Extrapulmonary tuberculosis

Angela Houston

Derek Clive Macallan

Abstract

Extrapulmonary tuberculosis (EPTB) now represents about half of all diagnosed cases of TB in the UK and is seen increasingly in patients with immunosuppression or HIV. It is usually caused by reactivation of latent infection and may cause disease at almost any site in the body. Most common sites include lymph nodes (19%), pleura (7%), gastrointestinal tract (4%), bone (6%), CNS (3%) and genitourinary system (1%). Its manifestations depend on the site of disease, making diagnosis challenging as EPTB may 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 steroid therapy is of proven value in TB pericarditis and meningitis.

Keywords tuberculosis; extrapulmonary tuberculosis; granuloma; HIV; lymphadenitis; miliary TB; pericarditis; spondylodiscitis; Xpert MTB/RIF

What's new?

- The incidence of extrapulmonary TB (EPTB) in the UK is increasing year-on-year
- Rising HIV prevalence and expanding use of immunomodulatory drugs such as anti-tumour necrosis factor have contributed to the increase in EPTB
- Novel molecular diagnostics including nucleic acid amplification tests (NAAT) and antigen detection assays have improved detection of TB and massively accelerated detection of drug resistance
- Multi-drug resistant EPTB (as for pulmonary disease) is increasing — highlighting the need for samples for NAAT/culture

Introduction

The most common site for infection with *Mycobacterium tuberculosis* (TB) is the lungs (representing about 51% of UK cases[1]), but dissemination may occur to any part of the body, resulting in extrapulmonary tuberculosis (EPTB). Most common sites include lymph nodes (19%), pleura (7%), the gastrointestinal tract (4%), bone (6%), CNS (3%) and genitourinary system (1%) (Figure 1).[1] Disseminated or miliary disease (~3% of UK cases) can also affect any organ. EPTB is under-recognized and diagnosis is often delayed, so it is important to appreciate the variety of different organ-specific clinical scenarios with which it may present, as well as the non-specific systemic symptoms of TB, such as fevers, night sweats and weight loss.

Angela Houston *BSc(Hons) MBchB DTM&H MRCP(UK) MSc FRCPath is an SpR in Infectious Diseases and Medical Microbiology, Clinical Infection Unit, St George's Hospital, London, UK. Conflicts of interest: none declared.*

Derek Clive Macallan *MA PhD DTM&H FRCP is Professor of Infectious Diseases and Medicine, St George's University of London, London, UK. Conflicts of interest: none declared.*

General principles of EPTB

Epidemiology

The incidence of TB in the UK has been increasing over the last decade and with it the incidence of EPTB, which represents about half of all diagnosed TB cases.[1] The most important risk factors for EPTB are shown in Table 1. Immunodeficiency increases both the risk of TB occurring (either primary or reactivation TB), and the risk of extrapulmonary spread, if active disease does occur. 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 for pulmonary disease, the inflammatory response to mycobacterial invasion usually takes the form of granuloma formation. Although other diseases, such as sarcoid, can generate granuloma, caseation is strongly indicative of TB. Pus formation is characteristic and may cause extensive tissue damage; the absence of an acute inflammatory infiltrate explains why such abscesses may be 'cold'. Disease may range from multi-bacillary, as in miliary disease, to paucibacillary, where a very small number of bacteria generate a disproportionate destructive local inflammatory response.

Diagnostics

As for TB in general, the importance of obtaining a positive culture cannot be over-estimated, not least to exclude drug-resistant TB. EPTB is often hard to diagnose by microscopy because tissue may be difficult to sample and tissue bacillary burden is often low. Characteristic histology (granuloma ± caseation) and imaging may be sufficient to mandate treatment whilst awaiting cultures. Novel molecular diagnostics have advanced our ability to detect and define TB (Table 2). Currently, the most promising of these is the Xpert MTB/RIF,[2,3] although the next few years will see more diagnostic tests emerge from the development pipeline.[4]

Treatment

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

Proportion of TB reported to Public Health England 2000-2011

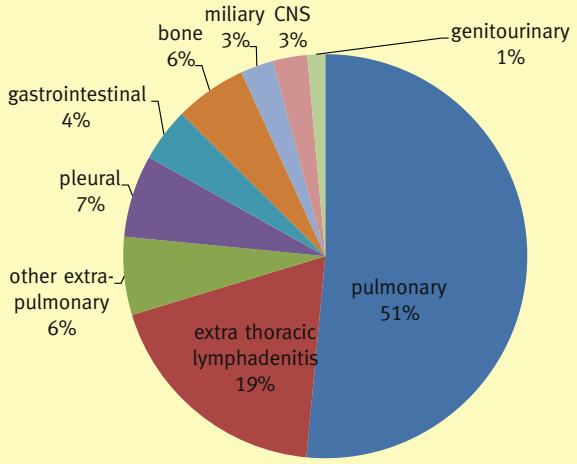

Figure 1

(E): HRZE is given for a 2-month intensive phase, followed by HR for 4 months (continuation phase).[8]

Specific extrapulmonary TB syndromes by disease site

Miliary TB

Miliary TB results from massive lympho-haematogeneous spread throughout the body. It accounts for 3% of EPTB cases and is associated with immunodeficiency. Infection is multi-bacillary, with foci in many organs and mortality is high.[9] The term 'miliary' (Manget, 1700) refers to the resemblance of pulmonary and hepatic nodules to millet seeds. Classically, these appear on chest radiology as multiple small (≤2 mm), discrete opacities.

TB lymphadenitis

Lymphadenitis is the most common presentation of EPTB in both children and adults (19% of UK TB cases). It usually represents reactivation from latent TB, although cervical disease may be caused by local spread from direct infection of tonsils or adenoids. The most common sites are the anterior or posterior cervical and submandibular nodes.

TB lymphadenitis is usually painless. On palpation, nodes are firm but groups may become matted together with induration of overlying skin. Tissue necrosis with formation of fluctuant abscesses is common and abscesses may discharge with sinus formation. Symptoms depend upon site: mediastinal TB lymphadenitis may present with dysphagia or recurrent laryngeal nerve involvement; abdominal/peritoneal disease, usually affecting periportal, mesenteric or peri-pancreatic nodes, often causes non-specific abdominal pain. Ultrasound or computerized tomographic (CT) imaging may show matted mesenteric lymph nodes with fat stranding and oedema. Rarely, enlarged lymph nodes cause obstructive symptoms in the liver (presenting with jaundice) or renal vasculature.

Fine-needle aspiration (FNA) of the affected node is recommended for mycobacterial molecular diagnostics and culture, and to exclude differentials such as malignancy or other infections (e.g. *Bartonella, Toxoplasma*) (Table 2).[10] Excision biopsy may be considered if the diagnosis is in doubt. The yield of acid-fast bacilli (AFB) from a smear is poor but increases in patients co-infected with HIV.[10]

TB lymphadenitis often follows a waxing and waning course, even during treatment. Worsening on treatment may be attributable to paradoxical reactions (an enhanced immune response to dying mycobacteria). Aspiration of abscesses may relieve symptoms temporarily, although repeated aspiration carries a small risk of sinus or fistula formation. Treatment is with standard quadruple therapy; the benefit of corticosteroids is debatable, although they do seem to expedite symptomatic improvement.

Pleural TB

Symptoms of pleural TB include pleuritic chest pain and breathlessness, associated with fevers and night sweats. Radiology may show pleural effusions, even in the absence of lung parenchymal changes. The pleural fluid is an exudate with high protein, low glucose and often lymphocytosis. AFB are rarely visible but pleural fluid becomes culture positive in up to 75% of patients; adenosine deaminase analysis is useful, having an 88% sensitivity for TB diagnosis.[11] Diagnosis can also be aided by pleural biopsy (for histology and culture) and the use of video-assisted

Risk factors for extrapulmonary tuberculosis

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

Table 1

New developments in the diagnosis of extrapulmonary tuberculosis

- Automated DNA tests (e.g. Xpert MTB/RIF) are rapid tests (~2 hours) that detect the presence of MTB DNA and test for mutations in the *rpoB* gene
- In extrapulmonary samples, the overall sensitivity is 77.3–95% and specificity 99–100%, equivalent to tuberculosis (TB) liquid culture[3,5]
- *rpoB* mutations identify 95% of resistance to rifampicin (taken as an indicator of multi-drug resistant TB). This represents a huge advance in TB diagnostics
- Urine enzyme-linked immunosorbent assay (dipstick) tests (*Determine TB-LAM*) detect the mycobacterial cell wall lipopolysaccharide antigen, lipoarabinomannan (LAM). Although still in development, they have potential as a low-cost, point-of-care test to detect disseminated TB in highly immunosuppressed patients (advanced HIV with CD4 count <200 cells/mm^3 – also those most likely to benefit from prompt treatment)[6,7]

Table 2