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Comparison of the Histopathological Observation in Pulmonary Tuberculosis between Elk (*Cervus canadensis*) Naturally Infected with *Mycobacterium bovis* and Human with *Mycobacterium tuberculosis*

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Abstract

Introduction: Bovine tuberculosis (TB) is an infectious disease caused by *Mycobacterium bovis* (*M. bovis*) and human TB by *Mycobacterium tuberculosis* (*M. tuberculosis*). The difference in lung pathology between bovine and human TB is not fully understood. In this study, the histopathological lung observations of elk naturally infected with *M. bovis* were examined and compared with those of humans with pulmonary TB infected with *M. tuberculosis*. **Materials and Methods:** Tuberculous lung lesions from elks and human patients were processed for the paraffin sections. The prepared sections were stained with hematoxylin and eosin (H & E) or Ziehl-Neelsen or Masson's trichrome staining. The histopathological findings were compared between elk and human. **Results and Discussion:** Upon gross examination, the lesions in the elk lung demonstrated chronic granulomatous caseous necrotizing tuberculous pneumonia with numerous caseous granulomas and some cavities, similar to those observed in the human TB lung. Microscopic examination revealed a general granulomatous inflammatory process characterized by the accumulation of alveolar macrophages and bronchial obstruction by granulomatous tissues, observed in both elk and humans. However, two differences were noted between *M. bovis* and *M. tuberculosis* infections in the morphological patterns of granulomas and cavities. First, while elk lung lesions manifested only primary-type granulomas, human pulmonary lesions contained both primary-type and post-primary granulomas, showing traces of alveolar structures in the central caseous region. Second, nearly all cavities observed in elk lung lesions showed an eroded connection to adjacent bronchioles, whereas no erosion into bronchioles was found in any human cavity. **Conclusion:** The reasons for the differences in lung pathology between *M. bovis* and *M. tuberculosis* infections are discussed in detail.

Keywords

Pulmonary Tuberculosis, Elk, *Mycobacterium bovis*, *Mycobacterium tuberculosis*, Histopathology

1. Introduction

M. bovis and *M. tuberculosis* are the primary cause of bovine and human pulmonary TB, respectively [1]. *M. bovis* has a wide range of hosts and infects many domestic and wild mammals [1]-[3]. The general pathological features of bovine TB in cattle are similar to those of human TB and are shared with most other affected domestic species [4] [5]. Tuberculosis lesions in cattle are initiated by infectious bacilli in the lungs and associated lymph nodes. Gross lesions appear as firm nodules, white to yellowish in color. Microscopic lesions demonstrate that the macrophages and the epithelioid cells as the activated macrophages form the center of tubercles, which is surrounded by a layer of lymphocytes and monocytes. The tubercle develops peripheral fibroplasia and central caseous necrosis. Most pulmonary lesions of *M. bovis*-infected farmed elk resemble TB in cattle [4]-[6].

In Korea, approximately 30,000 deer, including elks, are bred on 1500 small farms [7]. Deer are usually not raised for meat production but for the use of their antlers in oriental medicine. Unlike dairy cattle, the tuberculin skin test (TST) is not mandatory for diagnosing TB in farmed deer in Korea. Consequently, there is limited data on TB in deer. TB in elk was first reported in Korea in 2002 [8]. Recently, Kang *et al.* randomly investigated the incidence of TB in elk using an antibody-based immunoassay targeting the major antigens of *M. bovis*, MPB70, and MPB83 across the country, finding that approximately 20% of the tested animals were seropositive [9]. Today, due to its economic and public health significance, TB is emerging as an important infectious disease problem in the elk industry in Korea [9].

The formation of lung granulomas has been considered the hallmark of pulmonary TB, and cavity formation has traditionally been thought to occur when caseous granulomas erode into adjacent airways [10]-[13]. This theory was supported by animal studies. In a rabbit model, infection with *M. bovis* leads to the development of caseating granulomas, which form cavities through erosion into adjacent bronchi [11] [14]. This concept has been widely accepted as the standard paradigm of TB pathogenesis and has been believed by almost all scientists in TB research. However, a research group led by Hunter recently argued that postprimary TB caused by *M. tuberculosis* begins as an exudative bronchopneumonia process rather than from caseating granulomas [15]-[18]. According to their findings, the disease progresses to caseous pneumonia, followed by liquefaction, fragmentation, and cavity formation due to coughing. Additionally, historical literature from the pre-antibiotic era on human postprimary TB supports their assertion [19].

Cavity formation renders immune accessible lung tissue into immune-sheltered surfaces in direct connection with the external environment [12]. Therefore, the process of cavity formation could be targeted for vaccine development to prevent disease transmission or for new drug development.

In this manuscript, we first describe the histopathological features of lung lesions caused by naturally occurring *M. bovis* infection in elk and compare them with those observed in patients with human pulmonary TB caused by *M. tuberculosis*. We provide histopathological evidence that elk and human TB develop granulomas and cavities through different mechanisms, challenging the long-held belief that cavity formation results solely from caseating granulomas. Our findings suggest that this process is specific to *M. bovis* infection and does not apply to human pulmonary TB caused by *M. tuberculosis*. These insights may contribute to the development of new vaccines or drugs for both bovine and human pulmonary TB.

2. Methods

2.1. TST for the Elks

From April 2007 to September 2007, 62 elk from four farms in Korea were tested using the TST, which was performed according to U.S. Department of Agriculture guidelines using the comparative cervical tuberculin test [9]. In brief, 0.1 mL of bovine purified protein derivative and 0.1 mL of avian purified protein derivative were injected intradermally into the cervical region of the animals, approximately 12.5 cm apart. The skin thicknesses at the injection sites were measured 72 h later. The results were interpreted as positive when the skin thickness at the bovine injection site was more than 4 mm greater than that at the avian injection site, as inconclusive when the skin thickness at the bovine injection site was 1 to 4 mm greater than the avian reaction, and as negative when the skin thickness at the bovine injection site was less than or equal to the skin reaction at the avian injection site.

2.2. Necropsy and Histopathology

Ten TST-positive animals were sacrificed, and a postmortem examination was conducted. Lesion samples from the lungs were collected, fixed in 10% neutral-buffered formalin, routinely processed, and embedded in paraffin. The paraffin sections were stained with hematoxylin and eosin (H & E) for histopathological examination. Ziehl-Neelsen and Masson's trichrome staining was performed to identify mycobacterial bacilli and fibrotic regions, respectively.

2.3. Identification of *M. bovis* in the Lesions by Multiplex PCR

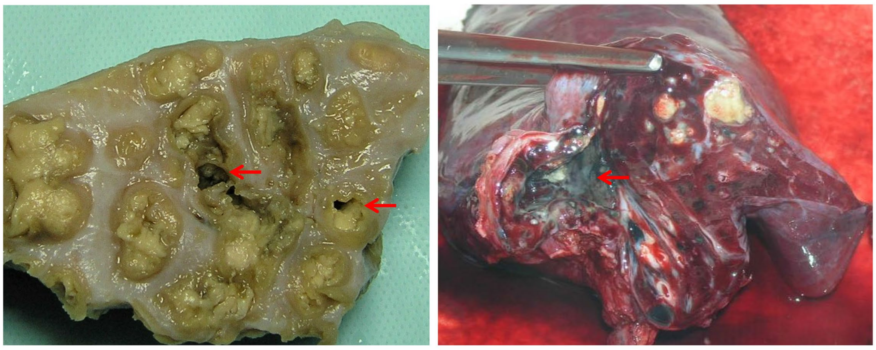
Caseous specimens from the elk lungs were collected in grinder tubes and homogenized. After centrifugation, the precipitates were collected in tubes. DNA was extracted using the QIAamp DNA FFPE Tissue Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. Multiplex PCR was performed as described elsewhere [20]. The primers used in the study included a common forward primer, CSB1 (5'-TTCCGAATCCCTTGTGA-3'), and two reverse primers, CSB2 (5'-GGAGAGCGCCGTTGTA-3') specific to *M. bovis* and CSB3 (5'-AGTCGCGTGGCTTCTCTTTTA-3') specific to *M. tuberculosis*. The product size amplified with primer sets CSB1 and CSB3 was 262 bp, and the PCR product generated by primer sets CSB1 and CSB2 was 168 bp. The PCR conditions included initial denaturation at 95˚C for 5 min, followed by 40 cycles of annealing at 53˚C for 30 sec, and extension at 75˚C for 5 min. Amplicons were analyzed by electrophoresis on a 1.5% agarose gel. Unique amplification products of either 168 bp (*M. bovis*-specific) or 262 bp (*M. tuberculosis*-specific) were compared with those of the respective reference species.

2.4. Human Histologic Specimens of Pulmonary TB

For human histopathological examination, lung tissue sections were obtained from the International Tuberculosis Research Center. Resected human lung tissues from patients with TB who underwent surgery were transferred from the National Masan Tuberculosis Hospital to the International Tuberculosis Research Center. All the surgical patients had multidrug-resistant or extremely drug-resistant TB. The indications for surgery included patients with persistent positive sputum despite chemotherapy and those at high risk of relapse due to a persistent cavity, even after achieving negative sputum conversion. All patients underwent a preoperative chest X-ray and high-resolution chest computed tomography, which demonstrated well-localized cavitary pulmonary TB confined to only the portion of the lung that was subsequently removed surgically. The use of these human tissues was approved by the Institutional Review Board of National Masan Tuberculosis Hospital (IRB-05-E01). Slides from 30 patients were stained with H & E for histopathological examination.

3. Results

Macroscopically, the lung specimens were consolidated, and the cut surface of the lung showed cavities and well-circumscribed granulomas in both elk (**Figure 1(a)**) and human TB (**Figure 1(b)**). The granulomas contained a creamy white caseous material. Elk lung specimens also exhibited fibrotic thickening of the interlobular septa and tuberculous nodules (**Figure 1(a)**). The cavities in both elk and human lungs had an open space at the center, and their inner surfaces contained bright white caseum with a friable consistency (**Figure 1(a)** and **Figure 1(b)**). In the case of elk specimens, to confirm the identification of the causative agent of the infection, caseous lesions were collected and processed for DNA extraction. As shown in **Figure 2**, the cause of infection in the animals was identified and confirmed as *M. bovis* using PCR.



(a) (b)

Figure 1. Resected lung specimens of active pulmonary tuberculosis in elk (a) and in human (b), naturally infected with *Mycobacterium bovis* and *Mycobacterium tuberculosis*, respectively. The lung tissues show cavities (arrows) and multiple tuberculous granulomas with central caseous necrosis.

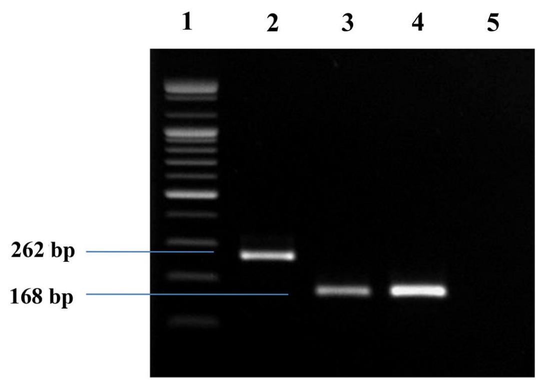
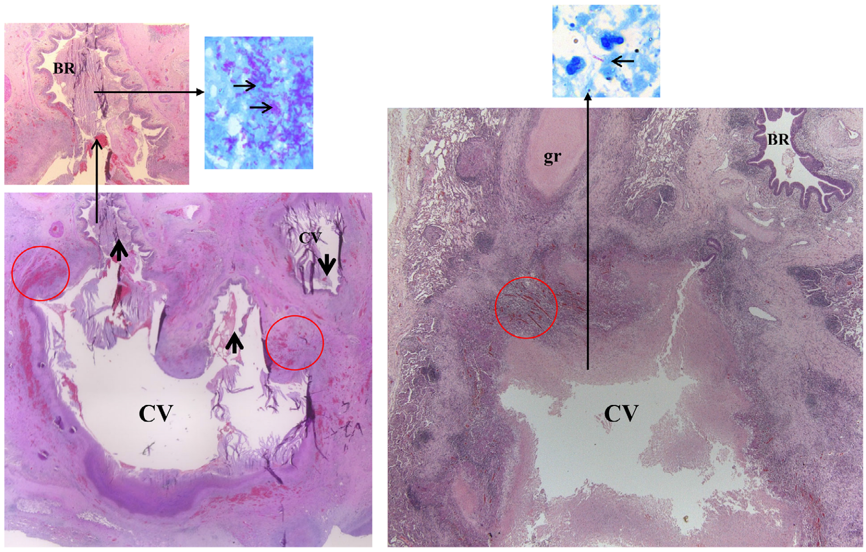


Figure 2. Confirmation of *Mycobacterium bovis* infection in elk through differential detection of *Mycobacterium bovis* and *Mycobacterium tuberculosis* by multiplex PCR. Lane 1: 100 bp ladder, Lane 2: *Mycobacterium tuberculosis* H37Rv, Lane 3: *Mycobacterium bovis*, Lane 4: lung lesion sample from elk, Lane 5: negative control.

Cavity formation is a typical feature of pulmonary TB in both animals and humans. In this study, the histopathological features of the cavities developed by *M. bovis* infection in elk were compared with those caused by *M. tuberculosis* infection in humans to investigate any differences. First, the interior surface of the cavity wall was covered with necrotic cellular debris, known as caseum (**Figure 3(a)** and **Figure 3(b)**). However, a significant difference in cavity formation was observed between elk and humans. In elk, the cavity wall ruptured and eroded into the adjacent bronchioles, leading to the discharge of infectious necrotic material into the bronchial airways (**Figure 3(a)** and **Figure 4**). By contrast, no adjacent eroded bronchioles were observed in the human cavity (Figure 3(b)). We examined about 30 human cavity sections, but no connections to the bronchioles were found. Liquefaction leading to cavity formation within the TB lesions was followed by massive mycobacterial proliferation, and numerous acid-fast bacilli were observed in the necrotic caseum of elk (Figure 3(a)). However, only a few acid-fast bacilli were found in the cavity caseum of patients with TB (Figure 3(b)).



(a) (b)

Figure 3. Comparison of the microscopic observations of tuberculous cavities (CV) between elk and human (H & E 12.5×). In elk (a), one big cavity is connected (arrow heads) into two small adjacent bronchioles (BR) and a small cavity in the upper right is also shown to be eroded into a bronchiole. Highly proliferated acid-fast bacilli (AFB) are seen in the necrotic materials in bronchiole (short arrows) (AFB stain 1000×). In a human cavity (b), no connected bronchioles to the cavity are observed. A few AFB were found in the caseum of cavity (AFB stain 1000×). A typical caseous granuloma (gr) is seen close to the cavity. Proliferation of the blood vessels was shown in the cavity wall both in elk and in human (red circles).

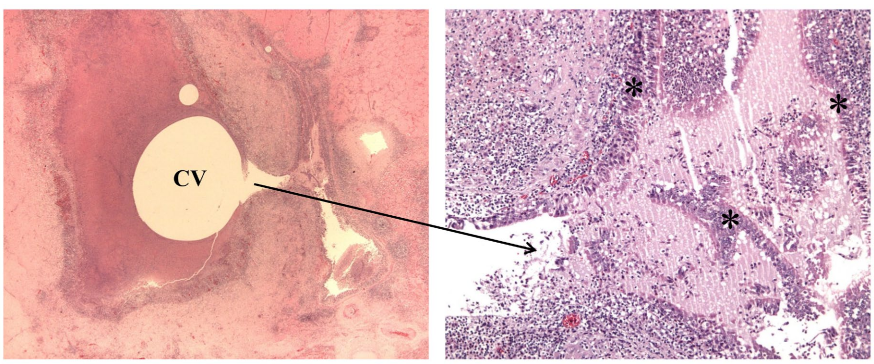


Figure 4. Microscopic feature of a cavity (CV) eroded into an adjacent bronchiole in elk (left, H & E 12.5×). Liquefied necrotic materials were drained into the bronchiole (right, H & E 100×). The bronchial epithelia are seen (*).

Typical caseous TB granulomas, composed of central caseous necrosis, a layer of cellular infiltrates (including epithelioid histiocytes and lymphocytes), and a surrounding rim of peripheral fibrosis, were observed in both elk and human lungs (**Figure 5(a)** and **Figure 5(b)**). These granulomas were confined to the fibrotic layer of the normal-appearing lung regions. The fibrotic rim of the granulomas was confirmed by trichrome staining, which detected collagen in blue (**Figure 5(c)** and **Figure 5(d)**). However, different patterns of granulomas were observed in the histopathological findings of human lung lesions. In contrast to elk granulomas, which exhibited a homogenous morphology of central caseous necrosis (**Figure 5(c)**), some human granulomas showed traces of alveolar structures within the caseous necrotic area (**Figure 5(d)**).

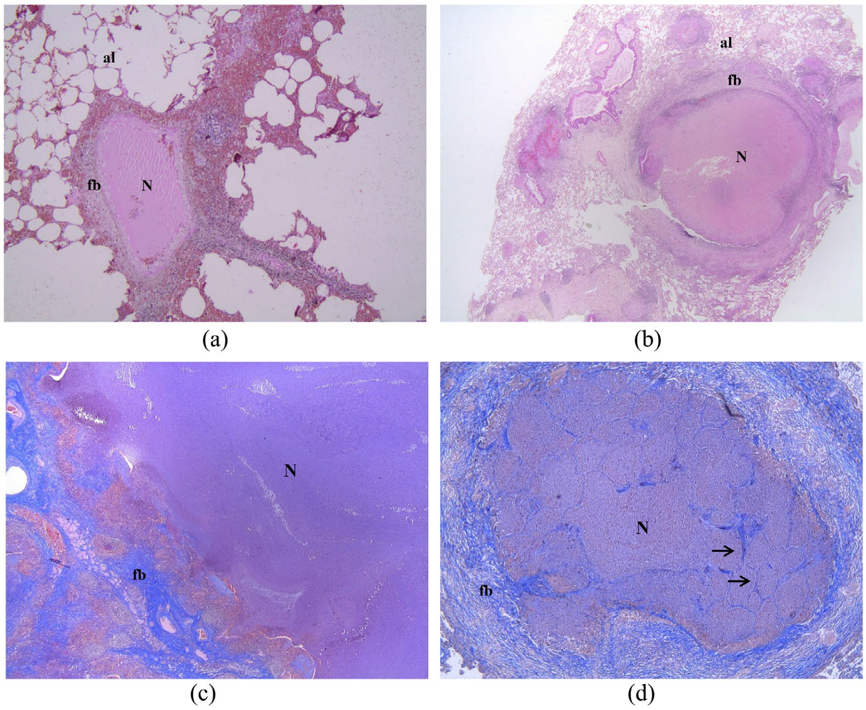


Figure 5. Comparison of the microscopic observations of tuberculous granulomas between in elk ((a) & (c)) and in human ((b) & (d)). A small and typical caseous necrotic granuloma showing the central necrosis with amorphous eosinophilic debris (N) and a layer of cellular infiltrates is surrounded by a fibrotic rim (fb) in elk (a) (H & E 40×) and in human (b) (H & E 12.5×). This well-organized granuloma is delineated from the surrounding normal lung parenchyma showing alveoli (al). The Masson's trichrome staining shows the collagenous areas of fibrosis (fb) in blue both in elk (c) and in human (d) (Magnification, 40×). Differently from the homogenous caseum of the granuloma in elk, the trace of alveolar structures (arrows) is observed in some granulomas in human.

The regions of exudative alveolar inflammation showed thickened alveolar walls with vasodilation, severe edema, fibrinous exudate, ruptured interalveolar septa, and an influx of chronic inflammatory cells, including numerous alveolar macrophages, in the alveolar spaces of both elk (**Figure 6(a)**) and humans (**Figure 6(b)**). Another characteristic feature of pulmonary TB is bronchial obstruction.

In elk, endobronchial TB with bronchiole obstruction by granulomatous tissue was observed, and the surrounding area showed granulomatous tissue composed of epithelioid histiocytes mixed with multinucleated giant cells and lymphocytes (**Figure 6(c)**). Similar findings were observed in human TB lesions (**Figure 6(d)**).

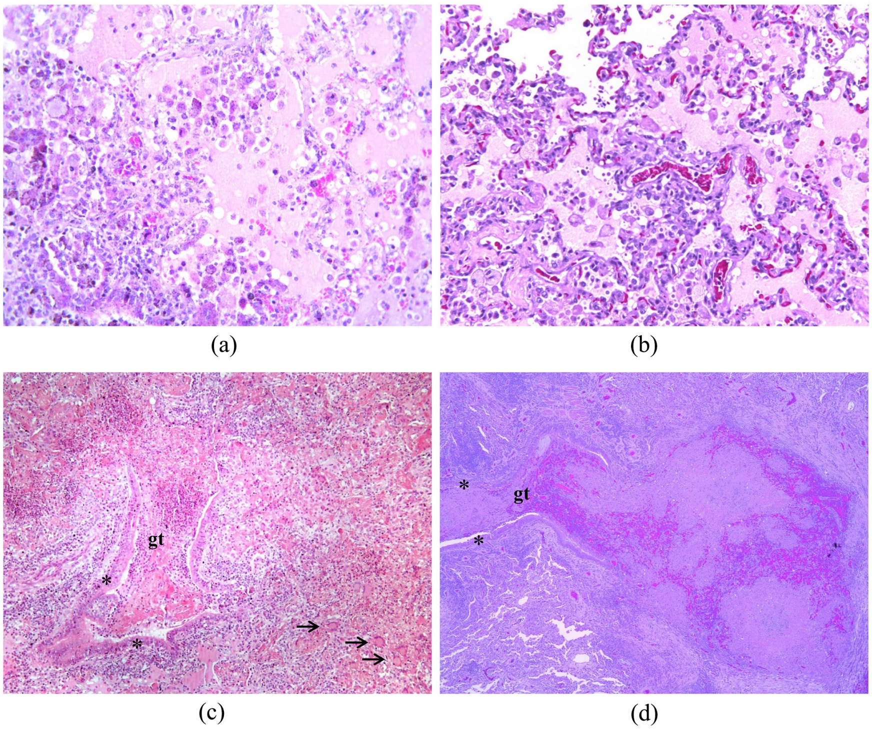


Figure 6. Histologic observations of tuberculous pneumonia showing the stage of exudative alveolar inflammation and endobronchial tuberculosis in elk ((a) & (c)) and in human ((b) & (d)). The thickened alveolar walls with vasodilation, severe edema, fibrinous exudate, ruptured interalveolar septa, and the influx of chronic inflammatory cells, including numerous alveolar macrophages in the alveolar spaces are seen in elk (a) and in human (b) (H & E 200×). Endobronchial tuberculosis with the obstruction of a bronchiole by granulomatous tissue (gt) is observed in elk (c) (H & E 100×) and in human (d) (H & E 40×). Note the bronchial epithelia (*). The surrounding area of the obstructed bronchiole shows the consolidated granulomatous tissue composed of epithelioid histiocytes mixed with multinucleated giant cells (arrows) and lymphoid cells.

4. Discussion

Bovine TB caused by infection with *M. bovis* affects not only the lungs but also the draining lymph nodes and many other organs, whereas the lesions of human pulmonary TB caused by *M. tuberculosis* infection, also known as post-primary or adult TB, are typically restricted to the lungs [4] [5] [15]. Therefore, in spreading infectious bacilli to new hosts, *M. tuberculosis* is transmitted only through aerosols, whereas cattle infected with *M. bovis* shed organisms in aerosols, respiratory secretions, feces, urine, and milk. For this reason, only the lung lesions in elk TB were presented and compared with those in human pulmonary TB in this study to investigate whether there are any histopathological differences between

M. bovis and *M. tuberculosis* infections.

M. bovis-infected lung lesions in elk manifested all stages of active TB development. During the early and exudative stages, vasodilation of the alveolar capillaries and alveoli filled with fibrinous exudate and alveolar macrophages were observed in elk. Similar findings have also been observed in human lung lesions. Bronchial obstruction by endobronchial TB is a specific and consistent finding in human pulmonary TB. In the present study, the lung lesions in elk also showed bronchial obstruction with chronic granulomatous tissue, which is consistent with the findings in human lungs. During the productive stage, the typical and well-demarcated caseous granulomas were easily found in both elk and humans. However, another type of granuloma was observed in *M. tuberculosis*-infected human lungs that was not found in elk. Elk lungs had only primary granuloma, which shows homogenous and amorphous caseous necrosis at the center of the granuloma. By contrast, in addition to primary-type granulomas, human pulmonary TB also manifests post-primary-type granulomas. Post-primary granulomas are well described elsewhere [15]-[19]. Canetti (1955) detailed the formation of granulomas in human pulmonary TB, also known as post-primary TB, based on his experiences with 1500 autopsies of tuberculous individuals [19]. Post-primary granulomas begin from caseous pneumonia, not from the granulomatous process. During caseation, the alveolar cells and leukocytes lose their contours and nuclei. The alveolar septa rapidly lose their capillaries, but their elastic fibers remain because of their great resistance to the caseation process. In this scenario, pneumonia-induced inflammation leads to the formation of post-primary granulomas. In contrast to human TB, *M. bovis* does not produce post-primary TB in any species [15], but only produces primary TB, which can develop into caseating primary-type granulomas, as shown in **Figure 5(a)** and **Figure 5(c)**. Histologically, the center of a caseating granuloma in primary TB is amorphous, whereas that of post-primary TB contains remnants of the alveolar walls, as shown in **Figure 5(d)** [17].

Another difference observed between elk and human TB pathologies in this study was the different histological patterns of the cavities. It is widely accepted that cavities develop by erosion of granulomas into the bronchiole, and the necrotic material is discharged into the airways, resulting in the spread and transmission of infection [14] [21]. In fact, almost all the cavities found in elk lesions in this study showed a morphology consistent with this description and demonstrated a connection with the adjacent airways by erosion. Necrotic material containing numerous bacilli was observed being discharged from the cavity into the adjacent bronchi or bronchioles in elk. The process of erosion from the caseous granuloma is well described elsewhere [5] [13] [22]. First, the caseous material of the granulomas softens, and liquefaction occurs. The exact cause of liquefaction is poorly understood, but the pathophysiological sequence is consistent with the present knowledge. The macrophages accumulated by the antigens of the tubercle bacilli become highly activated, and they release high levels of proteolytic and hydrolytic enzymes, such as proteinases, nucleases, and lipases. These enzymes play major roles in the liquefaction of solid caseous material. The wall of a nearby bronchus or bronchiole is eroded by the tissue damaging delayed-type hypersensitivity reaction to the accumulated antigens of the tubercle bacilli. The bronchus or bronchiole ruptures, and the liquefied caseum is discharged into the airway.

By contrast, no eroded connections from the cavities to the bronchi were observed in human TB lungs. More than 30 cavities were examined in human lung tissues, but none showed such connections. On the other hand, fewer tuberculous bacteria were found in human lesions compared to those in elk. The human lung specimens were taken during surgery, not from autopsies as in elk. All surgical patients with TB are typically treated with chemotherapy for a couple of months before surgery to reduce the bacterial burden, which helps minimize post-operative complications. Therefore, it is assumed that the drug treatment process resulted in a decreased number of AFB in the lesions.

Unlike *M. bovis*-infected animals, which develop only primary TB, humans infected with *M. tuberculosis* manifest two stages of the disease process: primary and post-primary TB [15]-[18]. Post-primary TB always follows primary TB and develops after host immunity has been established, either by the reactivation of latent organisms or by new infection from the environment. Cavity formation in human TB begins from caseous pneumonia, not from granulomas, and the cavities arise from the dissolution of caseous pneumonia, which is then coughed out [15]-[19]. Granuloma formation in human post-primary TB occurs when necrotic caseation is retained in the lung without liquefaction, inducing inflammation that eventually becomes surrounded by fibrosis [19]. Therefore, it is true that primary granuloma is the key lesion in *M. bovis*-infected bovine TB for developing cavities by erosion into the adjacent airways, but human pulmonary TB manifests a completely different mechanism of cavity development by coughing up the liquefied caseated material into the airway [15]-[18]. The formation of cavities by erosion of caseating granulomas accurately describes those formed by *M. bovis*, [14] but not by *M. tuberculosis*. The strong evidence observed in the present study regarding the differences in differentiating granuloma types between elk and humans supports this concept.

Nonetheless, the differences in histopathology may not have any clinical significance, as the mode of transmission of infection is the same in both animals and humans. Typically, infectious mycobacterial bacilli are released into the airways and transmitted to other hosts. However, understanding the different pathological mechanisms involved in cavity formation would be highly beneficial in establishing a foundation for vaccines and new drug research aimed at preventing infection transmission [23]. To bridge the gap in knowledge regarding human postprimary TB, further studies are needed. However, human tissue samples with postprimary TB are rarely available, and no recognized animal models exist for human pulmonary TB. Therefore, developing appropriate animal models for postprimary TB is essential for advancing future research.

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Contribution of the Authors

Study design: BYJ, SYE; Laboratory techniques: MSH, SSK, SKL; Data analysis: SNC, SYE; Review & editing: BYJ, SYE.

Conflicts of Interest

The authors declare no conflicts of interest.

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