Extrapulmonary tuberculosis

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Abstract

Extrapulmonary tuberculosis (EPTB) now represents over half of all diagnosed cases of TB in the UK and is increasingly seen in patients with immunosuppression or HIV. It is usually caused by reactivation of latent infection and can cause disease at almost any site, most commonly the lymph nodes (23%), pleura (8.2%), gastrointestinal tract (5.9%), bone (6.7%), central nervous system (4.4%) and genitourinary system (2.1%). Manifestations depend on the site of disease, making diagnosis challenging as EPTB can mimic many other diseases. Hence TB should be considered in the differential diagnosis of any sick patient. A diagnosis of EPTB should trigger a search for concomitant pulmonary disease, which has implications for infectivity, and an HIV test (as with any TB diagnosis). Obtaining appropriate samples for microbiological diagnosis is vital for effective management, especially as drug resistance becomes more common. Treatment is generally with standard quadruple therapy for 6 months (extended in TB meningitis); adjunctive corticosteroid therapy is of proven value in TB pericarditis and meningitis.

Keywords Extrapulmonary tuberculosis; granuloma; HIV; lymphadenitis; miliary tuberculosis; MRCP; pericarditis; spondylodiscitis; tuberculosis; Xpert MTB/RIF®

Introduction

The most common site for infection with *Mycobacterium tuberculosis* worldwide is the lungs, but dissemination can occur to any part of the body, resulting in extrapulmonary tuberculosis (EPTB). In the UK, the proportion of EPTB has increased relative to that of pulmonary tuberculosis (TB). In the UK, the most common sites of infection include the lymph nodes (23%), pleura (8.2%), gastrointestinal tract (5.9%), bone (6.7%), central nervous system (CNS; 4.4%) and genitourinary system (2.1%) (Figure 1).[1] Disseminated or miliary disease (approximately 3%) can also affect any organ. EPTB is under-recognized as symptoms are often non-specific, so diagnosis is often delayed. Therefore, it is important to appreciate the variety of different organ-specific clinical scenarios with which it can present, as well as the non-specific systemic symptoms of TB, such as fevers, night sweats and weight loss.

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Key points

- Symptoms of extrapulmonary tuberculosis (EPTB) are often non-specific, and clinical presentation can mimic that of other diseases, making diagnosis challenging and potentially delayed
- HIV and expanding use of immunomodulatory drugs such as anti-tumour necrosis factor have contributed to the increase in EPTB
- Always try to get samples for microbiology in patients with suspected TB; this is even more important in the current era of increasing incidence of multidrug-resistant tuberculosis (TB)
- Always look for pulmonary TB in patients with EPTB as concurrent pulmonary TB has implications for infectivity, isolation and contact tracing
- Always perform an HIV test in anyone with TB
- Check vitamin D concentration, and replace it if low in patients with TB

General principles of EPTB

Epidemiology

TB remains a major global health problem: an estimated 10.4 million new cases were reported worldwide in 2015.[2] Although the incidence of TB overall in the UK has been gradually decreasing over the past few years, 58.3% of cases reported in England in 2015 were extrapulmonary;[1] this proportion has increased since 2005. The most important risk factors for EPTB are shown in Table 1. Immunodeficiency increases the risk of both TB (primary, reactivation) and extrapulmonary spread if active disease occurs. In otherwise healthy people, most EPTB is presumed to arise from reactivation of latent infection, acquired during a primary infection that could have occurred many years earlier.

Pathology

As with pulmonary disease, the inflammatory response to mycobacterial invasion usually takes the form of granuloma formation. Although other diseases, such as sarcoid, can generate granulomas, caseation is strongly indicative of TB. Pus formation is characteristic and can cause extensive tissue damage; absence of an acute inflammatory infiltrate explains why such abscesses can be 'cold'. Disease can range from multibacillary, as in miliary disease, to paucibacillary, in which a very small number of bacteria generate a disproportionate destructive local inflammatory response.

Diagnostics

The importance of obtaining a positive TB culture cannot be over-estimated, not least to exclude drug-resistant TB. EPTB is often hard to diagnose by microscopy because tissue can be

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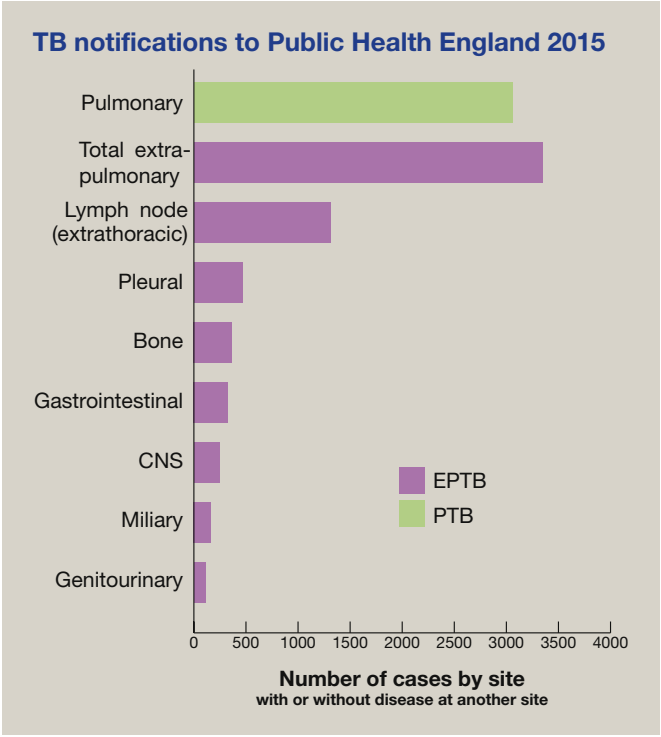

Figure 1

Risk factors for EPTB

- HIV infection
- Tumour necrosis factor-α antagonists (e.g. infliximab)
- Corticosteroids
- Malignancy
- Female sex
- Non-smoker

Table 1

difficult to sample and tissue bacillary burden is often low. Characteristic histology (granuloma ± caseation) and imaging may be sufficient to mandate treatment while awaiting cultures. See Table 2 for the recommendations for diagnostic sampling in EPTB.

Molecular techniques have advanced diagnostic abilities and are now part of routine practice in diagnosing TB. Xpert MTB/RIF® is a rapid automated diagnostic test that detects the presence of *M. tuberculosis* DNA as well as mutations in the *rpoB* gene (which confers rifampicin resistance). With EPTB samples, Xpert MTB/RIF® has a high specificity but limited sensitivity compared with standard culture.[4]

The use of whole-genome sequencing (WGS; Table 3) in higher income settings is the latest advance in TB diagnostics. It is used in research and epidemiology; it is not yet in mainstream use in clinical settings but is being rolled out in reference labs by Public Health England. It will be particularly valuable for contact tracing and identifying drug resistance earlier (see Further reading).

Diagnostic recommendations for different sites in suspected EPTB (summary of National Institute for Health and Care Excellence guidelines)[3]

Suspected site of EPTB	Imaging	Specimen	Test
Pleural	Chest X-ray Bronchoscopy	Pleural biopsy	Microscopy Culture Histology
		Pleural fluid	Microscopy Culture Cytology
CNS	CT MRI	Biopsy suspected tuberculoma	Microscopy Culture Histology
		Cerebrospinal fluid	Microscopy Culture Cytology
Lymph node	Ultrasound CT MRI	Biopsy	Microscopy Culture Histology
		Aspirate	Microscopy Culture Cytology
Pericardial	Echocardiogram	Biopsy of pericardium	Microscopy Culture Histology
		Pericardial fluid	Microscopy Culture Cytology
Gastrointestinal	Ultrasound CT Laparoscopy	Biopsy of site of disease (e.g. omentum, bowel, liver)	Microscopy Culture Histology
		Ascitic fluid	Microscopy Culture Cytology
Genitourinary	Ultrasound Laparoscopy Intravenous urography	Early-morning urine Biopsy from site of disease (e.g. renal biopsy)	Culture Microscopy Culture Histology
Bone/joint	X-ray CT MRI	Biopsy of bone Aspirate of fluid or abscess	Culture

CT, computed tomography; MRI, magnetic resonance imaging.

Table 2

Treatment

The treatment of EPTB is the same as for pulmonary TB, except that the duration of treatment is extended for disease at some sites (12 months for TB meningitis; some advocate extended treatment for TB of bone). Standard TB treatment comprises four drugs: isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E): HRZE is given for a 2-month intensive phase, followed by HR for 4 months (continuation phase). Corticosteroids are generally only used adjunctively in TB meningitis and pericardial TB as there is proven value in these sites (see Further reading).

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