Original Article

Differentiation of Crohn's disease from intestinal Tuberculosis and Ulcerative Colitis: a single tertiary centre experience in Nepal

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Abstract

Introduction: Differentiating intestinal luminal tuberculosis from Crohn's disease (CD) is an important clinical challenge of considerable therapeutic significance. Likewise differentiating ulcerative colitis from Crohn's disease with colonic or ileocolonic involvement is difficult. The aim of this study was to investigate the clinical, endoscopic, radiologic and histological features that will help to differentiate Crohn's disease from intestinal luminal tuberculosis as well as from ulcerative colitis.

Methods: A total of 40 patients diagnosed with Crohn's disease, Intestinal luminal TB and Ulcerative colitis who were admitted under the Gastroenterology Department TUTH from July 2017 to February 2018 were included in this retrospective study. Clinical, endoscopic, radiologic, histopathologic and microbiologic features as well as response to treatment of these patients were studied in detail.

Results: Among 40 patients, Intestinal TB was diagnosed in 52.5% patients, ulcerative colitis in 32.5% patients and Crohn's disease in 15% patients. There was a higher incidence of fever, night sweats, lung involvement and ascites in Intestinal TB whereas diarrhea, perianal disease, hematochezia and extraintestinal were predictive for Crohn's disease. Similarly on colonoscopy involvement of IC valve, patulous IC valve and transverse ulcers favored a diagnosis of intestinal TB in contrast to Crohn's disease where longitudinal ulcers, aphthous ulcers, cobblestone appearance and rectal involvement were seen.Similarly the diagnosis of Ulcerative colitis was favored by rectal involvement and contiguous involvement whereas patients with Crohn's disease had significantly more deep ulcers, cobblestoning, skip areas and ileal involvement.

Conclusions: Crohn's disease must be differentiated from Intestinal luminal TB and Ulcerative colitis before treatment. According to our study, a combination of clinical, endoscopic, serologic, radiologic, histopathologic and microbiologic features can be utilized in order to reliably predict and distinguish Crohn's disease from Intestinal luminal TB and from Ulcerative colitis. In complicated cases deep enteroscopy and surgery may be needed before a confident diagnosis is reached.

Introduction

Intestinal tuberculosis (ITB) is caused by the tubercle bacillus entering the gastrointestinal tract. The presence of the tubercle bacillus can trigger inflammatory changes including serosal and submucosal edema, cellular infiltration, and lymphatic hyperplasia.[1] Crohn's disease (CD), a chronic inflammatory bowel disease characterized by transmural inflammation and granuloma formation, can affect the entire gastrointestinal tract from the mouth to the anus.[2] Its etiology is not fully understood. The differential diagnosis between the two diseases can bemade on the basis of certain specific findings such as acid-fastbacilli (AFBs) and granulomas with caseous necrosis in ITB. However, these findings are positive in less than 50% of patients[3], and there is currently no definitive diagnostic test for CD. Also, importantly, the two diseases have confusingly similar clinical, endoscopic, and pathological manifestations and are often very difficult to distinguish in clinical practice.[4]

Diagnosis of gastrointestinal intestinal tuberculosis is often suspected on clinical, radiologic and endoscopic features, but histologic or microbiologic proof of the disease is often difficult to achieve. Therefore the majority of patients are treated using anti-tubercular therapy (ATT) on presumptive diagnosis only. In Nepal, as more and more cases of IBD which closely mimics GI tuberculosis are being recognized, the differentiating parameters become important. In cases of misdiagnosis as GI tuberculosis, unnecessary treatment with ATT poses a risk of toxicity, and treatment of the primary disease, such as Crohn's disease, is delayed. In contrast, treatment with steroids can be disastrous if GI tuberculosis is missed.

Inflammatory bowel diseases (IBD) encompasses a group of diseases, triggered and perpetuated by a variety of diverse genetic, environmental and immunologic factors that share similar clinical manifestations and which primarily affect the small intestine and colon.[5] The two most common entities of IBD, ulcerative colitis (UC) and Crohn's disease (CD) are more common in developed countries than developing countries.[6] According to recent studies, the incidence of IBD is increasing in developing countries.[7] In comparison to Western countries, there are limited data regarding the epidemiology, clinical features and causes of IBD in these regions. Therefore additional studies that emphasize clinical features and differentiation between UC and CD are needed to elucidate its pattern.

Thus, the aim of this study was (i) to investigate the value of clinical, endoscopic, radiologic and histological and microbiologic features in patients with intestinal luminal tuberculosis, Crohn's disease and Ulcerative colitis. (ii) to identify features that may help in differentiation of intestinal tuberculosis form Crohn's disease and that between Ulcerative colitis and Crohn's disease.

Methods

A retrospective analysis of 40 consecutive patients diagnosed with CD (n = 6) and ITB (n = 21) and UC (n=13) who were admitted under the Gastroenterology Department TUTH from July 2017 to February 2018 was done. The patients were also analyzed for response to treatment. Informed consents were signed by patients.

All data regarding the patients were recorded in a structured manner that included the patients' demographic, clinical, laboratory, endoscopic, radiological, and pathological data. In clinical evaluations, detailed information regarding any history of similar illnesses with symptoms such as abdominal pain, diarrhea, constipation, hematochezia, fever, sweating, and weight loss was obtained from all patients. In laboratory and radiological evaluations, white blood cells (WBCs), hemoglobin, platelets, protein, albumin, C-reactive protein, erythrocyte sedimentation rate, mantoux test, abdominal lymphadenopathy, ascites, and a suspicion of pulmonary tuberculosis during the initial diagnostic period were reviewed. Colonoscopic findings such as aphthous ulcers, transverse ulcers, longitudinal ulcers, deep ulcerations, cobblestone appearance, pseudopolyposis, stricture, mucosal bridge, patulous ileocecal valve, and involvement in segmental lesions of the bowels were also reviewed. If biopsy specimens had been obtained from patients, histological evaluations such as granulomas (caseous or non-caseous necrosis), AFB staining, polymerase chain reaction for Mycobacterium tuberculosis (TB-PCR), cryptitis, crypt abscess, and crypt atrophy were evaluated. The activity and severity of IBD were determined by the Crohn's Disease Activity Index and the Truelove and Witt's classification of UC.

The diagnostic criteria for CD conformed to the consensus on the management of CD in Europe and the Asia-Pacific region, that is, a combination of clinical, endoscopic, radiological and histological features.[8] The diagnostic criteria for ITB are as follows: (i) presence of caseating granuloma (ii) demonstration of AFB on smears or histological sections, (iii) positive culture for AFB, (iv) histologically or microbiologically confirmed TB at an extra-intestinal site, and (v) positive TB-PCR. For a definite diagnosis of ITB, one or more of these criteria had to be fulfilled, except for a complete response to treatment. Patients with presumed GITB unconfirmed by histology or microbiology but had response to standard ATT regimen were also included.

Statistical analysis was carried out on various clinical, radiologic, endoscopic, histologic and microbiologic features comparing all three groups, using Student's t-test and χ 2 tests, as appropriate. A P-value of <0.05 was considered statistically significant. The value of p1 indicates a comparison of intestinal TB and CD and p2 indicates a comparison of UC and CD.

Results

A total of 40 patients with intestinal TB and IBD were included in this study (mean age: 35.79±12.7 years). There were 22 males and 18 females with male to

female ratio of 1.22:1. Epidemiologic and clinical characteristics of the studied population are presented in Table 1. The patients were divided into three groups as follows: (i) Intestinal TB: n = 21 (52.5%), mean age = 35.2 ± 13.9 years, male to female ratio (M : F) = 1.33:1; (ii) Crohn's disease: n = 6 (15%),mean age = 34.6 ± 12.7 years, M : F = 1:1; (iii) Ulcerative colitis: n = 13 (32.5%), mean age = 37.3 ±11.5 years, M : F = 1.16:1. No statistically significant difference was found between the age and sex distributions of all three groups (Table 1).

Table 1 Clinical and demographic features in all the study groups

Characteristics	GITB (n=21)	Crohn's Disease (n=6)	Ulcerative colitis (n= 13)	p1	p2
Age (mean ± SD [years])	35.2 ±13.9	34.6 ± 12.7	37.3 ± 11.5	NS	NS
Sex (male : female)	1.33:1	1:1	1.16:1	NS	NS
Mean duration of symptoms (months)	6	24	5	S	S
Abdominal pain (%)	76	83	15	NS	S
Fever (%)	61	16	7	S	NS
Night sweats (%)	52	16	0	S	NS
Weight loss (%)	52	66	23	NS	S
Diarrhea (%)	28	66	61	S	NS
Constipation	14	16	15	NS	NS
Abdominal lump (%)	14	16	0	NS	NS
Intestinal obstruction (%)	4	16	0	NS	NS
Rectal bleed (%)	4	33	92	S	S
Fistula (%)	0	33	0	S	S
Ascites (%)	38	0	0	S	NS
Lung involvement (%)	33	0	0	S	NS
Anemia (%)	52	66	53	NS	NS
HIV seropositivity (%)	14	0	0	NS	NS
Smoking history	9	16	23	NS	NS
First degree relatives of IBD	0	0	7	NS	NS

Table 2 Radiological features in the study groups

Barium studies/ computed tomography/ Ultrasound findings (%)	GITB (n=21)	Crohn's Disease (n=6)	P
Short segmental involvement	14	66	S
Intestinal wall thickening/stricture	52	66	NS
Abdominal mass	14	16	NS
Mesenteric thickening	47	16	NS
Ascites	38	0	S
Abdominal lymph node	47	33	NS
Abnormal ileocecal junction	66	16	S
Comb sign	0	50	S

Table 3 Endoscopic features in the study groups

Characteristics (%)	GITB (n=21)	Crohn's Disease (n=6)	p
Longitudinal ulcers	4	66	S
Transverse ulcers	47	16	S
Aphthous ulcers	14	33	NS
Cobblestone appearance	4	50	S
Patulous/deformed ileocecal valve	61	16	S
Pseudopolyps	33	33	NS
Stricture	38	50	NS
Skip lesions	19	66	S
Nodularity	38	16	NS
Granulomas on biopsy	61	16	S

Comparison between intestinal TB and Crohn's disease

On comparing the clinical features (intestinal TB vs Crohn's disease) fever (61% vs 16%), night sweats (52% vs 16%), ascites (38% vs 0%) and lung involvement (33% vs 0%) were significantly more common in intestinal TB whereas rectal bleeding (33% vs 4%), perianal or enteroenteric fistula (33% vs 0%) and diarrhea (66% vs 28%) were significantly more common in Crohn's disease. There were no significant differences in abdominal pain, weight loss, abdominal lump, intestinal obstruction, or anemia between both the groups. The mean duration of symptoms before reaching a diagnosis was significantly longer in Crohn's disease patients (6 months vs 24 months; Table 1).

Among the radiological features, ascites (38% vs 0%), and abnormal IC junction (66% vs 16%) were significantly more common in intestinal TB whereas short segmental involvement (66% vs 14%) and comb sign (50% vs 0%) were significant for Crohn's diseases. Other features, such as stricture (52% vs 66%), mesenteric thickening (47% vs 16%),mass(14% vs16%) and lymphadenopathy (47% vs 33%) were present equally in both groups(Table 2).

Among the endoscopic features (Table 3), transverse ulcers (47% vs 16%), and patulous/deformed IC valve (61% vs 16%) were significantly more common in intestinal TB whereas longitudinal ulcers (66%vs 4%), cobblestone appearance (50% vs 4%) and skip lesions(66% vs 19%) were significantly more common in Crohn's disease. Aphthous ulcers, pesudopolyps, strictures and nodularity were not significantly different between both the groups. In the histopathology presence of granuloma correlated with intestinal TB as opposed to Crohn's disease (61% vs 16%).

One case of Crohn's disease underwent surgery for intestinal obstruction and the resected specimen was available for histopathological analysis. In 2 cases of Crohn's disease, patients underwent double balloon enteroscopy for evaluation of small intestinal strictures and biopsy sampling.

Comparison between Ulcerative colitis and Crohn's disease

There were 13 patients diagnosed with Ulcerative colitis and 6 patients with CD who were included in this study. The mean age at onset of IBD in CD cases was 32.6 ± 12.7 years, for UC it was 36.9 ± 11.5 years and the difference was not statistically significant. A first degree relative of IBD was present in only 1 case of UC but none in CD. The median time interval from initiation of symptoms to diagnosis was significantly longer in Crohn's disease vs UC (24 months vs 5 months).

In a comparison between the clinical characteristics and presentation of CD and UC (Table 1), it was noted that patients with CD had a significantly higher incidence of abdominal pain/cramping (83% vs 15%), weight loss (66% vs 23%), and fistula (33% vs 0%) whereas rectal bleeding was significantly higher in UC patients (92% vs 33%). There was no significant difference between UC and CD patients with regards to fever, diarrhea, anemia, smoking history or family history of IBD.

On comparing the endoscopic features (Crohn's disease vs UC) ileal involvement (83% vs 7%), deep ulcers (83% vs 15%), cobblestoning (66% vs 7%), and skip areas (83% vs 7%) were significantly more common in Crohn's disease whereas rectal involvement (92% vs 16%) and contiguous involvement (92% vs 16%) were significantly higher in UC patients (Table 4).

Based on colonoscopic findings in UC (Table 5), E3 disease (pancolitis) was present in 6 cases, E2 disease (involvement limited to the colorectal distal to the splenic flexure) was present in 5 cases and E1 disease (Involvement limited to the rectum) was present in 2 cases.According to Truelove-Witts classification the disease severity was moderate in 6 patients and severe in 7 patients. 2 cases with pancolitis presented with relapse while another case with pancolitis was steroid dependent.The most common clinical manifestation of the patients in this study was bloody diarrhea followed by abdominal cramping, anorexia, and weight loss. Symptoms of urgency and tenesmus and a sense of incomplete evacuation were present in 5 patients.

Extra intestinal manifestations were seen in 38% of UC patients and in 33% of those with Crohn's disease. There was no significant difference in the presence of extraintestinal features in UC vs Crohn's disease patients. Among the extra-intestinal manifestations of IBD, arthritis was the most frequent as observed in 38% of UC and 33% of Crohn's disease patients. Anterior uveitis was the next common with 23% in UC patients and 33% Crohn's disease patients (Table 6).

Table 4 Endoscopic features in the IBD patients

Characteristics (%)	Ulcerative colitis (n=13)	Crohn's disease (n=6)	p
Rectal involvement	92	16	S
Ileal involvement	7	83	S
Deep ulcers	15	83	S
cobblestoning	7	66	S
Contiguous involvement	92	16	S
skip areas	7	83	S
Granulomas	0	16	NS

Table 5 Disease extent and severity in the IBD patients

	Ulcerative colitis (n=13)		Crohn's disease (n=6)	
Extent (%): Montreal classification	E1	46	L1	33
	E2	38	L2	16
	E3	15	L3	50
Severity (%):	Mild	0	CDAI: Mild	0
	Moderate	53	CDAI: Moderate	50
	Severe	46	CDAI: Severe	50

Table 6 Extra-intestinal manifestations of IBD patients

	Ulcerative colitis (n=13)	Crohn's disease (n=6)
Arthritis (%)	38	33
Eye disorders (%)	23	33
Hepatobiliary (%)	23	0
Fistula (%)	0	33
Skin disorders (%)	15	16
Aphthous ulcers	15	16

Discussion

Differentiating intestinal tuberculosis (ITB) from Crohn's disease (CD) remains a challenging clinical problem in Nepal where Intestinal TB is prevalent and CD incidence is increasing. A definite diagnosis of ITB depends on methods that have unsatisfactorily low sensitivities, including 5.3–37.5% for acid-fast bacilli tissue staining[9], 23–46% for mycobacterial culture[10], and 36.4–67.9% for PCR[11]. Therefore, ITB still cannot be confidently excluded even when all the above results are negative, thus the current Asia-Pacific guidelines recommend 8–12 weeks of empirical antituberculosis treatment for patients with diagnostic uncertainty, owing to the potentially fatal complications if immunosuppressive agents are wrongly prescribed to ITB patients.[12] However, antituberculosis treatment can cause many side effects and facilitate the development of Mycobacterium tuberculosis drug resistance.

Additionally, 8–12 weeks of empiric antituberculosis treatment can delay proper CD treatment and lead to severe flares and complications. Therefore, many studies have been undertaken to identify features that can differentiate between these two diseases, and have found that individual clinical, endoscopic, imaging, and serologic laboratory findings help to guide physicians in selecting empirical treatment.[13]

Conclusion

As seen in our study, the following features should make a clinician alert for the suspicion of Crohn's disease as opposed to intestinal TB initially or in subsequent follow up: (i) longer mean duration of symptoms (ii) the presence of diarrhea; (iii) rectal bleed; (iv) perianal disease;(iii) endoscopic features such as longitudinal ulcers, cobblestoning and skip lesions; (v) the absence of large or confluent granuloma on histology and negative AFB smear; (v) the absence of involvement of the peritoneum, abdominal lymph node or site of extraintestinal tuberculosis, such as extra-abdominal lymph node, lungs, or pleura; and (vi) no response to ATT. Similarly features that predict the presence of Crohn's colitis from Ulcerative colitis include (i) absence of rectal involvement; (ii) presence of ileal involvement; (iii) deep ulcerations; (iii) cobblestoning; and (iv) skip lesions. The severity of illness and the presence of extraintestinal manifestations were not significantly different in Crohn's disease vs Ulcerative colitis.

Conflict of interest: None declared

Reference

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