Review Article

Granulomatous colitis: Can pathology help in differentiating intestinal tuberculosis from Crohns 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 Crohns 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 mesalamine 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 cobble stoning 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 biologicals 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).

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

Table 1. Causes of granuloma formation in the gastrointestinal tract

The granuloma which is the histological hall mark of both these diseases, have proved to have several morphological differences. The presence of numerous, larger confluent and caseating granulomas are more frequently encountered in ITB (Figure 1) whereas the granulomas of CD are more ill defined or poorly organized and smaller (Figure 2).

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 drawbacks 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-

med ITB (25) and 15 – 65% of patients with CD (26). Hence the need to identify other histological parameters useful in the differential diagnosis. These include the presence of a conglomerate of epithelioid histiocytes lining the inflammatory granulation tissue (Figure 3) which is due to the partial breaking down of granulomas which form the base of ulcers in ITB (Figure 4).

The presence of focally enhanced inflammation (Figure 5) either in the form of destruction or over running of an isolated crypt by inflammation or aggregates of acute or chronic inflammatory

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.

	Pulimood et al (South India)		Kirsch et al (South Africa)		Hewavisenthi (Sri Lanka)	
Histological parameter	ITB N=20	CD N=20	ITB N=18	CD N=25	ITB N=20	CD N=12
Characteristics of granulomas						
Granuloma present	100%	55%	78%	28%	95%	25%
Average size	>400um		0.05mm (Area)		>400um	
Average no / section	5.35	0.75	2.85	0.6	5.1	0.5
Granulomas > 5 per biopsy	40%	0%	44%	24%	50%	0%
Caseation	40%	0%	22%	0%	45%	0%
Confluence	60%	0%	50%	0%	65%	0%
Other histological features						
Disproportionate submucosal inflammation	65%	5%	67%	10%	NA	NA
Ulcers lined by epithelioid histiocytes	45%	5%	61%	8%	65%	0%
Architectural distortion in non inflamed areas	0%	62%	NA	NA	0%	58%
Enhancement of chronic inflammation	20%	50%	NA	NA	15%	66%

Table 2. Histological parameters helpful in differentiating ITB from CD

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)

Biopsy specimens from endoscopically uninvolved mucosa with chronic inflammatory changes and architectural distortion (Table 2) suggest that the disease process in Crohn's disease involves larger areas of the intestine. In contrast, ITB presents as an area of localised infection with a more severe granulomatous response. The significantly higher prevalence of deep ulcers and disproportionate submucosal inflammation in ITB also suggest more intense disease activity. The presence of crypt distortion and inflammation in areas of non inflamed and endoscopically normal mucosa seen in CD also emphasizes the need for clinicians to biopsy endoscopically normal areas to help in the differential diagnosis. Another feature of interest is the presence of pseudopyloric metaplasia / ulcer associated cell lineage (UACL) which was present more often in our cohort of CD patients (Figure 7). The presence of UACL is a reparative reaction of the intestinal mucosa to injury and ulceration and is possibly more frequent in CD patients because it is of a longer duration at presentation and diagnosis.

The presence of granulomatous vasculitis or collections of mononuclear cells around vessels (Figure 8) is also a useful feature in CD. The results of one study suggest that the majority of granulomas in Crohn's disease originate within walls of blood vessels and that the intestinal microvasculature contains an early element in the pathogenesis of CD (27). However this form of vasculitis is seen more often in the submucosal and deeper vessels and is therefore not a feature consistently identified in mucosal biopsies.

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.

References

1. Hewavisenthi SJDeS. Interpretation of Colorectal mucosal biopsies: A systematic approach. *Journal of Diagnostic Pathology* 2001; 2: 2-10.
2. Navaneethan U, Cherian JV, Prabhu R, Venkataraman J. Distinguishing Tuberculosis and Crohn's Disease in developing countries: How certain can you be of the diagnosis? *Saudi Journal of Gastroenterology* 2009; 15(2): 142-144.
3. Horvath KD, Whelan RL. Intestinal tuberculosis: Return of an old disease. *American Journal of Gastroenterology* 1998; 93: 692-696.
4. Tonghua L, Guozong P, Minzhang C. Crohn's disease: Clinicopathologic manifestations and differential diagnosis from enterocolonic tuberculosis. *Chinese Medical Journal* 1981; 94: 431-440.
5. Amarapurkar DN, Patel ND, Rane PS. Diagnosis of Crohn's disease in India where tuberculosis is widely prevalent. *World Journal of Gastroenterol*

ogy 2008; 14: 741–746.

6. Patel N, Amarapurkar D, Agal S, Baijal R, Kulshrestha P, Pramanik S, Gupte P. Gastrointestinal luminal tuberculosis: establishing the diagnosis. *Journal of Gastroenterology and Hepatology* 2004; 19: 1240–1246.

7. Nagi B, Kochhar R, Bhasin DK, Singh K. Colorectal tuberculosis. *European Radiology* 2003; 13: 1907–1912.

8. Wills JS, Lobis IF, Denstman FJ. Crohn disease: state of the art. *Radiology* 1997; 202: 597–610.

9. Epstein D, Watermeyer G, Kirsch R. Review article: the diagnosis and management of Crohn's disease in populations with high-risk rates for tuberculosis. *Alimentary Pharmacology and Therapeutics* 2007; 25: 1373–1388.

10. Leighton JA, Shen B, Baron TH, Adler DG, Davila R, Egan JV, et al. ASGE guideline: endoscopy in the diagnosis and treatment of inflammatory bowel disease. *Gastrointestinal Endoscopy* 2006; 63: 558–565.

11. Almadi MA, Ghosh S, Aljebreen AM. Differentiating intestinal tuberculosis from Crohn's disease: a diagnostic challenge. *American Journal of Gastroenterology* 2009; 104: 1003–1012.

12. Kim BG, Kim YS, Kim JS, Jung HC, Song IS. Diagnostic role of anti-Saccharomyces cerevisiae mannan antibodies combined with antineutrophil cytoplasmic antibodies in patients with inflammatory bowel disease. *Diseases of the Colon Rectum* 2002; 45: 1062–1069.

13. Ghoshal UC, Ghoshal U, Singh H, Tiwari S. Anti-Saccharomyces cerevisiae antibody is not useful to differentiate between Crohn's disease and

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intestinal tuberculosis in India. *Journal of Postgraduate Medicine* 2007; 53: 166–170.

14. Makharia GK, Sachdev V, Gupta R, Lal S, Pandey RM. Anti-Saccharomyces antibody does not differentiate between Crohn's disease and intestinal tuberculosis. *Digestive Diseases and Sciences* 2007; 52: 33–39.

15. Morgan MA, Horstmeier CD, DeYoung DR, Roberts GD. Comparison of a radiometric method (BACTEC) and conventional culture media for recovery of mycobacteria from smear-negative specimens. *Journal of Clinical Microbiology* 1983; 18: 384–388.

16. Gan H, Ouyang Q, Bu H, Li S, Chen D, Li G, Yang X. Value of polymerase chain reaction assay in diagnosis of intestinal tuberculosis and differentiation from Crohn's disease. *Chinese Medical Journal (Eng)* 1995; 108: 215–220.

17. Amarapurkar DN, Patel ND, Amarapurkar AD, Agal S, Baigal R, Gupte P. Tissue polymerase chain reaction in diagnosis of intestinal tuberculosis and Crohn's disease. *Journal of the Association of Physicians of India* 2004; 52: 863–867.

18. Pulimood AB, Amarapurkar DN, Ghoshal U, Phillip M, Pai CG, Reddy DN et al. Differentiation of Crohn's disease from intestinal tuberculosis in India in 2010. *World Journal of Gastroenterology* 2011; 17: 433–443.

19. Tandon HD, Prakash A. Pathology of intestinal tuberculosis and its distinction from Crohn's disease. *Gut* 1972; 13: 260–269.

20. Price AB, Morson BC. Inflammatory bowel disease: the surgical pathology of Crohn's disease and ulcerative colitis. *Human Pathology* 1975; 6: 7–29.

21. Lockhart-Mummery HE, Morson BC. Crohn's disease of the large intestine. *Gut* 1964; 5: 493–509.
22. Pulimood, AB , Ramakrishna, Kurian G, Peter S, Patra S, MathanV, Mathan M. Endoscopic mucosal biopsies are useful in distinguishing granulomatous colitis due to Crohn's disease from tuberculosis. *Gut* 1999 October; 45(4): 537–541.
23. Kirsch R, Pentecost M, Hall PdeM, Epstein DP, Watermeyer G, Friederich PW. Role of colonoscopic biopsy in distinguishing between Crohn's disease and intestinal tuberculosis. *Journal of Clinical Pathology* 2006 August; 59(8): 840–844.
24. Hewavisenthi J. Differentiation of Crohn's disease from Tuberculosis – can pathology help? *Proceedings of the Asia Pacific Digestive week* 2011; 213.
25. Pettengell KE, Larsen C, Garb M, Mayet FG, Simjee AE, Pirie D. Gastrointestinal tuberculosis in patients with pulmonary tuberculosis. *Queensland Journal of Medicine* 1990; 74: 303–308.
26. Tanaka M, Riddell RH. The pathological diagnosis and differential diagnosis of Crohn's disease. *Hepatogastroenterology* 1990; 37: 18–31.
27. Wakefield AJ, Sankey EA, Dhillon AP, Sawyerr AM, More L, Sim R et al Granulomatous vasculitis in Crohn's disease. *Gastroenterology* 1991; 100: 1279-1287.