

Endoscopic differentiation of Colonic Tuberculosis (CTB) and Crohn's Disease (CD) in tuberculosis endemic area.

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Abstract

Aim: To define the endoscopic features and distribution of colonic tuberculosis (CTB) and Crohn's disease (CD) for early diagnosis.

Methods: All adult patients referred for colonoscopy for CTB and CD was included. Demographic and colonoscopy features were recorded and biopsy taken.

Results: Ninety patients, of which 48 in CTB were enrolled. In CTB, lesions were mainly located on the right colon and ulcers were single or three to five, size more than 5 cm, irregular in shape, yellow glistening in color, circumferentially oriented, border indistinct with nodular component. CD involved both side of the colon and ulcers were more than five in number, linear or oval in shape, less than 2 cm, longitudinal orientation, dirty yellow color and intervening mucosa contain aphthous ulcers or cobble stoning

Conclusion: Colonic tuberculosis and Crohn's disease has distinct endoscopic and distribution pattern with some overlap. Colonoscopy and biopsy is an important diagnostic tool for early diagnosis in CTB and CD.

Keywords: Colonic tuberculosis, Crohn's disease, Intestinal tuberculosis, Colonoscopy.

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Introduction

Colonic tuberculosis (CTB) and Crohn's disease (CD) are important chronic granulomatous disorders of the large Intestine. Although both of these entities are found all over the world, their relative proportion varies in different regions. In developing countries CTB is more prevalent but Crohn's disease also do exist [1-4] whereas in the developed world, tuberculosis is re-emerging because of HIV infection and rise in the immigrant population from the tuberculosis endemic area and ageing population [5]. Both of these conditions may affect the large intestine with significant overlap in clinical presentation, distribution, radiological features and appearance on colonoscopy. In many cases, differentiation of these two disorders has become diagnostic challenge for clinicians [6-10].

Colonoscopy is a quick and effective tool for investigating colonic lesions where direct examination up to terminal ileum can be performed in a well prepared patient. In trained and expert hands, colonoscopy is a fairly safe procedure where not only morphological feature of the lesion can be defined but, one can also take tissue specimen for histopathology and acid fast bacilli (AFB) culture. In different studies, based upon colonoscopic finding and biopsy, early and definitive diagnosis of CTB and CD has been made [11-13]. In many situation, where biopsy specimen is inadequate, non-representative or histopathology report is inconclusive to differentiate between these two conditions, the endoscopic visual appearance of the lesion might be of help in clinical judgement and diagnosis.

In order to make an early diagnosis, it is important to define the visual characteristics and distributions of the colonic lesions in CTB and CD as both of these conditions are prevalent in our region. The aims of this study were to define the endoscopic features and the distribution of CTB and CD for early diagnosis and to validate the description with already defined colonoscopic features of these conditions from different set of population.

Methods

Adult patients presented to Aga Khan University hospital Karachi, Pakistan, for colonoscopy with suspected colonic tuberculosis or Crohn's disease between January 2011 till December 2015 were considered for inclusion in the study. Patients less than 18 years of age, poor bowel preparation, or when full colonoscopy could not be performed due to any reason or where colonoscopy showed no mucosal lesion up to terminal ileum were excluded from the study. Patients were prepared for colonoscopy starting on clear liquid diet for two days and sodium phosphate (NaP) administered in two doses of 45 mL each, containing 10.8 g disodium phosphate and 24.4 g sodium dihydrogen phosphate dihydrate. According to the protocol, the first dose was given in the evening before the examination (20:00hrs), and the second on the morning before the procedure (07:00hrs). Each dose was diluted in 120 mL of water followed by another 240 mL of water to make sure that stool passed are clear and watery in consistency.

Demographic data regarding age, gender, presenting complaints, duration of symptoms, previous or family history of tuberculosis was recorded. After taking informed consent colonoscopy was

performed with Olympus video scope up to the caecum and when possible retrograde examination of terminal ileum was also performed. During forward and backward movement of the scope, entire colonic mucosa, hepatic and splenic flexures were carefully examined for any lesion. Colonoscopic lesions were described on the basis of pre-defined proforma which included location of the lesion, number, size, shape and axis of lesion, base, borders and depth of the lesion was also described.

The appearance of the surrounding mucosa, friability, vascularity, contact bleeding, cobble stoning, presence of aphthous ulcers, skip lesion or continuous mucosal involvement, fistulae, stricture if any, deformity of caecum or ileocaecal valve were described. The terminal ileal lesions were also described as per colonic lesions. Multiple biopsies were taken from the lesions and surrounding mucosa in formalin for histopathology and in 0.9% normal saline for assessment of Acid Fast Bacilli (AFB) culture.

The diagnosis of tuberculosis was suspected in the presence of positive quantiferon test (interferon gamma release assay) for tuberculosis, positive staining for acid-fast bacilli (on crush biopsy smears, positive culture for Mycobacterium tuberculosis, presence of MTB by PCR or Gene-Xpert, caseation and necrosis in granulomas, confluent granulomas, multiple granulomas, large granuloma size, disproportionate sub mucosal inflammation [14,15]. Presence of microgranulomas, nonconfluent granulomas, single granulomas and architectural distortion distant from granulomatous inflammation favored Crohn's disease [16]. These patients were started on treatment and followed up in the clinic for at least one year and response to the treatment was documented. In case the patient did not respond to the treatment and diagnosis was reconsidered or alternate diagnosis was made, was also documented. The study was approved by the ethical review committee (ERC) of the institution

Statistical Analysis

The Statistical package for social science (IBM SPSS Statistics Version 19) was used for data analyses. Descriptive analysis of socio-demographic variables was done and means and standard deviations (SD) were calculated for quantitative variables and proportions for categorical variables. Continuous variables were compared using Student t-test and categorical variables were compared by chi-square or fisher exact test and 95% confidence intervals (CI) were calculated for each association. All P-values were two sided and considered as statistically significant if $P < 0.05$. Univariate and multivariate analysis was done and for contrasts of continuous variables, an independent sample t-test was used to assess the difference of means. Variables found to be statistically significant in the univariate analysis were included in a multivariate stepwise logistic regression model. The model was constructed to identify independent factors associated with CTB or CD. A multivariable logistic regression analysis was performed with an entry probability of 0.05. The regression coefficients of the final multivariable logistic model were taken as the weights for the respective variables and a score for each patient was calculated. Receiver-operating characteristic (ROC) analysis was performed on these scores to assess the ability to discriminate CTB from CD.

Results

Total patients enrolled in the study were 132 and 42 were excluded as they were not fulfilling inclusion criteria and 90 patient fulfilled the inclusion criteria. Out of 90 selected patients, 48 were in CTB and 42 in CD. The mean ages of the patients with CTB and CD was 34.23 ± 14.45 and 41.45 ± 13.4 ($p < 0.01$) years. In gender distribution male patients in CTB and CD were 27 (56.3%) and 20 (47.6%) ($p < 0.41$). Demographic features and endoscopic characteristics are shown in the Tables 1-3.

Colonoscopic features of tuberculosis

Numbers of ulcers in CTB were either single 13 (27%) or ranged from two to five 35 (73%) patients. The shape of these ulcers were circular or oval 11 (23%) and linear or irregular 37 (77%).

Table 1. Characteristics of study population.

Characteristics	Total Patients n=90	Colonic TB n=48	Crohn's Disease n=42	p-value
Age, in years with SD and range	37.6 ± 14.3; 15-76	34.2 ± 14.4	41.4 ± 13.4	0.01
Gender				
Male	47 (52.2)	27 (56.3)	20 (47.6)	0.52
Female	43 (47.8)	21 (43.8)	22 (52.4)	
No. of ulcers				
Single	13 (14.4)	13 (27.1)	0	<0.001
2-5	59 (65.6)	34 (70.8)	25 (59.5)	
>5	18 (20)	1 (2.1)	17 (40.5)	
Shape of ulcer				
Circular or Oval	43 (47.8)	11 (22.9)	32 (76.2)	<0.001
linear	47 (52.2)	37 (77.1)	10 (23.8)	
Size of ulcer				
1-2 cm	44 (48.9)	14 (29.2)	30 (71.4)	<0.001
3-5 cm	46 (51.1)	34 (70.8)	12 (28.6)	
Axis of ulcer				
Horizontal	60 (66.7)	45 (93.8)	15 (35.7)	<0.001
Longitudinal	30 (33.3)	3 (6.3)	27 (64.3)	
Base of ulcer				
Yellow	58 (64.4)	44 (91.7)	14 (33.3)	<0.001
Dirty yellow	32 (35.6)	4 (8.3)	28 (66.7)	
Border of ulcer				
Flat and Sharpe	16 (17.8)	5 (10.4)	11 (26.2)	0.14
Raised and irregular	20 (22.2)	11 (22.9)	9 (21.4)	
Indistinct	54 (60)	32 (66.7)	22 (52.4)	
Depth of ulcer				
Flat	3 (3.3)	0	3 (7.1)	0.09
Superficial	87 (96.7)	48 (100)	39 (92.9)	
Surrounding mucosa				
Normal	21 (23.3)	18 (37.5)	3 (7.1)	<0.001
Hyperemic	23 (25.6)	16 (33.3)	7 (16.7)	
Nodular	15 (16.7)	14 (29.2)	1 (2.4)	
Aphthous ulcer	31 (34.4)	0	31 (73.8)	
Intervening mucosa				
Normal	65 (72.2)	39 (81.3)	26 (61.9)	<0.001
Erythematous	10 (11.1)	9 (18.8)	1 (2.4)	
Cobble stoning	15 (16.7)	0	15 (35.7)	
Ulcer bleed				
Yes	15 (16.7)	3 (6.3)	12 (28.6)	0.009
No	75 (83.3)	45 (93.8)	30 (71.4)	
Location of ulcer				
Left side of colon	7 (7.8)	2 (4.2)	5 (11.9)	<0.001
Right side of colon	44 (48.9)	43 (89.6)	1 (2.4)	
Both sides of colon	39 (43.3)	3 (6.3)	36 (85.7)	

Table 2. On multivariate analysis, factors predicting Crohn's disease from colonic TB.

Characteristics	Odd ratio (95% CI)	p-value
Location of ulcer		
1-2 area	1.0	<0.001
3 and more areas	201.12 (10.22-3954.28)	
Shape of ulcer		
Linear	1.0	<0.006
Oval	65.30 (3.24-1316.30)	
Axis of ulcer		
Horizontal	1.0	<0.007
Longitudinal	42.81 (2.83-647.09)	
Base of ulcer		
Yellow	1.0	<0.02
Dirty yellow	24.46 (1.54-388.54)	

The size of the ulcer ranged from 1-2 cm in 14 (29.2%) and 2-5 cm in 34 (70.8%). The axis of the ulcer was horizontal in 45 (93.8%) and longitudinal in 3 (6.2%). The base of the ulcer was yellow glistening in 44 (91.7%) and dirty yellow in 4 (8.3%). The border of the ulcer was flat and sharp in 5 (10.4%) raised and irregular in 11 (23%) and indistinct in 32 (66.6%). All the ulcers in CTB were superficial. The mucosa surrounding the ulcer was normal in 18 (37.4%), red and swollen in 15 (31.3%) and nodular in 15 (31.3%) (Figures 1 and 2).

Colonoscopic features of Crohn's disease

Numbers of ulcers in CD were either 2-5 in 24 (57.1%) or more than 5 in 18 (42.9%) patients. The shape of ulcer was circular or oval in 32 (76.2%) and linear or irregular 10 (23.8%). The size of the ulcer ranged from 1-2 cm in 30 (71.4%) to 2-5 cm in 12 (28.6%). The axis of the ulcer was horizontal in 15 (35.7%) and longitudinal in 27 (64.3%). The base of the ulcer was yellow glistening in 14 (33.3%) and dirty yellow in 28 (66.7%). The border of the ulcer was flat and sharp in 11 (26.2%) raised and irregular 9 (21.4%) and indistinct in 22 (52.4%). Ulcers in the CD were flat in 3 (7.1%) and superficial in 39 (92.9%). Mucosa surrounding the ulcers was normal in 3 (7.1%), red and swollen in 8 (19.1%) and contained aphthous ulcers or cobble stoning in 31 (61.9%). At the time of examination, 22 (52.3%) ulcers had some degree of bleeding (Figures 3 and 4).

Distribution of lesions in Crohn's disease and colonic tuberculosis

Crohn's disease involved more than one area of the colon both on the right and left side whereas in CTB the lesions predominantly affect the right side and in rare case the left side was also involved. Distribution of CD and CTB respectively were rectum (62.2 vs. 18.8%, $P<0.001$), sigmoid colon (66.0 vs. 11.3%, $P<0.001$), descending colon (60.3 vs. 13.2%, $P<0.001$), ascending colon (64.1% vs. 43.4%, $P=0.03$), ileocecal region (88.6 vs. 92.4%, $P=0.5$), terminal ileum (24.5 vs. 15.0%, $P=0.2$). In CTB ileocaecal valve usually was deformed, patulous or destroyed with fish-mouth opening whereas in CD ileocecal valve was spared (Figures 5 and 6).

Discussion

In developing countries, colonic tuberculosis (CTB) and crohn's disease (CD) are two important diseases involving the large intestine with overlap in clinical features, radiological

Table 3. Differentiating features of colonic tuberculosis and Crohn's disease ulcers.

S. No	Characteristics of lesion	Colonic TB	Crohn's disease
1	Number	Single or multiple	Multiple
2	Size	Variable	Variable
3	Location	Superficially located	Superficially located
4	Surface	Yellow and glistening	Dirty yellow
5	Axis	Circumferentially oriented	Longitudinal orientation
6	Surrounding mucosa	Normal/nodular	Inflamed
7	Aphthous ulcers	Uncommon	Common
8	Cobble stoning	not seen	Cobble stoning present
9	Nodular component	Commonly present	Rarely seen
10	Ileocecal valve	Usually deformed and destroyed	Ileocecal valve is usually spared
11	Disease distribution	Usually right side of colon	Multiple areas and both side of the colon is involved

findings and endoscopic appearance [17] as the treatment differs significantly so early and correct diagnosis is important to save the life of the patient and to avoid complications. In this review from an TB endemic area where Crohn's disease also do exist, we demonstrated some important visual features and distribution of the lesions on colonoscopy examination and by correlating these findings in an appropriate clinical setting, we can differentiate between CTB and CD in significant number of Patients.

In this five years study we enrolled 48 consecutive patients with CTB and all of them were presented for the first time for colonoscopy and another 42 patients with CD either presented for the first time or they are already in our follow up pool and had their repeat colonoscopy for relapse of symptoms during this time period. Although number of patients is nearly equal in these two groups but new cases of CTB were more than CD patients which is in concordance with the prevalence of these two diseases in this part of the world.¹⁸

In this study more male patients had CTB than female patients may be due to difference in health seeking behavior or male being active member had more chances for external exposure and TB contact as compared to female. Similar finding were reported by a study from our region [18].

The median age of the patient was 34 years at diagnosis in CTB which is equivalent to the other observations in previous reports [19].

In this review, we found that characteristic lesion of CTB are usually single, but it may be multiple, mainly involving the ileocecal region, but rarely may also involve the left side of the colon. The size of the lesion in CTB was variable; it was superficially located in most of the patients and circumferential or transverse in orientation, with nodular component in a significant number of the cases. Surrounding mucosa in CTB cases was inflamed in majority of the patients.

In other studies, colonic tuberculosis lesions on colonoscopy are described as circumferentially or transversely placed ulcers, nodularity and hypertrophy of the mucosa with inflammation, mass like lesion with distortion and deformity of caecum and ileocaecal valve [20,21]. Our findings are consistent with these reports.

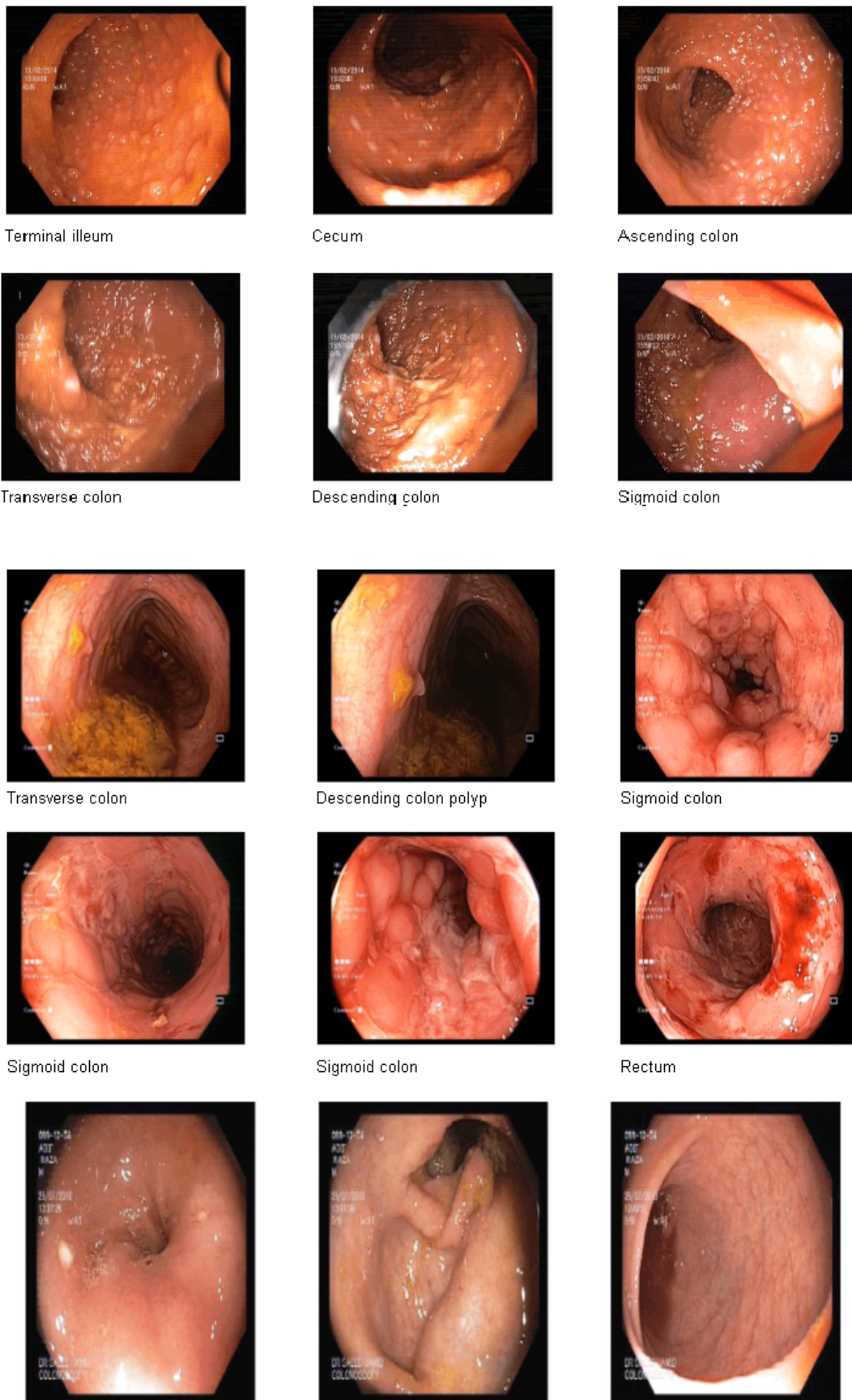


Figure 1. Cobble stoning, aphthous ulcers and skip lesions in Crohn's disease.

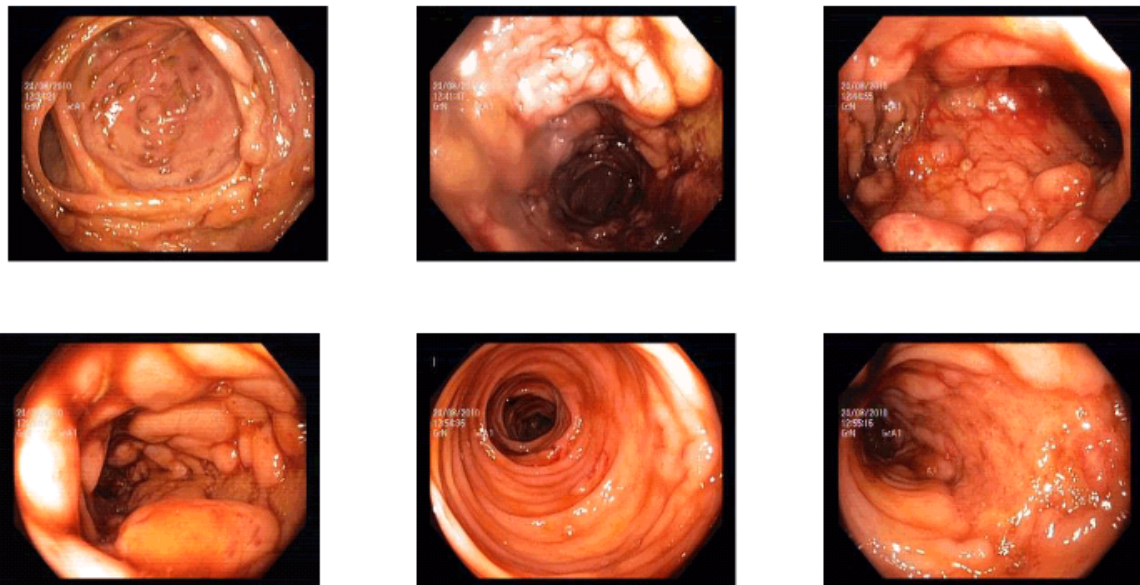
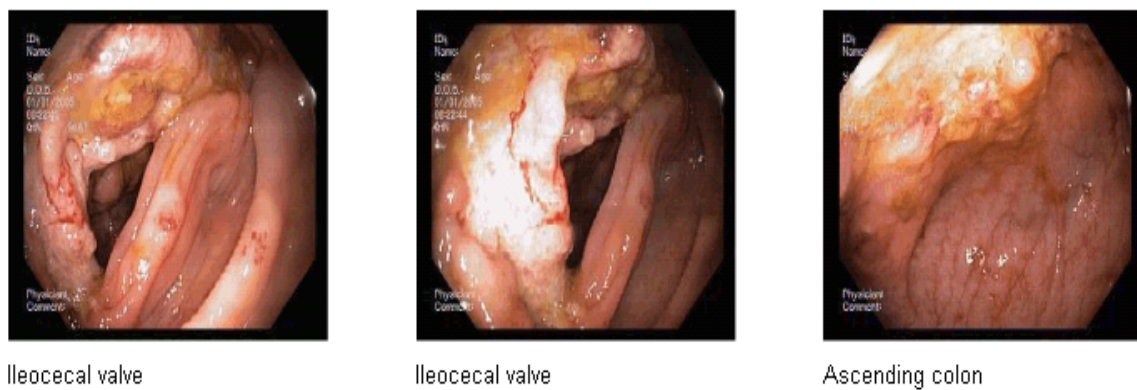


Figure 2. Pseudo polyps, ulcers and cobble stoning in Crohn's disease.

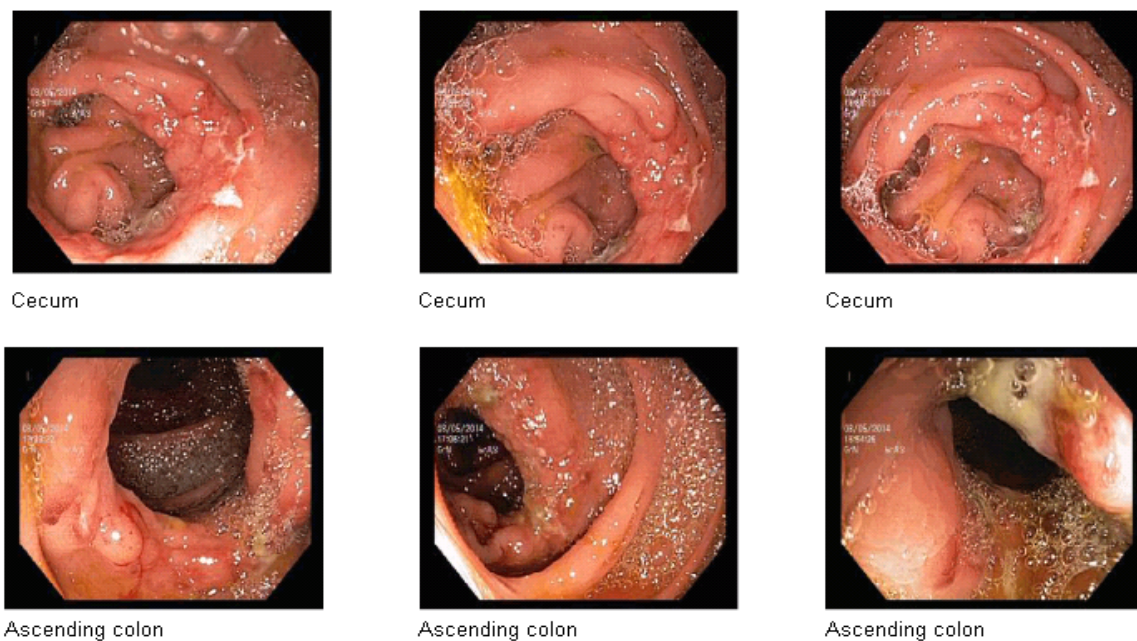


Ileocecal valve

Ileocecal valve

Ascending colon

Figure 3. Tuberculosis involvement of caecum and ileo-caecal valve.



Cecum

Cecum

Cecum

Ascending colon

Ascending colon

Ascending colon

Figure 4. Tuberculosis involvement of caecum and ileo-caecal valve.

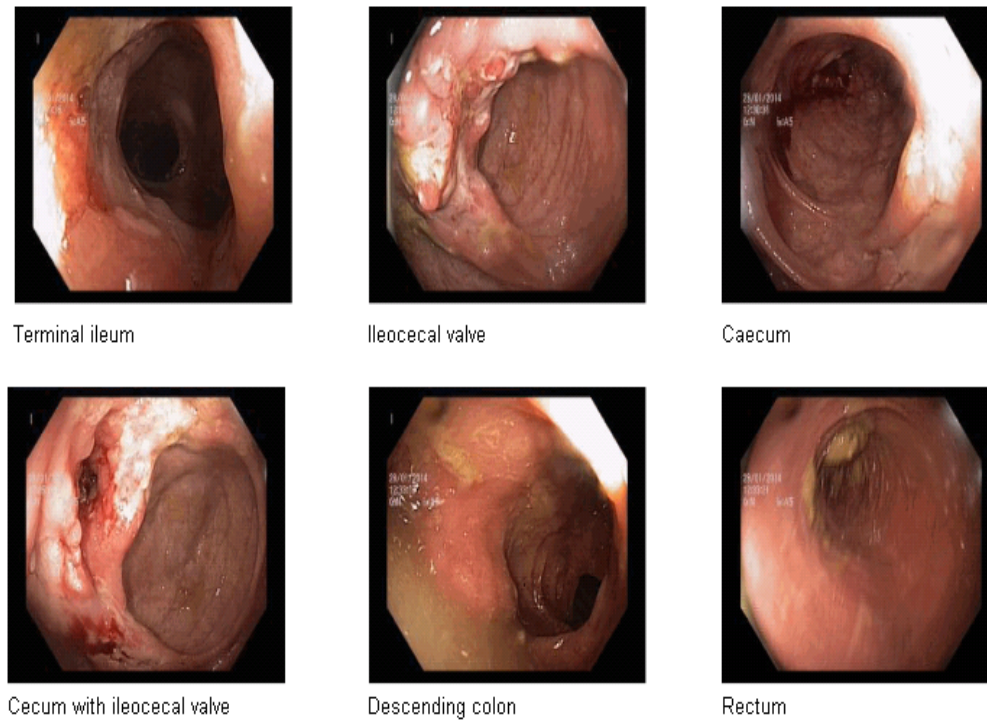


Figure 5. Tuberculosis involvement of caecum and ileo-caecal valve.

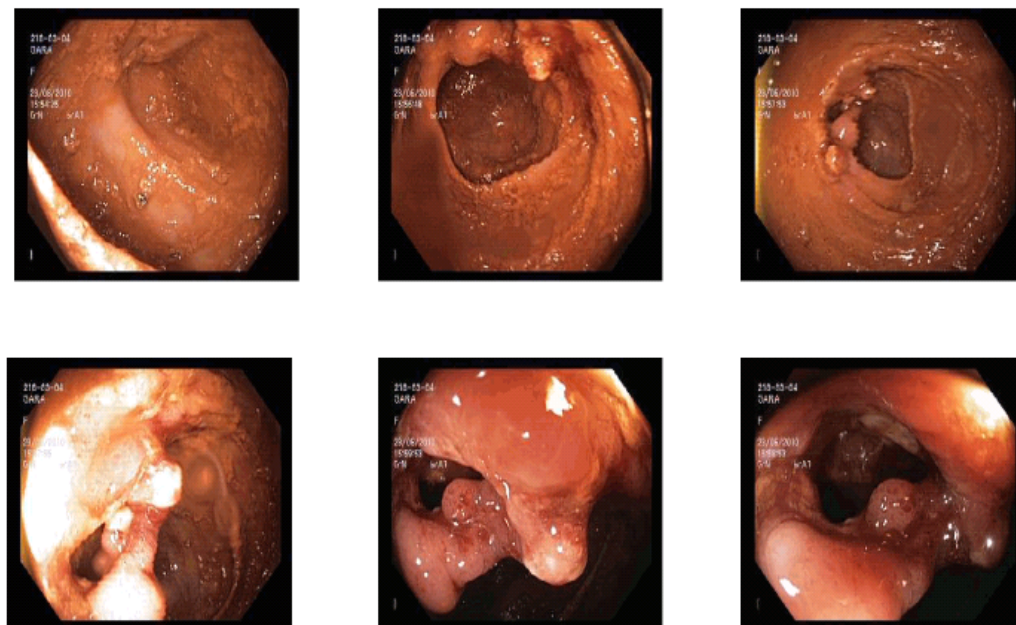


Figure 6. Tuberculosis nodules and ulcers in caecum and ileo-caecal valve.

Although nodular mucosa may be a typical finding in CTB but should be interpreted with caution by taking proper biopsy as many other diseases like colorectal carcinoma may mimic these nodular lesions [22].

Common involvement of CTB at ileocecal area is thought to be due to relative stasis and prolonged contact of AFB to the mucosa in this region and presence of more lymphoid follicle in sub mucosa of the intestine. Transverse location of the CTB ulcer is one of the reasons for predisposition to colicky abdominal pain, acute or sub-cute intestinal obstruction in the patients with CTB [17].

Another study from China, where 30 patients enrolled each from tuberculosis and Crohn's disease, the authors did not find any significant difference in the endoscopic, features between the CTB and CD9 [23].

In another study from Korea, characteristics features of CTB were involvement of less than four segments of colon, patulous ileocecal valve, transverse ulcers, and pseudo polyps for intestinal tuberculosis [24]. Majority of these features except pseudo polyps were present in our series of the patients with CTB.

In this review characteristic feature of CD lesions were multiple in numbers, involving many areas in right and left side of the colon and variable size. These lesions were superficially located, longitudinal orientation and their intervening mucosa in significant number of the patients contains aphthous ulcers and cobble stoning.

On multivariate analysis, we found that independent factors to determine the diagnosis of CD are more than three area of colon involvement, oval or circular shape ulcers, longitudinal in orientation with dirty yellow base.

In literature CD ulcers are described as, aphthoid or longitudinal, serpiginous or deep fissuring ulcers, skip lesion and a cobblestone appearance are commonly present [16-19].

Lee et al. from Korea reported that their diagnosis of crohn's disease was correct in 87.5% of patients when the diagnosis was made on the basis of four features, namely anorectal lesions, longitudinal ulcers, aphthous ulcers and cobbles toning [23].

In our review, at the time of examination, 12 (28.6%) patients with CD and 3 (6%) patients in CTB ulcers had some degree of bleeding. CD patient may present with bleeding per rectum during relapse of disease and in CTB, the patient may also have history of bleeding per rectum which at time may be massive. Pathogenesis in these patients may be obliterative endarteritis.²⁴ Our patient had mild degree of bleeding per rectum both in CTB and CD.

Conclusion

CTB and CD are important, but distinct disease entities of the large intestine. Colonoscopy is quick method of diagnosing these two conditions. In an appropriate clinical situation, if the lesion on colonoscopy are involving less than three areas of colon, localized to ileocecal region, superficially located and circumferential or transversely oriented with nodular component we are most likely dealing with colonic tuberculosis. On the other hand if the lesion are involving more than three areas of colon, oval or circular in shape, longitudinally oriented, with their intervening mucosa containing aphthous ulcers and cobble stoning and with dirty yellow base in appropriate clinical situation, we are most likely dealing with Crohn's disease. This is a single center study with small sample size and results needs reconfirmation with multicenter study and larger patient population.

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