

Case Report

The role of cartridge-based nucleic acid amplification test (CBNAAT) in early diagnosis of extra pulmonary tuberculosis – a case report

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Abstract – Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. It primarily affects the lungs, leading to Hemoptysis, which is the most frequent manifestation. When organs other than the lungs, pleura, such as lymph nodes, abdomen, reproductive organs (testicles, ovaries), skin, meninges, bones, and joints are affected, it is called extrapulmonary tuberculosis (EPTB). Recently, the Cartridge-based Nucleic Acid Amplification Test (CBNAAT) has shown higher sensitivity and specificity than other diagnostic tests in individuals with active and latent tuberculosis infection. This case highlights the importance of early and rapid diagnosis of tuberculous cervical lymphadenitis (scrofula) in a 38-year-old female using a cartridge-based nucleic acid amplification test (CBNAAT) and its treatment with antitubercular drugs, followed up 2 months after antitubercular drug treatment.

Introduction

Tuberculosis (TB) is a contagious infectious microbial disease caused by *Mycobacterium tuberculosis*, an acid-fast bacillus, and is part of a group of microorganism classified as the *Mycobacterium tuberculosis* complex [1]. According to the India Tuberculosis (TB) report-2023, approximately 0.172 million tuberculosis cases per million people were affected by tuberculosis in 2022 [1]. India is active in its pace to end tuberculosis (TB) by 2025 [1]. The government of India also aids in counteracting this tuberculosis by providing free antitubercular drugs in primary healthcare centers. Among all tuberculosis infections, over 15% occur in the extrapulmonary region [2].

Extrapulmonary Tuberculosis involves organs other than the lungs, such as the meninges, lymph nodes, reproductive organs, abdomen, joints, vertebral spine, skin, and bones [3]. Immunocompromised patients with tuberculosis (TB) are more likely to experience extrapulmonary symptoms, have a higher risk of latent disease reactivation, and acquire disseminated illness [4]. Worldwide, tuberculosis kills more than one million people per year, according to the latest estimates [5].

Although tuberculosis is curable, it remains challenging to detect, treat, and avoid its spread [5]. An initial evaluation is essential because samples such as sputum are typically difficult to obtain, and extrapulmonary lesions are paucibacillary [5]. Recently, nucleic acid amplification tests have enabled rapid and accurate detection of extrapulmonary tuberculosis [6].

According to the World Health Organization, approximately 2 million people die each year from tuberculosis, and 8 million people have active tuberculosis. Lifetime active tuberculous infection is possible in one out of every ten patients infected with *Mycobacterium tuberculosis* (TB). The likelihood of active tuberculosis increases in the first year following infection; however, for the majority of individuals, the disease does not manifest itself until much later [7].

Observation

A 38-year-old female presented to the Outpatient Department of Oral Medicine and Radiology with a chief complaint of swelling and pain in her neck for the past 1 month. The pain was gradual in onset, moderate in intensity, continuous in frequency, aggravated on bending forward, and occasionally relieved by warm water compression application. The patient also reported symptoms that were associated with frequent

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Fig. 1. Enlarged right supraclavicular lymph node.

vomiting, malaise, and lethargy. When probing history further, the patient reported that her grandmother at home had frequent bouts of cough for several years. Her medical history revealed hypothyroidism and irregular menstrual cycles over the past 4 months. On extraoral clinical examination, an enlarged supraclavicular lymph node was present on the right side of the neck, 1.5 cm above the sternoclavicular end of the right clavicle. The lymph node measured approximately 2×2 cm in size. The skin over the surface of the right supraclavicular lymph node had the same color as the surrounding skin but was stretched (Fig. 1). On palpation, the right supraclavicular lymph node was matted, firm in consistency, and tender.

Intraoral examination revealed dental caries in the right and left mandibular first molars, and root stumps in the right mandibular second molar. Based on these clinical findings, a provisional diagnosis of cervical lymphadenitis was made. Extrapulmonary tuberculosis and infected lipomas were considered as differential diagnoses. Intraoral examination revealed carious tooth 36,37,46, root stump 47 (Fig. 2A). Intra-oral periapical radiography revealed diffuse radiolucency in the crown portion involving the enamel, dentin, and pulp with an ill-defined radiolucency and loss of the lamina dura about the right mandibular first molar and root-like radiopaque structure with an ill-defined periapical radiolucency concerning the right lower second molar (Fig. 2B).

Based on these radiographic findings, Dental caries with chronic periapical abscess in right mandibular first molar was made. There was a marked elevation of C-reactive protein (CRP) in our case, 15.4 mg/L (normal C-reactive protein below 10 mg/L), and the erythrocyte sedimentation rate (ESR) was 25 mm (normal ESR range 0-20 mm/hr). Acid-fast bacilli staining

of sputum was negative. The tuberculin skin test (TST) result showed a positive outcome with 25 mm swelling and induration at the injection site 2.5 cm away from the left antecubital fossa along the long axis of the flexor aspect of the left forearm (Fig. 3).

Color Doppler Ultrasonography (USG) of the swelling on the right side of the neck revealed an ill-defined hypoechoic area with fluid collection surrounded by areas of inflammation in the right lower cervical neck space, posterior to the sternocleidomastoid muscle, and lateral to the right internal jugular vein. The sinus tract originated from the collection of matted cervical lymph nodes in the lateral aspect of the neck above the supra-clavicular region and extended up to the acromion process of the right scapula (Fig. 4).

Cartridge-based nucleic acid amplification test (CBNAAT) was positive for *Mycobacterium tuberculosis* (MTB) aspirated from the neck swelling with 9.4×10^2 colony forming units/mL (CFU/mL) (Fig. 5).

Based on investigations and clinical findings, a final diagnosis of extrapulmonary tuberculosis involving the right supraclavicular lymph node was made. The patient was prescribed an antitubercular drug regimen: rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, and ethambutol hydrochloride 275 mg for 6 months. The swelling over the neck subsided two months after initiating antitubercular medication. (Fig. 6).

Discussion

Mycobacterium tuberculosis is a non-motile, aerobic, rod-shaped bacterium that belongs to the Family- *Mycobacteriaceae* Genus- *Mycobacterium*, order *Actinomycetales* Class- *Actinomycetes*. Pulmonary tuberculosis refers to the condition in which the lungs are affected by tuberculosis. Active tuberculosis (TB) involves the multiplication of tuberculosis microorganisms when the immune system fails. When tuberculous microorganisms enter the lymphatics or bloodstream, involve two or more non-neighbouring sites, and disseminate to different organs, "disseminated tuberculosis" is employed. Tuberculous lymphadenitis can also occur as the first sign of a primary infection caused by nontuberculous *mycobacteria* acquired through direct transmission from the mucous membranes of the oropharynx [4].

Extrapulmonary tuberculosis is a term used to describe tuberculosis that affects organs other than lungs. Extrapulmonary tuberculosis includes tuberculous intrathoracic lymphadenitis or tuberculous pleural effusion without any obvious lung parenchymal abnormalities seen on chest X-rays [5]. Tuberculosis of the lymph nodes may develop as a primary infection or a clinical manifestation of a systemic condition.

Initially, the lymph nodes become enlarged, firm, mobile, and discrete; later, peri-adenitis occurs where the nodes are fixed to each other and the surrounding tissue; then, central softening occurs due to caseous necrosis, followed by collar-stud abscess and sinus tract formation [5].

Infection is transmitted by droplets containing *M. tuberculosis* microorganisms. Macrophages engulf and destroy the bacterium *Mycobacterium tuberculosis* (MTB). However, if

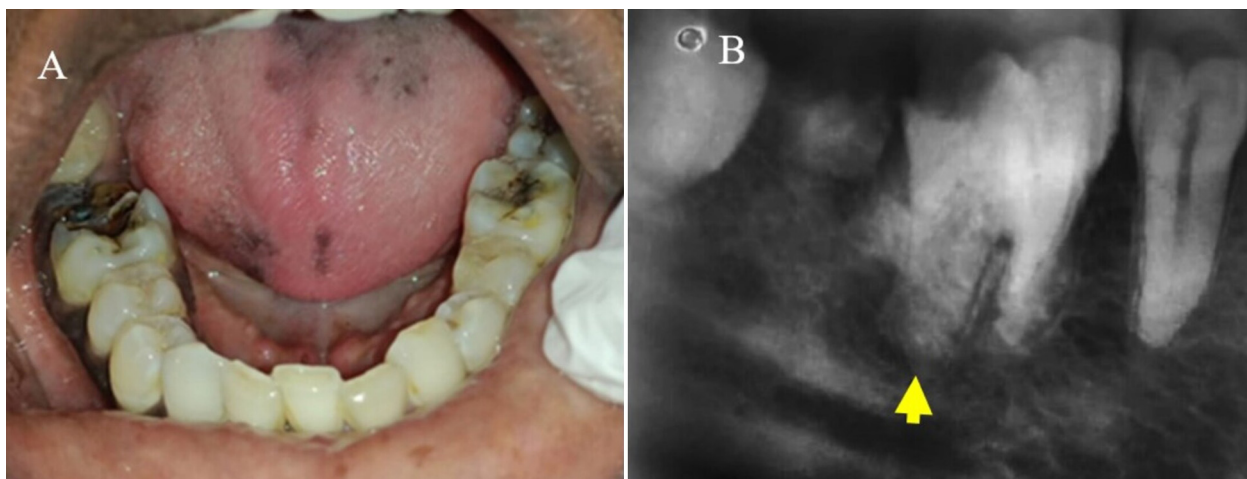


Fig. 2. A. Dental caries right mandibular first molar, B. Ill-defined radiolucency in periapical mesial root apex region in right mandibular first molar.



Fig. 3. Tuberculin skin test.

macrophages do not engulf bacilli due to immunocompromised states, such as acquired immunodeficiency syndrome (AIDS) or uncontrolled diabetes, they reach the lung alveoli and multiply rapidly. During the initial infection, *Mycobacterium tuberculosis* bacteria spread via the blood and lymphatic system, affecting the cervical lymph nodes and lungs [6], and rarely manifests with routine constitutional symptoms, such as pyrexia, malaise, anorexia, and weight loss, along with clinical signs and symptoms related to the affected organ system [7].

Except for groups that received Bacillus Calmette Guérin (BCG) vaccination after infancy, Interferon-Gamma Release Assays (IGRAs) offer a higher positive predictive value owing to

their increased specificity. Both the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are valuable for detecting latent tuberculosis infection (LTBI). Screening for latent tuberculosis infection (LTBI) is essential for individuals with identifiable risk factors that increase their likelihood of developing the disease, such as recent infection, young age, and immunosuppression [8]. Our patient presented with enlarged right cervical supraclavicular lymph nodes fixed to the underlying structures, which is the second stage of tuberculosis. She had no prodromal symptoms of fever or malaise. Vague clinical presentations with the absence of constitutional symptoms of tuberculosis such as fever, weight loss, unpredictable distribution of *Mycobacterium tuberculosis* microorganisms, few bacteria-paucibacillary nature of the disease, difficulty in acquiring suitable and sufficient samples such as sputum, and limited effectiveness of traditional microbiological procedures such as ziehl-neelsen sputum smear microscopy, culture contribute to the challenges in the diagnosis of extrapulmonary tuberculosis (EPTB).

The choice of diagnostic method is contingent upon the impacted organ system. Various techniques, such as nucleic acid polymerase chain reaction amplification test, interferon-gamma release assay (IGRA), and immunological test-tuberculin test involving the skin, are employed to ascertain the diagnosis of extrapulmonary tuberculosis (Tab. 1) [8,9]. The Cartridge-Based Nucleic Acid Amplification Test (CB-NAAT) is an automated diagnostic tool that uses cartridges to detect the presence of latent and active *Mycobacterium tuberculosis* and rifampicin drug-resistant strains by amplification of DNA. The World Health Organization (WHO) recommends CB-NAAT as an initial diagnostic test to detect extrapulmonary tuberculosis. It provides rapid results within 2 h, which is definite and promising [10,11].

The Extended Focused assessment with sonography for human immunodeficiency virus (HIV) and tuberculosis (e FASH) is an ultrasound protocol specifically developed to identify extrapulmonary tuberculosis. FASH is indicated in

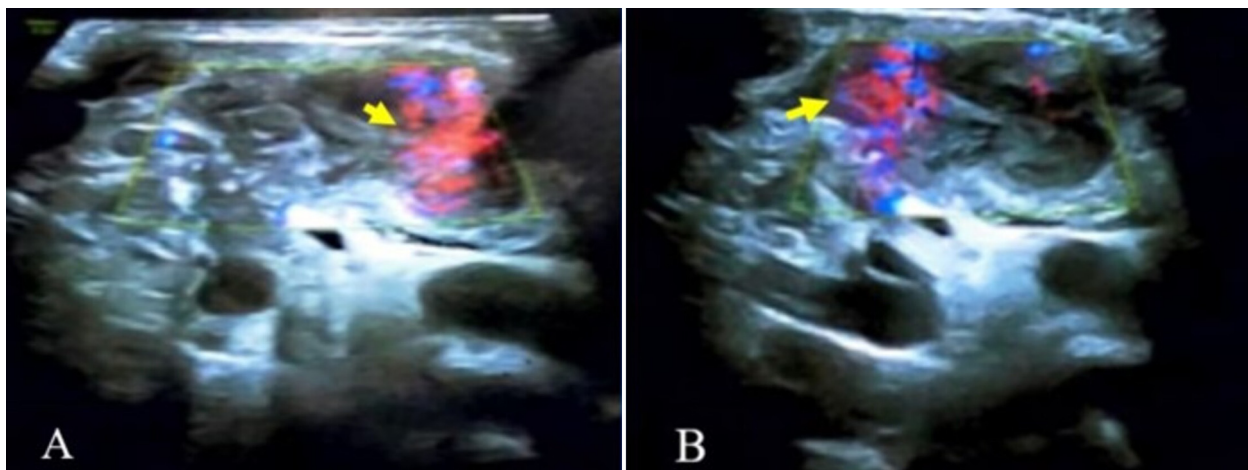


Fig. 4. Color doppler ultrasonography revealed a hypoechoic area in the right lower cervical neck space (increased color doppler flow) (yellow arrow).

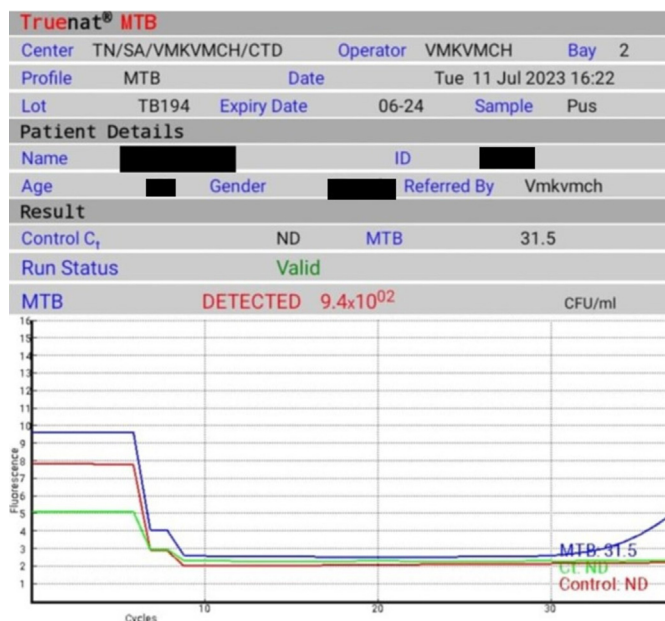


Fig. 5. Cartridge-based nucleic acid amplification test result.

suspected pleural and pericardial effusions, enlarged axillary, abdominal, nuchal, cervical lymph nodes, splenomegaly, hepatomegaly, and ascites caused by extrapulmonary tuberculosis [12]. Ultrasonography is a diagnostic tool for identifying and distinguishing extrapulmonary symptoms. It is also accessible and valuable in economically challenging places with resource limited settings worldwide [12]. The extended focused assessment with sonography for Tuberculosis (eFASH) procedure consists of an ultrasound evaluation of the chest, cervical lymph node, and the breadth of the inferior vena cava to determine if there is right heart failure in Extrapulmonary tuberculosis (EPTB) [12].

Conventional therapy for pulmonary tuberculosis consists of a two-month regimen of quadruple therapy with isoniazid (INH), ethambutol (EMB), rifampicin (RMP), and pyrazinamide



Fig. 6. 2 months post-treatment follow-up showed complete resolution of the neck swelling.

(PZA), followed immediately by four months of administration of rifampicin (RMP) and isoniazid (INH). Tuberculosis affecting the bones and joints requires 9 months of antitubercular drug regimen. Tuberculosis of the central nervous system, which results in meningitis, requires an antitubercular treatment regimen of 12 months [13]. Most adverse effects, such as nausea, vomiting, and skin rash, are related to the gastrointestinal system. However, a more severe and rare side effect of antitubercular drug is the occurrence of significant liver damage, characterized by a substantial increase in liver enzymes to levels three to five times higher than the average. Severe hepatic toxicity occurs in approximately 2.4% of cases and may necessitate temporary cessation of antitubercular medication [13].

Prior research has documented that 16–20% of cases of extensively drug-resistant tuberculosis (EP-TB) exhibit collective drug resistance. Among the instances of drug-resistant extrapulmonary tuberculosis (DR EP-TB), investigations have demonstrated the highest level of resistance to isoniazid (8–14%), whereas the occurrence of rifampicin monoresistance (2.4–3.9%) and multi-drug resistance (MDR) (2.0–10.0%)

Table 1. Diagnostic modalities for Extrapulmonary tuberculosis.

Tests	Description
The extended focused assessment with sonography for tuberculosis (eFASH)	In patients with tuberculosis, extended focused examination with sonography aids in determining the size of enlarged intraabdominal, axillary, nuchal, cervical lymph nodes, hepatomegaly, splenomegaly and thickening of terminal ileal wall.
Tuberculin skin test (TST)	A 0.1 ml intradermal injection of tuberculin pure protein derivative (PPD) is administered to the inner surface of the forearm as part of the Tuberculin Skin Test (TST). The induration reactions are measured within 48 to 72 h following intradermal injection of pure protein derivative (PPD). An induration measuring 5 mm or more is a positive test result for contagious tuberculosis.
Cartridge-based nucleic acid amplification test (CBNAAT) (Gene Xpert MTB/ RIF assay / TruNAT®MTB)	An automated molecular technique that uses Polymerase-chain reaction (PCR) and fluorescent probe. It provides rapid test results within 2 h.
Interferon-Gamma Release Assays (IGRAs)	Interferon-Gamma Release Assays (IGRAs) are blood tests employed to help diagnose tuberculosis (TB) caused by <i>Mycobacterium tuberculosis</i> infections. When diagnosing active and latent tuberculous infection, these assays quantify the immune response to particular antigens produced by <i>M. tuberculosis</i> bacteria.
QuantiFERON®-TB Gold In-Tube test (QFT-GIT)	It identifies <i>in vitro</i> responses to peptide antigens associated with tuberculosis (TB) infection by measuring interferon-gamma levels <i>via</i> enzyme-linked immunosorbent assay (ELISA) in one antigen tube.
QuantiFERON®-TB Gold Plus test	Interprets peptides of tubercle bacilli to stimulate both CD4 + and CD8+ T cells in two antigen tubes (TB1) and (TB2), potentially increasing the sensitivity for detecting both active and latent infections of <i>Mycobacterium tuberculosis</i>
T-SPOT®.TB test (T-Spot)	The T-SPOT.TB test detects <i>M. tuberculosis</i> -sensitized T cells using enzyme-linked immunospot technology (ELISPOT). It assesses interferon-gamma (IFN- γ) reactions to antigens unique to <i>Mycobacterium tuberculosis</i> (TB).

cases were relatively low [14]. The duration and effectiveness of treatment for extrapulmonary tuberculosis (EPTB) vary greatly depending on the organ implicated and the type of clinical manifestation [14]. Swift diagnosis and precise treatment are crucial to prevent the detrimental progression of tuberculosis and its spread to other individuals. Tuberculosis should always be considered in patients with ambiguous symptoms, and is regarded as a potential alternative diagnosis. Identifying latent tuberculosis and determining its treatment pose challenges owing to the absence of specific biomarkers and the limited availability of pertinent data from clinical studies [14]. Diagnostic and treatment decision-making for latent tuberculosis remains challenging owing to the absence of precise biomarkers and relevant clinical trial evidence [15].

Clinical significance

The case highlights the occurrence of tuberculous cervical lymphadenitis in a patient who visited the outpatient department of oral medicine for a dental check-up without

any constitutional symptoms such as fever, weight loss, malaise, night sweats, and fatigue. Rapid early diagnosis of extrapulmonary tuberculosis (EPTB) using cartridge-based nucleic acid amplification test (CBNAAT) is essential.

Conclusions

Thorough knowledge of extrapulmonary tuberculosis is essential for dental practitioners. Lymphadenitis of the cervical lymph nodes (scrofula) is the sole symptom of extrapulmonary tuberculosis infections without characteristic constitutional symptoms, such as cough, weight loss, night sweats, general malaise, fatigue and fever. Undoubtedly, the cartridge-based nucleic acid amplification test (CBNAAT) provides rapid early diagnosis of extrapulmonary tuberculosis. It aids in the initiation of antitubercular drug therapy without delay, thereby preventing further spread of this dreadful infectious microbial disease, which leads to mortality if left untreated.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability statement

The data will be made available upon request from the corresponding author.

Author contribution statement

Ramachandra Reddy Gowda Venkatesha: Concept, Design, Supervision; Karthik Rajaram Mohan: Literature collection, Literature review, Correction of Manuscript, Editing, Design; Vinitha Ganesh: Writing Manuscript, Design, Collection of Clinical Photographs; Saramma Mathew Fenn: Literature review, Literature collection, Editing; Reethika Rathan: Conceptualization, Design, Literature collection; Sabitha Gokulraj: Literature Review, Editing.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

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