Extrapulmonary tuberculosis

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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

Introduction
The most common site for infection with Mycobacterium tuberculosis (TB) is the lungs (representing about 51% of UK cases), 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). 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.

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. 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, although the next few years will see more diagnostic tests emerge from the development pipeline.

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

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. 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). 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.

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 lymphcytosis. 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. 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.
- 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, lipid arabinomannan (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/mm³ — also those most likely to benefit from prompt treatment)

Table 2
thoracic surgery (VATS). The differential diagnosis for pleural effusion is obviously wide, notably including para-pneumonic effusions, adenocarcinoma and malignant mesothelioma.

**Spinal and bone TB**

TB affecting bones accounts for 12% of EPTB cases and 6% of all TB notifications in the UK. The most common site of infection is the spine (9% of EPTB), followed by other large joints such as the hip, knee and shoulder. Spinal TB comprises several pathological entities including vertebral osteomyelitis, spondylitis and discitis (or spondylodiscitis, “Pott’s disease”) (Figure 2). The infection usually begins in the anterior aspect of the vertebral body adjacent to the subchondral plate, spreading to the adjacent disc, although in children the sequence may be reversed, progressing from vascularized disc to bone. Progressive bone destruction may lead to vertebral collapse and kyphosis with spinal gibbus formation (anterior angulation). Destructive cold abscesses may form and commonly extend into adjacent ligaments and soft tissues, especially the psoas muscle (psoas abscess). Narrowing of the spinal canal by deformity, abscess-formation, granulation tissue or direct dural invasion may result in spinal cord compression, a neurosurgical emergency.

Typically there is a long history (≥6 months) of fluctuating non-specific back pain, accompanied by constitutional symptoms. Plain X-rays may be deceptively normal and CT or magnetic resonance (MR) imaging is often needed for diagnosis. Aspiration of collections and/or biopsy of the affected bone may aid diagnosis and drainage may expedite recovery. TB treatment should be started immediately with standard quadruple therapy for 6–9 months. Adjunct corticosteroids are recommended if there is evidence of CNS or dural involvement. Joint management with orthopaedic or neurosurgeons experienced in the management of TB spine is essential to assess spinal stability and the need for external support or operative stabilization.

TB affecting other bones and joints is less common. Most cases present with bone or soft tissue swelling, often with sinus formation. There is no clear evidence to support the role of surgery and drainage or sinus repair. Sinus formation can be particularly troublesome and can take months if not years to heal, even with fully drug-sensitive organisms.

**Abdominal TB**

Gastrointestinal TB has a predilection for the terminal ileum; thickening or ulceration in this area may easily be mistaken for Crohn’s disease. Conversely, large bowel disease may be diagnosed radiologically as cancer. Complications include perforation and TB peritonitis. Diagnosis is difficult as symptoms (abdominal pain, fevers, weight loss) are non-specific. Radiological findings may include bowel thickening, lymphadenopathy, ascites, free gas suggestive of perforation, and abscess-formation, but the most important diagnostic aspect is a high index of suspicion in patients with risk factors for TB. Laparoscopic or colonoscopic biopsies are useful for histology and culture.

**Urogenital TB**

Urogenital TB comprises renal disease, ureteric disease and genital infection. The diagnosis of renal disease is easily missed, as back or flank pain, dysuria or constitutional symptoms occur in only 30% of patients. Renal TB is usually unilateral and rarely causes renal failure; the exception is tuberculous interstitial nephritis, which may affect both kidneys. Renal abscesses (Figure 3) may destroy the entire renal parenchyma. Pelvocalyceal involvement may result in thickening of the collecting system; more distally, ureteric fibrosis and stricture formation may cause hydronephrosis, whereas TB of the bladder wall may lead to fibrosis. Genital tract infection is unusual but most commonly affects the prostate of men or endometrium of women. Ovarian, tubal and testicular disease may result in infertility.

Depending on site, diagnosis depends on a combination of early-morning urine samples (EMUs) (when the concentration of AFBs in the urine is highest), biopsies and radiology. EMUs are insensitive but molecular tests may improve diagnostic yield (Table 2). Renal biopsy may show granulomatous interstitial nephritis, often with multifocal caseous necrosis. Cystoscopy with biopsies of bladder or ureteric/prostate tissue may also be helpful. Imaging or the renal tract may show a characteristically ‘beaded’ ureter (ureteritis cystica).

**Pericardial TB**

Although rare (accounting for <1% of EPTB), pericardial TB merits consideration because it is potentially life-threatening. TB pericarditis can present either acutely, with massive pericardial fluid accumulation causing cardiac tamponade, or sub-acutely.
with constrictive pericarditis. In acute disease, the chest X-ray shows cardiomegaly (Figure 4) and echocardiography reveals a large pericardial effusion. Aspiration/drainage may control the acute situation but surgical intervention (forming an open pericardial window to prevent fluid reaccumulation) may also be required (and also provides tissue for histology/culture). Corticosteroids expedite clinical recovery and reduce mortality.18

Other forms of extrapulmonary TB

Tuberculous meningitis is not discussed here as it is covered in MEDICINE 41(12): 683-685. Other EPTB sites that merit consideration include TB of the larynx because of its very high infectivity; cutaneous TB, either as primary disease, ‘scrofuloderma’, or local spread from adjacent affected organs; and adrenal involvement which, although rare, can result in acute adrenal insufficiency or the syndrome of inappropriate anti-diuretic hormone (SIADH) secretion.19 Non-specific syndromes such as haemophagocytic syndrome have also been described in EPTB.

Conclusion

TB can affect any part of the body, hence this review cannot be exhaustive. EPTB is a great imitator and can easily be misdiagnosed. Key aspects of management include a high index of suspicion for the disease, particularly in those with epidemiological risk factors or who are immunosuppressed, and taking appropriate specimens for histology and culture. Therapeutic outcomes are generally good, provided diagnosis is prompt and complications can be avoided (Table 3).

Medical emergencies in extrapulmonary TB — the ‘alarm bells’

Syndromes or complications that need urgent intervention include:

- Miliary disease may paradoxically worsen on treatment initiation — consider corticosteroids
- TB meningitis — beware of increased intracranial pressure (see MEDICINE 41(12): 683-685)
- Check for spinal cord compression in spinal TB — consider surgical decompression and add corticosteroids
- Look for cardiac tamponade in pericardial TB — give corticosteroids and consider drainage/pericardiectomy
- Hydronephrosis in renal/urogenital TB may need stenting
- Adrenal disease may precipitate an Addisonian crisis, which is easy to overlook — corticosteroid replacement may be required
- Beware of vascular obstruction due to mass lesions (cold abscesses) or lymphadenopathy

Table 3

Other forms of extrapulmonary TB

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REFERENCES


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**Practice points**

- Always try to get samples for microbiology in patients with suspected TB; discuss appropriate sampling with a microbiology doctor first
- Always look for pulmonary TB in patients with extrapulmonary TB as concurrent pulmonary TB has implications for infectivity, isolation and contact tracing
- Always perform an HIV test in anyone with TB
- early-morning urine samples should be taken in patients with suspected renal TB
- Be aware of increasing incidence of multi-drug resistant TB
- Check and replace vitamin D, if low, in patients with TB