DIAGNOSTIC CHALLENGE OF GASTROINTESTINAL TUBERCULOSIS: A REPORT OF 34 CASES AND AN OVERVIEW OF THE LITERATURE

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Abstract. We report 34 cases of gastrointestinal TB from Malaysia and present an overview of the diagnostic challenges. A concerted effort is necessary to improve the existing diagnostic methods, and develop and evaluate newer diagnostic tools through well designed multi-center studies.

INTRODUCTION

Tuberculosis (TB) has reemerged as a deadly pandemic in recent years. Nearly 2 billion people, constituting one third of the world's population are infected with tuberculosis (TB) (WHO, 2005a, 2007). TB kills over 5,000 people every day and nearly 2 million every year (WHO, 2006). TB alone causes 5% of all deaths worldwide, 9.6% of deaths in adults (the economically important age class between 15 and 59 years) (NIAID, 1999). TB is the leading cause of death among all women, especially the young (NIAID, 2001; WHO, 2005b). TB affects the poorest and marginalized population, breaks the social fabric and undermines the gains of global economic development. According to a WHO 2008 report, the estimated number of TB cases prevalent in the world was 14.4 million in 2006. Of these, the number of new cases was alarmingly high at 9.2 million. Africa, Southeast Asia and the Western Pacific accounted for 83% of all cases globally (WHO, 2008).

In countries with comprehensive diagnostic and reporting systems, extra-pulmonary TB (EPTB) accounts for 15-20% cases reported, particularly in people with HIV infection. In Cambodia the percent of EPTB cases rose from 9.8% in 1998 to 15.1% in 2002 of the total TB cases (WHO, 2005c). EPTB can involve any organ and is more difficult to diagnose than pulmonary tuberculosis (PTB), often requiring invasive procedures to obtain diagnostic specimens and more sophisticated laboratory techniques than sputum microscopy. The diagnosis can be elusive necessitating a high index of suspicion (Golden and Vikram, 2005). More often it is diagnosed on the basis of clinical experience which may lead to diagnostic errors (WHO, 2005c). According to Akgun *et al* (2005) gastrointestinal tuberculosis (GITB) is responsible for 1% of all cases of TB. Data describing the incidence or clinical spectrum of gastrointestinal tuberculosis is scarce and the details are unavailable (Leung *et al*, 2006). This information is important since it significantly impacts patient survival (Novak *et al*, 2007). Apart from mortality, it may result in

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unnecessary surgery (Uzunkoy *et al,* 2004). Autopsies of patients with pulmonary TB before the era of effective treatment demonstrated intestinal involvement in 55-90% of fatal cases. The previously noted frequent association between PTB and GITB no longer prevails, and only a minority of patients with abdominal tuberculosis now have abnormal chest findings. In less than 50% of patients with GITB the lungs are affected (Goic-Barisic *et al,* 2006; Leung *et al,* 2006).

REPORT OF 34 CASES OF GITB

A total of 34 cases were studied, 22 from Respiratory Medical Institute, Kuala Lumpur, and the rest from Alor Star Hospital, Kedah State, Malyasia. There were 19 male and 15 female patients. The median age was 37 and the ages ranged from 14 to 74 years. A majority of the patients (58%) were in the 30 to 40 years age range. The most cases were Malays (*n* = 25), Chinese (*n* = 4), Indians (*n* = 3), indigenous (*n* =1) and Indonesian (*n* = 1). The modes of presentation were pain in the right iliac fossa (*n* = 9), bowel obstruction (*n* = 9), abdominal pain (*n* = 7), diarrhea (*n* = 6) and ascites (*n* = 4). The sites of TB involvement were: cecum (*n* = 13), ileum (*n* = 10), mesenteric lymph nodes (*n* = 9), small intestine excluding terminal ileum (*n* = 7) and ascending colon (*n* = 6). Twenty-three of the cases were diagnosed based on histopathological tissue examination, which was suggestive of TB (caseating and non-caseating granulomatous inflammation). In 3 cases the presence of acid- fast bacilli was demonstrated on histological section by Ziehl-Nielsen staining. Other cases were diagnosed by overall clinical features and/or imaging findings which supported the diagnosis of TB. Chest radiography was suggestive of PTB in 16 cases (47%). All patients responded to anti-tuberculosis therapy. There were no deaths.

OVERVIEW OF DIAGNOSTIC CHALLENGES OF GITB

GITB is caused by Mycobacteria, which include *M. tuberculosis, M. africanum* (human reservoir) and *M. bovis* (cattle reservoir). The bacteria can spread from a primary lung focus or ingestion of bacilli in sputum from an active pulmonary focus or direct extension from the regional lymph nodes or genitourinary system (Bolukbas *et al,* 2005; Leung *et al,* 2006). In the gastrointestinal tract, any area from mouth to anus can be involved, apart from the peritoneum and pancreatobiliary system. However, in the biliary system, gallbladder TB is uncommon as intact gallbladder mucosa is resistant to *Mycobacterium tuberculosis* due to the presence of concentrated bile acids in the gall bladder lumen (Kapoor *et al,* 2006). The ileocecal area is the most commonly reported site for involvement because of the apparent affinity of the TB bacillus for lymphoid tissue and areas of physiological stasis facilitating prolonged contact between the bacilli and the mucosa (Bolukbas *et al,* 2005; Golden and Vikram, 2005; Leung *et al,* 2006). The various methods of diagnosis are clinical, imaging, endoscopy, histopathology, culture and molecular methods, such as PCR.

Clinical diagnosis

Clinical diagnosis is difficult because of non-specific symptoms, like chronic abdominal pain, weight loss, fever, diarrhea, constipation, or blood in the stool. It may mimic other abdominal diseases, such as other infections (amebiasis, yersiniosis), tumors, periappendiceal abscesses and Crohn's disease (CD). Differentiating between TB and CD is important since steroid treatment can be life saving in CD and lethal in intestinal TB (Chatzikostas *et al,* 2002; Martinez *et al,* 2003). Besides the difficulty in clinical diagnosis, it is often delayed due to the absence of specific biological markers, long incuba-

tion time for cultures and non-specific imaging findings increase the morbidity associated with this treatable condition (Vogel and Bous, 2008). The isolation of *M. tuberculosis* is not an easy process and granulomas may not be found in the intestine, but are usually found in the mesenteric lymph nodes. Intestinal obstruction is the most common complication (Makanjoula, 1997).

Imaging

The various imaging methods used are barium meal, intestinal or colonic double contrast enema, hypotonic duodenography and CT scan. Intestinal radiological examination is of great significance in assessing intestinal tuberculosis by demonstrating mucosal alterations, ulcers, bowel deformations, lesions and fissures (Yu *et al,* 2001). Barium contrast studies show strictures, deformed cecum, incompetent ileocecal valves or fistulas, bowel wall thickening and obstruction (Makanjuola, 1997; Yu *et al*, 2001). Yu *et al* (2001) reported that the sensitivity and specificity for the diagnosis of GITB with CT is low and the lesions in the small intestine are not easily identifiable. More useful in diagnosing GITB with CT is the presence of lymphadenopathy. A CT scan can be used to evaluate intestinal involvement, which is important for early diagnosis of GITB (Chatizkostas *et al,* 2002). To improve the diagnosis, a combination of other radiological procedures and CT scan need to be carried out.

Endoscopy

Colonoscopy with procurement of biopsy specimens is currently considered the most valuable diagnostic tool for identifying lesions in the colon and terminal ileum (Leung *et al,* 2006). The colonoscopic findings are transverse ulcers with surrounding hypertrophic mucosae and multiple erosions. The ulcers are typically oriented in a direction perpendicular to the longitudinal axis of the colon and tend to be segmental. This orientation is said to be related to the arrangement of the sub-mucosal lymphatic structures, which are thought to be the primary site of gastro-intestinal involvement (Makanjoula, 1997). Other endoscopic findings include strictures, polypoid lesions and fibrous strands (Leung *et al,* 2006). Martinez *et al* (2003) reported the presence of circular ulcers, small diverticulae (3-5mm) and firm sessile polyps. The TB positivity with the presence of granulomas is highly variable (Makanjoula, 1997), ranging from 0% to 45% of cases (Kim *et al,* 1998; Leung *et al,* 2006). The positivity rate can be improved by taking adequate tissue, more biopsies with a greater number taken from the rectum to the ileum, deeper biopsies from ulcer bases and diseased mucosa (Shah *et al,* 1992; Pulimood *et al,* 2008). This is evidenced by the more frequent presence of GITB obtained from surgically resected specimens than on colonoscopic biopsy material, reflecting the predominance of granulomas in the deeper layers (Leung *et al,* 2006).

Histopathology

Definitive diagnosis is based on histopathology, AFB smears, and culture of biopsy specimens obtained by colonoscopy or laparotomy. Typical granulomas and acid-fast bacilli (AFB) are not invariably detected in affected tissues. Pulimood *et al* (2005) reported that on mucosal biopsies, in addition to AFB detection, large granulomas, more than four sites with granulomatous inflammation, caseation, bands of epithiloid histiocytes in ulcer bases and granulomatous inflammation in cecum are in favor of a diagnosis of GITB. The identification of AFB on colonoscopic biopsy has been reported with variable frequency (0-36%) (Leung *et al,* 2006). The establishment of diagnosis by a combination of histology and culture varies from 40% to 80% and is dependent on

the site where the biopsy was taken from (Settbas *et al*, 2003).

Culture

Routine tests for the diagnosis of TB, such as AFB smear examination and culture, lack sensitivity and are time consuming. The use of fluorescence techniques for smear examination and BACTEC for culture enhance the rapidity of diagnosis and yet the sensitivity of these techniques in the diagnosis of GITB is poor due to the paucibacillary status (Amarpurkar *et al*, 2008). *M. tuberculosis* was cultured from mucosal biopsy in one-third of patients with colononic tuberculosis (Balamurugan *et al*, 2006).

Polymerase chain reaction (PCR)

The PCR based diagnostic method is capable of detecting 10fg (equivalent to about 2 mycobacterial genomes) in a reaction and (9 organisms of *M. tuberculosis*) in a 5 micrometer section of a paraffin embedded specimen (Tzen *et al*, 2006). PCR of mucosal biopsy specimens diagnoses colonic tuberculosis in 45% to 64% of cases (Gan *et al*, 2002; Balamurugan *et al*, 2006). PCR though specific, has a low sensitivity (Amarpurkar *et al*, 2008). The *M. tuberculosis* genome has been demonstrated in the mucosal biopsies of two-thirds of patients with colonic tuberculosis (Balamurugan *et al*, 2006). PCR amplification of IS 6110 for *M. tuberculosis* in fecal samples was evaluated for the diagnosis of GITB the sensitivity and specificity were 88% and 100%, respectively. In comparison, the sensitivity for histopathology was 50% and culture was 33%. The PCR test had the advantage of using a non-invasive sample, which is subject to less sampling error in comparison to mucosal biopsy (Balamurugan *et al*, 2006).

Serology

Although many serological tests have been developed and are commercially available, these are far from satisfactory for the diagnosis of tuberculosis (Woods, 2002; Amarpurkar *et al*, 2008).

Newer methods

In spite of using a combination of diagnostic modalities, many cases remain undiagnosed, posing a diagnostic challenge. In this scenario, the utility of newer tests used to evaluate latent tuberculosis infection (LTBI), the gamma interferon assay and ELISPOT-TB needs to be ascertained. The Quantiferon TB gold uses an enzyme linked immunosorbent assay (ELISA) to measure antigen specific production of interferon gamma by circulating T cells in whole blood. The T spot TB uses the ELISPOT technique to measure peripheral blood mononuclear cells that produce interferon gamma and uses *M. tuberculosis* specific antigens ESAT 6 and CFP-10 (Ravn *et al*, 2005). Caputo *et al* (2008) used the Quantiferon TB Gold assay in the diagnosis of two cases of GITB and were of the opinion it may hold promise for use in intestinal inflammatory diseases, when TB is suspected, but the conventional work up is not diagnostic. The cost of the newer tests are prohibitive and their utility in the diagnosis of GITB needs to be evaluated by multi-centric studies in different endemic areas.

In the scenario of difficult challenge of diagnosing GITB, a prompt response to anti-TB therapy has conventionally been accepted as a ground for diagnosis. This becomes more relevant, when differentiation between GITB and Crohn's disease needs to be made and to avoid unnecessary surgery.

In view of the increasing incidence PTB pulmonary and EPTB, and specifically the diagnostic challenge posed by GITB, a concerted effort is necessary to improve the existing diagnostic modalities in terms of specificity, sensitivity and developing newer diagnostic tools.

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