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CHALLENGES IN DIFFERENTIATING GASTROINTESTINAL TUBERCULOSIS AND CROHNS DISEASE IN A TERTIARY CARE HOSPITAL

Gastroenterology

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ABSTRACT

Background: Tuberculosis (TB) still continues to be a global health concern. In India, where Crohn's disease (CD) cases are on rise, it is difficult to diagnose and manage gastrointestinal tuberculosis (GITB).Final diagnosis is based on a combination of the clinical history with endoscopic studies, culture and PCR, biopsy pathology, radiological investigations and response to therapy.Early mucosal response at two-three months is a marker of response. Early differentiation is important in preventing the delay in the diagnosis and avoiding a complicated course. **Aim of the Study:** To identify the differentiating factors between GITB and CD. To correlate between important patient characteristics, symptoms, serology, imaging, colonoscopy, histology, response to treatment and final diagnosis. **Methods:** Patients who have features of both TB and CD and have difficulties in diagnosis, managing at our centre are included. Patients was diagnosed presumably with TB and CD based on symptoms, serology, imaging, colonoscopy, histology, response to treatment and final diagnosis was based on response to therapy.A total of 30 patients were analyzed. **Results:** Mean VF/SC was 0.54. 9(30%) patients were found to have VF/SC more than 0.63 and 8 (88%) of these turned out to be CD. Stricture was seen in total 13 (43%) patients. >3cm stricture was seen in 9 (30%) patients and <3cm in 4 (13%). Final diagnosis of CD was made in 7 (77%) of these who have >3cm stricture and in 1(20%) who have <3cm stricture.Final diagnosis of TB was made in 18 (64%) patients and CD in 12 (36%). **Conclusions:** Diagnosis is challenging because of paucity of bacilli in samples acquired and is aided by serology and imaging.VF/SC ratio and long segment stricture (>3cm) are two features in imaging which may distinguish CD from TB with high specificity.

KEYWORDS

Crohn's disease, Gastro intestinal Tuberculosis, Long segment stricture, VF/SC ratio

INTRODUCTION

Crohn's disease (CD) and Intestinal tuberculosis (ITB) are chronic granulomatous diseases effecting entire GIT with a predilection to terminal ileum[1]. However, both have overlapping features like clinical symptoms, radiology, endoscopy and histology[2]. Therefore, it's highly essential to explore an effective method for differentiating CD from ITB.

Existing diagnostic tests are difficult to differentiate CD from ITB. It is due to their low sensitivities, such as acid-fast bacilli, mycobacterial culture, polymerase chain reaction[3,4,5]. ATT treatment may lead to side-effects and serious complications[6]. In people who are at risk for ITB a CD diagnosis should be made after careful interpretation[7]. Visceral fat has been linked with many inflammatory conditions such as nonalcoholic steatohepatitis and IBD, especially Crohn's disease.It has also been shown that fibrofatty proliferation is seen at an increased frequency in patients with CD as compared to ITB. Intestinal TB being an infectious disease is associated with malnutrition, would be associated with lesser amount of visceral adipose tissue. The ratio of visceral fat area and subcutaneous fat area and length of stricture is measured on computed tomography which may help to differentiate[8].

A South Korean study from Seo H et al shows that 11% of TB patients were misdiagnosed as CD, while around 18% of CD patients received the diagnosis of TB[9]. Misdiagnosis of CD results in delayed treatment for IBD with a risk of disease progression and stricture formation. There is a risk of adverse effects, including hepatotoxicity due to ATT[10,11,12]. Improvement in CD symptoms and a decline in inflammatory markers with ATT are also seen in few studies[13,14,15]. However, there are adverse consequences of administering ATT in CD. In Aggarwal P et al. study which assessed the response of tubercular intestinal strictures to ATT, it was found that in spite of mucosal healing, fibrotic strictures persisted in nearly 75% of patients, indicating that ATT was unable to resolve the underlying fibrotic process in majority of patients. Though intestinal inflammation ignites the fibrotic response, intestinal fibrosis is a dynamic process, which when advanced, becomes independent of inflammation, and there has been minimal success in reversing established and advanced fibrosis. ATT rather appeared to accelerate the fibrosis development and progression in CD patients. Banerjee R et al. report suggested that the empirical ATT is an important contributor to the diagnostic delay. It may result in stenotic complications and need for surgery[16].While this could be a consequence of a diagnostic delay or the 'fibrotic' effect of ATT, the study seemed to suggest that the cause is not related to the diagnostic delay[17].

We conducted a study on patients who have overlapping features of GITB and CD who received empirical ATT and followed up. Patient characteristics, symptoms, serology, imaging, colonoscopy, histology, response to treatment and final diagnosis are analyzed.

MATERIALS AND METHODS

Patient Selection: Patients who are diagnosed to have presumed TB in OP and IP from February 2023 to February 2024 are enrolled in the study.

Methods: Patient characteristics including the demographic data, symptom analysis, radiological findings, serology-based reports were taken in consideration for data analysis. Based on baseline characteristics all patients were diagnosed to have presumed TB and treated with ATT. Then patients are kept on close follow up for side effects and response to therapy was noted clinically, serologically. Colonoscopy was done 2-3 months after ATT to look for response. Characteristics of patients who turned out to be CD are noted and correlated.

Fat Tissue Measurement: Body fat distribution was assessed using CT with a 10 mm thick slice at the level of the fourth lumbar vertebra. The VF area was defined as all of the pixels with adipose tissue attenuation coefficients. The tomographic attenuation of adipose tissue was defined to be between -150 and -50 Hounsfield units. The SF area was defined as the adipose area between the two defined contours.

Statistics: Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) software version 23.0. Descriptive statistics were expressed as mean, standard deviation for continuous variables and frequencies and percentages for categorical variables.

RESULTS

Patient Characteristics: Total of 30 patients were characterized of which 12 were males (36%) and 18 were females (64%), with age distribution ranging from 11 to 60 years with mean age of 27 years.Symptom analysis was done which included abdominal pain (93%), weight loss (76%), fever (60%), diarrhea(46%), bleeding per rectum(36%) and abdominal distension (36%) in most of the patients. serology based reports include anaemia (73%), thrombocytosis (23%). Mantoux test was positive in 5 patients (18%). Hypoalbuminemia was seen in 53%. Inflammatory markers like CRP is elevated in 56% and ESR in 83%. The most common segment involved in colonoscopy and radiology was terminal ileum (80%). Significant mesenteric lymphadenopathy was seen in 70% and ascites in 36%. Mean VF/SC was 0.54. 9(30%) patients were found to have VF/SC more than 0.63 and 8 (88%) of these turned out to be CD. Stricture was seen in total 13 (43%) patients. >3cm stricture was seen in 9 (30%) patients and <3cm in 4 (13%). Final diagnosis of CD was made in 7 (77%) of these who have >3cm stricture and in 1(20%) who have <3cm stricture. Chest involvement was seen in 5 (16%) patients. Final diagnosis of TB was made in 18 (64%) patients and CD in 12 (36%). So misdiagnosis of TB was done in 12 patients (36%) which was high in present study.

Comparison Of Data

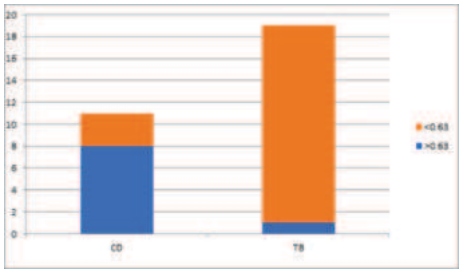

Chart 1 : Distribution based on the VF/SC and diagnosis

DISCUSSION

In present study,

FEATURES	TOTAL (30 patients)	TB (18 patients)	CD (12 patients)
CLINICAL FEATURES			
Abdominal pain	27 (90%)	15 (83%)	12 (100%)
Fever	17 (56%)	11 (61%)	6 (50%)
Weight loss	22 (73%)	15 (83%)	7 (58%)
Diarrhea	13 (43%)	7 (38%)	6 (50%)
Bleeding P/R	10 (33%)	5 (27%)	5 (41%)
Abdominal distension	10 (33%)	7 (38%)	3 (25%)
Tb contact history	6(20%)	4(22%)	2 (16%)
INVESTIGATIONS			
ESR	27 (90%)	18 (100%)	9 (75%)
CRP	16 (53%)	8 (44%)	8 (66%)
Anemia	21 (70%)	14 (78%)	7 (58%)
Thrombocytosis	6 (20%)	3 (16%)	3 (25%)
Mantoux	17 (57%)	13 (72%)	4 (33%)
hypoalbuminemia	15 (50%)	10 (56%)	5 (42%)
Lymphadenopathy	20(66%)	13(72%)	7 (58%)
Stricture	13 (43%)	6 (33%)	7 (58%)
Ascites	10 (33%)	7 (38%)	3 (25%)
Chest involvement	5 (16%)	3 (17%)	2 (16%)

STUDY	VARIABLES	CD	TB
Dawesh Prakash Yadav et al.	VF/SC	1.1	0.4
Jun Kwon Ko et al.	VF/SC	0.95	0.59
Saurabh Kedia et al.	VF/SC	0.99	0.47
Present study	VF/SC	0.81	0.45
Saurabh Kedia et al.	VF/SC >0.63	24 (72.7%)	5 (19.2%)
Present study	VF/SC >0.63	8 (66%)	1 (5%)

In present study mean VF/SC was 0.59. Mean VF/SC in CD patients is 0.81, whereas it is 0.45 in TB patients. Similar study by Dawesh Prakash Yadav et al. also showed that mean VF/SC in CD patients is 1.1, whereas it is 0.4 in TB patients. Similar study by Jun Kwon Ko et al. also showed that mean VF/SC in CD patients is 0.95, whereas it is 0.59 in TB patients. Similar study by Saurabh Kedia et al. also showed that mean VF/SC in CD patients is 0.99, whereas it is 0.47 in TB patients.

In present study VF/SC more than 0.63 was found in 8 (66%) CD patients, whereas it was found in only 1 (5%) TB patient. Similar study by Saurabh Kedia et al. also showed that VF/SC more than 0.63 was found in 24 (72.7%) CD patients, whereas it was found in only 5 (19.2%) TB patient

9(30%) patients were found to have VF/SC more than 0.63 and 8 (88%) of these turned out to be CD. 21 (70%) patients were found to have VF/SC less than 0.63 and 1 (4%) of these turned out to be CD.

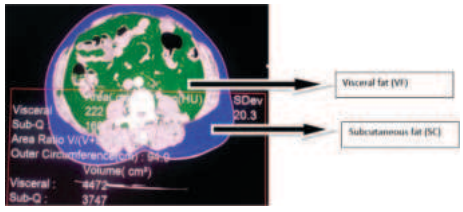

Figure 1 : CT abdomen showing visceral fat (VF), subcutaneous fat (SC), total fat (TF) area and their ratios in a patient with CD:
Green colour area shows visceral fat (VF) ; blue colour area shows subcutaneous fat (SC)

STUDY	VARIABLES	CD	TB
Saurabh Kedia et al.	Long segment stricture (>3cm)	57.6 %	7.7%
KS Madhusudan et al.	Long segment stricture(>3cm)	52.6%	16.1%
Present study	Long segment stricture(>3cm)	58%	11%

In this patient VF = 222 cm2 ; SC = 169 cm2 ; VF/SC ratio = 1.3

In present study long segment stricture was found in 58% of CD patients,whereas it was found in only 11% of TB patients. Similar study by Saurabh Kedia et al. also showed that long segment stricture was found in 57.6 % of CD patients,whereas it was found in only 7.7% of TB patients. Similar study by KS Madhusudan et al. also showed that long segment stricture was found in 52.6 % of CD patients,whereas it was found in only 16.1% of TB patients.

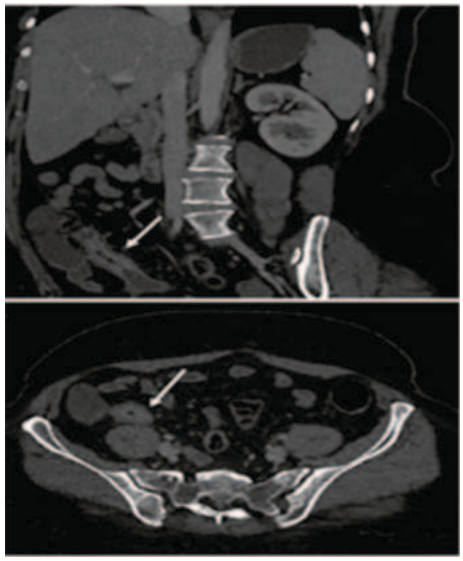

Figure 2 : Coronal and axial contrast-enhanced CT enterography images showing small segment stricture at ileum in a patient with GITB.

Endoscopic Findings - In present study most common segment involved is terminal ileum. ileocecal valve, transverse ulcers, nodularity were noted more in patients with TB compared to patients with CD. Longitudinal ulcers, aphthous ulcerations, mucosal bridge, cobblestone appearance were noted more in patients with CD compared to patients with TB.

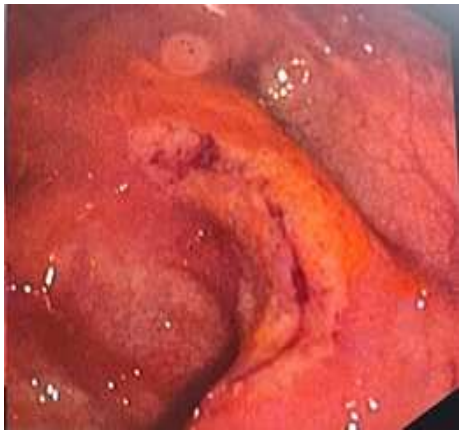

Figure 3 : Colonoscopy image showing transverse ulcer in a patient diagnosed to have GITB in caecum

Imaging - In present study node >1 cm in size with central necrosis, peritoneal ascites, chest X-ray/CT chest abnormalities, pulmonary TB, calcification, fibrosis were noted more in patients with TB compared to patients with CD. Changes in mesenteric fat, comb sign, presence of strictures, long segment involvement (>3 cm) were noted more in patients with CD compared to patients with TB.

Histopathology - In present study non specific findings were seen in 11(36%) patients. 7 (64%) of 11 were TB patients and 4 (36%) of 11 were CD patients. Biopsy findings more suggestive of TB were seen in 7 (23%) patients out of which 1 patient turned out to be CD. Biopsy findings more suggestive of CD were seen in 10 (33%) patients out of which 3 patients turned out to be TB. TB bacilli were positive in 2 patients.

Response to antitubercular therapy - In present study 18 (60%) patients responded to ATT at 2-3 months after therapeutic trial. 12 (40%) patients didn't respond to ATT trial after 6 months. 2 (6%) patients responded to ATT at 3 months but later noticed deterioration in symptoms finally turned out to be CD.

In the literature clinical features like fever, abdominal pain, wt loss, constipation, anorexia, intestinal obstruction, lung involvement, old age, immunocompromised are more likely to be seen in TB. Long duration, growth retardation, edema, rectal bleeding, diarrhea, EIMs, perianal symptoms, gastrointestinal bleeding, fistula more likely seen in CD.

Serological investigations - ESAT 6, CFP – 10, IGRA, CD4 + CD25 + FOXP3+ are more likely to be positive in TB. hsCRP>3 mg/L, anaemia, platelets >300*10^9/L, ASCA, hypoalbuminemia,high ESR, WBC >10*10^9/L are more likely seen in CD.

Endoscopic findings – colonoscopy findings like contracting diverticula, patulous ileocecal valve, transverse ulcers, ring-shaped ulcer, involvement of caecum and IC valve, nodularity more likely seen in TB. Longitudinal ulcers, aphthous ulcerations, mucosal bridge, cobblestone appearance, perianal lesions, skip lesions, irregular ulcer, stenosis and fistulas, involvement of rectum, sigmoid colon, descending colon, transverse colon, ascending colon, ileum more likely seen in CD.

Imaging - characteristics like lymph node >1 cm in size with central necrosis, peritoneal ascites, inflammatory masses, peritoneal nodules, concentric strictures, chest X-ray/CT chest abnormalities, pulmonary TB, calcification, fibrosis more likely positive in TB. Intestinal dilatation, fibrofatty proliferation, changes in mesenteric fat, comb sign, mural thickening with stratification in active inflammation, anal fistula or perianal abscess, intestinal fistula, adipose creeping sign, target sign, stricture, eccentric strictures, shortened mesentery, visceral/subcutaneous fat, asymmetrical wall thickening, long segment involvement (>3 cm), skipped lesions (>3) more likely seen in CD. The role of newer imaging techniques like contrast-enhanced intestinal ultrasonography, dynamic contrast enhancement (DCE) MRI, small intestine contrast ultrasound, hybrid PET/MRI and apparent diffusion coefficient (ADC) are considered.[18]

Histopathology - AFB stain, AFB culture, TB PCR, caseous necrosis, undetermined, linear ulceration with clusters of epithelioid histocytes, granulomas, >5 granulomas / biopsy site, large granulomas (> 200–400 μm), confluent, submucosal, well defined, surrounding cuffing lymphocytes more likely positive in TB. Microgranulomas, architectural distortion distant to granulomatous inflammation, focal enhanced colitis, cryptitis, crypt abscess, crypt atrophy, submucosal widening and fissures, neural hyperplasia, basal lympho-plasmacytosis, transmural inflammation likely seen in CD. Masson's trichrome staining and two-photon excited fluorescence imaging, second harmonic generation could be used. Recent study showed that collagen fiber and fiber deposits are significantly higher in GITB[19].

Response to antitubercular therapy - Mucosal healing with ATT is considered the gold standard as a surrogate for underlying GITB[20]. Early mucosal response to therapy by doing a colonoscopy at two months helps to differentiate GITB from CD. It could prevent the development of complicated CD course[21].

A dysregulated immune response is seen in CD. A dysfunction in terms of number, function and ability of the regulatory T cell (CD4+CD25+FOXP3+) to home to gut mucosa is recognised. Cut-off value of > 32.5% could differentiate GITB from CD with 90.6% specificity[22].

Mesenteric fat is driving force of inflammation in CD[23]. Saurabh Kedia et al. study reported that ratio of visceral fat (VF) to subcutaneous fat (SF) is higher in patients with CD. One of the study suggested that a combination of two radiological findings i.e. increased visceral fat and a long segment (>3 cm) involvement of the bowel wall, had high specificity for the diagnosis of CD[24].

However, there are few limitations of this study: 1) Sample size is small. 2) All the patients of TB and CD are not included in the study (included only challenging patients who have more number of overlapping features).

CONCLUSION

Differentiation of TB and CD is challenging most of the times.Worse outcomes (higher stricture formation and rates of surgery) were noted in patients with CD who received ATT trial before confirmation of CD.VF/SC ratio and long segment stricture (>3cm) are two features in imaging which may distinguish CD from TB with high specificity.

Author contributions: Vikas Reddy Venkannagari has conceptualized manuscript writing and made critical contributions in terms of management of the cases and revision of the manuscript. Bhashyakarla Ramesh Kumar and Uma devi malladi has contributed to manuscript writing and editing, compilation of the data, and literature review. Suraj Kumar Chimata and Sahitya Reddy Lingampally contributed to the manuscript's revision and management of cases.

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