

An Evidence-Based Clinical Pathway for the Diagnosis of Tuberculous Lymphadenitis: A Systematic Review

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Abstract

To achieve the World Health Organization end TB Strategy, early detection, and prompt treatment of not only pulmonary but also extrapulmonary tuberculosis (EPTB) should be achieved. The most common EPTB is tuberculous lymphadenitis, and the diagnosis is typically time-consuming. This review aimed to identify the best diagnostic pathway for preventing treatment delay and thus further complications. A systematic keyword search was done using four databases and other relevant publications and using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart to search for relevant articles that met the inclusion criteria. The quality of the articles was assessed using Newcastle–Ottawa Scale, and the articles were summarized based on the test for diagnosing tuberculous lymphadenitis. A total of ten articles were included for the synthesis of results, which compared the sensitivity and specificity of each diagnostic test for tuberculous lymphadenitis. The most promising test is the Xpert *Mycobacterium tuberculosis*/RIF, which has high sensitivity and specificity, but costs much more in comparison to the other tests. An ideal diagnostic method should include the combination of relevant patient history, clinical examination, and laboratory and radiological testing to avoid delays in treatment, misdiagnosis, and further complications.

Keywords: Clinical pathway, diagnostic pathway, extrapulmonary tuberculosis, tuberculous lymphadenitis

Submitted: 23-Dec-2019

Revised: 26-Jan-2020

Accepted: 25-Feb-2020

Published: 29-May-2020

INTRODUCTION

Infection caused by *Mycobacterium tuberculosis* (MTB) complex organisms is one of the top ten causes of death worldwide in recent years.^[1] Every year, millions of people develop a new tuberculosis (TB) infection and in 2018 alone, an estimated ten million people developed TB worldwide.^[2] TB can be broadly divided into two types: pulmonary TB and extrapulmonary TB (EPTB). Most efforts are expended for managing pulmonary TB, as it is a major public health concern. Nevertheless, the other, silent TB that contributes to the overall prevalence of TB should not be overlooked. EPTB is an infection also caused by MTB complex organisms, but to the parts of the body other than the pulmonary system.

EPTB can affect many organs, for example, the lymph nodes, nervous system, joints, genitourinary tract, bones, gastrointestinal system, and others. The infection can present on its own or concomitantly with pulmonary TB infection. In our local setting, the trend of EPTB is on the rise, with an increase of around 70% from 2005 to 2011 for newly

diagnosed cases.^[3] The most common type of EPTB is tuberculous lymphadenitis.^[4] A study in Spain has also shown a slow increase in EPTB cases over time (30.6% to 37.6% over 10 years).^[5] In Korea, EPTB comprises about 20% of the diagnosed TB cases. The more alarming feature is that it also shows an increasing trend over time. The most common type of EPTB in Korea is pleural EPTB, followed by that of the lymph nodes and gastrointestinal organs.^[6]

Tuberculous lymphadenitis is one of the more common types of EPTB in many countries and is often diagnosed very late, and diagnosis requires a high index of suspicion. Lymphadenitis

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Access this article online

Quick Response Code:



Website:
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DOI:
10.4103/ijmy.ijmy_207_19

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How to cite this article: Sivaratnam L, Nawi AM, Manaf MR. An evidence-based clinical pathway for the diagnosis of tuberculous lymphadenitis: A systematic review. *Int J Mycobacteriol* 2020;9:107-15.

can be caused by both the nontuberculous mycobacteria (NTM) and the MTB complex organisms. NTM causing lymphadenitis is commonly seen among children and should be ruled out at the soonest as the treatment differs for both. Most of the time, NTM infection would resolve spontaneously without treatment, whereas tuberculous lymphadenitis would require a prolonged duration of treatment. Tuberculous lymphadenitis is typically found in the cervical region, and involves unilateral and painless swelling.^[7] Apart from that, the clinician would also have to rule out other differential diagnoses before diagnosing tuberculous lymphadenitis. This could lead to delayed initiation of treatment.

The issue with most EPTB cases is late presentation and late diagnosis, which often leads to many complications.^[8] Physicians with a poor index of suspicion, coupled with the long duration of culture, add to the delay in treatment.^[8,9] Even though EPTB patients without concomitant lung infection are rarely contagious and a source of TB infection, we still need an efficient and systematic clinical care for these patients. From the natural progression of the disease, EPTB can either be a complication of PTB or the EPTB can progress and be disseminated to the lungs. As both ways can become an infectious disease, urgent care is needed in treating these patients. The patient factor is difficult to control, but awareness can be improved. Regarding the health-care delay, the time from when the patient first seeks treatment to the actual diagnosis and treatment can be reduced by educating staff and having a proper reference guideline or pathway to minimize misdiagnosis and avoid subjecting patients to unnecessary investigation and treatment.

The clinical pathway is currently used to help clinicians standardize case management; it involves an evidence-based pathway that has been well structured to help provide optimum treatment quality while keeping the cost to a minimum.^[10] The clinical pathway is typically a comprehensive process developed by a multidisciplinary team that is usually required in for managing that case. The aim of the present article is to review all evidence of the diagnostic pathway used and to identify the best pathway for diagnosing tuberculous lymphadenitis to prevent delayed treatment and further complications.

METHODS

A systematic review of the literature was done to identify studies that reported on any clinical pathway in the management of

tuberculous lymphadenitis. Here, we describe computerized methods for searching relevant information on the best means of diagnosing and treating tuberculous lymphadenitis. Four databases (PubMed, SCOPUS, MEDLINE and Ovid, and the Cochrane Library), with a guideline (the Malaysian clinical practice guidelines on EPTB), and a program were used for assessing the quality of the information. Further relevant articles were searched using the snowballing method. The search comprised a set of keywords that included terms related to tuberculous lymphadenitis and the clinical pathway together with their MeSH terms from 2014 until 2019. We used the following keywords: “tuberculosis” OR “tuberculous” AND “lymphadenitis” OR “lymphadenopathy” OR “lymph node enlargement” AND “clinical pathway” OR “care pathway.”

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used as the guideline to search for eligible articles. Table 1 shows the search summary according to each database; the PRISMA checklist is shown in Figure 1. The articles were screened by their title, followed by the abstract and full text. Only relevant articles were considered for analysis.

The inclusion criteria were: (a) reported on any clinical pathway/flow for treating tuberculous lymphadenitis, (b) published in 2014–2019, and (c) full article. The exclusion criteria were: (a) qualitative studies and commentary articles, (b) study in languages other than English, and (c) animal studies. In view of the rapid advancement of diagnosing techniques, where older methods may be obsolete, only articles from the last 5 years were selected.

Data synthesis and quality assessment

From the search summary using the PRISMA flowchart, an initial 3280 studies were retrieved using the keyword search; after much filtering, we identified an eventual ten articles for the final results synthesis. The findings from the ten selected articles were used in the pathway process and development. The quality of evidence of the observational studies was assessed using the Newcastle–Ottawa scale^[11] [Tables 2 and 3]. Studies that met at least five of the nine criteria were deemed of high quality.

RESULTS

For result analysis, we selected ten articles that described the testing requirements and comparison of testing to aid the

Table 1: Database Search Summary

Database	Number of articles before filter	Number of articles after filter	Number of articles accepted by title	Number of articles accepted by abstract	Number of articles accepted by full-text analysis
Medline and Ovid	3105	879	18	8	1
PubMed	8	6	3	0	0
SCOPUS	32	19	3	1	1
Cochrane library	125	75	1	1	0
Other sources	10	10	10	10	8
Total	3280	989	35	20	10

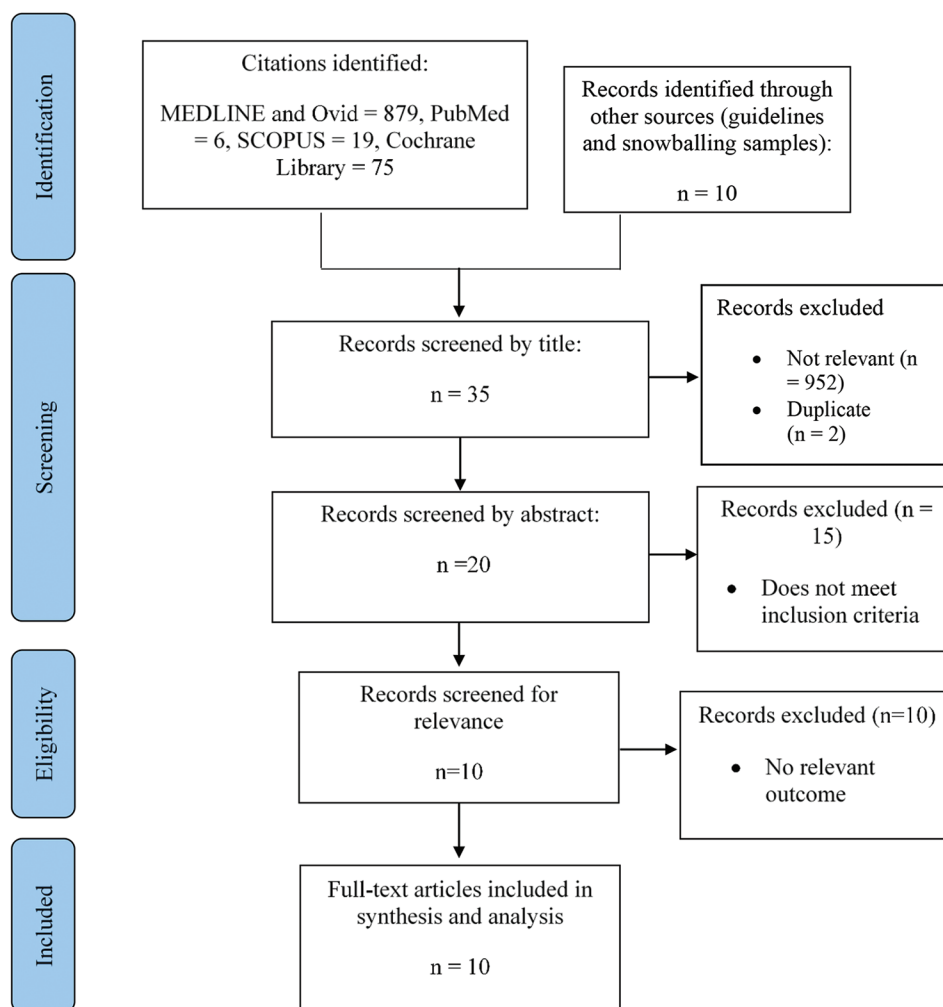


Figure 1: Preferred Reporting Items for Systematic Reviews and meta-analyses flow chart

diagnosis of tuberculous lymphadenitis. Two articles were case-control studies, four were cohort studies, three were report articles, and one was a clinical practice guideline. Most of the studies were from the UK (40%)^[12-15] and India (30%).^[16-18] The other studies were from Malaysia,^[3] Korea,^[6] and Turkey.^[19] All of the studies described similar investigation methods for diagnosing a suspected tuberculous lymphadenitis case. We compared the methods used for identification based on the time until results were obtained, and compared the sensitivity and specificity of each test used. The frequencies of the content of the articles are detailed in Table 4; the detailed findings of each article are summarized in Table 5 and the proposed diagnostic pathway for tuberculous lymphadenitis is detailed in Figure 2.

DISCUSSION

EPTB is an increasing problem worldwide today. As evidenced by a recent World Health Organization (WHO) report, as much as 15% of all TB cases are due to EPTB.^[1] Due to the limitation of late presentation, clinicians typically wind up treating a more complicated case, and thus morbidity increases. One method

for reducing the time to treatment is to ensure that clinicians have a high index of suspicion and order the appropriate treatment and start treatment promptly. With the diagnostic pathway, not only can the time to start treatment be shortened, but also as evidenced by using a clinical pathway, management among clinicians can be synchronized, and at the same time, costs can be minimized by avoiding unnecessary procedures.

As EPTB is not a main concern when dealing with TB, less effort has been expended on managing the disease. This is also the reason for the limited number of research articles specifically on EPTB as compared to pulmonary TB. Based on the available references, the first step in creating a clinical pathway can be achieved. Gathering all recent evidence that supports the pathway is valuable to the aim of reducing the delay in providing early treatment.

The evidence is then broken down to a few focused reviews in creating the diagnostic flow. First, once a patient is suspected to have tuberculous lymphadenitis, identifying the sample to be taken must be considered. Depending on the site of lymph node enlargement, there are many methods for obtaining the sample:

Table 2: Newcastle-Ottawa cross-sectional study

Number	Study	Selection		Comparability		Outcome		Quality score		
		Representativeness of the sample	Sample size	Nonrespondents	Ascertainment of the exposure (risk factor)	The study controls for the most important factor	The study controls for any additional factor		Assessment of the outcome	Statistical test
1	Asimacopoulos <i>et al.</i> ^[12]	*	*		**	*		**		7
2.	McAllister and MacGregor ^[13]	*	*		**	*		**		7

Table 3: Newcastle-Ottawa cohort study

Study	Selection		Comparability		Outcome		Quality score			
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome of outcome		Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
1	Gautam <i>et al.</i> ^[14]	*	*	*	**	*	*	*	*	8
2	Mittal <i>et al.</i> ^[15]	*	*	*	*	*	*	*	*	7
3	Meghji and Giddings ^[16]	*	*	*	*	*	*	*	*	7
4	Suzana <i>et al.</i> ^[17]	*	*	*	*	*	*	*	*	7

*: 1 point, **: 2 points

from a needle biopsy, excision, or a more invasive endoscopic or laparoscopic sampling.^[7] If the lymph node enlargement is visible, the best sampling technique is fine-needle aspiration (FNA), as it has been proven to be minimally

invasive.^[3,7,9,20] While it is claimed to be more sensitive, excision biopsy is a more invasive procedure, therefore it should be reserved if the FNA is inconclusive or if the patient has persistent lymph node enlargement despite completing treatment. FNA has been widely studied, and a 9-year study concluded that FNA is simple, is cost-effective, and can be done as an outpatient procedure, which is particularly useful in a resource-poor setting.^[21] There is good agreement for this evidence, and it is accepted by all countries, as advocated by the WHO.

Once clinical samples have been obtained, the best test for diagnosing tuberculous lymphadenitis is dependent on what is available in the current setting, what can be used, laboratory capacity, and operator expertise. The most basic test for diagnosing pulmonary TB is sputum microscopy for detecting the acid-fast bacilli, as both tuberculous and NTM are acid-fast. This test is fast and has high specificity and sensitivity. However, this is not true for EPTB infection, as the main issue in this case is the paucibacillary nature.^[20] Most EPTB patients are not smear positive; therefore, microscopy

Table 4: Frequency of main content in the selected articles

Content	Frequency described (number of articles)
Mantoux test	2
Biopsy	
FNA and excision biopsy	7
Nucleic acid amplification test	
Xpert MTB/Rif	3
Conventional PCR	3
Imaging	2
Treatment regimen/duration	3

FNA: Fine-needle aspiration, PCR: Polymerase chain reaction, MTB: *Mycobacterium tuberculosis*

Table 5: Summary result of articles

Author, country	Study design	Diagnosis			Suggestion	Treatment	
		Mantoux test	Biopsy <i>Mycobacterium</i> staining and culture	NAAT			
				Xpert MTB/RIF			PCR (conventional)
Lee ^[6] , Korea	Report		The first-line diagnostic technique Excision biopsy has the highest sensitivity, whereas FNA is less invasive and may be useful If FNA examination results are inconclusive, excision biopsy may need to be done Issues Low sensitivity - 0-40% Delayed results (2-8 weeks)	Assay, a novel automated, cartridge-based NAAT Xpert was highly sensitive for detecting TB in lymph node samples - 83.1% Pooled specificity of 98.7% for diagnosing EPTB	NAAT is used for rapid molecular detection and diagnosis of EPTB	6-month regimen	
Gautam <i>et al.</i> , ^[14] India	Cohort	31.42% positive	Detection rate: 17.85%	Interpretation of data was software based and not user dependent Detection rate - 25.71% Sensitivity - 80% Specificity - 86.89%	Detection rate, 20.71% Sensitivity - 68% Specificity - 89.57%	Combines clinical, radiological, and microbiological methods	6-month regimen
Ministry of Health, ^[3] Malaysia	Clinical practice guidelines		First-line diagnostic test Excision biopsy only when FNA is inconclusive or persistent lymph node despite full treatment			6-month regimen (2 months isoniazid, RIF, pyrazinamide, ethambutol I/4 months isoniazid, RIF)	

Contd...

Table 5: Contd...

Author, country	Study design	Diagnosis			Suggestion	Treatment	
		Mantoux test	Biopsy Mycobacterium staining and culture	NAAT			
				Xpert MTB/RIF			PCR (conventional)
Asimacopoulos <i>et al.</i> , ^[12] UK	Cross-sectional	52% positive	Tuberculous process seen in 79%			Diagnostic efficacy of FNA increases from 67% to 91% when cytological and microbiological modalities are combined	
Burrill <i>et al.</i> , ^[3] England	Report					Head-and-neck CT and MRI can be used for evaluation	
Engin <i>et al.</i> , ^[19] Turkey	Report					Head-and-neck CT and MRI can be used for evaluation	
Mittal <i>et al.</i> , ^[15] India	Cohort		Acid-fast bacilli detected on staining in 52% Positive culture, 60%		Positive - 60% Sensitivity - 88.23%	68% were diagnosed using a combination of staining, culture, and PCR	
McAllister and MacGregor, ^[13] UK	Cross-sectional		FNA Sensitivity - 53% Cytology - 27% Culture - 70% Excision biopsy Sensitivity - 91% Histology - 88% Culture - 69%			Specimens should be sent for both histopathology and microbiological analysis	
Meghji and Giddings, ^[16] UK	Cohort		FNA Cytology - 49% Culture - 40% Excision biopsy Histology - 97.6% Culture - 70.1%			FNA is minimally invasive and cost-effective If the first FNA is inconclusive, excision biopsy should be performed to save time	
Suzana <i>et al.</i> , ^[17] India	Cohort			Sensitivity - 89% Specificity - 74% (compared to culture)		Results are more rapid with higher accuracy	

NAAT: Nucleic acid amplification test, FNA: Fine-needle aspiration, EPTB: Extrapulmonary tuberculosis, CT: Computed tomography, PCR: Polymerase chain reaction, RIF: Rifampicin

for detecting acid-fast bacilli is neither highly specific nor highly sensitive, but it is a rapid method. A Canadian guideline mentioned that the sensitivity for sputum in a tuberculous lymphadenitis patient was only 5%–14%.^[22] This could be due to the portion of patients having co-infection of pulmonary TB and EPTB.

The next step typically involves cytology studies using the FNA specimen, or histopathology using an excision biopsy specimen, together with culture. Typically, both have very high sensitivity but low specificity for EPTB. This method is typically done for all new cases. The mode of detection is the identification of granulomas. This becomes problematic because it cannot specifically detect TB granulomas from other diseases that also feature the presence of granulomas in the tissue, such as nontuberculous mycobacterium infection

and leprosy, and occasionally syphilis, fungal infection, and brucellosis.^[23,24] On the other hand, culture specimens are usually highly specific but have low sensitivity, and the time for obtaining results is usually about 3–8 weeks.^[20,25] This greatly delays treatment for EPTB, thus increasing the complications of the disease.

New modalities have been researched for overcoming the issue of long waiting time for results, and molecular techniques have been developed. Using a nucleic acid amplification test such as the polymerase chain reaction can greatly increase sensitivity and dramatically reduce the turnaround time to about 6–8 h.^[26-28] As it is an amplification method, it can detect as few as ten mycobacteria, and this increases the sensitivity of the test.^[29] The newer modality is the Xpert[®] MTB/RIF assay, which is an automated cartridge-based method that enables

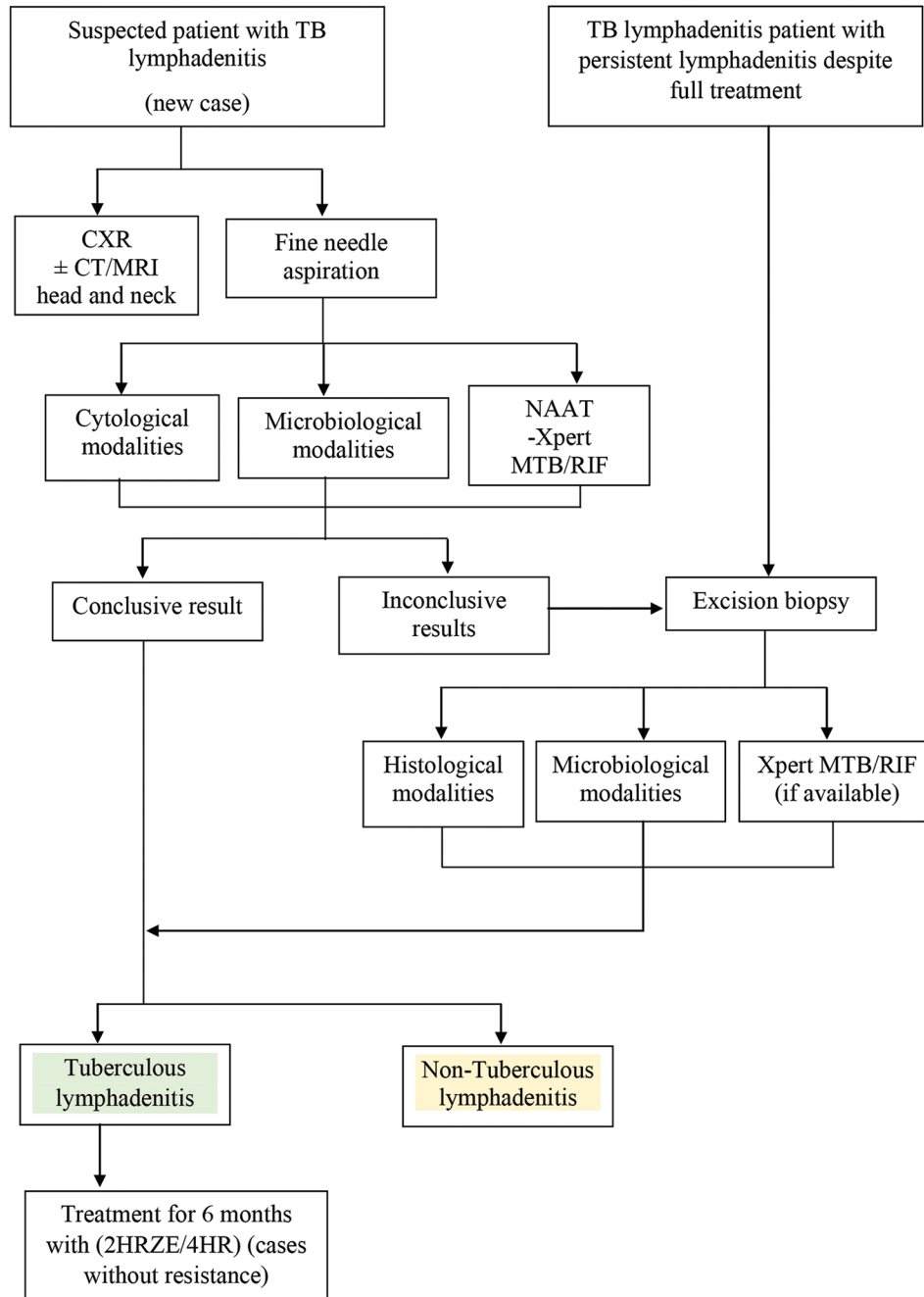


Figure 2: Diagnostic pathway for tuberculous lymphadenitis. NAAT: Nucleic acid amplification test, 2HRZE/4HR: 2 months isoniazid, rifampicin, pyrazinamide, ethambutol/4 months isoniazid, rifampicin

more rapid diagnosis^[6,30,31] and provides high sensitivity for detecting tuberculous lymphadenitis.^[6,23,30] This appears to be a promising method for the rapid detection of EPTB as compared to other methods; the only setback is that it is relatively costlier.^[23,27,32]

Others have compared these techniques, and one such review of 18 studies noted a pooled sensitivity of 83.1% for Xpert MTB/RIF as compared to culture specimens.^[31] The sensitivity and specificity of each test also increased when the tests are combined.^[7,30]

Table 6 shows the positive and negative traits of each test. Clearly, each test has its pros and cons, and using only one specific test for diagnosing tuberculous lymphadenitis is insufficient. Therefore, the ideal diagnostic test should be a combination of laboratory testing, together with relevant patient history and clinical examination.^[6,25,32]

Apart from the standard laboratory tests, additional radiological intervention can be used to support the diagnosis. Chest X-ray (CXR) is usually performed to rule out pulmonary involvement, as it is possible for a pulmonary TB patient to

Table 6: Advantages and disadvantages of each diagnostic test

Test	Advantage	Disadvantage
Microscopy	High specificity Short time for obtaining results	Low sensitivity
Cytology	High sensitivity	Low specificity
Histopathology	High sensitivity	Low specificity
Culture	High specificity	Low sensitivity Long time for obtaining results: 3-8 weeks
Nucleic acid amplification test (PCR-based)	High sensitivity and specificity	Costly
Xpert MTB/RIF	Short time for obtaining results: 6-8 h	

PCR: Polymerase chain reaction, MTB: *Mycobacterium tuberculosis*, RIF: Rifampicin

also have EPTB infection simultaneously. It can also be used to rule out any pleural, vertebral, or joint involvement. Even if the CXR is nonspecific for TB, the presence of cavitation, lymph nodes, and infiltrates is highly suggestive of TB infection. Computed tomography scan and magnetic resonance imaging can be used to aid in the diagnosis of EPTB.^[20,33]

Once a diagnosis is made, the recommended treatment for tuberculous lymphadenitis is 6-month first-line antitubercular treatment.^[3,7,20,32] The treatment includes 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) and 4 months of isoniazid and rifampicin (2HRZE/4HR) in cases where no resistance were detected. The required duration of treatment for tuberculous lymphadenitis was studied by comparing a 6- and 9-month regimen, which showed that both regimens were not greatly different. Both regimens had almost equal relapse and cure rates, but the authors noted that patients would prefer a shorter treatment duration and would be likely to follow the treatment and would have lower risk for adverse effects.^[32]

Limitation

One limitation of this study is the limited articles on EPTB infection and more specifically on tuberculous lymphadenitis. Most articles only compared one or two types of test, and not all tests were available for comparison of the best method. Apart from that, the studies were all different in terms of sample size, aim, and outcome.

CONCLUSION

Diagnosing tuberculous lymphadenitis would first require a high index of suspicion by the treating physician. With that, and the proper algorithm to follow, there would be no delays and clinicians would be able to ensure that all patients are treated as soon as possible and avoid complications brought on by delayed treatment, misdiagnosis and incorrect treatment, and complication of the progressing disease.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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