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ANALYSIS OF MEASURES TO IMPROVE THE CRITERIA FOR THE IMMUNOLOGICAL DIAGNOSIS OF TUBERCULOSIS OF PERIPHERAL LYMPH NODES AND NON-TUBERCULOUS LYMPHADENOPATHIES

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ABSTRACT

One of the most prevalent locations for extrapulmonary TB is the lymph nodes, especially the thoracic lymph nodes. However, nothing is known about Mtb infection in these organs. Lymph nodes are habitats for Mtb development and persistence in addition to being locations where the adaptive immune system is initiated. Granuloma growth brought on by Mtb infection disturbs and, if it grows large enough, destroys the lymph node's regular design, which is essential to its operation. Effective TB vaccines seem to stop Mtb from moving from the lungs to the lymph nodes in preclinical animals. Future studies evaluating the efficacy of vaccines and anti-TB drug treatments should take into account the effects on thoracic lymph nodes, not just the lungs. Finally, drug penetration to the lymph nodes is poor compared to blood, lung tissue, and lung granulomas. Reactivation of latent TB can begin in the lymph nodes, leading to dissemination of the bacteria to the lungs and other organs. Involvement of the lymph nodes may improve Bacille Calmette-Guerin (BCG) vaccine efficacy. More than 190 species of Mycobacterium are together referred to as non-

tuberculous mycobacteria (NTM). Most NTM infections have a non-specific clinical appearance, which frequently causes a delayed diagnosis. The fact that NTM organisms can be challenging to isolate adds even more complexity. Patients may find it difficult to tolerate the medications used to treat NTM infections, and extensive courses of anti-mycobacterial therapy are frequently necessary for sufficient suppression or eradication. In this article, we go over several NTM disorders, suitable diagnostic procedures, and treatment plans.

Introduction. In 2020, 1.3 million people died from tuberculosis (TB), and an estimated 10 million new cases of TB are reported annually. According to WHO data, extrapulmonary tuberculosis (EPTB) accounts for 18% of all TB cases; however, the percentage of recognized TB cases that include EPTB is significantly higher, rising from 17.4% (45,537) in 2011 to 20% (71,322) in 2016. The involvement of lymph nodes is the most prevalent type of EPTB. The most frequent cause of lymphadenopathy in low-income nations is tuberculous lymphadenitis (TBL). Because of the disease's paucibacillary origin, invasive sampling, and variable clinical presentation, TBL is difficult to diagnose [1,2,3]. Extrapulmonary tuberculosis (TB) is most frequently found in lymph nodes, especially thoracic lymph nodes. The infection caused by *Mycobacterium tuberculosis* (Mtb) in these organs is not well understood, yet. In addition to being the starting point of the adaptive immune system, lymph nodes are also Mtb growth and persistence habitats. A Mtb infection causes granulomas to grow, which disturb and, if large enough, replace the lymph node's natural architecture, which is essential to its operation. According to preclinical models, effective TB vaccinations seem to stop Mtb from moving from the lungs to the lymph nodes. Mtb proliferation and persistence occur in lymph node niches. Early human autopsy investigations discovered live Mtb in lymph nodes but no other indications of TB illness. Live Mtb could be present in lymph nodes that, upon physical examination by a qualified pathologist, seemed normal [4,5]. The most frequent location for *M. bovis* infection in cattle is the lymph nodes. Only one of the 15 cattle in a small investigation with lymph node evidence of bovine TB had a detectable lung infection. However, given that TB lesions can be tiny, some authors—quoted by Neill and colleagues—think that a more thorough examination of the cow's lungs should be carried out. It is well acknowledged that in bovine tuberculosis, lung lesions appear later in the infection process, while lymph nodes become infected earlier. Along with the lungs, lymph nodes are nearly invariably infected with Mtb in our experience dealing with nonhuman primates (NHPs). On rare occasions, we discover live Mtb bacilli in lymph nodes that do not appear to have a granuloma. It makes sense that Behr and Waters suggested that tuberculosis be classified as a lymphatic disease rather than just a pulmonary one in light of these findings. NTM infections can also be difficult to treat. Not all NTM species and medications of interest are available for antimicrobial-susceptibility testing (AST). When it is available, its clinical application is dubious and its reliability is not always guaranteed. Guidelines for the ideal number of medications and length of treatment are mostly dependent on opinion, and the ideal dosage of known anti-mycobacterial medications is uncertain [6,7,8]. Moreover, NTM infections are grouped

into a limited number of groups according to current criteria. As a result, aspects like virulence, pertinent host characteristics, resistance profile, and treatment response that vary among NTM species are not sufficiently addressed. Here, we outline our methodology for NTM infection diagnosis and management. There are published reviews on human TB lymphadenitis (TBLN) that concentrate on the disease's pathology, diagnosis, treatment, epidemiology, and clinical symptoms. Our goal is to explore the pathophysiology of Mtb infection in lymph nodes using research from both human and animal models. Future studies evaluating the efficacy of vaccines and anti-TB drug treatments should take into account the effects on thoracic lymph nodes, not just the lungs. Finally, drug penetration to the lymph nodes is poor compared to blood, lung tissue, and lung granulomas. Reactivation of latent TB can begin in the lymph nodes, leading to dissemination of the bacteria to the lungs and other organs [9,10,11,12].

The main purpose of the presented analytical manuscript is to summarize measures to improve the criteria for the immunological diagnosis of tuberculosis of peripheral lymph nodes and non-tuberculous lymphadenopathies based on reputable scientific research.

In order to diagnose non-tuberculous mycobacteria infections, there are no pathognomonic tests; instead, the clinical syndrome must be correlated with radiographic findings, followed by microbiologic confirmation of the etiologic agent. Because of the complexity of the diagnosis, specimen collection and testing may need to be repeated multiple times in order to confirm or rule out an NTM infection. Because of this, tests should be interpreted in consultation with specialists who have experience managing NTM infections, particularly if the microbiologic results do not match the clinical picture [13-16]. ***Microbiological diagnostics.*** Commonly found in soil and water, include (ing municipal and residential water supply systems, NTM are pervasive in the environment. Therefore, in order to minimize false positive results, care must be taken to ensure that biologic specimens are not contaminated by the environment. Almost any tissue or organ that is thought to be infected can yield specimens. Positive sputum culture results on at least two different times are required by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) recommendations for the diagnosis of pulmonary NTM infection. An alternative method of diagnosis is a single positive culture from a lower respiratory specimen, such as bronchial lavage or washing. More sputum cultures should be taken if there is a high clinical suspicion of lung NTM infection and the results of the initial tests are inconclusive (Table 1).

Table 1. Common mycobacterial infection symptoms that are not tuberculous [1,7,8,11].

№	Clinical Syndrome	Most Common Species	Other Species	Risk Factors/ Associations
1.	**Pulmonary44**	*MAC* *M. kansasii*	*M. abscessus*	α1-Antitrypsin deficiency
			M. fortuitum	Ciliary dyskinesia
			M. szulgai	Cystic fibrosis
			M. xenopi	GERD
			M. celatum	Bronchiectasis
			M. asiaticum	Pulmonary histoplasmosis
			M. shimoidei	Low BMI with scoliosis, pectus

				excavatum, mitral valve prolapse
		M. malmoense (Scandinavian Peninsula; Northern Europe)	Smoking or heavy alcohol use *(M. malmoense)* *Lymphopenia*	Smoking or heavy alcohol use (*M. malmoense*) Lymphopenia
2.	**Cervical Lymphadenitis3**	*MAC* *M. scrofulaceum*	*M. malmoense*	Children; 1–5 yrs Men with lung cancer
3.	**Skin, soft tissue infection**	*M. ulcerans*	*M. szulgai*	Bathing in water from bore holes insect bites
		M. kansasii	*MAC*	Possible association with pedicures
4.	**Tenosynovitis**	*M. marinum*	*M. terrae*	Exposure to fish tanks or other contaminated marine water sources
		MAC	*M. szulgai*	
		M. abscessus	*M. malmoense*	
			M. xenopi	
5.	**Bone disease**	*M. kansasii*	*MAC*	May occur via direct trauma or hematogenous seeding
		M. fortuitum	*M. xenopi*	
6.	**Disseminated disease**	**MAC**	*M. kansasii*	Severe Immunosuppression:
			M. chelonae	HIV infection/AIDS (CD4 count <50 cells)
7.	**Abscesses**		*M. haemophilum* *M. scrofulaceum*	SOT or stem cell transplant long-term, high dose steroids

Sputum is one clinical specimen that is particularly susceptible to contamination or bacterial overgrowth. To increase the microbiologic yield, concentration and disinfection methods are used when processing these specimens. Although N-acetyl-l-cysteine-NaOH-oxalic acid (NALC-NaOH-OxA) decontamination is frequently used, several investigations have raised concerns that it can compromise mycobacteria viability. Chlorhexidine is another decontamination technique that doesn't impact mycobacterial viability. The Clinical Laboratory Standards Institute (CLSI) has approved both of these techniques [11,14].

Testing for antibiotic susceptibility. Antimicrobial susceptibility testing (AST) guidelines have been published by ATS/IDSA and CLSI. Culture and growth using broth microdilution is the gold standard for assessing antimicrobial susceptibility. Generally speaking, only clinically relevant isolates should undergo NTM AST. For NTM species that are rarely harmful, as *M. gordonae, M. mucogenicum* or *M. terrae,* CLSI advises against susceptibility testing. Clinicians should be aware that there is no documented association between the clinical response to in-vitro susceptibility patterns for each species and anti-mycobacterial medication. For instance, with the exception of amikacin and macrolides,

there is no relationship between clinical response and *in vitro* minimum inhibitory concentrations (MIC) for isolates of *Mycobacterium avium complex* (MAC) [7-11].

Susceptibility testing against a larger panel of antimicrobials up front is advised for mycobacteria that are growing quickly. However, as most of these drugs lack a known MIC threshold for susceptibility or resistance, it is crucial to remember that the goal of this research is "to guide rather than dictate therapy." Clarithromycin, amikacin, tobramycin, cefoxitin, ciprofloxacin, imipenem, linezolid, moxifloxacin, tigecycline, clofazimine, trimethoprim-sulfamethoxazole, and doxycycline (or minocycline) are among the broader group of antimicrobials. Because of the erythromycin ribosomal methylase (erm) gene, all isolates of *M. abscessus* and *M. fortuitum* should also be regularly examined for inducible macrolide resistance. The organism is incubated with sub-inhibitory doses of clarithromycin for 14 days in order to test for inducible macrolide resistance [1-5].

NTM infection diagnosis by radiography. For pulmonary NTM disease, there is no pathognomonic radiographic pattern. Nodular bronchiectasis and fibro-cavitary disease are two radiographic features frequently seen in pulmonary NTM disease. It's also possible to discern a "mixed" pattern, which combines these two radiography patterns. NTM pulmonary fibro-cavitary disease: Men in their middle or later years who have underlying structural lung diseases like COPD or pneumoconiosis are more likely to develop fibro-cavitary disease. It is challenging to differentiate fibro-cavitary disease from endemic fungal infections and tuberculosis (TB) with a chest X-ray alone. Upper lobe-dominant cavities with thin or thick walls and surrounding pleural thickening are the hallmarks of this presentation. NTM is not frequently linked to calcified lymphadenopathy and related parenchymal infiltrates, which are typical of tuberculosis [6-12].

Examining the gamma and interleukin-2 pathways. NTM disease is more likely to affect some patients than others. The fact that many patients with positive tuberculin skin tests never develop active disease and that only a tiny percentage of patients who receive the bacille Calmette-Guerin (BCG) vaccination go on to develop disseminated BCG-osis serve as examples of this in other mycobacterial diseases. The type I cytokine system provides protection against mycobacterial infection; studies have demonstrated that lower immunity to mycobacteria results from abnormalities in the genes encoding IL-12, IL-23, and interferon-γ (INF-γ) receptors. "Mendelian susceptibility to mycobacterial disease" is the term used to describe patients who have these primary immunodeficiencies [1,4,7]. Patients who come with disseminated NTM infection without a known secondary cause should be evaluated for primary abnormalities in cell mediated immunity, even though this is not included in the 2020 or previous ATS/IDSA guidelines. This is especially true if family members are also unwell. Treatment choices may be influenced by this knowledge, which also informs prognosis. Other diseases such as CMV, human herpes virus-8, herpes simplex virus, Listeria, and Histoplasma infections can also affect these people [2,3,6].

Differentiating between colonization and infection. Environmental non-tuberculous mycobacteria are common, and the isolation of NTM species from non-sterile materials does not necessarily indicate infection. The majority of NTM isolated from a respiratory source might not fit the existing standards for NTM infection. NTM can colonize the respiratory system, particularly if there is underlying structural lung and/or airway illness. The most often reported NTM airway "colonizer" is MAC, however it's not always apparent if this is a low-grade infection or actual colonization. In pulmonary NTM disease, colonization without infection is an unproven idea; nonetheless, this does not

mean that all patients with NTM respiratory isolates need to be treated with antibiotics. A 2007 joint ATS and IDSA guideline created the current criteria for NTM pulmonary infections, which were updated in 2020 [1-7]. The most frequently observed and well-characterized NTM species—MAC, *M. kansasii* and *M. abscessus*—are inevitably the focus of these guidelines. Although there is little data and experience with these NTM species, it is likely that similar rules also apply to other, less well-known and uncommon NTM species. Microbiological, radiographic, and clinical correlation are necessary for the diagnosis of pulmonary NTM illness. To diagnose pulmonary NTM illness, all of these requirements must be satisfied because they are equally important [12,13].

Discussion. Other than Mycobacterium TB and Mycobacterium leprae, a collection of more than 190 species of Mycobacterium are together referred to as non-tuberculous mycobacteria (NTM). It is becoming more widely acknowledged that these organisms, which are found in soil and water supplies in particular, are the source of human illness. Infections caused by non-tuberculous mycobacteria can occur in both immunocompromised and healthy individuals. Diagnosing and treating NTM infections presents a significant number of obstacles. Most NTM infections have a non-specific clinical appearance, which frequently causes a delayed diagnosis. Due to varying growth requirements and times, it can be challenging to grow NTM from biological material for identification once it has been suspected [1-5]. Furthermore, molecular techniques that may not be generally accessible are frequently needed for the actual identification of the organism. Because NTM is so common in the environment, it can be difficult to distinguish between colonization and actual infection. Therefore, identifying NTM from biological material is not the same as diagnosing NTM infection. Identification of NTM infections by radiography. There is no pathognomonic radiographic pattern for pulmonary NTM disease. Fibro-cavitary disease and nodular bronchiectasis are two radiographic features frequently seen in pulmonary NTM disease. A "mixed" pattern, which combines these two radiographic patterns, may also be observed. Disease of the fibro-cavitary NTM lungs: Middle-aged or older males with underlying structural lung diseases like COPD or pneumoconiosis are typically affected by fibro-cavitary illness. With a chest X-ray, fibro-cavitary disease can be recognized, although it can be challenging to differentiate it from endemic fungal diseases and tuberculosis (TB). The top lobe predominates in this presentation, while the surrounding pleural thickening is surrounded by cavities with thin or thick walls. While calcified lymphadenopathy and related parenchymal infiltrates are common in TB, NTM is not frequently linked to these findings [6-10]. Separating colonization from infection

Infection is not always the result of isolating non-tuberculous mycobacteria (NTM) species from non-sterile materials. Current criteria for NTM infection may not be met by the majority of NTM isolated from a respiratory source. NTM can colonize the respiratory tract, particularly in cases of underlying lung and/or structural airway illness. It is unknown if MAC, the most frequently reported NTM airway "colonizer," is a low-grade illness or actual colonization. Antimicrobial treatment is not necessary for all patients with NTM respiratory isolates, even if colonization without infection is an unproven notion in pulmonary NTM illness. In 2007, ATS and IDSA jointly developed the current criteria for NTM pulmonary infections, which were later revised in 2020 [11-16]. From limited soft-tissue infiltration to widespread, life-threatening diseases, non-tuberculous mycobacterial infections are becoming a more significant cause of human illness. Because they are so common in nature, it might be difficult to distinguish between an actual NTM infection and contamination of biological samples. The radiographic and clinical characteristics are nonspecific, and the microbiologic diagnosis is laborious and not very

useful. Complex treatment involves long-term administration of multi-drug regimens with significant accompanying toxicity. Clinical results are frequently unsatisfactory, and it can be challenging to define therapy milestones [1,11,14,16].

Conclusion. In conclusion, there were notable variations between the two groups in terms of clinical symptoms, laboratory results, demographic and clinical data, and ATBL CT features. Consider the likelihood of tuberculosis in young male patients who report with distension and abdominal pain and whose CT scan reveals several enlarged lymph nodes in the mesenteric area with homogenous or heterogeneous enhancement. To confirm the diagnosis, further intestinal involvement investigation may be helpful. Hematogenous disseminated TB is likely if a patient has abdominal pain and distension along with coughing, sputum production, or superficial lymph node enlargement. If a CT scan shows several enlarged lymph nodes in different abdominal regions that are fused into mass with homogeneous or mixed enhancement, this is likely to be the case.

It is recommended to screen for PTB foci promptly. It is important to remember that ATBL is strongly suspected after several calcifications are discovered in the abdominal lymph nodes on CT scans. The clinical diagnosis of this symptom is significantly impacted. Gaining knowledge of these variations in ATBL brought on by hematogenous and non-hematogenous spread will help with early diagnosis and treatment, lower mortality and sequelae, and more effectively accomplish TB control and prevention objectives.

A growing number of human diseases are caused by non-tuberculous mycobacterial infections, which can vary from localized soft-tissue infiltration to widespread, life-threatening illnesses. Because of its widespread occurrence in nature, it might be difficult to distinguish between a genuine NTM illness and NTM biological sample contamination. The microbiologic diagnosis is laborious and not very useful, and the clinical and radiographic features are nonspecific. Treatment is complicated and involves long-term, multi-drug regimens with significant concomitant toxicity. Clinical results are frequently unsatisfactory, and defining therapy milestones is challenging.

References:

1. Ulain N, Ali A, Khan M, Ullah Z, Shaheen L, Shareef N, et al. (2022) Improving diagnosis of tuberculous lymphadenitis by combination of cytomorphology and MPT64 immunostaining on cell blocks from the fine needle aspirates. PLoS ONE 17(10): e0276064. https://doi.org/10.1371/journal.pone.0276064
2. Ganchua SKC, White AG, Klein EC, Flynn JL. Lymph nodes-The neglected battlefield in tuberculosis. PLoS Pathog. 2020 Aug 13;16(8):e1008632. doi: 10.1371/journal.ppat.1008632.
3. WHO. Global tuberculosis report 2019 2019. [cited 2020 Jul 30]. Available from: https://www.who.int/tb/publications/global_report/en/
4. Dijkman K, Vervenne RAW, Sombroek CC, Boot C, Hofman SO, van Meijgaarden KE, et al. Disparate Tuberculosis Disease Development in Macaque Species Is Associated With Innate Immunity. Front Immunol. 2019;10:2479 Epub 2019/11/19. 10.3389/fimmu.2019.02479
5. Sathkumara HD, Pai S, Aceves-Sanchez MJ, Ketheesan N, Flores-Valdez MA, Kupz A. BCG Vaccination Prevents Reactivation of Latent Lymphatic Murine Tuberculosis Independently of CD4(+) T Cells. Front Immunol. 2019;10:532 Epub 2019/04/06. 10.3389/fimmu.2019.00532

6. de Martino M, Lodi L, Galli L, Chiappini E. Immune Response to Mycobacterium tuberculosis: A Narrative Review. Front Pediatr. 2019;7:350 Epub 2019/09/12. 10.3389/fped.2019.00350
7. Zhang Z, Liu Y, Wang W, Xing Y, Jiang N, Zhang H, et al. Identification of Differentially Expressed Genes Associated with Lymph Node Tuberculosis by the Bioinformatic Analysis Based on a Microarray. J Comput Biol. 2020;27(1):121–30. Epub 2019/08/29. 10.1089/cmb.2019.0161 .
8. Kathamuthu GR, Moideen K, Sridhar R, Baskaran D, Babu S. Enhanced Mycobacterial Antigen-Induced Pro-Inflammatory Cytokine Production in Lymph Node Tuberculosis. Am J Trop Med Hyg. 2019;100(6):1401–6. Epub 2019/04/18. 10.4269/ajtmh.18-0834
9. Wong EA, Evans S, Kraus CR, Engelman KD, Maiello P, Flores WJ, et al. IL-10 Impairs Local Immune Response in Lung Granulomas and Lymph Nodes during Early Mycobacterium tuberculosis Infection. J Immunol. 2020;204(3):644–59. Epub 2019/12/22. 10.4049/jimmunol.1901211
10. Diedrich CR, Rutledge T, Maiello P, Baranowski TM, White AG, Borish HJ, et al. SIV and Mycobacterium tuberculosis synergy within the granuloma accelerates the reactivation pattern of latent tuberculosis. bioRxiv. 2020. 10.1101/2020.02.21.959353
11. Darrah PA, Zeppa JJ, Maiello P, Hackney JA, Wadsworth MH 2nd, Hughes TK, et al. Prevention of tuberculosis in macaques after intravenous BCG immunization. Nature. 2020;577(7788):95–102. Epub 2020/01/03. 10.1038/s41586-019-1817-8
12. Clinicoepidemiologic considerations in the diagnosis of tuberculous lymphadenitis: evidence from a high burden country, Assefa, Wubshet et al. International Journal of Infectious Diseases, Volume 124, 152 – 156.
13. Shetty, D., Vyas, D. Combination method for the diagnosis of Tuberculous lymphadenitis in high burden settings. Surg Exp Pathol 5, 11 (2022). https://doi.org/10.1186/s42047-022-00111-z
14. Zhu, Xl., Liu, Xy., Wen, L. et al. Clinical and CT characteristics of abdominal tuberculous lymphadenopathy: a comparative analysis of hematogenous and non-hematogenous dissemination. BMC Infect Dis 25, 710 (2025). https://doi.org/10.1186/s12879-025-11101-3
15. Tahtabasi M, Sahiner F. Tuberculous and non-tuberculous cervical lymphadenopathy incidence and distribution in Somalia from 2016 to 2020: A review of 241 cases. World J Otorhinolaryngol Head Neck Surg. 2022 May 5;8(4):361-369. doi: 10.1016/j.wjorl.2021.03.001.
16. Pennington KM, Vu A, Challener D, Rivera CG, Shweta FNU, Zeuli JD, Temesgen Z. Approach to the diagnosis and treatment of non-tuberculous mycobacterial disease. J Clin Tuberc Other Mycobact Dis. 2021 May 8;24:100244. doi: 10.1016/j.jctube.2021.100244.