Review Article

PATHOLOGY OF TUBERCULOSIS

Yoshinori KAWABATA

Abstract Tuberculosis, particularly pulmonary tuberculosis, is a serious disease in humans. Although its pathology was mostly established by 1950, many subjects remain unsolved including the causes of various types of caseous necrosis (such as the primary focus, caseous pneumonia, necrosis in immunocompromised patients, necrosis following exudation, and necrosis following production), the cause of lytic changes of caseous necrosis, and the original portion, manner, and causes of reactivation. In this article, I emphasize the diversity of host-parasite relationships associated with the degree of cellular immunity, and also try to explain the reasons for the various reactions of the host.

Key words: Tuberculosis, Pathology, Pathogenesis, Reactivation, Immunohistochemistry

1. Introduction

Tuberculosis, particularly pulmonary tuberculosis, is a serious disease in humans. The hypothesis that the pathology of tuberculosis develops in three stages was proposed by Ranke[1] in 1916 and the pathology of tuberculosis was mostly established by 1950[2)~4)]. Following an primary infection by *Mycobacterium tuberculosis* (Mtb), approximately 90% of patients contain Mtb by forming the primary complex (the primary focus and thoracic lymph node lesions). Only several percent develop primary tuberculosis following primary infection and several percent develop chronic tuberculosis after a latent period. The original portion of chronic pulmonary tuberculosis currently is not confirmed yet. The primary subjects of this review of tuberculosis will be primary infection, primary tuberculosis, original portion of reactivation, chronic pulmonary tuberculosis, and tuberculosis in immunocompromised patients. The genetic basis (such as expression of virulence lipids) and manipulation of Mtb to humans, and their effects to host-parasite relationship are beyond the scope of this review.

2. Process and pattern of inflammation

The inflammatory response to pathogenic substances begins with the exudation of the inflammatory cells and blood plasma into the lesion, followed by production (repair when there is tissue damage) and ends with scar formation, called, respectively, the exudative stage, the productive stage, and the scar stage. The productive stage is divided into the proliferative stage (epithelioid cell, a specialized type of macrophage (Mϕ) showing epithelial like cell connections to each other, granuloma formation or epithelioid cell layer formation around caseous necrosis) and the productive stage (reticulin network formation and collagen deposition in and around a granuloma or around caseous necrosis, which is a type of coagulation necrosis) in tuberculosis. In some patients, an abnormal inflammatory process leads to abscess formation and caseous necrosis followed by encapsulation. The inflammatory response is categorized into two major patterns; an exudative reaction/lesion, represented by severe exudation with subsequent caseous necrosis represented by caseous pneumonia[3)4)], and a productive reaction/ lesion represented by rapid formation of epithelioid cell granulomas that are formed after cellular immunity is established in tuberculosis[3)].

3. Primary infection and primary tuberculosis

a. Primary infection

Various Mtb and Mϕ relationships have been reported after primary infection in the lungs and cell culture systems, such as the death (oncosis or necrosis, apoptosis, etosis, and pyroptosis) of Mϕ and living Mϕ (activated, efferocytotic, and autophagic) until the development of caseous necrosis[5)~10)]. Previous studies reported that the primary focus and thoracic lymph nodes suddenly undergo caseous necrosis 4-6 weeks after primary infection, and this is histologically characterized by necrosis following exudation (E necrosis), showing a preserved lung structure without the production of reticulin fibers or collagen fibers before

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necrosis[3)4)11)]. The volume of a lesion of caseous necrosis is approximately the volume of a single acinus, which is 3 to 4 mm in diameter[3)]. The next step involves the formation of an epithelioid cell layer that surrounds the caseous necrosis. Over time, calcification and ossification also occur in the caseous necrosis. However, lymphocytes or Mϕs have not been detected in the calcified primary complex by immunohistochemical methods, because they lose antigenicity.

Lin et al. reported caseous necrosis (although the underlying pattern were not described in their study, it appeared to be E necrosis because of the primary focus) in the lungs as early as 4 weeks after infection, and this was accompanied by T-cell activation and the expression of chemokines including interferon-γ (IFN-γ) in cynomolgus macaques (primates)[12)]. Non-calcified, encapsulated E necrosis (including the primary focus) contained $CD4^+$ and $CD8^+$ lymphocytes, eosinophils (immunostaining using EG2; an antibody to the eosinophilic cationic protein), Mϕs, and Mtbs (immunostaining using an antibody to the Bacille de Calmette et Guérin/BCG) (Fig. 1, 2), but no neutrophils (immunostaining using an antibody to neutrophilic elastase)[13)14)]. In addition, tumor necrosis factor-α (TNF-α), interleukin-4, and IFN-γ have been detected in caseous necrosis using frozen sections[14)]. Lin et al. detected TNF-α in necrosis and IFN-γ around necrosis[12)].

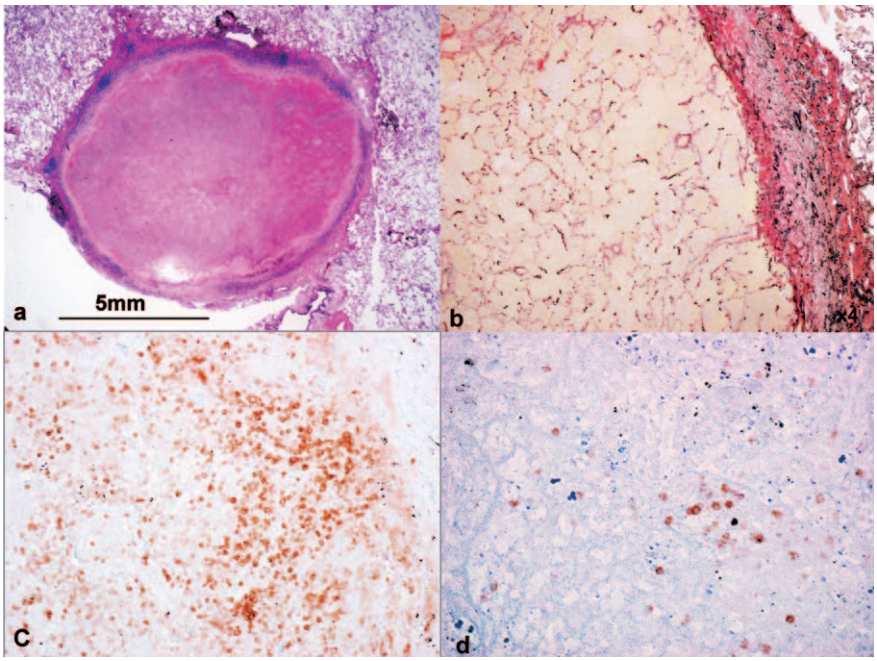

Fig. 1 Immunohistochemical features of necrosis following exudation (E necrosis) (including what are thought to be histological features of the primary focus).
a. Productive-stage caseous necrosis approximately 1 cm in diameter. Bar 5 mm. Hematoxylin Eosin staining (HE), ×10.
b. The lung structure is preserved and no fibrosis is noted in necrosis. Elastica van Gieson staining (EvG). ×40.
c. The exudation of many $CD4^+$ cells before necrosis. Immunostaining using an antibody to CD4, ×200.
d. The exudation of $CD8^+$cells before necrosis. Immunostaining using an antibody to CD8, ×400.

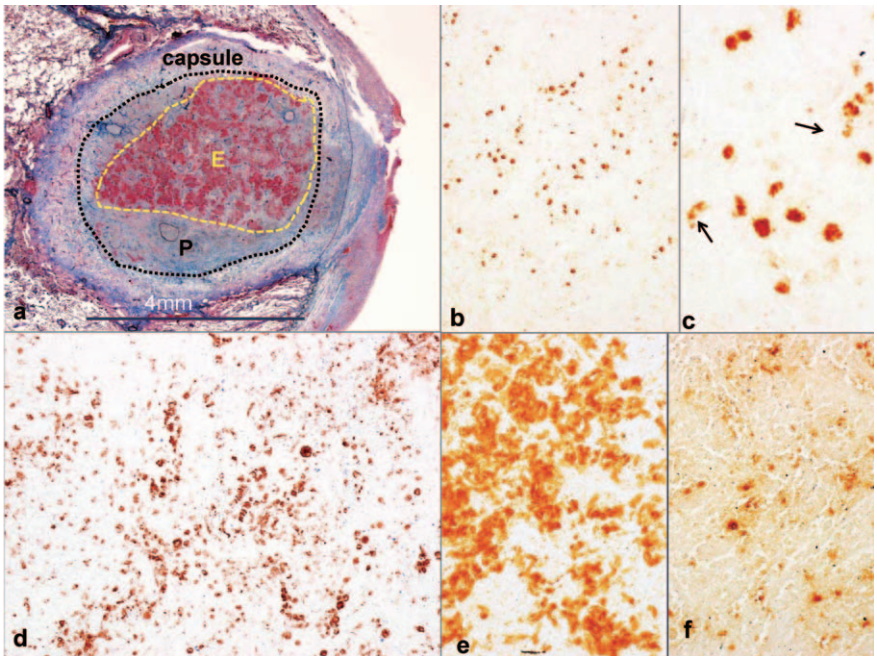

Fig. 2 Immunohistochemical features of E necrosis.
a. Productive-stage encapsulated caseous necrosis of approximately 7 mm in diameter was composed of central E necrosis (yellow circle) surrounded by necrosis following productive reaction (P necrosis) (black circle). Bar 4 mm. Elastica Masson staining, ×15.
b & c. Eosinophils with occasional degranulation (arrow) in E necrosis, but not in P necrosis. Immunostaining using EG2, ×150 & 600.
d. Many macrophages (Mϕs) with the occasional loss of the cell structure in E necrosis, but not in P necrosis. Immunostaining using an antibody to CD68, ×200.
e & f. Mainly intracellular, a large number of Mtbs in E necrosis, not in P necrosis (many Mtbs confirmed by Ziehl-Neelsen staining (ZN) in e, but not in f). Immunostaining using an antibody to Bacille de Calmette et Guérin, ×400.

I think human beings fight against Mtb using every defense mechanism, mainly cellular immunity, which results in caseous necrosis containing numerous numbers of Mtb in the primary complex (about 10^4 Mtb/1 necrotic lesion in primates[12]). Unfortunately the initiation events for the development of caseous necrosis following primary infection are unknown in humans.

We need the number of (intracellular and extracellular) Mtbs and cells and their functions including, a) the state of Mϕs: the death (oncosis, apoptosis, etosis, and pyroptosis) of Mϕ and living Mϕ (activated, efferocytotic, and autophagic), b) various $CD4^+$ cells (including Th1, Th2, and Th17), $CD8^+$ cells, NK cells, B cells, and other lymphocytes and their functions such as the release of cytokines, c) the presence of neutrophils, as in the primate model[12], d) the degree of eosinophils with degranulation, and e) the presence of acute microthrombosis just before necrosis. Primates are the best model for investigating the early events following infection[12)15)], and the events that occur just before caseous necrosis need to be investigated using recently developed modern techniques and methods. Then we can understand how caseous necrosis occurs.

English-language articles have speculated that caseous necrosis develops as a result of a) delayed-type hypersensitivity (DTH)[16], especially the action of TNF-α[17], b) apoptosis of Mϕs and T cells[18)19)], or c) the action of various lytic enzymes from inflammatory cells. Many molecular genetic analyses have recently been reported using the caseous necrotic lesion[20)~22)].

b. Primary tuberculosis

Four types of early-onset (primary) tuberculosis are known to occur after primary infection; 1) breakdown with cavitation of the primary focus and continuous aerogenous spreading, 2) tuberculosis of thoracic lymph nodes with occasional subsequent bronchial perforation, 3) early hematogenous spreading through tuberculosis of subclavicular lymph node (early miliary tuberculosis), and 4) unilateral tuberculous pleuritis. More than 1 type of primary tuberculosis can occur at the same time. In early miliary tuberculosis, small central caseous necrosis can be formed in the exudative stage, which is followed by the proliferative stage surrounded by the epithelioid cell layer (Fig. 3). Non-necrotizing epithelioid cell granulomas are also formed when a sufficient cellular immune response has been established, and when only a few Mtb/1 focus have been disseminated.

Primary tuberculosis was reported to originate mainly from a primary focus in the upper lobes (especially an apex)[3)23)24)], while the primary focus itself was located in the subpleural lung equally throughout the lobes and predominantly in the lower lobes because of their larger volume[23]. This is called (one type of) apical predisposition.

The degree of lymph node involvement following primary infection varies. In autopsies of patients with primary tuberculosis, 100% of thoracic lymph nodes are involved[3)25)], but 35% of patients who died of chronic pulmonary tuberculosis did not have findings of calcified, thoracic lymph node lesions[25]. Autopsy cases of primary tuberculosis who died from causes other than tuberculosis showed that more than 80% of patients had only 1 or 2 involved lymph nodes[26]. This finding suggests that only a limited numbers of cases of latent infection had hematogenously disseminated lesions at the time of primary infection.

4. Reactivation and chronic pulmonary tuberculosis

a. Three types of caseous necrosis

Caseous necrosis has been divided into 3 types[3]; E

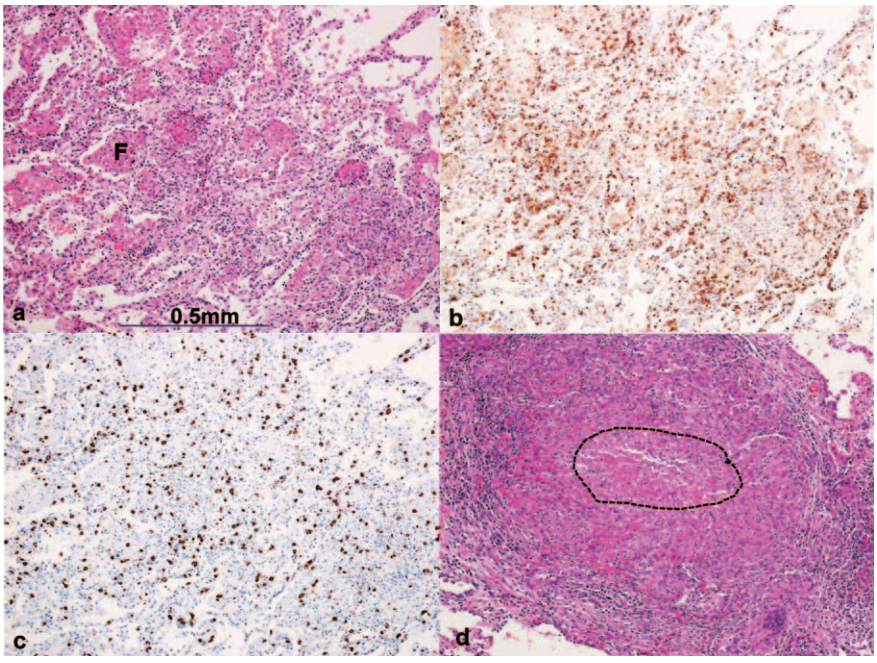

Fig. 3 Early miliary tuberculosis.
a. Exudation of fibrin (F) into the alveolar lumina and exudation of cells into the alveolar lumina and walls at the exudative stage. Bar 0.5 mm. HE, ×100.
b. Many $CD4^+$ cells in the alveolar lumina and walls. Immunostaining using an antibody to $CD4^+$ cell, × 100.
c. Many $CD8^+$ cells in the alveolar lumina and walls. Immunostaining using an antibody to $CD8^+$ cell, × 100.
d. Central caseous necrosis (dotted circle) surrounded by an epithelioid cell layer at the proliferative stage. HE, ×100.

necrosis (Fig. 1), necrosis following production (P necrosis) (Fig. 4ab), and refilling following the lysis of necrosis and discharge (L necrosis) (Fig. 4cd). As stated previously, elastic and reticulin fiber stainings (Elastica van Gieson staining et al. and reticulin staining) confirm that lung structure is preserved in E necrosis. The lung structure is not preserved in P necrosis because of fibrosis associated with epithelioid cell granuloma formation or encapsulation around E necrosis before caseous necrosis. And the lung structure disappears in L necrosis because of lysis or softening[3] and discharge of necrotic material with subsequent refilling of the necrotic material[3)27)28)]. Lymphocytes, Mϕs, and Mtbs are usually not detected in P necrosis, while small numbers of cells and Mtbs are frequently detected in L necrosis[13)14)].

b. Original portion of and progression to chronic pulmonary tuberculosis

Gideon et al. reported that the activation of latent tuberculous infection can occur years or decades after the primary infection in humans, which suggests that latent infection is a dynamic process between the host immune system and bacterial replication[29)]. Risk factors for reactivation include immunosuppression associated with human immunodeficiency virus (HIV) infection, steroids, or anti-TNF-α therapy; malnutrition, smoking, alcohol, diabetics, renal failure, and malignancy[29)].

(1) Original portion or source of chronic pulmonary tuberculosis

Regarding the original portion of chronic pulmonary tuberculosis following latent infection, Mtb was considered to be remain dormant and reside within old lesions either in the primary focus or aerogenously spreading lesions[3)23)] or hematogenously spreading lesions[30)31)] in the upper lobes of the lung for a long time with subsequent exacerbation (apical predisposition).

New theories have recently been proposed, namely, 1) postprimary tuberculosis begins as lipid pneumonia with subsequent caseous pneumonia in 2007[32)33)], 2) a dynamic reinfection hypothesis in 2009[34)35)], and 3) a necrosis-associated extracellular cluster theory followed by vascular thrombosis and pneumonia in 2016[36)]. The first two theories emphasize that Mtbs reside in foamy Mϕs[37)] without being attacked by cellular immunity and these foamy Mϕs somehow move to the apex with the subsequent formation of tuberculous lesions.

The reactivation of the primary focus or its aerogenously spreading lesions in the apex appears to be the most likely source because a) primary tuberculosis mostly begins in the upper lobes[3)23)], b) chronic tuberculosis mostly begins in the upper lobes, with scant hematogenous spreading[23)], c) the location of the first aerogenously spreading lesion after formation of the primary focus is mainly in the upper lobe[3)24)], d) thoracic lymph node lesions are mild or absent following primary infection without primary tuberculosis or in cases of chronic tuberculosis[23)26)], e) the reactivation of latent infection derives from the primary focus and hematogenous spreading is limited in primates[38)], and f) the primary focus and its spreading lesions contain large numbers of Mtbs and have diameters similar to an acinus[3)], in contrast to hematogenously spreading lesions with few Mtb and diameters of up to 300 μm[3)].

(2) Speculated progression to chronic pulmonary tuberculosis from a small lesion of caseous necrosis (necrotizing granuloma)

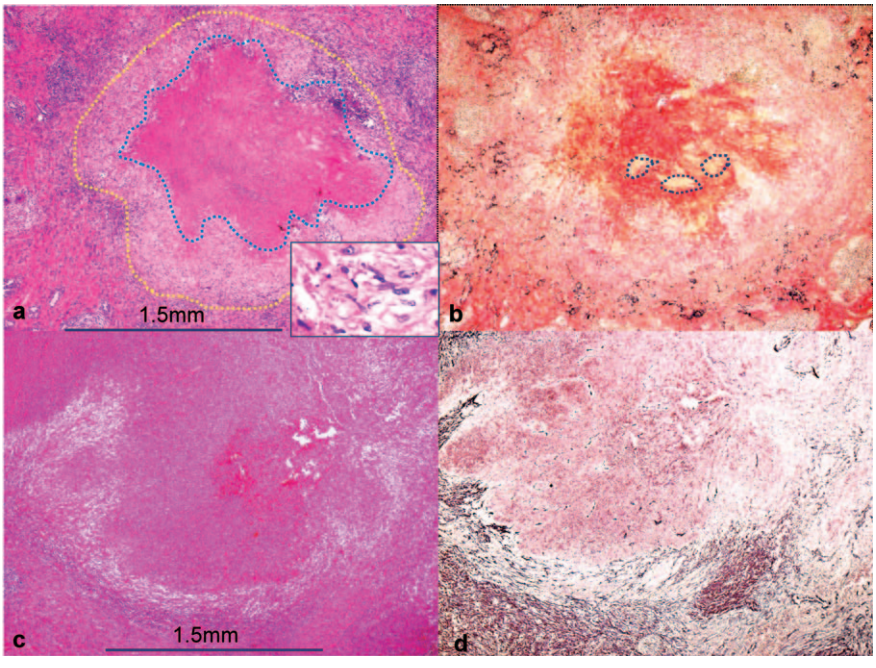

Fig. 4 Another type of caseous necrosis.
a. P necrosis. Well-formed, 2.6-mm sized, encapsulated, productive-stage caseous necrosis. Yellow circle: boundary of necrotizing granuloma, blue circle: caseous necrosis itself. Bar 1.5 mm. HE, ×40. Insert. An epithelioid cell layer surrounding caseous necrosis. HE, ×400.
b. The lung structure is not preserved because of fibrosis before necrosis. The dotted circle is a speculated epithelioid cell granuloma (yellow color). This finding indicates confluent epithelioid cell granulomas with massive surrounding fibrosis completely underwent caseous necrosis. EvG, ×40 (a, b. the same area. a case from Dokkyo Medical University, Koshigaya Hospital).
c. L necrosis. A portion of well-formed, encapsulated, productive-stage caseous necrosis. Bar 1.5 mm. HE, ×40.
d. The lung structure has disappeared because of lysis, the area has refilled with necrotic material. Reticulin staining, ×40 (c, d. the same area).

Our group previously examined encapsulated necrotizing granuloma in lobectomized cavitary pulmonary tuberculosis patients using elastic and reticulin staining. Various combinations were detected, such as E necrosis ＋ P necrosis, E necrosis＋P necrosis＋L necrosis, and others[13] (Fig. 5). This finding indicates that even a tiny (～2-mm diameter) necrotizing granuloma enlarges to greater than 5-mm in diameter by P necrosis surrounding E necrosis, and the presence of L necrosis indicates lysis or softening and subsequent aerogenous spread to the surrounding or to distant lung tissue. Therefore, latent infection is a constant dynamic process and not a stable state. An encapsulated necrotizing granuloma of greater than 5-mm in diameter is usually composed of more than 2 types of necrosis, and the coalescence of 2 or more neighboring lesions of E necrosis surrounded by P necrosis has been frequently observed (unpublished data). Furthermore, the importance of coalescence has been reported from different standpoints[39].

My hypothesis of reactivation is as follows (Fig. 6): a) frequently there are neighboring aerogenously spreading lesions (S) during the course of a primary infection (PF), b) each lesion is encapsulated, c) P necrosis develops and an enlarged necrotizing granuloma communicates with the membranous bronchiole (MB). This could be the morphological basis of reactivation. I wish to propose the hypothesis of dynamic reactivation, but do not rule out the other process of reactivation.

Lysis is an another process that is closely related to

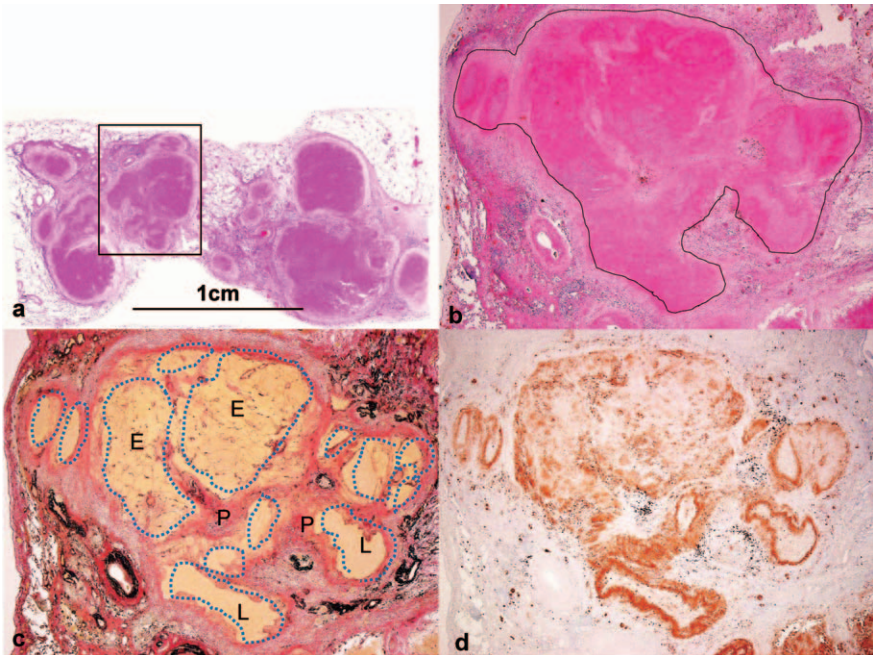

Fig. 5 Repeat necrosis resulted in multiple, confluent, necrotizing granulomas.
a. Multiple, confluent, encapsulated necrotizing granulomas of less than 1 cm in diameter. Bar 1 cm. HE, Panoramic view.
b. An approximately 7-mm sized, irregularly shaped, productive-stage, encapsulated lesion (dotted circle) showing different colors in caseous necrosis (box of a). HE, ×20.
c. This lesion is composed of many small necrotizing granulomas of E and L necrosis and also P necrosis surrounding E and L necroses. E: E necrosis, P: P necrosis, dotted circle; each small necrotizing granuloma. EvG, ×20.
d. Each necrotizing granuloma is surrounded by an epithelioid cell layer. Immunostaining using an antibody to CD68, ×20.

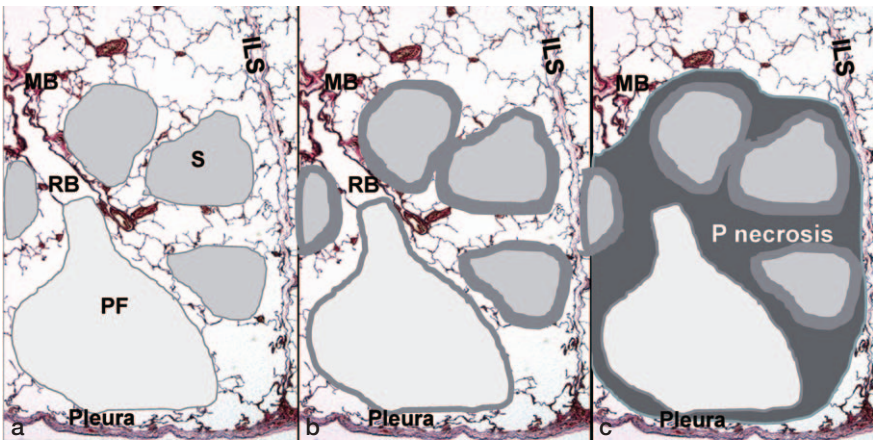

Fig. 6 Speculated process of large necrotizing granuloma formation.
a. At the time of primary infection, an acinar-sized primary focus (PF) communicating with a respiratory bronchiole (RB) is formed. Small aerogenously spreading lesions (S) are formed in the same lobule. They are outlined by a pleura and an interlobular septum (ILS). MB: membranous bronchiole.
b. Each necrotizing granuloma is encapsulated by thick fibrous tissue.
c. P necrosis develops around each necrotizing granuloma, and then this conglomerates into a single large necrotizing granuloma that communicates with the membranous bronchiole (MB). This is the morphological basis of reactivation.

reactivation characterized by the massive infiltration of neutrophils[3)4)34)] and eosinophils[14)]. The infiltration of these granulocytes begins from the capsule into caseous necrosis (Fig. 7) and the lung structure or fibrosis in necrosis then disappears. Continuous P necrosis and lysis with the discharge of necrotic material can stimulate cellular immunity, which might account for a continuously positive IFN-γ releasing assay or positive tuberculin reaction. Ford et al. suggested that Mtb actively replicate during the entire course of clinical latency and this is balanced by robust killing of Mtb[40)].

(3) Cause of P necrosis and lysis

Epithelioid cell granuloma formation with or without caseous necrosis is followed by fibrosis that surrounds the granuloma (encapsulation), which results in containment of Mtb.

Why does P necrosis occur after containment? What kinds of host-parasite relationships are involved? At present I cannot provide the answers. Lytic activity of neutrophils and eosinophils, and the subsequent discharge of necrotic material through the bronchiole or bronchus leads to cavitation and the re-growth of Mtb begins[41)42)]. What kinds of host-parasite relationships cause lysis? P necrosis and lysis are pathological processes essential for reactivation. Furthermore, the mechanisms by which immunocompromised states such as decreased $CD4^+$ cells or decreased TNF-α levels[43)~45)]

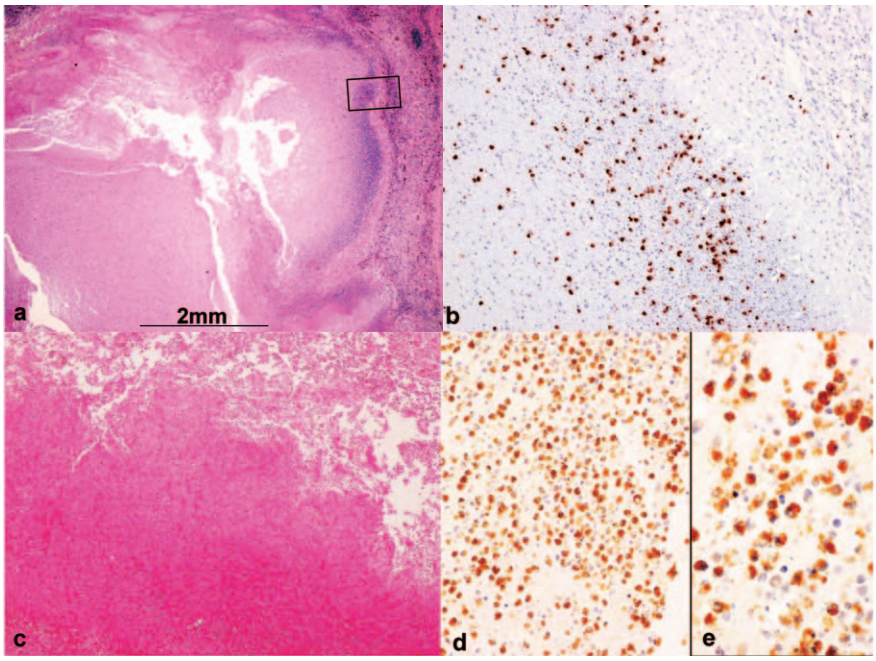

Fig. 7 Lysis and discharge of necrotic material.
a. A lytic lesion proved by EvG (loss of structure) shows a basophilic necrotic layer near the fibrotic encapsulation. Bar 2 mm. HE, ×20.
b. Infiltration of many neutrophils into the basophilic layer (box of a). Immunostaining using an antibody to neutrophilic elastase, ×150.
c. A productive-stage cavitary lesion showing lysis proved by EvG. HE, ×60.
d & e. Infiltration of large numbers of eosinophils into the area of lysis and discharge shown in c. Immunostaining using EG2, ×150 & ×600.

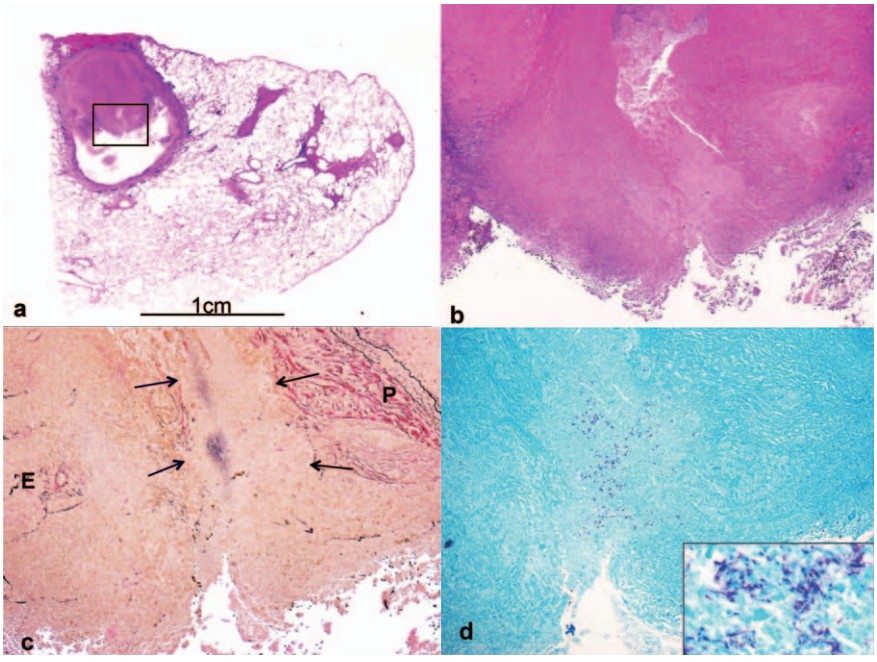

Fig. 8 Cavitation.
a. An approximately 1-cm sized, productive-stage cavity in the lung. Bar 1 cm. HE, Panoramic view.
b. Surface of the cavity (box of a). HE, ×40.
c. Nearly the same area shown in b. Arrows indicate the boundary of L necrosis, and other areas show E and P necroses. EvG, ×80.
d. Many Mtbs proliferate at the region of L necrosis and not on the surface of the cavity in this case. ZN, ×100. Insert ×800 (a case from Fukujuji Hospital).

pathologically increase reactivation have not yet been clarified; therefore, further studies are warranted.

c. Cavity formation and aerogenous spreading

Cavitation (Fig. 8) with regrowth of Mtb and subsequent aerogenous spreading of Mtb are the main features of chronic active pulmonary tuberculosis.

Aerogenous spreading lesions were herein divided into 3 types in the normal immune state. 1) A productive reaction/change is characterized by mild exudation (mainly inflammatory cells) during the exudative stage (Fig. 9), with subsequent epithelioid cell granuloma formation with or without small central caseous necrosis during the proliferative stage. This lesion is well formed, with clearly demarcated borders, and either single or confluent up to one lobule in diameter during the proliferative stage. This lesion finally disappears or hyalinizes. 2) An association with fibrinous exudation is characterized by the exudation of fibrin and inflammatory cells with or without small central necrosis during the exudative stage. Unabsorbed fibrins result in distinct fibrosis around single or multiple epithelioid cell granulomas with or without small caseous necrosis. 3) Caseous pneumonia is characterized by massive exudation and caseous necrosis during the exudative stage (exudative reaction) (Fig. 10). For each type of aerogenous spread, the

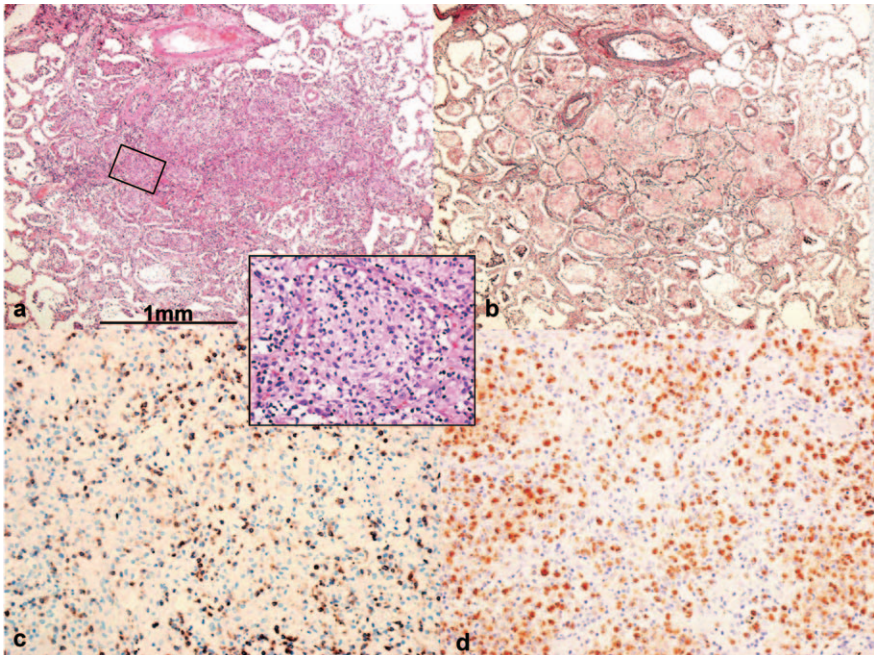

Fig. 9 Productive reaction/change in the exudative stage.
a. One, acinar-sized, exudative-stage, aerogenously spreading lesion with a productive reaction. Bar 1 mm. HE, ×40.
b. The lung structure is well preserved (the same with a) with the absence of reticulin fiber formation in the alveolar lumina, which indicates the exudative stage. Reticulin staining, ×40.
c. Moderate numbers of $CD4^+$ cells in the alveolar walls and lumina. Immunostaining using an antibody to CD4, ×200.
d. Alveolar lumina were filled with Mϕs. Immunostaining using an antibody to CD68, ×200. Insert. Alveolar lumina were filled with Mϕs showing structural organization resembling an early-stage epithelioid cell granuloma. HE, ×200.

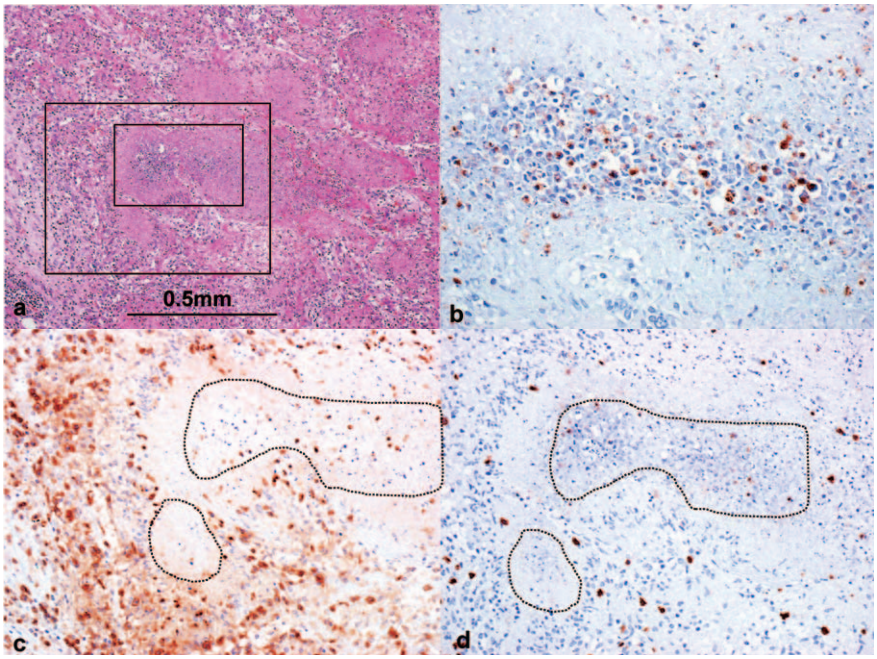

Fig. 10 Histology of a caseous pneumonic lesion.
a. One, lobular-sized, exudative- to proliferative-stage, caseous pneumonic lesion with negative Mtb by ZN. HE, ×100.
b. The center of necrosis is infiltrated by neutrophils (inner box of a). Immunostaining using an antibody to neutrophilic elastase. ×400.
c. Exudation of $CD4^+$ cells to the lesion, but devoid of a necrotic area (dotted circle) (outer box of a). Immunostaining using an antibody to CD4, ×200.
d. Weak exudation of $CD8^+$ cells to the lesion, but devoid of a necrotic area (dotted circle) (outer box of a). Immunostaining using an antibody to CD8, ×200.

exudation of $CD4^+$ and $CD8^+$ cells is noted in non-necrotic areas at the exudative stage, while the infiltration of neutrophils is observed only in necrotic areas (Fig. 10).

d. Tuberculous pneumonia or caseous pneumonia

Tuberculous pneumonia or caseous pneumonia occurs when one of the thoracic lymph node lesions erodes into a bronchus, or when a primary infection develops cavitation or when there is chronic cavitary pulmonary tuberculosis and subsequent massive aerogenous spreading. Rarely caseous pneumonia can occur from an unknown original portion. The cause of caseous pneumonia was previously attributed to be DTH[16)17)], which is seen in young immunocompetent person[2)3)]. It is reasonable to consider DTH as for reason of caseous pneumonia when a massive amount of necrotic material and significant numbers of Mtbs spread through a perforated bronchus or cavity. However, caseous pneumonia has been reported in the elderly patients and patients with underlying pulmonary or systemic diseases[46)]. Fig. 11 shows the pathological features of a middle-aged patient with chronic obstructive pulmonary disease who presented with lobar caseous pneumonia of the unknown original portion with the infiltration of large numbers of necrotic Mϕs; the infiltration of $CD4^+$ cells, $CD8^+$ cells, and neutrophils; and the proliferation of moderate numbers of Mtbs. The various mechanisms involved in the development of caseous pneumonias remain to be clarified.

e. Miliary tuberculosis of the chronic onset

This type of miliary tuberculosis is a result of destruction of the vasculature of each organ affected by tuberculosis (lung, bone, and others), with subsequent entrance of Mtb into the blood stream[3)]. Approximately 40% of miliary nodules are located at the peripheral acinar area, and exudation of Mtb from postcapillary venules has been speculated[47)].

The natural course of this type of miliary tuberculosis varies, mainly based on a patient's immunological state and the degree of vascular destruction. A mild to moderate degree of dissemination is more likely to be upper lobe-dominant with formation of well marginated miliary nodules (Fig. 12a) composed of well-formed epithelioid cell granulomas with or without small central caseous necrosis. Rarely, natural cure (Fig. 12bc) has been seen in immunocompetent patients. "Typhobacillosis"[3)48)] is occasionally seen in immunocompromised patients. It characteristically shows a rapidly overwhelming course, with abscess-like lesions without epithelioid cell layer formation of various sizes (Fig. 13). "Nonreactive tuberculosis" has also been reported. It follows various clinical courses and partly overlaps with "typhobacillosis"[49)]. The complication of acute respiratory distress syndrome on miliary tuberculosis results in a poorer prognosis[50)].

f. Pathological findings in immunocompromised patients, particularly acquired immunodeficiency syndrome (AIDS) patients

In prevalent countries, HIV and Mtb coinfections have serious impacts[51)~54)].

Clinically, patients show severe and unusual manifestations; predominantly extrapulmonary and disseminated lesions. Chest radiography shows lower lobes predominance, diffuse infiltration, intrathoracic adenopathy, and a rather low incidence of cavity formation[55)~58)].

Pathological features generally depend on the degree of immunodeficiency, particularly regarding the number of peripheral blood $CD4^+$ cells and levels of TNF-α in the lesion[59)60)]. The following characteristic histological features

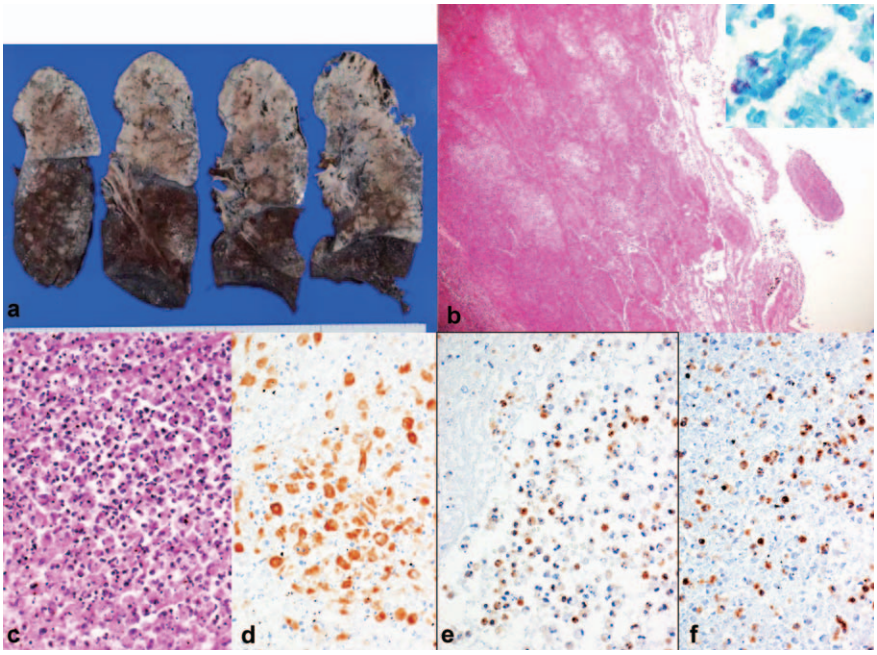

Fig. 11 Pathological features of caseous pneumonia.
a. Macroscopic features of caseous pneumonia involving the entire left upper lobe and the portion of the left lower lobe.
b. Caseous pneumonia in the emphysematous lung. HE, ×40. Insert. Mtb by ZN, ×800.
c. Caseous pneumonia is composed of complete necrosis (homogenously necrotic cells and others), degenerated cells with occasional nuclear debris, and fibrin. HE, ×200.
d. The presence of Mϕs varies area to area. Immunostaining using an antibody to CD68, ×200.
e. Neutrophils are seen mainly in degenerated area. Immunostaining using an antibody to neutrophilic antibody, ×200.
f. $CD3^+$ cells were noted in both areas but degree of infiltration varies. Immunostaining using an antibody to CD3, ×200 (A case from the Kawaguchi Municipal Medical Center).

are present: poorly organized or absent epithelioid cell granulomas, non-reactive lesions, abundant necrosis (not typical for caseous necrosis) with neutrophils and/or nuclear debris, and large numbers of Mtbs[52)58)~61)]. Fig. 14 shows a cavity wall composed of Mϕs (14a), with numerous Mtbs (14b). This finding can be called a type of nonreactive lesion with cavity formation, and is accounted for by the nearly complete loss of cellular immunity. Fig. 15ab shows coagulation necrosis of inflammatory cells and the infiltration of neutrophils. Fig. 15c shows a nodular lesion composed of spindle-shaped Mϕs (confirmed by immunostainings) without epithelioid cell transformation and intracellular acid-fast bacilli by Ziehl-Neelsen staining (insert).

The discrepancy between frequent pathological necrosis and insignificant radiological cavitation remains to be clarified.

5. Summary

Host-parasite relationships are complicated. Following primary infection, Mtb can proliferate in the Mϕs without strong resistance and then spread through thoracic lymph nodes. After the establishment of cellular immunity, the primary complex undergoes caseous necrosis with subsequent epithelioid cell layer formation and the proliferation of Mtb is prevented (state of containment). Only a small number of individuals show early tuberculosis. Chronic pulmonary

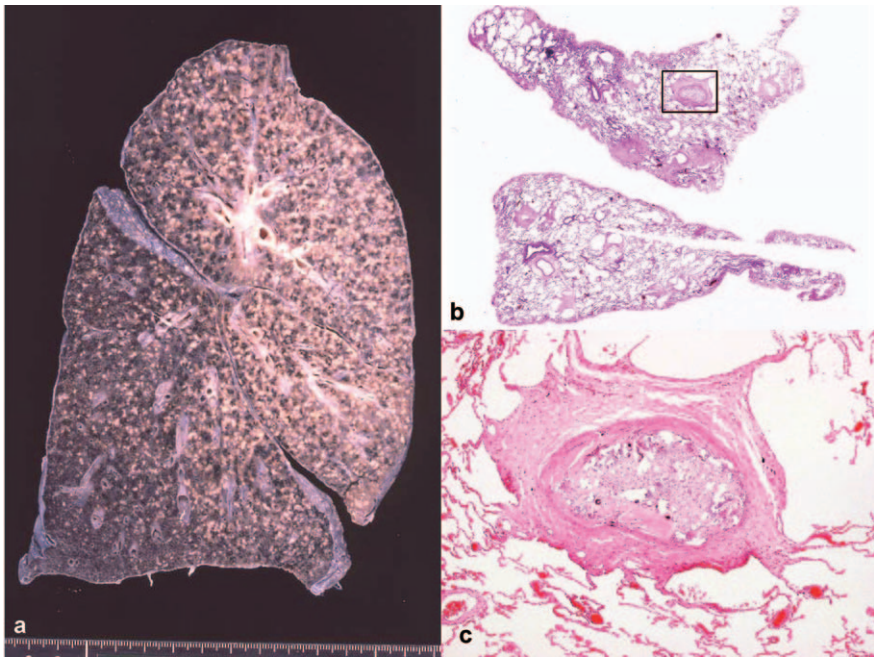

Fig. 12 Pathology of miliary tuberculosis (autopsy case and naturally cured, biopsy case).
a. Macroscopic features of miliary tuberculosis with numerous, small, yellowish nodules in the right lung.
b. Healed miliary tuberculosis with a few acellular fibrotic nodules (surgical lung biopsy). HE, Panoramic view.
c. One calcified necrotic lesion with fibrous encapsulation (box of b). HE, ×40.

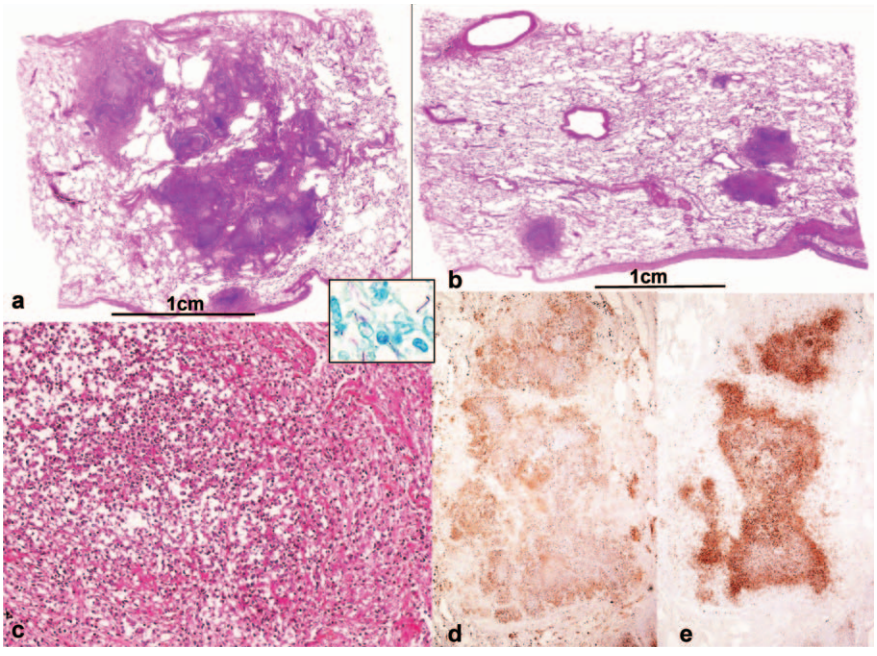

Fig. 13 The autopsy case of miliary tuberculosis (typhobacillosis).
a & b. Disseminated nodules of various sized (including up to a 1-cm sized), conglomerated nodules in the lung. Bar 1 cm. HE, Panoramic view.
c. Each lesion is mainly composed of necrotic tissue with many degenerated cells without a surrounding epithelioid cell layer. HE, ×150. Insert. Mtb by ZN, ×1600.
d. Mϕs were observed mainly around the necrotic area.
e. Numerous neutrophils were observed in the necrotic area.
d & e. Immunostaining using an antibody to CD68 and neutrophilic elastase, ×20 (a case from Tobu Chiiki Hospital).

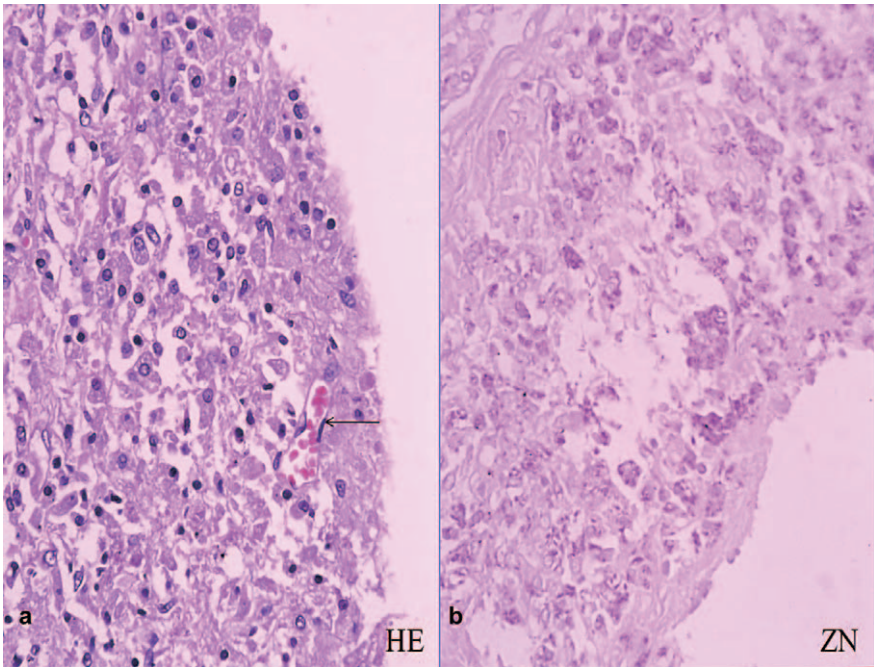

Fig. 14 Cavity in an acquired immunodeficiency syndrome (AIDS) patient.
a. The wall of the cavity is mainly composed of Mϕs without fibrosis, but a small blood vessel (arrow) is seen in the cavity wall. HE, ×400.
b. Proliferated Mtbs in Mϕs. HE+ZN, ×400 (a case from Dr. TV Colby).

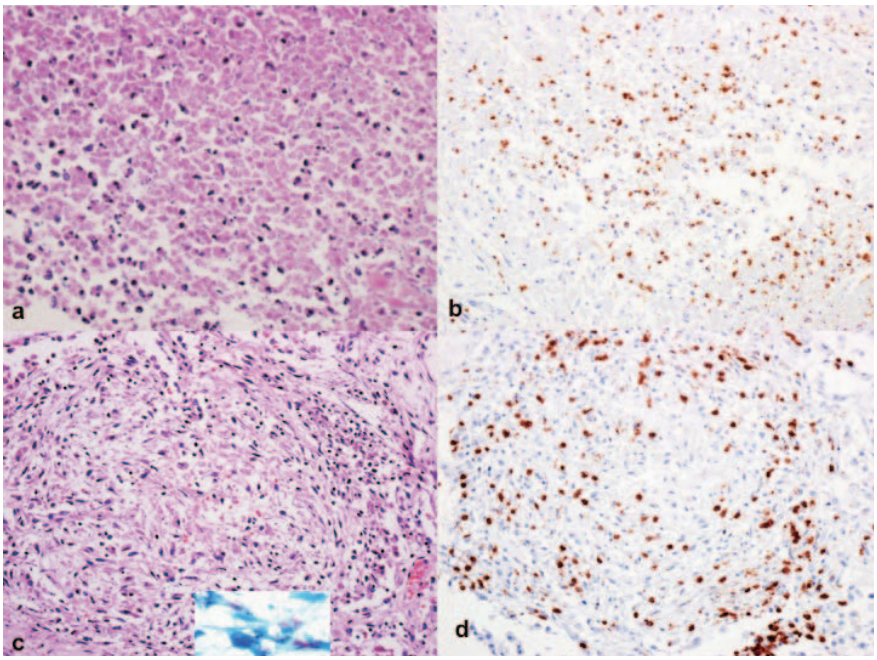

Fig. 15 Two types of tuberculous lesions in an AIDS case.
a. Coagulation necrosis composed of degenerated and dead inflammatory cells. HE, ×400.
b. Degenerated cells with condensed nuclei were mainly neutrophils in this area. Immunostaining using an antibody to neutrophilic elastase, ×200.
c. An approximately 1-mm sized, nodular lesion composed of spindle cells without epithelioid cell transformation (proved to be Mϕs by immunostaining). HE, ×200. Insert. Mtb by ZN in the lesion. ×800.
d. Infiltration of $CD8^+$ cells. Immunostaining using an antibody to CD8, ×200 (A case from NHO Tokyo National Hospital).

tuberculosis seems, and I believe, to be reactivation of an old lesion mainly in the apex with subsequent cavity formation. New, aerogenously spreading lesions are well-formed epithelioid cell granulomas with/without small, central caseous necrosis when Mtb numbers are limited. When more than moderate amount of necrotic material and Mtbs are aspirated, caseous pneumonic lesions are formed. Epithelioid cell granuloma formation is blocked in hosts with severe immunodeficiency. Both caseous necrosis (E necrosis) and epithelioid cell granulomas seem to be superb defense mechanisms, whereas P necrosis and lysis do not seem to be defense mechanisms and are a major cause of reactivation.

Apoptosis is now considered to be the main cause of cell death and tissue necrosis in tuberculosis. However, I could not confirm whether degenerated cells with fragmented nuclei or completely necrotic cells are actually apoptotic cells.

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— 第92回総会教育講演 —

肺結核症の病理

河端　美則

要旨：結核症，特に肺結核症は人類にとり深刻な疾患である。結核症の病理は1950年代にほぼ確立されている。しかしながら多くの課題が未解決のままである。それらは各種の乾酪壊死（初感染巣，乾酪性肺炎，免疫不全状態での壊死，滲出性反応後の壊死，増殖性反応後の壊死，その他）の原因と機序，軟化融解の原因と機序，それに加え内因性再燃の部位，機序と原因などである。今回の講演では，初感染の経過，初感染発病，慢性肺結核症の発症機序として筆者が確信している初感染巣あるいはその散布巣からの内因性再燃説と他の諸先生の再燃説による空洞化への進展過程の解説，空洞からの散布病変の諸相，散布病変の極型としての乾酪性肺炎，空洞からの散布と違うが慢性粟粒結核症，ならびに免疫不全状態での肺病変を解説した。講演全体を貫き宿主寄生体相関の多彩さを強調した。その多彩さは主に細胞性免疫の程度と関連しており，具体的にどのような形態を示すかを示した。なお菌の性状と遺伝子発現などは宿主寄生体相関において大切だが，筆者の能力の問題もありそれは今回の講演の対象外とした。

キーワーズ：結核症，病理，病因，再燃，免疫組織化学