Intestinal tuberculosis: a diagnostic challenge – case report and review of the literature
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Even though tuberculosis is considered rare in developed countries, its rising incidence, especially in high-risk populations, places intestinal tuberculosis in the differential diagnosis of patients with atypical abdominal symptoms or signs. We, herein, report the case of an immunocompetent woman, from a nonendemic area, who developed intestinal tuberculosis, emphasizing the diagnostic challenges caused due to nonspecific symptoms, inconclusive clinical, laboratory, and imaging findings, which could not rule in or rule out tuberculosis. Antituberculosis treatment was administered based on endoscopic findings and histological features of mucosal biopsies, which were indicative of intestinal tuberculosis, and the patient showed a marked clinical and laboratory improvement. We also review the evidence with regard to the diagnostic accuracy of the different available tests for intestinal tuberculosis.

Introduction
One-third of the world’s population is infected with tuberculosis (TB) [1]. In Western countries, TB rates are low and the disease is mainly diagnosed in immigrants and in immunosuppressed individuals. However, in the European Union, total TB deaths exceeded those attributed to HIV infection [2]. Intestinal TB is the sixth most common presentation of extrapulmonary TB [3]. It presents with diverse clinical manifestations and mimics other clinical entities. Laboratory tests and imaging techniques have limited accuracy for the diagnosis of intestinal TB. Therefore, diagnosis of intestinal TB is a challenge for physicians, and a high index of suspicion is essential. We, herein, present the case of an immunocompetent patient, from a non-TB endemic country, who developed intestinal TB. Anti-TB treatment was initiated based on endoscopy and histological findings even though all diagnostic tests were negative.

Case study
A 38-year-old woman presented to the emergency department complaining of abdominal pain, fever up to 38°C, weight loss of 6 kg, and diarrhea for the last 20 days. She had not traveled abroad recently. She reported the use of antiepileptic medications. Physical examination showed marked discomfort on the right lower abdominal quadrant and laboratory tests revealed leukocytosis (white blood cells: 12 800/µl, neutrophiles: 82%) and increased erythrocyte sedimentation rate and C-reactive protein levels. Chest X-ray showed a small circumferential lesion in the upper left lobe, which resembles an old granuloma. Abdominal X-ray showed signs of partial bowel obstruction of the terminal ileum. The patient underwent an abdominal computed tomography, which revealed mesenteric lymphadenopathy, ascites, and possibly a tumor in the cecal region. Diagnostic paracentesis of ascetic fluid revealed a serum-ascites albumin gradient of less than 1.1 g/dl and 1500 cells (65% lymphocytes). The patient also underwent colonoscopy, which revealed fragile mucosa with multinodular appearance, circumferential superficial ulcers, and hemorrhagic lesions. Histologic evaluation of multiple mucosal biopsies excluded the presence of malignancy but disclosed granulomatous inflammation possibly due to infection with Yersinia enterocolitica. Accordingly, the patient was treated with intravenous ciprofloxacin, but had a poor response. Colonoscopy was repeated and upper endoscopy was also performed. The endoscopic findings in the large bowel worsened whereas similar lesions were identified in the stomach and the duodenum. Mucosal biopsies raised the suspicion of TB (Figs 1 and 2), although the possibility of Crohn’s disease could not be excluded. Multiple laboratory tests for TB were performed, including a tuberculin skin test (TST), determination of adenosine deaminase levels in the ascetic fluid, acid-fast bacilli smear examination, as well as culture and polymerase chain reaction (PCR) of biopsy samples for Mycobacterium tuberculosis, but yielded negative results. Owing to further deterioration of her clinical status the patient was...
empirically given triple anti-TB treatment (i.e. isoniazid, pyrazinamide, and rifampicin). Ten days after treatment initiation the patient showed a marked clinical and laboratory improvement. Follow-up after 4 months showed excellent response to treatment; repeat colonoscopy was normal whereas TST was strongly positive. After 1 year of anti-TB treatment the patient remained asymptomatic with normal endoscopic and histological findings.

Discussion

This case study illustrates the importance of considering intestinal TB in the differential diagnosis of patients presenting with nonspecific abdominal signs and symptoms. It demonstrates the development of intestinal TB, with simultaneous involvement of multiple areas of the gastrointestinal tract, in an immunocompetent individual from a non-TB-endemic region, and the lack of sensitivity of TST, cultures, and serological tests in the diagnosis of TB. It also underlines that despite negative tests, early anti-TB therapy can be initiated when clinical, endoscopic, and histological features are suggestive of the diagnosis.

Although intestinal TB is relatively uncommon in developed countries, the incidence of TB is increasing considerably during the last decades mainly due to immigration and HIV infection. Especially in populations such as immigrants and institutionalized or immunosuppressed individuals, the risk of TB is even higher [3,4]. The incidence and the severity of intestinal TB is increased in immunosuppressed patients, and has more rapid progression due to deficient immune response [3]. However, our patient neither belonged to these groups nor had contact with individuals from these populations. Intestinal TB is caused by *M. tuberculosis* and it can either be a primary infection or a secondary infection after reactivation of latent pulmonary infection. Potential routes of infection are hematogenous spread from a pulmonary focus, ingestion of bacilli present in sputum or contaminated milk, lymphatic spread from infected lymph nodes and, rarely, spread from adjacent organs [3].

The ileocecal area is the most common site of infection as it is rich in lymphoid tissue and a region of physiologic stasis, but any region of gastrointestinal tract, from esophagus to the rectum, can be involved [3]. Our patient presented with simultaneous involvement of multiple areas of gastrointestinal tract, which has been rarely reported in the literature [5].

Clinical manifestations of intestinal TB are nonspecific and progress slowly, as a result, patients usually have symptoms for many weeks before seeking medical attention. In previous case series, patients with intestinal TB reported chronic abdominal pain, fever, weight loss, changes in bowel habits, abdominal mass, ascites, nausea, and vomiting [6–8]. Intestinal TB can also be complicated with obstruction, malabsorption, intestinal hemorrhage, perforation, and fistula formation. Several studies reported that women are more frequently affected and this has been attributed to malnutrition, poor access to health care facilities, and contiguous spread from tuberculous salpingitis [7]. Several diseases can mimic intestinal TB. Crohn’s disease is also a chronic granulomatous disorder with clinical, radiological, endoscopic, and pathological features similar to intestinal TB, making differential diagnosis between the two entities difficult [9]. Differential diagnosis also includes malignancies, *Y. enterocolitica* infection, lymphoma, amebiasis, histoplasmosis, and fungal infections [3].

Conventional laboratory tests are nonspecific and do not contribute to the differential diagnosis. Elevated erythrocyte sedimentation rate, high C-reactive protein levels, anemia, and lymphopenia or lymphocytosis are common laboratory findings [8,10]. In female patients, serum cancer antigen 125 levels may be raised, leading to a misdiagnosis of ovarian cancer [3].
The TST is the most widely used test for TB infection and relies on a competent delayed-type hypersensitivity reaction to the tuberculin. However, it has low sensitivity in patients with generalized or antigen-specific immunosuppression and poor specificity in patients with prior Bacille Calmette-Guérin vaccination or exposure to nontuberculous mycobacteria. Immunosuppression can be caused by malnutrition, intestinal parasitic infection, chronic diseases, and HIV infection [11]. The false-negative TST result in our patient, who was immunosuppressed due to extensive TB, was therefore not surprising. Furthermore, shortly after treatment initiation the TST became positive. When ascites is present, measurement of adenosine deaminase level is a fast and accurate test with high sensitivity, ranging from 93 to 100%, and specificity, ranging from 92 to 100%, which can adequately confirm or rule out the diagnosis of TB [12]. However, in nonendemic areas sensitivity is lower especially in the presence of cirrhosis [13].

Recently, two new blood tests [interferon-γ-release assays (IGRAs)] have been developed as alternatives to TST. They detect interferon-γ released from lymphocytes in response to stimulation by \textit{M. tuberculosis}-specific antigens. However, these tests are not available in our institution. A meta-analysis confirmed that IGRAs have excellent specificity that is unaffected by Bacille Calmette-Guérin vaccination. However, sensitivity of IGRAs is not consistent across different populations. In particular, sensitivity tends to be lower in countries with low incidence of TB and in individuals with advanced disease, malnutrition, and HIV-associated immunosuppression. In addition, IGRAs cannot distinguish active from latent TB [14,15]. Very few studies have assessed the sensitivity and specificity of these tests in intestinal TB, and their role in the diagnosis of intestinal TB is unclear [16].

A minority of patients with intestinal TB report prior history of TB infection and more than 50% have a normal chest X-ray [17]. Our patient’s chest X-ray showed a granuloma in the left upper lobe of the lung that could not be confirmed as a pulmonary focus of TB. Abdominal ultrasound is an inexpensive, noninvasive technique that can detect ascites and lymphadenopathy. The asymmetric thickening of the bowel wall in the ileocecal region and mesenteric thickening accompanied by enlarged mesenteric lymph nodes are indicative of intestinal TB [18]. An abdominal computed tomography scan may also reveal ascites, bowel wall thickening, mesenteric thickening, and lymphadenopathy with central areas of low attenuation due to caseation and calcification [19]. Although ultrasound and computed tomography findings are largely nonspecific and may also be seen in cancer, Crohn’s disease, lymphoma, and amebiasis, when combined with other clinical and laboratory findings can be a valuable tool for the diagnosis of intestinal TB.

Endoscopy should be performed in all patients with suspected intestinal TB. The pattern of distribution, the type of lesions, the histologic findings, and the microbiological cultures can be valuable diagnostic tools. Upper gastrointestinal endoscopy demonstrates single or multiple ulcers and hypertrophic nodular lesions, sometimes complicated with pyloric stenosis [20]. Colonoscopy and examination of the terminal ileum usually reveal segmental lesions whereas very few patients present with pancolitis. As mentioned above, the ileocecum is the most commonly affected site, but the colon and the small bowel can also be involved in varying degrees. However, the appearance of lesions is more important than the distribution in the differential diagnosis of TB. Endoscopic features include circumferential superficial ulcers, in contrast to the linear ulcers present in Crohn’s disease, which are surrounded by nodular and inflamed mucosa. Destruction of the ileocecal area, strictures, pseudopolyps and hyperemic mucosal nodules, isolated or in clusters, can also be present [21]. Multiple biopsies from both the lesions and endoscopically normal areas increase the diagnostic yield [22]. The pathognomonic features of caseous necrosis and presence of acid-fast bacilli are identified only in a minority of biopsy specimens [23]. Retrospective studies suggest confluent, large granulomas as indicative of TB, although granulomas are only found in 50–80% of mucosal biopsies from patients with TB [24,25]. Other histological features characteristic of TB are ulcers lined by bands of epithelioid histiocytes, disproportionate submucosal inflammation, and submucosal granulomas [22,26].

Acid-fast bacilli smear examination with conventional Ziehl-Neelsen staining is another routinely performed test for the diagnosis of TB that provides immediate results but lacks sensitivity. Culture of biopsy material remains the gold standard but is time-consuming, requiring 4 to 6 weeks to provide conclusive results [27]. A study reported positive cultures from mucosal biopsies in only one-third of patients with colonic TB [28]. In contrast, PCR for \textit{M. tuberculosis} on biopsy specimens can be helpful and can provide rapid diagnosis of TB with high specificity and positive predictive value up to 100% [29]. However, recent data reported poor sensitivity, especially in extrapolmonary TB, suggesting that PCR can diagnose but cannot rule out TB [30]. It is interesting that studies reported the presence of \textit{M. tuberculosis} DNA in lesions with and without granulomatous inflammation [27,31]. Nevertheless, despite negative histology or culture, the initiation of anti-TB therapy is recommended in patients with endoscopic findings suggestive of intestinal TB [25].

Even when all available diagnostic tests are applied, the diagnosis of intestinal TB can still remain uncertain. Our patient did not have any risk factors for TB infection and did not report any personal or family history of TB. Clinical symptoms and signs were nonspecific, except for ascites, which is more common in intestinal TB whereas
it is rarely seen in uncomplicated Crohn’s disease [32]. Routine tests for the diagnosis of TB were negative. Furthermore, imaging findings did not assist the differential diagnosis. In contrast, endoscopy revealed a type of lesion and a pattern of distribution that were not typical of Crohn’s disease. Nodular lesions in the stomach, superficial ulcers surrounded by nodular, inflamed mucosa segmentally distributed in the colon, and histology findings from biopsies with large and confluent granulomas were indicative of intestinal TB. Although Crohn’s disease could not be ruled out, and diagnosis could not be confirmed by any laboratory test, a therapeutic trial of anti-TB treatment was decided based on clinical, endoscopic, and histological features. The response to treatment was prompt with improvement of both clinical and laboratory findings.

In conclusion, this case report underlines that intestinal TB should be considered in the differential diagnosis of patients with nonspecific abdominal symptoms or signs, even in patients who do not belong to high-risk populations. Our case report also supports the findings of previous studies that reported the inadequacy of existing diagnostic tests for intestinal TB. It emphasizes the importance of histologic findings and the role of endoscopy with multiple biopsies as a useful diagnostic modality for intestinal TB. Finally, it supports the role of empirical anti-TB treatment when endoscopic and histologic findings are indicative of TB, even when the diagnosis cannot be confirmed with any diagnostic test.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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