Granulomatous colitis: Can pathology help in differentiating intestinal tuberculosis from Crohn’s disease?

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Granulomatous colitis: A granuloma is defined as a collection of modified epithelioid histiocytes. In the gastrointestinal tract, there are numerous conditions that can give rise to granuloma formation and also contain structures which mimic a granuloma (1) (Table 1). Of these, the two conditions considered most important are intestinal tuberculosis (ITB) and Crohn’s disease (CD). Both conditions present with similar clinical, endoscopic and radiological findings. The problem of differentiating ITB from CD is by no means unique to those practicing in the developing countries such as ours where ITB is common. Though the clinicians in the developing countries face the brunt of the problem, it has now become a global challenge. This is mainly due to the re-emergence of TB in the west, in the wake of the acquired immunodeficiency syndrome epidemic (2,3) and the more frequent recognition of CD in many tropical countries such as Sri Lanka where it was previously under diagnosed.

Though these two conditions share many similarities the treatment and the disease outcome are completely different. ITB is an entirely curable disease, CD, in contrast, is a progressive and relapsing illness. Secondly most CD patients respond to mesalazine preparations, immunotherapy or steroid treatment, a small proportion even respond to antituberculous therapy (ATT), making the issue even more confusing (2). Conversely, steroid therapy will do more harm than good in individuals with ITB. CD also requires life-long treatment and follow up. Thus, distinguishing between these two diseases is crucial. In fact, a large number of patients with CD are initially misclassified as having ITB in regions where TB is endemic, before they are treated for CD because of failure to improve with ATT. There are high rates of misdiagnosis in both conditions. For example, 65% of CD had been misdiagnosed as TB, as reported from China (4). Conversely, steroid therapy will do more harm than good in individuals with intestinal TB.

A variety of clinical, endoscopic, radiological and histological features have been recommended for the differentiation of these two conditions. Some of these will be briefly discussed, whilst the emphasis of this article will be on histological differentiation of ITB from CD. These histological features will be compared with the author’s data of a cohort of Sri Lankan patients.

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Clinical radiological and endoscopic features of ITB and CD

Clinical features: Clinical features of both diseases include constitutional symptoms (fever, anorexia and weight loss), symptoms due to mucosal ulceration (haematochezia, diarrhoea and malabsorption), symptoms due to transmural involvement (distention, abdominal pain vomiting, a palpable lump; intestinal perforation and fistula formation) and extra-intestinal manifestations such as arthritis and sclerosing cholangitis in the case of CD and multi organ involvement in TB. A family history of inflammatory bowel disease (IBD) in the case of CD or a history of family contacts in the case of TB may be obtained (5,6).

In patients with CD the duration of illness is generally more than 12 months while it is shorter, lasting around 6 to 7 months in ITB (5). Diarrhea and haematochezia are more commonly seen in CD while fever, ascitis and co-existing TB at other sites are seen in ITB. Perianal disease, malabsorption and recurrence of disease after surgery favor a diagnosis of CD.

Radiological features: Imaging plays an important role in diagnosing and differentiating ITB from CD (7,8). Barium examination is the mainstay for the evaluation of the intestinal tract whilst computed tomography (CT) is useful for the evaluation of extra-intestinal pathologies. ITB strictures are typically short, concentric and smooth in outline with significant pre-stenotic dilatation. In CD, strictures are usually long, eccentric with sacculations at the anti-mesenteric border and without significant pre-stenotic dilatation. Aphthous ulcers and an ulceronodular pattern in the small intestines and cobblestoning of the large intestines are almost pathognomonic of CD in the appropriate clinical setting. Tubercular ulcers are less common and tend to be round to oval in configuration. Perforation and fistulae are more often encountered with CD, while enteroliths are more common in ITB (7,8). In computerized tomography mural thickening with vascular engorgement of the mesentery (comb sign) and mesenteric fibrofatty proliferation are characteristic signs of CD.

Endoscopic features: Characteristic endoscopic features have been described in ITB and CD (9,10). Transversely placed ulcers, nodularity and hypertrophic lesions resembling masses are characteristic of TB. Aphthoid or longitudinal, deep, fissuring ulcers and a cobblestone appearance are said to be more typical of CD on endoscopy. Very few studies have directly compared these or evaluated their diagnostic value and inter-observer agreement.

Laboratory investigations: Abnormalities in routine blood tests such as total and differential leukocyte count, raised ESR, C-reactive protein and low haemoglobin are seen in the active phase of both ITB and CD (5,11). Anti Saccharomyces cerevisiae antibody (ASCA) is a non-specific antibody resulting from macromolecular transport of food antigens, due partly to an increase in intestinal permeability. In one study on a small number of patients, only one of 14 (7%) patients with ITB had a positive result for ASCA in contrast to 49% with CD (12) and there
fore, the authors recommended use of this test for differentiation between CD and ITB. However two larger studies from India showed that ASCA was not useful in differentiating between CD and TB (13,14). Since patients with both ITB and CD have chronic inflammatory lesions of the small intestine, with an associated increase in small intestinal permeability, the ASCA test being positive in the both conditions is to be expected (13). The most reliable method to differentiate between ITB and CD is demonstration of acid-fast bacilli (AFB) either in smears or by culture. However, smears and cultures demonstrating Mycobacterium tuberculosis (MTB) have low sensitivity. Identification of AFB on intestinal biopsies has been reported with variable frequency (25%-36%) (5,11). The use of fluorescent stain for the diagnosis of ITB increases sensitivity but lacks specificity and results are still poor due to the pauci-bacillary nature of the disease (5). Furthermore, Mycobacteria take a very long time (4-6 weeks) to grow in culture. The time to recovery of Mycobacteria from culture has been shortened to 2-3 wk by the use of automated culture systems such as BACTEC, Mycobacteria growth indicator tube (MGIT), MB/BacT mycobacterial detection system and the ESP culture system II (15). The sensitivity of the BACTEC system was found to be poor for the diagnosis of ITB (5,6). The TB polymerase chain reaction (PCR) assay is based on augmenting oligonucleotides found in MTB chromosomes that are highly specific for the organism. TB PCR analysis of endoscopic biopsy specimens or surgical specimens can be done quickly and results can be obtained within 48 h (16). This test is very specific for TB but occasionally may be positive in patients with CD (17). Sensitivity of this test is modest (16,17). The in situ TB PCR technique needs to be improved for better sensitivity. As currently used, TB PCR on biopsy samples has a high positive predictive value but a very low negative predictive value.

Quantiferon TB Gold (QFT-G, Cellestis Limited, Carnegie, Victoria, Australia) is an in vitro ELISA which detects the release of interferon-gamma after stimulation by MTB antigen. The advantages of QFT-G include lack of cross-reaction with BCG and most nontuberculous mycobacteria (except for M. kansasii, M. szulgai and M. marinum), avoidance of reader bias and the need for only a single patient visit. The limitations include the need for incubation within 12 hours of blood collection and its inability to differentiate infection with TB from latent TB infection. Its sensitivity for latent TB infection seems to be less than that of the tuberculin skin test. The role of QFT-G in intestinal tuberculosis is not clear. The test may have a possible role in follow up of patients on antituberculous therapy (ATT), in the diagnostic dilemma of CD versus ITB and may be undertaken prior to starting biologics in CD patients (18).

Pathological features: In surgical resection specimens the macroscopic features of ITB include ulceration, short strictures and marked thickening of the bowel wall due to inflammation, fibrosis and or adhesions. The ulcers are transverse, often circumferential with ill defined sloping or overhanging edges. The surrounding mucosa may show flattening of folds, ulcers, erosions
and pseudopolyps. The serosal surface may show 2-5 mm sized nodules and adhesions. The regional lymph nodes are invariably enlarged and may show caseation (19).

Macroscopically, CD also shows bowel wall thickening, skip lesions and strictures, but the latter are longer than in TB. Fat wrapping is common, as are adhesions, fistulae, sinuses and extra-intestinal abscesses (20). Mucosal aphthous ulcers are seen at an early stage, and coalesce to form larger stellate ulcers. Deep, longitudinal, fissuring ulcers are characteristic of CD, as well as smaller longitudinal ulcers separating oedematous or uninvolved mucosa to create a cobblestone appearance (21).

In practice however, pathologists will be faced with making this differential diagnosis in the context of endoscopic mucosal biopsies where the small sample size and superficial nature of the specimen makes this task difficult. The histological features studied in mucosal biopsies of different cohorts of patients from India, South Africa and Sri Lanka are summarized in table 1. (22-24).

Table 1. Causes of granuloma formation in the gastrointestinal tract

| Infective | Tuberculosis |
|-----------|--------------|
| Atypical Mycobacteria |
| Chlamydia |
| Yersinia |
| Schistosomiasis |
| Fungal infection |
| Rare - Salmonella, Campylobacter |
| Crohn's disease |
| Sarcoidosis |
| Malakoplakia |
| Diversion colitis |
| Barium granuloma |
| Pathological mimics |
| Histiocytic response to a ruptured crypt |
| Diverticular disease |
| Ulcerative colitis |
| Effects of tangential sectioning of a crypt |

Fig 1. Caseating and confluent granulomas in ITB(H&EX10)

Fig 2. Vague and ill defined granuloma of CD(H&EX10)

These microgranulomas often <200μm in size are mainly mucosal and submucosal in location. However one of the draw backs in relying on the morphology of the granulomas is that these are found in only 50 – 80% of the intestinal biopsies of patients with clinically confi-
cells around an isolated group of crypts or the presence of focal activity around crypts has been variously termed individual crypt pick out or focally active colitis. This feature is more consistently present in CD (Table 2).

Disproportionate submucosal inflammation is where the degree of submucosal inflammation exceeds that of the overlying and adjacent non-ulcerated mucosa (Figure 6). This feature appeared to be more frequent in the ITB patients from both South India and South Africa.

| Histological parameter | Pulimood et al (South India) | Kirsch et al (South Africa) | Hewavisenthhi (Sri Lanka) |
|------------------------|------------------------------|-----------------------------|---------------------------|
|                        | ITB N=20                     | ITB N=18                    | ITB N=20                  |
|                        | CD N=20                      | CD N=25                     | CD N=12                   |
| **Characteristics of granulomas** |                      |                             |                           |
| Granuloma present     | 100%                         | 78%                         | 95%                       |
| Average size           | >400um (>0.05mm (Area))      | 0.05mm                      | >400um                    |
| Average no / section   | 5.35                         | 7.28                        | 5.1                       |
| Granulomas > 5 per biopsy | 40%                         | 44%                         | 50%                       |
| Caseation              | 40%                          | 22%                         | 45%                       |
| Confluence             | 60%                          | 50%                         | 65%                       |
| **Other histological features** |                      |                             |                           |
| Disproportionate submucosal inflammation | 65%                          | 67%                         | NA                        |
| Ulcers lined by epithelioid histiocytes | 45%                          | 61%                         | 65%                       |
| Architectural distortion in non inflamed areas | 0%                          | NA                          | NB                        |
| Enhancement of chronic inflammation | 20%                          | NA                          | NA                        |

Table 2. Histological parameters helpful in differentiating ITB from CD
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Fig 3. Histiocytes lining the inflammatory granulation tissue in ITB(H&EX10)

Fig 4. A breaking down granuloma forming the base of an ulcer in ITB(H&EX10)

Fig 5. Focal active colitis in CD(H&EX10)

Fig 6. Disproportionate submucosal inflammation (H&EX10)

Fig 7. Pseudopyloric metaplasia / ulcer associated cell lineage (H&EX10).

Fig 8. Granulomatous vasculitis (H&EX10)
In summary, more numerous, larger, confluent and caseating granuloma favour a diagnosis of ITB whilst the presence of focal enhancement of chronic inflammation and architectural distortion in endoscopically normal areas appear to favour CD. This is possibly in keeping with the different disease activities of the two conditions in which ITB is a more localized infection with a more severe granulomatous response and CD is a more widespread disease with involving a larger area of the gastrointestinal tract. A multi disciplinary approach taking into consideration the clinical, radiological, endoscopic and histological findings will help differentiate ITB from CD in a majority of cases.

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