Intestinal tuberculosis and Crohn's disease: the importance and difficulty of a differential diagnosis

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ABSTRACT

Tuberculosis (TB) is the most prevalent infection worldwide and affects one third of the population, predominantly in developing countries. Intestinal TB (ITB) is the sixth most frequent extra-pulmonary TB infection. Crohn's disease (CD) is a chronic inflammatory bowel disease that arises from the interaction of immunological, environmental and genetic factors. Due to changes in the epidemiology of both diseases, distinguishing CD from ITB is a challenge, particularly in immunocompromised patients and those from areas where TB is endemic. Furthermore, both TB and CD have a predilection for the ileocecal area. In addition, they share very similar clinical, radiological and endoscopic findings. An incorrect diagnosis and treatment may increase morbidity and mortality. Thus, a great degree of caution is required as well as a familiarity with certain characteristics of the diseases, which will aid the differentiation between the two diseases.

Key words: Intestinal tuberculosis. Crohn's disease. Differential diagnosis.

INTRODUCTION

Both Crohn's Disease (CD) and intestinal tuberculosis (ITB) are chronic granulomatous diseases that affect the gastrointestinal tract and present a challenge for a differential diagnosis. Both may present similar clinical, radiological and endoscopic findings. However, they can be differentiated according to their evolution and management. Therefore, caution is imperative in order to make a correct diagnosis (1).

One third of the world population is infected with TB (1), predominantly in developing countries. It is important to note that extra-pulmonary TB (EPTB) affects only 20% of immunocompetent patients, while 50% of immunocompromised are affected (2). Intestinal tuberculosis represents the sixth most frequent extra-pulmonary TB and is observed in 11% of patients. Crohn's disease (CD) is a chronic inflammatory disease of an unknown etiology that arises from genetic, environmental and immunological factors (3). TB is considered as a problem predominantly in developing countries and less so in western countries. However, the disease is changing geographically and the incidence in developed countries has been increasing during recent years (4,5).

According to data published in 2016 by the World Health Organization, TB will continue to be an important public health problem since over ten million people worldwide are infected. The greatest incidence is in Southeast Asia, the Americas and Africa. In Europe, the incidence is 32/100,000 inhabitants/year. Spain is considered to have a low incidence of TB, with fewer than 20 cases/100,000/year in 2013. However, until 2000, the incidence of TB in Spain was far greater, up to 40 cases/100,000 inhabitants/year. This explains the elevated frequency of latent tuberculosis infection (LTB) in our country (12.5-33.5%) (5-7).

This epidemiological change appears to be due to the appearance of new risk factors (both latent and active), in addition to the historic risks such as HIV infection or other immunocompromised conditions, as well as an increase in immigration from areas where TB is endemic, among others. Thus, the profile of the TB patient has changed. New risk factors have been identified such as travel to countries with an elevated incidence and the generalized use of immunosuppressive therapies and biological medication (8). This is particularly important since immunosuppressive treatments such as anti-tumor necrosis factor (anti-TNF), thiopurine, calcineurine inhibitors, methotrexate and corticosteroids all increase the risk of TB infection (9). Other factors

such as smoking and malnutrition, which are frequently seen in patients with CD, may also elevate the risk of reactivating LTB above 10% (10).

Riestra S. et al. carried out a retrospective study in four Spanish hospitals, comparing patients with inflammatory bowel disease (IBD) who subsequently developed TB with those who did not. The authors observed that the main risk factors in these patients included a recent hospitalization (in the previous six months) and anti-TNF treatment (in the previous 12 months). Furthermore, over half of patients treated with anti-TNF that were subsequently diagnosed with TB (53%) became infected a year after initiating treatment (11).

Furthermore, despite the recommendations for a national TB screening of patients with IBD, cases continue to appear, usually during treatment with anti-TNF medication. This may be due to various factors, which are mainly non-compliance or incorrect TB screening in IBD patients treated with biological therapies. In addition, 40-58% of TB cases in patients receiving anti-TNF treatment in Spain had not correctly followed the established guidelines (12). Furthermore, the low sensitivity of the PPD skin test in immunocompromised patients, such as those with IBD, may be another factor. Other possible causes may be errors in clinical history data collection or rare cases which appear after a year of anti-TNF treatment, which may be due to *de novo* infection (13,14).

Crohn's disease is increasing in countries where TB is endemic and in patients that originate from these areas, which further complicates a differential diagnosis. In recent decades, there has been an increase in the incidence of IBD in areas where the prevalence has historically been low, such as Southeast Asia, Africa and Eastern Europe (8,9).

With regard to ITB, *Mycobacterium tuberculosis* (Mtb) can reach the intestinal mucous via the ingestion of infected sputum in the case of concomitant, active pulmonary TB (20-25% of cases). Also, via the ingestion of milk contaminated with *Mycobacterium bovis,* which is very rare in developed countries due to hygiene measures and the pasteurization of milk. Furthermore, this can occur hematogenously, via an active pulmonary focus or disseminated infection. Contamination via direct contact with adjacent organs is very rare (2,15).

With regard to the pattern of distribution, the most common site of ITB is the small intestine (33.8%), followed by the peritoneum (30.7%), colon (22.3%), liver (14.6%) and foregut (8.5%). It is worth noting that the terminal ileum and ileocecal valve are the most common areas of infection, perhaps due to their elevated concentration of mucosa-associated lymphoid tissue (MALT) (9).

CLINICAL FINDINGS

TB has been called "the great pretender" due to its ability to mimic a wide array of symptoms and a non-specific presentation that makes a differential diagnosis difficult. Abdominal pain, predominantly in the right iliac fossa, is the most frequent symptom of intestinal TB (85%). Other symptoms include weight loss (66%), fever (35-50%) and diarrhea (20%). Intestinal perforation is rare (1-5%) and requires an immediate surgical intervention due to the risk of peritonitis (16,17). There are some clinical characteristics that point towards intestinal TB such as asthenia, high fever and persistent night sweats (with absence of infection or intra-abdominal abscess), peritoneal ascites or a more acute but slower evolution of symptoms (Table 1).

Crohn's disease may follow a similar symptomology with fever, chronic diarrhea and weight loss. However, these symptoms are more chronic and alternate with periods of clinical remission. The diagnosis of CD is reinforced by the presence of fistula, an abscess, bowel obstruction, bloody stools or perianal discomfort (16,18,19). Extra-intestinal manifestations are normally associated with CD but must be carefully evaluated since TB may also present symptoms related with the joints, eyes and skin, simulating extra-intestinal Crohn's disease symptoms. However, the presence of primary sclerosing cholangitis strongly suggests a diagnosis of CD (20). With regard to the risk of perforation, in theory the risk is lower for intestinal TB due to peritoneal fibrosis and the formation of intestinal adherences in this area. Nevertheless, a greater incidence of perforation in ITB has been observed (1-15%) compared to Crohn's disease (1.5-3%) (21-23) (Table 1).

LABORATORY FINDINGS

With regard to laboratory findings, there may be non-specific alterations such as an increase in acute phase reactants (ESR and CRP), anemia or changes in nutritional parameters such as hypoproteinemia, hipoalbuminemia or lower transferrin saturation.

The best-known tuberculin skin test (TST) is the Mantoux tuberculin skin test. This consists of an intradermal injection of 0.1 ml of purified protein derivative (PPD) tuberculin in the inner side of the forearm, which is subsequently read after 72 hours. If the size of the induration is 5 mm or larger, it is considered as positive (24,25).

In areas of low incidence of TB (< 10 cases per 100,000/year) and those where the vaccination is available, a positive Mantoux test is more likely to be a false positive. Another drawback is the possible anergy in immunocompromised patients, such as HIV positive patients or those undergoing immunosuppressive treatment, which can give false negatives (25). Therefore, a repeat TST within 7-10 days is advised in IB patients undergoing immunosuppressive treatment, in order to increase antigen reactivity, known as the booster effect. A repeat TST within 7-10 days following a negative TST allows a diagnosis in up to 14% of patients (14). It is important to note that the TST does not discriminate between active and latent Mtb infection or the effects of prior vaccination (9,19). TST produces a positive result in 50% of patients with ITB; its diagnostic value in this context is not well known (25).

On the other hand, new laboratory techniques have been developed, such as the *IGRA (Interferon Gamma Release Assay).* This allows the detection of interferon-γ produced by lymphocytes exposed to MT. This test has a greater sensitivity and specificity with respect to TST (81% and 85%, respectively) and is associated with a lesser degree of false negatives in immunocompromised patients (26-28). The main advantages of IGRA tests compared to TST are the greater objectivity in result interpretation (without the need for a second reading) and the absence of effects due to prior vaccination. Nevertheless, IGRA tests do not differentiate between active and latent infection and the results may be influenced by immunosuppressive treatments (29,30).

There are two tests currently available. The QuantiFERON-TB Gold, which is licensed in the US, Europe and Japan (Cellestis LTD, Carnegie, Australia) and T-SPOT.TB (Oxford Inmunotec Global PLC, UK), which is licensed in Europe, US, Japan and China. These

tests use ELISSA and ELISPOT techniques, respectively. The most frequently used in our case is QuantiFERON-TB Gold, which has demonstrated a sensitivity of 86% and a specificity of 93%. The main advantage of these tests is their elevated negative predictive value (NPV) of 91-94%, which allows us to reliably discard ITB in the case of a negative result (30,31).

Despite the known effects of immunosuppressive drugs on IGRA tests, the combined use of IGRA and TST improves TB screening in CD patients undergoing immunosuppressive treatment, thus increasing the number of patients diagnosed with latent TB. Arias-Guillén et al. observed that positive TSTs were far less common in patients treated with two or more immunosuppressive drugs. Furthermore, the IGRA detected ten cases of latent tuberculosis infection in these patients that was not detected by TST (32).

Due to all these factors, CD patients undergoing immunosuppressive treatment (thiopurines, methotrexate and/or corticosteroids) subsidiary to anti-TNF inhibitors should undergo a double latent TB screening with both TST and IGRA tests, preferably on the same day. Alternatively, cultivation of *Mycobacterium tuberculosis* may be performed on intestinal samples obtained via colonoscopy with a recommended six samples from the biopsy. However, the sensitivity of this is low, with positive results in 25-35% of cases. Furthermore, the test takes a considerable amount of time of 3-8 weeks, representing a low diagnostic value (16,33).

A promising alternative solution is the use of polymerase chain reaction (PCR) tests for Mtb (PCR-Mtb) on intestinal mucosal samples (obtained via endoscopy or surgery) or fecal samples. Several studies have evaluated the role of PCR-Mtb for the diagnosis of ITB, with mixed results. Ramadass et al. reported a sensitivity and specificity of 79% and 88% in the analysis of fecal PCR respectively, whereas Gan et al. reported a sensitivity and specificity of 64.1% and 100%, respectively, using PCR of intestinal mucous samples (34,35).

Jin et al. performed a systematic review and meta-analysis of nine studies and observed that the PCR-Mtb had an elevated specificity (95%) and could differentiate between ITB and CD. However, a negative result does not exclude an ITB diagnosis due to the low sensitivity (47%) (36). Another advantage of the PCR-Mtb test is the speed

at which the results are obtained, in just 48-72 hours.

The presence of anti-*Saccharomyces cerevisiae* antibodies (ASCA+) is typical in cases of Crohn's disease, with an elevated specificity of 83%. However, the isolated findings of ASCA are not useful for the differential diagnosis of CD and TB due to the low sensitivity (33%) for CD, and it may also have similar positive results to patients with tuberculosis (2). However, combined ASCA and IGRA testing increases the diagnostic yield. In patients with ASCA+ and QuantiFERON-TB negative, the sensitivity and specificity of CD diagnosis increases to 44.4% and 96%, respectively (37-39).

HISTOLOGICAL FINDINGS

Both Crohn's disease and intestinal tuberculosis form part of the granulomatous enteritis group, although the mechanism of the granuloma formation is different in each case. Intestinal tuberculosis favors the use of macrophage and lymphocytes, camouflaging it from the hosts' immune system. However, there is a depleted intestinal barrier and increase in antigen permeability in CD, which produces an exaggerated immune response with the formation of granulomas (40).

The presence of caseating granulomas has historically been the gold standard to confirm intestinal TB. However, these symptoms are only found in a small proportion of patients (22-40%) (15,41,42) and it is also possible to find non-necrotising granulomas. Therefore, it is necessary to concentrate on other characteristics of ITB granulomas which can be more helpful for a differential diagnosis, such as their size, number and distribution. Typically, ITB presents multiple (five or more per area), confluent and very large (> 400 μm) granulomas (15,41). CD presents disorganized, non-confluent and small granulomas (< 200 μm) that affect the mucosal layer (Fig. 1).

Other indicators in the diagnosis of ITB include disproportionate inflammation of the surface submucosa and the presence of clusters of epithelioid histiocytes. The latter are associated with higher diagnostic specificity of 94% (43). Finally, techniques such as immunohistochemistry (IHC) to identify markers such as CD73 may also be useful. CD73 is expressed in the mesenchymal stem cells that surround the granulomas formed by ITB. They are not present in those related with CD (44).

RADIOLOGICAL FINDINGS

With regard to image diagnosis, a CT scan of the thorax is essential. This will show findings that are typical of concomitant pulmonary TB in up to 25% of cases. Nevertheless, a normal thoracic CT scan does not rule out intestinal TB. Image findings are similar in both Crohn's disease and intestinal tuberculosis. However, there are characteristics that may aid their differentiation. Therefore, an abdominal CT scan is recommended which assists in the evaluation of the extent of the disease, as well as the degree of affectation of other organs and structures such as the mesentery, peritoneum and lymph nodes.

The diagnosis of intestinal TB is strongly supported by certain characteristics such as the asymmetric thickening of the intestinal wall (generally less than 6 mm), peritoneal ascites and the presence of adenopathy in the area of the right colic artery (larger than 1 cm, either calcified or with a necrotic center). However, the presence of symmetric thickening of the intestinal wall, generally greater than 6 mm with transmural affectation and inflammatory changes in the pericolic fat and mesentery are more frequent in CD (6,15,18). The presence of fistulas and abscesses is significantly more frequent in patients with CD (45,46). However, there is some controversy with regard to the usefulness of these in the differential diagnosis, as some studies have shown a similar frequency for abscesses and fistulas in Crohn's disease and intestinal TB (47).

ENDOSCOPIC FINDINGS

Finally, a complete colonoscopy with ileoscopy is crucial for a differential diagnosis as both diseases occur principally in the ileocecal area. Generally, characteristic findings of intestinal tuberculosis include at least four sections of the colon with transvers ulcers and scars affected, an incompetent ileocecal valve and single, short stenosis with the presence of contracting diverticula (Fig. 2).

In Crohn's disease, however, longitudinal aphthous stomatitis is more frequent, with discontinuous serpiginous ulcers ("cobblestone"), stenosis of the ileocecal valve and associated perianal symptoms (8). One of the great advantages of endoscopy is that it allows the sampling of the mucosa and ulcerations, which aids a diagnosis. A minimum of six samples of intestinal mucosa are recommended. Ho Bae et al. initially developed

an endoscopy score to differentiate between intestinal TB and Crohn's disease, obtaining a sensitivity for CD of 65% and 97.5% for TB. The authors also proposed the validation of a new combined score based not only on endoscopy but also on radiological and laboratory findings, which increased the diagnostic precision to 96.3%. This is very useful for the differential diagnosis of Crohn's disease and intestinal tuberculosis. Each parameter counts as one point in the case of CD or one point is deducted if it is compatible with intestinal TB. The expected probability of CD with 0-2 points was above 90% (48).

TREATMENT

Finally, treatment strategies vary significantly in both diseases. Corticosteroids, immunosuppressive drugs and biological agents are used in Crohn's disease. The latter has been associated with a significant risk of reactivating latent TB, possibly leading to extra-pulmonary infection and drastically worsening the prognosis. The use of anti-tubercular therapy in Crohn's disease also delays optimal management and increases the rate of antibiotic resistance. For this reason, screening for latent TB is widely recommended prior to commencing anti-TNF treatment (4). The use of corticosteroids and anti-TNF alfa medication is also associated with an increased risk of intestinal perforation in patients with intestinal TB. The role of corticosteroids in the treatment of TB is controversial. However, it is recommended in cases of pericardial tuberculosis and tuberculous meningitis, where a reduction in mortality and morbidity has been demonstrated in both cases (49). For all these reasons it is vitally important to wait for complementary test results and remain circumspect with regard to the diagnosis of high risk patients and those suspected of having TB. It is also important to avoid the use of systemic corticosteroids based exclusively on endoscopic findings. When an intestinal tuberculosis diagnosis is confirmed, the treatment of choice is antibiotics (isoniazid, rifampicin) for the first two months, followed by pyrazinamide and ethambutol for the following four months.

Epstein et al. proposed a possible diagnostic-therapeutic treatment algorithm for patients with inflamed ileal conduit or ileocecal valve, where histological and microbiological results were inconclusive due to the absence of caseating granulomas

or BAAR in intestinal biopsy. Particularly, in immunocompromised patients or those originating from a country where TB is endemic. When there is an elevated suspicion of intestinal TB based on the clinical and endoscopic findings, it is particularly important to take into account the epidemiological circumstances of the patient and their history in addition to the radiological findings. This includes previous TB, active pulmonary TB with thoracic lesions, HIV infection and a positive latent TB test results, etc. The recommended treatment in these patients is anti-tubercular therapy for two months and a subsequent re-evaluation. Treatment completion is recommended in those patients who show clinical-analytical improvement.

Nevertheless, specific treatment for CD should commence (systemic or low bioavailability corticosteroids) followed by re-evaluation after two months in certain cases. For example, immunocompetent patients with no prior history of TB and a normal thoracic radiography and a negative latent TB test but clinical and endoscopic findings consistent with CD. Finally, in patients with a dubious diagnosis who do not respond favorably to initial treatment, laparoscopy should be considered, with a subsequent biopsy (15).

Recently a new algorithm has been proposed by V. Pratap Mouli et al. for cases of a differential diagnosis between intestinal tuberculosis and Crohn's disease. This group proposed to initiate tuberculosis treatment in doubtful cases and re-evaluate the clinical response after two, three and six months of treatment. In patients with no clinical improvement or who deteriorate, a new colonoscopy and biopsy should be performed to discard other possibilities such as CD. In this study, 37% of CD patients improved clinically after six months of anti-tubercular treatment. This may have been due to the fact that both diseases are granulomatous and Crohn's disease often shows spontaneous remission in up to 20% of cases (50).

However, this study showed a very low correlation between the clinical response and endoscopic treatment. One hundred per cent of intestinal TB patients showed mucosal healing after anti-tubercular treatment, whereas only 5% of Crohn's disease patients showed mucosal healing, 87% had no change and 8% deteriorated. Due to all of the above reasons, endoscopy is recommended independently of the clinical response to treatment in order to differentiate between both diseases. Finally, surgical procedures

are reserved for intestinal tuberculosis patients with complications such as abscesses, fistulas, intestinal obstruction or perforation.

CONCLUSIONS

Differential diagnosis between intestinal tuberculosis and Crohn's disease is particularly difficult and often presents a real challenge, particularly when treating immigrant patients from areas where TB is endemic or immunocompromised patients. An incorrect diagnosis may prolong the disease and favor complications such as intestinal perforation or disseminated TB. Maintaining caution with regard to a diagnosis based on physical exploration combined with radiological, endoscopic and histological findings is of utmost importance. This ensures a definitive diagnosis and the initiation of a specific treatment as soon as possible. It is important not to start treatment based exclusively on endoscopic findings, particularly in high-risk patients. In doubtful cases, initiating anti-tubercular treatment for 2-6 months with a re-evaluation of the clinical response may be effective. It is particularly important to evaluate the endoscopic results, since it has been shown that the great majority of ITB patients present endoscopic cure following treatment, unlike CD patients.

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Table 1. Endoscopic, clinical, radiological and histological characteristics of intestinal tuberculosis and Crohn's disease

Variables	Intestinal tuberculosis	Crohn's disease
Endoscope		
Longitudinal aphthous stomatitis	+	+++
"Cobblestone" mucosa	+	+++
Incompetent ileocecal valve	+++	+
Stenosis and fistulas	-	+++
Contracting diverticula	++	-
Scars and pseudopolyps	+	++
Clinical		
Diarrhea	++	+++
Rectal bleeding	+	++
Fever	+++	+
Perianal symptoms	-	++
Abdominal pain	++	++
Radiology		
Lymphadenopathy greater than 1 cm	+	-
Lymph node with central necrosis	+	-
Peritoneal ascites	+	-
Changes in mesenteric fat	-	++
Histology		
Large, confluent granulomas	+++	-
Caseous necrosis	++	-
Disproportionate submucosal inflammation	+++	+

Linear ulceration with clusters of epithelioid histocytes	+++	+

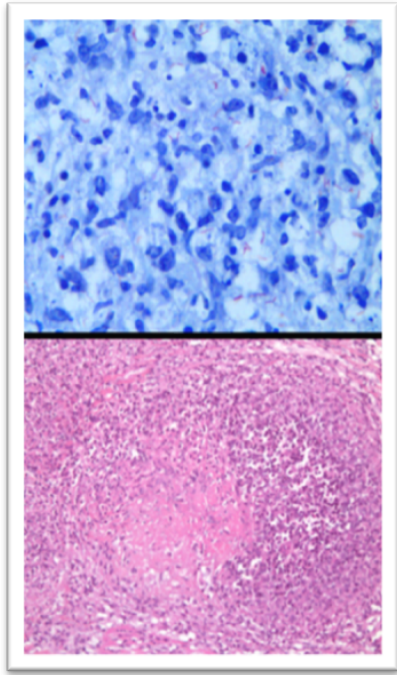| Linear ulceration with clusters of epithelioid histocytes	+++	+

Fig. 1. A. Ziehl-Neelsen stain showing abundant acid-fast bacilli. B. Caseating granuloma and abscessing with a notable inflammatory infiltration of polimorphonuclear leukocytes (PMN).
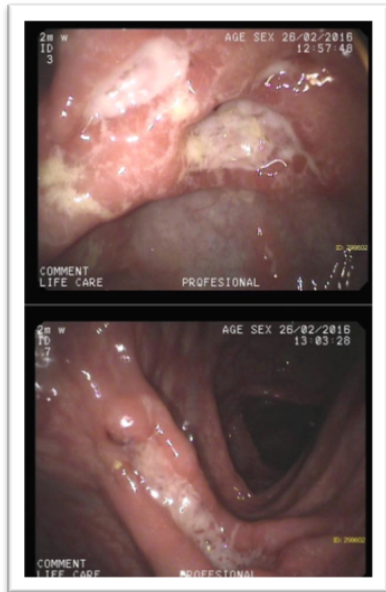
Fig. 2. Deep, transverse geographic ulcers in a patient with intestinal tuberculosis.