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Tuberculosis of the gastrointestinal tract and associated viscera

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ABSTRACT

Tuberculosis involvement of the gastrointestinal tract, peritoneum, and associated viscera is an uncommon but well described entity. While peritoneal tuberculosis and tuberculous enteritis are more common, involvement of the esophagus, stomach, colon, rectum, anus, liver, bile ducts, gallbladder, and pancreas can occur. Diagnosis is challenging as cases often mimic neoplasm or inflammatory bowel disease. In this review we outline the pathogenesis, clinical presentation, diagnostic testing, and treatment strategies pertaining to such cases.

Introduction

Tuberculosis (TB) is a global epidemic. In 2015, the WHO estimated there were 10.4 million new cases of TB and 1.4 million deaths worldwide. This included 1.2 million new cases and 0.4 million deaths in patients co-infected with human immunodeficiency virus (HIV) [1]. TB disproportionately affects patients afflicted by poverty, regardless of where they live in the world [2]. Although TB is much less common in the United States, it continues to be a public health concern. In 2014, the CDC reported 9421 new cases of TB in the United States (66% of which occurred among foreign born people) and in 2013 the CDC reported 555 deaths due to TB [3].

Given its prevalence and often non-specific presentation, cases of extrapulmonary tuberculosis (EPTB) are often difficult to diagnose and manage. Here, we present an overview of extra-pulmonary tuberculosis involving the peritoneum, gastrointestinal tract and associated viscera including the liver, bile ducts, pancreas, and gallbladder.

Overview

TB of the gastrointestinal tract, peritoneum, and associated viscera (collectively known as abdominal TB) is the sixth most frequent form of EPTB after lymphatic, genitourinary, bone, miliary, and CNS tuberculosis [4]. Peritoneal TB is the most common presentation of abdominal TB. Epidemiologic data suggests a predominance of peritoneal tuberculosis and tuberculous enteritis in younger patients less than 45 years of age [5,6]. TB may manifest in any location throughout the luminal gastrointestinal tract from the oral cavity to the rectum, although certain locations, such as the ileocecum are more common. There are common features that pertain to abdominal TB regardless of the anatomical site involved.

Pathogenesis

Abdominal tuberculosis develops from invasion of pathogenic bacteria, triggering damaging granulomatous inflammation. Such invasion and inflammation can lead to ulceration, bleeding, and perforation. The spread of pathogenic bacteria to the gastrointestinal tract occurs via four main routes. These routes of acquisition include swallowing of contaminated respiratory tract secretions, hematogenous spread from active pulmonary infection, contiguous spread from adjacent infected viscera or lymph nodes, and uncommonly ingestion of contaminated unpasteurized dairy products [7–9]. When contaminated sputum or food is ingested pathogenic bacteria invade through the intestinal epithelium and into the submucosa. Areas within the gastrointestinal tract containing high concentrations of lymphoid tissue and M-cells, such as the terminal ileum, are particularly susceptible to invasion [5]. In addition to inflammatory damage of the gastrointestinal tract wall, pathologic involvement of the gastrointestinal vasculature occurs. This is evidenced by histopathologic studies of mesenteric vessels in patients with tuberculous enteritis. When examined microscopically these vessels show granulomatous inflammation within the arterial wall and thrombosis with the arterial lumen. Thus, ischemia may exacerbate the gastrointestinal damage initiated by this localized granulomatous

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inflammation [4].

Testing

Tuberculin skin testing (TST) and interferon gamma release assay (IGRA) are usually positive in cases of abdominal tuberculosis. However, a positive result cannot distinguish between latent and active infection, and negative TST or IGRA does not exclude active tuberculosis infection. This limits their utility in diagnosis of active abdominal TB [8]. Smear microscopy and mycobacterial culture should be performed in all cases of suspected TB infection. Histologic examination should be performed if tissue is obtained. The gold standard for diagnosis is positive culture growth. However, the clinical utility of culture is limited by its relative low yield and the prolonged period (often weeks) required for growth to be detected [10]. For example, in cases of peritoneal tuberculosis, culture of ascitic fluid and tissue sampling has a sensitivity of only 35%6. As such, adjunctive testing may be considered when possible. The Xpert MTB/RIF (Xpert) assay is a nucleic acid amplification test that identifies the presence of Mycobacterium tuberculosis DNA, while having the additive benefit of detecting gene mutations conferring rifampin resistance. The assay uses five molecular probes targeted to the 81 bp rpoB core region [11]. The pooled sensitivity of the Xpert assay in lymph node samples, gastric aspirates, and ascitic fluid samples is 96%, 78%, and 59% respectively [10,12]. There is limited data regarding the sensitivity in fecal samples although one small study found sensitivity to be 100% and 50% in patients with sputum positive and sputum negative disease respectively [13]. Such data on testing extra pulmonary samples is not robust and limited to international studies, and the Xpert assay is currently only approved for use on respiratory samples in the United States. Due to such limitations, PCR testing of extra pulmonary samples is often done using 'home grown' laboratory developed molecular assays using unique proprietary primers. Such differences in testing make comparison of PCR testing used throughout the United States quite difficult.

Treatment

The current INDEX-TB guidelines for treatment of EPTB recommend standard treatment for all forms of abdominal TB. This consists of two months of four drug therapy (rifampin, isoniazid, pyrazinamide, ethambutol) followed by four months of two drug therapy (rifampin, isoniazid) [14]. These guidelines carefully note that this recommendation is largely extrapolated from study of pulmonary TB treatment, and that there is a paucity of data specific to treatment of abdominal TB. Providers should employ directly observed therapy (DOT) as outlined by the World Health Organization (WHO). Although DOT has not been extensively studied in abdominal TB, we advocate for the use of observed therapy based on its demonstrated benefit in patients with pulmonary tuberculosis. This recommendation aligns with the current Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) guidelines [15].

A clinical dilemma that can occur is how to approach treating a patient with active pulmonary TB who also reports abdominal symptoms. While treatment of active pulmonary TB is adequate to treat most manifestations of coexisting abdominal disease, care should be taken to assess for abdominal complications that may not respond fully to drug therapy. Such complications may require endoscopic or surgical interventions, and are discussed in detail in the following sections.

Drug resistance

Single and multi-drug resistant TB (MDR-TB) infections are becoming more common. In 2017, the WHO estimated an incidence of 601,000 MDR-TB cases worldwide. Rapid molecular drug susceptibility testing is recommended for patients who have been previously treated for tuberculosis, have been in contact with patients with known MDR TB, those who were born in or spent more than one year in a country with a moderate TB incidence ($\geq$20 cases per 100 000 people or a MDR TB prevalence greater than 2%), or HIV co-infected patients [16]. If culture growth is available causative organisms can be tested for drug susceptibility, allowing for tailored drug therapy. Recommendations regarding specific drug regimens for MDR-TB are beyond the scope of this review [17].

Tuberculosis of the gastrointestinal tract, peritoneum, and associated viscera

Peritoneal tuberculosis

Peritoneal tuberculosis is a manifestation of EPTB that requires a high degree of suspicion to diagnose. Diagnosis is often delayed weeks to months after the onset of symptoms [18,19]. One contributing factor to this delay is the presence of overlapping conditions (such as cirrhosis) that may provide an explanation for a multitude of patient symptoms. Peritoneal tuberculosis affects both sexes equally, and most commonly impacts those 35–45 years old [6]. Risk factors for developing peritoneal TB include states of immunosuppression (most prominently HIV/AIDS), kidney failure requiring dialysis, cirrhosis, and malnutrition [20,21].

Peritoneal infection most commonly results from hematogenous dissemination, although direct spread from involved areas of the gastrointestinal tract may occur. Concomitant pulmonary disease exists in 14% of patients 6. Once infected, the peritoneal membrane becomes thickened and hypervascular, and there is formation exudative proteinaceous ascites in most cases.

Three patterns of peritoneal TB are classically described. This includes a pattern of thickened peritoneum with ascites and scattered tubercular nodules; thickened peritoneum with ascites but without tubercles; and markedly thickened peritoneum with extensive fibrous adhesions and a relative absence of ascites. This third type is also known as a fibroadhesive, dry, or plastic pattern and corresponds to the classically described 'doughy abdomen' on physical exmaination [22,23]. This fibroadhesive pattern is least common, occurring in only 5–13% of peritoneal TB cases [22].

The clinical presentation of peritoneal TB is non-specific, often manifesting with an insidious development of systemic symptoms. The most common signs and symptoms include ascites (73%), abdominal pain (65%), weight loss (61%), fever (59%), diarrhea (21.4%), and constipation (11%). Lab testing is non-specific although normocytic anemia, thrombocytosis, monocytosis, and elevated erythrocyte sedimentation rate are characteristic [6].

Diagnostic paracentesis should be performed in all patients with ascites in whom peritoneal tuberculosis is a consideration. Ascitic fluid is typically straw colored but can be hemorrhagic in some cases. An ascites protein level $\geq$2.5 g/dL, serum albumin to ascitic fluid albumin ratio (SAAG) of less than 1.1 g/dL, elevated adenosine deaminase level $>$30 U/L, and a cell count of 500–1500 cells/mm3 with lymphocytic predominance is indicative of peritoneal TB. While ascitic fluid protein level $\geq$2.5 g/dL and SAAG $<$ than 1.1 g/dL is present in essentially all cases of peritoneal TB, it is not necessarily unique to peritoneal TB. This can be due to the presence of a co-existing condition such as cirrhosis, heart and renal failure which can confound basic peritoneal fluid analysis. While positive culture is considered the gold standard, ascitic fluid and tissue culture have low yield (sensitivity 35%), and may take weeks to show growth. Only 3% of samples are smear positive (with Ziehl–Neelson stain) [6]. Molecular testing of ascitic fluid samples using a PCR assay can be considered as an adjunctive test [10,12].

Ultrasound and computerized tomography (CT imaging) are useful in identifying disease features, but perhaps the greatest utility of these modalities is identification of target sites for fluid and tissue sampling. Characteristic CT findings include ascites, mesenteric lymphadenopathy, a thickened hypervascular peritoneum, tubercular nodules,