Diagnosis and management of intra-abdominal tuberculosis

Intra-abdominal tuberculosis is the term used to describe infection of the intra-abdominal solid organs, peritoneum and the gastrointestinal tract with *Mycobacterium tuberculosis*. The abdomen is the sixth most common extrapulmonary site after lymphatic, genitourinary, bone, joint and meningeal infection (Chaudery et al, 2010). Pulmonary tuberculosis is accompanied by intra-abdominal tuberculosis in 11% of cases (Kapoor, 1998), but intra-abdominal tuberculosis can occur in the absence of pulmonary tuberculosis (Kruijshaar and Abubakar, 2009).

Intra-abdominal tuberculosis is on the rise both globally and in the UK, therefore clinical suspicion in patients presenting with abdominal pain, fever, night sweats, weight loss and sub-acute gastric obstruction (*Table 1*) should be heightened. Globally, increasing incidence has been attributed to poverty and co-existing HIV infection, while rising incidence in the UK has largely been attributed to imported disease (Kruijshaar and Abubakar, 2009). Other risk factors for developing intra-abdominal tuberculosis include diabetes mellitus and iatrogenic immunosuppression.

Intra-abdominal tuberculosis is difficult to diagnose and, clinically, is easily mistaken for inflammatory bowel disease, with histological appearances very similar to those found in Crohn's disease (*Table 2*) (Jadvar et al, 1997). Therefore clinical history, including ethnicity, travel, contact history and HIV status, may point to a diagnosis of intra-abdominal tuberculosis, and failure to consider the infection may lead to significant delay in diagnosis. Initiation of immunosuppressive therapies for presumed inflammatory bowel disease will aggravate symptoms and could precipitate miliary tuberculosis and death.

This article provides an overview of epidemiology, pathophysiology, clinical presentation, differential diagnoses and interpretation of diagnostic tests in the context of peritoneal, intestinal and hepatic tuberculosis, aiming to raise the profile of the infection and better equip clinicians to make the diagnosis.

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Epidemiology

Despite global efforts to reduce the incidence of tuberculosis, in 2015 the World Health Organization (2016) estimated there were 10.4 million new cases, resulting in 1.8 million deaths worldwide. Poverty and co-existent HIV infection most commonly predispose to infection, but diabetes mellitus, malignancy, peritoneal dialysis and immunosuppressive therapies are also associated.

In the UK the highest rates of tuberculosis are among non-UK nationals (Nayagam et al, 2016) and are therefore thought to be imported. Extra-pulmonary disease, including intra-abdominal tuberculosis, is increasing in the UK (Kruijshaar and Abubakar, 2009). Intra-abdominal tuberculosis accounts for 5% of cases admitted to London hospitals (Nayagam et al, 2016) and can occur in the absence of active pulmonary disease. Women are twice as likely to develop extra-pulmonary disease (29.9% where n=9806/26 302) than men (16.6% where n=16 496/26 302) and may be at greater risk of intra-abdominal tuberculosis (Forssbohm et al, 2008). Intra-abdominal tuberculosis can occur in patients of any age, but is most commonly seen in those aged 21–40 years (Kapoor, 1998).

Table 1. Clinical signs and symptoms associated with intra-abdominal tuberculosis

Systemic manifestations of disease	Low-grade fever	
	Night sweats	
	Anorexia	
	Weight loss	
	Lethargy	
	Malaise	
Non-specific gastric symptoms	Abdominal pain	
	Distention or localized swelling	
	Nausea	
	Vomiting	
	Change in bowel habit	
Site-specific gastric symptoms	Peritoneal disease	'Doughy abdomen'
		Ascites
	Intestinal disease	Diarrhoea or constipation
		Rectal disease – minor per rectal bleeding
	Hepatic disease	Right upper quadrant pain
		Jaundice (rare)
		Ascites (rare)
		Hepatosplenomegaly (rare)

Pathophysiology

Intra-abdominal tuberculosis describes infection of the peritoneum, gastrointestinal tract and visceral organs including the liver, spleen, pancreas and intra-abdominal lymph nodes, but not the renal tract (Kapoor, 1998). Intra-abdominal infection is thought to be caused by haematogenous spread from the pulmonary system or other infected organs. However, it may also be caused by ingestion of either infected food, or sputum in patients with active lung disease (Jadvar et

Table 2. Features to help distinguish intra-abdominal tuberculosis from Crohn's disease

	Crohn's disease		Intra-abdominal tuberculosis	
Clinical manifestations	Fever occurs in active disease		Fever, when present, is high (>38.5°C) or swinging (not a consistent finding)	
	Weight loss		Weight loss – over a protracted course	
	Abdominal pain		Diffuse abdominal pain	
	Diarrhoea (bloody)		Diarrhoea (rarely bloody) or constipation	
	Extra-intestinal manifestations	Peri-anal fistulae	Extra-abdominal manifestations	Peri-anal fistulae are rare
		Eye disease		Pulmonary tuberculosis on chest X-ray
		Rheumatological manifestations		
Findings on imaging (ultrasound, computed tomography or magnetic resonance imaging)	Symmetrical bowel wall thickening		Asymmetrical bowel wall thickening	
	Lymph nodes – pericaecal, small, homogenous		Lymph nodes – mesenteric, large, necrotic centres	
	Engorged mesenteric vessels with associated fatty infiltration		Focus of inflammation most commonly occurs around the caecum and terminal ileum	
	No ascites		Ascites	
Endoscopy findings	Apthous ulcers (mouth)		No apthous ulcers	
	Ulcers are longitudinal and penetrate the lamina propria		Ulcers are transverse and do not penetrate the lamina propria	
	'Cobblestone' mucosa with associated 'skip lesions'		Hypertrophic mucosa	
	Preserved ileocaecal valve		Destruction or widening of the ileocaecal valve	
	Anorectal disease is common		Anorectal disease is rare	
Histopathology findings	Granulomas	Are non-caseating	Granulomas	Occur in <30% of cases and are pathognomonic for tuberculosis
		Are singular		Are confluent
				Are caseating
		Do not stain for acid-fast bacilli		Stain for acid-fast bacilli

From Ahuja (2017)

al, 1997; Rasheed et al, 2007), or by direct transmission from adjacent infected organs (Kapoor, 1998).

Once in the gastrointestinal tract bacilli enter the lymphatic system, via Peyer's patches, in macrophages and are carried to mesenteric lymph nodes (Kapoor, 1998). Here they can remain dormant or cause inflammation leading to swelling, fibrosis and ulceration.

The most common sites of involvement are the ileum and ileocaecal region, followed by the small intestine (Kapoor, 1998). Splenic involvement is usually associated with hepatic infection. The stomach and oesophagus are rarely affected as they contain little lymphoid tissue.

Clinical presentation: an overview

Clinical symptoms vary widely, are non-specific and cannot be relied upon to make a diagnosis (*Tables 1* and *2*). Systemic symptoms often have an insidious onset and include low-grade fever, night sweats, anorexia, weight loss, lethargy and malaise.

Non-specific gastrointestinal symptoms include abdominal pain and swelling, nausea, vomiting and change in bowel habit. Pain is the most common feature and can be caused by luminal blockage, stricture, mesenteric adenitis or peritoneal infection (Rasheed et al, 2007).

Certain symptoms are more commonly associated with site-specific infection. For example, infection involving the large or small bowel can result in chronic diarrhoea or constipation (Ahuja, 2017). Rectal involvement can cause minor per rectal bleeding (Kapoor, 1998) and fistulae. The classically described, but rarely felt, 'doughy abdomen' is associated with peritoneal disease (Ahuja, 2017), specifically the fibrotic-fixed type, while jaundice is most commonly described in patients with hepatic involvement.

Differential diagnosis

The diagnosis of intra-abdominal tuberculosis is challenging. Known as the 'great mimicker' (Chaudery et al, 2010), intra-abdominal tuberculosis is often mistaken for Crohn's disease, lymphoma or other gastric malignancies (Hu et al, 2009) (*Table 3*). Surgical causes of 'the acute abdomen' must also be ruled out. It is essential to take a thorough social, contact and travel history, as this, in the context of the patient's demographics, may indicate a higher clinical suspicion for intra-abdominal tuberculosis.

Diagnostic overview

In the event of diagnostic suspicion, a systematic approach to clinical investigation should be adopted, commencing with routine tests and progressing to more specific investigations.

Full blood count, white cell differential, C-reactive protein, urea and electrolytes and liver function tests may all aid diagnosis of infection. A common combination of

Table 3. Common differential diagnoses

Inflammatory bowel disease (specifically Crohn's disease)
Malignancy
Lymphoma
Surgical 'acute abdomen'
Carcinomatosis (in the context of miliary hepatic tuberculosis)

findings in intra-abdominal tuberculosis include low haemoglobin level in the context of raised C-reactive protein levels and erythrocyte sedimentation rate (Rasheed et al, 2007). However, it must be acknowledged that a multitude of infectious agents can produce a similar pattern in these non-specific markers of infection. Mycobacterial blood cultures are of limited utility.

The use of Mantoux skin testing in diagnosis of intra-abdominal tuberculosis is unreliable, as results are often negative even in the presence of intra-abdominal tuberculosis (Uygur-Bayramiçli et al, 2003).

Imaging should include chest X-ray to identify primary lung disease, although intra-abdominal tuberculosis can occur in the absence of pulmonary disease and chest radiographs may only be abnormal in 15–50% of cases (Rasheed et al, 2007). Ultrasound scanning and computed tomography of the abdomen will identify ascites or specific tissue involvement.

Site-specific tuberculosis: clinical presentation and investigation

Intestinal tuberculosis

The most common sites of involvement are the ileum and the ileocaecal region, followed by the small intestine (Kapoor, 1998). Tuberculous infection of the gastric mucosa results in ulceration, inflammatory infiltrates and resultant strictures (Rasheed et al, 2007). Patients commonly present with abdominal pain, change in bowel habit (diarrhoea or constipation), abdominal mass in the right iliac fossa (Rasheed et al, 2007) and occasionally with overt signs of obstruction. In the event of rectal involvement minor per rectal bleeding can occur. Signs, symptoms and investigations can be deceptively similar to those seen in malignancy and Crohn's disease, and differentiating the cause remains the clinician's greatest challenge (Jadvar et al, 1997).

Ultrasound can identify thickened bowel loops, enlarged abdominal lymph nodes and ascites (Spalgais et al, 2017). Ascites rarely occurs in Crohn's disease and warrants further investigation for intra-abdominal tuberculosis in the context of other suggestive factors.

Abdominal and pelvic computed tomography imaging should be carried out, even if the patient is a woman and of reproductive age. Findings characteristic of intra-abdominal tuberculosis include ascites, fibrinous stranding, a pelvic mass and calcified or enlarged retroperitoneal lymph nodes (Chaudery et al, 2010).

Barium studies demonstrate intra-luminal changes, but cannot differentiate intra-abdominal tuberculosis from Crohn's disease (Rasheed et al, 2007). Equally, endoscopy commonly provides inconclusive results, identifying aphthous ulcers, skip lesions, mucosal oedema and anal erosions, all of which can be seen in intra-abdominal tuberculosis and Crohn's disease (Rasheed et al, 2007). Endoscopic biopsies can be obtained for culture, Gram and Ziehl–Neelsen stain and histology.

In the event of diagnostic uncertainty, despite the above investigations, exploratory laparoscopy or laparotomy should be performed. This allows visualization and directed biopsy of the peritoneum and organs.

Histology can be challenging to interpret as both intra-abdominal tuberculosis and Crohn's disease cause granuloma formation. However, in tuberculosis granulomas tend to be submucosal, confluent and caseating, whereas in Crohn's disease granulomas involve the mucosa, are small and tend not to caseate (Ahuja, 2017).

Peritoneal tuberculosis

Peritoneal infection occurs in 38% of cases (Uygur-Bayramiçli et al, 2003), most commonly in association with other forms of gastric tuberculosis (Jadvar et al, 1997). It is classified into three types: wet, plastic or dry, and fibrotic-fixed (Jadvar et al, 1997).

Wet peritoneal disease is the commonest form and is characterized by abdominal pain, ascites and fever. The plastic or dry type is caused by the presence of caseating nodules, causing peritoneal inflammation. This results in formation of dense adhesions. The fibrotic-fixed type causes adhesions resulting in formation of omental masses, to which the bowel becomes tethered. This can cause sub-acute intestinal obstruction (Kapoor, 1998). The doughy abdomen can be palpated in these patients (Ahuja, 2017).

Peritoneal disease can be difficult to differentiate, both clinically and radiologically, from malignancy (specifically peritoneal carcinomatosis) and lymphoma (Kapoor, 1998). Ultrasound scanning can identify stigmata of intra-abdominal tuberculosis: ascites containing fine fibrous strands and lymphadenopathy with hypoechogenic cores indicative of caseation (Kapoor, 1998; Rasheed et al, 2007). Computed tomography imaging may reveal lymphadenopathy, fibrous matting, ascites, nodules and inflammation extending from the peritoneum into the extra-peritoneal cavity (Kapoor, 1998). It is crucial to obtain tissue diagnosis and computed tomography-guided biopsy. Paracentesis should be performed if ascites is present.

Ascitic fluid should be analysed for differential cell count, cytology, albumin and protein concentration (to determine serum–ascites albumin gradient) and adenosine deaminase levels. Cirrhotic liver disease must be identified or ruled out before results are interpreted.

In the context of intra-abdominal tuberculosis and in the absence of hepatitis, the protein content of ascitic fluid should be >3.0 g/dl, making the serum–ascites albumin gradient <1.1 g/dl. Cell content would typically demonstrate a lymphocytosis of 140–4000 cells/mm3. In non-cirrhotics elevated adenosine deaminase levels has high sensitivity and specificity when diagnosing intra-abdominal tuberculosis. However, sensitivity falls to approximately 30% in cirrhotics (Ahuja, 2017).

Culture from ascitic fluid has a yield of only 3%, and can take up to 8 weeks for a positive culture to be obtained (Chaudery et al, 2010). Polymerase chain reaction or cytology of ascitic fluid allows for more rapid diagnosis (Chaudery et al, 2010). Gram and Ziehl–Neelsen stain should also be performed.

Exploratory laparoscopy or laparotomy may be necessary if diagnostic doubt remains despite the above investigations. Laparoscopic peritoneal biopsy has a high diagnostic yield.

Hepatic tuberculosis

Hepatic disease can be either localized or miliary, but the miliary form is more common. The liver is affected in approximately 80% of patients with disseminated tuberculosis, through haematogenous spread by the hepatic artery (Ahuja, 2017). Patients may present with right upper quadrant pain, nausea, weight loss and fever. Less common signs include jaundice, ascites and splenomegaly (in 30% of cases) (Ahuja, 2017).

Computed tomography is superior to ultrasound scanning for identification of hepatic disease and can be used to guide liver biopsies. Miliary disease appears as a multitude of low-attenuation foci on

computed tomography (Kapoor, 1998), which may be mistaken for metastatic disease, sarcoid and lymphoma (Kapoor, 1998).

Clinicians must differentiate liver cirrhosis from intra-abdominal tuberculosis. In intra-abdominal tuberculosis ultrasound scanning will demonstrate smooth hepatomegaly with either miliary (micronodular) or macronodular appearances (Jadvar et al, 1997). It will also identify ascites. Paracentesis should be performed in patients with ascites.

Liver biopsy is the diagnostic gold standard and should be sent for culture, Ziehl–Neelsen staining and polymerase chain reaction.

Management

Antimicrobial therapy is the mainstay of treatment. The antibiotic regimen is the same as that used to treat pulmonary tuberculosis (rifampicin and isoniazid for the duration of treatment with additional pyrazinamide and ethambutol during at induction). Duration of therapy is commonly 6 months, but some clinicians use an extended antibiotic course to reduce the risk of relapse (Jullien et al, 2016). Directly observed therapy has improved adherence to treatment regimens and, possibly, overall cure rates (Rasheed et al, 2007).

Symptoms, particularly fever and night sweats, usually resolve within a few weeks of commencing antimicrobials. If symptoms fail to improve within this timeframe, alternative diagnoses such as lymphoma, malignancy or Crohn's disease should be re-considered (Ahuja, 2017).

Healing can promote fibrosis and scar tissue. This can inadvertently lead to worsening of strictures and subsequent obstruction. In this case surgical intervention is necessary (Ahuja, 2017). Steroids, when used under specialist guidance, in conjunction with antituberculous therapies can reduce the aforementioned complications and associated mortality (Alrajhi et al, 1998).

Conclusions

Intra-abdominal tuberculosis describes tuberculous infection of the intra-abdominal solid organs, peritoneum and the gastrointestinal tract, which can occur in the absence of pulmonary tuberculosis. Incidence in the UK is increasing, largely as a result of imported disease, and should therefore be considered as a differential in patients presenting with abdominal pain, weight loss, fever and night sweats.

Non-specific signs and symptoms complicate diagnosis. Intra-abdominal tuberculosis can mimic Crohn's disease, with similarities in clinical presentation and histology. Failure to consider intra-abdominal tuberculosis as a differential could lead to misdiagnosis and incorrect management, precipitating patient death.

Computed tomography of the abdomen is the gold standard imaging modality. As women show a propensity for extrapulmonary tuberculosis they are at greater risk of developing intra-abdominal tuberculosis. Therefore, where clinical index of suspicion is high, computed tomography of the abdomen should be performed in women of reproductive age.

Ascites and tissue samples should be examined for acid-fast bacilli by Ziehl–Neelsen staining, culture and polymerase chain reaction. Where initial investigations prove inconclusive exploratory laparotomy should be considered.

Once a diagnosis has been made patients should be commenced on appropriate antituberculous therapy for a minimum of 6 months. Concurrent use of steroids, under specialist supervision, can reduce complications and mortality. Use of directly observed therapy improves treatment outcomes. **BJHM**

Conflict of interest: none.

KEY POINTS

- Diagnosis of intra-abdominal tuberculosis is often significantly delayed and must be included in the differential diagnoses of inflammatory abdominal presentations.
- Key questions are social (country of origin), contact, travel, vaccination history and HIV status. Features of the clinical history will raise the index of suspicion for intra-abdominal tuberculosis.
- Key clinical features are insidious weight loss, night sweats, fever, abdominal pain, nausea (+/- vomiting), change in bowel habit, abdominal mass, 'doughy abdomen' and ascites.
- Commonest sites of infection are the ileum and ileocaecal regions, and the peritoneum.
- Paracentesis should be performed in patients with ascites. Ascitic fluid should be sent for differential cell count, Gram and Ziehl–Neelsen staining and culture. Computed tomography of the abdomen is gold standard and, where there is strong clinical suspicion of intra-abdominal tuberculosis, should be performed on women of reproductive age.
- Multi-drug therapy should be started and maintained for a minimum of 6 months. Concurrent use of steroids, under specialist supervision, can reduce complications and mortality.

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