Vascular, Cardiac Valve, and Metabolic Diseases

14

Sudden death prompting a judicial postmortem can be attributed to natural causes arising from a spectrum of vascular, cardiac valve, and metabolic diseases. The diseases most frequently reported in the forensic literature can only be diagnosed in part using macroscopic methods; however, cardiac valve disease in particular often demonstrates macroscopic findings. Suspected diagnoses require microscopic confirmation. In this context, almost all vascular, cardiac valve, and metabolic diseases demonstrate a histological and partly also immunohistochemical correlation. Occasionally, congenital vascular and cardiac valve diseases, as well as metabolic diseases undetected until postmortem, are the cause of sudden death, e.g., congenital heart defects, endocarditis, or aortic coarctation (Lynch et al. 2008; Karayel et al. 2006); endocardial fibroelastosis is rarely reported in the literature.

Undetected lethal cardiac valve disease primarily affects children and relatively young people with congenital cardiac valve defects, acquired cardiac valve stenosis, or cardiac valve insufficiency. Macroscopically detectable anomalies in coronary arteries in particular are also rare (Schmitt 1973). In contrast, arteriosclerotic aneurysms are unproblematic; however, their distinction from primary vasculitides is occasionally challenging (Desinan et al. 2010; Dettmeyer et al. 2006, 1998a).

Congenital and, more rarely, iatrogenic vascular anomalies can lead to lethal complications; primary among these are gross congenital malformations of the heart and vascular system. Severe malformations quickly become clinically symptomatic, while less life-threatening malformations can long remain undetected. Cases of sudden death associated with intracerebral hemangioma and arteriovenous malformations have also been reported (see Chap. 20). In the case of hemangioma, cavernous hemangioma needs to be differentiated from capillary hemangioma.

14.1 Vascular Diseases

The following potentially lethal vascular diseases are particularly noteworthy:

- General atherosclerosis (very common), including cerebral sclerosis, carotid and renal artery sclerosis, etc.
- Coronary sclerosis (see Chap. 13)
- Various forms of aneurysm which are either congenital or which develop in the setting of atherosclerosis
- Special forms of dissecting aneurysm in the setting of, e.g., idiopathic cystic medial necrosis (Erdheim–Gsell), Marfan syndrome, Ehlers–Danlos syndrome, and, rarely, syphilis (lues)

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- Arteritides and/or angitides as isolated or system disease (Wang et al. 2002)
- Congenital vascular anomalies such as capillary or cavernous hemangioma or arteriovenous tumors
- Rare syndromes with vascular involvement which, in individual cases, can be the cause of sudden death, e.g., Osler–Weber–Rendu syndrome (Byard et al. 2001)

A comprehensive list of all possible vascular diseases and their potentially lethal variants is beyond the scope of this work. Atherosclerotic lesions and their complications are the most common. In a number of cases, vascular disease has been proven as the cause of pregnancy-related sudden death (Risse et al. 2010; Risse and Weiler 1987). In addition, there are very rare findings of, e.g., coronary artery fibromuscular dysplasia as a cause of death (Zack et al. 1996). Also, cases of lethal complications of arteriovenous malformations, e.g., rupture and spontaneous hemothorax (Ishikawa et al. 2010), have been reported.

Posttraumatic arterial rupture may also be significant in terms of insurance law, particularly in cases where a two-stage event is suspected; in this case, a histomorphological correlation should be provided where possible. Thus, in initially incomplete rupture of the aorta, thrombosed ruptured fissure, partially necrotic vascular wall, and focal linear necrosis of the aortic muscle, for example, have all been described. In addition to the detection of micromorphologic signs of trauma, histological investigation also serves to exclude/include preexisting vascular diseases (trauma-related degenerative lesions in elastic fibers, acidic mucopolysaccharide deposition, microcystic lesions, and inflammatory processes). The final rupture of the remaining layers is mainly thought to be due to posttraumatic necrosis. A significant degree of atherosclerosis partly favors the onset of rupture, a fact that should be considered when giving an opinion in civil litigation (Brinkmann 1974). The same problem associated with expert opinions is also valid, e.g., for two-stage ruptures or dissecting aneurysms of the carotid or vertebral arteries following trauma or chiropractic intervention.

14.1.1 General, Coronary, and Cerebral Sclerosis

Sudden or unexpected death from natural causes may be the result of a wide range of sometimes extraordinary disorders. Although atherosclerotic coronary artery disease is by far the most frequent cause of sudden death, there are a number of differential diagnoses to consider:

Severe forms of general atherosclerosis with stenosing coronary sclerosis and cerebral sclerosis are diseases which, as a result of long-standing hypertension, nicotine abuse, metabolic disorders, or diabetes, among others, can lead to vascular wall rupture, stenosis, thrombosis, etc., with lethal hemorrhage, as in the case of massive intracerebral hypertonic hemorrhage. Severe atherosclerotic findings are often observed histologically:

- Rarefaction of the arterial media with elastic fiber fragmentation
- Intimal fibrosis, cholesterol crystal deposition
- Basophilic, partly tubular wall calcification
- High-grade atherosclerotic vascular narrowing

However, sudden cardiac death in relatively young men with no coronary atherosclerosis has also been reported. This type of sudden unexplained death has been known as “Pokkuri death syndrome” (PDS) in Japan, “Lai Tai” in Thailand, “bangungut” in the Philippines, “dream disease” in Hawaii, and “sudden unexpected nocturnal death syndrome” among South Asian immigrants in the USA (Nakajima et al. 2010).

14.1.2 Aneurysms

Aneurysms which can lead to lethal complications, generally hemorrhage following rupture, include:

- Atherosclerotic aneurysms, in particular infrarenal aortic aneurysms
- Congenital, occasionally multiple, aneurysms, e.g., of aortic, coronary, or cerebral arteries
- Aneurysms of the heart wall, generally following previous myocardial infarct

- Dissecting aneurysms, generally of the aorta, but rarely also of other arteries (splenic or coronary arteries, etc. (D'Ovidio et al. 2015)
- Iatrogenic aneurysms (Lau 2002)
- Ductal aneurysm

All forms of aneurysm can thrombose as a secondary event or even demonstrate accompanying inflammatory reactions. These inflammatory infiltrates are often encountered only focally and need to be distinguished from primary inflammatory vascular disease, which could itself be the cause of the aneurysm. Unusual localizations of aneurysms have also been described in the recent forensic literature (Desinan et al. 2010; Kodikara and Sivasubramanium 2009). In some cases, histological investigations can reveal, e.g., vasculitis or fibromuscular dysplasia as the cause of (dissecting) aneurysm or provide evidence of thrombosis and fungal colonization (Ortmann et al. 2010; Hagemeier et al. 2009).

14.1.3 Dissecting Aortic Aneurysm in Idiopathic Cystic Medial Necrosis

Aortic dissection is defined as follows: penetration of blood into the vessel wall through a tear in the intima, forming a split between coats or medial laminae that may be complicated by rupture; it is due to degeneration of connective or elastic fibers of the media, and the main predisposing factors include hypertension, Marfan syndrome, idiopathic cystic medial necrosis, pregnancy, some congenital cardiovascular diseases, as well as damage due to arterial catheterization or aortic valve surgery (Desinan et al. 2010; Dermengiu et al. 2009). In individual cases, consideration should be given to whether aortic dissection could have occurred in the setting of resuscitation measures (Patterson et al. 1974; Nelson and Ashley 1965). Erdheim–Gsell medial necrosis is a significant cause of aortic dissection and aortic rupture, and there is only a short time window available between onset of symptoms and administration of the necessary treatment (Maeso Madronero et al. 2000).

An acute dissection of the ascending aorta must be treated surgically as soon as possible, since the mortality rate in untreated dissections increases by 1–2% hourly. A higher frequency of medial degeneration associated with hypertension is well known (Carlson et al. 1970; Gore 1953; Rottino 1939). A long history of hypertension is reported in nearly 90% of all cases of aortic dissection (Stegmann 1987).

Dissecting aortic aneurysm is known as a cause of sudden unexpected death; however, clinical symptoms may be confused with those of myocardial infarction (Stegmann 1987). Dissection extending to the pericardium leads to acute pericardial tamponade; ruptures in the (usually left) pleural cavity or free abdominal cavity are less common. Entry and exit sites of aortic dissection are often in the ascending aorta (type A); aneurysms not involving the aorta are classified as type B (Li et al. 2015). Whether a genetic component is a causal factor in aortic dissection is currently the subject of discussion (Robertson et al. 2016). When reaching the origin of the ascending aorta, a dissecting aneurysm can lead to luminal compression in the large branching coronary arteries resulting in acute death. Cases where hemorrhage is absent are known as "bloodless aortic dissection" (Dettmeyer et al. 1998b; Dickens and Khoo 1993; Cambria et al. 1988).

In cases of "bloodless aortic dissection," an alternative pathophysiological mechanism must be discussed: increasing hypertension during progressive extension of the dissection, followed by sudden disruption of the subendothelially localized cardiac conduction system. The aortic dissection may also cause variations in blood pressure due to the undulating surface of the intimal layer, which may be enhanced by simultaneously increasing blood levels of catecholamines due to intensive chest pain. A comparative mechanism of sudden heart failure has been proposed in cases of aortic stenosis and coarctation of the aorta, which are known to cause sudden death (Frank et al. 1973).

Idiopathic medial necrosis is a frequent cause of dissecting aneurysm (Fig. 14.1) (Maeso Madronero et al. 2000; Leu and Leu 1988).

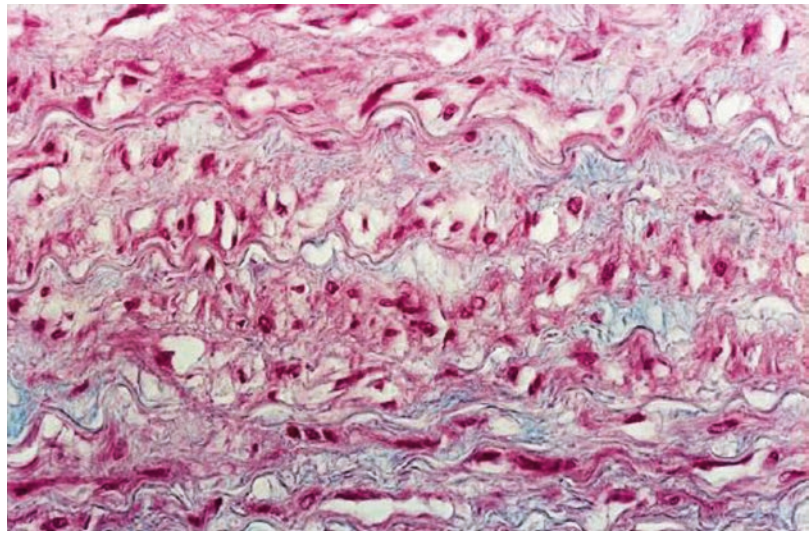

Fig. 14.1 Idiopathic microcystic medial necrosis as the cause of a dissecting aneurysm (H&E ×400)

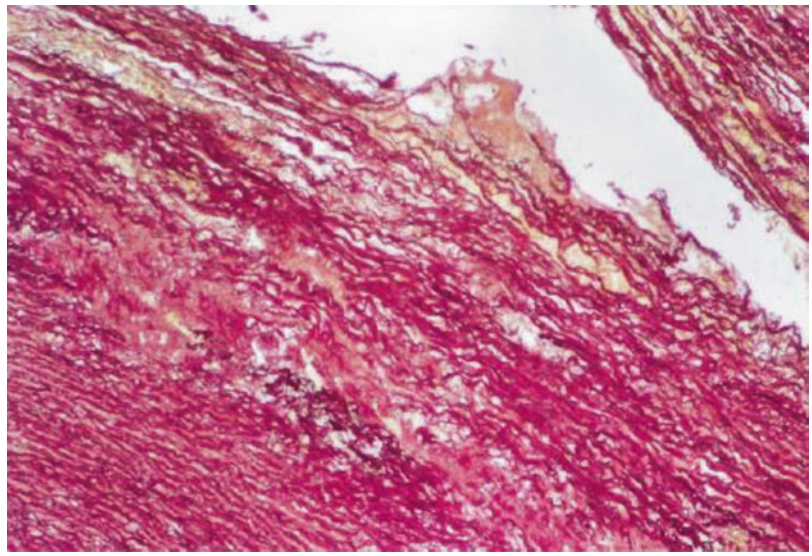

Fig. 14.2 Dissecting aneurysm of the descending aorta with longitudinal splitting of the vascular wall and fragmentation of elastic fibers in idiopathic medial necrosis (Elastica van Gieson ×40)

It was first described by Gsell (1928) and Erdheim (1929a, b) as a disease entity of the aortic vascular wall (Guitierrez et al. 1991; Hirst and Gore 1976). Pathogenetically, it leads to destruction of the aortic or arterial media with destruction of smooth muscle fibers, mesenchyme, and elastic fibers (Fig. 14.2). The degree of severity can vary greatly. Histologically, noninflammatory mucoid degeneration in the arterial media with only scant rarefaction and splitting of elastic fibers is seen; this can be easily detected using Elastica van Gieson staining. Necrosis and microcysts can only be detected in some cases; the extracellular matrix contains Alcian Blue-positive mucopolysaccharides (chondroitin sulfuric acid), starting most likely in the inner third of the arterial media (Fig. 14.3). In the case of extensive findings, muscular, collagen, and elastic fibers which have been forced apart can be seen, even in the absence of light microscopic confirmation of necrosis of elastic elements (Bode-Jänisch et al. 2012; Jungmann et al. 2010; Schmidt et al. 1996; Nashima et al. 1990; Schnapka et al. 1983; Schlatman and

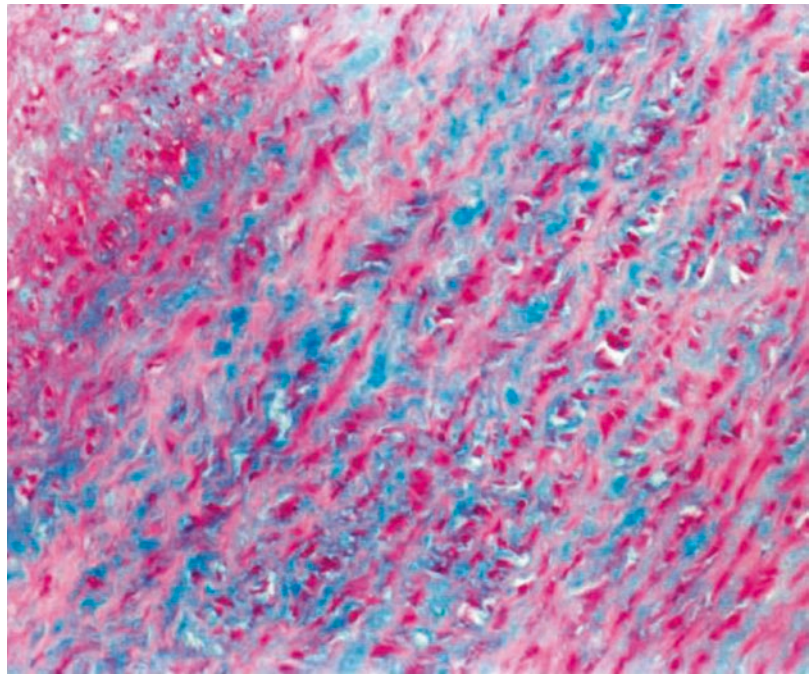

Fig. 14.3 Extensive Alcian Blue-positive mucopolysaccharides in the wall of the descending aorta in dissecting aortic aneurysm in the setting of idiopathic medial necrosis (×100)

Becker 1977; Brinkmann 1974; Anagnostopoulos et al. 1972; Burman 1960).

The severity of shrinkage and fragmentation of elastic fibers correlates with the extent of arterial intimal sclerosis, atrophy, and fibrosis of the muscular media. The vasa vasorum also demonstrates changes (Sorger 1968):

- Muscle hyperplasia
- Vascular ectasia
- Hyaline fusion of the vascular wall
- Endothelial swelling
- Intimal proliferation
- Intravascular thrombosis formation

Scant mucoid deposits can occur at any age and have no pathological relevance.

The term "segmental mediolytic arteritis"—often encountered in Anglo-Saxon countries—is ambiguous since no inflammatory vascular process is present (Lie 1992). Dissecting aneurysms are more rarely found in other arteries, such as the temporal, internal carotid, medial cerebral, basilar, coronary, splenic, femoral, anterior tibial, and vertebral arteries (Leu 1993). In such cases, histological investigation of vascular wall specimens can help clarify the cause. Cases of aortic dissection following cocaine consumption have been described (Palmiere et al. 2004).

14.1.4 Marfan Syndrome

Marfan syndrome is one of the most frequent genetic connective tissue disorders with a prevalence of 1 in 5000 Europeans (Wang et al. 2016; Hugar et al. 2014; von Kodolitsch and Robinson 2007; Byard 2006). It is an inherited connective tissue disorder with mutation on the fibrillin-1 gene (more than 500 identified mutations) (Klintschar et al. 2009; Byard 2006). Family clustering has been described (Hirani et al. 2008) and an autosomal dominant trait with complete penetrance but with phenotypic expression that varies considerably, both between and within families. Affected individuals develop varying patterns of organ involvement including the cardiovascular, ocular, skeletal, and pulmonary systems, as well as the skin and dura (Judge and Dietz 2005). Undiagnosed Marfan patients usually die from acute aortic dissection or rupture

and thus have an average life expectancy of about 32 years (Klintschar et al. 2009; Hirani et al. 2008; Hugar et al. 2014).

In Marfan syndrome, the aortic arch is particularly affected, demonstrating aneurysmal bulging which forms the point of origin of a dissecting aneurysm, as well as dilation of the aortic valve ring. Sudden, unexpected, and spontaneous rupture is possible (Bratzke and Wojahn 1977; Melsen 1973). If specimens are taken from the appropriate site, localized destruction of elastic fibers can be seen histologically (Elastica van Gieson staining).

The differential diagnosis between idiopathic cystic medial necrosis (Erdheim–Gsell) and changes seen in Marfan syndrome cannot be reliably made using histology, since both demonstrate loss and fragmentation of elastic fibers as well as pseudocystic areas in the aortic media with deposits of Alcian Blue-positive mucoid substances (Sariola et al. 1986; Saruk and Eisenstein 1977). However, in contrast to Marfan syndrome, there is no history of extravascular findings in idiopathic cystic medial necrosis, either in the deceased or their relatives. The differential diagnosis should take Ehlers–Danlos syndrome (Banaschak et al. 2002) or Loeys–Dietz syndrome into consideration; Marchesani syndrome also belongs to this group of diseases. Cases of familial dissecting aortic aneurysm have been reported (Schürch 1970). Even in younger people, a dissecting aneurysm should be considered (Gore 1953), whereby it is in precisely such cases that a genetic disposition is possible (Rippberger et al. 2009). In the case of death as a result of a ruptured dissecting aneurysm while performing an insured activity, issues relating to expert opinions may be raised, in some cases even medicolegal problems (Schmidt et al. 1996; Vock and Schulz 1986; Brinkmann 1974; Naeve and Brinkmann 1971). Distinction must be made in the differential diagnosis of dissecting aneurysm in the setting of atherosclerosis.

14.1.5 Ehlers–Danlos Syndrome

Ehlers–Danlos syndrome (EDS) is a connective tissue disorder characterized by the inability to produce sufficient amounts of collagen or a defect in the structure of collagen (Banaschak et al. 2002). EDS type IV, the vascular type, is marked by four clinical characteristics:

- Thin skin with visible veins
- Distinctive facial features
- Rupture of vessels and/or viscera
- Easy bruising/hematomas

While representing only 4% of the EDS cases, type IV poses the risk of premature death from spontaneous arterial, intestinal, or uterine rupture and may remain undiagnosed until postmortem examination (Shields et al. 2010; Prahlow and Wagner 2005; Wimmer et al. 1996). The median survival is approximately 48 years (Shields et al. 2010). Most deaths are caused by arterial dissection or rupture, involving a thoracic or abdominal vessel; cases with incidental myocardial infarction are rare (Gilchrist and Duflou 2005). There are also rare cases with type IV EDS presenting as sudden infant death (Byard et al. 1990) or leading to fatal hemoptysis (Yost et al. 1995). Additionally, there are reports where the cause of death was hemorrhage of the central nervous system. Histology and electron microscopy may demonstrate the findings of arterial wall thinning, decreased collagen content, and distorted collagen fibril structure. In routine histology (H&E, Elastica van Gieson), there are often no diagnostic microscopic pathological findings. Immunohistochemical detection of collagen type III reveals a significant reduction in the aortic media and adventitia, within the renal interstitium and the intrarenal vascular walls, as well as in the alveolar capillary regions of the lungs in particular (Banaschak et al. 2002). EDS can lead to myocardial infarction due to coronary artery dissection (Adés et al. 1995), to rupture of the coronary, thoracic, and other arteries (Aru et al. 1999; Collins et al. 1999; Evans and Fraser 1996; Nerlich et al. 1994), as well as to aneurysms of varying sizes (Eriksen et al. 1992). Nontraumatic vascular or bowel ruptures may cause sudden death even in children or adolescents (Aru et al. 1999; Kinnane et al. 1995; Soucy et al. 1990). The postmortem diagnosis can be supported by fibroblast cultures or by immunohistochemical examination of organ tissue (Reis et al. 1998). In rare

cases, EDS may simulate child abuse (Saulsbury and Hayden 1985; Owen and Durst 1984; Roberts et al. 1984). EDS can also cause sudden death in an infant in extremely rare cases (Byard et al. 1990).

14.1.6 Aneurysms in Other Arteries

In addition to atherosclerotic aneurysms of varying forms, other vascular wall changes can infrequently lead to dissecting aneurysms; primary vasculitides should be borne in mind in particular as the cause of secondary aneurysms. While aortic dissection frequently extends into its branches, isolated dissections of peripheral arteries, such as renal, coronary, pulmonary, and carotid vessels, are exceptional (Byard et al. 2017). In contrast, aneurysms of the visceral arteries are not a rare feature with the splenic artery being the most common site (Desinan et al. 2010; Thierauf et al. 2007; Saukko and Knight 2004; Merrell and Gloviczki 1992; Cosgrave et al. 1947). Ductal aneurysms are very rare. A primary defect in the internal elastic lamina of the ductal wall is assumed to be causal. A distinction is made between true ductal aneurysms, which can occur either as fusiform or dissecting variants, and so-called traction aneurysms, in which indentations in the aortic wall are drawn into the insertion of the ductus arteriosus (Früchtnicht and Albrecht 1998). Although atherosclerotic aortic aneurysms predominate in the majority of cases, there are reports on dissecting, as well as other, aneurysms, e.g., of the subclavian artery, the vertebral artery, the renal artery, the coronary artery (Makino et al. 2015; Jung et al. 2013; Erbersdobler and Tsokos 2006), or the splenic artery, sometimes in the setting of vasculitis (Desinan et al. 2010); isolated cases during pregnancy have also been reported (Srettabunjong 2013; Barbesier et al. 2013; Jung et al. 2013). For vertebral artery dissections, there are more reports on a traumatic cause of rupture (Kaiser et al. 2008; Galtés et al. 2012; Kristoffersen et al. 2012). As in basilar artery and coronary artery aneurysms, there is evidence of a genetic predisposition also in aortic dissection (Rippberger et al. 2009). In the case of traumatic aneurysm, histological tests should be performed to rule out primary vasculitis as a competing explanation for the aneurysm (Kaiser et al. 2008). The detection of hemorrhage at a survival time of approximately 3 days and longer, as well as the detection of siderophages, supports the assumption of a traumatic etiology of the aneurysm in the absence of primary vascular disease (Galtés et al. 2012; Kristoffersen et al. 2012; Kaiser et al. 2008) (Fig. 14.4).

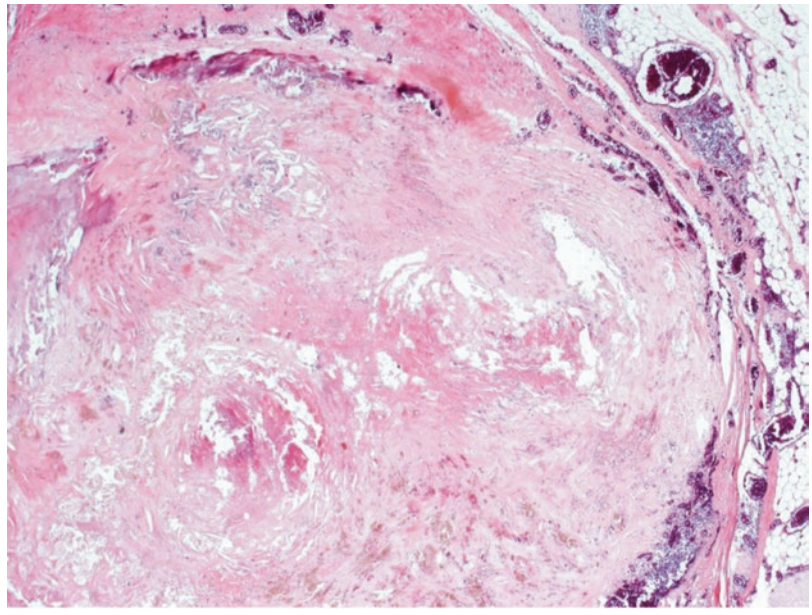

Fig. 14.4 Peripheral region of a thrombosed left circumflex artery aneurysm (H&E ×40)

14.1.6.1 Osler–Weber–Rendu Syndrome

Osler–Weber–Rendu syndrome, also known as *hereditary hemorrhagic telangiectasia (HHT)*, is a genetically inherited disease (Byard et al. 2001). Pulmonary arteriovenous malformations are predominantly found (Fig. 14.5); in the case of rupture or fistula formation, these can lead to hemothorax and death due to bleeding. More than half of all pulmonary arteriovenous malformations are seen in patients with Osler–Weber–Rendu syndrome (Ishikawa et al. 2010). If the pulmonary malformation is located in the subpleural region, rupture can rapidly result in hemothorax. If localized elsewhere in the lung, bleeding in peripheral branches of the bronchial tree and death due to blood aspiration are conceivable. From a differential diagnostic perspective, primary lung cancer, tumor metastasis, other vascular tumors (hemangiomas), and—as a rarity—extrauterine endometriosis in lung tissue (Morcos et al. 2006) should be considered.

In the differential diagnosis of Osler–Weber–Rendu syndrome, the *Klippel–Trenaunay syndrome*, a congenital angiodysplasia of venous vessels characterized by three main symptoms, cutaneous vascular nevi, hypertrophy of a limb, and varicosis or venous malformations, has to be pointed out (Pourhassan et al. 2007).

14.2 Arteritis

Of the underlying diseases with possible involvement of the coronary arteries, panarteritis nodosa, thromboangiitis obliterans, giant-cell arteritis (Shields et al. 2012; Pery et al. 1983), luetic arteritis (Frank et al. 1999; Glenewinkel et al. 1996), Takayasu's arteritis, Churg–Strauss syndrome (Schön et al. 2005), and rheumatic disease are mentioned in the literature.

14.2.1 Syphilitic Mesaortitis

Syphilitic aortitis is a complication of tertiary stage syphilis; histologically, up to 80% of patients show involvement of the cardiovascular system. Between 10 and 20 years may elapse from the time of infection to the clinical picture of syphilitic aortitis, although a faster disease course is possible. In addition to uncomplicated syphilitic aortitis, syphilitic aortic aneurysm, syphilitic endocarditis of aortic valve in particular with aortic insufficiency, as well as syphilitic

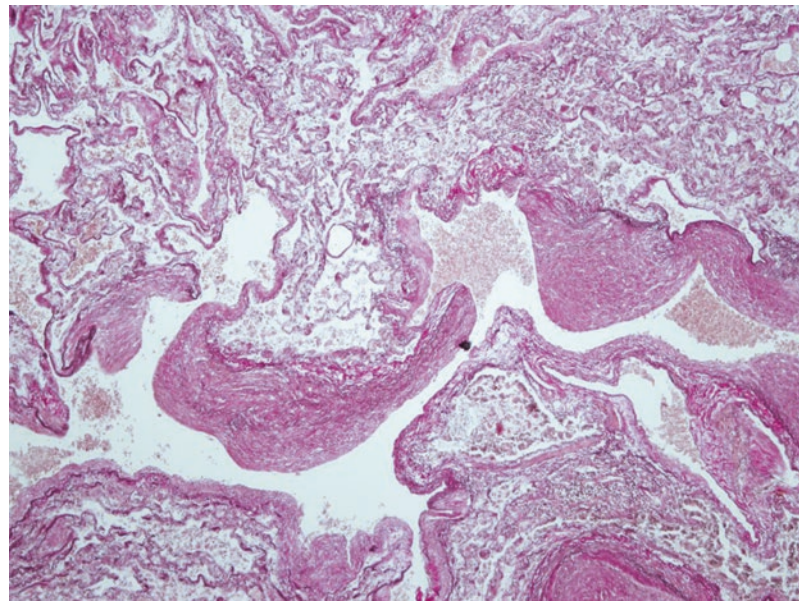

Fig. 14.5 Pulmonary *arteriovenous malformation* in Osler–Weber–Rendu syndrome with fatal blood aspiration following malformation rupture (Elastica van Gieson ×40)

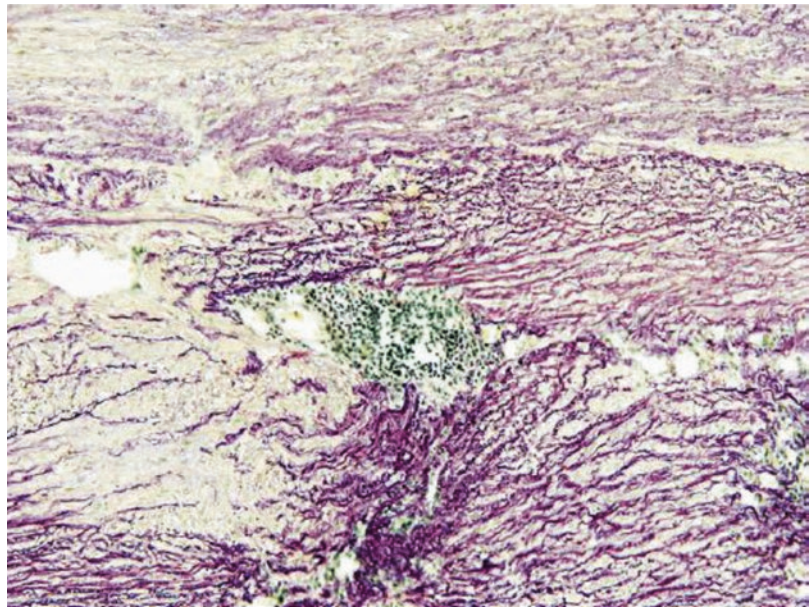

Fig. 14.6 Syphilitic aortitis with focal loss of fiber structures in the aortic media, as well as focal inflammatory infiltration with lymphocytes and plasma cells (Elastica van Gieson ×100)

coronary artery ostial stenosis may develop (Glenewinkel et al. 1996; Scharfman et al. 1950). The histological picture includes marked fibrous thickening of the aortic wall with lymphocytic and plasma cell infiltrates at the border between intima and media, in the media, and in the adventitial connective tissue (Fig. 14.6). These infiltrates may be more pronounced around the vasa vasorum. The elastic fibers of the aortic or arterial media are rarefied and fragmented and partially replaced by collagenous scar tissue. The histological picture described here, however, requires serological confirmation prior to a definitive diagnosis (Gormsen 1984).

14.2.2 Suppurative Aortitis in Atherosclerosis

The spectrum of rare primary inflammatory vascular diseases also includes suppurative arteritis, more rarely primary coronaritis (Dettmeyer et al. 1998a), and hypersensitivity angiitis. These vascular diseases can have a fatal outcome as a result of acute obturating thrombosis, vascular stenosis, or rupture. Histopathologically, granulomatous, giant-cell containing, and lymphoplasma cellular arteritis can be found (Cassling et al. 1985; Hushang et al. 1984). Only few cases describe inflammatory aneurysm of the abdominal aorta in the setting of existing coronaritis (Cohle and Lie 1988; Pereira et al. 1981).

The severity of the inflammatory process can vary greatly: on the one hand, findings may reveal scant inflammatory infiltration of the vascular wall and perivascular tissue, while on the other, dense lymphocytic infiltrates may be present accompanied by germinal center formation in longer disease courses. Hypersensitivity angiitis should be considered in the differential diagnosis if eosinophilic granulocytes are present. Nonspecific angiitis is frequently found, while suppurative aortitis in the setting of infected aortic atherosclerosis (Fig. 14.7), which can lead to vascular wall rupture, is rare (Eplinius and Hädrich 2014). Aortitis as the cause of death in infants is extremely rare (Schäfer and Püschel 1996).

14.2.3 Giant-Cell Arteritis

Intramyocardial vascular involvement in the context of systemic vascular wall inflammation is occasionally seen in the form of uncharacteristic and nonspecific vasculitis (Fig. 14.8; Table 14.1).

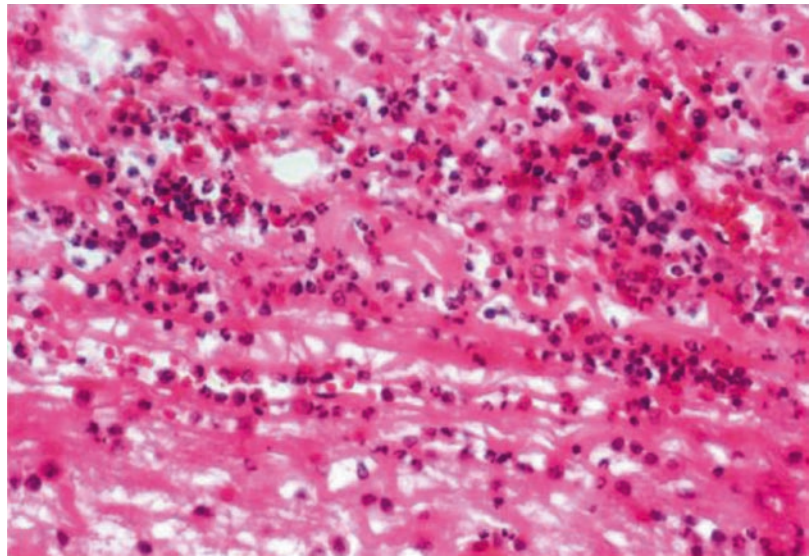

Fig. 14.7 Acute rupture of suppurative aortitis in severe atherosclerosis (H&E ×200)

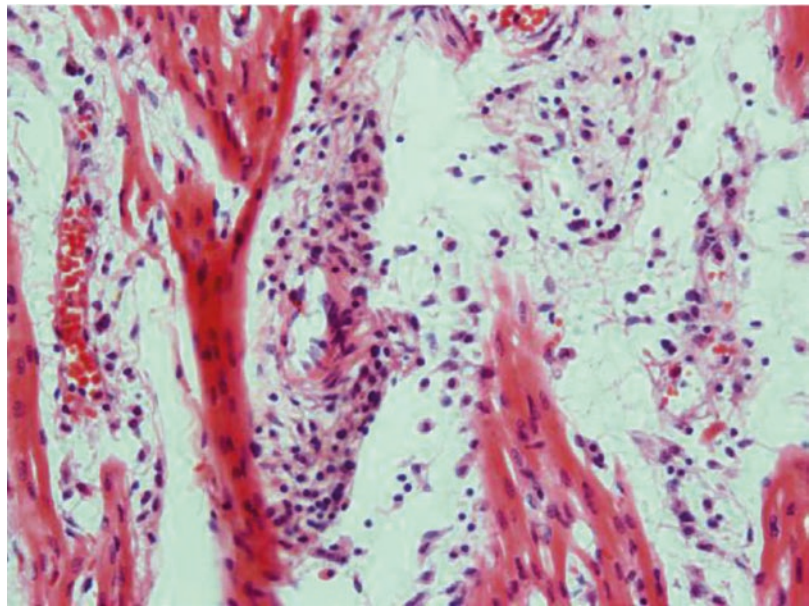

Fig. 14.8 Nonspecific vasculitis of peripheral intramyocardial arterial branches (H&E ×200)

Giant-cell arteritis occurs as temporal arteritis; the aorta is less frequently affected, as are the coronary arteries. Thus, giant-cell arteritis could be proven histologically as the cause of aortic rupture (Pery et al. 1983; Ainsworth and Gresham 1961); coronary artery involvement is also possible in giant-cell arteritis (Fig. 14.9) (Karger and Fechner 2006; Kumar et al. 2002). Giant-cell arteritis is an arterial disease of unclear etiology seen in the elderly, in the form of temporal arteritis and rheumatic polymyalgia (Salvarani et al. 2002). Appearing in almost all arteries, it was first described in 1932 (Horton et al. 1932). In the case of coronary artery involvement, myocardial infarction (Karger and Fechner 2006; Martin et al. 1980) or dissecting aneurysm (Magarey 1950) may result, both with fatal outcomes (Cohle et al. 1982).

Immunohistochemically, the giant cells react positively to the macrophage-specific antibody CD68 (Wagner et al. 1994) and are negative for the antibodies MRP 8 and 14 (Karger and

Table 14.1 Differential diagnosis of giant-cell arteritis

Term	Characteristic histological findings	Preferential localization
Syphilitic mesaortitis (mesaortitis syphilitica, lues)	Focal necrosis of the aortic media; lymphoplasma cellular infiltrate perivascularly around the vasa vasorum	Ascending aorta
Takayasu's arteritis	Granulation tissue with polynuclear giant cells, fibrosis of the aortic intima, elastic fiber degeneration, and fragmentation	Aortic arch, aortic arch arteries
Giant-cell arteritis	Giant cells (CD68+) in granulation tissue, intimal fibrosis, "skip" lesions, degeneration, and fragmentation of elastic fibers	Aorta, primarily large and medium arteries, rarely coronary arteries
Panarteritis nodosa	Fibrinoid necrosis, followed by scarred granulation tissue, and sectorial lesions	Medium and small muscle-like arteries
Coronaritis	As giant-cell arteritis; primary isolated coronaritis without giant cells, with thick lymphocytic infiltrate, and germinal centers	As giant-cell arteritis, usually involvement of all coronary artery; as primary arteritis, segmental involvement

Modified from Pery et al. (1983)

Fechner 2006). The cores of the giant cells are frequently arranged in a horseshoe or circular form. The giant cells are localized in close association to fragmented fibers of the internal elastic lamina (Kimmelstiel et al. 1952) and are often accompanied by a dense lymphocyte-rich inflammatory infiltrate of all three wall layers. Additionally, neutrophil granulocytes and macrophages can be observed. The arterial wall is thickened, and a concentric narrowing of the lumen by intimal hyperplasia may be present (Karger and Fechner 2006).

Churg–Strauss syndrome (CSS). This rare syndrome with an incidence of 1–3 cases per 1 million individuals per year is characterized by systemic eosinophilic granulomatous vasculitis, in later stages with involvement of all internal organs including life-threatening eosinophilic myocarditis. Inflammatory eosinophilic infiltrates can show granuloma-like arrangement and necrosis. Without histological examination of tissue samples, it is not possible to correctly diagnose eosinophilic myocarditis and/or perimyocarditis. The presence of extravascular eosinophilic blood cells appears to be the most relevant diagnostic criterium for Churg–Strauss syndrome. Most important differential diagnoses include rheumatologic diseases and allergic asthma (Schön et al. 2005; Noth et al. 2003).

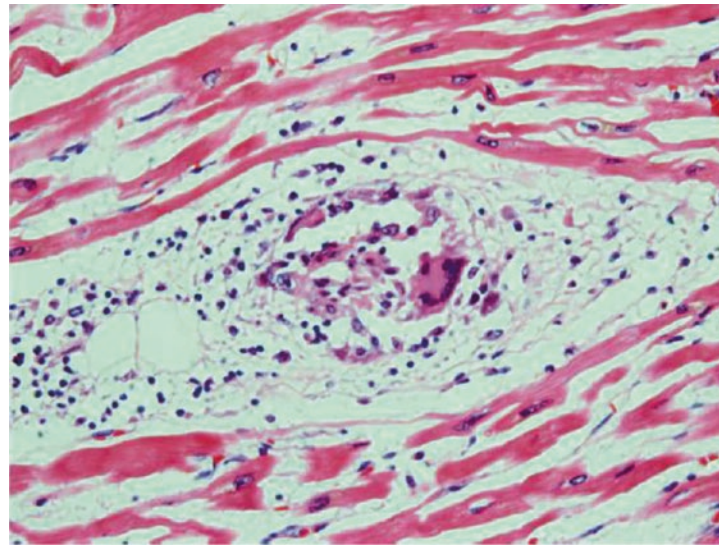

Fig. 14.9 Intramyocardial giant-cell arteritis in peripheral coronary artery branches (H&E ×200)

14.2.4 Isolated Coronary Arteritis

There are numerous case reports in the literature on inflammatory changes in the coronary arteries as a cause of sudden cardiac death (Inokuchi et al. 2014; Norita et al. 2012; Dettmeyer et al. 1998a; August and Holzhausen 1992; Fujita et al. 1992; Paul et al. 1990; Tanaka et al. 1988; Lie 1987; Mitchinson et al. 1984). Isolated coronaritis, however, is very rare. Macroscopically, marked thickening of the segmentally involved coronary wall is conspicuous, with clear luminal narrowing. Inflammatory changes can be seen in a circular pattern. Histologically, giant-cell arteritis of the coronary arteries or granulomatous arteritis may be present (Aufderheide et al. 1981). In the absence of evidence of polynuclear giant cells, and in the case of isolated, segmental involvement of the coronary arteries, coronaritis demonstrates a dense, primarily lymphocytic inflammatory infiltrate, in addition to which germinal centers may be present (Fig. 14.10), while densely aggregated hemosiderin deposits may be found in granulation tissue (Fig. 14.11). Pronounced coronaritis can be a plausible cause of death. Neutrophil granulocytes are barely detectable, while eosinophil granulocytes may be present in only scant numbers (Kajihara et al. 2013).

14.2.5 Takayasu's Arteritis

Takayasu's arteritis is a very rare, special form of arteritis, affecting women more commonly than men (Johnston et al. 2002; Gravanis 2000; Amano and Suzuki 1991; Lupi-Herrera et al. 1977; Rosen and Gaton 1972). Typically, segmental involvement of one artery is seen, while vascular occlusion is possible in smaller arteries. Coronary artery involvement can be the cause of sudden death (Krompecher et al.

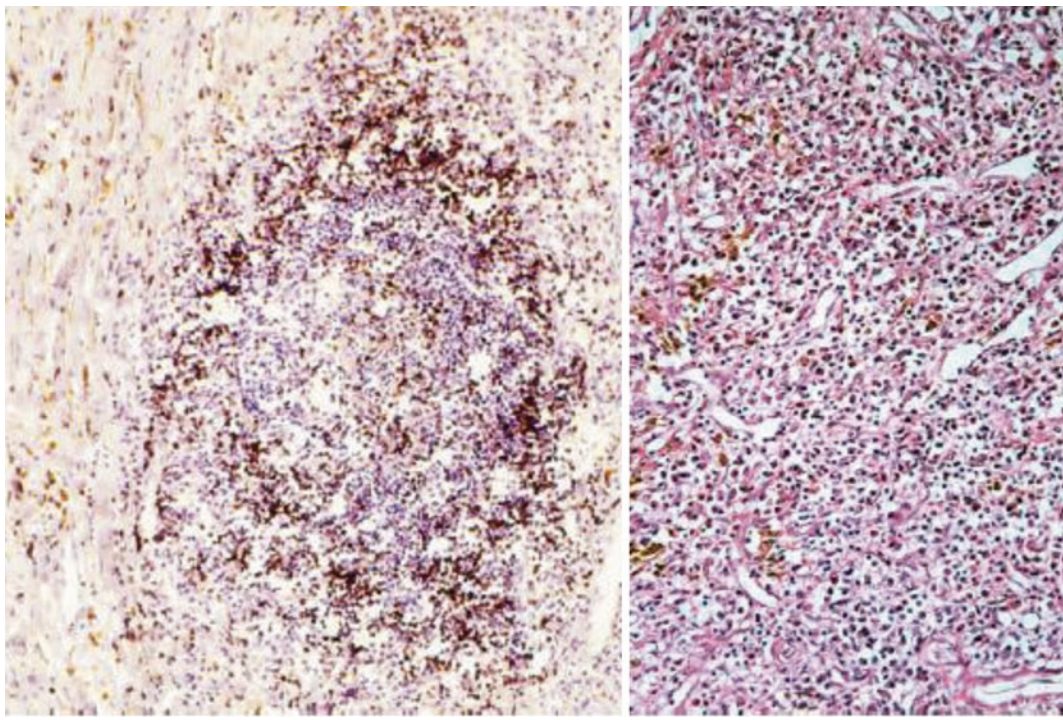

Fig. 14.10 Lethal coronaritis: pronounced stenosing coronaritis with germinal center formation in the circular, stenosing lymphoplasma cellular infiltrates within the vascular wall and in perivascular tissue; immunohistochemical detection of CD3+ T-lymphocytes (CD3 ×100; left); section of the left coronary artery wall with dense lymphoplasma cellular infiltration in loose granulation tissue (H&E ×200; right)

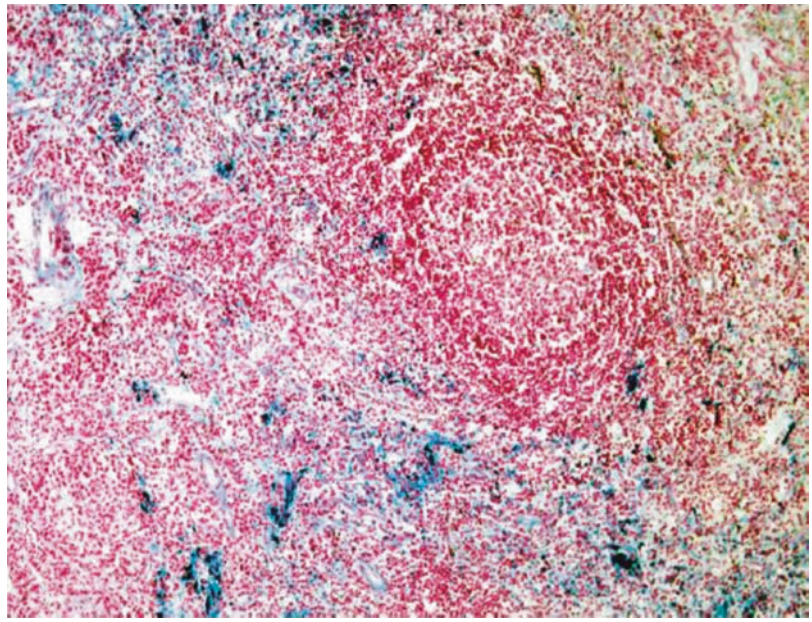

Fig. 14.11 Lethal coronaritis: inflammatory granulation tissue with densely aggregated lymphocytes, plasma cells, scant eosinophil granulocytes, and siderophages (Prussian blue ×200)

1984). Histologically, segmental lymphoplasma cellular inflammation of an artery wall section can be seen at acute and subacute stages; the arterial intima and adventitia in particular may be severely affected. Inflammatory cells may be embedded in a well-vascularized, fine connective tissue. Depending on stage, areas of fibrosis may already be found, while inflammatory cells can infiltrate the arterial media, which generally remains clearly discernible. Necrosis and granulomas are rare; single polynuclear isolated giant cells have been described. Approximately 30% of cases of Takayasu's arteritis show coronary artery involvement, the proximal sections being those mostly commonly affected. Isolated involvement of a cardiac artery is very rare (Seguchi et al. 1990; Rosen and Gaton 1972; Krompecher et al. 1984). Occasionally, the disease can involve the aortic base, with extension into the aortic valve, coronary arteries, and interventricular septum, causing sudden death. Segmental involvement of the abdominal aorta produces aneurysms. Newly formed lesions may be found in the splenic and renal arteries (Aufderheide et al. 1981).

14.2.6 Kawasaki Disease

Kawasaki disease (mucocutaneous lymph node syndrome, MLNS), first identified in 1967 by Tomisaku Kawasaki, is an acute systemic but self-limiting vasculitis of childhood that can result in coronary artery aneurysms, myocardial infarction, and sudden death in previously healthy children (Rowley and Shulman 2010; Wood and Tulloh 2009; Suzuki et al. 2000; Bayer Kristensen and Østergaard Kristensen 1994; Althoff 1990; Landing and Larson 1987; Tanaka et al. 1986; Missliwetz et al. 1981; Yutani et al. 1981; Kawasaki et al. 1974). In more than 20% of patients, severe inflammation of the vasa vasorum led to coronary arteritis with aneurysm formation, thrombosis, and severe fibrous stenosis (Fineschi et al. 1999). Morbidity and mortality are mainly associated with the development of coronary aneurysms (Canino-Rodriguez and Cox 2008; Murai et al. 1989; Schultz 1989). Of unknown etiology, it is the most common cause of acquired heart disease in young children (Ashrafi et al. 2007). The intense inflammatory process has a predilection for the coronary arteries, resulting in the development of aneurysmal lesions, arterial thrombotic occlusion,

or, potentially, sudden death. Giant aneurysms due to Kawasaki disease can rupture, presenting histological findings with aggregations of neutrophils containing myeloperoxidase and neutrophil elastase scattered in chains over the aneurysm wall. These findings suggest that destruction of the wall by an enzyme may cause aneurysm rupture (Sunagawa et al. 2008). Cases with late sudden death from obliteration of the lumen of the full length of the left anterior descending coronary artery are reported (McConnell et al. 1998). The clinical picture of Kawasaki disease varies greatly, and even extensive myocardial damage may be asymptomatic for many years (Kristensen and Kristensen 1994). Long-term follow-up of coronary artery lesions has revealed several characteristic features, including progressive localized stenosis, extensive recanalizations, and development of collateral arteries. Saccular aneurysms can be large with calcified, thin walls, composed of an internal fibrocalcified layer and an external thin tunica media (Fineschi et al. 1999). Late stages present without any signs of active inflammation. Usually, individuals affected were completely healthy, often asymptomatic, and without an identifiable risk factor for cardiovascular disease prior to the fatal event (Rozin et al. 2003). With regard to histological examinations, it is important to note that myocarditis also frequently occurs in the acute phase of Kawasaki syndrome, even in the case of prior normal echocardiography (Yoshikawa et al. 2006; Yonesaka et al. 1992). Juvenile periarteritis should be considered in the differential diagnosis (Missliwetz et al. 1981).

14.2.7 Drug-Associated Vasculitis

There are reports in the literature on necrotizing angiitis associated with drug abuse (Halpern and Citron 1971) and heroin-associated cerebral arteritis (King et al. 1978), as well on neurosurgical complications of heroin addiction including brain abscess and mycotic aneurysm (Amine 1997).

14.3 Heart Valve Defect: Endocarditis

Acute, frequently polypoid and occasionally bacterially infected inflammation of a heart valve (ulcerative polypoid endocarditis) is found primarily at the mitral and aortic valves. Macroscopic diagnosis can be confirmed histologically by evidence of partially fibrin-covered granulation tissue at the surface (Fig. 14.12), capillarization of valve tissue, and pos-

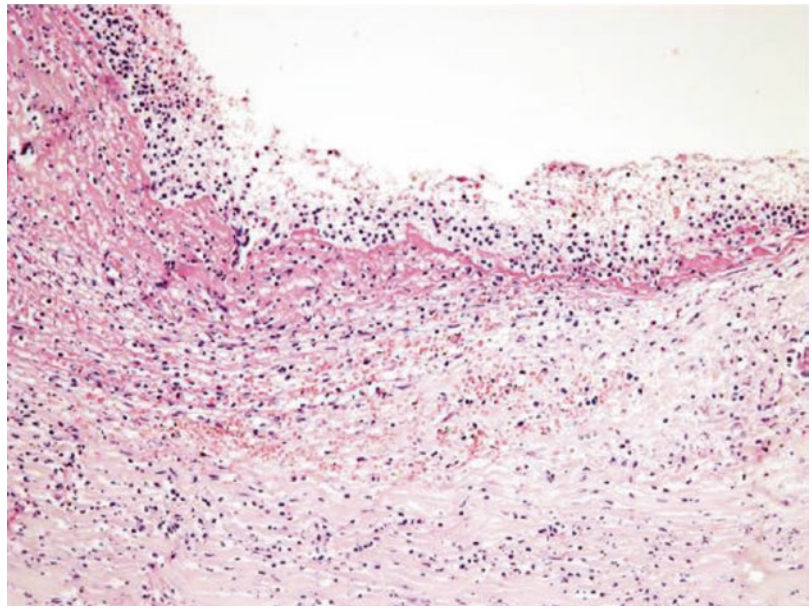

Fig. 14.12 Acute recurrent fibrinous endocarditis of the mitral valve: flat fibrin layer, infiltrated by a mixed-cell inflammatory infiltrate, edematous fibrous cardiac valve tissue (H&E ×100)

sible detection of an adherent thrombosis, in addition to which basophilic bacterial colonies can be seen in infective endocarditis. Inflammatory processes of longer standing may fibrose and reveal basophil calcium salt deposits (Fig. 14.13). Aortic bicuspid valve, infective endocarditis, and subaortic aneurysm appear to be associated (Saint-Martin et al. 2009). Post-inflammatory mitral valve stenosis can lead to hemosiderin-laden macrophages in the lungs (Fig. 14.14).

14.4 Amyloidosis

The spectrum of potentially lethal metabolic diseases relevant in forensic practice covers a multitude of diseases. In addition to congenital metabolic diseases or mitochondrial diseases [e.g., medium-chain acyl-CoA dehydrogenase deficiency (MCAD) in neonates and infants], diabetes (see Chap. 16), and mucoviscidosis, sudden unexpected death also occurs in various forms of

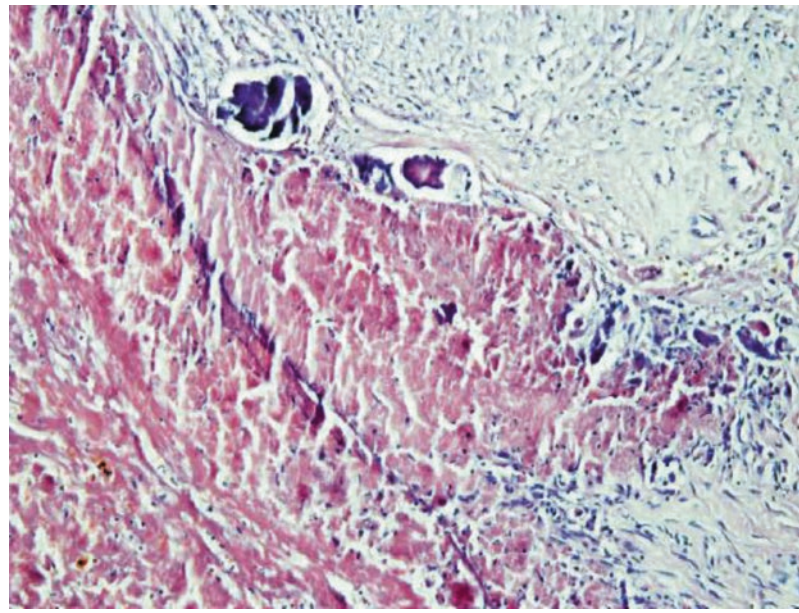

Fig. 14.13 Endocarditis of the aortic valve with dystrophic basophil calcification of the valve ring (H&E ×100)

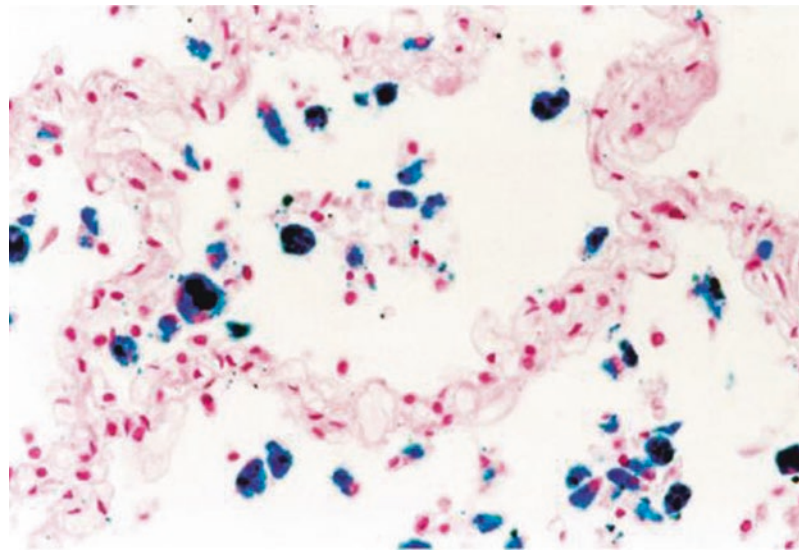

Fig. 14.14 Multiple hemosiderin-laden macrophages in the lungs following post-inflammatory mitral valve stenosis (Prussian blue ×400)

amyloidosis, Addison's disease (see Chap. 16), undetected pheochromocytoma (see Chap. 16), or cases of sudden death due to Fabry disease, which is regarded as an underdiagnosed disease (Hoffmann and Mayatepek 2009).

Amyloidosis. Amyloidosis is a multisystem disease. Amyloid deposits are found in various organs or organ systems. Amyloids are proteins of varying chemical structure, which forms the basis for the amyloid classification (Röcken 2009). In this context, a letter code is used, whereby, e.g., "A" represents amyloid fibril protein and the abbreviation "TTR" represents the precursor protein transthyretin (formerly prealbumin). Approximately 75 amyloid TTR variants have been identified to date (Merlini 2003).

Amyloidosis is a chronic disease which can long remain symptom-free and undetected; hereditary forms are also known (Gertz 1992). The distribution and extent of amyloid deposits determines the disease course, occasionally also the acuteness of death, particularly in the case of cardiac involvement (Röcken 2008). Amyloidosis is only macroscopically suspected in severe forms; here the conspicuously light red tissue has a markedly hardened consistency, in particular the spleen (so-called ham spleen), and the myocardium has a rubbery consistency.

Amyloid deposits can be detected in all organs and organ systems as homogeneous eosin red glycoprotein complexes using conventional amyloid staining or Congo red staining. Characteristic apple-green deposits are seen when visualized through crossed polarimetric filters; in fluorescence microscopy, amyloid deposits have a yellowish-orange color. The distribution pattern of the amyloid deposits in the organism enables typing as, e.g., cardiovascular-type amyloidosis (Kieninger et al. 2010). Amyloidosis can exhibit different protein structures and, likewise, can be classified on this basis, e.g., AA amyloidosis or ATTR amyloidosis. The most common systemic variant is an immunoglobulin-derived light chain (AL) amyloidosis (Morgenthal et al. 2016). A classification of myocardial amyloidosis based on the intensity of amyloid deposits has been proposed, whereby the degree of deposition was evaluated on the basis of visual judgment. At grade I, less than 25% of the myocardial area consisted of amyloid; at grade II, 25–50%; and at grade III, more than 50% (Kieninger et al. 2010). A distinction is made between various amyloid types depending on distribution patterns. In cardiovascular amyloidosis, primarily arteries have thickened vascular walls, containing striped, semicircular Congo red-positive amyloid deposits in the vascular wall media (Figs. 14.15 and 14.16); massive

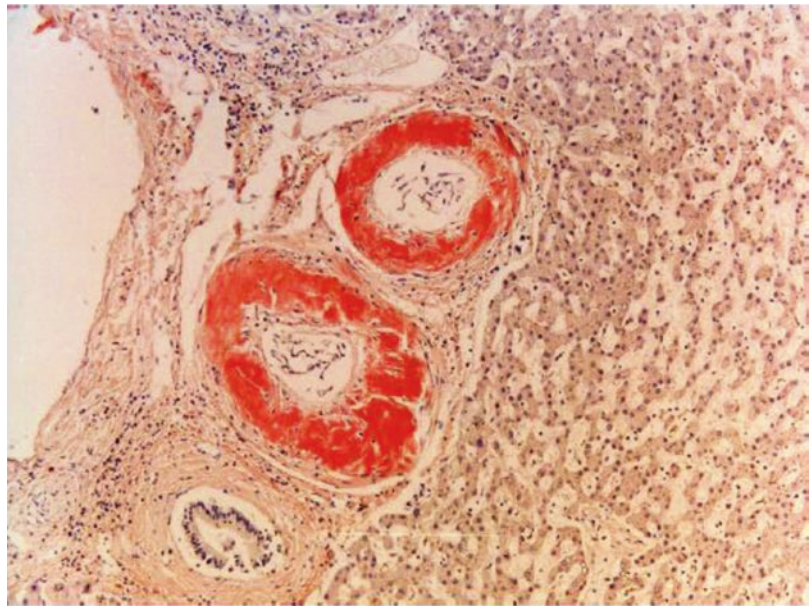

Fig. 14.15 Vascular amyloidosis with striped, Congo red-positive amyloid deposits in intrahepatic vascular branches (Congo red ×200)

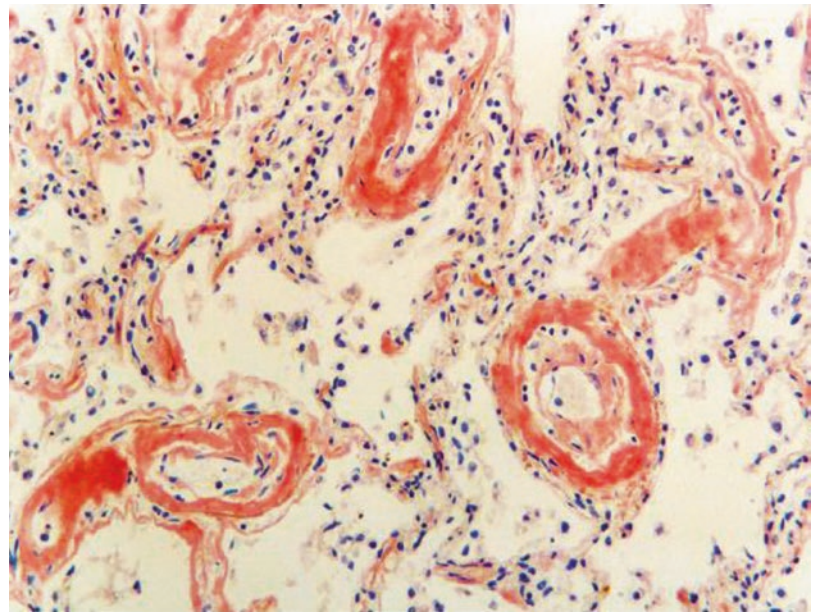

Fig. 14.16 Intra pulmonary vascular amyloidosis (Congo red ×200)

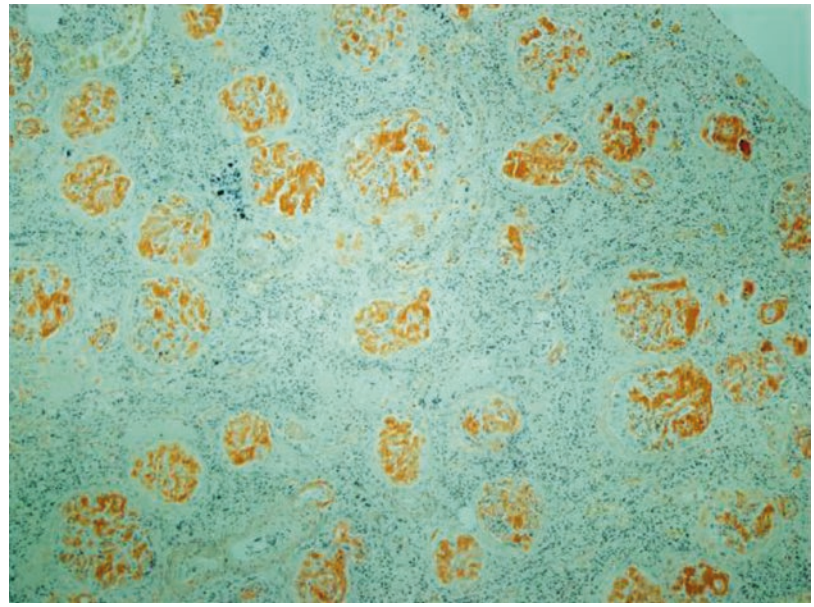

Fig. 14.17 Intrarenal amyloidosis with involvement of the glomeruli (Congo red ×40)

involvement of renal glomeruli also is possible (Fig. 14.17). In the myocardium, these deposits can be detected in the interstitium, leading to restrictive cardiomyopathy. In this context, the contractile function of cardiomyocytes is impaired to the same extent as the cardiac conduction system and cardiac microcirculation. Distinct amyloid deposits could represent a plausible explanation for acute rhythmic cardiac death (see Chap. 1, Fig. 1.3) (Gertz 1992; Hassan et al. 2005; Dröber et al. 2010).

The prognosis of cardiac amyloidosis depends on the nature and origin of the amyloid protein deposited (Kieninger et al. 2010). Patients with cardiac amyloidosis can show persistent elevated troponin levels. Therefore, it is important to consider cardiac amyloidosis in

patients with troponin elevation and heart failure (Kraemer et al. 2009).

Other vascular and metabolic diseases can explain sudden unexpected death (e.g., mucoviscidosis, etc.). In this respect, diseases are also encountered in forensic practice for which a histological and immunohistochemical correlation can be found in the relevant general and specialized forensic literature.

14.5 Hemochromatosis

Hereditary hemochromatosis is a frequent autosomal recessive disease which causes iron overload of various organs. Symptoms and organs involved can vary, and only a minority develops liver cirrhosis and pancreatic fibrosis. However, the life expectancy of persons with moderate or subclinical symptoms is reduced (Niederau et al. 1985). Although there are cases with myocardial damage leading to cardiomyopathy with an increased risk of sudden cardiac death, there are only single case reports in the forensic literature (Klintschar and Stiller 2004). Microscopically, the liver will show micronodular cirrhosis with portal fibrosis containing slight inflammatory infiltration. Prussian blue and therefore iron-positive granules may be abundant in phagocytes and bile duct epithelia (Fig.14.18). Iron may also

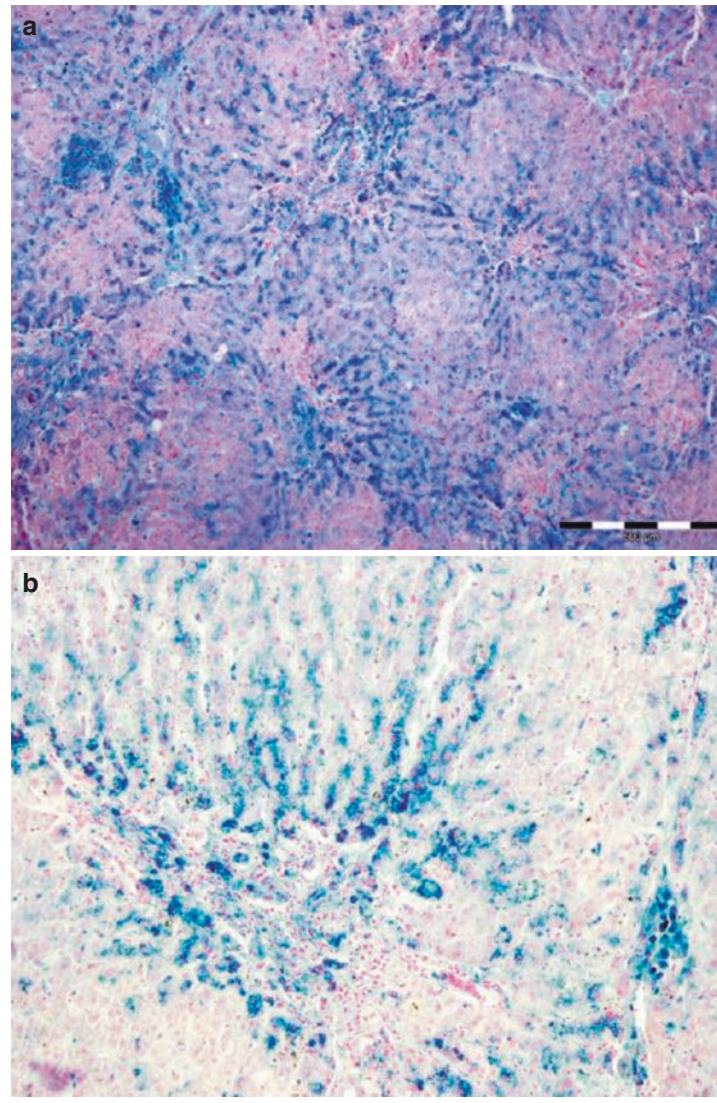

Fig. 14.18
Hemochromatosis with (**a**) iron overload and beginning liver cirrhosis (Prussian blue ×100) and (**b**) multiple iron-positive granules in hepatocytes, phagocytes, and bile duct epithelia (Prussian blue ×200)

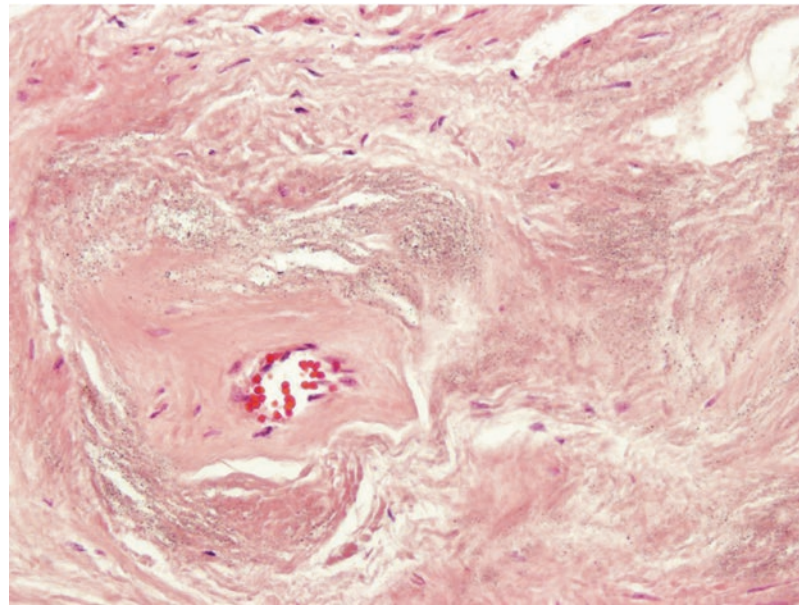

Fig. 14.19 Ochronosis with fine, dustlike blackish-brown deposits in collagenous scar tissue within the myocardium (H&E ×400)

be present in all other parenchymal organs. Iron-containing granules in the myocardium, combined with marked dilation and disconnection of the muscle fibers accompanied by microfocal necrosis, may explain sudden cardiac death (Klintschar and Stiller 2004; Passen et al. 1996).

14.6 Ochronosis

Ochronosis is a rare, congenital, autosomal recessive metabolic disease with an incidence of between 1:250,000 and 1:1,000,000. It is characterized by an accumulation of homogentisic acids in the body and their excretion in urine (*alkaptonuria*). When polymerized homogentisic acids are deposited in collagen-containing tissue (sclera, skin, hyaline cartilage, blood vessel intima, intervertebral discs), these tissues take on a blackish-brown color—a finding that is macroscopically patent at autopsy in advanced cases (Breer et al. 2012). From a histopathological perspective, dust-like blackish-brown deposits are seen particularly in intervertebral disc tissue and joint capsules. Deposits in thyroid tissue in the setting of ochronosis can cause the clinical picture of "black thyroid," as also described in minocycline use (see Chap. 16). In individual cases, deposits are found even in small areas of fibrotic scarring within the myocardium (Fig. 14.19). Other manifestation sites of ochronosis can include, e.g., the coronary arteries, the aortic wall, and the dura mater.

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