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THE PATHOLOGY OF TUBERCULOSIS 4

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4.1 THE MORPHOLOGY OF GRANULOMATA

The histological features of tuberculosis are characteristic and similar in all sites of infection. The hallmark of active infection is the necrotizing epithelioid cell granuloma. It is also important to point out that tuberculous granulomata are identical morphologically and immunologically to granulomata due to other infectious causes such as histoplasmosis and blastomycosis[1]. Before describing the pathology of tuberculosis, some general points will be covered.

The predominant cells in all granulomata, whether organized into epithelioid cell foci or not, are non-lymphoid mononuclear cells[2,3]. This diverse group, known as the reticuloendothelial or mononuclear phagocyte system[4], includes blood monocytes, tissue macrophages (or histiocytes), and organ-specific forms such as the Kupffer cells of the liver. In epithelioid cell granulomata they are represented by macrophages, epithelioid cells and giant cells of predominantly Langerhans type[2,5,6]. The nuclei of these giant cells are arranged in an arc around central granular cytoplasm. Tuberculous granulomas typically show necrosis; as described later this is due to the inherent toxicity of the bacilli and the release of cytokines such as tumour necrosis factor and interleukin-1[7].

Mononuclear phagocytes arise from immature bone marrow precursors, circulate briefly as monocytes and then populate the tissues as macrophages. They are capable of rapid differentiation and activation. Mackaness[8] used the term 'activation' to describe increased activity against ingested pathogens; such macrophages can be recognized functionally[9] and morphologically[10].

An epithelioid cell granuloma consists of a collection of partly or highly specialized mononuclear phagocytes in response to a persistent inflammatory agent. Epithelioid cells appear large with abundant eosinophilic cytoplasm and show indistinct cell boundaries[11]. Enzyme histochemistry and immunochemistry support the concept that the cell population of a granuloma is mixed, with different activities of cells in varying regions of the granuloma.

Inclusions, such as asteroid or Schaumann bodies, may be found in the giant cells in long-standing granulomatous inflammation. Asteroid bodies are also seen in giant cells and are formed from a radial arrangement of cytoskeletal elements. Schaumann bodies are laminated calcified bodies 10–100 μm in diameter found within epithelioid cells and giant cells. They may lie free in areas of fibrosis and indicate previous granulomatous inflammation. They show a central crystalline core containing iron and calcium. They are probably of lysosomal origin[12]. They have been reported as occurring in up to 6% of tuberculous granulomata.

On electron microscopy, macrophages have a deeply indented nucleus with fairly dense chromatin. A nucleolus may be prominent. Mitochondria are relatively numerous.

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Strands of rough endoplasmic reticulum and lysosomes lie in the cytoplasm. Variable numbers of microfilaments and microtubules are also present throughout the cytoplasm.

The most striking feature is the presence of large numbers of cytoplasmic vacuoles[13,14]. These inclusions are circular or elongated and measure 0.05–0.25 μm in diameter. Some are electron dense and resemble lysosomes. The majority, however, contain fluffy material that appears homogenous. This latter type of vacuole appears to be unique to epithelioid cells[15,16]. Fragments of micro-organisms may be seen within these vacuoles[17]. Epithelioid cells show prominent rough endoplasmic reticulum and Golgi lamellae, therefore suggesting that in epithelioid cell granulomas macrophages change from a predominantly phagocytic to a secretory role[18,19]. Well-developed epithelioid cells show numerous cytoplasmic projections, which frequently interdigitate and occasionally form junctions[19,20]. This feature accounts for the indistinct and cytoplasmic boundaries of epithelioid cells seen on light microscopy.

The intercellular junctions that form between epithelioid cells resemble desmosomes. Subplasmalemmal densities present on the opposing cells closely relate to a plaque of electron-dense extracellular material. Immature cells in granulomata generally lack such membrane interconnecting elements. Isolated subplasmalemmal linear densities of the type seen in relation to intercellular junctions in granulomas are frequently seen in cells of the mononuclear-phagocyte system[21]. The large number of junctions between epithelioid cells suggests cell-to-cell communication is prominent. Adhesion molecules are associated with these junction complexes. Cell adhesion due to these molecules has been localized by immunocytochemistry, in particular integrin VLA-3[22]. This integrin is strongly associated with intercellular contact sites. Subplasmalemmal densities are associated with areas of the cell membrane where cytoskeletal filaments relate to the extracellular matrix[23].

4.2 THE IMMUNOLOGY OF GRANULOMATA

The immunological response to tuberculosis is almost entirely cell-mediated, the epithelioid cell being the effector cell. Macrophages in association with a delayed hypersensitivity reaction show increased phagocytic and intracellular killing ability[24]. There is substantial evidence that the mononuclear and epithelioid cells seen within granulomata are derived from the bone marrow via the circulation. Cells of the mononuclear phagocytic system from different anatomical sites show marked functional and phenotypic differences[25]. This heterogeneity may reflect either the influence of environmental factors stimulating circulating monocytes to differentiate in a particular way, or the existence of different macrophage subsets[26]. Different subsets of macrophages are seen in B and T cell-dependent areas of peripheral human lymphoid tissues[27]. Further evidence that epithelioid cells are derived from monocytes is provided by the retention of the monocyte–macrophage marker RFD-2 by epithelioid cells throughout granulomata[28]. Epithelioid cells also show the macrophage marker OKMI[29,30]. However, mononuclear phagocytes in the centre and periphery of granulomata differ in their immunological phenotype[31]. Activated macrophages and epithelioid cells within the centre of granulomata strongly express HLA-DR and show marked acid phosphatase activity. In the periphery of granulomata there is an additional population of non-lymphoid HLA-DR positive cells, which show only a small degree of acid phosphatase activity. These cells appear to function as antigen-presenting cells[32]. Epithelioid giant cells also strongly

express HLA-DR, and may also function as antigen-presenting cells[30].

4.2.1 THE ROLE OF T CELLS

The feature that distinguishes hypersensitivity granulomata from non-specific foreign-body type granulomata is the presence of lymphocytes (Plate 3). In hypersensitivity type epithelioid cell granulomata, lymphocytes are seen in close association with the activated macrophage–monocyte cells. These T cell–macrophage interactions are important in the immunology of tuberculosis[33]. The majority of lymphocytes seen in epithelioid cell granulomata are T cells[34]. These cells show features of activation[35]. A higher proportion of CD4 helper cells are present in the centre of granulomata than at the periphery[36]. CD8 suppressor and B cells tend to be associated with epithelioid cells at the periphery, particularly in tuberculosis[37], where occasionally they form a mantle separating the granuloma from the surrounding tissue[30]. Paradoxically, some CD4 helper cells can show suppressor functional activity. These features support the concept that a function of a granuloma is the formation of an isolated microenvironment[38] with immunoregulation occurring at the periphery. Some workers have emphasized the role of T lymphocytes in granulomatous inflammation, hypothesizing that these cells may initiate epithelioid cell granulomata[39,40]. In tuberculous granulomata, T lymphocytes produce interferon-1[41]. There are reports, however, of epithelioid cell granulomata being induced in the absence of T cell function[42]. The importance of cytokine activity in granulomata is shown by the suppressive role of corticosteroids. The macrophages in granulomata show decreased activation and number in the presence of steroids in experimental situations. There is also decreased tissue necrosis, with steroids showing an anti-inflammatory effect[43]. The release from granulomata of cytokines such as tumour necrosis factor and gamma interferon may be responsible for systemic effects such as fever in tuberculous infection[44].

Studies have shown that there is T cell receptor gene restriction in individuals with tuberculosis[45]. It is of interest that gamma-delta T cells are increased in the peripheral blood; this is a feature seen in mycobacterial infections[46]. Gamma-delta lymphocytes react to mycobacterial antigens[47]. They appear not to be increased in number in the granulomata themselves[48]. Some mononuclear cells in granulomata stain for S100 antigen, a marker of certain members of the mononuclear macrophage system, in particular Langerhans cells and so-called T-zone histiocytes. These are believed to function as antigen-presenting cells. Epithelioid cells and the monocytes in granulomata strongly express leucocyte function associated antigen-1 (LFA-1) and its ligand intercellular adhesion molecule-1 (ICAM-1). This supports the view that the monocyte-macrophage cells in granulomata are involved in antigen presentation.

The concept of high- and low-turnover granulomas was introduced by Spector [49–51]. 'High' turnover granulomata are dependent on continued recruitment from the bone marrow. Most foreign-body type granulomata are of 'low'-turnover type. These differ in being very long lived with a low level of monocyte recruitment and minimal fibrosis. The lack of fibrosis in foreign-body granulomata may be due to the low level of macrophage turnover with subsequent small amounts of free lysosomal enzymes and other fibrogenic substances[52]. In the case of high-turnover granulomata it appears that activated macrophages stimulate the proliferation of fibroblasts[53]. For example, by secreting fibronectin, activated macrophages attract fibroblasts and by secreting a growth factor the absolute number of fibroblasts is increased[54]. Granulomas have therefore been classified by the presence or

absence of an associated immunological response[55]. They fall into two main groups: immunological or hypersensitive type[56] and the non-immunological foreign-body type.

4.3 THE PATHOLOGY OF TUBERCULOSIS

Tuberculosis can cause lesions in any tissue or organ of the body, but most frequently involves the lung. In view of this, the following account will focus mainly on this organ. Other organ sytems will be then be described.

4.3.1 PULMONARY TUBERCULOSIS

(a) Primary tuberculosis

The pathology of tuberculosis takes into account the inherent virulence of the organism, the immunity of the person infected, the development of hypersensitivity and the formation of epithelioid cell granulomata. Primary tuberculosis is the first infection of an unsensitized host. Tubercle bacilli usually enter the lung via the airways, and when in small groups of one to three can reach the alveolar spaces[57] in droplets smaller than 5 μm in diameter. The very early cellular reaction in tuberculosis is not known, but it is probable that neutrophils are responsible for phagocytosis initially, and macrophages are recruited later. They are then phagocytosed and the majority of the organisms will be killed. This has been termed stage I of the disease[57,58]. However, a proportion of the bacilli will survive and replicate within the macrophages and cause cell death (stage II). Further monocytes are recruited from the circulation and transform into macrophages, but unless they are activated they are inefficient at destroying the tubercle bacilli. Chemotactic factors such as complement component C5a and various cytokines such as monocytic chemotactic protein 1 (MCP-1) recruit macrophages[59]. Acid-fast bacilli are easily seen at this stage. Tubercle bacilli are transported via lymphatics to regional lymph nodes, in which epithelioid cell granulomata develop. Granulomata develop typical central necrosis as delayed hypersensitivity to the bacilli develops (stage III). This takes about 2–4 weeks, as measured by the tuberculin test. The necrosis in the granulomata is most probably due to local toxic lysosomal or cytokine effect rather than ischaemia. Tuberculous bacilli are also directly cytotoxic. The epithelioid cells that result are much more efficient at killing the intracellular bacilli. The majority of the bacilli are now extracellular and have a reduced ability to multiply and are more difficult to find at microscopy. A spectrum of reactivity to the tubercle bacilli appears to exist[60]. There may be a florid granulomatous reaction with few identifiable bacilli comparable with tuberculous leprosy. The other end of the spectrum is the presence of quiescent macrophages with abundant necrosis and large numbers of bacilli[60–62] (Plate 4).

This initial focus of caseous bronchopneumonia together with the lymphadenopathy is known as a Ghon complex. This type of infection is seen mainly in early childhood in endemic areas with a maximum incidence at 1–3 years[63]. The lymph nodes on the same side as the Ghon focus form a mass usually larger than the Ghon focus. Histologically there is marked fibrinous exudate and numerous acid-fast bacilli surrounded by granulation tissue. Connective tissue stains will show that initially the underlying lung architecture is preserved. Features correspond to the grey hepatization phase of lobar pneumonia. Infection may be centred on blood vessels[64]. The primary pulmonary focus is usually unilateral and found in a subpleural position above or below the lobar fissure between the upper and lower lobes, or less commonly the basal part of the lower lobes. Grossly it appears as a yellow-white area of softening 10–20 mm in diameter surrounded by a grey capsule. The soft area represents the 'caseous' necrosis. There may be an associated pleural effusion.

Similar primary complexes occur in organs infected by less frequent routes of infection, such as the gastrointestinal tract, oropharyngeal lymphoid tissue and the skin. Regional lymph nodes are involved by lymphatic transport of bacilli from the initial site of infection.

From the lymphatics, the bacilli enter veins and spread to other parts of the body, including the lungs, the brain, kidney and bone. If bacilli enter a pulmonary artery, spread to other parts of the lung will result. The systemic haematogenous stage is frequently marked by acid-fast bacilli in the urine. Despite this wide distribution, in the majority of cases the infection is controlled and lesions resolve without clinical features. Areas of infection smaller than a millimetre in size resolve with no fibrosis. Larger areas of infection, greater than 5 mm across show fibrosis and dystrophic calcification and occasionally ossification. They have the appearance of friable white material surrounded by a grey capsule with fibrosis in the adjacent lung. These larger lesions appear to be a source of reactivation. Hilar lymph nodes typically show dense hyaline fibrosis. In the infant, however, there may be uncontrolled proliferation of the tubercle bacilli; the Ghon focus may penetrate a blood vessel or bronchus to cause bronchopneumonia and other satellite lesions or 'miliary' disseminated disease such as meningitis, or renal disease. Infected organs show numerous small, white nodules resembling millet seed. Oesophageal perforation has also been rarely described [65].

Congenital tuberculosis is rare and generally lethal. Infection appears to be by a haematogenous route or from aspiration of infected amniotic fluid[66].

(b) Secondary tuberculosis

After resolution of the primary infection, small numbers of bacilli survive within the scarred foci for many years. The majority of infections, at least 90%, do not progress any further. Reactivation of the disease (post-primary or secondary tuberculosis) occurs when host resistance is impaired. This may be due to immunosuppression from any cause, including malnutrition, alcoholism, malignant disease, silicosis, diabetes[67] and acquired immune deficiency syndrome (AIDS). Post-primary pulmonary tuberculosis may also be the result of further infection from an exogenous source. This disease is mainly a disease of the elderly[68], who were infected at a young age when tuberculosis was more common. It is usually seen in the apical or posterior segments of the upper lobes (Simon's foci) 10–20 mm from the pleura and apical segments of the lower lobes. Clinically the disease presents as an acute necrotizing pneumonia (Plate 5). Hilar lymphadenopathy is not a prominent feature. In view of the sensitivity of the host there is a very florid response to the bacilli, with marked caseous and liquefactive necrosis. The liquefaction and cavitation is due to the hydrolysis of protein, lipid and nucleic acids by the enzyme products of large numbers of macrophages recruited in view of the hypersensitivity of the host[69]. The organisms are able to multiply extracellularly in large numbers. This is stage IV of the disease as described by Lurie. The lesion often ruptures into a bronchus and may result in progressive pulmonary tuberculosis localized to one area of the lung. Endobronchial and endotracheal infection may result. Large numbers of bacilli are usually present in the sputum. There may be a dominant florid hypersensitivity reaction to this liquefied material in the distal lung, particularly in children. Diffuse bronchopneumonia can occur. A tuberculous empyema may result if the secondary lesion ruptures into the pleural cavity. Organisms may be coughed up and infect the larynx or be swallowed and infect the lymphoid tissue of the gastrointestinal tract. Other paths of spread within the lung are via arteries, with miliary spread to all

parts of the lung, or via a pulmonary vein with dissemination to all areas of the body. Common sites of spread are the bone marrow, eye, lymph nodes, liver, spleen, kidneys, adrenal, prostate, seminal vesicles, uterine tubes, endometrium and the meninges. The eye is another important site of involvement. The disease may then progress in any one of these organs to dominate the clinical picture. Common sites of isolated infection are cervical lymph nodes (scrofula), meninges, kidney, adrenals, bones, uterine tubes and the epididymis. Diagnosis of such extrapulmonary sites often requires biopsy [70].

In renal disease, infection of the renal pelvis and the bladder may result. Tuberculosis of the uterine tubes may spread to the endometrium and the adjacent pelvic structures. In infection of the spine (Pott's disease), the disease may spread along the psoas fascia along a tract opening in the groin. Chronic tuberculous infection is a well-known cause of reactive systemic amyloid (secondary, AA type).

In severely immunosuppressed individuals, particularly in AIDS, in view of the reduced T lymphocyte population there is almost a total absence of granulomata and large numbers of mycobacteria proliferate uncontrolled within macrophages. Rarely patients show loss of skin sensitivity and loss of cell-mediated immunity to the mycobacteria[71].

Another rare form of disseminated spread of infection is cryptic disseminated tuberculosis. This occurs in immunodeficient individuals and the elderly. Very small lesions are present with large numbers of bacilli[72]. The cause of such reduced response to the infection is not known but may be due to abnormal expression of HLA-DR gene products[73].

Secondary lesions are associated with a great deal of lung destruction. Much of the destruction may be due to overproduction of cytokines such as tumour necrosis factor[74].

The liquified cavity becomes surrounded by dense fibrous tissue. It is lined by caseous material with soft nodules and may contain remnants of pulmonary vessels. Cavities usually measure from 3–10 cm across. If they are developing they have thin walls; more chronic cavities are surrounded by fibrosis. Pulmonary artery aneurysm[75] and bronchopleural fistula[76] are complications that may result. A late problem with a chronic cavity is colonization by a fungus such as aspergillus with the development of a mycetoma.

4.4 SYSTEMIC INVOLVEMENT IN TUBERCULOSIS

The more common sites of involvement are described.

4.4.1 LYMPH NODES

Lymph nodes may become an isolated site of disease in secondary tuberculosis; involvement of cervical nodes is termed 'scrofula'. A sinus may develop, connecting with the skin. Cervical lymphadenopathy may occur in primary tuberculosis where the site of infection is the oropharynx, including the tonsil. The nodes may become adherent and form a multinodular mass that may imitate metastatic carcinoma.

Lymph nodes infected with tuberculosis may enlarge when antituberculosis chemotherapy is started. It is suggested that the breakdown of degenerating bacilli stimulates cell-mediated immunity[77].

4.4.2 SKIN

Primary tuberculosis of the skin is very rare and is usually the result of direct inoculation. The lesion develops within 2–4 weeks after the inoculation. The earliest response is a neutrophilic reaction with necrosis and ulceration. Macrophages are recruited and necrotizing epithelioid cell granulomata develop.

Miliary tuberculosis of the skin can occur in primary pulmonary tuberculosis and is characterized by numerous micro-abscesses surrounded by macrophages containing acid-fast bacilli.

Involvement of the skin in secondary tuberculosis is manifested by lupus vulgaris. These chronic lesions are found on the head and neck as red-brown patches with nodules. Well-formed epithelioid cell granulomata with Langerhans giant cells are seen histologically, although necrosis is minimal. Acid-fast bacilli are rarely seen.

Occasionally disseminated skin lesions are seen in active tuberculous infection. They show well-formed granulomata without acid-fast baciili. Regression occurs on treatment and they probably represent a local response to fragments of tuberculous antigenic material[78]. They are known as tuberculids (papulonecrotic, lichen scrofulosorum and erythema induratum). Necrosis and vasculitis may be seen.

4.4.3 CENTRAL NERVOUS SYSTEM

Tuberculous meningitis may occur after the escape into the subarachnoid space of bacilli from a focus of infection in the meninges or cortex. There is a diffuse meningitis with severe inflammation and fibrin exudation and eventual fibrosis. Nerves and blood vessels may be compromised; obliterative endarteritis develops. A rare form of tuberculosis in an epidural site may result from spread of tuberculous infection from the middle ear. Subdural tuberculosis manifests as large confluent plaques of exudate.

Tuberculomas are localized space-occupying masses within the brain tissue with central necrosis and surrounding granulomatous inflammation. In adults they are supratentorial while in children they tend to occur in the posterior fossa. Old lesions may calcify. In only half the cases is there a previous history of tuberculosis[79].

A hypersensitivity phenomenon manifesting as acute haemorrhagic leucoencephalopathy may occur in tuberculous patients. This may also be associated with upper respiratory tract infections due to organisms other than tuberculosis and in septicaemia. There is diffuse oedema, focal demyelination and a perivascular macrophage reaction. Spinal cord involvement has been described[80].

4.4.4 FEMALE GENITAL TRACT

(a) Uterine tubes and ovary

Primary tuberculosis is rare; secondary infection is almost always by the haematogenous route. The uterine tubes are the most common site of infection. Although a pulmonary lesion may not be evident, involvement of the peritoneum or kidneys may be present. Lymphatic spread from primary intestinal infection may occur or there may be direct spread from the bladder or gastrointestinal tract.

As the disease becomes chronic, there is thickening and nodularity of the tube. Dense fibrous adhesions between the ovary and tube develop, and the fimbriae and ostium may obliterate. The ovary can be involved by direct spread from the uterine tube, but this is less common than tube involvement itself[81]. It is rare to see necrotizing granulomata within the ovarian stroma. The uterine tube can dilate and form a hydrosalpinx. Mucosal granulomata are seen, which extend into the muscle wall and to the serosa. They can become confluent and cause obstruction. The granulomata ulcerate and infectious material is released into the tube lumen. Tubal obstruction is almost always the end result of this process[82]. Calcification is common in old lesions.

(b) Endometrium

Involvement of the endometrium follows infection of the uterine tubes. The resulting

granulomatous inflammation may be focal and poorly formed in view of the monthly shedding of the endometrium. The inflammation can, however, be diffuse with numerous necrotizing granulomata. The only manifestation of the disease may be a chronic endometritis with plasma cells. The inflammation is normally superficial: deep granulomatous inflammation is rare[83]. Reactive changes may be seen in the adjacent endometrial glands. Placental tuberculous infection is rare[84]. Infection of the cervix and vulva may follow tuberculous endometritis. Tuberculous cervicitis may resemble carcinoma macroscopically.

4.4.5 KIDNEY AND MALE GENITAL TRACT

Tuberculosis of the kidney results from secondary spread from a pulmonary site and it may be either unilateral or bilateral. The resulting necrotizing granulomata involve the cortex and medulla and eventually rupture into the renal pelvis.

Tuberculous cystitis, epididymitis and orchitis may result from this. Tuberculous epidiymitis may also originate from the prostate. In haematogenous spread, the head of the epididymis is most frequently involved, the vas being spared. In spread from the prostate, both the vas and tail are involved. Testicular involvement may simulate a neoplasm.

4.4.6 BONE AND JOINT

Tuberculosis at these sites is normally secondary by the haematogenous spread from the lung. The most common site involved is the spine, in the area of the tenth thoracic vertebra, although any bone may be involved. There is bone destruction with replacement by caseous inflammation. A paravertebral abscess may result. Spinal cord compression is a recognized complication. The infection can track along anatomical planes to discharge a distance from the involved bone.

Poncet's disease may occur in association with tuberculosis. Hypertrophic osteoarthropathy may also occur where pulmonary disease is long-standing or extensive. Organisms are not found at the involved sites and the conditions probably have an immunological basis. Tuberculous arthritis may originate in the synovium itself or develop from direct spread from tuberculous arthritis. The knee and hip joints are the most commonly involved sites. The end result is joint restriction or ankylosis.

4.4.7 GASTROINTESTINAL

As with the lung, tuberculosis can be divided into primary and secondary types. Tuberculosis can affect any part of the gastrointestinal tract, but it is most commonly found in the terminal ileum and ileocaecal region. It is rare to see tuberculosis in the colon and rectum. Acute obstruction and perforation are frequent complications. The differential diagnosis of tuberculosis always includes Crohn's disease. Tuberculosis can cause single or multiple strictures with mucosal ulceration. The ulcers tend to be annular in distribution, the base being raised. The submucosa is characteristically obliterated in tuberculosis, with severe associated fibrosis. This fibrosis results in hypertrophic or ulceroconstrictive forms of the disease. Fissures and fistulae are rare. Granulomata are well formed, found in Peyer's patches and lymphoid follicles, and almost always are found in regional lymph nodes. Enterocolitis may result from acute infection and perforation with the development of peritonitis, and ascities may occur. In peritonitis the surface is studded with myriads of tubercles, which can fuse to form caseous masses. Involvement of the greater omentum predominates.

Anorectal tuberculosis is common in areas with a high incidence of pulmonary and intestinal tuberculosis[85]. One clinical type is in patients presenting with active tuberculosis with anal ulceration in which acid-fast

bacilli are numerous. The second clinical type is more chronic with marked fibrosis and fistulae in which bacilli are sparse; differentiation from Crohn's disease is difficult.

Gastric tuberculosis is almost always secondary and presents with chronic ulceration associated with destruction but minimal fibrosis. A tuberculous mass may develop at the pylorus. Regional lymph nodes are normally involved[86].

4.4.8 CARDIOVASCULAR

Tuberculous pericarditis is associated with generalized infection; myocarditis is less frequent. Constrictive pericarditis with heart failure may result. Although involvement of small vessels is common in tuberculosis, large vessel involvement is rare. The aorta is most commonly involved.

4.4.9 ENDOCRINE

The adrenal is the most frequently involved endocrine gland and tuberculosis is a typical cause of Addison's disease. In extensive multi-system disease, the adrenals are spared. In contrast to this, when the adrenals are involved and destroyed by necrotizing granulomatous inflammation, extra-adrenal tuberculosis is rare[87]. Involvement of the pituitary, in particular the hypophysis, follows pulmonary infection.

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