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SMALL INTESTINE (J SELLIN, SECTION EDITOR)

Differential Diagnosis of Crohn's Disease Versus Ileal Tuberculosis

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Abstract Both intestinal tuberculosis and Crohn's disease are chronic granulomatous inflammatory diseases of the bowel having overlap of clinical, endoscopic, radiological, and histological features. Differentiating between the two disorders is relevant not only in Asian countries but also in the West. In spite of diagnostic criteria for both diseases being available, still the dilemma of segregating the two diseases remains. Nearly one third of the patients with Crohn's disease may receive anti-tuberculosis treatment also. Diagnosis should be based on the combination of all disease-specific and corroborative evidences.

Keywords Intestinal tuberculosis · Crohn's disease · Differentiation · Tuberculosis

Introduction

Tuberculosis has resurrected as one of the major public health threats facing the world. It continues to be a major cause of morbidity and mortality in developing countries. Also, its incidence is increasing in the developed countries due to the large-scale global immigration, the AIDS pandemic, emergence of multi-drug resistant (MDR) and extensively drug resistant (XDR) tuberculosis, and frequent use of drugs like biologicals [1]. The incidence of intestinal tuberculosis (ITB), a common form of extrapulmonary tuberculosis, has increased in parallel with the overall increase in prevalence of tuberculosis. The incidence of Crohn's disease (CD) has also increased over the past several decades all over the world, including those areas where the disease has been conventionally reported to be rare [2, 3].

Distinguishing CD from ITB is challenging as both diseases have similar radiological, endoscopic, and histologic features. A high index of suspicion is paramount as otherwise it may result in medical mishap. In case of misdiagnosis of ITB, unnecessary anti-tubercular drugs pose a risk of toxicity and treatment of the actual disease is delayed. In contrast, treatment with steroids and immunosuppressants for a mistaken diagnosis of CD can lead to fatal dissemination of tuberculosis. It is well known that the differentiation of CD from ITB cannot be made on single index evaluation of a patient as no single pathognomonic test is available for either of the two diseases. Hence, all clinical and diagnostic evidences need to be considered for reaching at the diagnosis. This review discusses various parameters that aid in differentiating between two closely resembling diseases.

Clinical Presentation

Both conditions are characterized by insidious onset of symptoms like abdominal pain, anorexia, weight loss, altered bowel habits, rectal bleeding, fever, and sometimes the presence of an abdominal lump. However, certain features such as severe abdominal pain, high-grade fever >38.5 °C (in the absence of abdominal abscess), poor appetite, and obstructive symptoms favor ITB [1, 4]. Peritoneal involvement with ascites would also favor a diagnosis of ITB, but as it is often not present, it is not very discriminatory. On the contrary, chronic diarrhea with

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or without blood, aphthous ulcers, perianal disease, and enteric fistulae favor CD [5]. Extra-intestinal manifestations (EIMs) such as pyoderma gangrenosum, uveitis, primary sclerosing cholangitis, oral aphthous ulcers, arthralgia/arthritis, or ankylosing spondylitis go more in favor of CD. Nevertheless, involvement of other organs by tuberculosis with its associated immune phenomenon such as reactive arthritis (Poncet's disease), skin, eye, and liver is known to occur and should not be misinterpreted as EIMs [6]. A previous or family history of tuberculosis, history of chronic immunosuppression, and an origin from area of high tuberculosis endemicity are all suggestive of tuberculosis rather than Crohn's disease. Another subtle difference is the duration of symptoms which may be longer in CD as compared to ITB where these may range from 1 month to 1 year.

Serological Tests and Culture

The laboratory differentiation between ITB and CD has not had great success with routine blood tests being too nonspecific. Also, various serological markers such as the antineutrophil cytoplasmic antibodies, the peri-nuclear and the cytoplasmic variants (p-ANCA and c-ANCA), and the IgA and IgG subtypes of anti-*Saccharomyces cerevisiae* antibodies (ASCA) have limited diagnostic value for either of these conditions. Studies have shown that ASCA is not useful in differentiating between ITB and CD as nearly half of patients with ITB may be ASCA+ and hence should not be relied upon [7]. The most reliable method to diagnose ITB is to find *Mycobacterium tuberculosis* bacilli in the intestinal tissue either by demonstration of acid fast bacilli (AFB) using conventional Ziehl-Neelsen stain or AFB culture. However, mycobacteria take 4–6-week time to grow in culture. Recent methods of culture like BACTEC, Ogawa, mycobacterium growth indicator tube (MGIT), MB/BacT mycobacterial detection system, and ESP culture system II are rapid though sensitivity varies. These systems need to be evaluated specifically for ITB [8–10]. Other molecular methods like DNA probes, ribosomal rRNA-based probes, and gene amplification methods seem promising. However, as ITB is a paucibacillary disease, sensitivity of detecting *M. tuberculosis* in tissue specimens remains low. Culture of biopsy specimens can also be useful in identifying MDR and XDR strains of mycobacteria [11].

Tuberculosis polymerase chain reaction (PCR) assay is based on the amplification of oligonucleotides found in chromosomes of *M. tuberculosis* that are highly specific for the organism. PCR analysis of endoscopic biopsies should be done routinely as the results are available within 2–3 days. PCR positivity is not influenced by presence of granulomas or caseation necrosis [12, 13]. This emphasizes the usefulness of this test even where histology does not show granulomas. TB PCR is very specific for tuberculosis but rarely has been reported to be positive for CD. Fecal PCR for *M. tuberculosis* IS6110 to distinguish Crohn's disease from ITB has been reported from India, but this needs further validation [14]. A new technique "in situ PCR" is being studied to overcome the drawbacks of conventional PCR [15, 16].

Endoscopic Features

Ileo colonoscopy is crucial for the diagnosis of both ITB and CD as brunt of disease in both conditions is around the ileocecal area. When ITB affects the colon, it can present in various ways as segmental ulcers, inflammatory strictures, or hypertrophic lesions resembling nodules, polyps, and masses (Fig. 1). ITB is seen more in the right side of the colon and follows a decreasing trend from the right to left side of the colon [17, 18]. Rarely diffuse involvement of colon resembling pancolitis may occur in ITB. Anorectal involvement, aphthous ulcers, deep longitudinal ulcers, and cobblestone appearance were all significantly more common in patients with CD than in patients with ITB [19] (Fig. 2). Predominant ileal involvement with sparing of cecum is likely to occur in CD rather than ITB where IC valve gets involved early. Similarly, early involvement of multiple segments will favor the diagnosis of CD rather than ITB. The extent of ileal involvement in ITB is shorter as compared to CD. In contrast, ITB usually has less than four segments involved, a patulous ileocecal valve, transverse ulcers, and more scars.

Video capsule endoscopy has been used to evaluate small bowel involvement in CD more commonly than ITB. Nonetheless, it was found that ulcers in ITB were characteristically shallow with an irregular "geographic" border, were usually not larger than 1–2 cm in length, and were transverse rather than the typical longitudinal ulcers seen in the CD [20].

Pathological Features

Differentiation based on histopathology of the diseased area is very important in both ITB and CD but challenging as both conditions are characterized by chronic granulomatous inflammation with overlapping histological features (Table 1). The features specific for ITB are the presence of acid-fast bacilli and caseous necrosis. Nevertheless, these classical features are present in less than one-third cases of ITB. Pulimood et al. [21] have in addition reported confluent large granulomas, >4 sites of granulomatous inflammation, bands of epithelioid histiocytes lining ulcers, submucosal granulomas, and disproportionate submucosal inflammation as favoring diagnosis of ITB. Features seen more frequently in CD include small, loose, infrequent non-caseating granulomas, architectural distortion extending into areas distant from

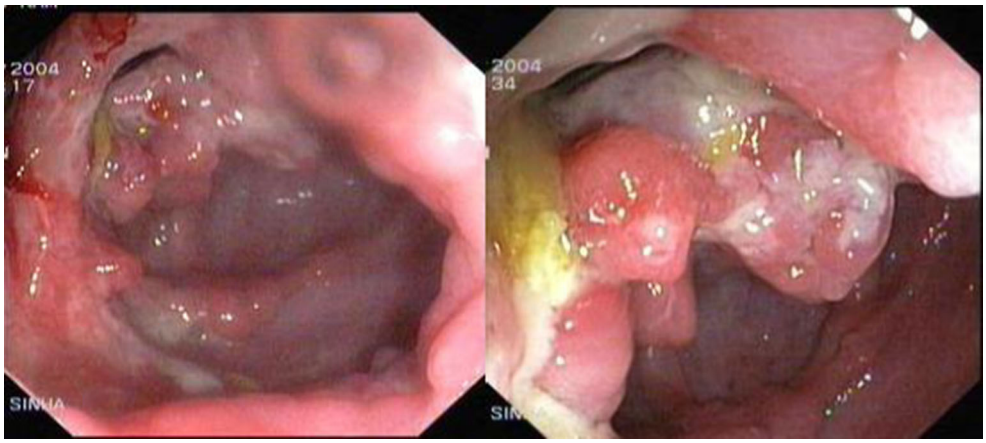

Fig. 1 Ulcero-nodular lesion involving ileocecal valve and caecum in intestinal tuberculosis

granulomatous inflammation, and evidence of focally enhanced colitis [22, 23]. Moreover, inflammatory changes may occur not only in endoscopically diseased area but in normal-looking area also. Hence, multiple biopsies (6–10 in number) should be included from both endoscopically involved and distant and not involved segments.

Imaging Studies

The radiological armamentarium for evaluating tuberculosis of the small bowel (SBTB) includes barium studies (small bowel follow-through, SBFT), CT (multidetector CT, CT enterography, and CT enteroclysis), ultrasound (sonoenteroclysis), and magnetic resonance imaging (MRI; enterography and enteroclysis). Descriptive patterns of ileocecal involvement suggestive of tuberculosis include Fleischner's sign (thickened patulous ileocecal valve combined with a narrowed terminal ileum), and Stierlin's sign (a rapid emptying of contrast through a gaping ileocecal valve into a shrunken cecum). The most common abnormality seen on CT enterography is short-segment strictures with symmetrical concentric mural thickening and homogeneous mural enhancement. Other findings include lymphadenopathy, ascites, enteroliths, peritoneal thickening, and enhancement [24]. Features of CD include symmetrical bowel wall thickening, fibrofatty proliferation of the mesentery known as creeping fat, regional mesenteric nodes measuring 3–8 mm, and enlarged mesenteric vascular bundles in the involved mesentery known as the Comb sign [25–27]. Extra-intestinal features of CD such as fatty liver, gallstones, primary sclerosing cholangitis, and sacro-ileitis may also be noticed in imaging modalities. Besides CT enterography, MR enterography has also been evaluated to characterize ITB and CD. One of the few drawbacks compared with computerized tomography is that magnetic resonance imaging cannot detect small calcification within nodes or masses. However, magnetic resonance enteroclysis is increasingly being used to image the small intestine for diagnosis and assessment of small intestinal CD, but little data exist regarding its use in ITB and this requires further study [28]. Complex perianal fistula detected on magnetic resonance of the pelvis is highly suggestive of

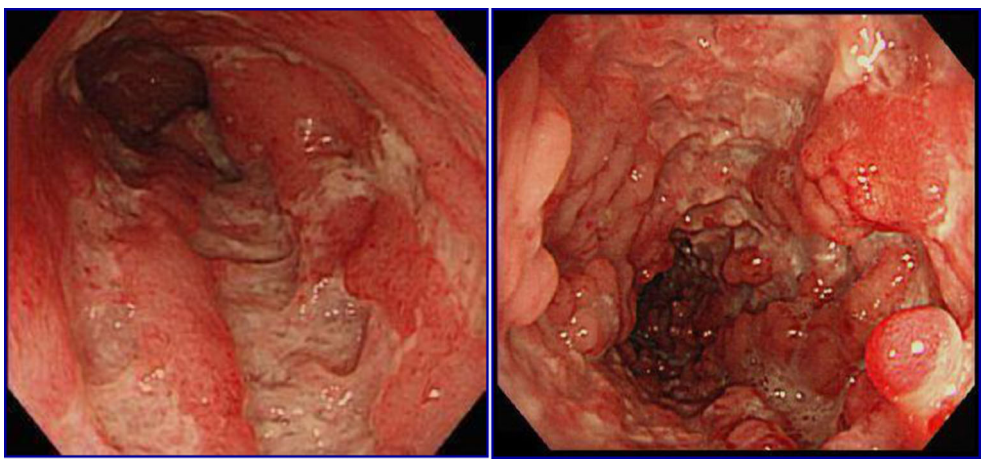

Fig. 2 Longitudinal deep ulcers in Crohn's disease

Table 1 Differences between ITB and CD

Parameter	Intestinal tuberculosis	Crohn's disease
Age	Any	Young
Gender	Male=Female	Female>Male
Disease course	Chronic, continuous	Relapses and remissions
Duration of symptoms	Shorter	Longer
Clinical presentation (frequency and chronological order)	Pain abdomen, fever, poor appetite, chronic diarrhea	Chronic diarrhea, hematochezia, abdominal pain, poor appetite, fever
Endoscopic features	Transverse ulcers, nodules scars, short segment strictures. Ileocecal valve almost always diseased	Longitudinal ulcers, aphthous ulcers, cobblestoning, perianal disease. Long segment of ileal involvement with sparing of ileocecal valve
Histological features	Granulomas (caseating, large, confluent, and more in number). Mucosal architectural loss only close to granulomas. Prominent submucosal inflammation	Granulomas (non-caseating, small, loss, and infrequent). Focally enhanced colitis. Mucosal architectural loss present even distant from granulomas
Radiological features	Short strictures, deformed ileocecal valve, lymphadenopathy with hypodense centers, thickened peritoneum	Long segment strictures, multiple sites involved, Comb sign, perianal disease
Tissue TB PCR and culture	Positive	Negative

CD. Evidence of past or active tuberculosis on chest X-ray will favor associated ITB, but this is rarely present nowadays.

Role of Laparoscopy

Laparoscopy has an established role in diagnosing peritoneal tuberculosis, but its role in diagnosing ITB is less certain. Thickened peritoneum with tubercles found in mesentery, omentum, and other solid organs will favor the diagnosis of tuberculosis. Creeping fat associated with transmural inflammation has been classically noticed in Crohn's disease. However, mesenteric fat wrapping has also been reported in patients with tuberculosis [29].

The Tuberculin Skin Test (TST)

This skin test has been extensively studied in patients with pulmonary tuberculosis. The traditional cut-off used is 10 mm. But increasing this to 15 mm increases the specificity but at the cost of sensitivity [30]. The value of this test specifically for ITB is not established. False-positive results may occur due to previous BCG vaccine exposure (up to 15 years), non-tuberculosis mycobacteria, and in low endemicity areas. Similarly, false-negative results may occur in patients on immunosuppressants, extreme malnutrition, and other immunocompromised states. However, this test, if positive, provides supportive evidence to the diagnosis of tuberculosis though negative test does not rule out the disease.

Interferon γ Release Assays (IGRA)

In an attempt to overcome the problem of TST, IFN-γ-based assays have been developed to evaluate for tuberculosis. These assays determine the magnitude of interferon γ release by T cells upon stimulation by *M. tuberculosis* antigens in vitro. Two types of tests are available, QuantiFERON-TB Gold (Cellestis, Carnegie, Australia) and T-SPOT. *TB* (Oxford Immunotec, Oxford, UK) [31, 32].

The main advantages of these tests are (i) no cross-reaction with BCG and most non-tuberculosis mycobacteria, (ii) complete in a single visit, and (iii) malnourished and immunocompromised patients can be evaluated. However, these assays fail to differentiate between latent and active tuberculosis and cannot predict progression of latent tuberculosis. In case of borderline values of IGRA, one has to rely more on TST and clinical judgment [33]. The precise role of these assays in the diagnosis of TB remains unsettled.

Anti-tubercular Therapeutic Trials

Although anti-tubercular therapy trial was used in the past to differentiate between the two diseases in countries with high prevalence of tuberculosis, but this should not be taken as a standard practice. Partial response to anti-tubercular therapy (ATT) in patient with actual Crohn's disease and emergence of MDR tuberculosis restricts the usefulness of response to ATT as a way of establishing the diagnosis of tuberculosis [34]. To make the matter more complex, the patients with CD being treated with immunosuppressants have a higher risk of

acquiring all infections including tuberculosis. This can lead to the co-existence of two diseases. In addition, reactivation of tuberculosis needs to be more aggressively searched in countries where tuberculosis is endemic. In spite of the availability of a wide range of investigations, uncertainty about ITB vs. CD remains in nearly one third of the patients. Such patients may be considered for ATT first. However, re-evaluation at 8–12 weeks is crucial for decision regarding continuation of ATT or switching to treatment for CD.

Conclusion

Differentiation between ITB and CD is very challenging but crucial as fall outs of wrong diagnosis can be devastating. In the absence of a single pathognomonic clinical feature or diagnostic test, the diagnosis of either disease should be based on all the evidences. A detailed clinical evaluation and corroborative tests are mandatory before initiating specific therapy.

Compliance with Ethics Guidelines

Conflict of Interest Ajit Sood, Vandana Midha, and Arshdeep Singh declare no conflict of interest.

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