Pathology of Fulminant Myocarditis

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Although prominent achievements have been made in the identification, diagnosis, and treatment of myocarditis, the pathological diagnosis of myocarditis is still a difficult problem due to continuous changes of the diagnosis criteria, classification, and pattern of infection. Sobernheim first proposed the diagnosis of myocarditis in 1837. In 1858, the famous German pathologist Virchow popularized the diagnosis of myocarditis. In 1912, Herrick noted the morphological characteristics of ischemic myocardial necrosis. Since then, the diagnosis rates of myocarditis have decreased significantly. The advent of transvenous endomyocardial biopsy (EMB) in 1962 changed the knowledge of the pathophysiology, etiology, and therapeutics of myocarditis. In 1984, eight cardiac pathologists gathered in Dallas, USA, and developed the morphological standards and Dallas Criteria for the diagnosis of myocarditis in EMB samples. Subsequently, the Dallas Criteria was accepted and promoted by the National Institutes of Health, and is still the standard for the identification of myocarditis by pathologists. According to the histological characteristics in EMB and the clinical manifestations, in 1991, Lieberman classified myocarditis into fulminant myocarditis, acute myocarditis, chronic active myocarditis, and chronic persistent myocarditis.

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6.1 Overview of the Pathology of Myocarditis and Fulminant Myocarditis

According to the Dallas Criteria [1], myocarditis can only be diagnosed if myocyte necrosis, degeneration, or both associated with an inflammatory infiltrate adjacent to the degenerating or necrotic myocytes can be demonstrated. However, the morphology of myocardial damage in myocarditis differs from that in ischemic heart disease. According to the types of infiltrated inflammatory cells, myocarditis can be subdivided into lymphocytic, eosinophilic, neutrophilic, giant cell, granulomatous, and mixed cell types. According to the area of inflammatory cell infiltration, myocarditis can be classified into interstitial, perivascular, and endocardial types. According to the severity of cardiac lesions, myocarditis can be divided into slight, mild, moderate, and severe degrees. According to the distribution of inflammatory cell infiltration, myocarditis can be divided into focal, confluent, or diffuse types. Borderline myocarditis refers to a subtype of focal inflammatory cell infiltration

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in the interstitial myocardium, but without obvious myocardial necrosis. According to the Dallas Criteria [1], myocarditis is divided into active, recurrent, rehabilitative, and marginal subtypes, and persistent cardiac viral infection without inflammatory cell infiltration is defined as non-inflammatory viral cardiomyopathy.

Myocarditis is one of the most common causes of sudden cardiac death, especially accounting for sudden deaths in children and young people. Domestic reports stated that the rate of myocarditis detected in autopsies was 2.8%, while in foreign countries it was 4–9%. This rate increased up to 20% in the sudden deaths of children.

Based on etiology, myocarditis is divided into infectious and non-infectious categories. Myocarditis induced by different causes manifest differently in etiologies, pathophysiological mechanisms, and pathological changes(Table 6.1) [2, 3].

6.1.1 Infectious Myocarditis

Infectious myocarditis is caused by an infection of pathogenic microorganisms including viruses, bacteria, fungi, parasites, and so forth. Viral and bacterial myocarditis are the most common types of myocarditis [4]. The main pathogens of infectious myocarditis include the following categories:

1. Viruses. Coxsackie virus, echovirus, adenovirus, cytomegalovirus, varicella-zoster virus, simple herpes virus, Epstein-Barr virus, measles virus, rubella virus, polio virus, influenza virus, acute encephalitis virus, respiratory syncytial virus, arena virus, dengue fever virus, hepatitis virus, human immunodeficiency virus, Junin virus, coronavirus, rabies virus, yellow fever virus, smallpox virus, and so forth.

Table 6.1 The classification and etiology of myocarditis [2, 3]

Types of myocarditis	Etiology	Important examples of myocarditis
Infectious myocarditis	Viruses Pyogenic bacteria Specific bacteria Fungi *Rickettsia* Parasites	Coxsackie viral myocarditis Septic myocarditis Tuberculous myocarditis Diphtheria toxic myocarditis Fungal myocarditis *Rickettsia* myocarditis Chagas myocarditis Toxoplasmosis myocarditis Trichinosis myocarditis
Myocarditis with systemic disease	Collagen-associated vascular disease Acute rheumatic fever Pregnancy	SLE Rheumatic myocarditis Perinatal myocarditis
Granulomatous myocarditis		Sarcoidosis Idiopathic giant cell myocarditis
Drug/toxin-induced myocarditis	Antibiotics, diuretics, antitumor drugs, catecholamines Chemical poisons or heavy metals (phosphine, arsenic, lead, etc.) Biological toxins (venomous snakes, spiders, scorpions, bee bites or stings)	Drug allergic myocarditis
Others	Physical factors (radiation) Transplantation-associated myocarditis	

2. Bacteria. *Streptococcus, Staphylococcus, Pneumococcus, Meningococcus, Mycobacterium, Diphtheria*, Brucella, *Neisseria gonorrhoeae, Haemophilus, Vibrio cholerae,* Listeria, *Actinomycetes, Tularea*, *Salmonella*, Whipple, *Campylobacter*, and so forth.
3. Spirochetes. *Leptospira, Treponema pallidum, Borrelia burgdorferi*, and *Treponema pallidum.*
4. Rickettsia. *Coxiella burnetii*, Rocky Mountain spotted fever, and tsutsugamushi disease.
5. Fungi. *Candida, Mucor, Aspergillosis, Coccidia, Blastomyces, Cryptococcus, Histoplasma*, and so forth.
6. Protozoa/helminth. *Trypanosoma, Toxoplasma, Cysticercosis, Sarcosporidium, Schistosome, Echinococcus, Paragonimus, Trichinella,* Filariasis, roundworms, and so forth.

6.1.2 Non-infectious Myocarditis

1. Systemic disease-associated or immunoreactive myocarditis such as systemic lupus erythematosus (SLE), rheumatism, rheumatoid disease, drug allergic myocarditis, nodular polyarteritis, dermatomyositis, Kawasaki disease, perinatal cardiomyopathy, thrombotic thrombocytopenic purpura, and so forth.
2. Myocarditis caused by physical or chemical factors such as drugs (toxins), heavy metals, biological toxic substances, metabolic disorders (uremia, hypokalemia), and physical injuries.
3. Other types such as sarcoidosis, idiopathic giant cell myocarditis, and so forth.

The clinical manifestations of myocarditis are diverse, ranging from asymptomatic to severe arrhythmia, acute heart failure, cardiogenic shock, and even death. The EMB is the "gold standard" for the clinical diagnosis of myocarditis.

Pathological lesions vary significantly in myocarditis. In some cases, it shows diffuse damage such as myocardial relaxation, lack of elasticity, decreased ventricular tension and compliance, and cardiac enlargement and dilation of the chambers. In other cases, there are myocytic edema, dissolution, necrosis, and interstitial inflammatory infiltration that may lead to acute heart failure, pulmonary edema, cardiogenic shock, or even death. If the disease affects the cardiac conduction system, it can cause various degrees of atrioventricular block, and even ventricular fibrillation which may induce Adam–Stokes syndrome or sudden death.

Myocarditis is usually characterized by myocardial architectural displacement and the presence of focal mononuclear cells and lymphocytes that cause encroachment or scalloping of the sarcolemmal membrane of myocytes, the fragmentation of myocytes with remnants of cytoplasm or bare nuclei, or diffuse infiltration and even the replacement of myocytes by inflammatory cells in severe cases. Extensive myocytolysis and necrosis are rare. The use of Masson's trichrome is helpful in difficult cases because damaged myocytes display a basophilic tinctorial quality [4].

It should be noted that, in terms of pathological diagnosis, the interpretation of myocardial inflammatory cell infiltration must be cautious, because in approximately 5–10% of non-myocarditis deaths (such as mechanical injury, poisoning, etc.), more-or-less focal inflammatory cell infiltrations are present in the myocardial interstitium without myocardial degeneration or necrosis. Only in circumstances where the lesions are severe enough to induce clinical symptoms can the diagnosis of myocarditis be taken into consideration. Under physiological conditions, there are also a few lymphocytes under the endocardium, usually less than 5 cells/mm^2. In 1999, the World Heart Association Consensus Meeting issued a quantitative immunohistopathology standard for myocarditis, which is defined as inflammatory cell infiltration >14/mm^2 [5]. Fulminant or acute progressive myocarditis usually manifests rapid clinical progress and the diffuse infiltration of inflammatory cells in biopsy specimens. The latest diagnostic criteria for fulminant myocarditis was defined as >50/mm^2 inflammatory cell infiltration with obvious myocardial necrosis [6].

The differences between myocarditis and myocardial inflammatory responses, which are two distinct types of pathological changes, should also be noted. In situations such as myocardial infarction or myocardial degeneration, inflammatory responses exist during the clearance of necrotic myocytes, but small focal infarcts usually lie along the coronary arteries. In diseases with systemic leukocytosis such as leukemia and parasitic infections, there are eosinophilia, leukocytosis in the myocardium or small blood vessels, and even scattered or small focal aggregations in the myocardial interstitium, but this is generally not accompanied by myocardial necrosis. In addition, clarifying the pathological characteristics of viral, bacterial, fungal, and parasitic myocarditis in the acute phase, especially pathogen detection in myocardial lesions, will be helpful in the diagnosis and differential diagnosis of myocarditis.

6.2 Pathological Characteristics of Myocarditis of Different Etiologies

6.2.1 Viral Myocarditis

Viral myocarditis is the most common cause of lymphocytic myocarditis. Many viruses can cause different degrees of myocarditis; the most common types are Coxsackie virus groups A and B, echovirus, and adenovirus [2, 4]. The pathogenic mechanism of viral myocarditis includes the direct damage of myocytes by the virus, and through autoimmune responses or inflammatory mediator-induced (such as interleukin-6, interferon, etc.) specific antiviral immune responses. Acute viral myocarditis refers to those who experience a disease course within 3 months.

Pathological Changes A general examination shows that the shape of the heart can be normal or enlarged with dilated chambers (obviously in the left ventricle). The heart weight is slightly increased. No obvious thickening of the ventricular wall is observed, but it shows flattened papillary muscles and trabeculae carneae cordis as well as soft and loose myocardial textures. Faint color and interstitial edema appear in anatomic sections, along with gray-white or gray-yellow spot-like lesions and focal hemorrhages or hemorrhagic necrosis (Fig. 6.1) [7].

Generally, lesions are worse in the left ventricle than in the right, worse in the ventricles than

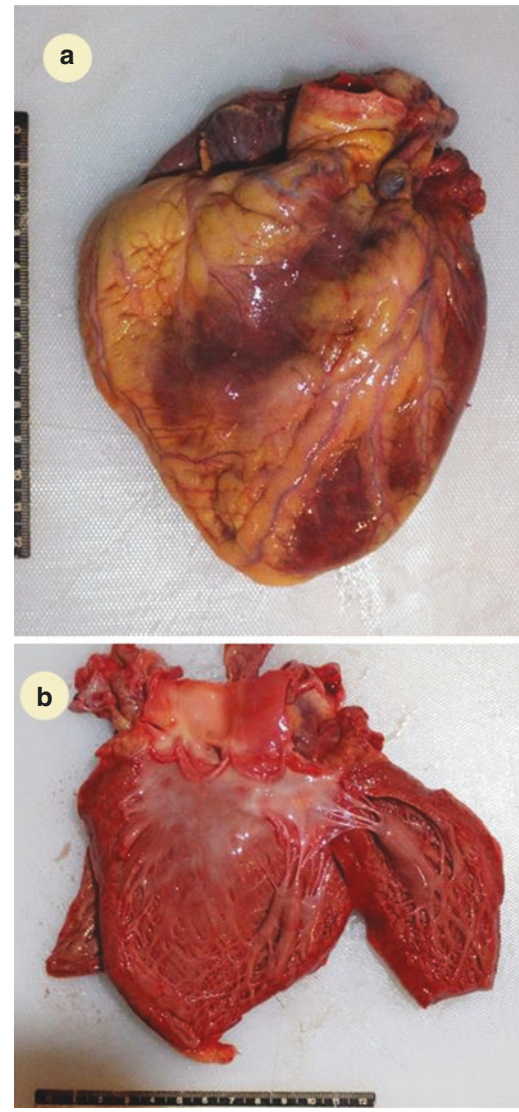

Fig. 6.1 Fulminant myocarditis (female, 30 years old, died 3 days after onset). (**a**) The heart is slightly enlarged (320 g) with a soft texture; (**b**) The section view from panel **a** shows enlargement of the left ventricle, flattened papillary muscles, and trabeculae carneae cordis with light color

in the atriums, and slightly worse in the subendocardial layer than in the outer layer. In most cases, the lesions are widely distributed and diffuse from inside to outside, and are often accompanied by fibrinous pericarditis and exudative pericardial effusion. Auricular or intraventricular thrombosis is uncommon. Compensatory hypertrophy may be present in the chronic phase.

Cardiac Histopathological Examination In the acute phase, degeneration/necrosis occurs in cardiomyocytes, which may involve a single cell or a small group of myocardial fibers. The cardiomyocytes may disintegrate into flakiness or partially dissolve, and even worsen to extensive necrosis, with interstitial and perivascular inflammatory infiltrates predominated in monocytes, lymphocytes, and plasma cells (Fig. 6.2). Neutrophils and eosinophils can be seen occasionally. The chronic phase is manifested by the formation of granulation tissue and interstitial fibrosis (Fig. 6.3), which are mainly concentrated in the muscle bundles and around small blood vessels, and even extended to the endocardium. Scattered small scars may exist (Fig. 6.4). Compensatory cardiomyocyte hypertrophy or degenerative calcification may also be present. In some cases, there may be a few instances of mononuclear, lymphocyte-based inflammatory infiltration. Myocardial necrosis is more obvious and extensive in fulminant myocarditis, with widened myocardial interstitium, edema, and multiple flaky or diffuse inflammatory infiltration.

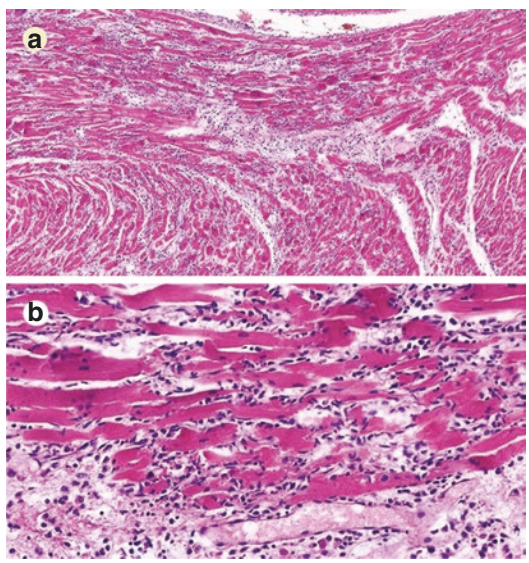

Fig. 6.2 Acute viral myocarditis (male, 13 years old, sudden death). (**a**) Necrosis of myocytes, with extensive infiltrates of monocytes and lymphocytes (HE 40×); (**b**) Necrosis of myocytes, with extensive infiltrates of monocytes and lymphocytes (HE 100×)

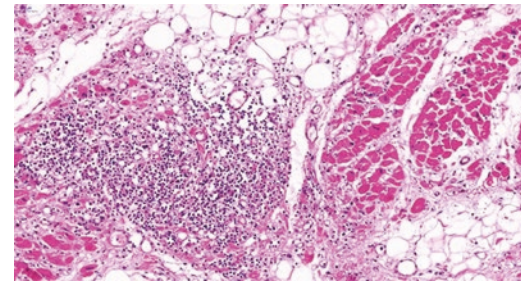

Fig. 6.3 Subacute viral myocarditis (female, 26 years old, sudden death). It shows a necrotic myocardium replaced by granulation tissue and infiltrates of monocytes and lymphocytes (HE 200×)

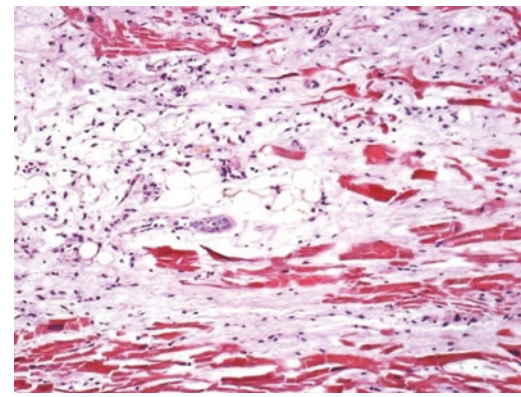

Fig. 6.4 Chronic viral myocarditis (male, 28 years old, sudden death). It shows interstitial fibrosis with infiltrates of monocytes and lymphocytes (HE 40×)

We conducted immunohistochemical examinations of heart specimens from cases of deaths caused by viral myocarditis. The results show that almost all cases have CD68-positive macrophage infiltration, and CD3 and CD4/CD8-positive T cells are present in most cases. Different numbers of CD56-positive natural killer cells and myeloperoxidase (MPO)-positive neutrophils can be found, while CD19-positive B cells are rare or absent (Fig. 6.5).

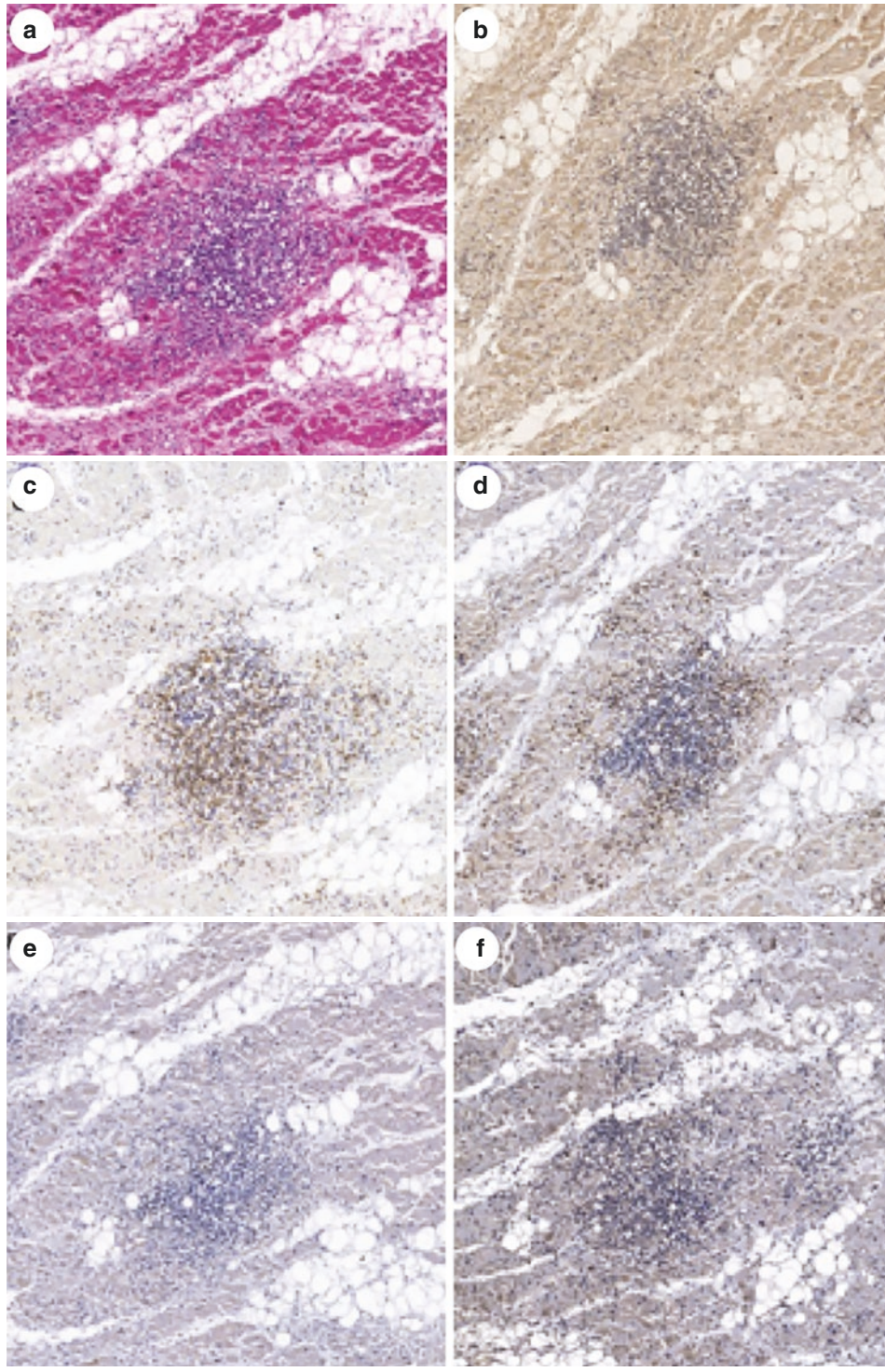

Fig. 6.5 Cell types of inflammatory infiltrates in viral myocarditis. It shows the necrotic cardiomyocytes with infiltrates of massive CD3/CD4/CD8-positive T cells and CD68-positive macrophages, and a few CD19/CD56-positive lymphocytes and MPO-positive neutrophils. (**a**) HE staining; (**b**) CD3; (**c**) CD4; (**d**) CD8; (**e**) CD19; (**f**) CD56; (**g**) CD68; (**h**) MPO

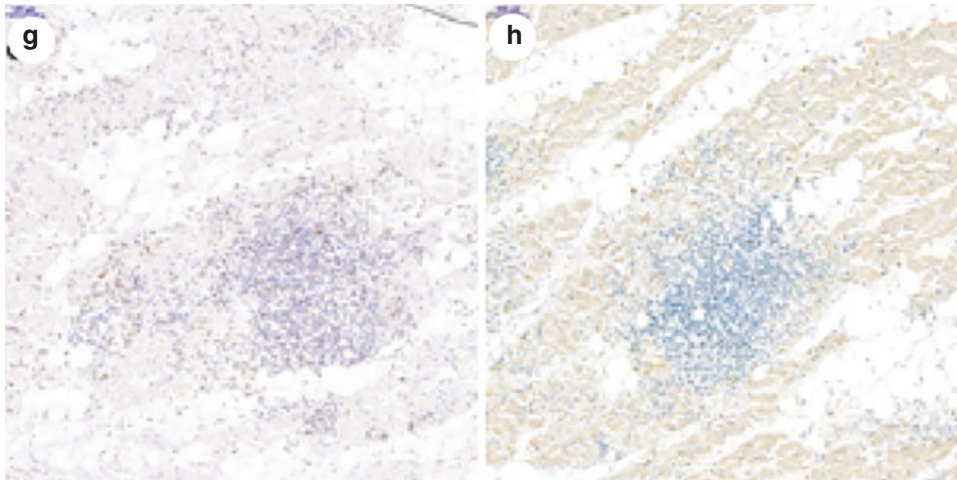

Fig. 6.5 (continued)

The posterior wall of the atrium, ventricular septum, and apical area are usually involved in adult viral myocarditis, and occasionally the cardiac conduction system is affected. When the atrioventricular node and the subendocardial myocardium are affected, inflammatory infiltrations can be found within the cardiac conduction system, such as in the atrioventricular node, atrioventricular bundle (His bundle), and its branches. The cardiac conduction cells may also undergo edema and coagulative necrosis. In some cases of sudden death from myocarditis, the inflammation in the sinus node, atrioventricular bundle, and left and right bundle branches is more serious than that of myocardial inflammation (Figs. 6.6 and 6.7). Even focal myocarditis in the conduction system or adjacent areas (Fig. 6.8) may lead to severe arrhythmia or sudden death. In samples from deaths caused by viral myocarditis, the immunohistochemical examinations of the cardiac conduction system also showed multiple mononuclear cells and lymphocyte infiltrations (Fig. 6.9).

The invasion of a virus into the human body will cause viremia (virusemia), which will then involve multiple organs or the target organs of the virus. Some patients with viral myocarditis may also have pathological damage to the brain, liver, lungs, and other organs, causing changes in relative tissues and cells including inflammation, edema, and necrosis, and leading to viral encephalitis (Fig. 6.10), viral hepatitis [8] (Fig. 6.11), viral pneumonia, and so forth [9].

Borderline myocarditis refers to a small amount of lymphocyte-based inflammatory infiltration without myocardial cell damage in endocardial biopsy examination. If repeated biopsies show persistent lymphocytic infiltration, it is called persistent myocarditis; sparse infiltration of lymphocytes indicate a recovery period of myocarditis, and a lack of inflammatory infiltration indicates that the myocarditis has been cured.

Note that false positives or other lesions should be excluded in endocardial biopsies. Common situations include: a few lymphocytes observed in normal myocardial interstitium but less than 5/mm^2 [10]; normal cells in the interstitium are mistaken for lymphocytes, such as endothelial cells, smooth muscle cells, mast cells, and so forth; extramedullary hematopoietic cells that appear in the necrotic area of ischemic heart disease are mistaken for lymphocytes in myocarditis [11]; the focal infiltration of monocytes and lymphocytes in the interstitium and fibrotic area of dilated cardiomyopathy, which can be distinguished from myocarditis by the absence of cardiomyocyte damage; the excessive secretion of vasopressin/catecholamines by

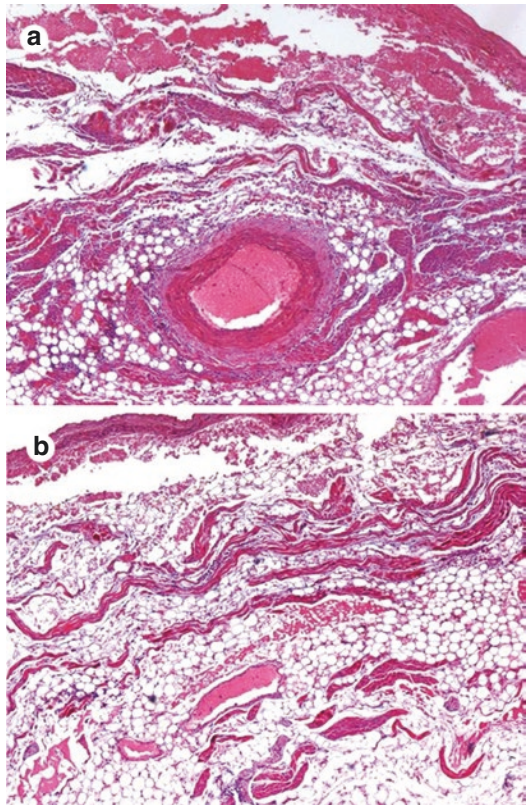

Fig. 6.6 Myocarditis with the cardiac conduction system affected (male, 52 years old, sudden death during antipsychotic treatment). (**a**) Infiltration of monocytes and lymphocytes around the sinus node artery, with hemorrhage (HE 40×); (**b**) Edema within the sinus node, with infiltration of monocytes, lymphocytes, and hemorrhage (HE 40×)

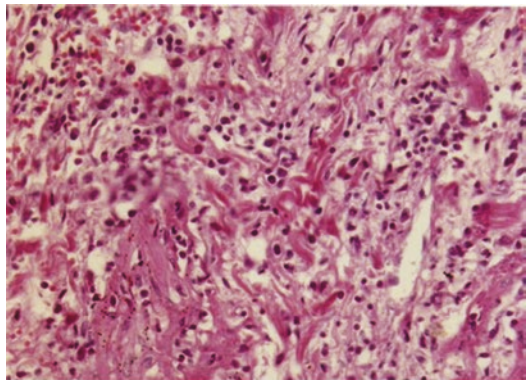

Fig. 6.7 Viral myocarditis (male, 25 years old, sudden death after fainting). Degeneration/necrosis of conduction cells in the atrioventricular node, with the infiltrate of monocytes and lymphocytes (HE 250×)

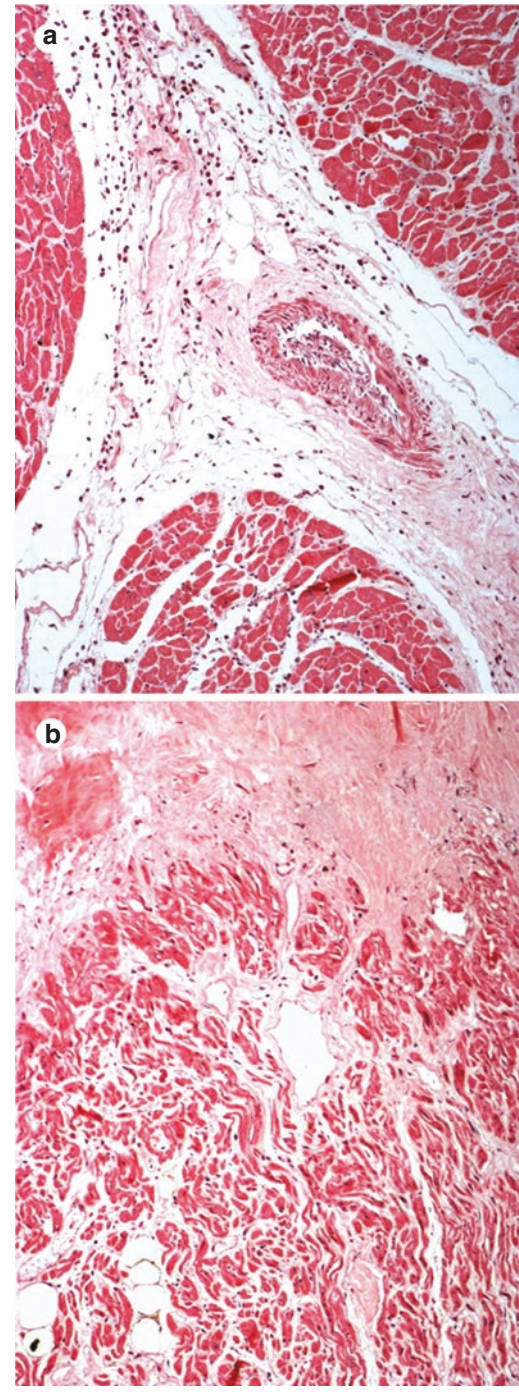

Fig. 6.8 Focal viral myocarditis (male, 40 years old, sudden death). (**a**) Focal infiltration of monocytes and lymphocytes under the His bundle on the top of the ventricular septum; (**b**) No inflammatory infiltration in the His bundle near the cardiac conduction system (HE 100×)

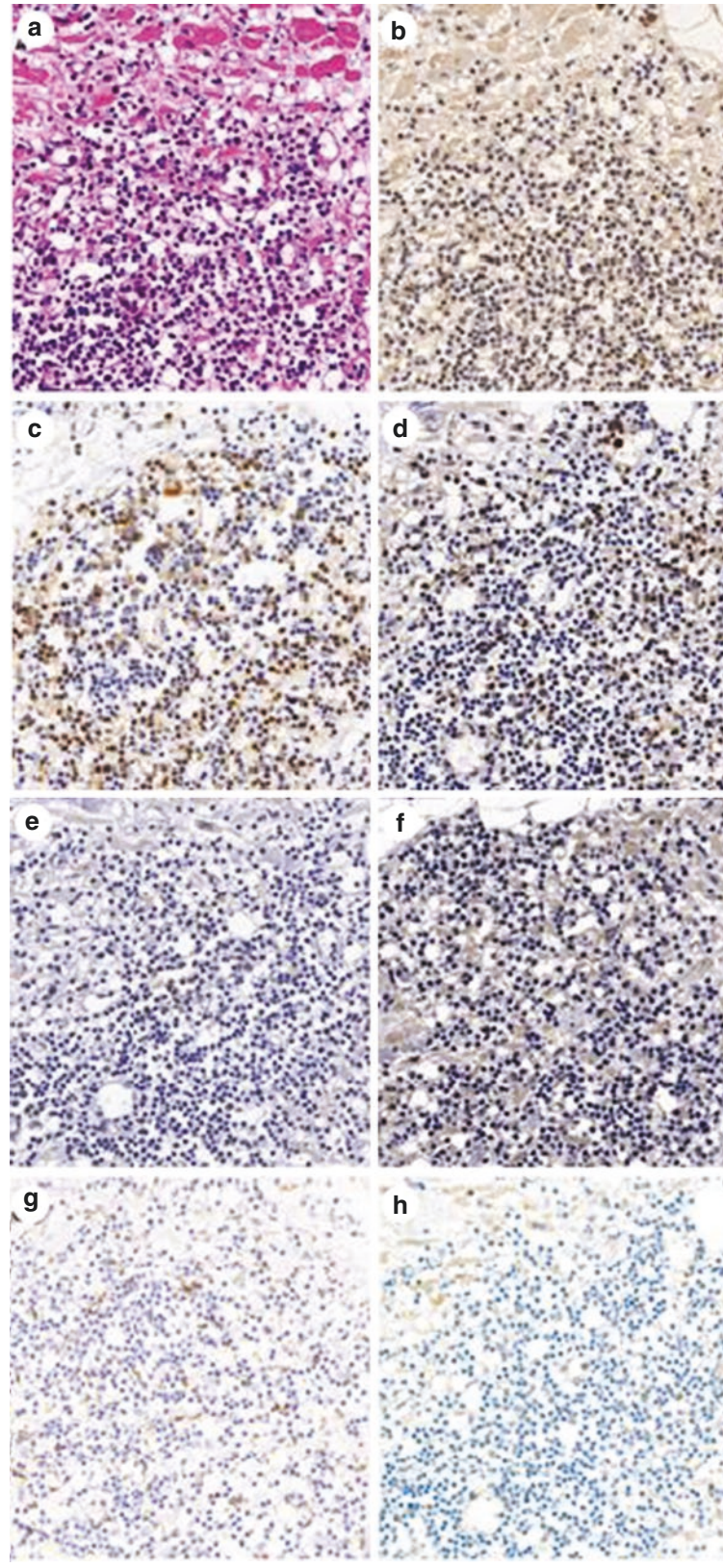

Fig. 6.9 Cell type of infiltration in the His bundle in viral myocarditis. Necrotic myocardium with infiltrates of massive CD3/CD4/CD8-positive T cells and CD68-positive macrophages, as well as a few CD19/CD56-positive lymphocytes and MPO-positive neutrophils. (**a**) HE staining; (**b**) CD3; (**c**) CD4, (**d**) CD8; (**e**) CD19; (**f**) CD56; (**g**) CD68; (**h**) MPO

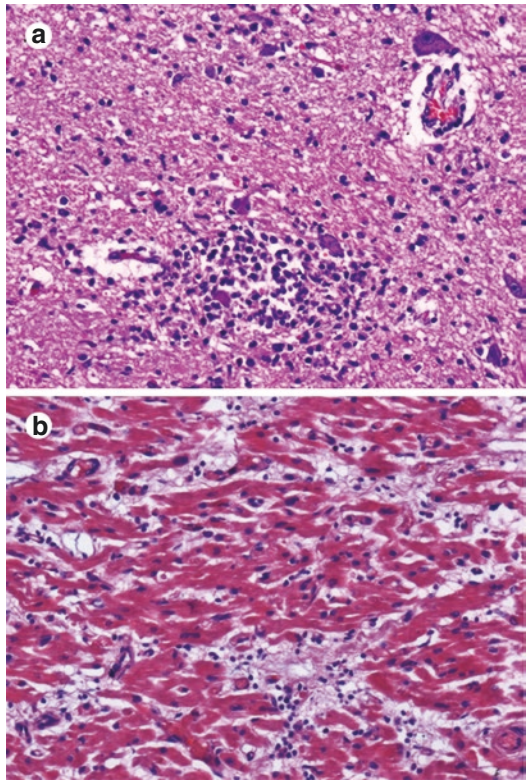

Fig. 6.10 Viral encephalitis combined with myocarditis (male, 2 years old, died after 3 days of fever). (**a**) Viral encephalitis (medulla oblongata); (**b**) Viral myocarditis (HE 200×)

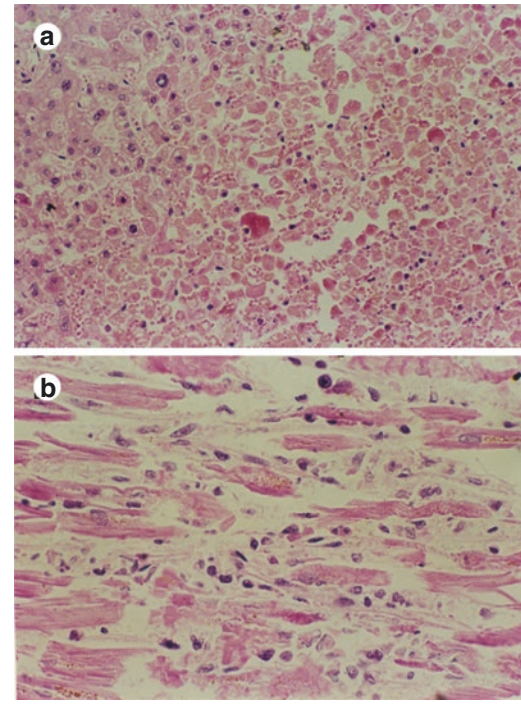

Fig. 6.11 Acute severe hepatitis B combined with myocarditis (female, 53 years old, death after 2 days of right upper abdominal pain). (**a**) Severe viral hepatitis, massive necrotic hepatocytes (HE 200×); (**b**) Viral myocarditis, necrotic cardiomyocytes with infiltrates of monocytes and lymphocytes (HE 400×)

pheochromocytoma cells may cause a rupture of cardiomyocytes and a few infiltrates of monocytes and lymphocytes in the interstitium, showing pathological changes similar to myocarditis [12], which can be distinguished by the distribution of the damaged area and the types of inflammatory cells. For identification, the characteristic of vasopressin/catecholamine-induced lesions is that myocardial injury is mainly manifested around interstitial arterioles with mixed inflammatory infiltration of neutrophils and lymphocytes; Masson's trichrome staining can be used to distinguish punctuated pathological calcification of cardiomyocytes and toxoplasma myocarditis. Typically, an endocardial myocardial biopsy will not locate tumor metastasis, but lymphocytic and hematopoietic malignant tumors such as leukemia and lymphoma can cause atypical changes in the subendocardial cardiomyocytes, but myocardial damage is rare. Immunohistochemical staining and genetic testing can help to differentiate from myocarditis and determine whether it is benign or malignant.

Clinically, it is difficult to definitely diagnose viral myocarditis. The increased viral titer in serum will provide a certain amount of help. An endocardial biopsy is crucial to confirm the diagnosis, but it is still difficult due to the limitations of specimen collection. The positive rate of virus detection is low in endocardial biopsy specimens, and the in situ nucleic acid hybridization, polymerase chain reaction-single strand conformation polymorphism analysis (PCR-SSCP), nested PCR, and other technologies can be helpful in improving the success rate of virus detection.

6.2.2 Bacterial Myocarditis

Bacterial myocarditis refers to myocardial inflammatory lesions caused by direct bacterial infection of the myocardium, the effects of toxins produced by bacteria, or due to allergic reactions induced by products from bacteria. Most bacterial myocarditis is purulent. Myocarditis induced by tubercle bacilli, *Corynebacterium diphtheria*, and *Bacillus typhia* can also be seen. Bacterial myocarditis is less common than viral myocarditis, and the underlying mechanisms of bacterial myocarditis include direct bacterial invasion, bacterial toxins, immune response, and so forth [13].

In recent years, the number of patients with bacterial myocarditis has continued to increase due to the increased incidence of immune system impairments [14]. Usually, cases of suspected bacterial myocarditis based on clinical tests are rarely diagnosed [15]. Although endocardial myocardial biopsies show high specificity, their sensitivity is low; thus, the diagnosis of bacterial myocarditis is rarely confirmed before the patient dies [16].

According to the size of the lesions, bacterial myocarditis can be divided into diffuse and localized myocarditis. According to pathological characteristics, it can be classified into substantial myocarditis with myocardial degeneration and interstitial myocarditis with interstitial damage; according to the course of disease, it can be divided into acute and chronic bacterial myocarditis. The healing of bacterial myocarditis generally occurs through the repair of granulation tissues and the formation of scars.

The pathological changes of suppurative and tuberculous myocarditis are described in the following sections.

1. Suppurative myocarditis (pyogenic myocarditis), also called myocardial abscess, refers to myocarditis characterized by a large number of neutrophils in the myocardium and the formation of pus. It is often a complication of purulent bacterial infection in other parts. The pathogens of suppurative myocarditis primarily contains *Staphylococcus aureus, Streptococcus, Pneumococcus,* and *Meningococcus*. Most cases of suppurative myocarditis are the consequences of sepsis, including acute angina, tonsillitis, pneumonia, epidemic cerebrospinal meningitis, urinary tract infection, metritis, mastitis, and even postoperative bacterial infections [17]. Bacterial endocarditis can also lead to suppurative myocarditis. Bacteria can be seen in suppurative myocarditis using bacterial culture and (or) microscopic examination.

   Pathological changes: Generally, multiple abscesses of different sizes can be found on the surface and cross sections of the heart. Usually, myocardial abscesses are numerous and small in size, within 1 cm in diameter, and most are round or pin-shaped yellow-green lesions, and are difficult to notice unless examined by microscope; on a few occasions, cord-like purulent bands can be seen, and dark red hemorrhagic reaction zones exist around the abscess. Pus exists in large abscesses and invades the entire layer of the ventricular wall, and can even cause heart rupture. A thin layer of fibrous tissue occasionally forms after the healing of an abscess, and the layer gradually bulges under the pressure of the ventricle, finally forming an aneurysm. Death may result due to cardiac tamponade when the acute rupture of the ventricular wall or an aneurysm occurs. In addition, abscesses in the myocardial wall can invade the epicardium, where fibrin is locally attached. Abscesses can also break into the pericardial cavity, resulting in purulent pericarditis.

   Histopathological examination of the heart: There is interstitial neutrophil infiltration or multiple small abscesses. Sometimes bacterial colonies will be found in the center of abscesses. These colonies are metastatic bacterial colonies from sepsis or suppurative embolus from bacterial endocarditis (Fig. 6.12). Myocardial interstitial edema is obvious. Thrombosis or various emboli can be observed in small blood vessels, such as bacterial emboli, pus emboli, hyaline thrombus, and so forth. The affected cardiomyocytes often undergo degeneration and necrosis (Fig. 6.12d). In some cases, bacterial endocarditis or valvulitis can be seen, and serious

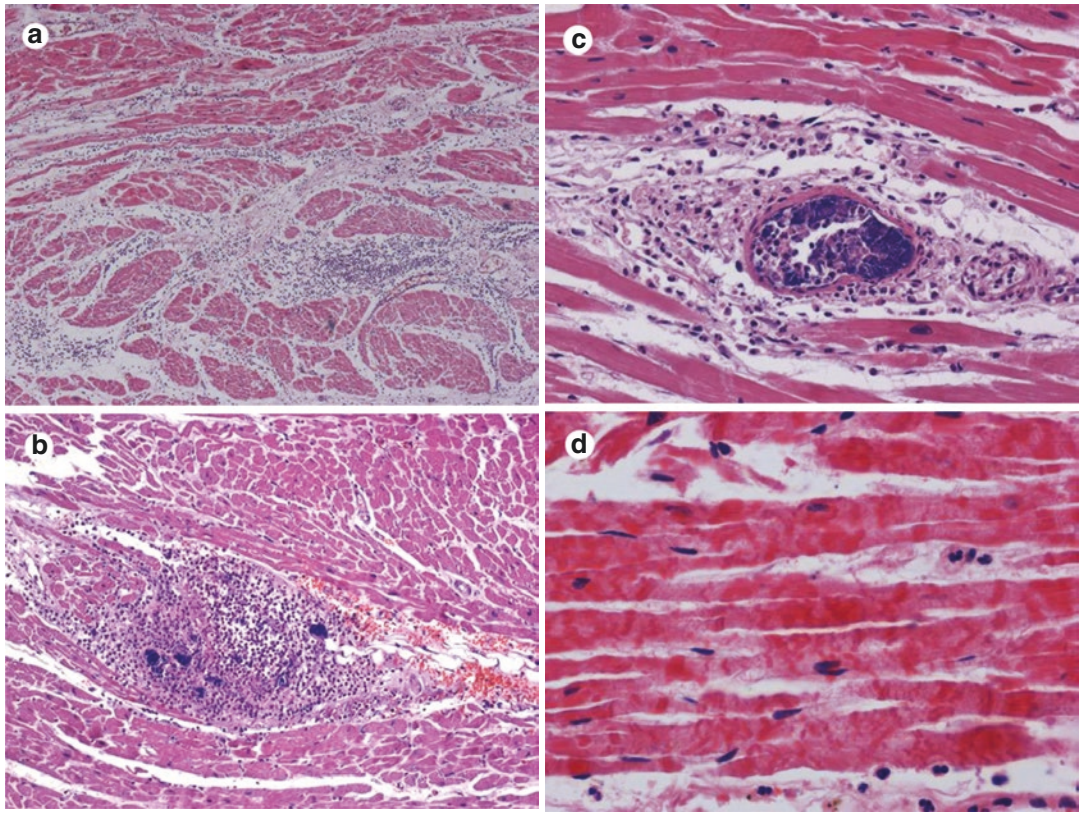

Fig. 6.12 Suppurative myocarditis. (**a**) Diffuse infiltrates of massive neutrophils in interstitium (HE 40×); (**b**) Formation of small abscess with necrosis of cardiomyocytes. The bacterial colonies and hemorrhagic zones are shown (HE 200×); (**c**) Pus embolus and bacterial embolus within a small vessel, with inflammatory infiltrates and tissue edema (HE 400×); (**d**) Necrosis in the contraction zone of the papillary muscle with scattered infiltrates of neutrophils (HE 200×)

consequences or sudden death may result if the cardiac conduction system is invaded or small abscesses have formed (Fig. 6.13). If the course of disease is prolonged, fibrosis and the organization of myocardial tissue will occur, leading to granulation tissues and scars.

2. Tubercular myocarditis, also known as myocardial *Tuberculosis*, is a special type of myocarditis caused by mycobacterium *Tuberculosis*. It is rare in clinical practice, and mostly stems from the blood transmission of primary *Tuberculosis* or the direct spread of tuberculous pericarditis and epicarditis. Characteristic tubercles can be seen in lesions, which mainly affect the pericardium, while heart valves and cardiomyocytes are rarely involved. It is very difficult to diagnose tuberculous myocarditis before death, and it is usually found in autopsies. Myocardial *Tuberculosis* was found to account for 0.25–0.28% of tubercular cases by autopsy.

Pathological changes: Tuberculous myocarditis is classified into nodular, miliary, and diffuse types; the nodular type is the most common.

- Nodular type: This is also known as tuberculoma. It is mostly located in the right atrium, and the nodules are round or oval, grayish-yellow, and solid, with a diameter of 1–7 cm. Nodules may be surrounded by fibers of different amounts, with yellow-white caseous necrotic material filled in the center. The nod-

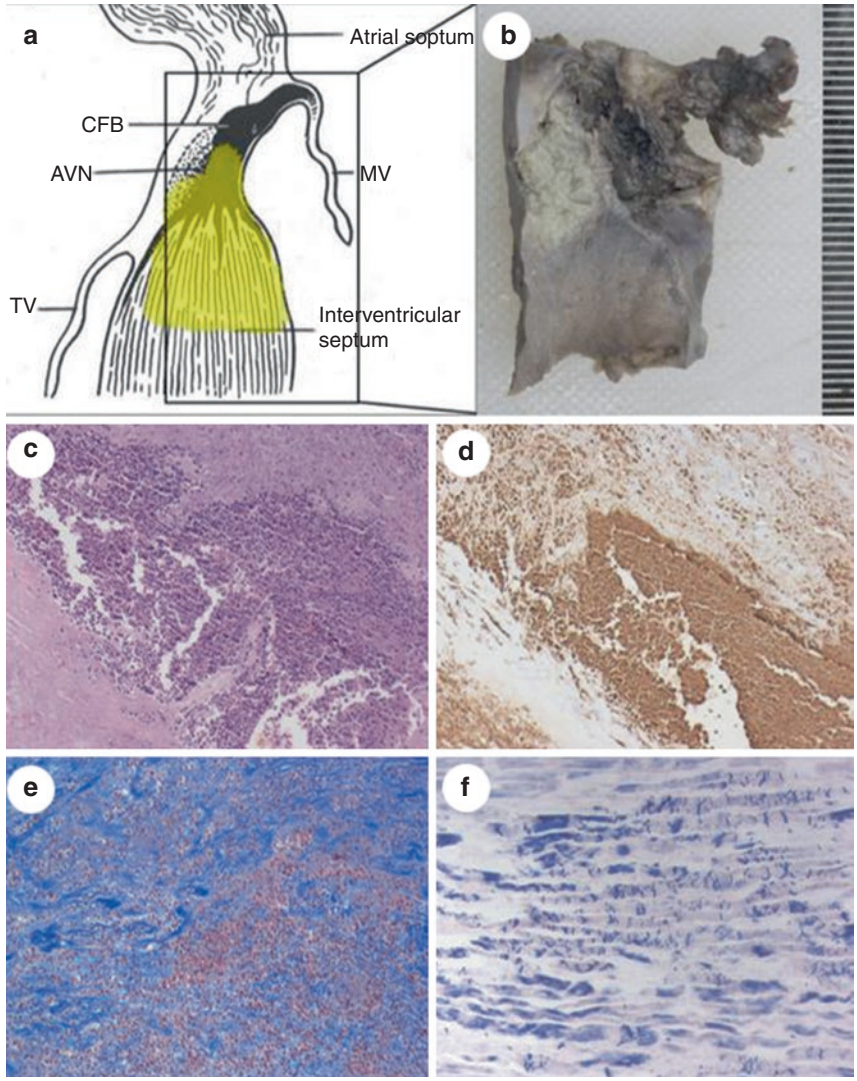

Fig. 6.13 Bacterial endocarditis with invasion of the atrioventricular node and abscesses in the interventricular septum. (**a**) A diagram of the atrioventricular septum and the location of an abscess (the area in yellow); (**b**) The top part of the interventricular septum; bacterial endocarditis of the mitral valve (MV) and a small pale abscess are shown; (**c**) An abscesses in the interventricular septum with massive infiltrates of neutrophils (HE 100×); (**d**) Immunohistochemical staining of MPO-positive neutrophils in a continuous slide (SABC 100×); (**e**) Necrosis of conduction cells in the atrioventricular node (AVN) with massive infiltrates of neutrophils (Masson 100×); (**f**) Multiple necroses in contraction bands of the left ventricle (PTAH 100×). PTAH, Mallory Phosphotungstate Hematoxylin

ules are either single or multiple. Ulcers or thrombosis may form when the endocardium is involved. The centers of nodules under microscopic views are mainly composed of caseous necrotic materials with a few Langhans giant cells on the edge of necrotic foci and fibrous tissues around the outer layer. There is lymphocyte infiltration in the fibrous tissues and the adjacent myocardium.

- Miliary type: Commonly found in patients with miliary *Tuberculosis*. The number of nodules varies, and they are mostly located in

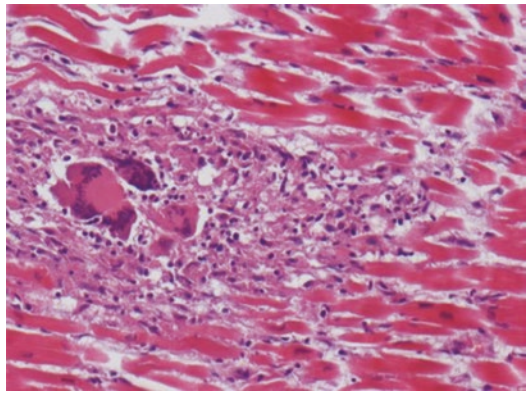

Fig. 6.14 Tubercular myocarditis (male, 40 years old, died from systemic miliary *Tuberculosis*). A myocardial *Tuberculosis* nodule with caseous necrosis and Langhans giant cells in the center, and necrosis in ambient cardiomyocytes (HE 400×)

the epicardium and endocardium. The nodules have a grayish-yellow, translucent appearance with diameters of 1–3 mm. The nodules can only be found under microscopic examinations, located in the connective tissues between muscle bundles, and are mostly distributed along the blood vessels, with caseous necrosis or several Langhans multinucleated giant cells in the center of nodules surrounded by many proliferated epithelioid cell and lymphocytes. Necrosis may appear in ambient cardiomyocytes (Fig. 6.14).

- Diffuse type: This type is rare and is usually caused by the expansion of pericardial *Tuberculosis*. The myocardium with lesions is grayish-yellow and distributed in stripes. Under the microscope, the myocardial tuberculous granulation tissues show diffuse hyperplasia, mainly composed of epithelial cells, lymphocytes, and multinucleated giant cells, with varying degrees of caseous necrosis. Mycobacterium *Tuberculosis* can often be detected here.

6.2.3 Fungal Myocarditis

Fungal myocarditis generally refers to an inflammatory lesion of the myocardium caused by a fungal infection. It is commonly seen in patients with prolonged use of antibiotics, adrenocortical hormones, and immunosuppressants. Therefore, fungal myocarditis is often part of systemic fungal infections. The pathogens mainly consist of *Candida* and *Mucor*. Primary fungal myocarditis is extremely rare. Fungal toxins may induce necrosis of cardiomyocytes, leading to inflammation of the myocardium.

Pathological changes: Generally, myocardial lesions of fungal myocarditis show no difference from fungal infections of other organs. In most cases, purulent or hemorrhagic necrotic foci of varying sizes are present in the heart.

Histopathological examinations: In the early stage, inflammatory lesions scatter in the interstitium, then spread and merge. The appearance of lesions varies according to different pathogens. Some have prominent hemorrhaging and necrosis but mild inflammation, while others are dominated by neutrophil infiltration accompanied by tissue necrosis and abscess formation. In the center of the necrosis foci, liquefaction emerges rapidly to form pus cavities with massive neutrophil infiltration and remaining blood vessels. The foci contain many fungal filaments and spores, such as *Aspergillus, Candida*, and *Mucor*. It is easier to find fungal hyphae in the acute phase. In the chronic phase, there are obvious macrophage infiltration, granulomatous transformation, and even multinucleated giant cells. Even *Tuberculosis*-like nodules may exist in the chronic phase, but the necrosis is not as severe as that in *Tuberculosis*, and mycobacterium *Tuberculosis* is absent. These are the main points for the identification and differentiation between fungal and tuberculous myocarditis. (Fig. 6.15).

Common fungi show certain microscopic characteristics. For example, aspergillus hyphae are mainly mycelium, and HE staining exhibits blue-purple with uniform diameters of 7–10 μm. The mycelial branches are radially arranged at an acute angle of 45°. Spores and hyphae can be seen in *Candida*. The spores are round or ovoid, and the hyphae are straight and slender with a separated appearance. It is clearer to display *Candida* with Gram or silver stain. *Mucor* is more likely to invade blood vessels. Its hyphae are mostly distributed in the blood vessel wall

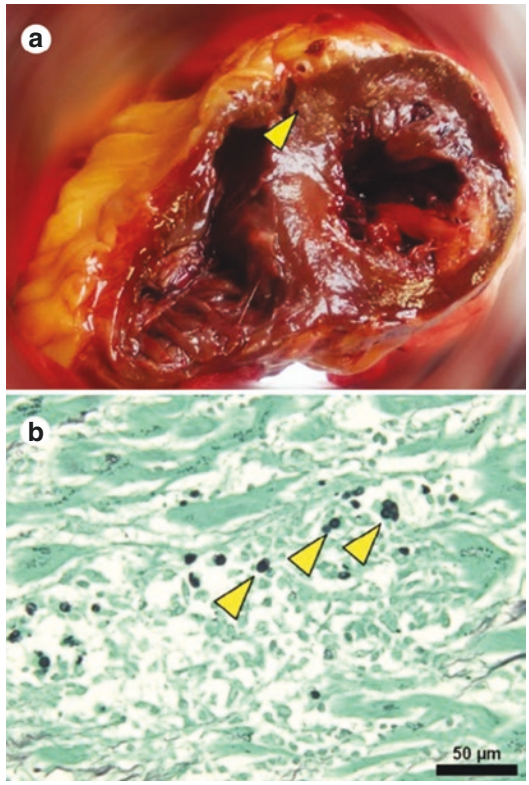

Fig. 6.15 Fungal myocarditis (male, 79 years old, died after 21 days of antibiotic therapy; *Candida albicans* was found in blood and urine cultures) [18]. (**a**) A small nodule in the cross section of the heart (yellow arrow); (**b**) The accumulation of fungi in the nodule (yellow arrow; Grocott methenamine silver stain)

or vascular cavity. The hyphae are thick and not separated, with a diameter of 6–40 μm. The width of hyphae is uneven with many wrinkles, and the few but blunt branches distribute in right angles, without spores.

6.2.4 Systemic Disease-Associated Myocarditis

Myocarditis can also occur in some systemic autoimmune diseases and perinatal women. In the former situation, it is common in connective tissue diseases such as SLE, rheumatoid arthritis, polymyositis/dermatomyositis, thrombotic thrombocytopenic purpura, Wegener's granulomatosis, ankylosing spondylitis, and mixed connective tissue disease. Among these diseases, SLE, rheumatoid arthritis, and polymyositis/dermatomuscular account for most of the related myocarditis. As for myocarditis in perinatal women, it is so-called perinatal myocarditis, also known as perinatal cardiomyopathy.

In immune-mediated myocarditis, it shows pathological characteristics of a large number of monocyte and lymphocyte infiltration. Lupus myocarditis, rheumatic myocarditis, and perinatal myocarditis will be described here.

1. Lupus myocarditis indicates a severe condition in SLE. It may be the first manifestation of SLE, and may also occur during the follow-up period, especially in untreated patients with SLE. The heart lesions in SLE includes pericarditis, myocarditis, endocarditis, and vascular diseases, of which lupus pericarditis is the most common (Fig. 6.16). Although the incidence of heart lesions is lower than that of skin and kidney damage, it still constitutes up to 50% of lesions.

   The pathogenesis of SLE contains systemic disorders characterized by cell damage caused by immune complexes among which anti-nuclear antibodies play a vital role. Anti-nuclear antibodies attack degenerated or damaged cell membranes. Once these antibodies gain access to the nucleus, the swelling, fragmentation, and dissolution of the nucleus will be induced. After this process, it will form a kind of uniform, structureless, round-shaped small body.

   These bodies will be eliminated from the cells. These bodies are purple-red in HE staining; thus, they are called lupus or hematoxylin bodies, which are characteristic evidence for the diagnosis of SLE. Lupus bodies have a chemotactic activity to neutrophils and macrophages; thus, it can promote phagocytosis in the presence of complements. Once a cell undergoes endocytosis of lupus bodies, it will be called a lupus erythematosus cell or lupus cell (Fig. 6.16a). The pathological changes of SLE vary, but there is no specific changes of SLE, except for lupus cells. Acute necrotic arteritis and arteriositis are the main lesions of

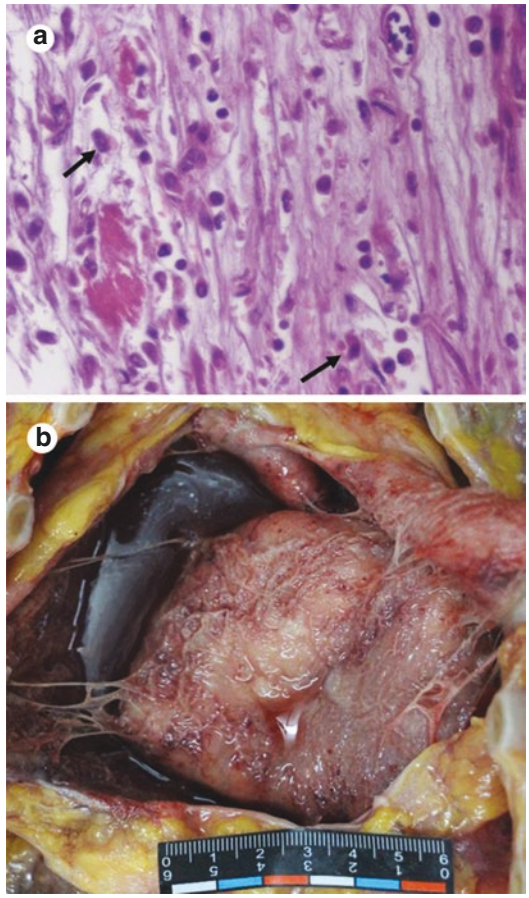

Fig. 6.16 SLE (female, 64 years old; she had SLE for more than 10 years, and died during infusion when the disease worsened). (**a**) Lupus cells are occasionally seen (black arrow) (HE 400×); (**b**) Villous heart and pericardial effusion

this disease. In the active stage, it is mainly fibrinoid necrosis; in the chronic stage, the blood vessel wall becomes fibrotic, with narrowed lumens and lymphocytes, edema, and an increased matrix around the vessels.

Pathological changes: The heart is generally enlarged in lupus myocarditis, and may be accompanied by pericardial effusion and villous heart (Fig. 6.16b). The endocardium is focally thickened, and the heart valve may become involved in non-bacterial verrucous endocarditis (Libman–Sacks endocarditis). The neoplasms often invade the mitral or tricuspid valve [19].

Histopathological examinations: Fibrinous pericarditis is characterized by fibrinous necrosis under the microscope, accompanied by mixed inflammatory infiltrates and granulation tissues (Fig. 6.17); lymphocytic myocarditis (similar to viral or idiopathic myocarditis) is present in the myocardium, and manifests with the extensive degeneration of cardiomyocytes, intermittent edema, lymphocyte infiltration, and so forth. (Fig. 6.18) [19].

Fibrinous vasculitis is another histological feature of SLE. The lesion mainly involves

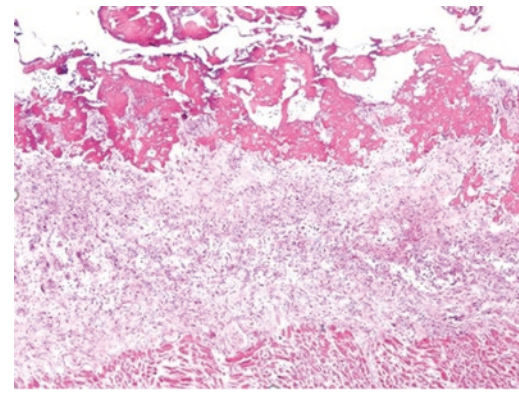

Fig. 6.17 Lupus pericarditis and lupus myocarditis. The fibrinoid necrosis of the pericardium and formation of granuloma (HE 40×)

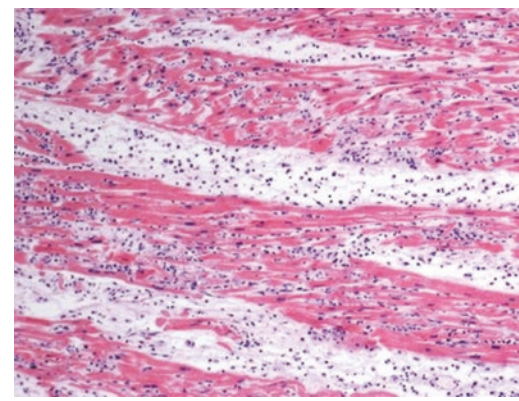

Fig. 6.18 Lupus myocarditis (male, 24 years old, diagnosed with SLE for 7 months, died after a severe fever). Focal necrosis of the ventricular cardiomyocytes with edema and massive infiltrates of monocytes and lymphocytes (HE 40×)

the small and middle arteries, where the blood vessel walls are replaced by amorphous fibrinoid substances. In lupus myocarditis, fibrinous vasculitis can be observed in the small arteries within the myocardial interstitium, which means fibrinous necrosis of the blood vessel walls with lymphocytes infiltration and perivascular edema. This illness is characterized by permanently existing antigens and uncleared immune complexes. Immunofluorescence will show the depositions of immunoglobulin, complement, and fibrinogen, which indicate that the disease is caused by immune complexes, which is how to differentiate it from viral myocarditis. In advanced stages of fibrinous vasculitis, the myocardial intermural arteriole may develop into "onion-skin" arteriopathy; even the arteries of the cardiac conduction system will be involved, which may cause severe arrhythmia or sudden death (Fig. 6.19).

For the endocardium, microscopic examination will find focal fibrosis with infiltrated monocytes and lymphocytes (Fig. 6.20). If non-bacterial valvular verrucous endocarditis is accompanied, the vegetations of valves are composed of fibrin, necrotic debris, and inflammatory cells.

Lupus myocarditis is often associated with coronary arteritis which leads to thickening of the arterial intima and narrowing of the lumen,

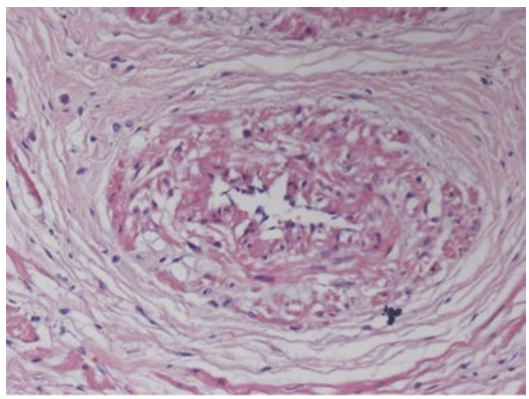

Fig. 6.19 Lupus myocarditis (male, 16 years old, died during wrestling). Obstruction of the sinus node artery which show edema and "onion-skin" arteriopathy (HE 400×)

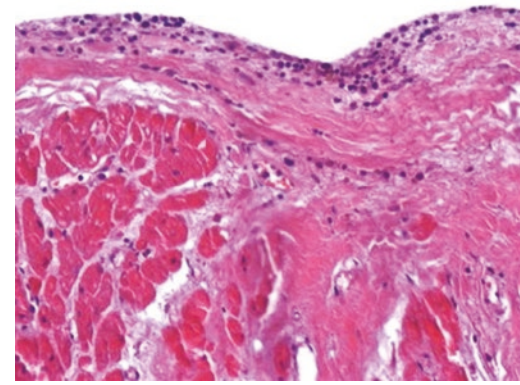

Fig. 6.20 Lupus endocarditis (male, 24 years old, diagnosed with SLE for 7 months, died after a severe fever). The focal thickening of the endocardium and a few infiltrates of monocytes and lymphocytes (HE 100×)

even causing diffuse small myocardial infarction foci and other lesions.

Attention should be paid to the differences between lupus myocarditis and drug-related myocarditis, especially in patients with SLE who are treated with quinidine. However, if no lupus body or lupus cells are found, it is difficult to distinguish lupus myocarditis from rheumatoid myocarditis. Cellulose vasculitis is not a unique characteristic of SLE, as it is also seen in rheumatoid disease, polyarteritis nodosa, and so forth; thus, it requires differential diagnosis between all the abovementioned diseases.

2. Rheumatic myocarditis is the main pathological manifestation of rheumatic carditis in the acute phase of rheumatic heart disease, which also includes rheumatic endocarditis, rheumatic pericarditis, and so forth. Rheumatic heart disease is the most common acquired heart disease in the world, and it is an important cause of disability and mortality in children in developing countries [20]. Rheumatic heart disease is caused by group A streptococcus hemolyticus-induced upper respiratory tract infections (acute pharyngitis, tonsillitis) and rheumatic fever. When the carbohydrates in the bacterial cell wall cross-react with the valvular tissue, acute rheumatic heart disease may occur, such as rheumatic myocarditis [21]. Up to 55% of patients with rheumatic

fever have antigen-antibody complexes in their endocardial tissues, and deposited complements in the perivascular connective tissues and sarcomeres; 65–80% of children with rheumatic fever have clinical manifestations of rheumatic carditis.

Pathological changes: In the early stage, the changes in the cardium are not obvious. If rheumatic endocarditis is combined, there will be swelling of the valves and decreased transparency. Miliary-sized (approximately 1–3 mm), off-white, translucent, verrucous vegetations can be seen on the surface of valves (white thrombus), which often arrange like beads on a string at the atresia edge of the valve. If repeated onsets eventually lead to chronic rheumatic valvular disease, the mitral valve is the most susceptible, followed by the aortic valve. There is diffuse fibrous hyperplasia of the valve leaflets and chordae, which may fuse and cause valvular stenosis and/or insufficiency. In the late stage, focal thickening of the left ventricular and atrial endocardium, fibrosis, mural thrombosis, flattened papillary muscles and fleshy columns, hypertrophy, and dilatation of cavities are also commonly present.

Histopathological examinations: The most important feature of rheumatic myocarditis is rheumatic granuloma (Aschoff body) in the myocardial interstitium, followed by diffuse interstitial myocarditis (Fig. 6.21a, b).

The formation of Aschoff bodies contains a series of pathological processes, namely, the fibrinous necrosis of collagen fibers, followed by the development of granulomas and finally fibrosis. Thus, myocarditis also manifests corresponding characteristics of sequential pathological changes according to the course of disease, such as fibrinoid necrosis of collagen fibers, perivascular Aschoff bodies, and thin, spotted myocardial fibrosis with perivascular scars.

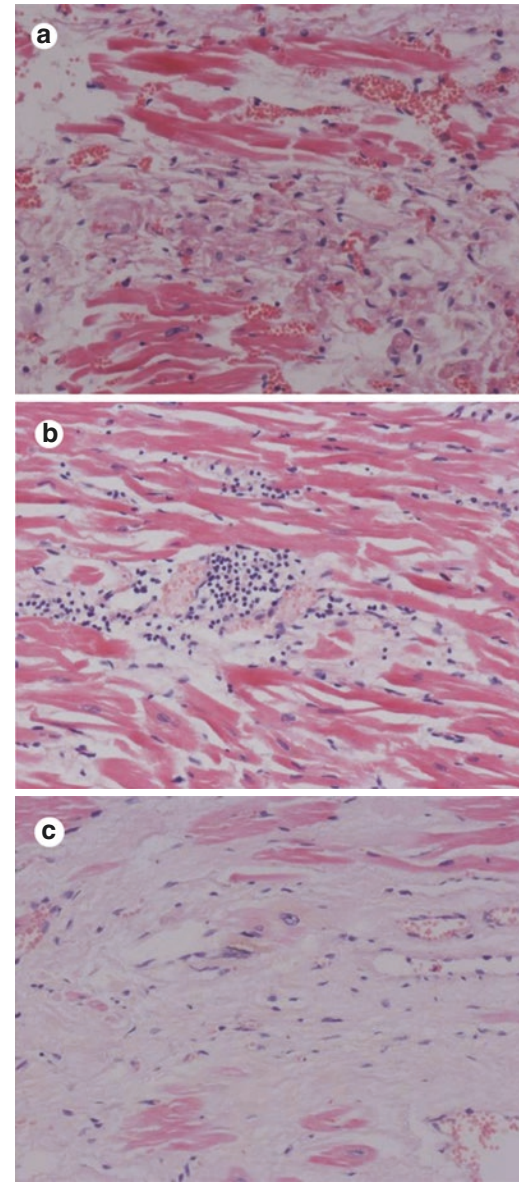

Fig. 6.21 Rheumatic myocarditis (male, 48 years old, sudden death). (**a**) Fibrous necrosis and rheumatic body in the interstitium (HE 200×); (**b**) Infiltrates of lymphocytes in the interstitium (HE 200×); (**c**) Gradual fibrosis in the interstitium, and several rheumatic cells can be found (HE 200×)

In the early phase of rheumatic myocarditis, namely, the degeneration and necrosis phase, the swelling of cardiomyocytes, interstitial edema, fibrinous necrosis, and myxoid degeneration can be found. One to two months after the onset of clinical symptoms, it enters the granuloma stage when Aschoff bodies appear inside and around the fibrous necrosis foci, and especially around small blood vessels. Aschoff bodies are characteristic for diagnosis under microscopic examination, which manifest with oval macrophages, lym-

phocytes, plasma cells, and so forth that gather near the small vessels in the interstitium. If the macrophages engulf cellulose-like necrotic material, they will transform into rheumatic cells (Aschoff cells). Rheumatic cells are large, round, or polygonal, with rich and homogeneous cytoplasm. They have large, round, or oval nuclei with clear nuclear membranes, and chromatin concentrates in the center with filiform radiations to the nuclear membrane, so that the cross section of the nucleus looks like an owl-eye, often called an awl-eye cell; for the longitudinal section of a long nucleus, it looks like a caterpillar, hence it is called a caterpillar cell. Besides the above-mentioned mononuclear cells, rheumatic cells can also be dual or multinuclear, and these are called Aschoff giant cells. Immunohistochemistry confirmed that rheumatoid cells are of monocyte-macrophage origin, but not cardiomyocyte origin. The granuloma stage lasts for 2–3 months and then enters to the fibrosis stage. At this time, the cellulose-like necrosis is dissolved and absorbed, and the nuclei of rheumatic cells may become densely stained with an unclear structure. The rheumatic cells will transform into fibroblasts and the granulomas gradually become fibrotic and form small spindle-shaped scars that will eventually be replaced by collagen scar tissue (Fig. 6.21c). Most patients will finally develop chronic rheumatic heart disease (especially valvular heart disease).

In children, it shows cardiomyocyte edema and steatosis, fasciculate fibrous necrosis of the left atrial cardiomyocytes, and significant interstitial edema. It may present diffuse interstitial myocarditis with infiltrations of many lymphocytes, eosinophils, and even neutrophils.

Aschoff bodies are specific in the pathological diagnosis of rheumatic myocarditis. They may appear in the myocardium, endocardium, and epicardium, especially in the left ventricular wall, mitral valve attachments, the connective tissue triangle in the root of the aorta, and papillary muscles. It can also affect the cardiac conduction system (Fig. 6.22). It could be the cause of ectopic excitatory foci with tachycardia or atrial fibrillation in rheumatic myocarditis.

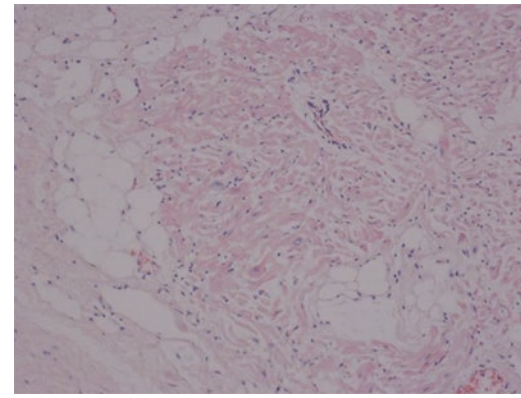

Fig. 6.22 Rheumatic myocarditis with the cardiac conduction system involved (male, 48 years old, sudden death). Infiltrations of macrophages and lymphocytes in the His bundle (HE 40×)

3. Perinatal myocarditis, or peripartum cardiomyopathy (PPCM), is a rare disease that usually occurs in the final month of pregnancy or 5 months after delivery. These patients show myocardial dysfunction and dilation secondary to left ventricular systolic insufficiency, while other causes of heart failure are excluded. Its incidence is between 1:4000 and 1:300, and is more common in women over the age of 30. The risk factors include obesity, a history of myocarditis, smoking, alcoholism, multifetal pregnancy, an elderly mother, malnutrition, pregnancy-induced hypertension (gestational hypertension) or eclampsia, metabolic disorders (such as gestational diabetes), and so on. Possible causes include viral infections, nutritional deficiencies, coronary artery disease of small vessels, and immune responses to myometrial or fetal antigens. Recent studies believe that the pathogenesis is related to the imbalanced myocardial microvascular angiogenesis during pregnancy that results in myocardial ischemic damage. Between 5% and 30% of patients with perinatal cardiomyopathy are accompanied by lymphocytic myocarditis, and occasionally with dilated cardiomyopathy complicated with myocarditis. It is as yet unclear whether perinatal myocarditis/cardiomyopathy is a unique

type of heart disease independent of idiopathic dilated cardiomyopathy or idiopathic lymphocytic myocarditis.

Pathological changes: No specific pathological changes. Usually the heart enlarges with dilation of the cavities. The lesions are focal and irregular, and may involve only the left ventricle or both ventricles. The cut surface of the myocardium may be pale or with a few gray stripes. If the right ventricle is involved in PPCM, it is associated with ventricular tachyarrhythmia [22].

Histopathological examination: Hypertrophy, edema, and focal necrosis of cardiomyocytes can be observed, with circular vacuoles in the cytoplasm. There are also interstitial edemas, focal hemorrhages, and focal fibrosis, with several scattered infiltrations of neutrophils, lymphocytes, and plasma cells, as well as perivascular inflammation. (Fig. 6.23).

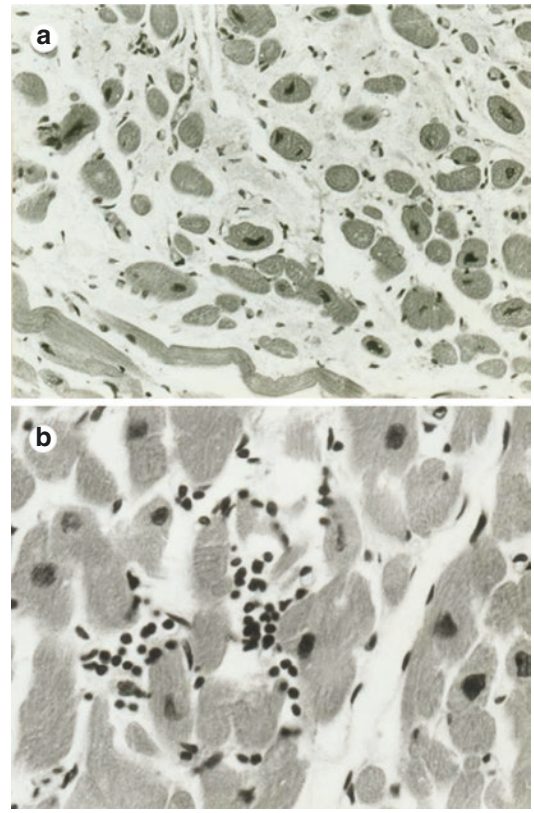

Fig. 6.23 Perinatal myocarditis (female, 21 years old, sudden death in the eighth month of pregnancy) [23]. (**a**) Hypertrophy of cardiomyocytes, interstitial edema, and fibrosis with scattered infiltrates of monocytes and lymphocytes (HE 200×); (**b**) Hypertrophy of cardiomyocytes and interstitial infiltrates of monocytes and lymphocytes (HE 400×)

6.2.5 Granulomatous Myocarditis

Granulomatous myocarditis is characterized by the appearance of giant cells in the inflammatory foci and the formation of granulomas, including two types: cardiac sarcoidosis and giant cell myocarditis.

1. Cardiac sarcoidosis is a type of granulomatous disease of unknown cause with multi-organ or multi-system involvement, which is characterized by the formation of non-caseous granulomas. The clinical symptoms are non-specific and easy to misdiagnose. Some research suggests that there is an immune dysfunction in the local environment of sarcoid granulomas, which is related to the cell-mediated immune responses to a certain unrecognized antigen. It is also related to systemic immune abnormalities and genetic factors. Although 90% of sarcoidosis primarily affects the lungs, 20–30% of sarcoidosis will affect the heart and is known as cardiac sarcoidosis (sarcoidosis of heart). Most patients with cardiac sarcoidosis have subclinical manifestations, less than 5% of patients show clinical symptoms, and a few patients only have heart disease without systemic disease. Since this disease involves the myocardium, it may lead to conduction block or arrhythmia. Atrioventricular block and tachycardia accounts for 75% of patients with arrhythmia, and sudden death will occur in approximately 2% of patients.

   Pathological changes: General examination: The myocardial section shows tough, small, gray-white nodular granulomas, mainly distributed in the ventricular septum, left ventricular wall, and papillary muscles, which needs to be distinguished from metastatic and fibrous tumors of the heart. The positive rate of EMBs of the right ventricle is usually less than 50%. When the myocardium is completely affected, the heart is enlarged and

becomes fibrotic, similar to dilated cardiomyopathy, with a few manifestations similar to restrictive cardiomyopathy.

Histopathological examination: There are several subtypes of pathological manifestations according to the results of EMBs, namely, typical non-caseating granuloma, lymphocytic myocarditis, dilated cardiomyopathy, or normal myocardium. The microscopic characteristics are similar to those of extracardiac sarcoidosis. The cardiac nodules can exist in isolation, or merge with each other to form a large lesion area, forming epithelial-like cellular granulomas that mainly contain non-caseating necrosis (Fig. 6.24). The granulomas are small and regular in shape without obvious necrosis in the center. They contain dense epithelioid cells and multinuclear giant cells arranged in the structure of a circular or oval granuloma. There are vacuoles in the cytoplasm of multinuclear giant cells, and red stellate bodies can be found (asteroid body). Asteroid bodies are eosinophilic, with a small, dark, radially arranged prickle-like body in the center. However, the asteroid body is not a specific lesion of sarcoidosis. There are obvious fibrosis around the granuloma with scattered monocytes and lymphocytes and rare eosinophils. Multiple isolated granulomas may fuse, and the surrounding fibrotic tissue will proliferate and envelop the granulomas. The granulomas wrapped in fibrous tissue will eventually become a hyalinized fibrous scar. Immunochemistry examination confirms that the granuloma is mainly composed of CD68-positive epithelioid cells, and the infiltrating lymphocytes are mainly CD4-positive T cells, while B cells are rarely seen. The endocardium and pericardium may also be involved. In most cases, myocardial hypertrophy and interstitial fibrosis emerge while endocardial thickening is present in only a few cases.

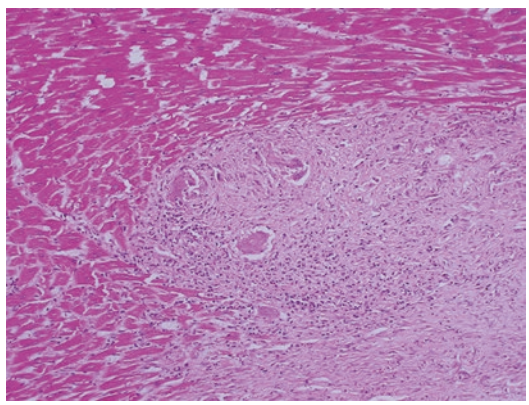

Fig. 6.24 Sarcoidosis in a heart. The formation of an epithelial-like cellular granuloma that mainly contains non-caseating necrosis, with multinuclear giant cells and lymphocytes (HE 100×)

Differential diagnoses of sarcoidosis usually involve infectious granulomatous heart disease, giant cell myocarditis, allergic myocarditis, and acute rheumatic fever. Infectious granulomas are rare in immune-healthy people; it requires routine staining of fungi and mycobacterium *Tuberculosis* for differentiation. In these infectious diseases, it usually manifests as a necrotic granuloma, such as *Tuberculosis* of the heart. For idiopathic giant cell myocarditis, it is characterized by multinuclear giant cells in the interstitium, usually without granuloma. For allergic myocarditis, there are collagen fibers in the center with infiltrations of many eosinophils, but multinuclear giant cells and fibrosis are rare. In acute rheumatic fever, the granulomatous lesions are often insignificant, and the giant cells are usually smaller than the multinuclear giant cells of sarcoidosis. In patients who received repeated biopsies, foreign body giant cells may be seen in the area around the catheter sheath. Myogenic giant cells will be observed in the marginal repair area of ischemic infarction, and lymphocytes and hemosiderin can be seen in the scar tissue. Granulomas can occur in metabolic diseases such as lipogranulomatosis, oxalosis, and gout, as well as in connective tissue diseases such as rheumatic heart disease, Wegener's granulomatosis, and Churg-Strauss syndrome. However, granulomas in cardiac sarcoidosis are usually focally distributed; thus, the possibility of cardiac sarcoidosis cannot be ruled out completely even if a biopsy is negative.

2. Idiopathic giant cell myocarditis, also known as isolated or Fiedler myocarditis, is a rare type of myocarditis. There are giant cells and

granulomas in the interstitial inflammatory focus. The cause is unknown and more common in young and middle-aged people between 20 and 50 years of age who are previously healthy. The clinical onset is rapid, with an acute and progressive course, and is usually fatal. For the fulminant type, the patients often die from heart dilation-induced acute heart failure and/or arrhythmia.

Idiopathic giant cell myocarditis has a poor prognosis, especially when accompanied by focal or even extensive myocardial necrosis; 20% of these patients have autoimmune diseases, such as ulcerative colitis, rheumatoid arthritis, myasthenia gravis, hyperthyroidism or hypothyroidism, and other concomitant diseases including drug allergies, thymoma, sarcoidosis, and so forth.

Pathological changes: The heart enlarges and the weight increases, with the main lesions concentrated in the myocardium. The endocardium and pericardium can also be affected. In the cutting surface of the heart, especially in the left ventricular wall and interventricular septum, there are fused or multifocal necrotic areas that are grayish-yellow or dark red and approximately ≥2 mm in diameter. Most of the four heart cavities are affected, and mural thrombus may emerge in some cases. In the late/repair phase, the ventricular wall decreases in thickness due to diffuse scarring. Due to the existence of visible island-like cardiomyocytes inside the fibrous scar tissue, it is not a true ventricular aneurysm.

Histopathological examination: The characteristic pathological change is the appearance of multinuclear giant cells (by fusion of macrophages) and necrosis of cardiomyocytes within the extensive inflammatory infiltration foci (Fig. 6.25). In the interstitium, there are multifocal or diffuse inflammatory infiltrations mainly consisting of lymphocytes, plasma cells, eosinophils, and macrophages, mixed with multinuclear giant cells. The size of multinuclear giant cells can reach 90 μm × 20 μm, with up to 20 nuclei in each cell, and they usually lie on the adjacent sarcolemma of necrotic cardiomyocytes. Extensive necrosis occurs in cardiomyocytes, which can be focal, map-like, or diffuse, accompanied by varying degrees of fibrosis. The necrotic myocardium is replaced by granulation tissue, and the boundary between necrotic and viable myocardial tissues is unclear.

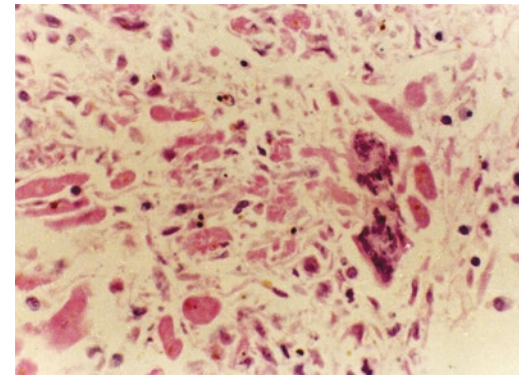

Fig. 6.25 Idiopathic giant cell myocarditis. Necrosis of the myocardium with interstitial infiltrates of lymphocytes and multinuclear giant cells (HE 400×)

Immunohistochemical stainings show that the multinuclear giant cells are CD68-positive macrophages, while they are actin-, desmin- and myosin-negative. Lymphocytes are mainly $CD3^+$ T cells, with rare B cells. $CD8^+$ T cells are much more numerous than $CD4^+$ T cells in the acute phase. During the repair phase, actin-positive macrophages are occasionally seen at the edge of inflammatory foci, indicating inflammatory damage to the cardiomyocytes.

If pathological examinations find myocardial necrosis and multinuclear giant cells in young patients, the diagnosis of idiopathic giant cell myocarditis should be considered when infectious diseases are eliminated.

The clinical diagnosis of idiopathic giant cell myocarditis requires a differential diagnosis from cardiac sarcoidosis. These two diseases share similar clinical features and general morphological appearances; thus, that they are often classified together. However, they are different diseases with significant differences in microscopic histopathological

characteristics and prognoses. First, the presence or absence of granulomas is the key distinguishing point of the histopathology. Second, there is more pronounced fibrosis in cardiac sarcoidosis than in idiopathic giant cell myocarditis, while few eosinophils are seen in cardiac sarcoidosis. The myocardial necrosis also differs: it is mass-shaped in cardiac sarcoidosis but band-shaped in idiopathic giant cell myocarditis.

6.2.6 Allergic Myocarditis

Allergic myocarditis, also known as hypersensitive myocarditis (hypersensitive myocarditis), refers to drug-induced hypersensitive myocardial inflammation with damage to the myocardium. It occurs rapidly after medication, and is a common adverse drug reaction. More than 40 kinds of drugs may cause allergic reactions, containing antibiotics, diuretics, and anti-allergic drugs [24]. The antibiotics include ampicillin, chloramphenicol, sulfonamides, and so forth. The anti-inflammatory drugs include phenylbutazone, indomethacin, and so forth. The rest are comprised of antidepressants such as amitriptyline, antiepileptic drugs such as phenytoin, and diuretics such as spironolactone. Seven percent of patients who have undergone heart transplantations will have allergic myocarditis, which may be related to the long-term use of dobutamine [24–28]. The clinical symptoms of allergic myocarditis include a skin rash, fever, increased eosinophils in peripheral blood, and occasional arrhythmia. It is usually not dose-dependent, and may occur at any period of medication use. This adverse reaction is usually benign, but in severe cases it may result in chronic heart failure or even sudden death.

Pathological changes: General examination shows that lesions are common in the left ventricular wall and the ventricular septum, resulting in dough-like myocardial softness with yellow-red spots.

Microscopic pathological changes: The lesion is transient interstitial myocarditis, and the main manifestations are inflammatory infiltrations around the small endocardial vessels and in the interstitium which mainly consist of eosinophils, as well as lymphocytes, plasma cells, and mast cells that may have degranulation (Fig. 6.26). The degeneration and necrosis of cardiomyocytes are mild. Occasional focal necrosis can resolve spontaneously after

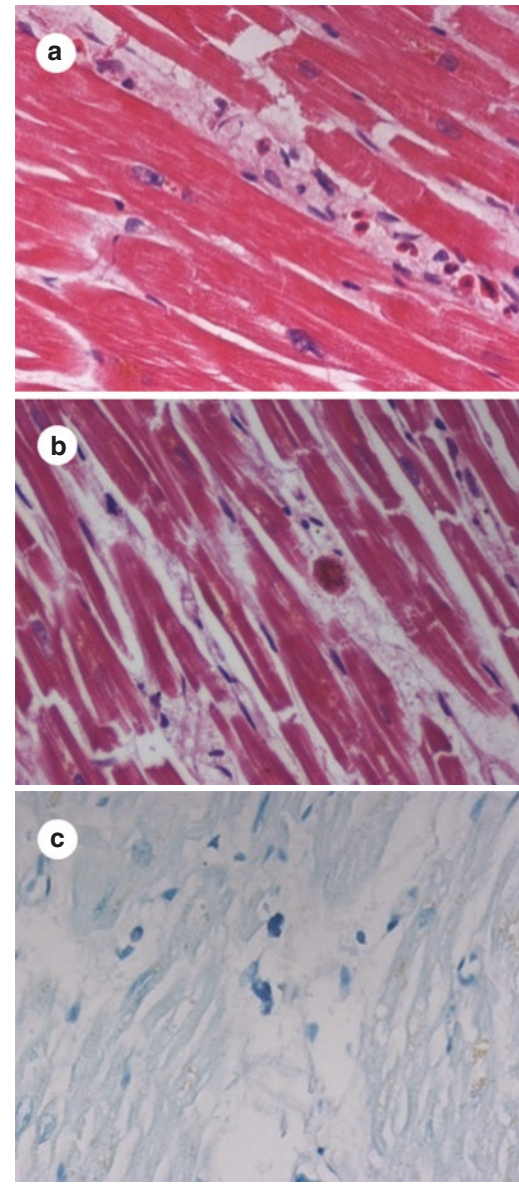

Fig. 6.26 Allergic myocarditis. (**a**) Infiltrates of eosinophils in the interstitium; (**b**) Infiltrates of mast cells and degranulation; (**c**) Infiltrates of mast cells and degranulation (Wright's staining)

ceasing the medication, leaving no fibrosis or fibrinous necrosis. Vasculitis or perivascular inflammation often occur within allergic myocarditis, but necrotic vasculitis is rare. The infiltrating lymphocytes are mainly T cells, with few B cells.

Allergic myocarditis lacks giant cell infiltration, which is the key point to distinguish it from drug-induced giant cell myocarditis. For the differentiation between allergic myocarditis and eosinophilic myocarditis, there is extensive myocardial necrosis, infiltrations of many eosinophils and inflammatory cells, and a lack of symptoms of systemic allergy in the latter [29, 30].

Eosinophilic myocarditis (Fig. 6.27) is sometimes called idiopathic eosinophilic endocarditis [31]. However, for some cases of eosinophilic myocarditis, when more eosinophils are detected in the myocardium, it should also be considered as allergic myocarditis, especially for myocarditis that responds to drugs. In some cases, immunohistochemical staining may provide evidence of IgE and allergic reactions, such as an increase of mast cells in the lung tissue. The evidence of contact with allergens should be investigated, if available. Eosinophilic myocarditis may be part of "drug-induced hypersensitivity syndrome" (DIHS), also known as a "drug rash with eosinophilia and systemic symptoms" (DRESS). This is a serious reaction that usually occurs one to eight weeks after medication, and is characterized by a fever, rash, and multiple organ failures. It is a type of immune response involving the activation of macrophages and T cells and the release of cytokines. No consensus has as yet been reached for the etiology of this disease.

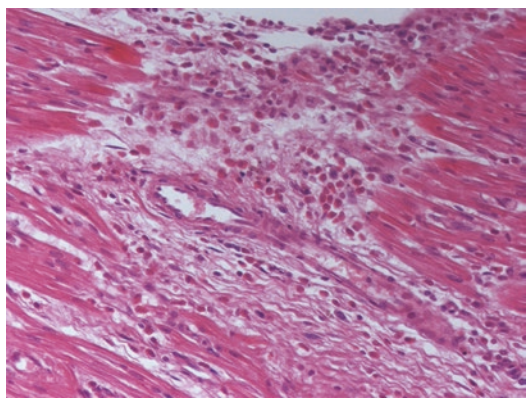

Fig. 6.27 Eosinophilic myocarditis. Necrosis of cardiomyocytes, infiltrations of massive eosinophils, and fibrosis (HE 200×)

6.2.7 Toxic Myocarditis from Snake Venom

Snake venom toxins can cause toxic myocarditis and damage to other organs after various venomous snake bites. Among them, a bite from a pallas pit viper, especially Ancistrodon acutus, may cause serious toxic myocarditis. The injured patient may die from heart failure, arrhythmia, and multiple organ failure [32]. The mechanism of toxic myocarditis from snake venom is related to the agkistrodotoxin which contains a variety of toxic components, such as anticoagulation and procoagulant toxins, hemorrhagic toxins, proteolytic enzymes, lecithinase A, and other toxic enzymes. These toxins can cause local bleeding and swelling, as well as myocardial damage. Therefore, in addition to local bleeding and blisters, the patient's clinical symptoms also include shortness of breath, chest tightness, progressive heart palpitations, and other manifestations of myocardial damage. A myocardial zymogram and a biochemical test will show an increase, and an ECG will show ST-T and/or rhythmic changes, and so forth.

Pathological changes: General examination shows myocardial congestion, edema, and multiple spotting hemorrhages in the epicardium and cut surface.

Histopathological examination: Infiltration of a small amount of monocytes and lymphocytes in the epicardium, with sarcolysis of some cardiomyocytes, eosinophilic enhancement of some myocardial sarcoplasm, contractile band or coagulative necrosis, interstitial edemas, spotting hemorrhages, and inflammatory infiltration dominated by neutrophils (Fig. 6.28),

as well as significant congestion in vessels. There is degeneration and necrosis in the heart conduction system including the sinoatrial node, atrioventricular node, and atrioventricular bundle cells, and is accompanied by interstitial hemorrhage and a small amount of inflammatory infiltration (Fig. 6.29).

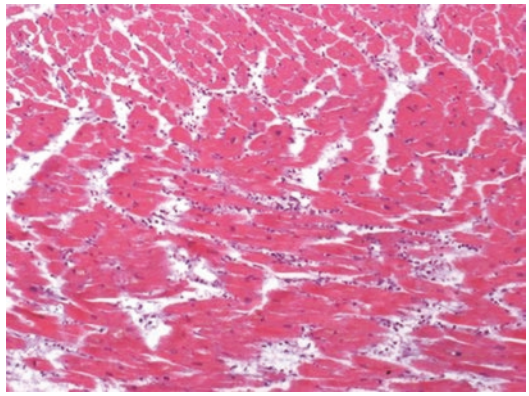

Fig. 6.28 Toxic myocarditis (female, 67 years old, died after a bite by Gloydius brevicaudus). Diffuse necrosis of the myocardium and interstitial infiltrations of neutrophils (HE 100×)

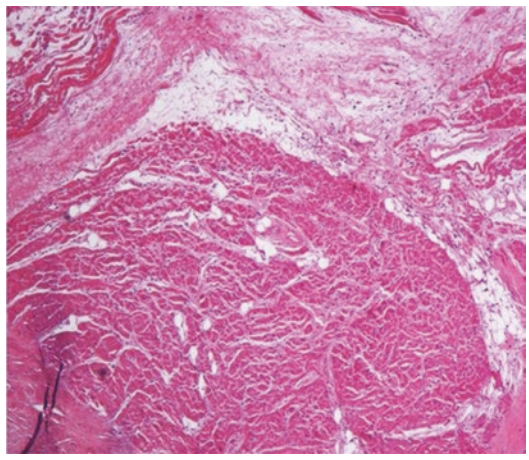

Fig. 6.29 Toxic myocarditis (male, 20 years old, died 1 day after a bite by Ancistrodon acutus). Interstitial hemorrhage, edema and inflammatory infiltrates in the His bundle (HE 40×)

6.3 Typical Cases

6.3.1 Case 1

Case Presentation

An 8-year-old girl had stomach discomfort in the morning and received treatments in a local clinic (no details for the medication), then she felt sort of relief. The patient complained of chill and nausea at 6 p.m. in the evening, and then received treatments in another clinic (injection with gentamicin plus metoclopramide, and one Huoxiang Zhengqi capsule taken orally). Repeated vomiting occurred since 9 p.m., and the patient had additional treatments in the second clinic in the next morning. The medication contained intravenous injection of gentamicin plus metronidazole, and half a pill of cimetidine for orally use. Then the patient went back home, feeling excessive fatigue. She did not eat anything since then, but drank water for 6 or 7 times. At approximate 7 p.m., the patient was found unconscious with decreased skin temperature. She was sent to a hospital immediately, but the ECG showed no electrophysiological signal already, with both corectasis. The declaration of clinical death was made.

Pathological Diagnosis

lymphocytic myocarditis (Fig. 6.30).

6.3.2 Case 2

Case Presentation

A 52-year old man was admitted to hospital because of fever (38.3 °C), chill, fatigue and poor appetite for 5 days. This patient was treated in a local clinic for 5 days (no details for the medication), but there was no improvement for symptoms. The body temperature increased up to 40 °C with listlessness and diarrhea (watery stool). The patient was sent to the hospital in early morning, and the temperature decreased to 36.7 °C after

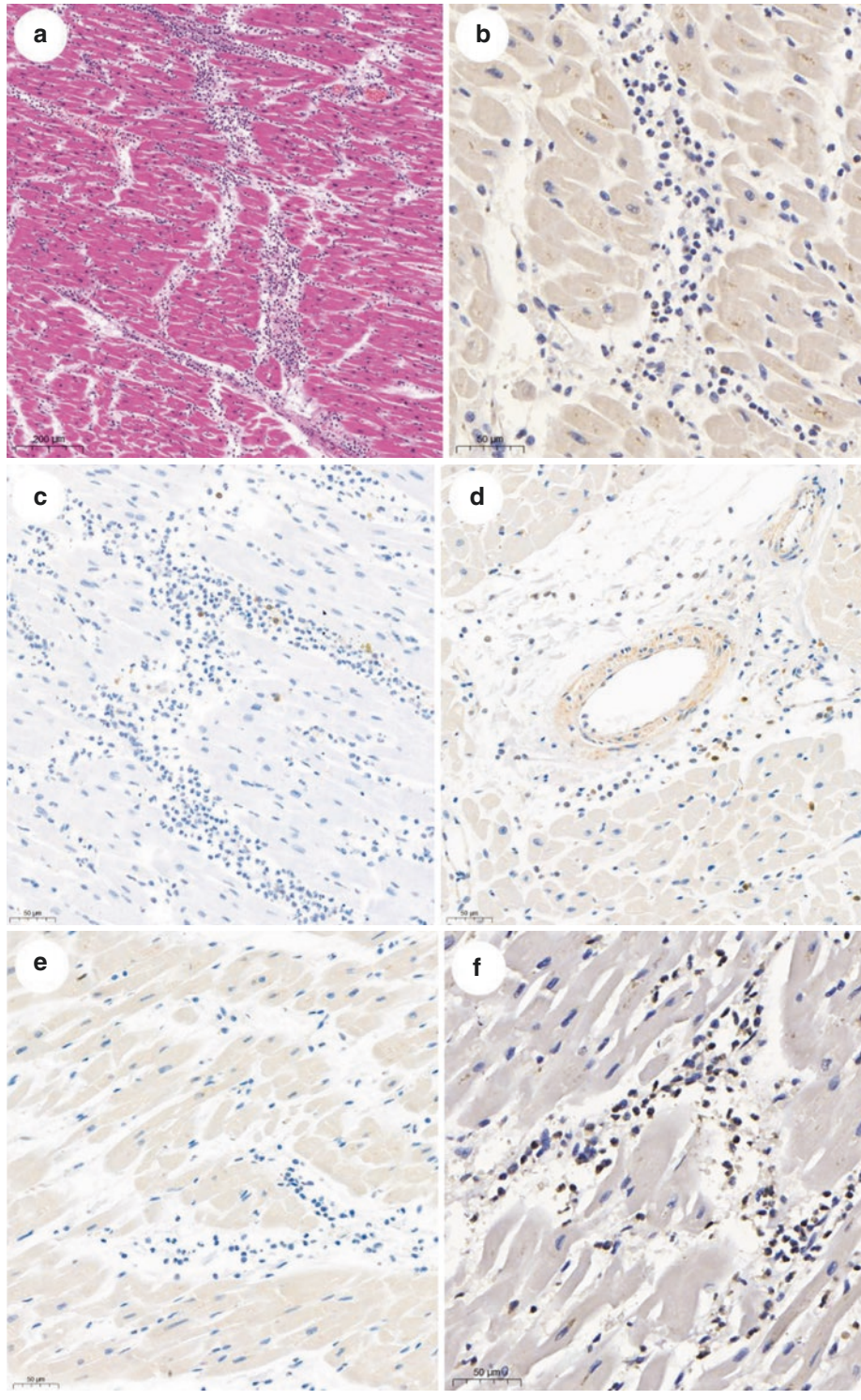

Fig. 6.30 Lymphocytic fulminant myocarditis. Cord-like necrosis of myocytes, with interstitial and perivascular infiltrates of massive inflammatory cells. Immunohistochemistry staining shows that the infiltrates consist of CD3 and CD4/CD8-positive T cells and MPO-positive neutrophils, while CD19-positive B cells are absent. (**a**) HE staining (50×); (**b**) CD3 (200×); (**c**) CD4 (200×); (**d**) CD8 (200×); (**e**) CD19 (200×); (**f**) MPO (200×)

treated with antibiotics, antipyretic and supportive care. In the morning, the patient had watery stool for 4 times with nausea and vomiting, and he was immediately given montmorillonite powder, berberine, potassium supplement, and infusion of piperacillin/ tazobactam plus inosine, vitamins C and B6. In the afternoon, the patient became sweated profusely, fidgety and cold in limbs. The blood pressure dropped to 70/30 mmHg with heart rate 152–172 bpm. Fluid infusion was conducted in two vessels with anti-shock therapies (dopamine and norepinephrine), and then the patient was transferred to a higher-level hospital. The blood pressure decreased to 47/33 mmHg in the transferal, followed by cardiac arrest. Tracheal intubation and cardiopulmonary resuscitation were immediately done. The heart rate was recovered, but the blood pressure was still undetectable. When arriving hospital, the patient was unconscious with both corectasis and cold body. CPR was conducted again with deep venous puncture, infusion of dopamine, dobutamine and norepinephrine, plus assisting breathing with ventilator. Despite all the treatments, cardiac arrest still occurred repeatedly, and it ended up with clinical death.

Supplementary Examination

Routine blood test: WBC 20.7 × 10^9/L, lymphocytes 10.2%, neutrophils 74.8%, platelets 9 × 10^9/L;

Blood biochemistry: AST 135 U/L, potassium 2.42 mmol/L, LDH 411 U/L;

Coagulation markers: D-D 23 mg/L, PT 17.1 s, PT-INR 1.39, APTT 89.6 s, TT 21.6 s;

Blood gas analysis: pH 6.661, pCO_2 140 mmHg, Lac 18 mmol/L, BE −42.9 mmol/L.

Pathological Diagnosis

Lymphocytic myocarditis (Fig. 6.31).

6.3.3 Case 3

Case Presentation

A 20-year-old man was admitted to hospital because of cardiac and respiratory arrest. He was treated in a local clinic for discomfort several days ago (no detail). At 5 pm in the day, a roommate found the patient appeared unconscious. After arriving in the school hospital, CPR was done for cardiac and respiratory arrest, and the patient was transferred to a higher-level hospital as soon as possible. The patient was in a coma with dilated pupils, undetectable blood pressure and pulse, and no electrophysiological signal in ECG. The diagnosis of sudden death was made.

Supplementary Examination

Routine blood test: WBC 22.26 × 10^9/L, neutrophils 73.4%, lymphocytes 23.4%, monocytes 2.9%;

Blood biochemistry: ALT 1583 U/L, AST 1604 U/L, BUN 12.7 mmol/L, Cr 327 μmol/L, potassium 10.6 mmol/L, blood glucose 14.3 mmol/L;

Myocardial injury markers: CKMB 12.23 ng/mL, myoglobin >1000 ng/mL.

Pathological Diagnosis

Lymphocytic myocarditis (Fig. 6.32).

6.3.4 Case 4

Case Presentation

A 29-year-old man got intravenous infusion because of “common cold” in a local clinic (no detail) in the morning. At about 11 a.m., dyspnea suddenly occurred, followed by unconsciousness. Cardiac and respiratory arrest and undetectable blood pressure was found when the patient was sent to a local out-patient department. CPR and oxygen inhalation were immediately done while the patient was transferred to a higher-level hospital. His heart rate was 139 bpm, and blood pressure was 97/50 mmHg (maintained by high dose of blood pressure elevating drugs) with both corectasis. The patient was also treated with tracheal intubation and ventilator -assisted breathing, blood transfusion, fluid infusion and supportive therapies. On the next day, cardiac arrests happen for 4 times from morning to dusk, and at every onset, he was rescued with CPR, injection of adrenaline calcium gluconate and pituitrin, infusion of sodium

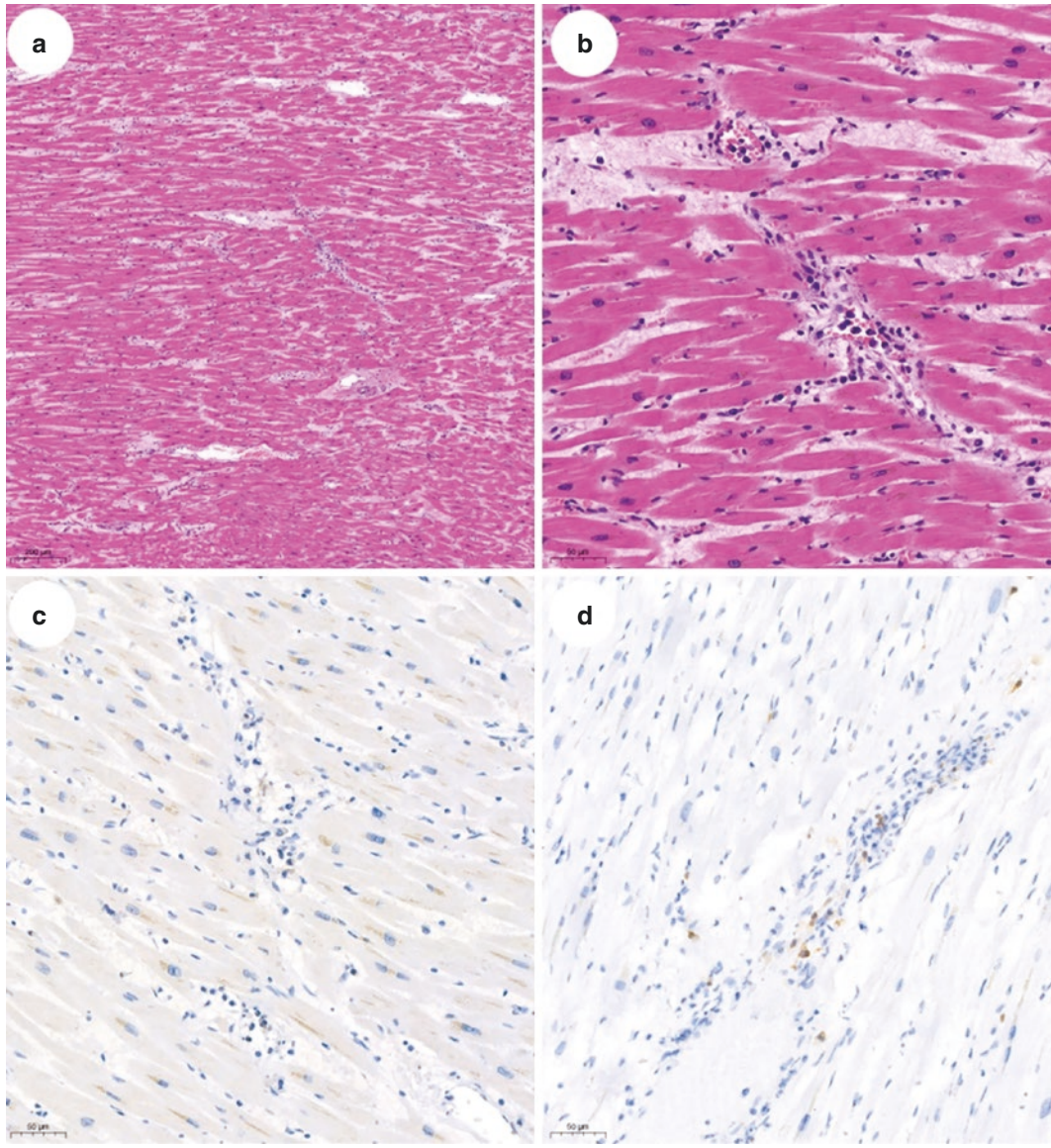

Fig. 6.31 Lymphocytic fulminant myocarditis. It shows multiple patches of necrosis of cardiomyocytes, especially predominant in the areas around small vessels, with interstitial and perivascular infiltrates of inflammatory cells. Immunohistochemistry staining shows infiltrates of mainly CD3 and CD4/CD8-positive T cells, CD19-positive B cells and CD68-positive macrophages. CD56-positive NK cells are rare. (**a**) HE staining (50×); (**b**) HE staining (200×); (**c**) CD3 (200×); (**d**) CD4 (200×); (**e**) CD8 (200×); (**f**) CD19 (200×); (**g**) CD56 (200×); (**h**) CD68 (200×)

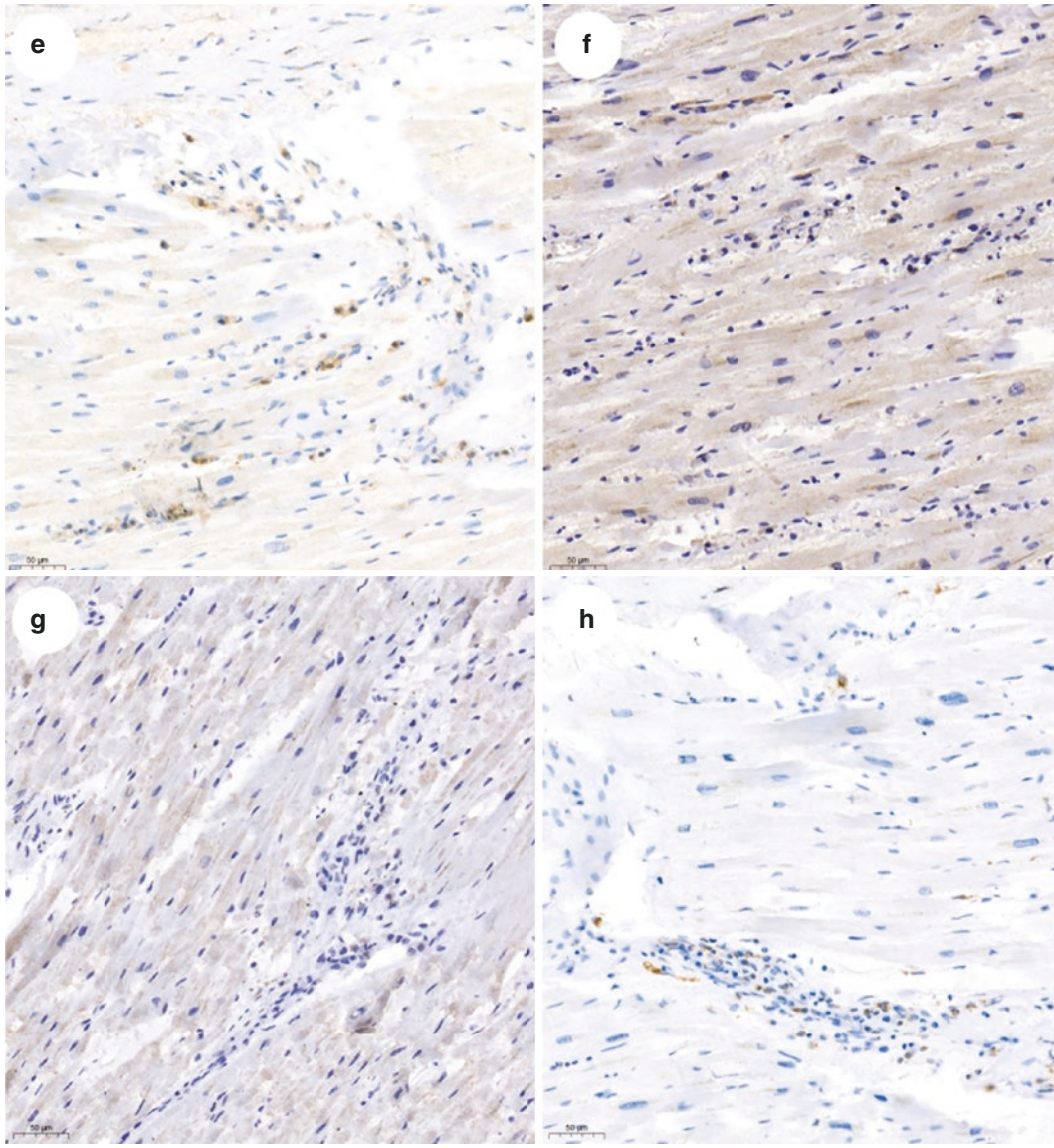

Fig. 6.31 (continued)

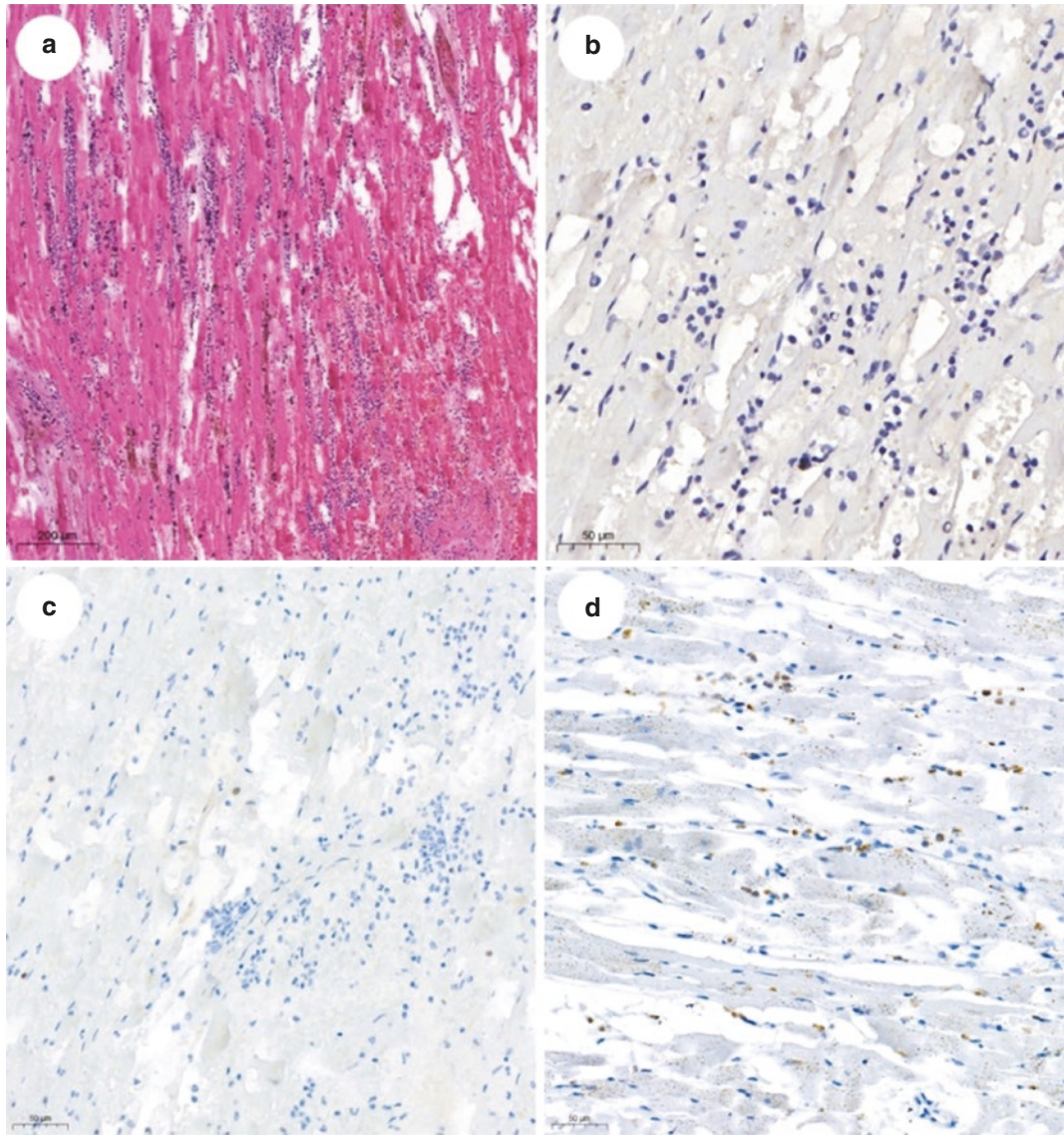

Fig. 6.32 Lymphocytic fulminant myocarditis. Necrosis of cardiomyocytes, with extensive infiltrates of inflammatory cells in interstitial areas. Immunohistochemistry staining shows infiltrates of CD3 and CD8-positive T cells, CD68-positive macrophages and MPO-positive neutrophils. CD19-positive B cells and CD4 -positive T cells are rare to see. (**a**) HE staining (50X), (**b**) CD3 (200X), (**c**) CD4 (200X); (**d**) CD8 (200X); (**e**) CD19 (200X); (**f**) CD68 (200X); (**g**) MPO (200X)

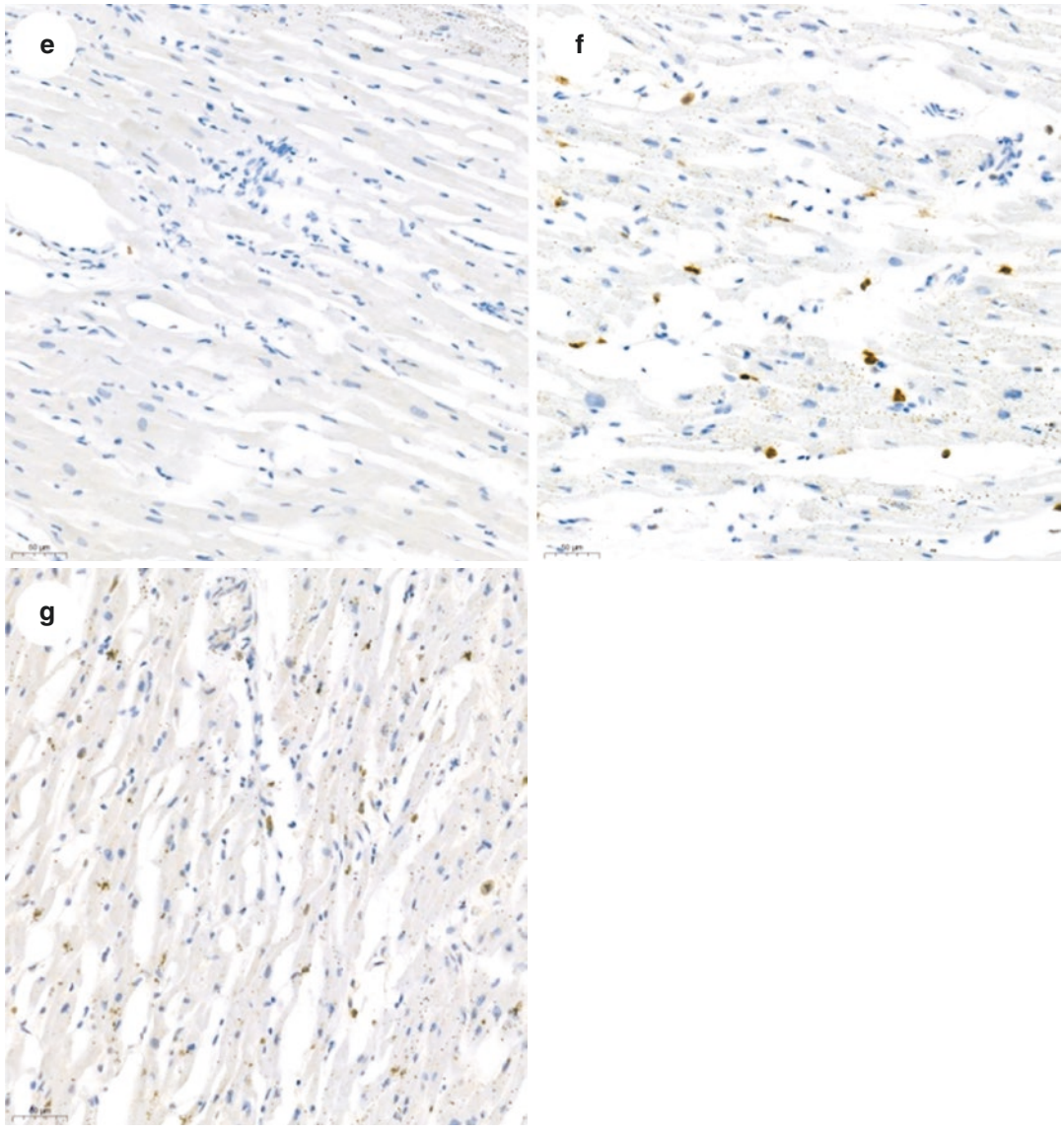

Fig. 6.32 (continued)

bicarbonate, pumping in with dopamine and electrical cardioversion. The heartbeat recovered for 3 times, but failed for the last time. Then the declaration of clinical death was made.

Supplementary Examination

Routine blood test: WBC 23.6 × 10^9/L, neutrophils 85%, lymphocytes 9.1%, monocytes 5.7%, platelets 61 × 10^9/L;

Blood biochemistry: ALT 955 U/L, AST 1005 U/L, LDH >1867 U/L, blood glucose 17.22 mmol/L;

Coagulation markers: PT >180 s, FIB <0.5 g/L, APTT >180 s, TT >180 s, D-D > 80 μg/mL, FDP >150 μg/mL, AT 30%;

Myocardial injury markers: cTnI >50,000 ng/mL, CKMB 126.6 ng/mL, myoglobin >1200 ng/mL;

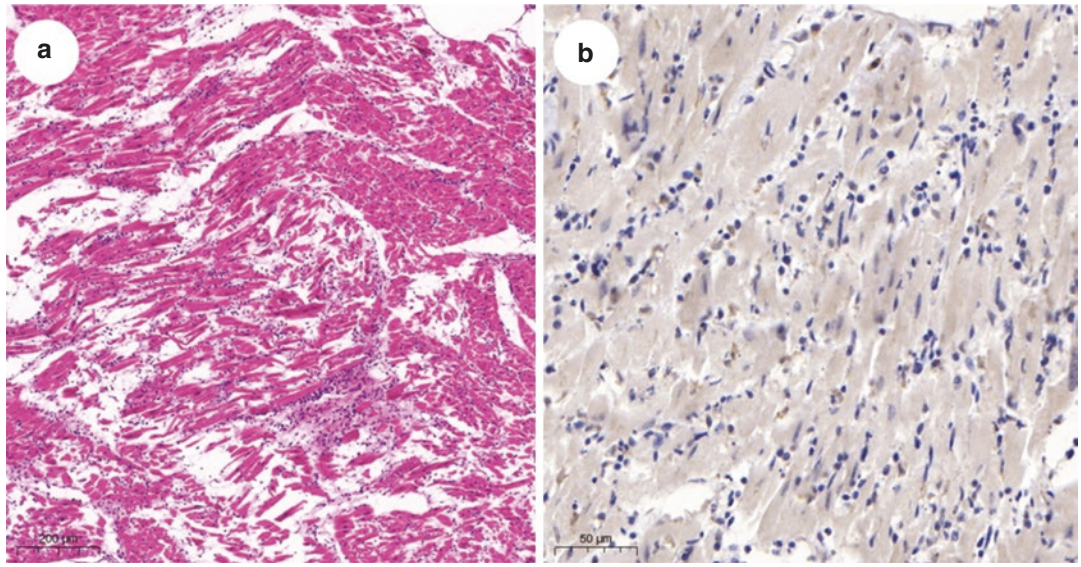

Fig. 6.33 Lymphocytic fulminant myocarditis. Multiple patches of necrotic and dissolved myocytes, with massive infiltrates of inflammatory cells. Immunohistochemistry staining shows infiltrates of MPO-positive neutrophils. (**a**) HE staining (50X); (**b**) MPO (200X)

Cytokines: IL-6 > 5000 pg/mL.

Pathological Diagnosis
Lymphocytic myocarditis (Fig. 6.33).

6.3.5 Case 5

Case Presentation
An adult male visited a local clinic in the morning for discomfort, and was diagnosed with "common cold with mild bronchitis". He was injected with one shot of andrographis paniculata nees, and givenorally-taken drugs including cefixime, Ganmao cough granules and others. Two additional shots of andrographis paniculata nees were injected at 6 p.m. in the evening and 8 a.m. the next day. At about 12 a.m., the patient retched severely and became critically ill (no detailed description), and the vital signs were undetectable when he was sent to hospital. Then the declaration of clinical death was made.

Pathological Diagnosis
Lymphocytic myocarditis (subacute phase) (Fig. 6.34).

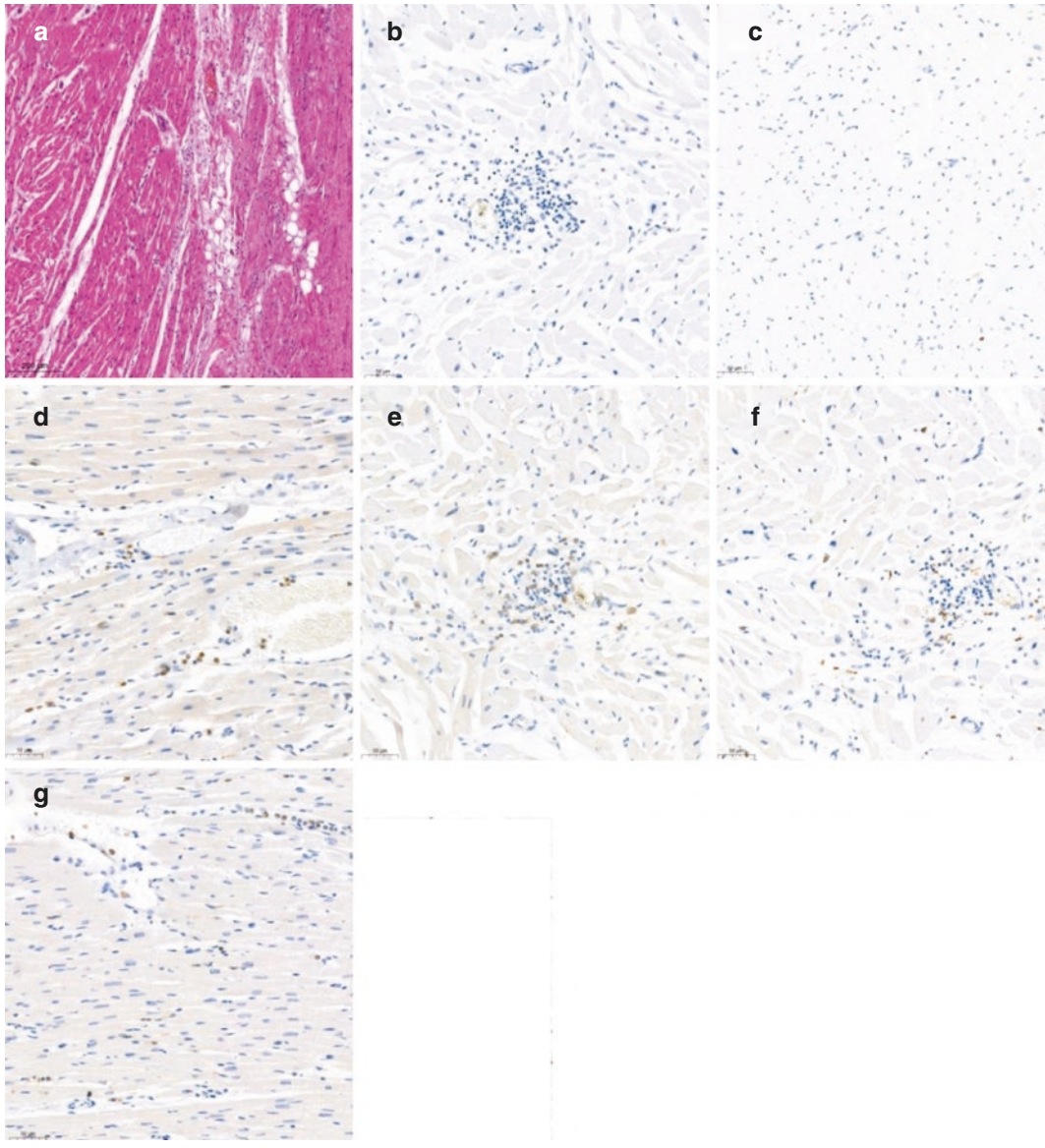

Fig. 6.34 Lymphocytic fulminant myocarditis (subacute phases). It shows necrotic and dissolved myocytes with infiltrates of inflammatory cells, formation of granulation tissue and fibrosis. Immunohistochemistry staining shows infiltrates of CD8-positive T cells and CD19-positive B cells, but CD4 -positive T cells are rare. CD68-positive macrophages and MPO-positive neutrophils are also present. (**a**) HE staining (50X); (**b**) CD3 (200X); (**c**) CD4 (200X); (**d**) CD8 (200X); (**e**) CD19 (200X); (**f**) CD68 (200X); (**g**) MPO (200X)

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