasculitis

Behçet's disease

Vasculitis affecting various-sized vessels occurs in patients with Behçet's disease [23]. This disease is characterized by recurrent oral and genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, and central nervous system (CNS) inflammatory lesions. Small-vessel vasculitis, arteritis, arterial aneurysms, and venous and arterial thromboangiitis may occur. Marked neutrophil infiltration with necrosis in the adventitia of small vessels suggests small-vessel necrotizing vasculitis (Supplementary Table S1).

Cogan's syndrome

The pathological basis of Cogan's syndrome is vasculitis with ophthalmic manifestations of interstitial keratitis and uveitis and otological manifestations of sensorineural hearing loss, tinnitus, and vertigo [24]. Various-sized arteries, including the aorta and medium- and small-sized arteries, are damaged. Aortic aneurysm and inflammation of the aortic and mitral valves are sometimes present (Supplementary Table S1).

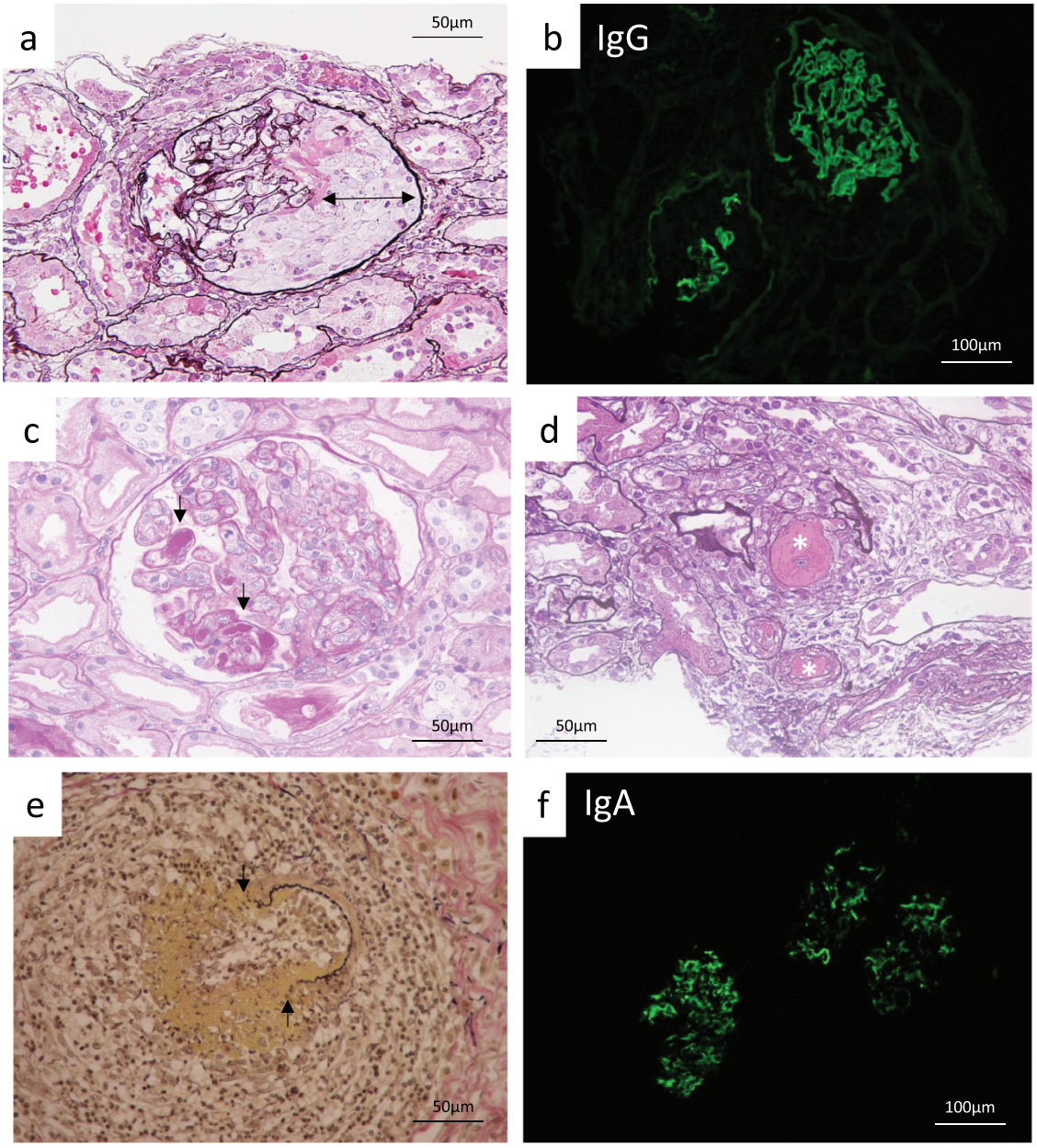

Figure 4. Immune complex small-vessel vasculitis.

(a) Anti-GBM disease of the glomerulus [periodic acid methenamine silver (PAM)–HE staining]. NCGN. The double-headed arrow indicates the formed cellular crescent. (b) Anti-GBM disease of the glomerulus (immunofluorescent staining for IgG). IgG deposition in linear arrays along the glomerular capillary loops. (c) Cryoglobulinemic vasculitis of the glomerulus (PAS staining). PAS-positive hyaline thrombi (arrows). (d) Cryoglobulinemic vasculitis of the kidney (PAM–HE staining). Hyaline thrombi that occupy interstitial arterioles (asterisks). (e) IgA vasculitis of the stomach (EVG staining). Disruption and loss of the elastic layer (arrows). (f) IgA vasculitis of the kidney (immunofluorescent staining for IgA). IgA deposition in the mesangium.

Single-organ vasculitis

Cutaneous leucocytoclastic angiitis

Cutaneous leucocytoclastic angiitis forms limited lesions in the skin [25]. The disorder manifests as small papular purpura, so-called palpable purpura, similar to IgA vasculitis, in the lower extremities. Subsequently, the lesions become plaque-like gangrenous lesions, nodules and purpura with skin necrosis, and skin ulcers. Although affected vessels confirmed by skin biopsy are usually small vessels, such as venules in all layers of the dermis, small-vessel vasculitis in the subcutaneous tissue is occasionally observed. Small-vessel vasculitis mainly with neutrophil infiltration with nuclear dust around the vessels is a typical feature of this disease (Figure 5(a)). Fibrinoid degeneration is also sometimes observed in the vessel wall. Direct immunofluorescence findings of skin biopsy specimens reveal the deposition of IgG, IgM, and C3, but not IgA, in the affected small-vessel walls in the dermis. Based on these findings, this disease is considered Coombs' type III allergic reaction, an immune complex reaction. Vascular impairment due to the migration of polymorphonuclear leucocytes to the vessel wall, lysosomes, and reactive oxygen species is thought to be involved.

Cutaneous arteritis

Cutaneous arteritis (CA) is vasculitis localized in the skin with no lesion in other organs, although histopathological findings

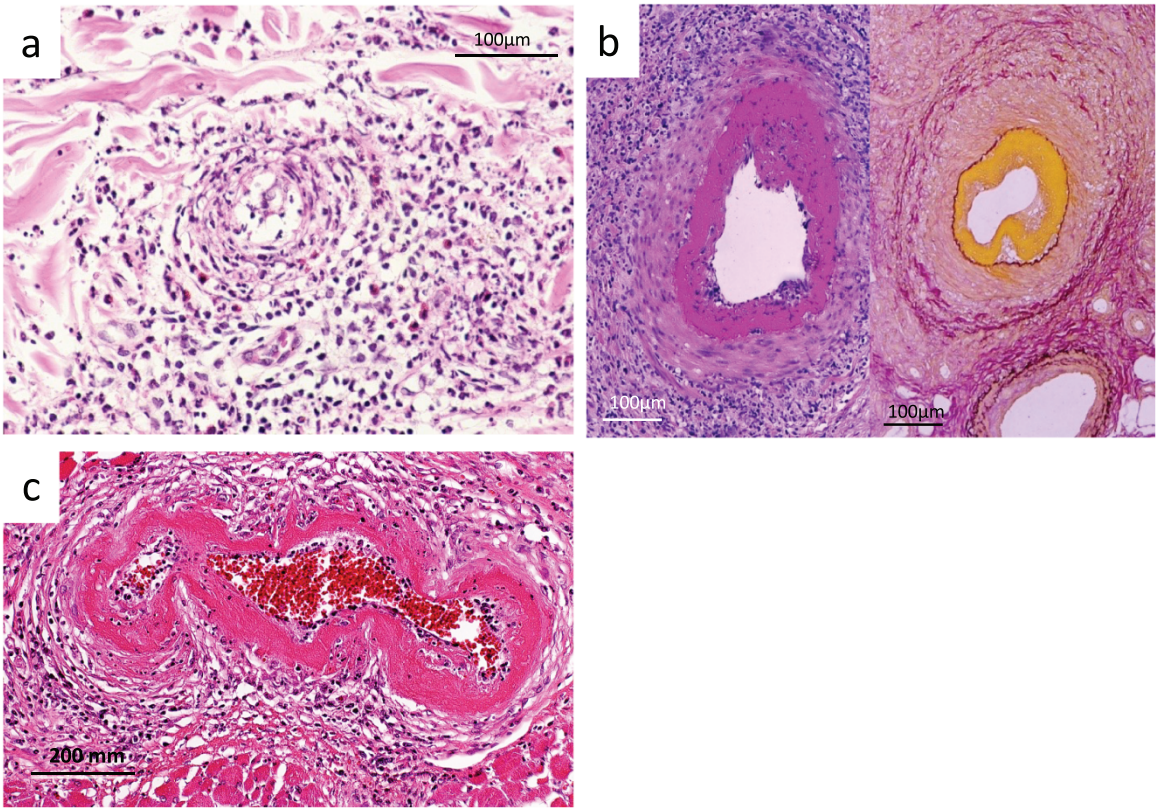

Figure 5. Other vasculitis.

(a) Cutaneous leucocytoclastic angiitis (HE staining). Small-vessel vasculitis with neutrophil infiltration with nuclear dust. (b) CA [HE staining (left) and EVG staining (right)]. Small arteries in the deep layer of the dermis or subcutaneous tissue are affected similarly to PAN. (c) Lupus vasculitis (HE staining). Necrotizing vasculitis.

of skin biopsy specimens are similar to PAN [25]. Skin symptoms include nodules (subcutaneous nodules), livedo, ulcers, and gangrene. Purpura, papules, white atrophy, and oedema have also been reported. Nodules occur in 90–100% of the cases and livedo occurs in 55–80% of the cases, and they occur most frequently in the lower extremities. The nodules are usually 1 cm or less in diameter, multiple, red or dark reddish-purple, and associated with spontaneous pain and tenderness. Small arteries in the deep layer of the dermis or the subcutaneous tissue are affected, as with PAN (Figure 5(b)). The disease is classified into four stages by Arkin: (1) degenerative stage, (2) acute inflammatory stage, (3) granulation tissue stage, and (4) healed granulation tissue stage [8]. Fibrinoid degeneration is present in the degeneration stage, and inflammatory cell infiltration mainly composed of neutrophils, bleeding, and disruption of the external elastic lamina is observed in addition to fibrinoid degeneration in the acute inflammatory stage. In the granulation tissue stage and healed granulation tissue stage, lymphocytes and macrophages become predominant, and thrombus and granulomatous changes are observed. The IEL is usually unaffected in CA. Deposition of immunoglobulins and complements on the affected vessel wall is only infrequently seen.

Primary CNS vasculitis

The diagnosis of primary CNS vasculitis (PCNSV) requires determining that CNS vasculitis is not a component of a systemic vasculitis, caused by infection, or associated with a systemic disease. The diagnosis is made according to Birnbaum's criteria [26]. Vasculitis is localized in small- and medium-sized meningeal and cortical vessels (Supplementary Table S1). PCNSV is pathologically classified into the following three types: (1) granulomatous vasculitis (58%) sometimes related to amyloid-β deposition, (2) lymphocytic vasculitis (28%), and (3) necrotizing vasculitis (14%).

Isolated aortitis

The presence of isolated aortitis is very difficult to determine [27]. Because there is no specific biomarker for TAK or GCA, it is impossible to know if isolated aortitis is a limited expression of TAK or GCA.

Vasculitis associated with systemic disease

Lupus vasculitis

Vascular lesions in systemic lupus erythematosus (SLE) are classified into three categories: (1) arteriosclerotic, (2) thrombotic, and (3) inflammatory types. In most cases, lesions are likely to manifest more than one category [28]. Histopathological findings in the inflammatory category generally include necrotizing vasculitis, arterial intimal thickening, and leucocytoclastic vasculitis (Figure 5(c)).

Rheumatoid vasculitis

Arteritis similar to PAN is present in most vasculitis associated with rheumatoid arthritis [29]. Small-sized arteries are slightly more likely to be damaged in rheumatoid vasculitis as

compared with PAN. Intrarenal arteries are not so affected, unlike in PAN (Supplementary Table S1).

Sarcoid vasculitis

Sarcoid granulomas (noncaseating granulomas in which the central part is composed of epidermoid cells and multinucleated giant cells with surrounding lymphocytes, macrophages, and fibroblasts) are often found around the pulmonary vessels. However, sarcoid vasculitis is a condition in which sarcoid granulomas involve the vascular wall, resulting in the destruction of vascular wall components such as the external elastic lamina and smooth muscle in the media (Supplementary Table S1) [30].

Vasculitis associated with probable aetiology

Hepatitis C virus-associated cryoglobulinemic vasculitis

After infection with hepatitis C virus, mixed type II cryoglobulin appears, which is deposited on arterioles and small arteries, causing vasculitis [31]. Electron microscopy reveals deposits typically with a cylinder-shaped structure (Supplementary Table S1).

Hepatitis B virus-associated vasculitis

PAN-like necrotizing arteritis sometimes develops with hepatitis B virus infection [31].

Syphilis-associated aortitis

Aortitis develops in patients infected with *Treponema pallidum* [32]. Infiltration of lymphocytes and plasma cells is mainly seen in the vasa vasorum of the adventitia. Patchy loss of elastic fibres and smooth muscle cells (SMCs) and scarring are found in the media (Supplementary Table S1).

Drug-associated immune complex vasculitis

Immune complex-mediated small-vessel vasculitis occurs in drug-induced SLE patients [33].

Drug-associated ANCA-associated vasculitis

Drug-associated ANCA-associated vasculitis is a new category of vasculitis introduced in the CHCC2012 [2]. MPO-ANCA appears to induce vasculitis in association with the use of the following drugs: (1) antithyroid drugs (propylthiouracil, benzylthiouracil, and methimazole), (2) antibiotics (minocycline, cefotaxime, nitrofurantoin, and garenoxacin), (3) immunosuppressants (D-penicillamine), (4) vasodilators (hydralazine), (5) antiarrhythmics (procainamide), (6) antihyperuricemics (allopurinol), (7) antiparasitics (levamisole), (8) antiepileptics (phenytoin), and (9) antirheumatics (sulfasalazine). The pathological feature of this condition resembles MPA (Supplementary Table S1). Vasculitis usually improves after discontinuation of the causative drug. Drug-induced inhibition of the degradation of neutrophil extracellular traps (NETs) may be involved in its mechanism of pathogenesis [34].

Cancer-associated vasculitis

Cancer-bearing patients sometimes develop cutaneous leucocytoclastic angiitis. The following criteria are required for the diagnosis of cancer-associated vasculitis: (1) vasculitis occurs within 1 year after the onset of cancer, (2) the condition of vasculitis is in conformity with that of cancer, and (3) drug- and infection-associated vasculitis can be completely excluded. Immune complexes are considered to be involved in this vasculitis [35]. Cancer-associated vasculitis is often seen with haematological cancers but rarely with solid cancers (Supplementary Table S1).

Vasculitis-related diseases and non-inflammatory vasculopathy not mentioned in the CHCC2012

Buerger's disease

This disease, also called thromboangiitis obliterans, is closely associated with smoking [36]. In the acute phase, inflammatory arterial thrombosis with microabscesses and granulomas is present. More neovascularization and cellular components are found in Buerger's disease than in usual non-inflammatory thrombosis. In the chronic phase, fibrous occlusion of vessels is observed. The IEL is intact or slightly damaged throughout the disease course (Supplementary Table S2).

Inflammatory abdominal aortic aneurysm

Marked fibrosis with mononuclear cell infiltration and lymphoid follicle formation occurs around an abdominal aortic aneurysm [37] (Figure 6(a)). Inflammatory abdominal aortic aneurysm (IAAA) is shown in some cases as an IgG4-related disease [38].

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is included in thrombotic microangiopathy and is caused by the loss or deficiency of the activity of a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13, a von Willebrand factor cleaving enzyme [39]. A common histological finding is small-artery thrombosis in organs throughout the body, such as the heart, the CNS, and kidneys (Figure 6(b)).

Antiphospholipid syndrome

Thrombus formation in arteries and veins is the primary histological finding of antiphospholipid syndrome (APS) [40]. The CNS and the placenta are the most common sites of thrombosis, although thrombosis can occur in various organs and tissues throughout the body. Thrombus-induced ischaemic enteritis often occurs in the gastrointestinal tract (Figure 6(c)).

Segmental arterial mediolysis

Segmental arterial mediolysis is a non-inflammatory disease involving arteries of internal organs and rarely coronary arteries. Vacuolation and mucinous degeneration of the arterial media are typical features of this condition [41]. Bleeding and dissection of the arterial wall and thrombosis are also observed. Arterial lesions begin with the cytoplasmic vacuolar degeneration of SMCs. Subsequently, fused vacuoles destroy the cell membrane, resulting in the lysis of the media. Bleeding within the arterial wall and fibrin deposition around the adventitia are also present. Transmural lesions create gaps in the arterial wall, which cause dissection and destruction of the arterial wall, resulting in major bleeding (Supplementary Table S2).

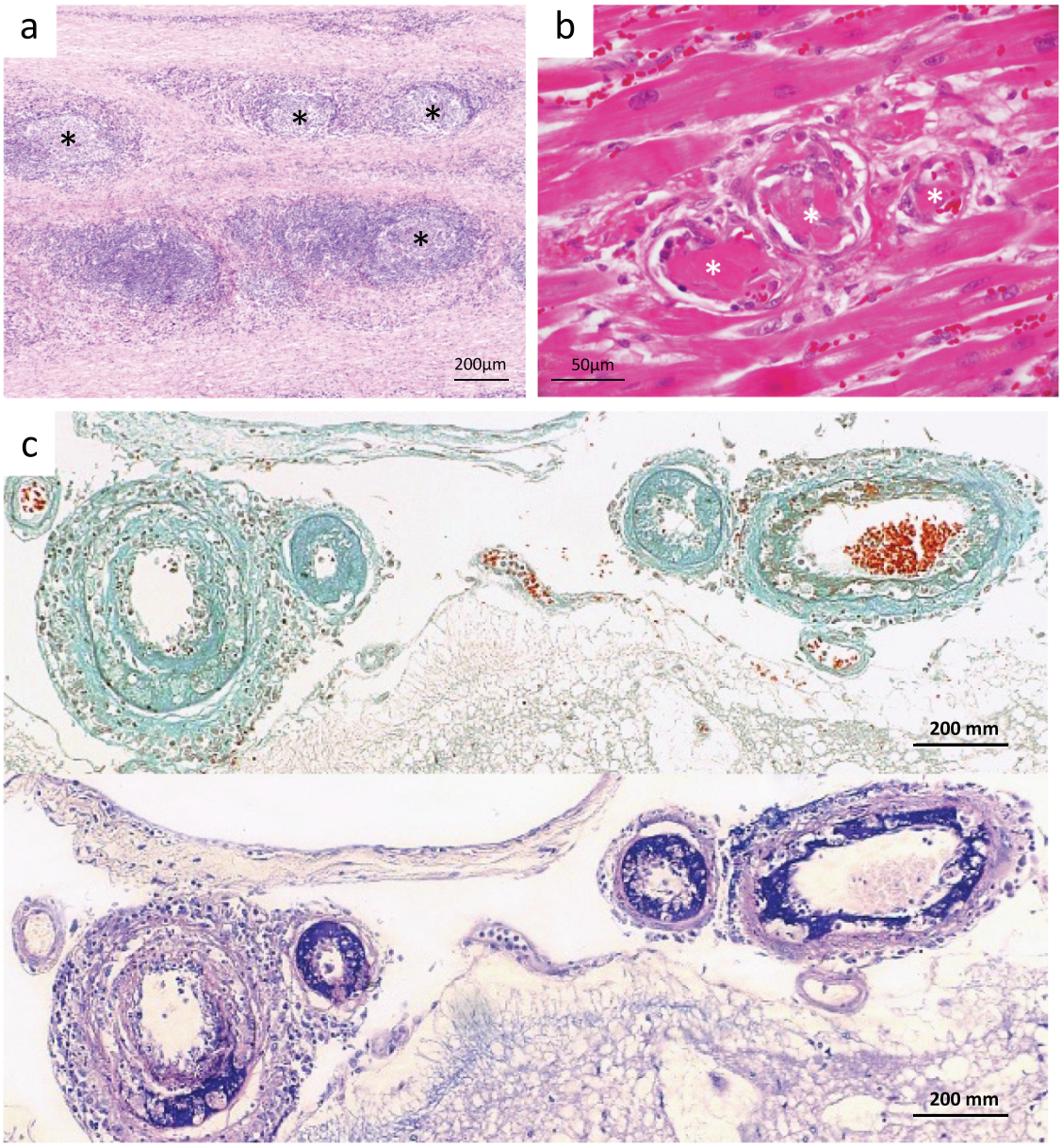

Figure 6. Vasculitis-related diseases.

(a) IAAA (HE staining). Marked fibrosis with mononuclear cell infiltration and lymphoid follicle formation (asterisks) around an abdominal aortic aneurysm. (b) TTP of the heart (HE staining). Thrombus in a small artery (asterisks). (c) Ischaemic enteritis based on APS (top, elastic Masson staining; bottom, PTAH staining). Fibrinoid necrosis is observed in PTAH staining.

Fibromuscular dysplasia

Fibromuscular dysplasia occurs most commonly in young women and affects most frequently the renal artery, followed by the internal carotid artery, visceral arteries, and very rarely the coronary artery. The vascular wall is irregular with a wavy (concave and convex) deformation [42, 43]. This deformation is observed most clearly or only in longitudinal sections of the affected vessel. Histologically, it is characterized by the abnormal proliferation of SMCs and fibrous tissue that often affect segmentally in the media of the small and medium-sized arteries (Supplementary Table S2).

Discussion

Although the CHCC2012 classification is easy to understand and is useful for organizing knowledge of vasculitis [2], diseases should be classified based on their pathogenesis ideally. However, the pathogenesis for most vasculitis has yet to be discovered, whereas breakthroughs have been made regarding limited types of vasculitis in recent years. For example, the pathogenicity of autoantibodies, such as ANCA and anti-GBM antibody, has been determined [44–46], and the discovery of the implication of NETs in ANCA-associated vasculitis has brought remarkable progress in understanding the pathogenesis of these diseases [47, 48]. Despite this recent progress,

further studies are needed before vasculitis can be classified according to the underlying pathogenesis.

The following pathological issues remain unsolved: (1) differentiating between TAK and GCA in the characteristics of their aortic lesions and (2) differentiating between PAN and CA in the characteristics of their skin lesions. The Clinical Pathology Group of the JPVAS has collected specimens of aortic lesions from GCA patients in whom GCA was diagnosed by biopsy of the temporal artery. A study comparing these to aortic lesions from patients with TAK is now ongoing, and it has been noted that the distribution of inflammation in the aortic wall may be distinct between the two. In contrast, a differential diagnosis between PAN and CA is made by careful observations of the clinical course because it is difficult to distinguish them from pathological findings. However, the application of artificial intelligence (AI) to pathological diagnosis has progressed rapidly, and its effectiveness has been recognized [49]. AI may be able to distinguish between them even if humans cannot discern any difference.

This review presented representative pathological findings of vasculitis and vasculitis-related diseases. This will be useful for clinicians to refer for typical pathological findings of vasculitis in daily practice.

Supplementary data

Supplementary data are available at *Modern Rheumatology* online.

Conflict of interest

None declared.

Funding

This project was supported by a grant from the Ministry of Health, Labour and Welfare of Japan to the Japan Research Committee of the Ministry of Health, Labour and Welfare for Intractable Vasculitis (20FC1044 and H29-nanchitou (nan)-ippan-018).

Data availability

The datasets gathered during the preparation of this manuscript are available from the corresponding author on reasonable request.

Authors' contributions

A.I., T.K., H.K., K.T., T.M., E.I., T.O., Y.O., M.O., M.K., D.N., and E.M. wrote the manuscript. M.H. supervised the project. All authors read the final version of the manuscript and provided critical feedback.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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