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Clinicopathological Profile of Tuberculosis and Non-Tuberculosis Chronic Granulomatous Lymphadenitis at the Department of Anatomic Pathology, Faculty of Medicine, University of Indonesia/Dr. Cipto Mangunkusumo Hospital from 2018 to 2022

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ABSTRACT

Background
Chronic granulomatous lymphadenitis (CGL) is an inflammatory condition associated with lymphoproliferative lesions, infections, and autoimmune diseases. One of the etiologies of CGL is *Mycobacterium tuberculosis* (MTB). According to WHO data in 2020, Indonesia still ranks third globally for TB cases. To ensure appropriate patients' treatment, there is a need to accurately diagnose TB lymphadenitis through clinicopathological. Therefore, this research aimed to determine the clinicopathological features that differentiate TB lymphadenitis from other types.

Method
This research was a retrospective analytical review and data were collected from the Department of Anatomic Pathology archives, Faculty of Medicine, University of Indonesia/Dr. Cipto Mangunkusumo Hospital for 5 years, from 2018 to 2022. Clinical data were obtained from electronic medical records. The histopathological assessment involved evaluating the presence of polymorphonuclear cells (PMN), giant cells, and central necrosis in CGL.

Result
A total of 156 CGL cases were identified, with 63.8% of TB lymphadenitis patients being female and the highest age group was <45 years old. No significant association was found between age, a history of autoimmune diseases, malignancy, and TB lymphadenitis. The most commonly involved lymph node location was in the neck area, with a proportion of 62.2%. There was a significant association between lymph node location and the occurrence of TB lymphadenitis ($p<0.003$). Other variables assessed included the presence of PNM cells (81.7%), giant cells (94%), and central necrosis (88.8%), with p-values <0.000 for each variable. The results showed a significant association between PMN cells, giant cells, and central necrosis with TB lymphadenitis.

Conclusion
The characteristics of the female gender, lymph node location, presence of PMN cells, central necrosis, and giant cells could be considered as features to assess for diagnosing CGL caused by MTB.

Keywords: Chronic granulomatous lymphadenitis, TB lymphadenitis, NTM lymphadenitis, KFD, CSD, toxoplasma lymphadenitis

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INTRODUCTION

Chronic granulomatous lymphadenitis (CGL) is an inflammation associated with lymphoproliferative lesions, infections, and autoimmune conditions.[1-3] CGL can be classified based on its etiology, which includes infectious and non-infectious. Infectious CGL can be further divided into suppurative caused by tularemia, cat-scratch disease, and non-suppurative caused by *Mycobacterium tuberculosis* (MTB), atypical mycobacteria, toxoplasma, and fungal infections.[4,5]

According to the World Health Organization (WHO) data in 2022, Indonesia still ranks third in the world for new tuberculosis (TB) cases.[7] In 2022, TB incidence reached 969.000, with 8% being extrapulmonary TB, including TB lymphadenitis, with an incidence rate of 354 /100.000 population. The number of deaths caused by TB reached 150.000 cases every years.[6] The diagnosis of extrapulmonary TB is based on clinical, bacteriological, and histopathological examinations. This shows that the recognition of the morphological features of TB lymphadenitis is an important modality in diagnosing TB accurately for appropriate patients management.[8]

Another common cause of CGL is Non-Tuberculosis Mycobacteria (NTM), with *Mycobacterium atypical* being one of the causative agents. In the United States, the incidence of NTM is 0.1-2 per 100.000 population, however, there is no available data on its prevalence in Indonesia.[9] Cat-scratch disease (CSD) is an inflammatory necrotic disease caused by *Bartonella henselae,* with an incidence rate of approximately 4.7 per 100.000 population in USA. CSD mainly affects younger patients, the highest incidence in the 5-9 year age group.[10]

Toxoplasma lymphadenitis is caused by *Toxoplasma gondii*. According to the Centers for Disease Control and Prevention (CDC) in 2018, an estimated 11% of the US population aged 6 years old and older were infected with Toxoplasma.[11] Generally, toxoplasma lymphadenitis can be diagnosed through histopathological examination and confirmed through serological testing.[1] Kikuchi-Fujimoto disease (KFD) is characterized by subacute necrotizing lymphadenopathy. This disease often occurs in young Asian individuals, under 30 years old,[12] with a higher incidence in females compared to males[9] and is generally a self-limiting disease.[12]

Histopathological examination of the lymph nodes is an important modality for determining the etiology and establishing the diagnosis. Correlation with clinical findings, serologic, radiological, and other supporting examinations is also expected to reach a specific diagnosis.

This retrospective research aimed to establish a definitive diagnosis and better understand the clinicopathological profile of TB and non-TB CGL in the Department of Anatomic Pathology, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo Hospital (FKUI/RSCM) in 2018-2022.

METHODS

This analytical retrospective research used samples from the archives of the Department of Anatomic Pathology, FKUI/RSCM, collected from 2018 to 2022. The inclusion criteria used were all tissues originating from lymph nodes, characterized by tissues lined by connective tissue stroma, and diagnoses with Lymphadenopathy, TB lymphadenitis, CSD, Toxoplasma lymphadenitis, or KFD. The exclusion criteria were core biopsy or fragmented tissue specimens without clear stroma and cases with unavailable, suboptimal, or non-representative slides. The sampling technique was consecutive, selecting all samples that met the inclusion and exclusion criteria.

This research recorded clinical data, including age, gender, history of autoimmune disease, history of malignancy, and location of lymph nodes. Histopathological data were obtained through morphological features from hematoxylin-eosin-stained slides. There were no histology criteria to clearly diagnose TB and non-TB. In this study, it is hoped that morphological feature can help to support the diagnosis. There were variables assessed included central necrosis, the presence of PMN cells, and giant cells.

A total of 156 cases met the inclusion and exclusion criteria, and the data obtained were analyzed using statistical analysis with SPSS version 25.0. Proportion comparison tests were performed using the Chi-square test, and when the Chi-square test assumptions were not met, Fisher exact test was used. The prevalence ratio was also determined. The results were considered statistically significant when the p-value was <0.05.

RESULT

This research found 180 CGL cases in the archival data from the Department of Anatomic Pathology, FKUI/RSCM, from January 2018 to December 2022. A total of 12

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samples were not available in the archives, 6 samples had a final diagnosis other than CGL, 4 samples were core biopsies or fragmented tissues, and 2 samples had faded staining. Therefore, the total number of samples that met the inclusion and exclusion criteria was 156 cases.

Table 1. Clinicopathological characteristics of TB and non-TB lymphadenitis.

Variable	N (%)
Age	
<45 years old	132 (84.6)
>45 years old	24 (15.4)
Gender	
Male	51 (32.7)
Female	105 (67.3)
History of autoimmune	
Yes	20 (12.8)
No	136 (87.2)
History of malignancy	
Yes	9 (5.8)
No	147 (94.2)
History of Family	
Yes	2 (1.3)
No	154 (98.7)
Location of the Lymph nodes	
Neck	127 (81.4)
Axilla	15 (9.6)
Inguinal and abdominal	14 (9)
PMN cells	
Yes	110 (70.5)
No	46 (29.5)
Central necrosis	
Central necrosis	98 (62.8)
No	17 (10.9)
Non-central necrosis	41 (26.3)
Giant cells	
Yes	84 (53.8)
No	72 (46.2)

Table 1 showed clinicopathological characteristics of samples used in this research. The distribution of demographic data in the 156 samples revealed that 84.6% of patients were under 45 years old and 67.3% were female. Furthermore, approximately 12.8% of patients had various autoimmune diseases, including Systemic Lupus Erythematosus (SLE), autoimmune hepatitis, systemic sclerosis, erythroderma, and Rheumatoid Arthritis (RA). Family history data did not show significant associations, with only 1.3% of data indicating a family history. The most common location of lymph nodes was in the neck area, accounting for 81.4% of cases, followed by axillary and inguinal areas, with proportions of 9.6% and 9%, respectively.

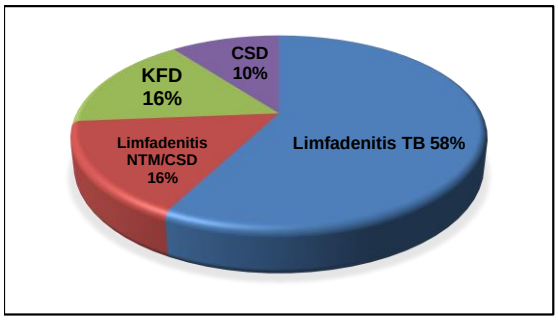

Figure 1. Presentation of TB and non-TB lymphadenitis.

The obtained data were subjected to bivariate analysis for each clinical and histopathological characteristic to assess their association with TB and non-TB lymphadenitis. Table 2 showed the results of the analysis using Chi-square and Fisher exact tests. Several categories showed p-values <0.05, including gender, lymph node location, presence of PMN, central necrosis, and giant cells.

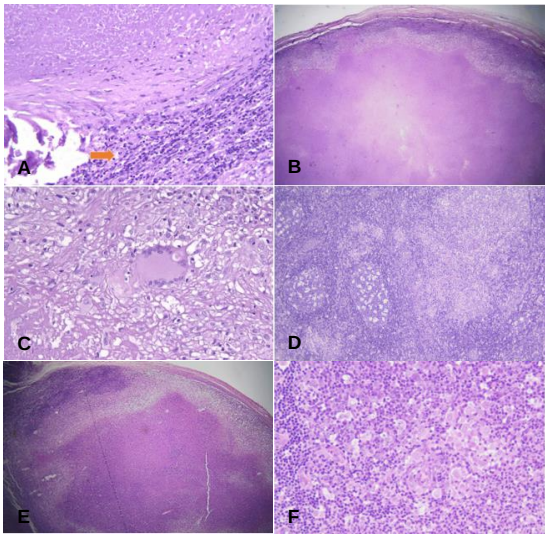

Figure 2. A. PMN cells in the periphery of TB lymphadenitis. B. Central necrosis in TB lymphadenitis. C. Langshan's giant cells in TB lymphadenitis. D. Focal necrosis in KFD. E. Stellate microabscess in NTM lymphadenitis. F. giant cells invade the centrum germinativum in toxoplasmas lymphadenitis.

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Table 2. Relationship between clinicopathological features and TB and non-TB lymphadenitis.

8.5	Chronic Granulomatous Lymphadenitis		Total (n%)	p-value	PR (CI 95%)
	TB (n%)	Non-TB (n%)			
Age					
<45 years old	75 (56.8)	57 (43.2)	132 (100)	<0.604[cs]	0.909 (0.645-1.282)
>45 years old	15 (62.5)	9 (37.5)	24 (100)		
Gender					
Male	23 (45.1)	28 (54.9)	51 (100)	<0.026[cs]	0.707 (0.505-0.988)
Female	67 (63.8)	38 (36.2)	105 (100)		
History of autoimmune					
Yes	14 (70)	6 (30)	20 (100)	<0.233[cs]	1.253 (0.906-1.731)
No	76 (55.9)	60 (44.1)	136 (100)		
History of malignancy					
Yes	6 (66.7)	3 (33.3)	9 (100)	<0.734[fs]	1.167 (0.720-1.891)
No	84 (57.1)	63 (42.9)	147 (100)		
History of Family					
Yes	2 (100)	0 (0)	2 (100)		
No	88 (57.1)	66 (42.9)	154 (100)	<0.509[fs]	
Location of the Lymph node					
Neck	79 (62.2)	48 (37.8)	127 (100)	< 0.003[cs]	
Axilla	9 (60)	6 (40)	15 (100)		0.101 (0.022-0.472)
Inguinal and abdominal	2 (14.3)	12 (85.7)	14 (100)		0.111 (0.18-0.685)
PMN cells					
Yes	89 (81.7)	20 (18.3)	109 (100)	< 0.000[cs]	38.3 (5.509-267.329)
No	1 (2.2)	46 (97.9)	47 (100)		
Necrosis					
Central necrosis	87 (88.8)	11 (11.2)	98 (100)	< 0.000[cs]	
No	0 (0)	17 (100)	17 (100)		
Non-central necrosis	3 (7.3)	38 (92.7)	41 (100)		
Giant cell					
Yes	79 (94.0)	5 (6)	84 (100)	< 0.000[cs]	6.15 (3.56-10.63)
No	11 (15.3)	61 (84.7)	72 (100)		

CS: Chi-square; FS: Fisher exact; PR: Prevalence Ratio; CI: Confidence Interval

DISCUSSION

TB had been found to be a commonly encountered disease in developing countries such as Indonesia. Histopathological examination was one of the modalities used to establish the diagnosis of TB lymphadenitis. The expertise of anatomical pathology specialists in recognizing important morphological features was found to be crucial in determining the etiology of lymphadenitis. In this research, 156 samples met the inclusion and exclusion criteria. However, the constraints encountered were limited clinical data and difficulty in evaluating some slides due to unavailability in the Department of Anatomical Pathology archives.

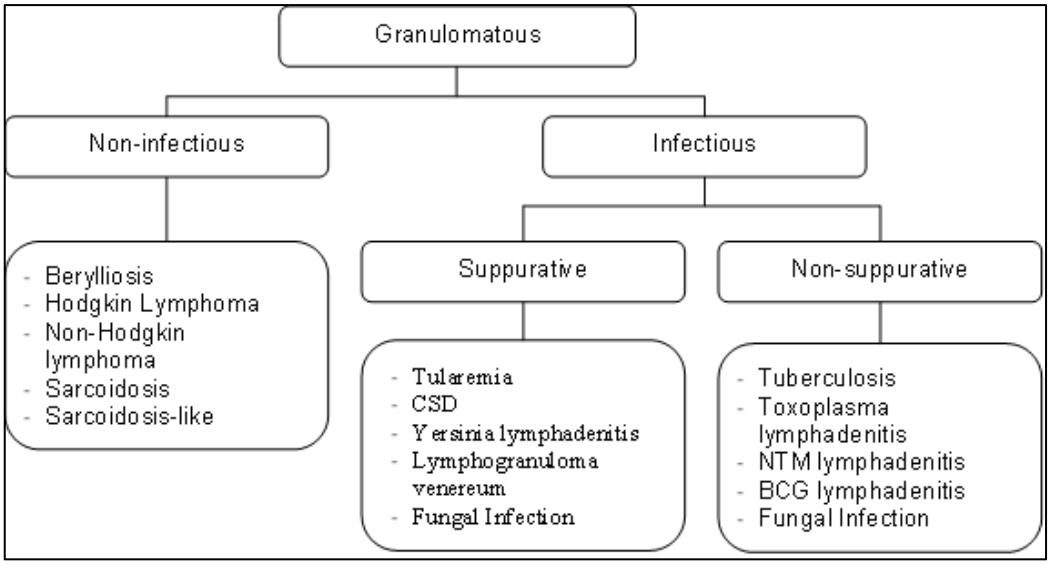

Figure 3. Approach to granulomatous lymphadenitis, modified from Asano et al.[4]

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Infectious CGL was classified into suppurative and non-suppurative types. Almost all of these lymphadenitis cases had central abscess/necrosis in the granuloma caused by gram-negative bacteria.[4] KFD, also known as histiocytic necrotizing lymphadenitis, was characterized by well-defined necrosis, nuclear debris, as well as the absence of eosinophils and neutrophils. The differential diagnosis of this disease included TB and CSD, therefore, KFD was included in this research.[12]

Age Characteristics

Mathiasen et al[16] found that the highest frequency of TB lymphadenitis occurred in individuals <45 years old, with a mean age of 32 years old.[16] Similarly, in this research, the cases of <45 years old reached 84.6% with a mean age of 29 years old. Raja et al[17] also showed that the highest incidence of lymphadenitis occurred in individuals <45 years old, with a mean age of 37 years old but no significant statistical relationship was found (p<0.604). CGL caused by CSD/NTM, toxoplasma, and Kikuchi showed a similar pattern as TB, where the <45 years old age group had a higher frequency compared to the >45 years old age group.[1,12.24]

Gender Characteristics

In this research, the female gender was more frequently affected by TB lymphadenitis than males, with a frequency of 63.8%. The bivariate analysis showed a p-value of <0.026, indicating a tendency towards the occurrence of TB lymphadenitis in female's gender. These results were supported by Kathamuthu et al[18] and Medeiros et al[1], where females were more susceptible to TB lymphadenitis than males, with a ratio of 2:1. This was related to differences in social, economic, and nutritional status, which were lower in females, leading to a higher incidence of TB lymphadenitis in females.[16]

Granulomatous lymphadenitis caused by NTM/CSD did not show gender differences, as some literature suggested no gender tendencies.[9] In this research, toxoplasma and KFD lymphadenitis showed a similar pattern, with female having a higher frequency of 56.2% and 68% compared to males, which was similar to the results of Bassett et al[24] and Perry et al[12].

Characteristics of History of Autoimmune Disease

This research further assessed the history of autoimmune diseases previously experienced by patients. The results showed that the prevalence of autoimmune diseases among patients with TB lymphadenitis was 9%. The history of autoimmune diseases had a p-value of <0.233, indicating that it did not have a significant relationship with the incidence of TB lymphadenitis. However, some literature suggested that autoimmune diseases were a critical process that worsened TB conditions and caused cavitation and transmission.[19,20,21]

History of autoimmune NTM/CSD lymphadenitis was found in 2 cases, about 1.2%, which was also reported by Mok et al[23], where a 1.5% incidence of SLE cases was accompanied by NTM infection. According to Vargas et al[22], autoimmune conditions were a risk factor that exacerbated disease development, including lymphadenitis and CSD.[22] SLE patients were also vulnerable to opportunistic infections, including NTM.[23]

A previous report found that immunocompromised conditions such as autoimmune diseases worsened the course of toxoplasma lymphadenitis but without any significant relationship.[24] It was consistent with this retrospective review, where only 1 patient with toxoplasma lymphadenitis and 3 (12%) KFD patients had a history of autoimmune disease. Perry et al[12] also discovered that 12% of KFD patients had a history of autoimmune diseases, indicating that KFD was associated with several systemic diseases, particularly SLE.[12]

Characteristics of a History of Malignancy

Previous investigations reported the relationship between TB lymphadenitis and malignancy, such as in leukemia and lymphoma with MTB reinfection. Agrawal et al[25] found 6 cases of TB lymphadenitis with a history of breast carcinoma. Kaplan et al reevaluated 58,245 cancer patients and discovered that 201 cases (0.3%) had TB, with the highest prevalence in Hodgkin's lymphoma and breast cancer. In this research, there were 6 patients with a history of malignancy, but the relationship was not statistically significant (p<0.734).[25]

Data on the characteristics of NTM in causing infections in patients with a history of cancer were still limited.[26] The investigation that examined cancer patients with lymph node enlargement caused by *B. henselae* bacteria found a history of exposure to cats, but no association was discovered with a family history of CSD.[27] Similarly, in this research, only 1 patient with a history of breast cancer had NTM/CSD lymphadenitis.

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Toxoplasma infection occurred acutely disseminated, leading to the involvement of the central nervous system, specifically in immunocompromised patients such as autoimmune diseases and AIDS.[1] Kalantari et al found no relationship between breast carcinoma and toxoplasma lymphadenitis. Same with this research, there was no significant association between history of malignancy and toxoplasma lymphadenitis.[28] There was one cases KFD with lymphoma, but according to Park et al[30] the relationship between KFD with malignancy history need to be studied futher.[29]

History of Family Characteristics

This research found a family history of TB and TB lymphadenitis in two patients, according to the data obtained from electronic medical records. However, there was no significant relationship found between family TB history and lymphadenitis (p <0.509). This was different from the literature, where almost one-third of TB lymphadenitis patients had a history of TB in their families.[9] This was due to limitations, such as incomplete medical records or history-taking documentation, leading to different results compared to previous research.

There was no significant association was found between family history and NTM/CSD lymphadenitis, toxoplasma lymphadenitis, and KFD. Similarly, Park et al[30] reported that no family history of the disease was found in NTM lymphadenitis. Both toxoplasma and CSD lymphadenitis were zoonotic diseases transmitted through cats and no research reported on the influence of family history on CSD infection.[27] KFD, commonly caused by infection and autoimmune diseases, was not found to be associated with a family history of the disease.[12]

Location of Lymph Node Characteristics

Approximately 62.2% of TB lymphadenitis cases were located in the neck area, followed by the axillary and inguinal regions. A significant relationship was found between the location of the neck area and the tendency for TB lymphadenitis compared to non-TB lymphadenitis, with a p-value of <0.003. Similarly, Shigeyuki Asano found that 90% of TB lymphadenitis cases were generally located in the head and neck.[9]

NTM/CSD lymphadenitis had also been found in the cervical, axillary, and inguinal areas, with proportions of 33%, 27%, and 18%, respectively.[4,9] Similarly, NTM/CSD lymphadenitis was found in various areas, with a more even distribution, including 48% in the neck, 20% in axillary, and 32% in inguinal areas. Toxoplasma lymphadenitis was located in the cervical area, and in this research, approximately 75% of lesions were found in the neck area, with the remaining in the inguinal. Among 25 KFD patients, 24 (96%) were in the neck area, and one was in the axillary. Perry et al also reported that approximately 60-90% of KFD cases were located in the cervical region, followed by axillary and supraclavicular areas.

Characteristics of PMN Cells

PMN cells were immune cells involved in the process of MTB infection that played a dual role in contributing to the formation of granulomas and tissue necrosis.[31] In this research, almost all cases showed the presence of PMN cells, which were mainly found in the outer layer of the granuloma and generally not clustered. Statistically, these results were significant and related to a p-value of <0.000, indicating their presence as a sign of MTB-induced lymphadenitis.

PMN cells were also found in NTM lymphadenitis, specifically in areas of necrosis. This did not indicate the presence of secondary infection but rather an inflammatory response to the bacteria.[1] Similarly, in early CSD lesions, necrosis was accompanied by a mixture of PMN cells. In the early phase, small abscesses with focal necrosis and PMN cell clusters developed under the subcapsular sinus, which progressed to the cortex and medulla.[1] In the re-evaluation of NTM/CSD lymphadenitis slides, PMN cells were generally found in 20 patients (80%), mainly in areas of necrosis.

Toxoplasma lymphadenitis did not form well-organized granulomas, induce necrosis, or be accompanied by neutrophils, eosinophils, and fibrosis.[4] In this research, no PMN cells were found in all patients with Toxoplasma lymphadenitis. A typical feature of KFD was the absence of neutrophils and eosinophils, which helped in diagnosing KFD in lymph nodes.[4,12] These results were similar to the previous research, where no PMN cells were found in all patients with KFD.

Characteristics of Central Necrosis

Both suppurative and non-suppurative forms of infectious CGL-induced central necrosis mediated by gram-negative bacteria. The persistence of antigens also stimulated macrophage activity, resulting in the production of tumor necrosis factor (TNF) and interferon-gamma (IFN-γ). These cytokines recruited

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circulating monocytes and neutrophils, leading to chronic inflammation. Activated Th1 cells and macrophages also induced the production of IFN-γ and TNF, initiating granuloma formation.[32]

In TB granulomas, necrosis occurred due to failure in controlling the infection, deficiency/excess of TNF, and deficiency of leukocytes to replace dead macrophages within the granuloma.[33,34] Subsequently, epithelioid granulomas became organized and delineated, progressing into caseous central necrosis. The characteristic feature of TB lymphadenitis was the presence of caseous central necrosis, surrounded by epithelioid cells and Langhans giant cells. In this research, approximately 88.8% of TB lymphadenitis patients had central necrosis in the granulomas, with a significant p-value of <0.000, indicating an association between central necrosis and TB lymphadenitis.

Approximately 7.3% of TB lymphadenitis cases had necrotic areas that did not form central necrosis, as explained by the chronicity of the disease. In the early phase of TB lymphadenitis, nonspecific changes were observed, with inflammatory cells infiltrating the periadventitial area, followed by abscess formation and necrosis. Differences in chronicity also contributed to the absence of central necrosis.

The presence of central necrosis in NTM/CSD lymphadenitis in this research was found in 11 patients (44%). The type of necrosis observed depended on the clinical phase at the time of histopathological examination. Lymphadenitis caused by NTM passes through suppuration without the formation of caseous necrosis. In the acute phase, NTM bacteria caused more exudative lesions and the neutrophils were also found in the necrotic areas.[1]

In CSD, infected lymph nodes passed through early, intermittent, and latent phases. During the early phase, there was follicular hyperplasia and an abundance of immune such as immunoblasts, histiocytes, macrophages, neutrophils, and plasma cells in lymphatic vessels, subcapsular sinuses, and paracortical areas. The intermittent phase (microabscess formation) was characterized by the presence of central necrosis with or without epithelioid granulomas. Clusters of neutrophils were found beneath the subcapsular sinuses and spread to the medulla. Central necrosis consisted of aggregates of neutrophils and fibrinoid material, which passed through suppuration. Furthermore, macrophages surrounded the abscess and formed granulomas (stellate microabscesses), rarely accompanied by Langshan's giant cells. In the final phase (latent), the merging of stellate microabscesses caused the formation of large irregular abscesses (geographic abscesses), followed by fibrosis.[4]

Infection of lymph nodes caused by Toxoplasma did not induce necrosis or fibrosis. According to Asano et al[4], necrosis was not a characteristic feature of Toxoplasma lymphadenitis, which was supported by previous research, where necrosis was generally not found in Toxoplasma lymphadenitis (87.5%). The two cases with necrosis were not central necrosis and both patients had a history of autoimmune disease and malignancy Mandal et al found necrosis in immunocompromised patients, which was supported by this research, as both patients had immunocompromised conditions.[35] However, histological discoveries of KFD showed focal necrosis with defined borders. The necrotic areas contain numerous karyorrhectic debris and histiocytes at the periphery of the necrosis. Similar to these findings, all KFD patients had necrosis without central necrosis.[12]

Giant Cell Characteristics

This research also evaluated the presence of giant cells derived from macrophages that were stimulated and transformed into epithelioid cells. Subsequently, adjacent epithelioid cells fused their membranes to form giant cells.[33] These cells were commonly found in TB but their absence did not exclude granulomatous inflammation caused by MTB or other infections with similar histological features, such as fungal infections.

In this research, a significant association was found between the presence of data cells and TB lymphadenitis (p<0.000). The results showed that approximately 87% of TB lymphadenitis was accompanied by giant cells. Similarly, Purbaningsih et al found the presence of giant cells as a sign in diagnosing TB lymphadenitis in 73.7% of cases.[36]

In NTM lymphadenitis, giant cells were also found but in small amounts (16%). Asano et al[12] discovered giant cells in the intermittent phase of CSD, although it was very rare,[4] as with NTM lymphadenitis.[9] Meanwhile, in toxoplasma lymphadenitis and KFD, giant cells were not found. Some literature stated that giant cells were not a feature of the picture of toxoplasma lymphadenitis and KFD.[4] Both

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toxoplasma lymphadenitis and KFD did not induce the formation of giant cells.[9]

CONCLUSION

In conclusion, this research showed a significant relationship between female gender characteristics, the location of the lymph nodes, specifically the neck area, the presence of PMN cells, central necrosis, and giant cells with TB lymphadenitis. These characteristics were expected to be considered as features to assess for diagnosing CGL caused by MTB.

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