7 Clinical Manifestations of and Laboratory Tests for Myocarditis and Fulminant Myocarditis

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Myocarditis refers to inflammatory injury of the myocardium caused by various factors. Its clinical manifestations are related to the severity of myocardial damage. Mild cases only manifest as increased heart rate and mild reduction of cardiac systolic or diastolic function, while severe cases present with cardiogenic shock, heart failure, malignant arrhythmia, and even sudden death [1].

Myocarditis can be categorized as infectious or non-infectious myocarditis according to etiology. Viral infections are the most common cause of infectious myocarditis. Other causes of infectious myocarditis include bacterial, fungal, spirochetal, rickettsial, protozoal, or helminthic infections, but which are relatively uncommon. Meanwhile, non-infectious myocarditis can be induced by drugs, toxicants, radiation, connective tissue diseases, systemic vasculitis, giant cell myocarditis, and sarcoidosis.

According to the clinical course, myocarditis can be divided into fulminant myocarditis, acute myocarditis, chronic active myocarditis, and chronic persistent myocarditis.

Fulminant myocarditis is the most severe and special type of myocarditis; its occurrence results from the combined action of direct viral cytopathogenic effects and the overexuberant antivirus immune response. Viral infections can induce cardiac damage either by direct virus replication/killing of infected cells or by immune-mediated tissue damage, which is mainly mediated by T cells. Besides, various inflammatory cytokines also participate in myocardial damage and microvascular injury, thus contributing to cardiac tissue damage and cardiac dysfunction. Fulminant myocarditis is characterized by an acute onset and a rapid progression. Patients soon develop hemodynamic instability (pump failure and circulatory failure) and severe arrhythmia after the onset of the illness, which can be accompanied by respiratory, liver, or kidney failure. The early mortality rate of fulminant myocarditis is extremely high. However, after active treatment, most patients have a good long-term prognosis once they have passed the acute risk period.

Fulminant myocarditis occurs throughout the year but most frequently during winter and spring. It affects people of all ages, and most cases occur in young adults who are generally in good health and without basic organic diseases. There is no reported obvious sex difference in the occurrence of fulminant myocarditis.

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7.1 Clinical Manifestations

The clinical manifestations of fulminant myocarditis vary greatly. It begins with prodromal symptoms of respiratory infections, followed by mild chest pain, palpitations, and transient electrocardiogram (ECG) changes and then progresses to life-threatening cardiogenic shock, malignant arrhythmias, and multiple organ dysfunction. Fulminant myocarditis is characterized by a sudden onset and a rapid progression.

7.1.1 Predisposing Factors

Factors that lead to the reduction of the systemic or local respiratory immune defense function, such as cold, sudden climate change, and excessive fatigue, can decrease patients' immunity and facilitate invasion of pathogens, which consequently leads to fulminant myocarditis. Predisposing factors exist at different stages of the disease. The first stage is the period before the onset of illness. Persistent or intense stress, such as fatigue and long-term overwork, is the most common cause of fulminant myocarditis. The second stage is when patients have already developed symptoms but are still at an early stage or in a mild state. Continuing to engage in high-intensity work can exacerbate the disease, and severe arrhythmia, shock, and sudden death may occur. Acute exacerbations are frequently present in various situations, such as physical education, military training, marathons, and other strenuous exercises.

7.1.2 Early Symptoms

Accurate knowledge and understanding of the early symptoms of fulminant myocarditis are extremely important for timely diagnosis. Different patients may have different early manifestations [2].

7.1.2.1 Respiratory Symptoms

Respiratory symptoms of fulminant myocarditis are uncommon and are generally mild, which is different from a "cold." Fulminant myocarditis can mimic a cold, manifesting as nasal congestion, runny nose, fever, headache, and other discomfort, followed by a mild, short-term cough, usually without sputum [3]. Different degrees of fever can occur, ranging from a temperature of 37–39 °C. However, some patients report short-term chills but deny fever, and they generally present with discomfort, such as chest tightness, chest pain, and shortness of breath. Notably, only approximately <50% of patients have respiratory infection, and this infection is generally mild and transient [4].

7.1.2.2 Gastrointestinal Symptoms

A small number of patients have mild diarrhea, often presenting as loose stools, which can last for 2–3 days. Most patients have poor appetite and anorexia and even develop nausea, vomiting, abdominal distension, and mild abdominal pain [5, 6].

7.1.2.3 Systemic Symptoms

Systemic symptoms mainly manifest as fever, fatigue, and dizziness. Over time, patients show an obvious lack of speech, obvious fatigue, and anorexia. Some patients prefer to lie supine because of low blood pressure and obvious dizziness when sitting or standing [7].

7.1.2.4 Symptoms of Myocardial Damage

Similar to the symptoms of myocardial infarction, a small number of patients present with chest pain at first, followed by persistent chest tightness. Chest pain occurs when inflammation involves the pericardium and/or pleura and can also be caused by inflammation-induced coronary artery spasm. Chest tightness and shortness of breath may be caused by myocardial damage. Some patients present with palpitations and blackouts, which are usually caused by arrhythmias, such as tachycardia or bradycardia. In severe cases, the symptoms may manifest as syncope or sudden death, and some patients have palpitations and syncope as their first symptoms [7].

7.1.3 Progressive Symptoms

After the occurrence of prodromes over a short period, patients' condition usually worsens, and patients soon show extreme fatigue, anorexia, dizziness, chest tightness, and palpitations. They usually prefer to stay in bed to save energy and even feel tired to open their eyes. Some patients develop syncope and arrhythmia repeatedly.

7.1.3.1 Symptoms of Myocardial Damage

A few days or 1–3 weeks after the onset of prodromal symptoms, patients develop dyspnea, chest tightness, chest pain, palpitations, dizziness, extreme fatigue, and anorexia, which are primary reasons for medical visits. One European study suggested that 72% of patients with fulminant myocarditis had dyspnea; 32% had chest pain; and 18% had arrhythmias. Statistics from the author's hospital show that approximately 90% of patients with fulminant myocarditis presented to or were referred to the hospital because of dyspnea or chest tightness accompanied by extreme fatigue, anorexia, and dizziness; meanwhile, 10% of patients presented to or were referred to the hospital because of syncope or after cardiopulmonary resuscitation.

Chest Pain and Tightness

The chest pain is intense and unbearable for most patients, with a sense of being on the verge of dying. It generally appears in the precordial area, behind the breastbone, and on both sides of the front chest. Numbness or tingling in the left wrist and fingers can also occur. The pain is persistent and cannot be relieved by medicine or rest. Some patients, especially elderly patients, show chest tightness and acute left heart failure.

Painless Myocarditis

Painless myocarditis occurs in a minority of patients who are commonly old, is accompanied by diabetes or severe infection, or develops in the perioperative period. In most patients, painless myocarditis is accompanied with cardiogenic shock, severe arrhythmia, or heart failure, which can cause sudden death. In some patients, the pain can be masked by symptoms, such as congestive heart failure, extreme fatigue, fear and nervousness, acute indigestion, and syncope.

Arrhythmia

Arrhythmia is very common and occurs in almost every patient with fulminant myocarditis. Various arrhythmias can be seen in patients with fulminant myocarditis, with sinus tachycardia as the most common type. Tachyarrhythmias include atrial flutter, atrial fibrillation, atrial tachycardia, ventricular tachycardia, and ventricular fibrillation. Inflammation and edema of the myocardium can affect the cardiac conduction system, causing sinus arrest, intraventricular block, and atrioventricular block. Patients can present with palpitation, dizziness, cold sweats, syncope, and even Adams–Stokes syndrome. In a very small number of patients, the symptoms exacerbate rapidly after the onset of the disease, with hemodynamic disorders and even cardiac arrest.

7.1.3.2 Hemodynamic Disorder

Hemodynamic disorder is an important feature that distinguishes fulminant myocarditis from acute myocarditis. Some patients rapidly develop acute left heart failure and cardiogenic shock and show signs of pulmonary congestion and shock.

Acute Heart Failure

Patients may present with severe dyspnea, orthopnea, cough with pink foamy sputum, shortness of breath, anxiety, profuse sweating, oliguria, or anuria. However, edema, liver enlargement, and jugular vein filling are rare because of reduced systemic blood vessel tone. Clinically, severe acute left heart failure is uncommon, and most patients can lie supine, which is related to total heart failure and peripheral vasodilatation.

Cardiogenic Shock

Patients may show clammy, pale, cyanotic, and cold limbs and weak pulse. When the blood pressure is extremely low, the peripheral blood pressure cannot be measured. Patients' peripheral circulation is also poor, and they may be unresponsive, confused, or even in coma [8, 9].

Adams–Stokes Syndrome

A few cases present with syncope or sudden death and are generally accompanied by severe arrhythmias, such as ventricular tachycardia, ventricular fibrillation, sick sinus syndrome, and third-degree atrioventricular block.

Notably, an abnormal cardiac pump function is the main cause of hypotension in fulminant myocarditis among the three basic determinants of cardiac output (myocardial contractility, cardiac preload, and cardiac afterload), while blood volume and vascular resistance also have contributions. Since most patients with fulminant myocarditis have no basic organic heart disease, the abnormal cardiac pump function is only manifested by diffuse reduction in myocardial contraction and decreased ejection fraction. However, because patients have no basic cardiac disease, the myocardial compensation mechanism is too late to establish; the disease progresses very rapidly; and cardiogenic shock is very easy to ignore.

7.1.3.3 Manifestations of Multiple Organ Involvement

Fulminant myocarditis can cause multiple organ dysfunction or failure, including abnormal liver function, abnormal kidney function, abnormal blood coagulation, and respiratory system dysfunction. Multiple organ dysfunction is most secondary to cardiac damage and cardiogenic shock at later stage, while virus erosion and immune response also play a very important role.

1. **In the presence of acute respiratory distress syndrome (ARDS)**, patients with fulminant myocarditis develop pump failure and cardiogenic shock. Under multiple conditions, such as ischemia, pulmonary congestion, and inflammatory storms, lung exudation occurs; tissue fluid increases; pressure increases; and exudation even penetrates the alveoli, leading to ARDS. Patients present with hypoxia and dyspnea, and the blood lactic acid level is increased. However, owing to extreme fatigue, patients have no strength to breathe, making breathing superficial or shallow. Doctors should pay great attention to this scenario and provide timely respiratory assistance. Prolonged severe shock and long-term use of norepinephrine and other vasoconstrictors can cause irreversible damage to multiple organs, including disseminated intravascular coagulation (DIC), ARDS, and severe leakage syndrome. In addition, a small number of patients may have a pulmonary infection, that is, pneumonia. Different types of pneumonia have different symptoms. Bacterial pneumonia accounts for 80% of adult infectious pneumonia cases and has a very high mortality rate among children, elderly patients, and patients with immunosuppression. Most patients have chills, fever, cough, sputum, and chest pain, while a few patients have hemoptysis and dyspnea. Other symptoms include nausea, vomiting, general discomfort, and muscle aches. Viral pneumonia is caused by a variety of viral infections, which mostly occur during winter and spring. The clinical manifestations are mainly cough, fever, dyspnea, cyanosis, and anorexia. Approximately 10% of patients with fulminant myocarditis also have pleural effusion. Pleural effusion is mostly bilateral and is caused by inflammation and leakage. If it does not form compression, no special treatment is needed, and it will disappear as the systemic inflammatory storm and myocardial inflammation attenuate.
2. **In the presence of an abnormal liver function**, only a very small number of patients have obvious liver damage in the early stage, which is related to the virus and inflammatory storm. However, inappropriate treatment regimens, such as the application of high-dose vasoconstrictors (e.g., noradrenaline) or prolonged shock, can result in liver damage and jaundice. The transaminase level can reach 8000 U/L, and in severe cases, bile/enzyme separation may occur. Hypoproteinemia due to decreased protein synthesis leads to systemic edema and even polyserous effusions. Decreased synthesis of coagulation factors leads to coagulation dysfunction, namely DIC. If it reaches this stage, the situation is difficult to reverse.
3. **In the presence of an abnormal renal function**, patients with fulminant myocarditis may

develop acute kidney injury, which is mainly caused by insufficient renal perfusion resulting in a low cardiac output. Some patients may have severe renal function injury; however, when the systemic symptoms are attenuated with mechanical support treatment, such as IABP, renal function gradually returns to normal after going through the oliguria and polyuria phases.

4. **In the presence of DIC**, the clinical manifestations of patients with fulminant myocarditis are complex and diverse, with the main manifestations including bleeding, shock, organ dysfunction, and anemia. The occurrence of DIC is directly related to prolonged shock, delayed diagnosis, and inappropriate treatment, such as long-term use of vasoconstrictors (e.g., norepinephrine or pituitrin). Therefore, they should be actively avoided.
5. **Thyroiditis, it** only occurs in a very small number of patients with fulminant myocarditis and is part of the inflammation. Various types of thyroiditis may occur, and the onset is insidious and often undetected. Sometimes, they are found accidentally during physical examination or when relevant clinical symptoms appear. Hashimoto's thyroiditis is the most common type, which may be characterized by diffuse thyroid enlargement with a hard texture and smooth surface, sometimes with nodules. It is generally painless or has mild tenderness. Local compression and systemic symptoms are not usually observed, while pharyngeal discomfort occurs occasionally. Thyroid function can be either normal or abnormal. Patients with hyperthyroidism can show hypermetabolic symptoms, such as fever, sweating, hand tremors, and weight loss. The goiter may enlarge, and vascular murmurs may occur.

In summary, the clinical manifestations of fulminant myocarditis vary greatly from individual to individual. Many patients have only low-grade fever, significant fatigue, anorexia, or mild diarrhea in the early stages. Objectively, patients are usually quiet, without pain or groaning. The symptoms can last for 3–5 days. Most primary diseases are ignored because the symptoms are mild and are generally not the main reason for the patients' visit. However, these are important clues for the diagnosis of myocarditis. Therefore, it is important to obtain a detailed medical history. If patients have the abovementioned symptoms and recover after taking medicine or receiving no special treatment for 2–3 days, the condition should be considered as a common cold. If patients do not recover, especially if the symptoms are aggravated, and symptoms, such as extreme fatigue, chest tightness, palpitations, and dizziness, occur, the possibility of fulminant myocarditis and investigation through related examinations or transfer to a higher-level hospital for diagnosis and treatment should be considered.

7.2 Physical Signs

7.2.1 Vital Signs

Patients usually exhibit severe changes in their vital signs. Abnormal blood pressure, respiration (fast or slow), and heart rate indicate hemodynamic instability, which is the most significant manifestation of fulminant myocarditis and an indication of the severity of the disease.

7.2.1.1 Fever

Some patients may have an increased body temperature, while other patients may not develop fever. The increase in body temperature caused by primary viral infection is generally not too high. However, when it is complicated by pulmonary (or other organic) bacterial infections, the body temperature can reach 39 °C or even higher. A very small number of patients may also experience a situation where the body temperature does not increase (below 36 °C), which indicates that the disease is extremely severe.

7.2.1.2 Hypotension

Patients with fulminant myocarditis can develop hypotension as a consequence of abnormal vasomotor systole resulting from severe cardiac dysfunction and systemic inflammatory storm. The blood pressure can be lower than 90/60 mmHg in most patients and can decrease to <70% of the

basal value in patients with previous hypertension. In severe cases, the blood pressure cannot be measured. Patients with hypotension or shock usually have an increased heart rate. However, there are also patients with hypotension presenting with no obvious increase in heart rate, while some patients even show bradycardia or conduction block resulting from myocardial inflammation. However, in these patients, the blood pressure will decrease markedly as the disease progresses, and shock may occur. Patients with severe hypotension may present with repeated ventricular tachycardia or ventricular fibrillation, which can easily lead to death.

7.2.1.3 Breathing Changes

Patients may show tachypnea (respiratory rate of up to 20–30 beats/min) or hypopnea (respiratory rate of <10 beats/min) in severe cases. Blood oxygen saturation is generally lower than 90%. Some patients manifest dyspnea and require mechanical ventilation.

7.2.1.4 Heart Rate and Heart Rhythm Changes

Sinus tachycardia (heart rate of >120 beats/min) is relatively common in patients with fulminant myocarditis. Bradycardia (heart rate of <50 beats/min) may also occur in some patients. Sinus tachycardia is a remarkable characteristic of fulminant myocarditis, and it is a normal response to shock. Half of patients have a markedly increased heart rate. In a resting state, the heart rate is above 80–100 beats/min, usually 100–150 beats/min, and even higher than 150 beats/min in a few patients. Although tachycardia (heart rate of >10 beats/min) that is not commensurate with increases in body temperature is not a specific sign of myocarditis, it is an important clinical clue for the diagnosis of myocarditis, which needs to be taken seriously. In addition to sinus tachycardia, other types of arrhythmias can also occur, including ventricular or supraventricular premature contractions, ventricular and supraventricular tachycardias, and ventricular fibrillation. Some patients present with bradycardia and conduction block as a consequence of conduction system damage caused by myocardial inflammation and myocyte edema. Among these, ventricular tachycardia and ventricular fibrillation are the most serious types of arrhythmias [10, 11].

7.2.2 Heart-Related Signs

7.2.2.1 Cardiac Size

The heart border does not usually enlarge (that is, the heart is not large); however, in a very small number of patients, the heart is enlarged at the early stage of the disease [12]. Patients with an enlarged heart can present with mitral or tricuspid valve insufficiency. Even so, since the contractility of the myocardium is extremely low, systolic murmurs at the apex of the heart or the left lower edge of the sternum are rarely heard. However, it has been reported that such murmurs were heard in a patient with fulminant myocarditis who developed papillary muscle and valve leaflet rupture during Impella treatment [13].

7.2.2.2 Heart Sounds and Murmurs

The apex beats are dispersed as a consequence of cardiac damage and decreased myocardial contractility. Muffled and dull heart sounds can be present in the early stage, and a third heart sound and gallop rhythm can often be heard. The first heart sound in the apical area is diminished or split. The heart can sound like a fetal heart. Pericardial friction sounds may be indicative of pericarditis. A well-trained physician, especially a cardiovascular physician, should be able to identify these abnormalities regardless of the chest wall thickness and patient sex and age. A slightly louder P_2 at the pulmonary valve can occur, but is usually not obvious. P_2 is not markedly enhanced even if heart failure is severe because the left and right sides of the heart fail simultaneously, and the pulmonary artery pressure may not increase considerably.

7.2.2.3 Cardiac Insufficiency

Lung rales may occur when left ventricular dysfunction is present. Rare patients can have distention of the jugular vein, hepatomegaly, a positive

hepatojugular reflux, and lower limb edema although right ventricular dysfunction occurs. However, all manifestations are uncommon because of systemic dilation and vascular leakage of the arteries and veins.

7.2.3 Lung Signs

Most patients can lie down or require bed rest, while a small number of patients prefer to be in a semi-recumbent position as a consequence of the presence of left heart failure. Patents may have dry/moist rales due to left heart failure or pneumonia (mainly viral in the early stage). However, most patients have no rales due to heart failure.

7.3 Laboratory Examination

Laboratory tests are essential for making a timely diagnosis of fulminant myocarditis.

7.3.1 Myocardial Injury Marker Cardiac Troponin I or T (cTnI or cTnT) Assessment

Both cTnI and cTnT are small molecule proteins that are specifically expressed in cardiomyocytes (molecular masses of 23.88 and 37 kDa, respectively). They can exist in both bound and free forms. When the myocardium is damaged, cTnI and cTnT are released into the circulation. The current detection methods can be performed rapidly and are sensitive, aiding timely detection and diagnosis. The cTnI or cTnT levels in patients with fulminant myocarditis are usually very high, and the level change is rapid. If it is not particularly high at the beginning, it will increase rapidly within a few hours. Protein levels beyond the detection threshold (e.g., >50,000 pg/mL) are common in patients with fulminant myocarditis [14]. Although an increase in the cTnI or cTnT level can also be seen in patients with acute myocardial infarction, the increase in patients with fulminant myocarditis is more obvious and is not commensurate with the damage site and area shown in the ECG. Another distinguishing factor between cardiac infarction and fulminant myocarditis is that the levels of creatine kinase isoenzymes increase along with the levels of cTnI or cTnT during myocardial infarction, while the increase in the levels of creatine kinase isoenzymes is usually not so significant during fulminant myocarditis [15].

Notably, unlike in acute myocardial infarction, the marked increase in the levels of cTnI or cTnT in fulminant myocarditis does not indicate a large area of myocardial necrosis. In fulminant myocarditis, immune cells and inflammatory storms affect the function and metabolism of cardiomyocytes, thus leading to the leakage of cTnI or cTnT from the cells. Because the damage is severe and affects the entire heart, the levels of cTnI or cTnT are high.

7.3.2 Brain Natriuretic Peptide (BNP) Assessment

BNP or NT-proBNP is a biomarker of cardiac dysfunction. It is released by cardiomyocytes when injured and is an indicator of decreased cardiac function and increased myocardial tension. Similar to the troponin levels, the plasma BNP or NT-proBNP levels of patients with fulminant myocarditis are also very high (usually reaching 1000 pg/mL and can reach >10,000 pg/mL); the levels are markedly higher in patients with fulminant myocarditis than in those with general myocardial infarction. Troponin and BNP are sensitive and reliable markers of myocardial damage and cardiac dysfunction, respectively. Their levels increase considerably in patients with fulminant myocarditis and change rapidly. The levels can also reflect the severity of the clinical condition of patients. When patients receive reasonable treatment and recover, the levels of troponin and BNP can rapidly decrease and restore to normal levels within 1–2 weeks. However, if the treatment is improper or not timely, their levels will remain relatively high. Persistently high levels of troponin and BNP are signs of poor prognosis [15].

7.3.3 Blood Routine Examination

Blood routine examination may be normal at the early stage. In some cases, the total white blood cell count and neutrophil count may increase, but which does not mean that the patient has a bacterial infection. Our observations show that the total white blood cell count increases in varying degrees in approximately 60% of patients; the neutrophil count increases in 70% of patients; and the white blood cell and neutrophil counts decrease in remaining patients. Attention should be paid to the possibility of a combined bacterial infection at a later stage. A small number of patients (25%) have a decreased platelet count, which may be related to thrombosis and platelet consumption caused by inflammation and shock [16].

7.3.4 General Biochemical Tests

General biochemical tests, including liver function tests, kidney function tests, and blood electrolyte tests, are necessary and need to be performed every day in the early stages of the disease. Some patients with fulminant myocarditis have varying degrees of liver damage and kidney damage at the onset of the disease. This may be because the disease (viral infection) also involves these organs. In rare cases, the serum levels of liver enzymes (alanine aminotransferase and aspartate aminotransferase) can be as high as 10,000 U/L, among which the level of aspartate aminotransferase seems to show a slightly more marked increase than do the levels of other enzymes [17]. Similarly, after reasonable treatment, the liver enzyme levels can rapidly decrease and return to normal levels earlier than the troponin levels. In general, the transaminase levels are normal or slightly elevated. However, prolonged shock and long-term use of high-dose norepinephrine can lead to liver ischemic necrosis. In these situations, the liver enzyme levels increase considerably; the liver enzyme/bilirubin levels are separated; and DIC occurs. In addition, the serum albumin level can be reduced, which is related to liver damage, reduced hepatocyte synthesis capacity, and vascular leakage. The blood lactic acid level should also be checked, as it reflects the tissue anaerobic metabolism level, that is, hypoxia, which is very helpful for selecting treatment programs and judging treatment efficacy.

7.3.5 Coagulation Function Tests

Coagulation function tests include assessment of the prothrombin time, activated partial thromboplastin time, D-dimer level, activated clotting time, thrombin time, fibrinogen content, and other indicators. Patients with fulminant myocarditis are prone to developing DIC, and heparinization is required during circulatory support treatment. Thus, close monitoring of coagulation function is necessary. Decreases in the fibrinogen level and platelet count; prolongation of the prothrombin time, activated partial thromboplastin time, and thrombin time; and increases in the D-dimer level are signs of DIC [18]. Ninety percent of patients with fulminant myocarditis have varying degrees of D-dimer level increase when they are admitted to the hospital, indicating that the coagulation process has already started. Therefore, measuring coagulation function is very important for timely detection and diagnosis of DIC.

7.3.6 Inflammatory Indicator Assessment

The detection of inflammatory indicators is particularly important because the core pathophysiological mechanism of fulminant myocarditis is excessive immune activation and inflammatory storm formation.

1. The high-sensitivity C-reactive protein level and erythrocyte sedimentation rate are important indicators that can reflect the severity of inflammation. Approximately 27% of patients with fulminant myocarditis have different degrees of erythrocyte sedimentation rate increase, and 90% of patients have elevated C-reactive protein levels, among a few patients with extremely high C-reactive protein levels. A follow-up study has shown that among patients with obvious elevated inflammatory indicators, the inflammatory indica-

tors generally decrease soon after the disease is controlled. Of note, levels of high C-reactive protein and erythorocyte sedimentation rate are not specific and therefore, they have no value for diagnosis.

2. The most importantly, levels of multiple cytokines and inflammatory mediators include interleukin-1 (IL-1), interleukin-6 (IL-6), and other interleukins, tumor necrosis factor alpha (TNF-α), and interleukin-33 receptor soluble ST2 (sST2) [19, 20]. Our research has shown that the levels of these cytokines and inflammatory mediators are markedly increased in patients with fulminant myocarditis, which plays an important role in the inflammatory storm, and have diagnosis value, especially sST2. When acute myocardial injury occurs (plasma cTnI and BNP levels significantly elevate),elevated cytokine levels, especially sST2, can help diagnosis of fulminant myocarditis. Also see Chap. 13.
3. Procalcitonin (PCT) is rapidly cleaved to calcitonin in healthy individuals. Thus, the serum PCT level is very low and cannot be detected. However, in an inflammatory state, especially during bacterial infection, various tissues and cells can produce PCT and even a large amount of undegradable PCT, thus increasing the level of PCT. If patients with fulminant myocarditis show elevated PCT levels, attention should be paid to the possibility of bacterial infection. However, our observation in 69 patients with fulminant myocarditis without bacterail infection found that PCT level is 2.917±1.544 ng/mL (reference level is < 0.05 ng/mL) at admission day, increases to 21.679±7.564ng/ml at next day and it is still 3.017±1.446 ng/ml at discharge, which suggests that elevated PCT level does not represent bacterial infection during fulminant myocarditis.

7.3.7 Pathogen Detection

Pathogen detection includes pathogenic nucleic acid detection, antigen detection, and antibody detection, which were discussed in the special chapter (see Chap. 4 Etiology and Detection Methods of Fulminant Myocarditis).

7.3.8 ECG

In patients with fulminant myocarditis, the manifestations on ECG vary greatly. Among them, QRS complex widening, voltage reduction, and ST segment elevation are the most common manifestations that mimic acute myocardial infarction (with or without lead selectivity) [21]. Manifestations similar to non-ST-segment elevation myocardial infarction are also present. Arrhythmias are very common, including sinus tachycardia and bradycardia, conduction block, various premature beats, atrial or ventricular tachycardia, and ventricular fibrillation (see Chap. 10 ECG manifestations in myocarditis).

7.4 Case Reports

Case 1 A 52-year-old man was admitted to the hospital because of syncope. He was in general good health and engaged in paperwork. Recently, one of his relatives has passed away. He helped organize the funeral and did not sleep for 3 days. After the funeral, he felt extremely tired and slept continuously for nearly 24 h. On the next day, he fainted suddenly when he got up to go to the toilet. The patient was brought to the hospital by his family. At admission, the patient was confused and felt fatigued with a heart rate of 100 beats/min and blood pressure of 70/50 mmHg. His heart sounds were considerably reduced, and a third heart sound and galloping rhythm could be heard. ECG showed V_1–V_5 ST segment elevation, which might indicate extensive anterior wall myocardial infarction. However, the emergency coronary angiography yielded normal findings. Echocardiography showed diffuse reduction in myocardial contraction, thickened ventricular septum (13 mm), and decreased ventricular ejection fraction (35%). The cTnI level was markedly increased. The patient was then diagnosed with fulminant myocarditis. The "life support-based comprehensive treatment plan" introduced in Chap. 15 was immediately conducted. The patient was treated with IABP, adequate doses of glucocorticoids, adequate doses of immunoglobulin, and oseltamivir p.o. After 12 days of treatment, his condition improved greatly, and the

ventricular ejection fraction recovered to 62%. Thereafter, he was discharged.

Case 2 A 33-year-old woman was admitted to the hospital because of syncope. She was a manager and worked continuously lately because it was at the end of the year. After the overwork, she felt fatigued and went home to sleep. She was awakened by the alarm clock at 8 o'clock the next day and fell down after sitting up. Thereafter, she fell asleep. Two hours later, she contacted a colleague and then lost consciousness. Her colleague brought her to the hospital immediately. ECG at admission showed a third-degree atrioventricular block. Her blood pressure was 50/40 mmHg, with very muffled heart sounds, decreased left ventricular diffuse movement, and decreased left ventricular ejection fraction (30%). The levels of cTnI and NT-proBNP were considerably increased, and the levels of inflammatory factors IL-1 and IL-6 were also remarkably increased. She was then diagnosed with fulminant myocarditis. After active treatment, including temporary cardiac pacing, IABP+ECMO, and immune regulation, she recovered and was discharged after 2 weeks.

Case 3 A 14-year-old girl was admitted to the CCU owing to cardiac arrest. She was a student who felt tired for several days during their final examination but still insisted on attending class. After an 800-meter running test, she suddenly felt chest tightness and discomfort, accompanied by dizziness and fatigue. The patient was immediately sent to the medical room. Her pulse was weak, and the pulse rate reached 150 beats/min, with a blood pressure of 40/20 mmHg. The patient was treated with vasoconstrictors and transferred to the CCU. However, she experienced cardiac arrest during transfer. CPR was performed, and 8 min later, the stroller arrived at the CCU. Persistent cardiopulmonary resuscitation was performed. Meanwhile, tracheal intubation, mechanical ventilation, and emergency bedside venous-arterial extracorporeal membrane oxygenation were urgently needed. Her heart beated again. Her cTnI level was 4434.6 pg/mL, while her NT-proBNP level was 452 pg/mL on admission. Cardiac ultrasonography showed a normal heart size and normal ventricular wall thickness. Left ventricular systolic function was markedly reduced (ejection fraction, 8%). Her cTnI level increased to >50,000 pg/mL 6 h later; other biomarkers, such as the sST2, IL-1, IL-6, and TNF-α levels, also increased markedly. A diagnosis of fulminant myocarditis was made.

Key Points

1. The clinical manifestations of fulminant myocarditis are variable. Fulminant myocarditis begins with prodromal symptoms of respiratory infections, followed by mild chest pain, palpitations, and transient ECG changes and then progresses to life-threatening cardiogenic shock, malignant arrhythmias, and multiple organ dysfunction. It is characterized by a sudden onset and a rapid progression.
2. Hemodynamic disorder is an important feature that distinguishes fulminant myocarditis from acute myocarditis. Since most patients with fulminant myocarditis have no basic organic heart disease, the myocardial compensation mechanism has not been established, and patients soon develop cardiogenic shock.
3. Laboratory tests, such as assessment of the cardiac troponin, brain natriuretic peptide, and inflammatory factor levels; ECG; and cardiac color Doppler ultrasonography, combined with evaluation of clinical manifestations, are essential for a timely diagnosis of fulminant myocarditis.

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