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 Pac-
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, Malaysia. 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 pancreaticobiliary 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 colonic tuberculosis (Balamurugan et al, 2006).

**Polymerase chain reaction (PCR)**

The PCR based diagnostic method is capable of detecting 10 fg (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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