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EDITORIAL

Interferon-gamma release assays as a tool for differential diagnosis of gastrointestinal tuberculosis

Tsvetelina Velikova, Anita Aleksandrova

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Abstract

In this editorial, we comment on an article published in a recent issue of the *World Journal of Clinical Cases*. There is a pressing need for reliable tools for diagnosing tuberculosis (TB) of the gastrointestinal tract. Despite advancements in the diagnosis and treatment, TB remains a global health challenge. Ali *et al* demonstrated that TB may mimic gastrointestinal conditions, such as gastric outlet obstruction, causing a delay in the diagnosis. Furthermore, the latter complication is frequently observed during infections, including *Helicobacter pylori*, and rarely is related to TB, as in the presented case. In line with this, we think that laboratory tests based on interferon-gamma release assays can be a helpful tool for diagnosing latent TB paced in the gastrointestinal tract. Innovative strategies and approaches for diagnosing latent/active extra pulmonary TB are crucial for establishing the diagnosis early and enhancing treatment strategies to mitigate the global burden of TB.

Key Words: Tuberculosis; Gastrointestinal tuberculosis; Interferon-gamma release assay; IGRA; Primary gastroduodenal tuberculosis; Gastric outlet obstruction; Case report

Core Tip: The diagnosis of abdominal tuberculosis (TB) is frequently delayed since there are no identifiable clinical signs and symptoms, and the illness might resemble other intra-abdominal disorders. In line with this, the most prevalent causes of gastric outlet obstruction are peptic ulcer disease and stomach cancer, and when excluded, TB infection should be added as a differential diagnosis. Assays of interferon-gamma release (IGRAs) have become a crucial diagnostic tool for latent TB infection. IGRAs have also been used to potentially distinguish between mimics such as Crohn's disease or other ascites-causing conditions and abdominal TB. Given that they are unaffected by the Bacille Calmette-Guérin immunization, these are considered beneficial.

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INTRODUCTION

The United Nations forged a commitment by all member states to eradicate tuberculosis (TB) by 2030 due to the disease's widespread prevalence[1]. Even though TB is most common in Asia and Africa, industrialized countries are also experiencing an increase in TB cases, primarily from latent TB (LTB), which is brought on by immune com promising conditions, the use of biologics, and migration[2].

One area of particular interest is elucidating the gastrointestinal (GI) form of TB. The World Health Organization's (WHO) primary strategy for controlling TB focuses on pulmonary TB, which is the primary manifestation of the pathogen. However, extra pulmonary TB (EXPTB) is becoming more well-recognized, with abdominal TB being one of the most typical appearances[3].

The GI system, peritoneum, abdominal solid organs, and abdominal lymph nodes can all be arbitrarily infected with abdominal TB. Moreover, the most frequent site of involvement for TB infections of the abdomen is the GI tract, although it might be challenging to identify GI TB due to it varied to non-specific clinical presentation. This leads to significant morbidity and a delay in diagnosis[3].

Thus, there is an urgent need for innovative research and studies aimed at unraveling latent TB, especially when this infection is not on the differential diagnosis list. Innate (mainly early on) and adaptive immunity play a combined role in the immune response the infected subjects use to regulate *Mycobacterium tuberculosis* (*M. tuberculosis*) replication. The term "latent tuberculosis infection" (LTBI) has historically been used to denote TB infection when there is no clinically apparent TB disease but rather a continuous immunological response to stimulation by *M. tuberculosis* antigens. Three antigens with a significant diagnostic potential were identified: ESAT-6, CFP-10 and TB 7.7, which can be detected by interferon-γ release assay (IGRA)[4]. The other screening test available for TB is the tuberculin skin test (TST)[5].

The minuscule numbers of bacilli in infected people have immunogenic antigens that trigger host responses, which can act as a stand-in for the bacillus itself when it comes to detecting TB infection, which is a paucibacillary state[6].

IGRA tests offer an alternative to the TST. There are now two commonly used commercially available IGRAs: Quanti Feron TB gold in a tube and T-SPOT. TB. IGRAs have some benefits compared to TST, including a higher specificity for Mtb and a lower risk of Bacille Calmette-Guérin (BCG) vaccination-induced cross-reaction. In nations with low to moderate TB burdens, IGRAs are now the primary diagnostic technique for LTBI[7,8].

However, several studies have demonstrated that TST and IGRA are not very good at predicting the development of active TB, as was also recently shown in a prospective study conducted on recent immigrants and TB contacts in an area with a low TB incidence. The Quanti Feron-TB gold positive predictive value (PPV) was 3.3%, but T-SPOT TB's claimed PPV was 4.2%, and TST's (where a 15 mm cut-off defined positivity) was 3.5%[9].

Jonas *et al*[10] showed that pooled estimates for the sensitivity of IGRA tests ranged from 0.81 (95%CI: 0.79-0.84) to 0.90 (95%CI: 0.87-0.92), and pooled estimates for the specificity of screening tests ranged from 0.95 to 0.99, leading to the conclusion that both screening tests for latent TB-TST and IGRAs were moderately sensitive and highly specific[10].

After this contemporary overview of the epidemiology, clinical characteristics of GI TB and challenging diagnosis of GI TB, it is clear why we focus on the case report of primary gastroduodenal TB and our expert opinion on how the use of IGRAs could be helpful in the diagnosis of such conditions.

PRIMARY GASTRODUODENAL TB PRESENTING AS GASTRIC OUTLET OBSTRUCTION

The case report by Ali *et al*[11], "Primary gastroduodenal TB presenting as gastric outlet obstruction (GOO): A case report and review of literature"[11], published in the *World Journal of Clinical Cases*, examined descriptively and in detail primary gastroduodenal TB in a young man.

We chose to cover this case report in our editorial because it is distinguished by its relevance. Ali *et al*[11] described a 23-year-old patient with recurrent epigastric pain, distension, nausea, vomiting, and weight loss. It was not clear from the paper why the anti-tubercular medication was planned, only that he had experienced similar symptoms during a prior stay in South Africa 8 months earlier, during which an endoscopy revealed pathological and inflammatory changes in the

distal gastric mucosa with negative *Helicobacter pylori* (*H. pylori*) result.

The authors also commented on the ways TB infection can occur in the GI, *i.e.*, ingestion of contaminated milk or food (primary TB), ingestion of contaminated sputum (secondary TB), hematogenous spread from a distant TB focus, or dissemination from infected neighboring foci *via* the lymphatic channels[12,13]. Therefore, the authors suspected TB because of the region of high prevalence of TB, and also the clinical picture of GOO.

It is well-known that when *M. tuberculosis* affects organs other than the lungs, it is referred to as EXPTB. An average of 15% of all TB cases reported to WHO were extra pulmonary, with estimates ranging from 8% to 24% worldwide[2].

However, the rate of GI TB is controversial. In India, considered one of the countries with the highest burden, 20% of TB cases were EXPTB (34%-lymphatic TB, 25%-pleural, 13%-abdominal) at nearly 13%[14,15]. The other country with a high burden, China, reported 31% EXPTB (341%-skeletal system, 26%-pleura, 14%-other, including abdominal)[16]. Pakistan reported 30% EXPTB (21%-abdominal, 29.6%-pleura, and 21.5%-lymphatic locations[17].

Countries with medium-sized TB burden demonstrated 13% EXPTB with 9% abdominal TB (6th most common site)[18], whereas low TB incidence countries (*i.e.*, the United States) reported 20% EXPTB of all TB cases (40%-lymphatic and 6%-abdominal)[19]. European countries showed 17% for EXPTB (3%-abdominal)[20].

In South Africa, a sub-Saharan country with a high TB and human immunodeficiency virus (HIV) burden, where the presented patient visited and stayed, 43% of all TB cases were EXPTB (28%-abdominal)[21]. It is essential to mention that TB+ and HIV+ populations reported 28% of EXPTB, with abdominal sites ranking third (11%)[22].

Additionally, the global prevalence of TB is declining overall while the percentage of EXPTB is increasing. In just ten years, this percentage increased from 16.4% to 22.4% in Europe[23].

In line with these statistics, IGRAs have become a crucial diagnostic tool for LTBI. IGRAs have also been used to potentially distinguish between mimics such as Crohn's disease or other ascites-causing conditions and abdominal TB. Given that they are unaffected by the BCG immunization, these are considered beneficial[24].

In a meta-analysis by Luo *et al*[25], which included 12 studies[25], the diagnostic accuracy of T-SPOT in peripheral blood and peritoneal fluid was evaluated. The pooled sensitivity and specificity of T-SPOT in peripheral blood for diagnosing peritoneal TB were 91% and 78%, respectively, with the pooled positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of 4.05 and 0.13, respectively. On the other hand, T-SPOT in peritoneal fluid showed pooled sensitivity, specificity, PLR and NLR of 90%, 78%, 6.35, and 0.14, respectively[25]. These results confirm that T-in both biological materials are sensitive for diagnosing TB peritonitis.

Another systematic review conducted by Su *et al*[26] showed that interferon-gamma levels in the ascitic fluid reported excellent sensitivity and specificity (93% and 99%, respectively)[26].

IGRAs have also been evaluated in several studies as a diagnostic tool to discriminate GI TB from Crohn's disease[27-29].

A recent meta-analysis by Xu *et al*[29] exerted a pooled sensitivity of 82.8% and a pooled specificity of 86.7[29]. These meta-analyses confirmed that IGRAs are an excellent supplementary modality for differentiating intestinal TB and Crohn's disease. Other studies, however, demonstrated poor sensitivity and specificity and questioned this test's utility [30].

The use of IGRAs should be used with caution because people with inflammatory bowel disease may also be exposed to TB in TB-endemic areas and may have a positive IGRA. Many patients with disseminated TB or malnutrition may not show immunological responsiveness when exposed to TB antigens[31].

Based on the currently available information, it is uncertain how useful IGRA is in diagnosing active abdominal TB and should not be used a standard procedure in TB-endemic areas. Nevertheless, given the previously noted limitations, it might play a part in ruling out TB if a Crohn`s disease diagnosis is taken into account in TB-endemic environments[24]. Finally, Ledesma *et al*[8] demonstrated that not all patients with a positive IGRA had the same chance of developing active TB, with higher IGRA values being closely linked to the development of the disease[8]. Consequently, further research on the role of IGRA tests in detecting and diagnosing GI TB is imperative to unravel the usefulness of these tests in the future.

The paper of Ali *et al*[11] addressed these issues, structured as case report. Although the paper fulfilled the criteria for case report presentation, it did not focus on the GI TB diagnosis by IGRA tests. However, as we mentioned above, it was not clear from the paper why the anti-tubercular medication was planned, and the therapy was started based on the previous similar symptoms during a prior stay in South Africa 8 months earlier, and endoscopic pathological and inflammatory changes in the distal gastric mucosa with negative *H. pylori* result. Therefore, one of the main limitations was the assumption of the diagnosis TB because of the region of high prevalence of TB, and also the clinical picture of GOO. Moreover, the authors did not state the limitation of their paper. However, the authors defend their assumptions and managed the case adequately. Furthermore, all the drawbacks of the paper are not fatal but a potential for future research.

CONCLUSION

Despite significant progress in the diagnosis and treatment of TB, it remains a formidable global health challenge. The study by Ali *et al*[11] highlights a critical issue where TB can masquerade as GI conditions like GOO, a relatively common condition during some infections, leading to diagnostic delays. Notably, GOO is commonly associated with infections such as *H. pylori* but seldom linked to TB, as evidenced in the case presented. Considering this, we advocate utilizing IGRAs as valuable tools for detecting latent TB in the GI tract. Embracing innovative strategies and diagnostic approaches for identifying latent or active EXPTB is paramount to achieving early diagnosis and improving treatment outcomes, thereby alleviating the global TB burden.

FOOTNOTES

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