Chapter 12
Cardiovascular Tuberculosis

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12.1 General

Tuberculosis (TB) is uncommon in developed countries. But it is still endemic and frequently seen in some areas of Africa and Asia. Besides, the increase in the number of immunocompromised patients, especially with HIV, is responsible for the increase in the incidence of tuberculosis and its complications. According to the World Health Organization (WHO), one third of the world's population has TB infection today, and it is the commonest cause of death among patients with infectious diseases [31].

Extrapulmonary TB is generally found in the pleura, lymph nodes, abdomen, and central nervous system [35]. The cardiovascular system is involved in 1–2% of the patients with TB [4, 27, 30, 33, 35, 50]. The incidence of cardiac TB in autopsies is about 0.25% [33]. It has been shown that the rate of cardiac involvement in patients who died from TB is approximately 2% [43]. Only 0.5% of the patients with extrapulmonary TB have cardiac involvement, and it is more frequently seen in immunocompromised patients [53]. The primary involvement site is pericardium [35, 50, 53]. Other forms of cardiovascular involvement including endocarditis, myocarditis, valvular or coronary involvement, arteritis, and aneurysms are extremely rare [27]. Myocardial involvement by TB may cause arrhythmias, sudden cardiac death, congestive heart failure, and aneurysms. Also, aortitis and arteritis may cause mycotic aneurysms, pseudoaneurysms, and rupture [43].

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12.2 Pericarditis

The pericardium is the most frequently involved cardiac tissue by TB. Pericarditis is seen in less than 1% of the patients with TB [23, 40]. In general, 10–11% of patients with pericarditis have TB etiology [23, 57]. Incidence of TB pericarditis is higher in the endemic areas; it has been reported that TB accounts for 40–70% of the patients with pericarditis in developing countries [40, 43, 50]. In contrast, only 4% of the patients with pericarditis have TB etiology in developed countries [40, 43]. Also, its incidence is higher in the areas where the human immunodeficiency virus (HIV) is epidemic [40, 57].

12.2.1 Pathology

TB pericarditis is always associated with an extracardiac infection focus located anywhere in the body [50]. It spreads to pericardium via three main routes: lymphatic spread (from paratracheal, peribronchial, and mediastinal lymph nodes), hematogenous spread (mainly in immunocompromised patients), or rarely direct contiguous spread from adjacent structures (lungs, pleura, and spine) [40, 43, 50]. Lymphatic and hematogenous spread are the main routes. Pathophysiology of the disease includes four stages: (i) fibrinous exudation with polymorphonuclear infiltration with relatively high number of mycobacteria; (ii) serous or serosanguineous effusions with lymphocytic infiltration (monocytes and foam cells); (iii) absorption of effusion leading to caseating granulomas and pericardial thickening due to fibrin and collagen deposition and fibrosis; and (iv) constrictive scarring with extensive calcification [9, 38, 40]. Fibrosis, adhesion, and calcification of the visceral and parietal pericardium create a rigid and contracted fibrocalcific envelope encasing the heart that restricts diastolic filling and eventually systolic ejection in the constrictive pericarditis stage [40].

   TB pericarditis is typically a paucibacillary condition [43]. Proteins of *M. tuberculosis* nestled in the pericardium trigger a T helper subtype 1 (TH-1) lymphocytes-mediated hypersensitivity reaction that stimulates cytokine release [9, 40, 43]. Cytokine release activates macrophages and induces pericardial inflammation and granuloma formation that causes exudative effusion and afterward consequences [40, 43]. Patients with TB pericardial effusions have a cytokine profile (tumor necrosis factor alpha and interleukin 1 and 2) and increased interferon-gamma production suggesting the occurrence of a hypersensitivity reaction orchestrated by the TH-1 lymphocytes [9, 40]. Most frequently implicated cytokine is TNF-α [57]. Cytokines may also cause fever, weight loss, and weakness [57]. Anti-myolemmal antibodies causing cytolysis may have a role in exudative pericarditis [40].

12.2.2 Clinical Properties

Although the course of the disease is mostly insidious and progresses to chronic constrictive pericarditis, acute and fulminant pictures related to pericardial tamponade may also be seen [7, 15]. Tamponade is considered to be the acute complication of TB pericarditis, while constrictive pericarditis is chronic complication [43]. The clinical picture is highly variable and includes acute pericarditis with or without effusion, cardiac tamponade, chronic pericardial effusion, acute constrictive pericarditis, subacute constriction, effusive-constrictive, or chronic constrictive pericarditis, and pericardial calcifications [37, 50]. It is generally manifested as one of four clinical syndromes: acute pericarditis, effusive pericarditis, myopericarditis, or constrictive pericarditis [43]. The usual presentation of the disease is pericardial effusion, constrictive pericarditis, or a combination of effusion and constriction [40]. The disease may progress more aggressively in immunocompromised patients (HIV, etc.); clinical presentations including dyspnea, hemodynamic instability, and myocardial involvement tend to be more severe [43].

12.2.2.1 Tuberculous Pericarditis and Pericardial Effusion

The onset of the disease is mostly insidious [7, 15, 40]. It usually manifests as a "slowly progressive febrile illness" [7]. Generally, the patients with TB pericarditis have weight loss, cough, dyspnea, orthopnea, chest pain, night sweats, fever, tachycardia, cardiomegaly, and pleural effusion [7, 23, 40, 51, 57]. The most frequent symptoms are cough, dyspnea, and fever [7, 40]. Chest pain is relatively seen less often [7, 43]. The patients usually have the symptoms of congestive heart failure without hypotension including sinus tachycardia, pulsus paradoxus (>12 mmHg), raised central venous pressure, palpable apical impulse, increased cardiac dullness, muffled heart sounds, pericardial friction rub, hepatomegaly, ascites, and peripheral edema [7, 15, 40, 43, 51, 57]. Right upper abdominal pain may be seen due to liver congestion [40]. Peripheral lymphadenopathy affecting the cervical glands has been reported [7]. Typical triad of acute pericarditis including chest pain, friction rub, and ECG changes are uncommon and seen in only 3–8% of the patients with TB pericarditis [43]. If pericardial fluid accumulation is quick or compensatory mechanisms are inadequate, hypotension and tamponade may occur [43]. Ten percent of patients with TB pericardial effusion have cardiac tamponade [40]. TB pericardial effusion is characterized by exudative nature that it contains high protein levels and an increased leukocyte count including mainly lymphocytes and monocytes and is frequently hemorrhagic [40]. There is no evidence of lung lesions in about half of the patients [23].

The underlying myocardium may be involved by inflammation of the pericardium. Elevated levels of biomarkers of myocardial damage (troponins, creatinine kinase, etc.), ECG changes related to myocardial injury, and impaired left ventricular systolic function may refer to the presence of myopericarditis [43].

12.2.2.2 Constrictive Pericarditis

Constrictive pericarditis occurs in 30–60% of the patients with TB pericardial effusion despite adequate treatment with antituberculous drugs and corticosteroids [9, 40]. It is considered one of the most important complications of TB. In developing countries, the most frequent cause of constrictive pericarditis is TB with a reported incidence of 38–83% [9]. The presence of tamponade at admission due to TB pericarditis is found to be correlated with development of subsequent constrictive pericarditis [57].

Parietal and visceral pericardia are thickened and fused as a result of fibrosis or fibrinous exudate induced by pericarditis [9]. This situation creates a rigid skin surrounding the heart which restricts diastolic filling of the ventricles and eventually decreases stroke volume of the heart as a result of Frank-Starling law. Inability of the ventricles to hold and pump enough volume of blood leads to congestive heart failure [9]. Long-standing constrictions may cause myocardial fibrosis and atrophy contributing heart failure and deteriorating the operative outcome [9].

The clinical picture may range from asymptomatic to severe constriction [40]. It may progress from an acute pericarditis to constriction phase passing through the effusion and absorption phases or may manifest as pericardial constriction without a history of acute pericarditis [9]. Pericardial knock, an early diastolic sound caused by rapid filling of the constricted left ventricle, and splitting of the second heart sound can be heard on auscultation. Low-voltage complexes and atrial fibrillation on ECG and enlarged cardiothoracic ratio on X-ray may be seen [40].

Although the TB pericarditis may have more aggressive clinical picture in immunocompromised patients, it has been reported that the incidence of constrictive pericarditis is significantly low in HIV-positive patients when compared to HIV-negative patients [9]. Because TB pericarditis and subsequent fibrosis and granuloma formation are mainly orchestrated by TH-1 cells, the presence of HIV infection decreases hypersensitivity reaction to the proteins of *M. tuberculosis* and the inflammatory process [9].

12.2.2.3 Effusive-Constrictive Pericarditis

Effusive-constrictive pericarditis (ECP) is a rare manifestation of TB caused by constriction of the visceral pericardium and compressive pericardial effusion [45]. It may occur during the continuum from pericardial effusion to constrictive pericarditis [45]. The prevalence of ECP is 4–4.5% [45]. The etiology is TB in 60% of all ECP cases [45]. Both effusion and visceral pericardial constriction increase pericardial pressure [40]. The treatment of ECP is difficult. Pericardiocentesis does not relieve pericardial pressure impairing the diastolic filling of the heart because fibrinous pericardial bands between thickened pericardial layers strictly loculate pericardial effusion preventing complete drainage of it [40, 45]. Also, pericardial pressure remains elevated after pericardiocentesis due to visceral constriction [40]. Elevated right atrial pressure persisting after pericardiocentesis despite intrapericardial pressure falling to near 0 mmHg is suggestive of ECP [45]. Similarly, the efficacy of

pericardiectomy in these patients is generally limited because removal of fibrinous exudate coating the visceral pericardium is almost impossible [40]. Visceral pericardiectomy may be performed in these patients to treat persistent heart failure [45]. Mortality rate is 4–50% [45].

12.2.3 Diagnosis

Chest radiography, ECG, and echocardiography are essential in the diagnosis and management of pericardial TB [43]. Chest X-ray shows an enlarged cardiac silhouette in more than 90% of cases [40]. It may also show radiological evidence of pulmonary TB and pleural effusions [7]. ECG changes including non-specific ST-T changes, QRS complex microvoltage, electrical alternans, and atrial fibrillation can be seen in patients with TB pericarditis [35, 40]. The presence of microvoltage on the ECG is usually related to pericardial effusion [40]. Echocardiography is an accurate and noninvasive method to diagnose pericardial effusion and constriction, but it is not suggestive about the etiology. Pericardial effusion with fibrinous strands between pericardial layers and pericardial thickening is frequently seen but not specific for TB pericarditis [7, 40, 51]. In constrictive pericarditis, thick fibrinous exudate in the pericardial sac or a thick skin surrounding the heart, which diminishes cardiac movements, is seen during echocardiography [40]. Also, CT scanning or MRI can be used to determine the presence of pericardial effusion, pericardial thickening, and mediastinal lymph nodes [7]. Mediastinal lymphadenopathy can be detected in almost all patients with TB pericarditis, and they regress or disappeared with antituberculous therapy which suggests TB etiology [7, 51]. The most frequently enlarged lymph nodes are the aortopulmonary (63%), paratracheal (52%), carinal (41%), pretracheal (26%), and hilar (15%) lymph nodes, respectively [7]. Nuclear imaging with gallium-67 and indium-111 scintigraphy can be used in the diagnosis of TB pericarditis, but its results do not reveal TB etiology [7]. Because proving the presence of TB in another organ in a patient with pericarditis is highly suggestive of the TB pericarditis, the presence of pulmonary or extracardiac TB should be explored with cultures and other techniques [7, 37]. Tuberculin skin test is not useful in diagnosis due to its high false-negative (25–33%) and false-positive (30–40%) results [37, 51, 57]. Negative test result does not exclude TB. But a strong positive test result should increase the suspicion of TB etiology [51]. Acid-fast bacilli should be searched in the sputum. It is positive in only 10–55% of the patients [40]. If the results of sputum and pericardial fluid examinations are inconclusive, gastric washings, urine culture, and right scalene lymph node biopsy may be used to identify the presence of acid-fast bacilli [7, 40].

The definitive diagnosis is mainly established by microbiological and pathological examination of the pericardial fluid and tissue to demonstrate TB bacilli or granulomas [7, 43]. Pericardiocentesis should be performed in all patients with suspected TB pericarditis [40]. Pericardial biopsy is generally recommended to obtain pericardial tissue sample [57]. Both procedures can be performed together by inferior pericardiotomy. This procedure also allows drainage of pericardial effusion for

treatment and prevents its reaccumulation [57]. Identification of *M. tuberculosis* in the pericardial fluid or tissue samples and identification of caseous granulomas in the tissue are required [37]. Culture of the pericardial fluid is more suggestive in the diagnosis of TB etiology than fluid smear and histology of the pericardium [7, 40, 51]. But isolating the organism or identification of caseous granulomas is often difficult. TB bacilli are detected in the pericardial fluid in only 0–42% of the patients by direct smear examination and in 53–75% by culture [40]. Also, it is not a timely method and may cause delays in diagnosis [57]. The diagnostic value of pericardial biopsy is about 10–64% [40, 51]. It provides positive results more frequently than pericardial fluid samples and should be performed [15, 57]. But it should be kept in mind that normal results obtained by the examination of pericardial fluid and tissue do not exclude TB pericarditis.

To improve diagnosis of TB pericarditis, a prediction model for endemic areas was suggested [51]. Scoring system has easily available five clinical and laboratory variables: 1 score for night sweats, 1 score for weight loss, 2 score for fever >38 °C, 3 score for white cell count $<10 \times 10^9$/L, and 3 score for serum globulin >40 g/L. It was shown that a total score of 6 or more in a patient with suspected pericarditis has a sensitivity of 86% and a specificity of 84% for the diagnosis of pericardial TB [51].

Traditional diagnostic tools are insufficient to diagnose pericardial TB [51]. Novel techniques including polymerase chain reaction (PCR) method to identify *M. tuberculosis*, enzyme-linked immunospot (ELISPOT) test detecting T cells specific for the *M. tuberculosis* antigen, adenosine deaminase activity (ADA), pericardial lysozyme, and interferon-γ concentration in TB pericardial effusion can be used [37, 40, 43, 51]. They provide rapid and accurate results for diagnosing pericardial TB. The genetic material belonging to *M. tuberculosis* bacilli is identified in pericardial fluid and tissue samples by PCR method [7]. Its diagnostic accuracy is close to conventional microbiological and pathological methods [7]. The sensitivity of the method is higher with tissue samples (80%) than with fluid (15%) [7, 40, 51]. Although it provides results more rapid than culture, high contamination rates and false-positive results (sensitivity 32%) make PCR unsuitable for daily clinical practice [7, 40, 51]. It was shown that elevated pericardial ADA (≥35 U/L) and interferon-γ levels (>200 pg/L) have high sensitivity (>90%) and specificity (>70%) rates for the diagnosis of TB pericarditis [7, 40]. ADA levels are associated with T-cell activity [7]. In a patient with high ADA level, bacterial pericarditis and neoplastic diseases should be excluded [51]. Interferon-γ is recommended as a more suggestive method [51].

12.2.4   Treatment

The treatment of TB pericarditis includes immediate combined drug therapy for different durations (6, 9, 12 months) [37, 38]. The goal of the treatment is both to treat the acute tamponade symptoms and to prevent the occurrence of constrictive pericarditis [57]. Antituberculous treatment increases survival significantly as shown by the mortality rates which has fallen from 80–90% in pre-antibiotic era to

8–17% in HIV-negative patients and 17–34% in HIV-positive patients currently but does not prevent the development of constrictive pericarditis [40]. A combined drug therapy consisting of rifampicin, isoniazid, pyrazinamide, and ethambutol for at least 2 months, followed by isoniazid and rifampicin lasting a total of 6 months, is suggested in extrapulmonary TB [40]. Steroids may be combined with antituberculous treatment to decrease mortality, the severity of symptoms, the rate of recurrence and rehospitalization, the incidence of constrictive pericarditis, and the need for pericardiocentesis or pericardiectomy [15, 37, 43]. But the adjunctive use of steroids is still controversial because they have been shown not to reduce mortality or need for pericardiectomy by some authors [15, 43, 57].

Open surgical drainage versus pericardiocentesis is another controversial issue in the treatment of TB pericarditis [57]. Early surgery including complete open drainage in TB pericarditis has been recommended by some authors to prevent repeated pericardiocentesis and development of chronic constrictive pericarditis [15, 38, 40, 57]. The presence of the opportunity to obtain pericardial biopsy during the procedure also favors open drainage [57]. In general, surgery is indicated in patients with pericardial effusion persisting despite medical treatment with or without repeated aspirations or with pericardial thickening and constriction [30]. The mortality rate in TB pericarditis may reach up to 85% in untreated patients [37]. It has been reported that average survival is 3.7 months in patients without specific treatment [7].

The treatment of constrictive pericarditis involves both antituberculous drugs for 6 months and pericardiectomy [40, 43]. There are some controversies about the timing of pericardiectomy. While some authors recommend immediate surgery for all patients with constrictive pericarditis, others recommend it for the patients in whom medical treatment fails [40]. But in latter recommendation, surgery should not be delayed if the patient has pericardial calcifications, a sequela of chronic disease [40]. Central venous pressure generally decreases on postoperative 2–4 days and returns to normal 4 weeks after surgery [9]. But about half of the patients have abnormal left ventricular diastolic filling after pericardiectomy, which is caused by myocardial fibrosis and atrophy or incomplete decortication [9]. Operative mortality of pericardiectomy is 3–16% and can reach up to 19% in patients with extensive calcification and adhesions [9, 40, 43]. Acute cardiac dilatation and failure may be seen following pericardiectomy, which is mainly arisen from the occurrence of myocardial atrophy [9]. Occurrence or worsening of mitral and tricuspid regurgitation after pericardiectomy due to ventricular dilatation or elongation of the papillary muscles can be observed [9].

12.3   Myocarditis

TB myocarditis was first reported by Maurocordat, a Turkish physician, in 1664 [35]. Although TB mainly involves the pericardium, the myocardium can rarely be affected [50]. The cause of higher affinity of *M. tuberculosis* to the pericardium rather than the myocardium is unclear [27]. Myocardial TB mostly occurs in an association with the pericardial disease [41]. Isolated TB myocarditis is extremely

rare with a prevalence of 0.2–2% [23, 41, 43, 50]. Involvement of coronary vessels and the endocardium by TB is exceedingly rare and usually associated with the infection located other parts of the heart [23, 50]. TB myocarditis is usually diagnosed postmortem with an incidence of <0.3% in all autopsies [35, 50, 54].

12.3.1 Pathology

The infection reach the myocardium via direct invasion from the pericardium or the pulmonary cavity, hematogenous spread, or retrograde lymphatic spread [35, 41, 43, 50]. The origin of the infection is pulmonary [35]. There are three types of involvement: (i) nodular tubercles (tuberculomas) characterized by central caseation, (ii) miliary tubercles resulting from hematogenous spread, and (iii) diffuse infiltration associated with tuberculous pericarditis rich in lymphocytes and giant cells [4, 12, 23, 27, 35, 41, 43]. Endocardial miliary tubercles, polyploid tubercles, tuberculous nodules on valves, and thrombi containing entrapped tubercle bacilli can be seen [23]. The most frequently affected heart chamber is left ventricle (68%). It can cause mitral and tricuspid insufficiency, but valvular stenosis and involvement of the semilunar valves are unusual [41].

12.3.2 Clinical Properties

The patients with TB myocarditis are usually asymptomatic [27, 41]. In contrast to pericarditis, myocarditis causes myocardial inflammation which can lead to serious complications including arrhythmias and heart failure [53]. Symptomatic patients may have atrial and ventricular tachyarrhythmias, ventricular fibrillation, conduction defects, long QT syndrome, congestive heart failure, dilated cardiomyopathy, ventricular aneurysms and pseudoaneurysms, superior vena caval obstruction, right ventricular obstruction, valvular dysfunction, coronary arteritis, and even sudden cardiac death [2, 4, 5, 13, 18, 21, 27, 33, 35, 41, 43, 54]. Accompanying pericardial involvement causing effusion, adhesions or constrictions complicates the symptoms of myocarditis [54]. The use of antituberculous drugs may cause arrhythmias including prolonged QT interval and torsade de pointes induced by isoniazid and moxifloxacin [35].

12.3.3 Diagnosis

The diagnosis of TB myocarditis is usually made at autopsy [41]. It should be suspected in patients with a history of TB exposure or from endemic areas presenting with nonischemic arrhythmias, congestive heart failure, or cardiogenic shock [27,

41, 42]. Cardiac MRI and late gadolinium enhancement have been reported to describe cardiac tuberculomas and myocardial infiltration [27]. If clinical suspicion is strong and imaging is suggestive for TB etiology, endomyocardial biopsy is indicated for early diagnosis [12, 27].

12.3.4   Treatment

The knowledge about the treatment of antemortem cases is limited and basically relies on empirical guidance [27]. The standard 4-drug antituberculous therapy is used to treat TB myocarditis and its complications [41, 43]. The duration of the therapy is unclear. Beta-blockers can be used to treat ventricular arrhythmias, but they have not been validated in this indication [27]. The efficacy of adjunctive steroids is also controversial [27].

12.4   Aortitis and Aneurysm

Mycotic aneurysm of the aorta secondary to TB infection was first described by Kamen in 1895 [8, 39, 60]. It is a very rare and life-threatening entity [3, 28, 36, 39, 49, 60]. The literature knowledge about the disease is mainly based on case reports [8, 39]. In the report of Parkhurst and Decker [48], TB aortic aneurysm was found in only 1 case (0.3%) among 338 aortic aneurysm cases detected in 22,792 autopsies between 1902 and 1951. This report belongs to a pre-antibiotic era, and it can be assumed that the incidence of aortic aneurysm secondary to TB infection is much less today due to the use of antituberculous drugs [20]. TB aortitis is seen 1% of the patients with latent TB [3]. The risk of aortitis and aneurysm is high in immunocompromised patients [36]. While case reports published in the pre-antibiotic era (before 1950) were mostly from autopsies, recent reports published in later years have shown that antemortem diagnosis and successful treatment of the disease have become possible due to enhanced imaging and surgical methods [8, 22].

12.4.1   Pathology

TB aortic aneurysms are seen in both abdominal and thoracic aorta with an equal frequency [3, 8, 36, 39, 43]. It can less frequently involve peripheral arteries including the subclavian, carotid, common iliac, hepatic, renal, femoral, and innominate arteries [3, 14, 16, 39]. TB infection reaches the aorta by means of two pathways: (i) commonly (in 75% of patients) direct invasion from an adjacent contagious lesion such as mediastinal lymphadenitis (63%), pulmonary lesions, empyema, pericarditis, spondylitis, or paravertebral abscess and (ii) rarely hematogenous or

lymphangitic spreading from primary lesions [8, 14, 16, 20, 22, 28, 32, 36, 39, 46, 47, 49, 60]. The descending aorta is more vulnerable to TB infection compared to the ascending aorta, which is represented by 46% of TB aortic aneurysms which are located at the descending aorta while only about 10% at the ascending aorta [8, 14, 28, 49]. This tendency may be explained by close proximity of the descending aorta to mediastinal lymph nodes [8, 14, 49]. Two specific groups of mediastinal lymph nodes located around the distal aortic arch and in the left pulmonary ligament are responsible for direct infection and aneurysm of the distal aortic arch and the supra-diaphragmatic aorta [46]. Infrarenal segment is the most frequent involvement site of the abdominal aorta [36].

Aortic infection is associated with aortic stenosis, mycotic aneurysm, pseudoaneurysm, or autoimmune aortitis [8]. Four types of TB involvement in the arterial system were described: (i) miliary infection of the intima, (ii) tubercular polyps attached to the intima, (iii) infection of several layers of the arterial wall, and (iv) aneurysm formation [8, 22, 47]. Besides, a stenosing type of TB aortoarteritis was described recently [8]. It may occur as a consequence of hypersensitivity reaction to TB antigens [36]. Stenotic lesions involving the aorta (acquired coarctation) or renal artery can cause hypertension [43, 49]. Direct hematogenous spread may cause infection in the tunica intima of the aorta, but invasion via vasa vasorum or lymphatics may extend the infection to the tunica media or adventitia [22, 32, 36, 39, 47]. TB bacilli may also lodge in an atheromatous plaque, which alters the resistance of the vessel wall to infection, and spread through the aortic wall [8, 32, 36].

Infection of the aortic wall results in tissue destruction and necrosis [16, 39]. Destruction of the aortic wall is followed by its expansion to form a true aneurysm, named mycotic aneurysm. On the other hand, if necrosis involves the entire thickness of the aortic wall, it may be ruptured resulting in either massive bleeding or the formation of a perivascular hematoma [3, 16, 22]. Resorption of the encapsulated hematoma and communication of the residual cavity with the aortic lumen produce a false aneurysm, which is referred to as pseudoaneurysm [16, 39]. In contrast to true aneurysms, pseudoaneurysms lack all three layers of the arterial wall, which creates a tendency to aneurysm rupture and fatal bleeding, and are generally saccular in shape [60]. Typically, calcification is absent in all TB aortic aneurysms [8]. Most of the TB aneurysms are solitary, false, and saccular with a high risk for rupture and fatal bleeding [8, 14, 20, 22, 36]. Another typical presentation of vascular involvement in pulmonary TB is Rasmussen aneurysm that is a form of arteritis occurred at the vessels located near the cavitations and that causes recurrent hemoptysis in these patients [55, 60].

Atypical species of Mycobacteria including Bacille Calmette-Guerin (BCG), an attenuated strain of *Mycobacterium bovis* for adjuvant immunotherapy of bladder carcinoma or melanoma, and *Mycobacterium avium-intracellulare* (MAI) have also been reported to cause aortic aneurysms and pseudoaneurysms [3, 39].

12.4.2 Clinical Properties

Clinical presentation of the disease ranges from asymptomatic to rupture, bleeding, and shock. The age of the patients with TB aortic aneurysm ranges 6–86 years old (mean 50 ± 16 years) [36]. Both gender are involved equally [36]. The patients have fever, weight loss, pulsatile or palpable mass, chest pain, dysphagia, hoarseness, stridor, hemoptysis, intestinal bleeding, fistula, abdominal pain, or back pain regarding the localization of the aneurysm [8, 14, 16, 20, 22, 28, 43]. Patients usually presented in three clinical scenarios: (i) persistent chest, back, or abdominal pain, (ii) major bleeding or shock, or (iii) rapidly expanding palpable or pulsatile mass [36]. Rupture of the aneurysm is associated with the high mortality rate. Rupture into the esophagus, jejunum, stomach, pulmonary tree, peritoneal cavity, duodenum, and colon has been reported [3]. Acute aortic syndromes including aortic dissection may be seen [49]. Aneurysms of the ascending aorta may extend to the aortic root and the sinus of Valsalva and may cause aortic valve insufficiency and cardiac tamponade [43, 47]. The most frequent causes of death are rupture with massive bleeding, miliary TB, and congestive heart failure [36].

12.4.3 Diagnosis

The diagnosis is difficult and should be established as early as possible to prevent rupture and associated mortality [49]. Presence of active TB or past history is helpful in directing the clinician for this challenging diagnosis. CT and MRI are recommended to detect aortitis and aneurysm [16, 22, 36]. Thickening of the aortic wall may refer to aortitis without etiology [49]. MRI is more sensitive in this setting [49]. The presence of contrast extravasation during imaging indicates aneurysm rupture and is an indication for emergency surgery [43]. Aortography was the primary diagnostic tool previously, but it has been replaced by ultrasonography, CT, and MRI which can easily detect the aneurysm by a noninvasive manner [16, 20]. Also, TB aneurysms may not have fill defect in angiography [36].

The definitive diagnosis can ultimately be established by histological examination of surgical specimens revealing granulomatous aortitis with caseous necrosis and positive acid fast bacilli on Ziehl-Neelsen staining [49]. Negative test results do not exclude the diagnosis of TB etiology.

12.4.4 Treatment

Neither medical nor surgical treatment alone is sufficient for a complete cure. Optimal therapy is the combination of both preoperative and postoperative antituberculous drugs and operative methods [8, 14, 16, 20, 22, 32, 36]. Once TB

aneurysm has been diagnosed, 4-drug treatment should immediately be started to cover the postoperative period, and the operation should be performed urgently [8, 14, 22, 36, 47]. The duration of antituberculous therapy is controversial, but it should be extended to at least 9–12 months in patients with severe systemic infection [3]. Some authors recommend lifelong antibiotic treatment after prosthetic graft implantation [3]. Prolonged antibiotic treatment should be preferred in patients with an extra-anatomic bypass to prevent blowout of the aortic stump due to recurrent infection [3].

Surgical options include extra-anatomic bypasses, in situ insertion of aortic conduits, patch closure or direct closure of the aortic rent, and endovascular aneurysm repair [3, 8, 22, 60]. The size of the aneurysm is not a limitation for the need of surgery, because even a small pseudoaneurysm down to 1 cm in diameter can rupture and cause fatal bleeding [22, 36]. Resection of the infected aortic segment with surrounding tissues and revascularization of the lower body with arterial reconstruction is the frequently performed procedure in such cases [20, 32, 60]. The extent of aortic wall resection should be decided with visual inspection rather than time-consuming frozen section and histologic study to shorten cross-clamp-related ischemia time [8, 22]. Insufficient resection of the rent margin which contains infective material is associated with recurrence [8]. The type of aortic repair is chosen according to the rent size: An interposition graft should be inserted in the presence of a large rent; otherwise a patch repair may be performed [8]. Usually, an interposition graft is required to reconstruct a true aneurysm, but patch or direct closure can be performed in pseudoaneurysms [20]. In the presence of active infection or abscess formation, complete resection of the aneurysm and extended removal of the infected tissue should be followed by an extra-anatomic bypass to keep prosthetic material away from the infection area [20]. Recurrence of aneurysm and graft infection can occur [60]. Preoperative antituberculous drugs and adjunctive procedures such as drainage of paraspinal abscess and antibiotic-soaked grafts may be helpful to prevent persistence or recurrence of the infection [10, 16, 20]. Close postoperative follow-up is required to detect recurrence [20, 22]. Mortality of the surgery is 14–20% and reaches up to 50% in emergent operations [3, 60]. Causes of perioperative mortality are massive gastrointestinal hemorrhage, aorto-enteric fistula, renal failure, rupture of another tuberculous aneurysm, and acute heart failure [16].

Currently, endovascular treatment of TB aneurysms is increasingly preferred method [14]. Debridement and removal of the infected tissue which is the main part of surgical success are impossible in the endovascular treatment [14]. In the presence of persistent infection, the efficacy of drug therapy decreases, and the risk of rupture and fatal bleeding increases [14]. For that reason, careful patient selection is the key element for the success of the treatment with stent-graft deployment [10]. The placement of intravascular prosthesis to treat TB aneurysms has been reported having a high risk of infection recurrence and bleeding [39]. Patients who are relatively sterile during the procedure have better results and lower long-term complications [10]. Also, endovascular treatment can be considered as a bridge to surgery or as a palliative destination therapy [32].

12.5   Takayasu Arteritis

Takayasu arteritis (TA) is a rare, large-vessel vasculitis of unknown etiology that primarily involves the aorta and its major branches including subclavian and carotid arteries. It is primarily an inflammatory disease causing chronic and progressive vessel wall inflammation which is responsible from concentric thickening of the vessel wall producing arterial stenosis with ischemic complications or aneurysm formation [26]. Clinical manifestations of TA are related to systemic inflammation and the site of vascular lesions. While systemic inflammation causes constitutional symptoms including fever, malaise, night sweats, anorexia, arthralgia, and lymphadenopathy, vascular complications include pulse defects, claudication, dizziness, visual disturbances, bruits, and blood pressure difference between the arms [34].

An association between TB and TA has been suggested for more than a half of century [19, 55, 58, 59]. There is a clinical correlation between two clinical entities without a proven causative mechanism [26]. The prevalence of TB is higher in patients with TA in comparison with the general population [19, 34, 59]. Case series from Asia, South America, and Africa have revealed that the frequency of TB in patients with TA ranged between 22 and 70%, while TB rates were 0.03–1.5% in the general population in these regions [19, 59]. Purified protein derivative (PPD) is positive in 81–100% of the patients with TA but 66% in normal controls [6, 59]. Also, hypersensitivity reaction to specific antigens of *M. kansasii* (84% vs 11%) and *M. avium* (78% vs 15%) is more frequently positive in TA than non-TA patients [6]. Active TA is more frequent in patients with TB lymphadenitis (21% in TA vs 1% in pulmonary TB) than with pulmonary TB [34]. TB lymphadenitis in para-aortic or mesenteric lymph nodes closely located to inflamed vessels in TA has been frequently reported [34]. PPD with induration over 10 mm is also more frequent (92.5% vs 89%) in TA patients with extrapulmonary TB [6]. Clinical and angiographic features of TA in patients with and without TB are indistinguishable [34]. Histopathological features of TA are similar to those of TB lesions including granulomatous inflammation and Langerhans-type giant cells [1, 24]. Gene sequences associated with *M. tuberculosis* including IS6110 and HupB genes were found within tissues of the aorta from patients with TA, which implies the relationship between arteritis and latent infection [55]. Demonstration of tubercular lymph nodes in the vicinity of arterial lesions and increased levels of agalactosyl IgG may also represent the association between TB and TA [1].

On the other hand, the use of anti-TNF therapy providing remission in TA patients is not associated with the occurrence of mycobacterial infections, which is reasonable to infer that if TA results from active or latent TB infection, anti-TNF agents should aggravate clinically evident TB [6]. Quantiferon-TB Gold test, which detects TB infection by measuring in vitro T-cell interferon-gamma release in response to antigens highly specific for *M. tuberculosis*, was shown to have similar positive results in TA and the controls indicating that the rate of TB infection in TA patients is not higher than the general population [24]. Any genetic relationship between TB (both pulmonary and extrapulmonary) and TA regarding HLA-B alleles

did not detected [56]. In patients with concomitant TA and TB, TB does not affect the clinical course of TA [34].

In TA, inflammation characterized by mononuclear (lymphocytes, macrophages, plasma cells, and giant cells) infiltration begins around the vasa vasorum at the medio-adventitial junction and involves the entire adventitial layer and outer third of medial layer [29, 55, 58]. The intimae remain normal until fibrosis involves it [55]. Granulomatous reaction with giant cells, laminar necrosis, fragmentation of elastic fibers, and loss of smooth muscle cells can be seen [58]. There is reactive fibrosis, medial scarring, and vascularization [58]. In the healing stage, fibrosis involves all three layers of the vessel [58]. Histopathological changes including intimal and adventitial fibrosis and medial degeneration resulted in stenosis or aneurysm formation [29]. The etiopathogenesis of the disease is still unknown, but an autoimmune basis related to genetic, infectious, or environmental factors is strongly suggested [58]. There is clinical relationship between TA and TB. In spite of this association, the exact link between TB and TA cannot be demonstrated until now.

It has been widely suggested that antigens of *M. tuberculosis* may stimulate T cells to produce autoimmune reaction against the vascular wall resulting in the onset of TA [6, 26, 59]. A significant increase in antibody titers against the proteins of TB bacilli including 65 kDa heat-shock protein (HSP65) has been found in patients with TA [19, 59]. HSP65 is the most frequently emphasized protein in this setting. Heat-shock proteins are found in a wide range of species extending from bacteria to humans and constitute an ancient intracellular self-defense system with scavenger activities to protect cellular proteins from denaturation [1, 6, 52]. They are expressed as a result of cellular stress including infections, increased blood pressure, overload of endoplasmic reticulum, oxidation/reduction imbalance, mechanical stress, and inflammation [6, 52]. It was shown that human 60 kDa heat-shock protein (HSP60) is homolog to HSP65, and both TA and pulmonary TB patients have higher prevalence of antibodies IgG isotype reactive to both HSP60 and HSP65 [1, 6]. These antibodies may have a cross-reaction with self-antigens of human vessels leading an autoimmune vessel damage and vascular disease [1, 6, 19, 29, 34, 59]. Not only in TA, HSP65 has been implicated in various rheumatic diseases in humans [1].

Another proposed mechanism is the increased levels of agalactosyl IgG which is markedly elevated in both mycobacterial disease and several autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease, and TA [59]. In addition, proinflammatory cytokines, including interleukin-18 and TNF-α, contributing immunity against TB infection and granuloma formation may contribute to pathogenesis of TA, because interleukin-18 and TNF-α are upregulated in patients with TA [59]. Although *M. tuberculosis* has never been demonstrated directly in the arterial tissues of patients with active or inactive arteritis [6], the presence of IS6110 and HupB gene sequences of *M. tuberculosis* in the aortic tissues of TA patients implies that TB may directly induce inflammatory reaction in TA without an autoimmune mechanism [34, 55]. Also, BCG vaccination was proposed for the etiology of TA [6, 29].

12.6   Atherosclerosis

Atherosclerosis is the main pathology of cardiovascular diseases which are responsible for one third of all deaths in the world according to the World Health Organization (WHO). Although there is no clinical evidence for increased atherosclerosis development in TB [52], it was shown that patients with pulmonary or extrapulmonary TB had a 40% increased risk for acute myocardial infarction and unstable angina pectoris and a 50% increased risk for ischemic stroke [19]. The relationship between TB and atherosclerosis is unclear, but it should be considered that some mechanisms seen in the course of TB may potentially be related to the occurrence or progression of atherosclerosis.

A connection between hardly growing intracellular organisms (cytomegalovirus, Herpes simplex virus, Chlamydia pneumoniae, and Helicobacter pylori) and atherosclerosis has been implicated due to their chronic or latent infection habit that may cause persistent inflammation leading to atherosclerotic plaque formation [19, 52]. Atherosclerosis is primarily an inflammatory disease. Activated leukocytes including T lymphocytes and macrophages and inflammatory markers including C-reactive protein, fibrinogen, serum amyloid, interleukins, TNF-α, and adhesion molecules are related to the progress of atherosclerosis [52]. *M. tuberculosis* has similar features with microorganisms which are accused of leading atherosclerosis and similarly induces chronic inflammation which may have a role in atherosclerosis.

Cross-reaction of antibodies to heat-shock proteins may be associated with atherosclerosis, because the endothelial cells express them when they are activated by various stressors [19, 61]. A significant correlation between anti-HSP65 antibodies and carotid atherosclerosis has been reported [19]. Patients with atherosclerosis have higher titers of antibodies against heat-shock proteins [52, 61]. Also, it was found that there are T cells specifically responding to heat-shock proteins in atherosclerotic plaques [61]. As mentioned above, antibodies produced against *M. tuberculosis* HSP65 can induce a self-reaction of T and B cells against human HSP60 through molecular mimicry which may play a role in the development of atherosclerosis [52]. The anti-HSP60 titers in the animals immunized with BCG vaccine were found to be correlated with atherosclerotic plaque formation [52].

TB induces free radical production such as reactive nitrogen intermediates (RNI) and reactive oxygen species (ROS), which enhance oxidative stress and decrease antioxidant activity in patients [17, 44]. Oxidation/reduction imbalance is associated with LDL oxidation which has a central role in the pathogenesis of atherosclerosis via endothelial dysfunction, expression of the adhesion molecules, and foam cell formation. Oxidation/reduction imbalance in TB patients may be associated with an enhanced susceptibility of LDL to oxidation predisposing TB patients to a higher risk of atherosclerosis [44].

12.7 Deep Vein Thrombosis

There are several classic risk factors for venous thromboembolism (VTE), and infection is considered one of them. Also, TB is an independent risk factor for VTE. Inflammation, stasis, and hypercoagulable state which occurred during the course of TB infection can cause VTE [25, 31]. In the report of Dentan et al. [11] involving the data of 33.048.852 in-patient and outpatient admissions, an association between pulmonary TB and VTE without underlying coagulation disorders was established. The prevalence of VTE in patients with TB is 2–4% [11, 25]. The risk of VTE in TB patients represented by odds ratio (OR) is close to that of neoplasia (1.55 vs 1.62) which is a well-known risk factor for VTE [11]. TB can produce a hypercoagulable state attributed to increased platelet aggregation; thrombocytosis; increased fibrinogen, factor VIII, plasminogen activator inhibitor 1 plasma, and antiphospholipid antibody levels; and decreased antithrombin III and protein C levels [11, 25, 31]. Besides, venous compression by retroperitoneal lymph nodes may cause stasis and thrombosis [11, 31]. Endothelial injury caused by TB bacilli and inflammation or the use of rifampin may take part in the pathogenesis of VTE [25]. In addition to deep vein thrombosis and pulmonary embolism, thrombosis of unusual sites including cerebral venous sinuses or hepatic vein has been reported in patients with pulmonary TB [25].

Hypercoagulable state is recovered following commencing antituberculous therapy [31]. The treatment of VTE in TB patients should include both anticoagulation and antituberculous therapies [25]. The maintenance of target INR level may be difficult, and a high dose of warfarin may be required due to hypercoagulable state induced by rifampicin, which is a cytochrome p450 inducer and increases clearance of anticoagulants [31].

VTE is an independent prognostic factor for TB patients and independently associated with mortality (OR = 3.87) [11]. Mortality is higher in patients with both TB and VTE (15%) than in patients with TB (2.7%) or VTE (2.5%) alone [11].

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