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What is the optimal diagnostic pathway in tuberculous lymphadenitis in the face of increasing resistance: Cytology or histology?☆,☆☆,★,★★

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ABSTRACT

Background: The London Borough of Newham has the highest rates of tuberculosis (TB) within Europe (116 per 100,000). There is a lack of guidance in lymph node (LN) TB on how to best obtain a positive culture, which is the gold standard in the face of increasing mycobacterial resistance.

Methods: An individual cohort study was carried out via a prospective local TB database capturing 90 cases of cervical LN TB over 34 months. We compared the diagnostic efficacy of fine needle aspiration (FNA) and excision biopsy of LN.

Results: FNA cytology revealed granulomata in 49%, acid-fast bacilli (AFB) in 8.6% and a positive culture in 40%. LN excision showed granulomata in 97.6%, AFB in 17.1% and a positive culture in 70.1%. There was an 18% resistance to first-line antimicrobials.

Conclusions: We describe our experience and suggest an algorithm for the culture of TB organisms to avoid a lengthy diagnostic process.

1. Introduction

Mycobacterial species first appeared 15,000 years ago [1]. *Mycobacterium tuberculosis* is an obligate aerobe and an acid-fast bacterium. Acid-fast bacilli (AFB) retain dyes when heated and treated with acidic organic compounds, which is the basis for pathologic identification [1]. The probability of developing active clinical tuberculosis (TB) following inhalation of an infectious droplet is less than 10% over a lifetime. Prevalence of TB depends on geographical location, strain type and immunosuppression. Human immunodeficiency virus (HIV) positive patients are twenty times more likely to develop TB [2,3].

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There are an estimated 8 million new cases of TB per annum worldwide [4]. In the United Kingdom (UK), the overall incidence of TB in 2012 was 13.9 per 100,000. Urban centres are reported to have higher incidences; the London Borough of Newham reported the highest rate of tuberculosis in the UK with 116.5 per 100,000 which is comparable to Nigeria and is the highest in Western Europe [5]. Extra-thoracic lymph node TB accounts for 20% of cases [4]. The cervical lymph nodes are the most frequently involved; historically referred to as scrofula [1,2].

Part of the success of the organism is in the delayed presentation. Patients are frequently asymptomatic; the lymph node may grow discretely, in isolation and is usually non-tender [6]. Constitutional symptoms of weight loss, fever, malaise and night sweats are seen in only a minority of patients [7,8].

130 years on from Koch's discovery of tubercle bacilli, the search for effective diagnostic methods continues [9]. There is currently no single point-of-access test available that correctly diagnoses mycobacterial infection and provides sensitivities to the common antimicrobials. There are a range of tests used in tandem to diagnose and screen for TB. Immunodiagnostic tests; QuantiFERON® Gold, QuantiFERON® Gold In-Tube and the T-Spot tests measure interferon-gamma and can confirm that a patient has either active or latent TB and thus play a supportive role in screening only [10,11]. The Mantoux tuberculin sensitivity test has significant cross-reactivity with other mycobacterium and will be positive if the patient has had a Bacillus Calmette-Guerin (BCG) vaccination, therefore its specificity is limited [10,11].

Establishing a firm diagnosis of lymph node TB is therefore difficult but may be achieved by tissue sampling through the identification of AFB on cytology or histopathology. Evidence of granulomatous inflammation on cytology or histology may also point towards TB but has the disadvantage of being non-specific [12]. The gold standard for diagnosis and treatment is a positive culture of the mycobacterial species. There is a lack of guidance on how to best obtain a positive TB culture, especially in the face of increasing mycobacterial resistance.

In the investigation of lymphadenitis, ultrasound (US) with fine needle aspiration (FNA) is usually the first-line diagnostic test. It is quick, cheap and relatively safe. Alternatively, excision biopsy yields increased histological, culture and microscopy sensitivities, however, it is costly, labour-intensive and carries complications [13–15]. These complications include infection, damage to nearby neurovascular structures and a persistent discharging sinus.

Current challenges in TB diagnostics include the diagnostic delay, the HIV epidemic and increasing drug resistance. Difficulty in detection and failure to treat all infectious cases of TB has led to the continued transmission of the disease [2]. We present a summary of the cases of lymph node TB in a suburb of London over 34 months.

2. Methodology

Data was collected from January 2011 to October 2013 via a prospective database of all identified TB cases within the catchment area of Newham. Patients in whom there was clinical suspicion of TB had an FNA, mainly with US, with the aspirate sent for AFB microscopy and TB culture.

In our department, aspirates undergo an Auramine and Ziehl-Neelsen stain at the TB microbiology laboratory to verify the presence of AFB. The aspirate is then concentrated and transferred to culture bottles, which are kept at a temperature of 37 °C for 42 days. Growth plates are read electronically. Specimens are then sent to a central reference laboratory for drug susceptibility testing which rapidly identifies *M. tuberculosis* complex and common non-tuberculous strains. Line probe assays LiPA (Innolipa, LiPA; Innogenetics, Ghent, Belgium) are used for the samples as they are seen as a rapid and sensitive tool in multidrug resistance TB (MDRTB). It involves an initial polymerase-chain-reaction (PCR) based technique followed by hybridisation to a LiPA membrane. PCR based tests for non-respiratory TB samples at the reference laboratory show a sensitivity of 71%, specificity of 92%, positive predictive value of 70% and negative predictive value of 93% [16]. Deoxyribonucleic acid (DNA) sequencing and phenotypic tests are performed when identification is not possible by PCR. Histopathology was considered positive when a sample contained Langerhan's giant cells and caseating granulomas or giant cells with caseating necrosis.

Electronic patient databases were used to confirm AFB results, culture sensitivities and HIV, hepatitis C and hepatitis B status. Patient notes were used to define exact timelines from first presentation at the ear, nose and throat (ENT) clinic through to discharge from the TB chest clinic.

3. Results

There were 114 patients with extrapulmonary lymph node TB, of which 90 had clinically abnormal cervical lymph nodes. The average age was 34.7 years old (range 15–67 years old). Fifty-four percent were male and 46% female. Only 10 patients (11.1%) were born in the UK; 32 patients were from Pakistan, 25 from India and Bangladesh collectively. Those not born in the UK immigrated on average 9 years before diagnosis. Four patients had previous TB, but all completed their original course of antimicrobials. Fifty-four percent had had a previous BCG vaccine. One patient was HIV positive and two were hepatitis B positive.

Seventy-one of the 90 patients with abnormal lymph nodes were initially seen in the ENT "two-week wait clinic" — a rapid diagnostic service for neck masses. The remainder were seen by other specialties and referred directly to the TB clinic or seen initially at the TB clinic and sent for investigations to the ENT department. The median time from presentation to ENT to treatment was 57 days.

Seventy patients (77.8%) initially had an US-FNA. Thirteen had a repeat US-FNA, mainly because the first FNA was non-diagnostic or not sent for TB culture. FNA cytology revealed granulomata in 49%, AFB on microscopy in 8.6% and a positive culture in 40%. Seven patients had a FNA of pus from a lymph node abscess. None of these seven samples revealed AFB on microscopy but six (85.7%) returned a positive culture. Of the 14 FNA samples that were positive for AFB on microscopy, 12 (85.7%) led to a positive culture diagnosis. Four patients underwent a core biopsy revealing granulomata in 50%, but no AFB on microscopy and no positive cultures. Forty-one patients (45.6%) had an excision biopsy of a lymph node, revealing granulomata in 97.6%, AFB in 17.1% and a positive