Vascular Lung Diseases 11

Here we will discuss infarct and thromboembolic disease, vasculitis, vascular malformations, and pulmonary hypertension. Vascular tumors have already been discussed.

11.1 Infarct and Thromboembolic Disease

Thromboembolism is a frequent event in older patients. Often the underlying disease is chronic heart failure with venous congestion. Thrombi are formed in the lower extremities but also in the pelvic region and give rise to emboli. Large emboli will get stuck in the large pulmonary arteries and cause sudden death with the symptoms similar to cardiac infarct. Smaller emboli might be pressed into smaller arteries and get stuck there. These emboli will cause a hemorrhagic infarct by occlusion of a pulmonary artery and retrograde influx of blood from the venous side as well as from bronchial arteries. Since the lung has a double system of blood flow, bronchial and pulmonary system ischemic infarcts do not occur – there is one exception, ischemic infarct in vasculitis.

11.1.1 Gross Examination and Histology

An infarct has a cuneiform appearance, the broad side is at the periphery, and the tip is where the artery is occluded. On cut surface the infarct is dark red with a hemorrhagic dark blue-red border. The consistency is firm.

On histology, the center of the infarct has lost staining of the cells (no nuclei visible), and the cells appear like ghost cells; however, the alveolar structure is still visible (Fig. 11.1). If the infarct is older, an inflammatory granulation tissue develops (usually a type of organizing pneumonia), which slowly will organize the infarct and replace it with scar tissue. Even as scar the cuneiform figure will remain. At the border of the infarct, numerous hemosiderin-laden macrophages will appear. Elastic stains can easily highlight obstructed arteries. Typically there are thick-walled arteries in the vicinity of the infarct, probably reflecting increased vascular pressure.

11.2 Vasculitis

11.2.1 Classification of Vasculitis

According to the Chapel Hill classification, there is primary systemic vasculitis and secondary (most often infection associated) vasculitis, and there is large medium and small vessel vasculitis [1]; the affection of arteries and veins is not further acknowledged. In this last update of the primary 1994 classification, changes were made such as granulomatosis with polyangiitis instead of Wegener's granulomatosis and eosinophilic granulomatosis with polyangiitis instead of

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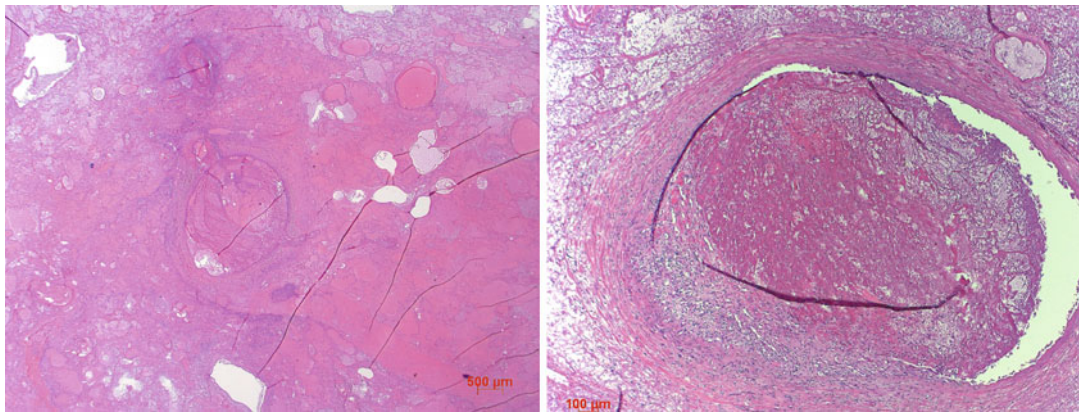
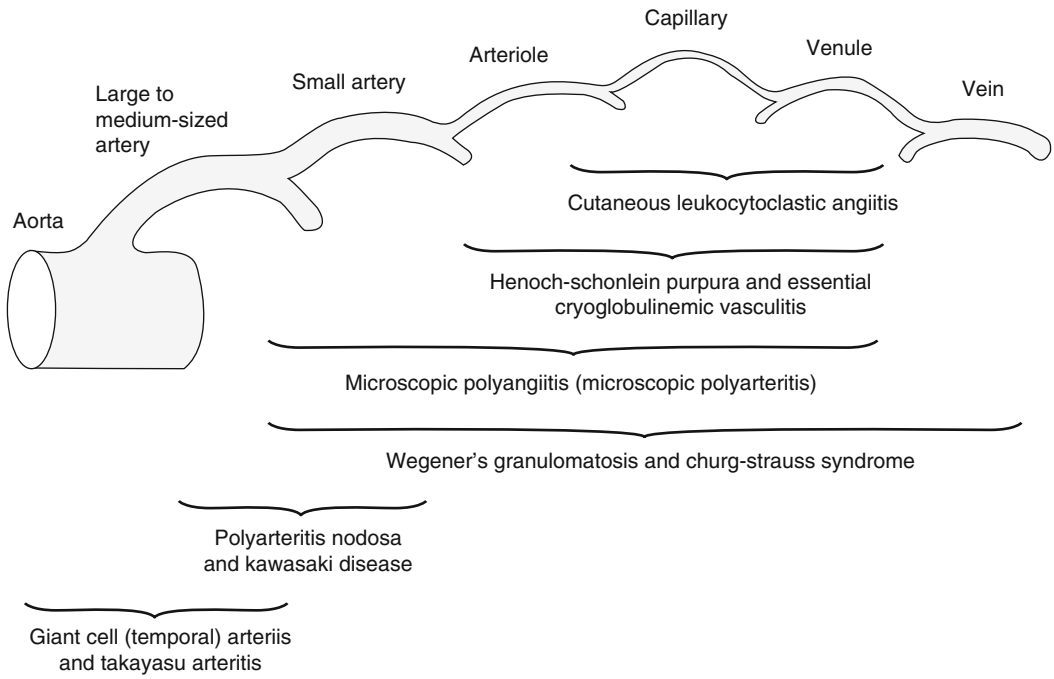


Fig. 11.1 Hemorrhagic infarct, left the infarct is seen with hemorrhage and the occluded artery, to the right an artery with a thromboembolus is shown, the embolus is already undergoing organization by granulation tissue. H&E, bars 500 and 100 µm

Churg-Strauss vasculitis. In addition, categories for variable vessel vasculitis and secondary forms of vasculitis were added. The lung is affected by a few variants of primary systemic vasculitis, which are discussed here. Secondary vasculitis will not extensively be discussed.

Schema of the classification of vasculitides according to the 1994 Chapel Hill classification: Vasculitides are grouped according to the size of the affected vessels; this classification was modified in 2012; however, the involvement of vessels is still the basis of the updated classification.

Jennette, Falk, et al., *Arthritis & Rheumatism*



11.2.2 Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA), formerly called *Wegener's granulomatosis*, affects medium to small arteries, arterioles, capillaries, venules, and small- to medium-sized veins. There are three main organ systems involved: mucosa of the upper airways, lungs, and kidneys. In some patients, only one organ system, in other patients two organ systems, and in some patients all three systems can be affected.

The vasculitis will cause vascular obstruction followed by occlusion, which finally will cause ischemic infarct if the vessel is large enough.

11.2.2.1 Clinical and Radiological Findings

Patients present with hemoptysis, fever may be seen, on serum examination antineutrophil cytoplasmic antibodies (ANCA) may be present; antibodies are a sign of the underlying vasculitis. Examination of ANCA antibodies will show more common anti-proteinase 3 (PR3) [2]. On X-ray and CT scan, classical GPA will show infarct with less dense center parts (Fig. 11.2). Several infarcts can be present. If only small vessels are affected, the CT scan is less characteristic with diffuse interstitial infiltrates. Usually both lungs are involved. In these cases hemoptysis will be more pronounced, and on BAL alveolar hemorrhage will be diagnosed.

For a clinical diagnosis, the following features are required: histopathological evidence of granulomatous inflammation, upper airway involvement, laryngo-tracheo-bronchial involvement, pulmonary involvement (X-ray/CT), antineutrophilic cytoplasmic antibody positivity, and renal involvement [3].

11.2.2.2 Gross Examination

If infarcts are present, these will have a similar cuneiform appearance as in hemorrhagic infarct; however, the cut surface is yellowish white with a hemorrhagic border. If only small vessels are involved, the cut surface shows hemorrhage without any further characteristics (Fig. 11.3).

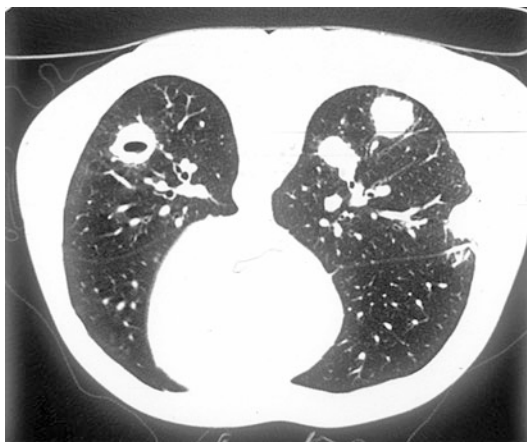


Fig. 11.2 Granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), in this CT scan there are nodular densities one of them with central necrosis, a typical finding in this disease

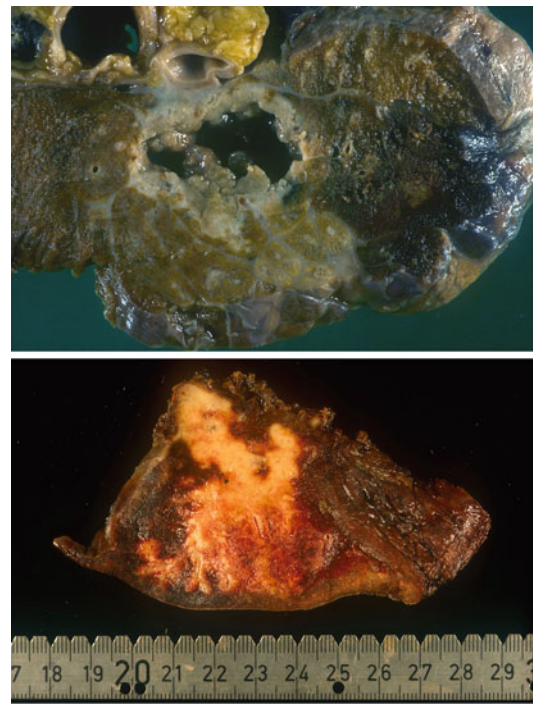


Fig. 11.3 GPA, macroscopic features of a case with large central necrosis (*upper panel*) and another case with ischemic infarct (*lower panel*)

11.2.2.3 Histology

The vasculitis is characterized by a destructive infiltration of the vessel wall by neutrophils, rarely also by eosinophils (Fig. 11.4). The vasculitis causes fibrinoid necrosis of the endothelium and bleeding, which depending on the size of the vessels can be focal or massive. The necrosis of endothelia is the most important sign of vasculitis, because in the differential diagnosis, transmigration of neutrophils in infections can be very prominent and therefore cannot be regarded as the proof of vasculitis. More often vasculitis causes thrombosis and vascular occlusion, which consequently lead to infarction and necrosis of the parenchyma. Since most often there is arterial occlusion, the infarcts are ischemic.

Epithelioid cell granulomas should be present in this new classification, as granulomatosis is now a requisite of the diagnosis (Fig. 11.5). Cases which present exclusively with vasculitis including those with capillaritis are now included into microscopic polyangiitis (see below).

In later stages, and under therapy, the neutrophils might be replaced by lymphocytes. In these cases, one has to exclude an infectious, mainly viral-induced secondary vasculitis (Fig. 11.6).

GPA usually presents with PR3 antibodies. ANCA testing nowadays is a routine in clinical practice. But be aware that ANCA can be negative in early stages of GPA, and ANCA can be positive in some infectious secondary vasculitis.

GPA can start with unspecific syndromes, even organizing pneumonia without vasculitis [4]; in these cases the patients should be observed until specific features will be present.

GPA patients will be treated primarily with corticosteroids; if non-responding, an immunosuppressive treatment with drugs like cyclophosphamide is the second choice.

11.2.2.4 Molecular Biology

GPA can be regarded as an autoimmune disease. ANCA directed against proteinase 3 (PR3) are preferentially associated with GPA. Anti-PR3 antibodies can activate neutrophils in vitro. A significant association of PR3-ANCA and HLA-DP and the genes encoding alpha-1 antitrypsin and PR3 have been found [2]. How these are associated with the production of autoantibodies is not understood. Lymphocytes are also involved in GPA, mainly lesional T cells, which exhibit pro-inflammatory properties and promote granuloma formation. Apart from T cells,

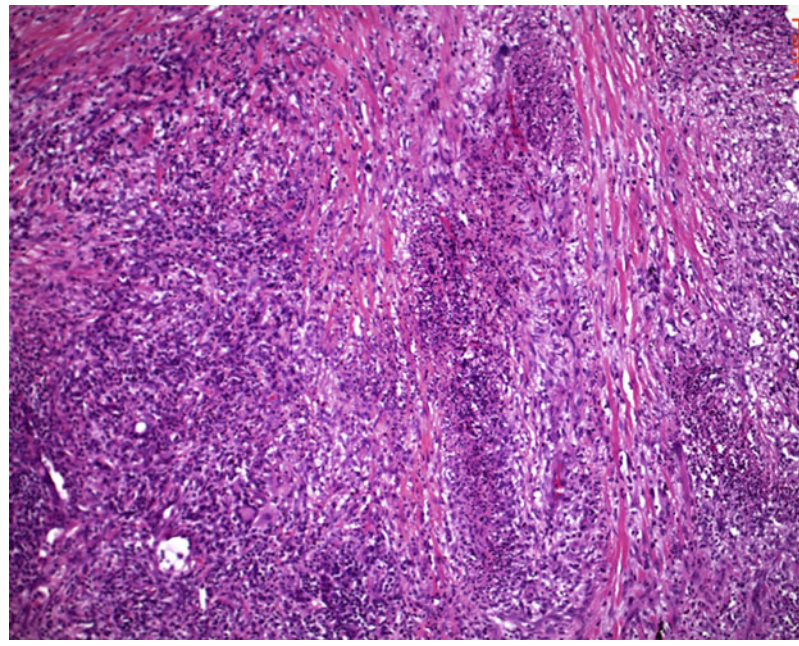


Fig. 11.4 Neutrophilic vasculitis in GPA. In the center a middle-sized artery is shown, which is completely destroyed by the infiltrating neutrophils. Some smaller arteries are seen right and lower left. On the left also an ill-formed epithelioid cell granuloma is visible. H&E, bar 100 µm

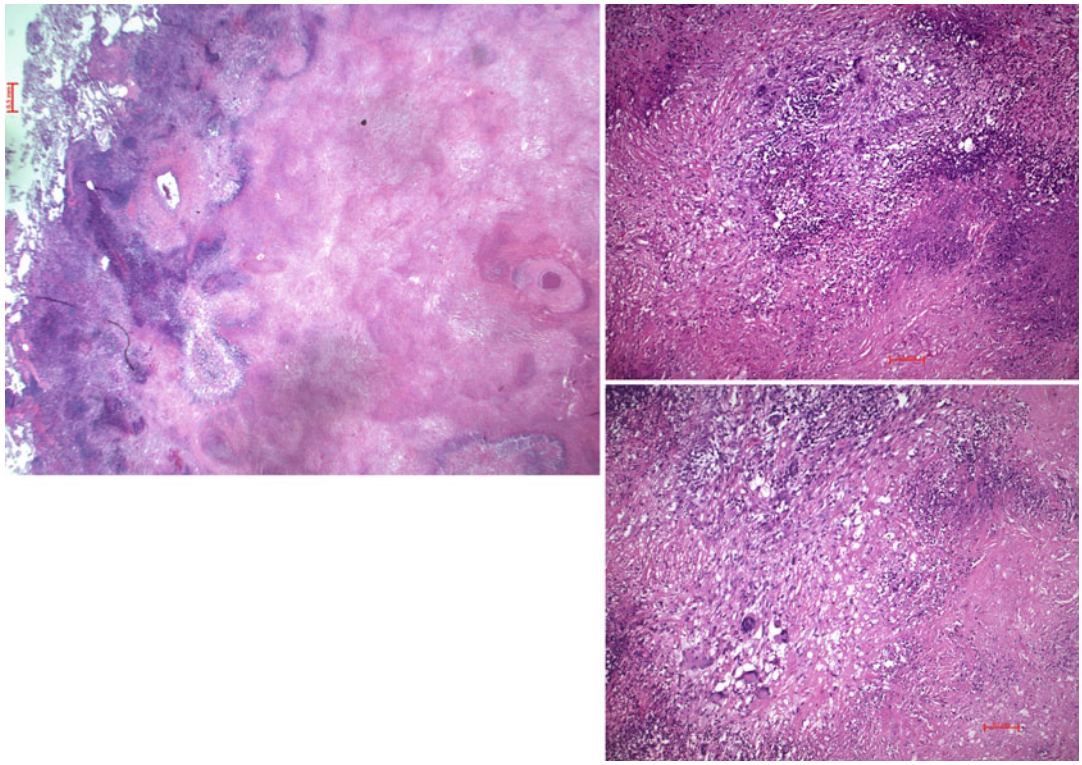


Fig. 11.5 GPA with a large ischemic infarct (*left*) and vasculitis with neutrophils as well as some epithelioid cell granulomas (*upper and lower right*). In both pictures also the edge of the infarct is visible. Granulomas in GPA are more loose, not as compact as in sarcoidosis or necrotizing sarcoid granulomatosis. H&E, bars 500 and 100 µm

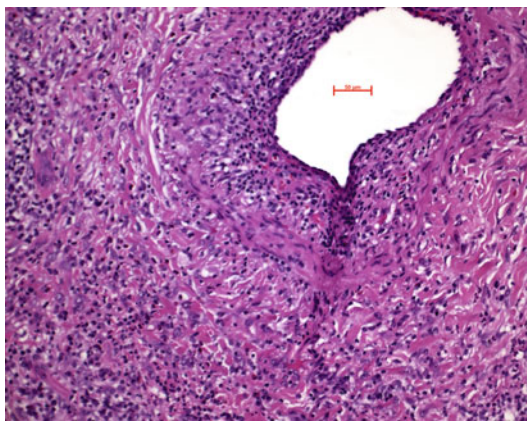


Fig. 11.6 Lymphocytic vasculitis in a case of GPA, the patient was already treated with high-dose corticosteroids. A few epithelioid cells and one giant cell can still be seen on the left. H&E, bar 50 µm

dendritic cells are abundantly present at the sites of inflammation and locally orchestrate the immune response [5].

11.2.3 Eosinophilic Granulomatosis with Polyangiitis (EGPA, Formerly Called Churg-Strauss Vasculitis)

11.2.3.1 Clinical Presentation

EGPA was first described in 1951 as a small- and medium-sized vessel vasculitis, characterized by an almost constant association with asthma and eosinophilia. Vasculitis typically develops in a previously asthmatic middle-aged patient. Asthma is severe, associated with eosinophilia and extrapulmonary symptoms. Some patients report allergic rhinitis without asthma. Most frequently EGPA involves the peripheral nerves and skin (allergic superficial eosinophilic vasculitis). Other organs such as the heart, kidney, and gastrointestinal tract, if affected, confer a poorer prognosis. In about 30–40 % of the patients, anti-myeloperoxidase (MPO) antineutrophil cytoplasm antibodies (ANCA) are present [2].

EGPA patients with anti-MPO ANCA suffered more, albeit not exclusively, from vasculitis symptoms, such as glomerulonephritis, mononeuritis multiplex, and alveolar hemorrhage, whereas ANCA-negative patients more frequently develop heart involvement [6, 7]. In recent time *EGPA* has been linked to new antiasthmatic drugs such as montelukast. However, new investigations have ruled out this as a possible cause of the disease [8].

Elevated IgG4 levels were found in active EGPA patients compared to controls. Serum IgG4 correlated with the number of eosinophils. During treatment and in disease remission, both IgG4 level and IgG4/IgG ratio dropped [9].

11.2.3.2 Radiology

The major findings at X-ray and CT scan are diffuse interstitial infiltrates; hemorrhage will be seen on CT scans (Fig. 11.7). If eosinophilic pneumonia is present, this will cause more density and focally also ground glass changes.

11.2.3.3 Gross Morphology

On cut surface, pneumonia (consolidations) and hemorrhage are the major, however, unspecific findings.

11.2.3.4 Histology

The hallmark is an eosinophilic vasculitis, again with destruction of the vessel wall and fibrinoid necrosis of the endothelium. Besides numerous eosinophils, also macrophages and histiocytes can be seen within these infiltrations. This causes focal bleeding if capillaries are affected and hemorrhage if larger vessels are involved. In older lesions or in patients under therapy, an eosinophilic infiltrate can persist up to 1 month, and hemosiderin-laden macrophages tell the story about previous bleeding. In florid cases there might be also an eosinophilic pneumonia with parenchymal necrosis. Granulomas are not associated with the vasculitis. In areas with parenchymal necrosis, a foreign body giant cell granulomatous reaction can be seen around the necrosis (Fig. 11.8).

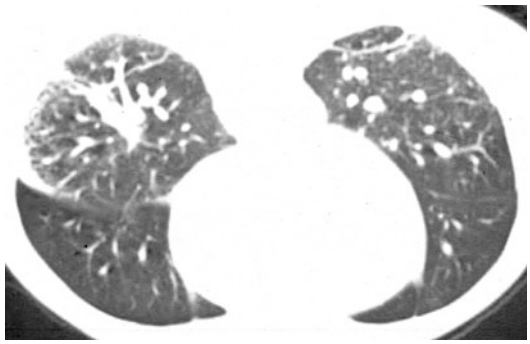


Fig. 11.7 CT scan of a case with eosinophilic granulomatosis with polyangiitis (EGPA). Note similar nodular densities, but usually there is no cavitation

11.2.3.5 Molecular Biology

A strong association with IL10 promoter polymorphisms was detected in EGPA. Other associations, including CTLA4, CD226, and copy number polymorphisms of FCGR3B need to be validated in further investigations [10].

11.2.3.6 Therapy

In most cases patients will respond to corticosteroid treatment, rarely an immunosuppressive therapy might be necessary. Encouraging results have been reported for the treatment of EGPA with rituximab or with the eosinophil-targeted antiinterleukin-5 agent mepolizumab [11].

The nomenclature remains a source of confusion: (1) Is vessel inflammation or the presence of ANCAs essential for the diagnosis of EGPA? (2) Are granulomas required for the diagnosis, and what type of granulomas should be seen? (3) Is eosinophilic pneumonia in EGPA another disease or just a variant? (4) Is hypereosinophilic syndrome a variant of EGPA?

As the understanding of the relation between the vasculitis and the eosinophilic proliferation is profoundly lacking, these questions so far cannot be answered.

11.2.4 Microscopic Polyangiitis

Microscopic polyangiitis (MPA) is a small vessel vasculitis, sometimes indistinguishable from GPA. Epithelioid cell granulomas and infarct-like necrosis are absent. In contrast to GPA, MPA is often limited to the lungs; however, it may

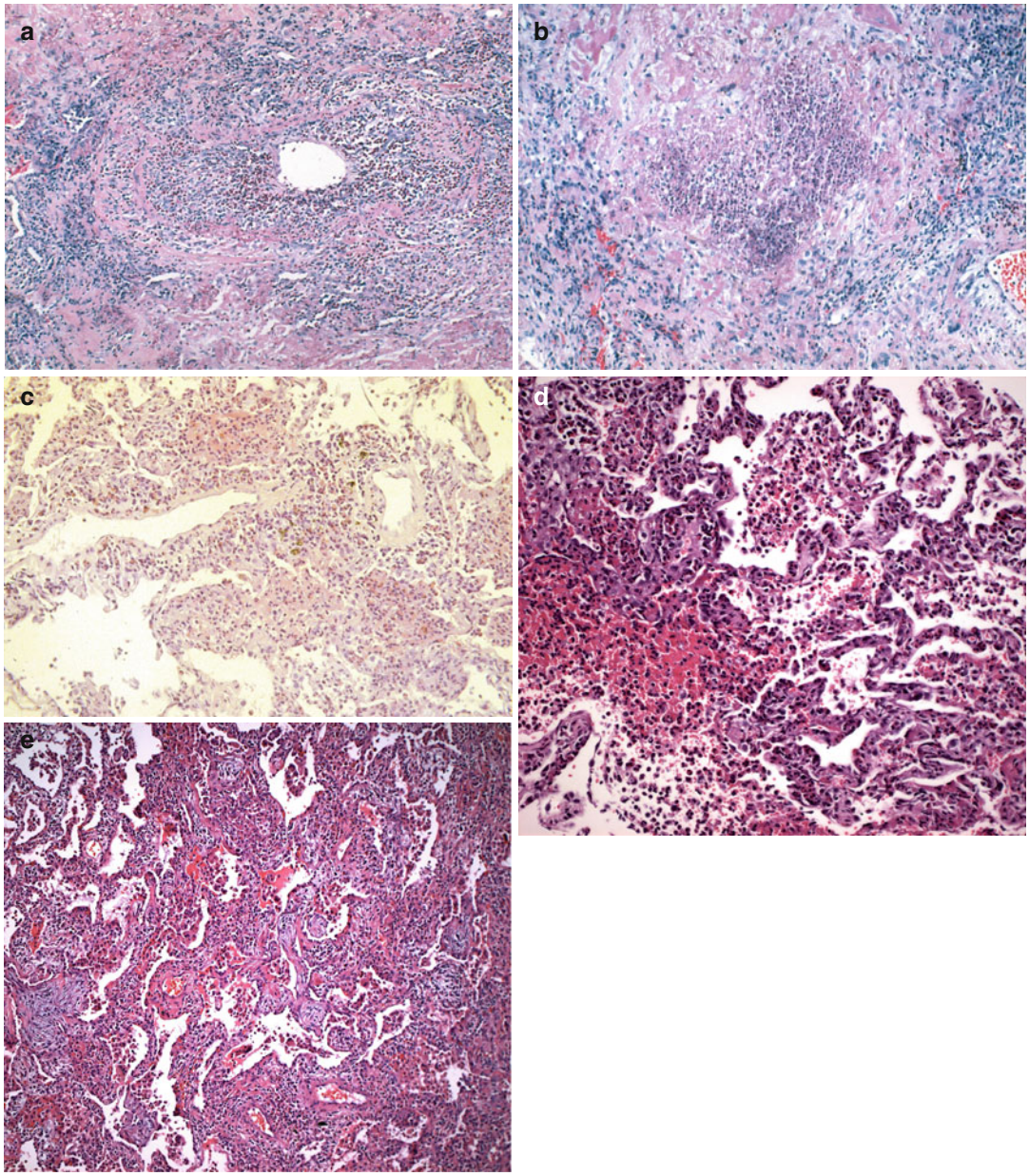


Fig. 11.8 EGPA illustrated with three cases. In (**a**) and (**b**) eosinophilic vasculitis is shown with a small necrotic focus and few scattered epithelioid and giant cells. In (**c**) a patient with EGPA was treated with corticosteroids for 2 weeks before the transbronchial biopsy was taken. This resulted that the vasculitis was no longer present (no endothelial necrosis, no infiltration of the vascular wall), but the eosinophilia could still be evaluated. In (**d**–**e**) an eosinophilic vasculitis is present, here predominantly as capillaritis. But there is also organizing pneumonia as a sign of a long-standing process with repair. H&E, ×50 and 100

involve the kidneys. Diffuse alveolar hemorrhage is most commonly seen in small vessel vasculitides, specifically MPA [12]. There is a wide variation of possible underlying diseases, but some might also be coincidentally associated with MPA. The most common are chronic airway diseases (CAD), where MPO-ANCA tended to be lower than in the non-CAD group. None of the patients in the CAD group had pulmonary hemorrhage or interstitial pneumonia. Also the outcome in the CAD group was better than in the non-CAD group [13].

There is also a geographic variance as MPA and MPO-ANCA were more common in Japan, whereas granulomatosis with polyangiitis and PR3-ANCA were more common in the UK [14]. This difference may at least in part derive from the difference in genetic background. In Japanese patients with MPA, HLA-DRB1*09:01 was increased as well as in MPO-ANCA-positive vasculitis. HLA-DRB1*09:01 is one of the most common HLA-DRB1 alleles in Asians but is rare in Caucasian populations [15]. In an attempt to identify autoantigens within the ANCAs, Regent et al. identified antibodies targeting lamin A, vimentin, alpha-enolase, and FUBP2 in patients with MPA. IgG from patients with microscopic polyangiitis reacted stronger against culture endothelial cells and induced a strong ERK phosphorylation in these cells [16].

In a European study on GPA and MPA patients, HLA-DP, SERPINA1, PRTN3, and HLA-DQ SNPs were more significantly associated with ANCA specificities (PR3 vs. MPO) than with the clinical syndromes [17]. In the study by Rahmatulla, these genetic variants were tested in GPA and MPA: CD226, CTLA-4, FCGR2A, HLA-B, HLA-DP, HLA-DQ, HLA-DR, HSD17B8, IRF5, PTPN22, RING1/RXRB, RXRB, STAT4, SERPINA1, and TLR9. Subdivision based on ANCA serotype matched better with these gene variants compared to clinical diagnosis. Within the identified 33 genetic variants, alpha-1 antitrypsin, the major histocompatibility complex system, and several distinct inflammatory processes play a major role [18].

11.2.4.1 Gross Morphology

In a VATS biopsy, there is hemorrhage without any specific morphology other than bleeding. The specimen should be sectioned in a 90° angle to the axis of the blood vessels to get the best cross sections of the larger vessels.

11.2.4.2 Histology

In MPA small vessels are involved. There is a neutrophilic rarely eosinophilic granulocytic infiltration within capillary walls, also arterioles and venules can be affected. Since necrosis of the endothelial cells will cause disruption of the vessel walls, focal bleeding (alveolar hemorrhage) will result. As this process recurs, macrophages are following and ingest the blood. The histological picture is not easy to interpret; however, a strictly to the capillary wall-associated granulocytic infiltration, and no outside accumulation within alveoli, as well as the scattered hemosiderin-laden macrophages will guide to the correct diagnosis (Fig. 11.9). Granulomas as well as infarct are absent.

11.2.4.3 Prognosis

A higher mortality is seen in patients with MPA-associated fibrosing interstitial lung disease (ILD) compared to those with peripheral nervous system involvement [19]. This was also confirmed in the study by Katsumata et al [20].

11.2.5 Panarteritis Nodosa

Panarteritis nodosa is a large, medium, and small vessel vasculitis, which very rarely affects the lungs. Within the Armed Forces Institute collection, there are only a few cases recorded involving the lungs. Organs most commonly affected are the gastrointestinal tract, arteries at the base of the

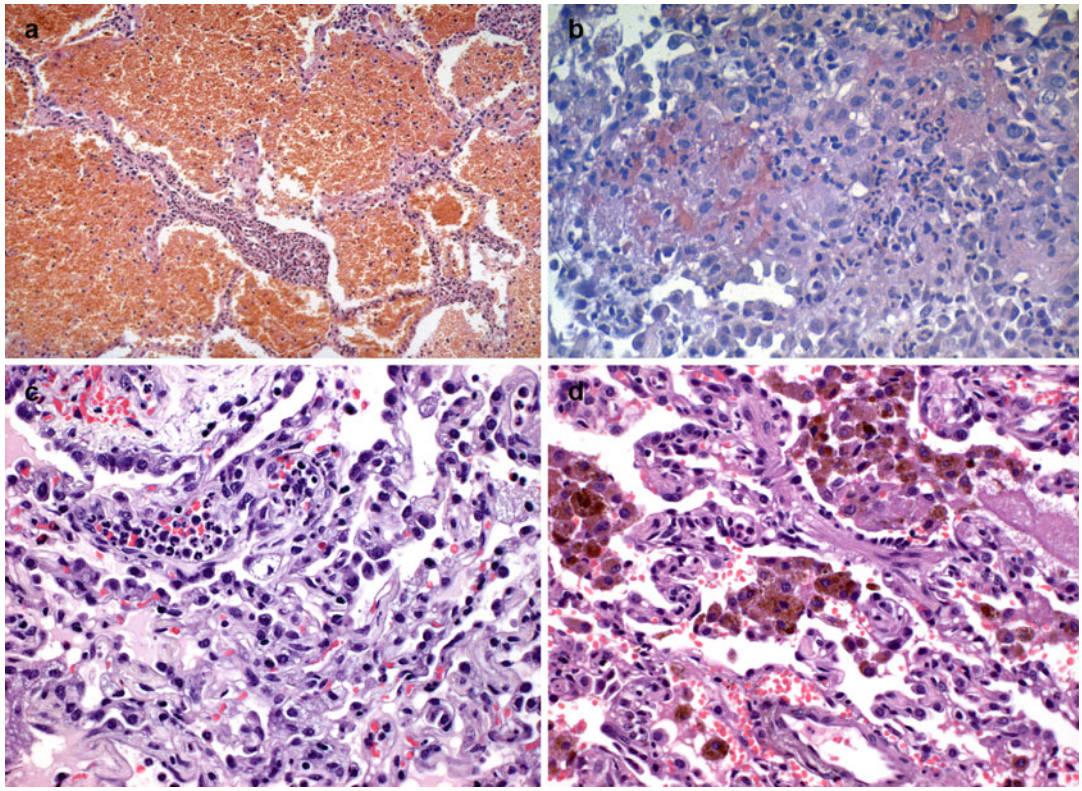


Fig. 11.9 Microscopic polyangiitis (MPA) illustrated by four cases. (**a**) A classical picture with capillaritis and alveolar hemorrhage. Due to the hemorrhage, the vascular pathology is almost highlighted. (**b**) The vasculitis is obscured by the hemorrhage; however, if one follows the alveolar septum, it becomes clear that the granulocytes are within and around the blood vessels, and the hemosiderin-laden macrophages represent former bleeding. (**c**) In this case the vasculitis is nicely shown and also the necrosis of endothelial cells. (**d**) Here hemorrhage is the only feature; the few scattered granulocytes within the capillaries are not diagnostic, because they are not associated with endothelial damage. Only clinical history and CT scan together with morphology could establish the correct diagnosis. H&E, Trichrome, ×50 and 100

brain, heart, liver, and spleen. To my knowledge only one definitely proven case has been published in the literature, which involved the lungs [12]. It is a neutrophilic granulocytic vasculitis, but during the course of the disease, also histiocytes are present too; the vasculitis is nodular and granulomatous, causing either stenosis with ischemic infarcts or dilation with aneurysm formation, rupture, and bleeding (Fig. 11.10).

The relevance of the classification system of vasculitides, relying on affected vessel size as the primary discriminator, is still questionable. Classification on ANCA-positive and negative vasculitis is a first step to get a better separation, and also the type of ANCA is clinically important. However, some entities remain ill defined: polyarteritis nodosa, microscopic polyangiitis, and adult immunoglobulin A vasculitis [21] (Table 11.1).

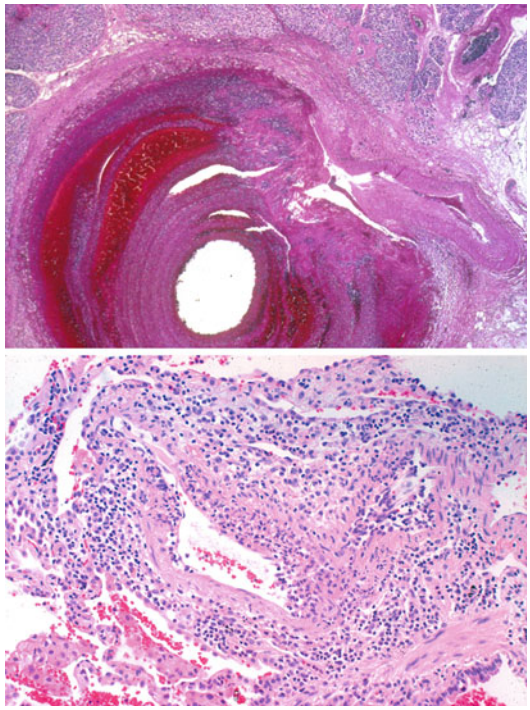


Fig. 11.10 Panarteritis nodosa involving the lung, an exceptional rare organ affection. *Top panel* shows a large artery with vasculitis and thrombosis. In the *lower panel*, a middle-sized artery is involved by a neutrophilic vasculitis with endothelial cell damage. H&E, ×12 and 200 (Case photographed at the AFIP during my stay there)

Table 11.1 ANCA and other autoantibodies in vasculitis and autoimmune diseases

GPA initial	PR3	50 %	MPO	<5 %
Generalized	PR3	90 %	MPO	<5 %
EGPA	PR3	20 %	MPO	20 %
MPA	PR3	10 %	MPO	60 %
PanA	PR3	<5 %	MPO	<5 %
SLE	PR3	–	LF/HLE/LZ	25 %
Sjøgren	PR3	–	LF/HLE/LZ	25 %
Polymyositis	PR3	–	LF/HLE/LZ	<10 %
Rheumatoid	PR3	–	LF/HLE/LZ	20–50 %

As a rule, infections should always be ruled out in cases with vasculitis before a systemic vasculitis is diagnosed.

11.3 Secondary Vasculitis with Infection

Most infections can cause a secondary vasculitis; in case of bacterial and fungal infections, these are usually granulocytic (neutrophilic) vasculitis, whereas viral infections cause lymphocytic vasculitis (Figs. 11.11 and 11.12). Parasitic infections come as eosinophilic vasculitis, similar to allergic reaction.

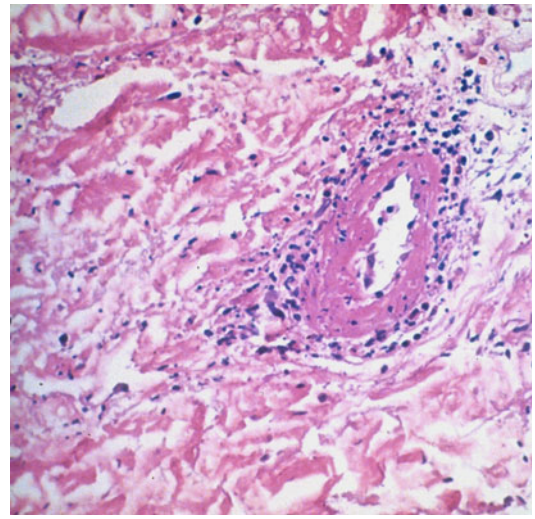


Fig. 11.11 Secondary vasculitis due to infection with herpesvirus, H&E, ×100

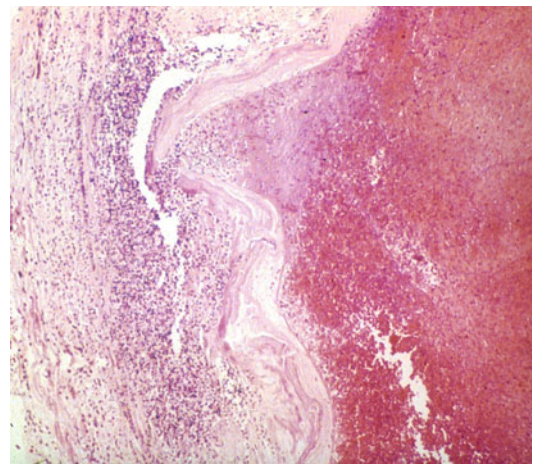


Fig. 11.12 Secondary vasculitis due to infection with *Staphylococcus aureus* infection and sepsis. H&E

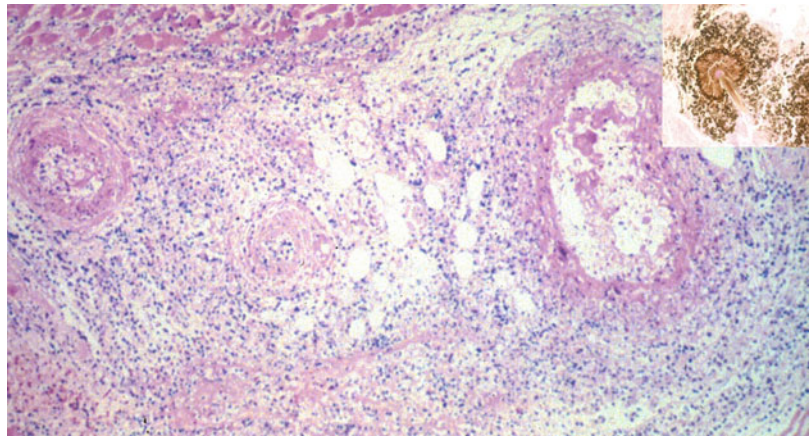


Fig. 11.13 Secondary vasculitis due to sepsis with an *Aspergillus* species in a child after chemotherapy for leukemia. *Inset*: a fruiting body of the fungus allowed a more specific diagnosis. H&E, Grocott, ×100 and 400

Most common secondary infectious vasculitides occur in tuberculosis, mycobacteriosis, almost all forms of fungal infections, and many viral infections. Of note some infectious vasculitides can also be ANCA positive, as we have seen in a case of infectious vasculitis caused by *Treponema pallidum*.

In children mycotic infections are seen in patients treated for leukemia and in bone marrow transplant (Fig. 11.13). In these cases processing of the tissue and diagnosis by the pathologist should be done as quick as possible, because these children are on a high risk of developing sepsis: all fungi grow toward high oxygen tension and therefore can invade the pulmonary vascular system within hours, resulting in bacteremia and sepsis.

11.4 Secondary Vasculitis Without Infection

These forms of vasculitis have been discussed in other chapters. Examples are vasculitis in sarcoidosis, necrotizing sarcoid granulomatosis, and hypersensitivity pneumonia. An unusual form of eosinophilic vasculitis has been described in a newborn with congenital chylothorax [22]. The vasculitis vanished after correction of the ductus thoracicus within a week (Fig. 11.14). Other forms of noninfectious vasculitis can occur in drug abuse, for example, in methadone abuse, where the filling material from the drugs is injected together with the drug into a vein. The filling material often contains talcum, which will cause a granulomatous vasculitis with foreign body giant cells. Another vasculitis can be induced by material from dialysis membranes. If used several times, polyhydrocarbon fragments

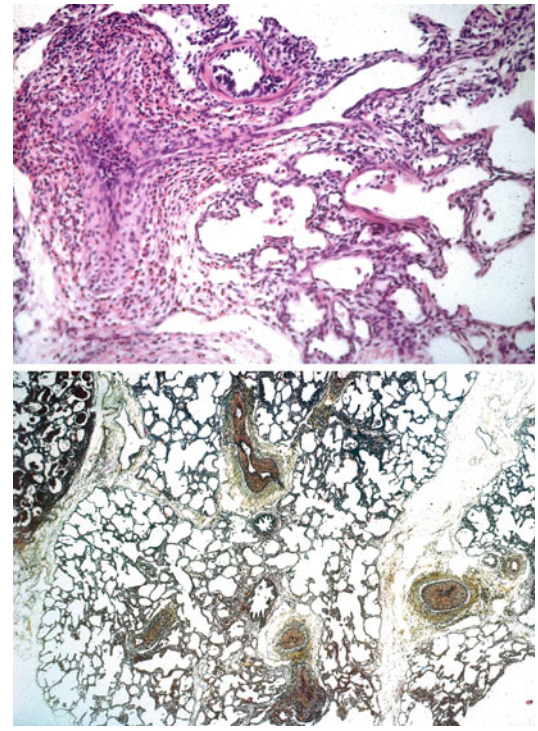


Fig. 11.14 Eosinophilic vasculitis due to chylothorax in a 2-day-old child. Note the dense eosinophilic infiltration confined to the blood vessels, whereas the alveolar tissue is normal. H&E and Movat stain, ×200 and 50

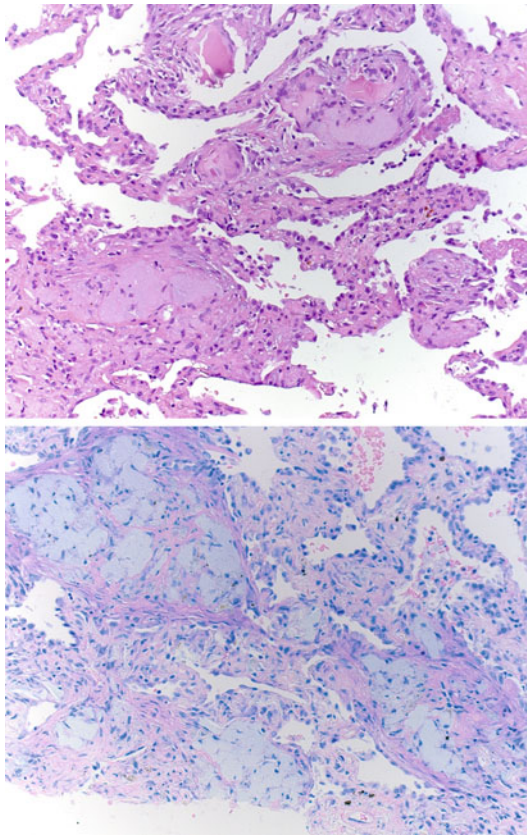


Fig. 11.15 Foreign body vasculitis caused by material dissolved from medical devices. The material looks amorphous eosinophilic and is surrounded by a macrophage reaction (*upper panel*). On PAS stain the material is negative (*lower panel*). H&E and PAS, ×200

can be dissolved and will circulate via the venous system, reaching the lung and will cause a macrophage vasculitis (Fig. 11.15).

11.5 Vascular Diseases and Malformation

Pulmonary arteries and veins can be affected by different malformations, which are at present ill defined. Usually patients present with alveolar hemorrhage, which sometimes can be life threatening. The underlying pathology can be capillary or cavernous hemangiomas, arteriovenous malformations, or angiomas but also rare diseases such as Marfan syndrome and Ehlers-Danlos disease type IV. Usually a careful examination is necessary to find the underlying cause of bleeding. This requires extensive sectioning. In my experience one should select those areas, where massive hemorrhage is present. Take many sections and start searching for malformations. In *Marfan disease* clinical information, if provided, might help a lot, so one can immediately focus on the large arteries and investigate the elastic laminae (Fig. 11.16). The formation of elastin is disabled, causing thin-walled large blood vessels, which easily rupture; in the lung mainly the large pulmonary arteries are affected; however, in these patients the symptoms are mainly due to aortic problems (rupture). In *Ehlers-Danlos disease IV*, the most important finding is thin-walled large arteries and ill-developed collagen in the adventitia. The synthesis of different types of collagen is blocked. In the lungs large pulmonary arteries are affected. Most important both diseases will manifest in a young-aged population.

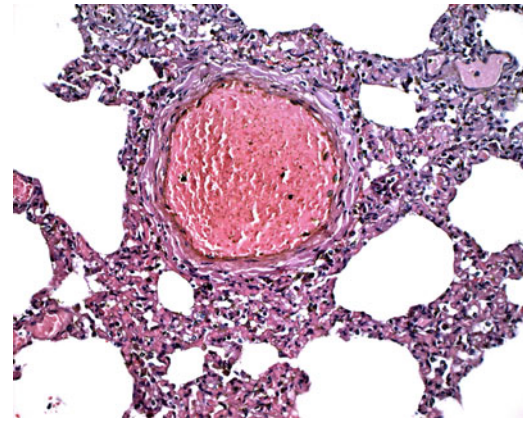


Fig. 11.16 Pulmonary involvement in Marfan disease. Note the thin-walled artery without a visible elastic lamina. Trichrome stain, ×200

Clinical symptoms are massive hemorrhage in young patients, which tend to be fatal. As this is a systemic disease, there is no option for treatment.

11.5.1 Histology

On low power examination, no abnormalities are seen. The bronchovascular bundles are well

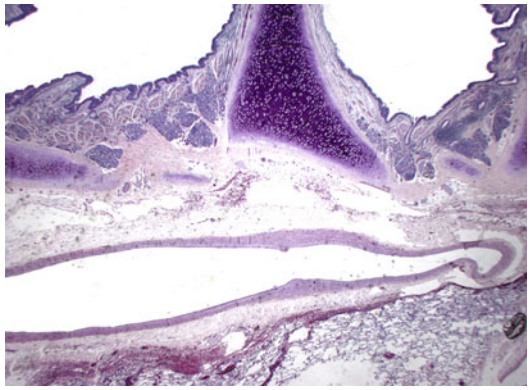


Fig. 11.17 Lung involvement in Ehlers-Danlos disease type IV. Here again a thin-walled artery is seen, but here the collagen fibers are reduced in number and they are functional impaired. H&E, ×12

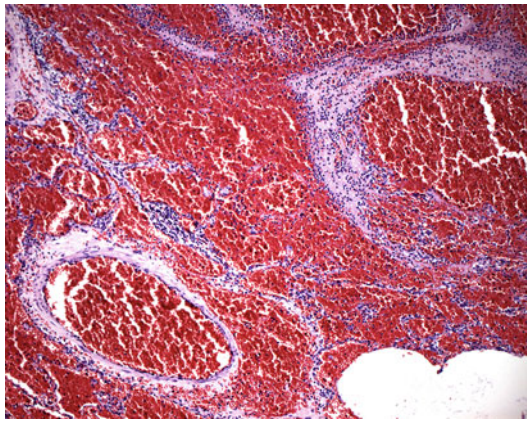


Fig. 11.18 Lung involvement in Ehlers-Danlos disease type IV. Here rupture of a small blood vessel is seen, which caused massive bleeding. H&E, ×50

structured; within the lung parenchyma, massive hemorrhage is the only finding. The abnormality, which will lead to further chemical investigation, is the thin wall of large pulmonary arteries seen on mesenchymal tissue stains such as Movat pentachrome. The intima is normal and the elastic laminae are normal, but the collagen is abnormally thin (Figs. 11.17 and 11.18). This combination together with the age of the patient and the rapid deterioration should cause chemical investigation for the underlying enzyme defect.

Mutation within the COL3AI gene results in the disorder of type III procollagen. The diagnosis is confirmed by demonstrating the synthesis of abnormal type III procollagen molecules from cultured dermal fibroblasts or by identifying the mutation in the COL3A1 gene [23]. Biallelic sequence variants have a significantly worse outcome than heterozygous variants for either null mutations or missense mutations, and frontoparietal polymicrogyria may be an added phenotype feature. This genetic constellation provides a very rare explanation for marked intrafamilial clinical variation due to sequence variants in COL3A1 [24].

11.6 Malformation and Systemic (Inborn) Vascular Diseases in Children

This has been already discussed in the chapter on childhood and will not further be treated here.

11.7 Pulmonary Hypertension

Pulmonary hypertensive diseases will not often be subjected to pathological analysis; however, the pathologist might be questioned in autopsy cases or in rare diseases with hypertension. Therefore we will describe the morphological changes to be seen in histological specimen to enable the pathologist to make the diagnosis of pulmonary hypertension and some variants. In some cases such as in systemic diseases or in autopsy cases with heart diseases, the pathologist can arrive at a diagnosis, which includes also the etiology of hypertension, but in biopsies the final diagnosis has to be established by a multidisciplinary team led by the clinician.

Pulmonary hypertension is defined as an arterial pressure of $\geq$25 mmHg under resting condition. There are also definitions for pre- and postcapillary hypertension, where >15 mmHg defines a postcapillary hypertension whereas precapillary hypertension is defined by $\leq$15 mmHg.

The severity of changes within the walls of pulmonary arteries can be graded, and to my experience the grading system by Heath and Edwards is most useful (Table 11.2).

Table 11.2 Grading of sclerosis according to Heath and Edwards [25]

Grade 1: medial hypertrophy and muscularization of arterioles
Grade 2: medial hypertrophy and intimal proliferation in small arteries
Grade 3: medial hypertrophy, intimal proliferation, and concentric laminar fibrosis
Grade 4: medial hypertrophy, intimal proliferation, and concentric laminar fibrosis and plexiform lesions
Grade 5: prominent plexiform and angiomatoid lesions, + hemosiderin deposition
Grade 6: as grade 5, + necrotizing arteritis

Primary pulmonary hypertension, veno-occlusive syndrome (diseases), and pulmonary capillary hemangiomatosis were originally considered separate diseases, although D. Dail many years ago pointed to a connection of these three in his thesis work. Primary pulmonary hypertension is caused by a vascular obstruction of medium to small blood vessels. As a reaction a secondary proliferation of small capillaries with a glomerulum-like appearance is started – the so-called plexiform lesion (Fig. 11.19). The driving forces are vascular factors such as VEGF, endothelin, endostatin, and their receptors (Fig. 11.19d). Small areas of necrosis can occur, and a hemangioma-like dilation of veins is typically found around these proliferations (Fig. 11.19e). Small areas of necrosis can occur. Larger arteries will show vessel wall thickening and stenosis. Bleeding and hemosiderin deposits can be found; however, no large hemorrhage will be seen.

Veno-occlusive disease is characterized by an occlusion of pulmonary veins, which are found along interlobular septa. Sometimes an elastic stain is necessary, to highlight remnants of these vessels (Fig. 11.20). Pulmonary capillary hemangiomatosis often can be found associated with the former two diseases. PCH is characterized by a proliferation of pulmonary capillaries typically in septa. There are at least doubled capillary beds (Fig. 11.21). The disease occurs in children and young adults and causes alveolar hemorrhage syndrome. To my experience and according to case reports in the literature, there are two probably separated forms: PCH associated with PAH ± VOD and PCH as an isolated tumorlike form.

PAH in collagen vascular disease, most often systemic sclerosis, is characterized by vessel wall thickening (grades 2–4). In some cases this thickening resembles sclerosis as in chronic vascular transplant rejection due to antigen-antibody complex deposition. Also vasculitis can occur.

PAH in intravenous drug abuse comes usually as foreign body giant cell vasculitis with obstruction of small arteries and capillaries. Plexiform lesions can be present in rare cases. The reason is embolization of tablet filling substances such as talcum. Another drug *Sauropus androgynus* inducing PAH was reported in Korea and Japan. This starts with myxoid changes in arteries and bronchioles, followed by eosinophilic vasculitis and bronchiolitis, and finally occlusion of bronchioles and blood vessels.

Signs of pulmonary hypertension including elastosis of the arteries are characteristically found in lung sequestration with and without CPAM. Elastosis (multiplicity of elastic layers), which is also present in other types of pulmonary hypertension, is most severe in sequestration and can be used as another aid in making the correct diagnosis.

PAH is also found in thromboembolic disease, even with plexiform lesions, but venous dilations associated with these lesions do not occur (Fig. 11.22) (Table 11.3).

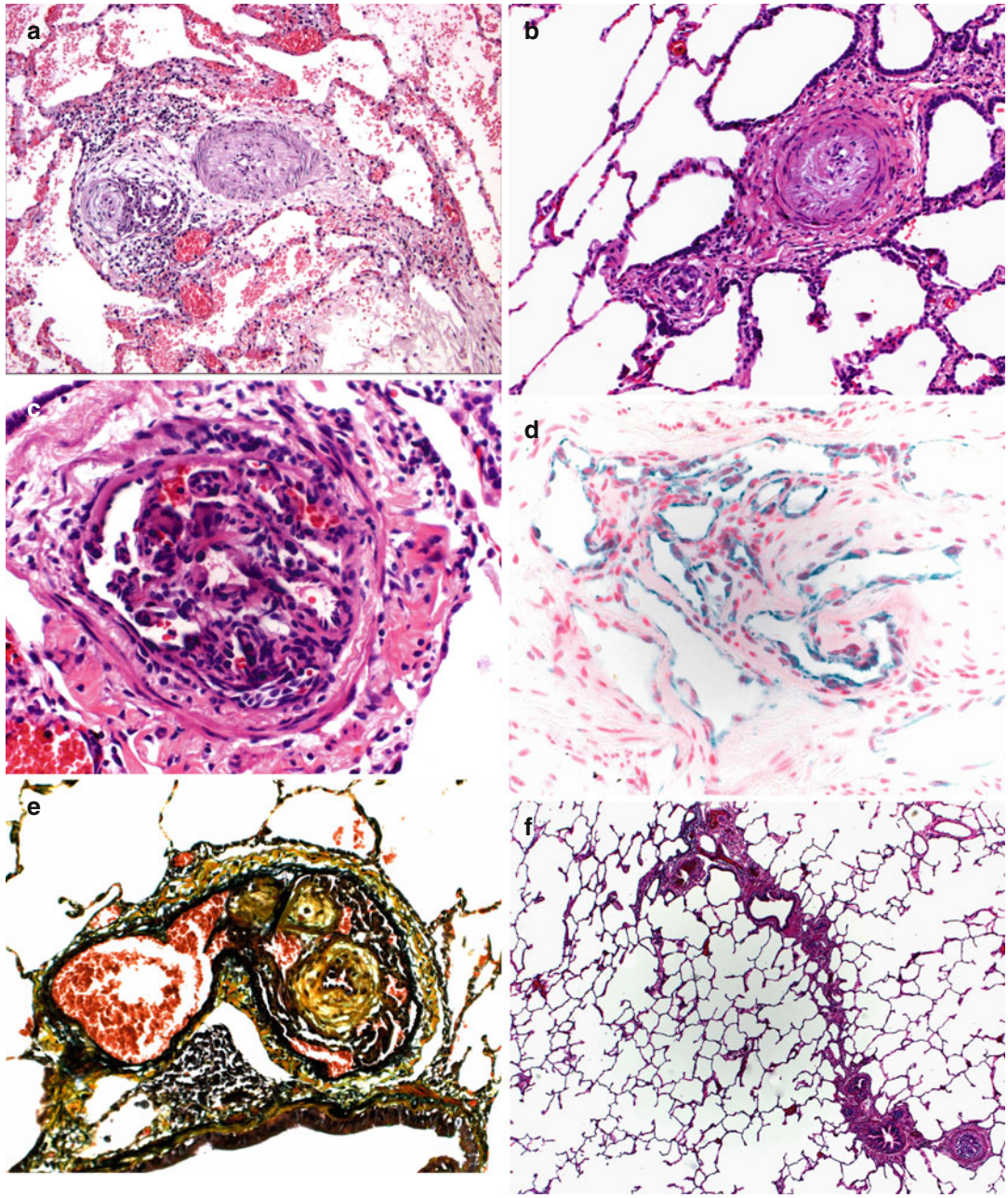


Fig. 11.19 Idiopathic arterial pulmonary hypertension. (**a**) Shows an occluded artery and adjacent a plexiform proliferation of primitive endothelial tubules and capillaries. (**b**) Another case of IPH with stenosis of the artery and early plexiform lesion. (**c**) Plexiform lesion within an artery, and (**d**) expression of VEGF in the endothelia of this plexiform proliferation. (**e**) A typical and diagnostic finding in PAH is a dilated vein adjacent to the obstructed artery. (**f**) Opening of arteriovenous anastomoses, probably "reuse of preexisting anastomoses from the fetal period." H&E, immunohistochemistry for VEGF, and Movat, ×50, 100, and 200

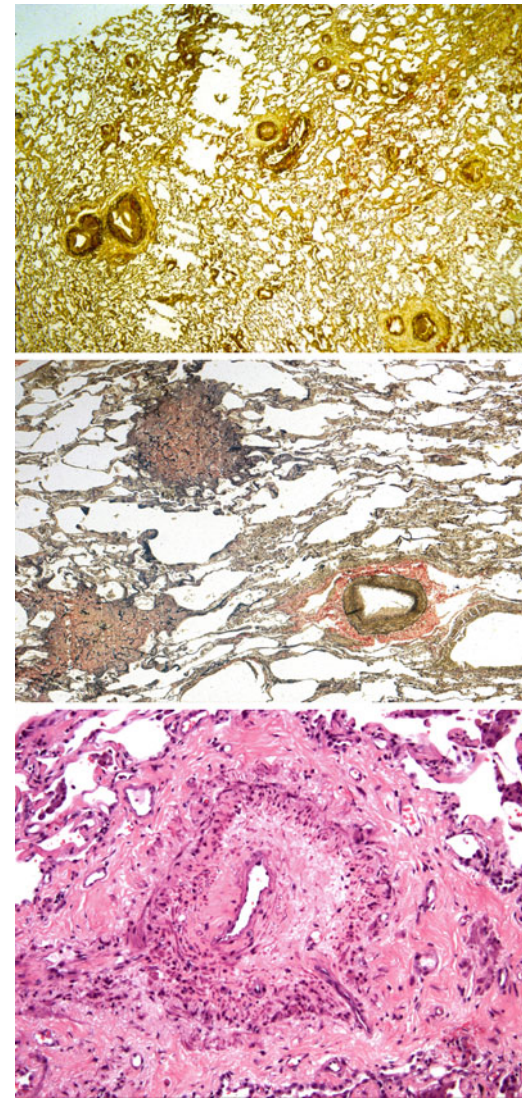


Fig. 11.20 Veno-occlusive disease: the overview in *top panel* shows an almost normal peripheral lung; however, the thickened and obstructed veins stick out. In the middle one artery with thickened wall is shown and two veins, which are occluded and therefore lost to circulation. In the *lower panel*, another vein is shown, which is severely obstructed. H&E, Movat, ×12, 50, 100

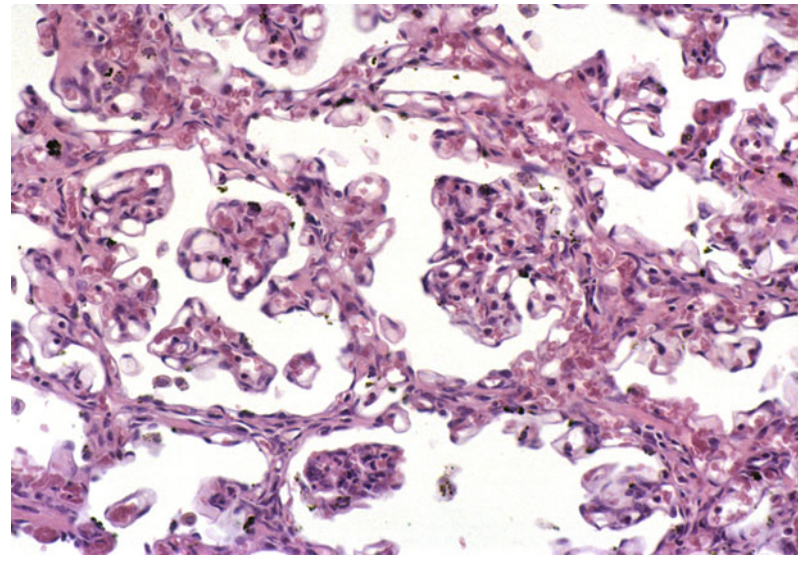


Fig. 11.21 Pulmonary capillary hemangiomatosis in a case of idiopathic arterial hypertension. There are many capillaries within an alveolar septum, best seen at cross sections in the middle of the picture. H&E, ×200

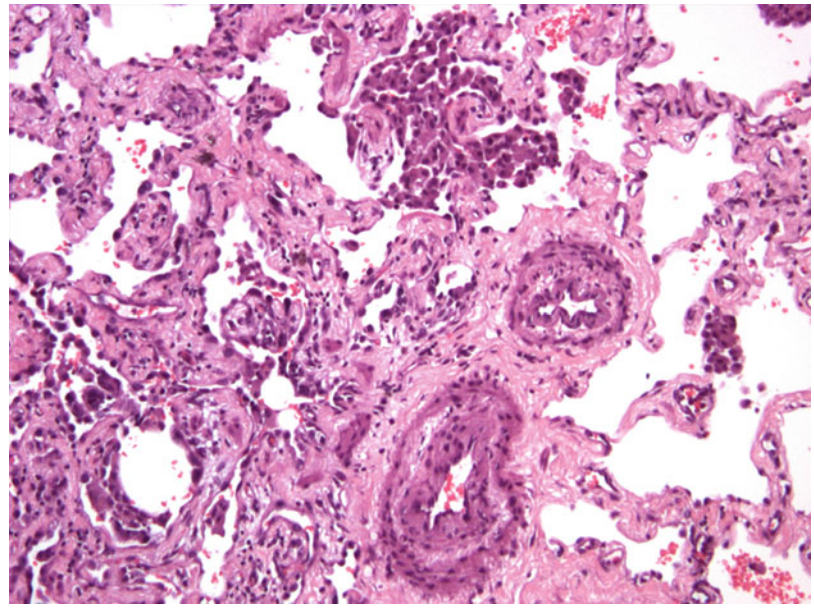


Fig. 11.22 Chronic thromboembolic disease and thickened arteries are seen and within the vessel wall some primitive endothelial proliferations, which will give raise to plexiform lesion later on. Note that there are no dilated veins. H&E, ×200

Table 11.3 The updated Venice classification 2012–2015 [26–29]

A1. Pulmonary arterial hypertension (PAH)
A1.1. idiopathic (iPAH)
A1.2. heritable
A1.2.1. BMPR2
A1.2.2. ALK1, endoglin ± hereditary hemorrhagic telangiectasia
A1.2.3. unknown
A1.3. drug and toxin induced
A.1.4. associated with
A1.4.1. connective tissue disease
A1.4.2. HIV infection
A1.4.3. portal hypertension
A1.4.4. congenital heart disease
A1.4.5. schistosomiasis
A1.4.6. chronic hemolytic anemia
A1.5. persistent pulmonary hypertension of the newborn
A1.6. pulmonary veno-occlusive disease (PVOD) ± pulmonary capillary hemangiomatosis (PCH)
A2. pulmonary hypertension in left heart diseases
A2.1. systolic dysfunction
A2.2. diastolic dysfunction
A2.3. valvular disease (Fig. 11.23)
A3. pulmonary hypertension associated with chronic obstructive pulmonary disease
A3.1. COPD
A3.2. ILD
A3.3. other pulmonary diseases with mixed restrictive and obstructive patterns
A3.4. sleep apnea syndrome
A3.5. alveolar hypoventilation
A3.6. high altitude sickness
A3.7. developmental abnormalities
A4. chronic thromboembolic pulmonary hypertension (CTEPH; Fig. 11.22)
There is no longer a differentiation into thromboembolic obstruction of proximal or distal pulmonary arteries

Table 11.3 (continued)

A5. pulmonary hypertension with unclear multifactorial mechanisms
A5.1. hematologic disorders as myeloproliferative diseases, splenectomia
A5.2. systemic disorders: sarcoidosis, Langerhans cell histiocytosis, LAM, neurofibromatosis, vasculitis
A5.3. metabolic disorders: glycogen storage diseases, Gaucher, others, thyroid diseases
A5.4. others: tumoral obstruction, fibrosing mediastinitis, and chronic renal failure on dialysis

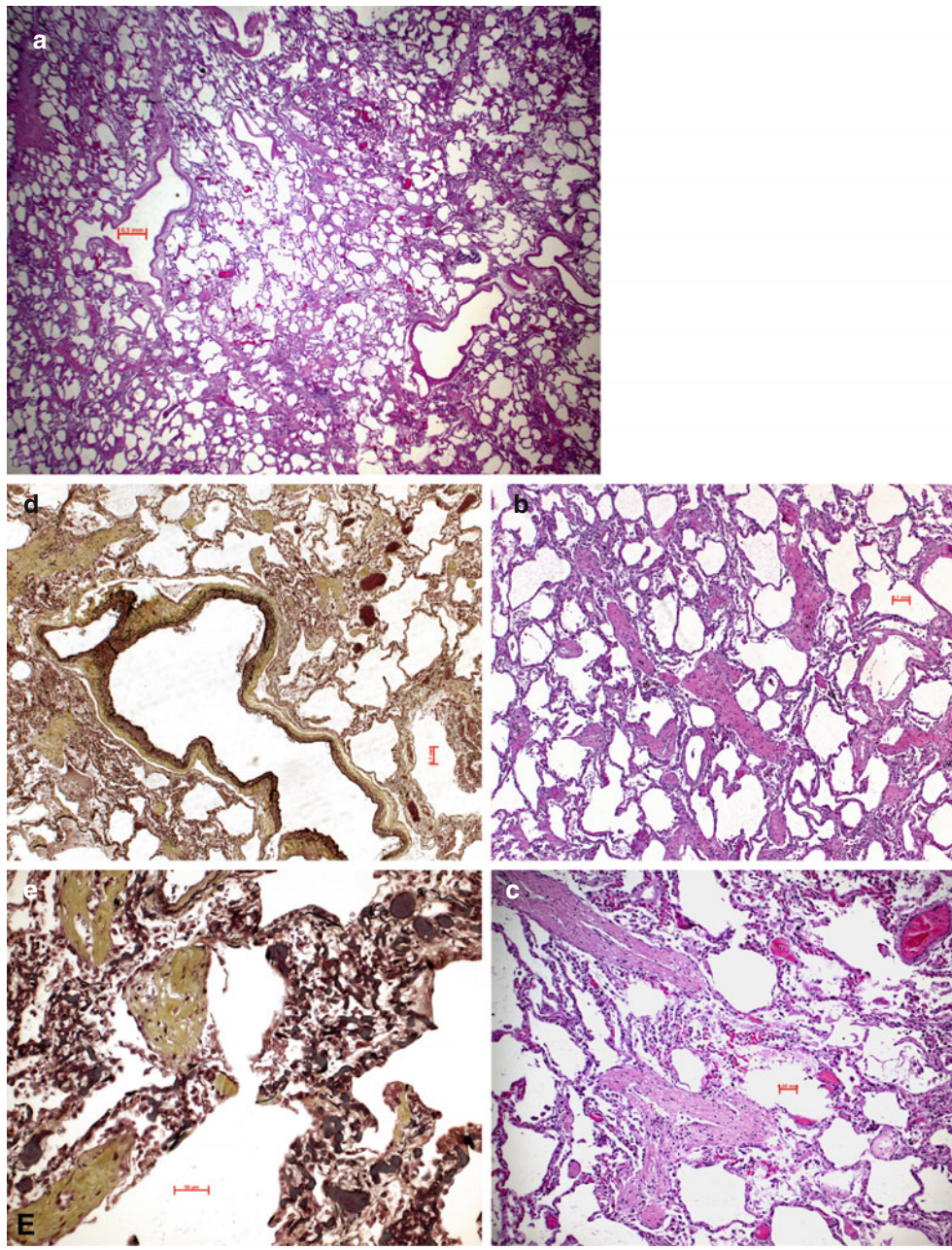


Fig. 11.23 Pulmonary hypertension in valvular disease. (**a**) Overview showing large dilated veins whereas everything else looks normal. (**b**, **c**) On higher magnification there are strands of fibrosed tissue, which show narrow lumina and represent severely stenosed veins. This morphology is also illustrated by Movat stain in (**d**, **e**) where also the dilation of the capillary bed is clearly seen. H&E, Movat, bars 500, 100, 50 μm

11.7.1 Mechanisms of PAH

Some reports have shed light to the mechanisms, but a final cause has not been discovered. Mutations in bone morphogenic protein receptor type II (BMPR2) have been discovered, and it has been shown that BMPR2 mutations in different exons result in altered function. However, BMPR2 mutations are found in only a minority of PAH patients [30, 31]. So it is speculated that disease modifier genes might exist. Activin-like kinase type I (ALK1) was found altered in hereditary hemorrhagic telangiectasia. Since both genes belong to the TGFβ family, this pathway might be most probably affected [31]. BMP receptors 1 and 2 associate to form homo- or heterodimers. BMP4, a ligand for BMPR2, inhibits the proliferation of arterial muscle cells from proximal pulmonary arteries but stimulates proliferation of peripheral arteries. In iPAH hypoxia induces production of endothelium-derived BMP4, associated with increased proliferation and migration of vascular smooth muscle cells.

The serotonin transporter (5-HTT) was found to be overexpressed in PAH [32]. Functional polymorphism of the 5-HTT gene promoter has been demonstrated in some patients, an increase of the expression of the 5-HT transporter (5-HTT) in others. This all result in an abnormally strong proliferative response to serotonin. Interestingly appetite-suppressant drugs are potent inhibitors of neuronal 5-HT uptake and inhibit 5-HTT.

In the downstream pathway, VEGF and VEGF receptors play an essential role in PAH. Also an increase of TXA_2 synthesis was shown in patients with iPAH, pointing to the involvement of thrombotic and inflammatory mechanisms [33].

PAH caused by antiphospholipid autoantibodies most likely is caused by fibrin thrombi causing widespread obstruction of small pulmonary arteries with concentric cellular and fibrous intimal hyperplasia (Fig. 11.24) [34].

In children the group of Fukushima studied the mechanisms of PAH with PVOD in left-to-right shunt of the heart. There was a predominant biosynthesis of TXA_2 over PGI_2, which might cause vasoconstriction in these infants [33]. Finally in a study on PCH, the authors reported on mutations in the eukaryotic translation initiation factor 2α kinase 4 (EIF2AK4) gene. EIF2AK4 potentially connects with BMPR2 to cause PCH. Mutant EIF2AK4 could promote proliferation of small pulmonary arteries by cross talk with mammalian targets of the rapamycin signaling pathway [35] (Table 11.4).

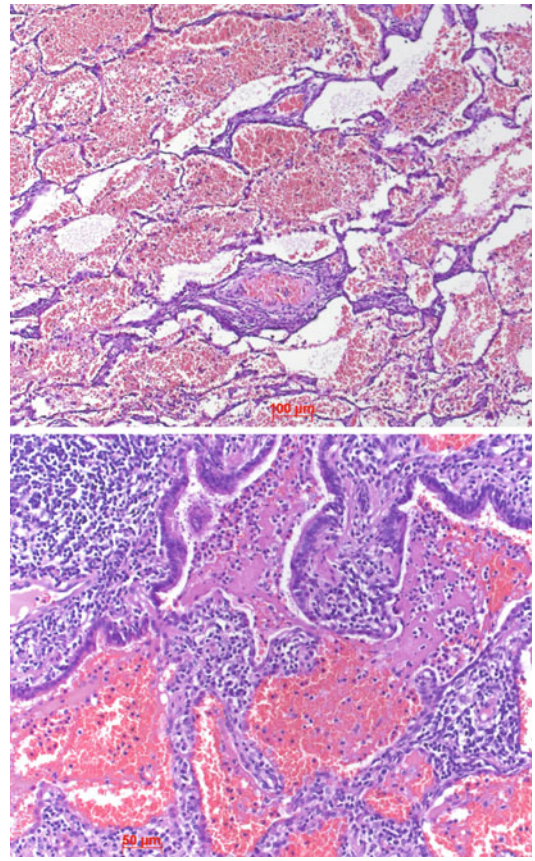


Fig. 11.24 Two cases of antiphospholipid antibody syndrome presenting with alveolar hemorrhage. In the case at the *top panel*, there is only hemorrhage and no other morphological feature. In the second case (*lower panel*), there is an additional lymphocytic pneumonia (LIP), which at least point to an immunological disorder. H&E, bars 50 and 100 µm

Table 11.4 How to diagnose vasculopathy

Pulmonary arteriopathy (pre- and intra-acinar arteries)
Subsets:
Pulmonary arteriopathy with isolated medial hypertrophy
Pulmonary arteriopathy with medial hypertrophy and intimal thickening (cellular, fibrotic)
Concentric laminar or eccentric, concentric non-laminar
Pulmonary arteriopathy with plexiform and/or dilation lesions or arteriitis
Pulmonary arteriopathy with isolated arteriitis
As above but with coexisting venous-venular changes (cellular and/or fibrotic intimal thickening, muscularization)
The presence of the following changes should be noted:
Adventitial thickening; thrombotic lesions (fresh, organized, recanalized, colander lesion); necrotizing or lympho-monocytic arteriitis; elastic artery changes (fibrotic or atheromatous intimal plaques, elastic laminae degeneration); bronchial vessel changes, ferruginous incrustation, calcifications, foreign body emboli, organized infarct; perivascular lymphocytic infiltrates
Pulmonary occlusive venopathy (veins of various size and venules) with or without coexisting arteriopathy
Histopathologic features:
Venous changes: intimal thickening/obstruction (cellular, fibrotic); obstructive fibrous luminal septa (recanalization)
Adventitial thickening (fibrotic); muscularization; iron and calcium incrustation with foreign body reaction:
Capillary changes: dilated, congested capillaries; angioma-like lesions
Interstitial changes: edema; fibrosis; hemosiderosis; lymphocytic infiltrates
Others: dilated lymphatic, alveoli with hemosiderin-laden macrophages, type II cell hyperplasia
Pulmonary microvasculopathy with or without coexisting arteriopathy and/or venopathy
Histopathologic features:
Microvessel changes: localized capillary proliferations within pulmonary interstitium; obstructive capillary proliferation in veins and venular walls
Venous-venular intimal fibrosis
Interstitial changes: edema, fibrosis, and hemosiderosis
Others: dilated lymphatics: alveoli with hemosiderin-laden macrophages; type II cell hyperplasia

11.8 Alveolar Hemorrhage

Alveolar hemorrhage syndrome (AHS) presents with bleeding in the lung parenchyma. In some patients, AHS will cause hemoptysis; in other patients, there is only sometimes blood found in expectorations. In BAL specimen there are red blood cells as well as hemosiderin-laden macrophages – this is essential to differentiate AHS from artificial bleeding induced by bronchoscopy or biopsy, as well as from aspiration from the upper respiratory tract. There are several underlying diseases, which can present with AHS. Within the differential diagnosis, they are vasculitis, primary systemic as well as secondary; pulmonary hypertension; autoimmune diseases including collagen vascular diseases; Goodpasture syndrome; antiphospolipid autoantibody syndrome (Fig. 11.24); infections such as tuberculosis, influenza virus, *Hantavirus*, SARS, dengue fever, and Nile virus fever; inhalation of herbicides and pesticides; and drug reactions, especially cytostatics.

11.9 Diseases of the Lymphatics (Adult and Childhood)

Tumors of the lymphatic system have been covered in tumors. Here we have to discuss malformation, obstruction, and inflammation.

11.10 Malformation

Malformation of the ductus thoracicus will cause obstruction of the lymphatic flow resulting in leakage of the fluid into the alveoli. The

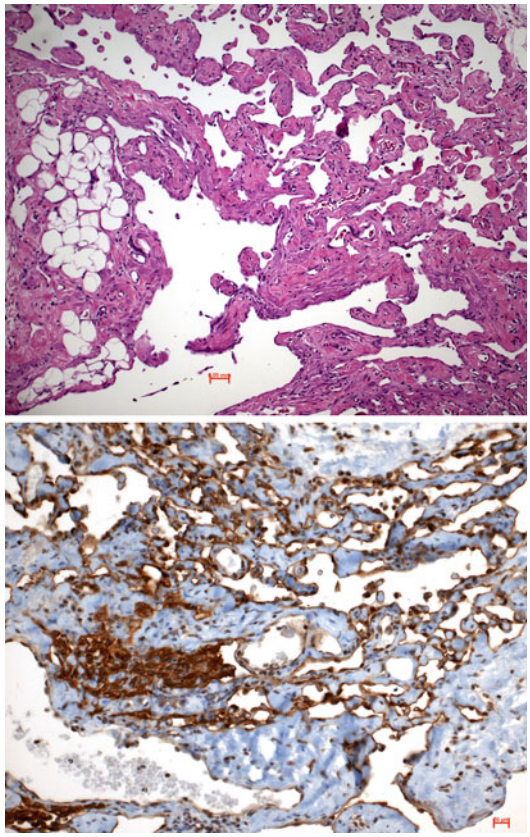


Fig. 11.25 Systemic lymphangiomatosis (Gorham-Stout syndrome) here presented in a resection from a cystic tumor of the mediastinum. In this 22-year-old male patient, there was bone disease and also lung involvement. *Upper* panel shows the lymphangioma-like histology. In the *lower* panel, the endothelia all express VEGFR3. Bars 50 and 20 μm

histological picture will resemble edema; however red blood cells are missing, whereas scattered leukocytes are encountered. The septa are widened by this fluid. Leakage can also affect the pleura causing chylothorax. This malformation can be focal, involving the lung and mediastinum, but exists also as a systemic form, Gorham-Stout syndrome [36, 37]. In this case also the bones and many other organs are affected too (Fig. 11.25). These patients present with symptoms related to loss of electrolytes and small peptides/proteins. Most prominent is albuminemia. Patients are of young age or children. The diagnosis can be made by CT scan, because the multitude of cystic-dilated lymphatics within the

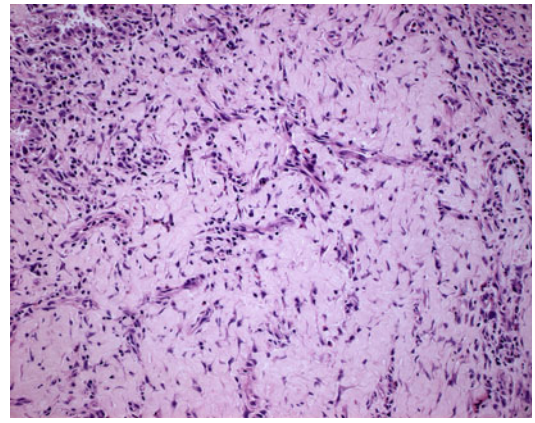


Fig. 11.26 Diffuse capillary lymphangiomatosis with many proliferating lymphatic vessels within a fibrotic tissue. The diagnosis will require immunohistochemical positivity for podoplanin and/or VEGF-C or VEGFR3. H&E, ×200

mediastinum will simulate a cystic tumor. The local form will present as lymphangiosis, with the characteristic proliferation of lymphatic vessels (Fig. 11.26). As an aid in the diagnosis, antibodies against podoplanin and VEGFR can highlight the lymphatics[3].

11.11 Obstruction

Several diseases can cause lymphatic obstruction. Here we will give a list of common and rare causes.

Lymphangioleiomyomatosis: The obstruction is caused by the proliferation of smooth muscle cells.

Tumors: Central tumors might directly compress lymphatics, or tumor cell clusters might obstruct lymphatics.

Parasites: Larvae as well as eggs can obstruct lymphatics. This is very common in tropical parasitic infection such as filariasis.

11.12 Inflammation

Lymphatics are always involved in any kind of infection. However, in common bacterial and viral infections lymphatics are usually not seen

due to their small size. An exception is granulomatous pneumonias such as tuberculosis and sarcoidosis, where the granulomas can be more easily seen centered on lymphatics.

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