



Tuberculous Lymphadenitis with Dark Specks Cytomorphology: Focus on the Presence of Eosinophils and History of Atopy in Children

Humairah Medina Liza Lubis^{1*}, Nurcahaya Sinaga², Emni Purwoningsih³, Qatrunnada Medina Salim⁴, Muhammad Fathurridha Arabia Salim⁴

¹ Department of Anatomical Pathology Faculty of Medicine Universitas Muhammadiyah Sumatera Utara Medan, Indonesia

² Department of Pediatric Faculty of Medicine Universitas Muhammadiyah Sumatera Utara Medan, Indonesia

³ Department of Biochemistry Faculty of Medicine Universitas Muhammadiyah Sumatera Utara Medan, Indonesia

^{4,5} Medical Education Faculty of Medicine Universitas Sumatera Utara Medan, Indonesia

ARTICLE INFO

Article history:

Received 21 January 2023

Accepted 1 April 2023

Published 10 June 2023

Keyword:

Children
dark specks
eosinophils
history of atopy
tuberculous lymphadenitis

ABSTRACT

Background. Research on eosinophils in lymph node cytology in tuberculous lymphadenitis (TBLN) patients with dark specks cytomorphology and its association with a history of atopies are still very little. Although neutrophils have been reported as predominant phagocytic cells in TB patients, eosinophils are also abundant in blood and lung tissue, but their role and pathogenesis are still unclear. Objective. To analyze the relationship between TBLN and eosinophils, dark specks, and history of atopy in pediatric TBLN patients. Methods. This study is a cross-sectional study of 35 indicative cytology results of patients with TBLN stained with May Grunwald Giemsa. Data on atopy history were measured by filling out the standard questionnaire of The International Study of Asthma and Allergies in Childhood (ISAAC). Results. Based on the cytological examination, 22 samples (62.9%) were found with positive eosinophils, and 13 samples (37.1%) with negative eosinophils. A total of 23 samples (65.7%) had a history of atopy. The Fisher's Exact Test results showed that TBLN with dark specks cytomorphology tends to find eosinophils with a test value of $p=0.001$, indicating a relationship between the two cytomorphological features. The results also showed a relationship between TBLN with dark specks cytomorphology with a history of allergies ($p=0.038$), and there was a relationship between the presence of eosinophils and a history of allergies ($p=0.001$). Conclusion. Tuberculous lymphadenitis with dark specks cytomorphology was significantly associated with eosinophils and a history of atopy.

This open access article is under the [CC-BY-SA](https://creativecommons.org/licenses/by-sa/4.0/) license.



Kata kunci:

Anak
bintik gelap
eosinofil
limfadenitis
tuberkulosis riwayat atopi

*) corresponding author

Dr. dr. Humairah Medina Liza Lubis,
M.Ked.(PA), Sp.PA
Department of Anatomical Pathology
Faculty of Medicine Universitas
Muhammadiyah Sumatera Utara, Medan,
Indonesia

ABSTRAK

Latar Belakang. Penelitian eosinofil pada sitologi kelenjar getah bening pada pasien limfadenitis tuberkulosis (LNTB) dengan sitomorfologi bintik gelap dan kaitannya dengan riwayat atopi masih terbatas. Meskipun neutrofil telah dilaporkan sebagai sel fagosit dominan pada pasien TB, eosinofil juga banyak ditemukan pada darah dan jaringan paru tetapi peran dan patogenesisnya masih belum jelas. Tujuan. Menganalisis hubungan antara LNTB dengan eosinofil, bintik gelap dan riwayat atopi pada pasien limfadenitis TB anak. Metode. Studi dilakukan secara cross-sectional dengan sampel 35 hasil sitologi indikatif pasien LNTB yang diwarnai dengan May Grunwald Giemsa. Data riwayat atopi diukur dengan pengisian kuesioner standar The International Study of Asthma and Allergies in Childhood (ISAAC). Hasil. Berdasarkan pemeriksaan sitologi didapatkan 22

Email: humairahmedina@umsu.ac.id
DOI: 10.30604/jika.v8i2.1790
Copyright 2023 @author(s)

sampel (62,9%) dengan eosinofil positif dan 13 sampel (37,1%) dengan eosinofil negatif. Sebanyak 23 sampel (65,7%) memiliki riwayat atopi. Hasil uji Fisher's Exact menunjukkan bahwa LNTB dengan sitomorfologi bintik gelap cenderung ditemukan eosinofil dengan nilai uji $p=0,001$, menunjukkan adanya hubungan antara kedua gambaran sitomorfologi. Hasil penelitian juga menunjukkan adanya hubungan sitomorfologi LNTB dengan sitomorfologi bintik gelap dengan riwayat alergi ($p=0,038$), dan ada hubungan antara adanya eosinofil dengan riwayat alergi ($p=0,001$). Simpulan. Limfadenitis tuberkulosis dengan sitomorfologi bintik gelap berhubungan secara signifikan dengan eosinofil dan riwayat atopi.

This open access article is under the [CC-BY-SA](https://creativecommons.org/licenses/by-sa/4.0/) license.



INTRODUCTION

The incidence of extrapulmonary tuberculosis (EPTB) in children has been increasing rapidly in recent years. This disease can involve multiple organs, and the most common is the lymph nodes, known as tuberculous lymphadenitis (TBLN) (Bayazit *et al.*, 2004; Mustafa *et al.*, 2005; Tadele *et al.*, 2014; Gupta and Bhake, 2017; Shah and Dani, 2017). Tuberculous lymphadenitis is caused by the reactivation of latent disease in a former lymph node infection or hematogenous reinfection. Signs and symptoms are chronic, painless swelling that persists and enlarges. The mass is known as a cold abscess because it is not accompanied by local discoloration and heat, and the overlying skin is purple (bluish-red) (Chao *et al.*, 2002).

The diagnosis of TBLN is based on the typical cytologic predominantly reactive with few clusters of epithelioid cells, multinucleated giant cells, and necrotic material with few epithelioid cells. Lubis *et al.* (2008) found a different microscopic picture beyond the conventional picture of TBLN in the form of dark specks (DS) between eosinophilic granular amorphous necrotic masses. Dark specks are containing dark chocolate particles in pinkish, homogenous, acellular, and well-circumscribed irregular mass on H&E stain (Figure 1) (Lubis *et al.*, 2008). Prasoon (2014) and Chikkannaiah (2015) reported an eosinophilic structure similar to DS cytomorphology, associated with the presence of Acid Fast Bacillus (AFB) in TBLN with specificity values of 58.33% and 39% (Prasoon *et al.*, 2014; Chikkannaiah *et al.*, 2015). Delyuzar (2019) reported that positive TB cases (DS features) compared to negative TB cases (without DS features) were found to have a high specificity value (>90) (Delyuzar *et al.*, 2019). Research conducted by Lubis *et al.* (2021) reported aspirating with dark specks that showed positive immunocytochemistry with rabbit polyclonal against *Mycobacterium tuberculosis* (Mtb) antibody (60%) (Lubis *et al.*, 2021). Therefore, the cytological appearance of DS is one of the diagnostic signs of TBLN and is used as an additional basis for establishing a cytological diagnosis of TBLN.

On TBLN with cytological appearance of DS, many eosinophils cytology was found, and requires pathological explanation. Eosinophils are also found in abundance in blood and lung tissue, but their role in its pathogenesis is still unclear. Eosinophilia in patients with pulmonary tuberculosis has been investigated in relation to the continued response to anti-TB chemotherapy and the initial allergic state of the organism (Kuzovkova *et al.*, 2016). Eosinophilia is associated with a cell-mediated T helper 2 (Th2) immune response, including the production of IL-5, which has the ability to degranulate and release cationic

granule proteins that are helminthotoxic and function to increase eosinophilopoiesis and eosinophil activation (Weller and Spencer, 2018). So far, eosinophils have been associated with their function as host protection, but several studies have reported that the increase in eosinophils in helminth infections has not been shown to have a protective effect. Cytokines produced by eosinophils (including IL-10 and IL-4) suppress the host response and have no impact on larvae (Huang *et al.*, 2014; Huang *et al.*, 2015).

Similar to neutrophils, eosinophils can work to phagocytize pathogens that attack and kill them intracellularly by sending Major Basic Protein (MBP) and Eosinophil Cationic Protein (ECP) to intracellular phagosomes (Malik and Batra, 2012; Germic *et al.*, 2019), thereby paving the way for subsequent antigen presentation (Shi *et al.*, 2000). In addition, eosinophils also use extracellular killing mechanisms by releasing cytotoxins through degranulation, releasing droplets through Eosinophil Peroxidase (EPO), and trapping extracellular DNA (Svensson and Wennerås, 2005; Yousefi *et al.*, 2008).

Lubis (2019) reports increased expression of IL-4 cytokines on TBLN with DS feature (Lubis *et al.*, 2021). Interleukin-4 plays an important role in the immune response to parasitic worms and allergic inflammation associated with atopy. Some researchers regard allergy as an imbalance to Th2, and recently immunologists have found a way to direct the Th2 allergic response toward amplification of the Th1 response to reduce the incidence of atopy. Several groups have tried to administer high doses of allergens to induce a Th1 response. Another group used the MTb vaccine to induce a stronger Th1 response at an early age (Berger, 2000).

In simple terms, to determine whether a person suffers from allergies or atopy is to see the presence of eosinophils in certain samples or by doing an Immunoglobulin E (IgE) examination. Eosinophils are a classic feature of infectious disease, and MTb infection frequently demonstrates the recruitment of eosinophils in naturally occurring human infections and experimental trials on animals. However, the precise function and role of eosinophils in the host immune response in TB are poorly understood. Several studies have stated that eosinophil protein is a mycobactericidal that can lyse MTb bacteria. In an *in vitro* study, EPO-induced surface changes were followed by MTb lysis, and EPO-containing macrophages exhibited strong antimycobacterial activity (Bohrer *et al.*, 2021). It was also found that eosinophils can release defensins in response to cell wall components of BCG or MTb, which can directly kill BCG *in vitro* (Driss *et al.*, 2009). Research conducted by Moideen *et al.* 2018 found a decrease in eosinophil granule protein with anti-tuberculosis treatment (ATT) (Moideen *et al.*, 2018).

This study was conducted to prove an increase in eosinophils in TBLN by the microscopic appearance of a DS necrotic mass and a history of atopy. This study is a preliminary study to establish whether there is a relationship between TBLN and the allergic process, especially in children, and an explanation of its pathogenesis so that treatment in TBLN is more focused on giving anti-allergic drugs compared to anti-tuberculosis drugs, which cause many adverse side effects.

METHODS

Sample Selection

This study was conducted using a cross-sectional approach to analyze the relationship between TBLN with eosinophils, dark specks, and atopy history in pediatric TBLN patients. The inclusion criteria of this study was the pediatric patients who have a lump that diagnosed as tuberculous lymphadenitis with DS who have a history of atopy. While the exclusion criteria were pediatric patients that diagnosed as non-specific infections and malignancies. Data on atopy history were measured by filling out the standard questionnaire of The International Study of Asthma and Allergies in Childhood (ISAAC). Cytology samples were obtained from private clinics and Muhammadiyah Hospital, North Sumatra. Fine needle aspiration biopsy was performed on the swollen neck, axillary, inguinal, supraclavicular, and submandibular lymph nodes in children aged 1-18 years. Microscopic examination was carried out at the Anatomical Pathology Laboratory, Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara.

Cytological Assessment

Before the cytologic examination, a fine needle aspiration biopsy was performed with history taking and by filling standard questionnaire adapted from The International Study of Asthma and Allergies in Childhood (ISAAC). Aspirate slides were stained with May Grunwald Giemsa, and microscopic examination at 400x magnification was performed in 10 random areas. The diagnosis of tuberculous lymphadenitis was made based on a microscopic appearance of dark specks between eosinophilic granular amorphous necrotic masses (Lubis *et al.*, 2008; Lubis *et al.*, 2021), and the appearance of eosinophils in the form of a nucleus segmented into two or more lobes connected by thin filaments, abundant cytoplasm containing many reddish-orange granules (Perkins *et al.*, 2018). The slides were read by an anatomical pathologist using the blind method.

Statistical analysis

Descriptive statistics were used to present cytologic features of dark specks and eosinophils, and history of atopy. Fisher's exact test was employed to examine the relationship of TBLN with dark specks cytomorphology and eosinophils, the relationship between TBLN with dark specks cytomorphology with a history of allergies, and relationship between the presence of eosinophils and a history of allergies. All the analyzis conducted in this study used IBM SPSS 20.

RESULTS AND DISCUSSION

This study involved 35 patients ranging from 1 to 18 years old, and the majority were aged 1-9 years were 20 cases (57.1%), and 10-18 years were 15 cases (42.9%). The ratio of women (22 cases=62.9%) to men (13 cases=37.1%) was 1.69:1. Lymph nodes were mainly involved in 23 cases were cervical (65.7%); 6 cases were submandibular (17.1%), 4 cases were supraclavicular (11.4%), 1 case was axillar (2.9%), and 1 case was inguinal (2.9%).

The examination results for the cytomorphological diagnosis of dark specks among eosinophilic granular amorphous necrotic masses in TBLN, the presence of eosinophils, and a history of atopy are shown in Table 1. There were TBLN with dark specks cytomorphology in 23 cases (65.7%), positive eosinophils in 22 cases (62, 9%) (Figure 1), and a history of atopy in 23 cases (65.7%).

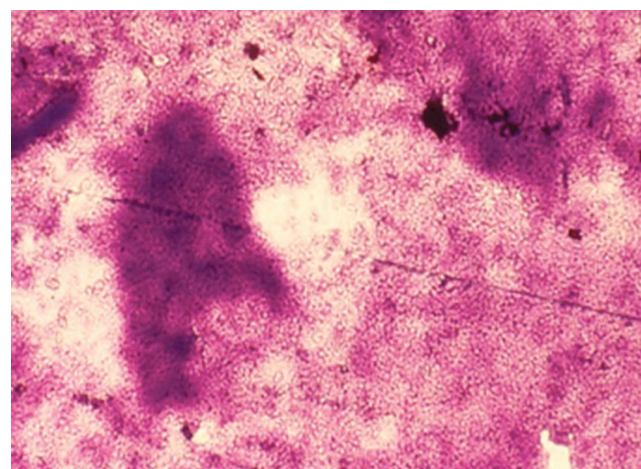


Figure 1. Aspirate of tuberculous lymphadenitis with dark specks (DS) cytomorphology (black aarrow), and group of eosinophils (black circle) (May–Grunwald Giemsa, 400×) (Lubis *et al.*, 2021).

Table 1. Examination of dark specks among eosinophilic granular amorphous necrotic masses, presence of eosinophils, and history of atopy in TBLN

Characteristics	Frequency (n)	Percentage (%)
Dark specks		
Absence	12	34.3
Presence	23	65.7
Eosinophils		
Absence	13	37.1
Presence	22	62.9
History of atopy		
Absence	12	34.3
Presence	23	65.7

An analysis of the relationship between TBLN DS with a history of atopy and between eosinophils and a history of atopy was performed (Table 2). TBLN with DS tends to find eosinophils with a test value of p=0.001, indicating a

relationship between the two cytomorphological features. The results also showed a relationship between TBLN and DS cytomorphology with a history of allergies (p=0.038), and

there was a relationship between the presence of eosinophils and a history of allergies (p=0.001).

Table 2.
The relationship between dark specks between eosinophilic granular amorphous necrotic masses and the presence of eosinophils, and atopy history in TBLN

Eosinophils	DS Positive (%)	DS Negative (%)	Total (%)	p-value*
Positive (%)	19 (54.3)	3 (8.6)	22 (62.9)	0.001
Negative (%)	4 (11.4)	9 (25.7)	13 (37.1)	
Total (%)	23 (65.7)	12 (34.3)	35 (100)	
History of Atopy				
Positive (%)	18 (51.4)	5 (14.3)	23 (65.7)	0.038
Negative (%)	5 (14.3)	7 (20)	12 (34.3)	
Total (%)	23 (65.7)	12 (34.3)	35 (100)	
Eosinophils	Positive Atopy History (%)	Negative Atopy History (%)	Total (%)	p-value*
Positive (%)	19 (54.3)	3 (8.6)	22 (62.9)	0.001
Negative (%)	4 (11.4)	9 (25.7)	13 (37.1)	
Total (%)	23 (65.7)	12 (34.3)	35 (100)	

*Fisher's exact test: p<0.05

This study showed an increase in eosinophils in field of view of the microscope. This study also showed a significant relationship between TBLN DS with a history of atopy and an increase in eosinophils with a history of atopy in pediatric patients. The specific immune response to MTb in the host is complex and involves several mechanisms. Chronic MTb infection creates an inflammatory environment that continuously develops in which to inhibit this development, the cellular response will be actively working. The cellular immune response in TB lasts 15-18 days after infection by involving dendritic cells that function to activate naive T cells, followed by the migration of activated T cells to the main site of infection. Inflammatory lesions are protected by the accumulation of activated T cells, macrophages, lymphocytes, and cytolytic-specific antigens. An increase in multifunctional T cells and a subset of functional T cells that produce the specific antigens interleukin (IL)-17, IL-22, and IL-23 were detected in MTb-infected individuals and is associated with an increase in granulocytes in TB granulomas, some of which are neutrophils and eosinophils (Caccamo *et al.*, 2010; Clemmensen *et al.*, 2021; Nogueira, Warren and Torres, 2021).

Eosinophils possess a large number of cell surface molecules, including Toll-like receptors, adhesion molecules, chemokines, complement, and chemotactic factor receptors, immunoglobulin receptors, apoptotic signaling molecules, prostaglandins, and leukotriene receptors (Barnig *et al.*, 2015). These cells have complex extracellular and intracellular features that enable them to react to the inflammatory environment. Eosinophils store various preformed proteins, including cationic proteins, EPO and eosinophil-derived neurotoxins, cytokines, chemokines, and growth factors. Eosinophils exhibit degranulation via cytolytic degranulation in response to stimuli. Human eosinophils possess lipid bodies that can be induced at

certain sites by forming eicosanoid mediators that are known to control bacterial infections (Vieira-De-Abreu *et al.*, 2005).

The increase in eosinophils in almost the entire microscopic field of view is because eosinophils exhibit bactericidal potential mediated through phagocytosis, respiration, and mobilization of cytotoxic proteins in the presence of bacterial infection (Ramirez *et al.*, 2018), which suggests a protective role of these cells in bacterial infection. Extensive necrotic in the form of amorphous eosinophilic granular mass is suspected to be a lipid body of eosinophils, which requires further examination. It can also be seen from the response to therapy given where in patients with a higher number of eosinophils with extensive necrotic masses, anti-tuberculosis treatment becomes more manageable and shows satisfactory results.

This study also showed a significant relationship between TBLN DS with a history of atopy and also an increase in eosinophils with a history of atopy in pediatric patients. It is obtained that children with a history of asthma are more dominant. Research by Kavut *et al.* (2012) CD14-159C/T polymorphism and high eosinophil count levels with tuberculosis infection are associated with atopy, especially in asthma (Baççioğlu Kavut *et al.*, 2012).

The history of atopy in this study was established based on the ISAAC questionnaire without conducting SPT and IgE level tests. Since the subject in this study was the local prevalence of TB, history of atopy, especially asthma, and socioeconomic status were relatively homogeneous. It was assumed that most subjects had initial exposure to infections and allergens. Further research will be conducted to prove whether there is a true relationship between TBLN and atopy history by using cytokine biomarkers to better understand the pathogenesis of this disease from an immunological perspective.

Research on the exact role and function of eosinophils in the host immune response to mycobacterial infection in TB remains should be carried out comprehensively both experimentally in experimental animals and clinically. The involvement of eosinophils and a history of atopy in the study were initial findings, suggesting the possibility of co-infection between TB and allergy. Antiallergic drugs can be considered in future management strategies apart from relying on BCG and ATT, but further research is needed. The extensive analysis and correlation between eosinophilia and TB represent a further goal to better understand the role of eosinophils during TB infection and disease progression.

LIMITATION OF THE STUDY

Since this study was conducted using a cross-sectional approach to analyze the relationship between TBLN with eosinophils, dark specks, and atopy history in pediatric, there was limited variables and indicators, especially related to confirmation by standard examination of atopy determination with IgE. Future studies will be more full of insights if consider broader indicators to definitive diagnosis of atopy.

CONCLUSION AND SUGGESTIONS

Tuberculous lymphadenitis with dark specks cytomorphology was significantly associated with eosinophils, and a history of atopy. This study can be considered to that treatment in TBLN is more focused on giving anti-allergic drugs compared to anti-tuberculosis drugs, which cause many adverse side effects.

ACKNOWLEDGMENT

The writers would like to thank the Faculty of Medicine Universitas Muhammadiyah Sumatera Utara, Medan, that provided research funds through the UMSU Internal Grant in 2021.

ETHICAL CONSIDERATION

This research has been approved by the ethics committee of the Faculty of Medicine, Universitas Muhammadiyah Sumatera Utara, under the ethical clearance number 579/KEPK/FKUMSU/2022.

REFERENCES

Baççioğlu Kavut, A. *et al.* (2012) 'Association between tuberculosis and atopy: Role of the CD14-159C/T polymorphism', *Journal of Investigational Allergology and Clinical Immunology*, 22(3), pp. 201–207.

Barnig, C. *et al.* (2015) 'Circulating human eosinophils share a similar transcriptional profile in asthma and other hypereosinophilic disorders', *PLoS ONE*, 10(11), pp. 1–17. doi: 10.1371/journal.pone.0141740.

Bayazit, Y. A., Bayazit, N. and Namiduru, M. (2004) 'Mycobacterial Cervical Lymphadenitis', *ORL*, 66, pp. 275–280. doi: 10.1159/000081125.

Berger, A. (2000) 'Science commentary: Th1 and Th2 responses: What are they?', *British Medical Journal*, 321(7258), p. 424. doi: 10.1136/bmj.321.7258.424.

Bohrer, A. C. *et al.* (2021) 'Eosinophils are part of the granulocyte response in tuberculosis and promote host resistance in mice', *Journal of Experimental Medicine*, 218(10). doi: 10.1084/jem.20210469.

Caccamo, N. *et al.* (2010) 'Multifunctional CD4+ T cells correlate with active Mycobacterium tuberculosis infection', *European Journal of Immunology*, 40(8), pp. 2211–2220. doi: 10.1002/eji.201040455.

Chao, S. S. *et al.* (2002) 'Tuberculous and nontuberculous cervical lymphadenitis: A clinical review', *Otolaryngology - Head and Neck Surgery*, 126(2), pp. 176–179. doi: 10.1067/mhn.2002.121912.

Chikkannaiah, P., Boovalli, M.M. and Venkataramappa, S. M. (2015) 'Eosinophilic Structure: Should it be Included in Routine Cytology Reporting of Tuberculosis Lymphadenitis?', 9(12), pp. 10–12. doi: 10.7860/JCDR/2015/15631.6862.

Clemmensen, H. S. *et al.* (2021) 'In vivo antigen expression regulates cd4 t cell differentiation and vaccine efficacy against mycobacterium tuberculosis infection', *mBio*, 12(2), pp. 1–16. doi: 10.1128/mBio.00226-21.

Delyuzar, D., Sinaga, BYM. and R, Y. (2019) 'The correlation between cytology of tuberculosis through eosinophilic mass containing brown particles feature and various bacterial strain', *International Journal of Scientific and Research Publications (IJSRP)*, 9(12), p. p9680. doi: 10.29322/ijsrp.9.12.2019.p9680.

Driss, V. *et al.* (2009) 'TLR2-dependent eosinophil interactions with mycobacteria: Role of α -defensins', *Blood*, 113(14), pp. 3235–3244. doi: 10.1182/blood-2008-07-166595.

Germic, N. *et al.* (2019) 'Regulation of the innate immune system by autophagy: monocytes, macrophages, dendritic cells and antigen presentation', *Cell Death and Differentiation*, 26(4), pp. 715–727. doi: 10.1038/s41418-019-0297-6.

Gupta, V. and Bhake, A. (2017) 'ScienceDirect Clinical and cytological features in diagnosis of peripheral tubercular lymphadenitis – A hospital-based study from central India', *Indian Journal of Rheumatology*, pp. 1–5. doi: 10.1016/j.ijrb.2016.11.032.

Huang, Lu; Gebreselassie, NG; Gagliardo, LF; Ruyechan, MC; Lee, NA; Lee, JJ and Appleton, J. (2014) 'Eosinophil-derived IL-10 supports chronic nematode infection', *J Immunol*, 193(8), pp. 4178–4187. doi: 10.4049/jimmunol.1400852.

Huang, L. *et al.* (2015) 'Eosinophils and IL-4 Support Nematode Growth Coincident with an Innate Response to Tissue Injury', *PLoS Pathogens*, 11(12), pp. 1–17. doi: 10.1371/journal.ppat.1005347.

Kuzovkova, S. D., Liskina, I. V and Rekalova, O. M. (2016) 'Participation and the possible role of eosinophils in the inflammatory process in chronic forms of pulmonary tuberculosis', pp. 1–6.

Lubis, H. M. D, Lubis, H. M. L, Lisdine and Hastuti, N. (2008) 'Dark specks and eosinophilic granular necrotic material as differentiating factors between tuberculous and non-tuberculous abscess', *Maj Patol Indonesia*, 2, pp. 49–52.

- Lubis, H. M. L. *et al.* (2021) 'Immunocytochemical Study of Rabbit-Polyclonal to Mycobacterium Tuberculosis, AB905: Improving Diagnostic of Tuberculous Lymphadenitis', *Mutiara Medika: Jurnal Kedokteran dan Kesehatan*, 21(2), pp. 95–101. doi: 10.18196/mmjkk.v21i2.11559.
- Lubis, H. M. L., Lubis, M. N. D. and Delyuzar, D. (2021) 'Interleukin-4 cytokine as an indicator of the severity of tuberculous lymphadenitis', *Open Access Macedonian Journal of Medical Sciences*, 9(A), pp. 82–86. doi: 10.3889/oamjms.2021.5667.
- Malik, A. and Batra, J. K. (2012) 'Antimicrobial activity of human eosinophil granule proteins: Involvement in host defence against pathogens', *Critical Reviews in Microbiology*, 38(2), pp. 168–181. doi: 10.3109/1040841X.2011.645519.
- Moideen, K. *et al.* (2018) 'Heightened systemic levels of neutrophil and eosinophil granular proteins in pulmonary tuberculosis and reversal following treatment', *Infection and Immunity*, 86(6), pp. 1–8. doi: 10.1128/IAI.00008-18.
- Mustafa, T., Stanley, J. and Sayoki, G. M. (2005) 'Immunohistochemical analysis of cytokines and apoptosis in tuberculous lymphadenitis', pp. 454–462. doi: 10.1111/j.1365-2567.2005.02318.x.
- Nogueira, M., Warren, R. B. and Torres, T. (2021) 'Risk of tuberculosis reactivation with interleukin (IL)-17 and IL-23 inhibitors in psoriasis – time for a paradigm change', *Journal of the European Academy of Dermatology and Venereology*, 35(4), pp. 824–834. doi: 10.1111/jdv.16866.
- Perkins, S. L. *et al.* (2018) *Hematology and Clinical Microscopy Resource Committee*.
- Prasoon, D; Agrawal, P. (2014) 'Correlation of eosinophilic structures with detection of acid-fast bacilli in fine needle aspiration smears from tuberculous lymph nodes: Is eosinophilic structure the missing link in spectrum of tuberculous lesion?', 31(3). doi: 10.4103/0970-9371.145647.
- Ramirez, G. A. *et al.* (2018) 'Eosinophils from Physiology to Disease: A Comprehensive Review', *BioMed Research International*, 2018(Figure 1). doi: 10.1155/2018/9095275.
- Shah, I. and Dani, S. (2017) 'Profile of tuberculous cervical lymphadenopathy in children', *Journal of Tropical Pediatrics*, 63(5), pp. 395–398. doi: 10.1093/tropej/fmx001.
- Shi, H. Z. *et al.* (2000) 'Lymph node trafficking and antigen presentation by endobronchial eosinophils', *Journal of Clinical Investigation*, 105(7), pp. 945–953. doi: 10.1172/JCI8945.
- Svensson, L. and Wennerås, C. (2005) 'Human eosinophils selectively recognize and become activated by bacteria belonging to different taxonomic groups', *Microbes and Infection*, 7(4), pp. 720–728. doi: 10.1016/j.micinf.2005.01.010.
- Tadele, A. *et al.* (2014) 'Immunocytochemical detection of Mycobacterium Tuberculosis complex specific antigen , MPT64 , improves diagnosis of tuberculous lymphadenitis and tuberculous pleuritis', pp. 1–10.
- Vieira-De-Abreu, A. *et al.* (2005) 'Allergic challenge-elicited lipid bodies compartmentalize in vivo leukotriene C4 synthesis within eosinophils', *American Journal of Respiratory Cell and Molecular Biology*, 33(3), pp. 254–261. doi: 10.1165/rcmb.2005-0145OC.
- Weller, P. F. and Spencer, L. A. (2018) 'Functions of tissue-resident eosinophils', 17(12), pp. 746–760. doi: 10.1038/nri.2017.95.Functions.
- Yousefi, S. *et al.* (2008) 'Catapult-like release of mitochondrial DNA by eosinophils contributes to antibacterial defense', *Nature Medicine*, 14(9), pp. 949–953. doi: 10.1038/nm.1855.