Diagnosis of Crohn's disease in India where tuberculosis is widely prevalent

Deepak N Amarapurkar, Nikhil D Patel, Priyamvada S Rane

Deepak N Amarapurkar, Nikhil D Patel, Priyamvada S Rane, Department of Gastroenterology, Bombay Hospital & Medical Research Centre, Mumbai 400025, India

Correspondence to: Dr. Deepak Amarapurkar, Department of Gastroenterology, Bombay Hospital & Medical Research Centre, D 401/402 Ameya RBI Employees Co-Op Housing Society, Plot No. 947-950, New Prabhadevi Road, Prabhadevi, Mumbai 400025, India. amarapurkar@gmail.com

Telephone: +91-22-24306262 Fax: +91-22-24368623

Received: July 14, 2007 Revised: November 28, 2007

Abstract

AIM: To define the parameters that positively predict diagnosis of Crohn's disease (CD) and differentiate it from gastrointestinal tuberculosis (GITB).

METHODS: This prospective study over 3 years was carried out in the consecutive Indian patients with definite diagnosis of CD and equal numbers of patients with definite diagnosis of GITB. Demographic, clinical, laboratory, morphological and histological features were noted in all the patients. Serological tests such as p-ANCA, c-ANCA, IgA ASCA and IgG ASCA, were performed. Endoscopic biopsy and/or surgical tissue specimens were subjected to smear and culture for acid-fast bacilli (AFB) and tissue polymerase chain reaction for tuberculosis (TB PCR). Diagnosis of CD and GITB was based on the standard criteria. Data were analyzed using univariate Chi-square test and multiple logistic regression (MLR).

RESULTS: The study is comprised of 26 patients with CD (age 36.6 ± 8.6 year, male:female, 16:10) and 26 patients with GITB (age 37.2 ± 9.6 year, male:female, 15:11). The following clinical variables between the two groups (CD vs TB) were significant in univariate analysis: duration of symptoms (58.1 ± 9.8 vs 7.2 ± 3.4 mo), diarrhoea (69.2% vs 34.6%), bleeding per rectum (30.7% vs 3.8%), fever (23.1% vs 69.2%), ascites (7.7% vs 34.6%) and extra-intestinal manifestations of inflammatory bowel disease (61.5% vs 23.1%). Of these, all except ascites and extra-colonic manifestations were found statistically significant by MLR. Accuracy of predicting CD was 84.62% based on the fever, bleeding P/R, diarrhoea and duration of symptoms while it was 63.4% when histology was reported as inflammatory bowel disease and 42.3% when there was recurrence of disease after surgery. Accuracy of predicting GITB was 73.1% when there was co-existing pulmonary lesions and/or abdominal lymphadenopathy; 75% when

tuberculosis was reported in histology; 63.4% when granuloma was found in histology; 82.6% when TB PCR was positive; and 61.5% when smear and/ or culture was positive for AFB. Serological test was not useful in differentiation of CD from GITB. Positivity rates for CD and GITB were: p-ANCA- 3.8% and 3.8%, c-ANCA- 3.8% and 0%, IgA ASCA- 38.4% and 23.1%, and IgG ASCA- 38.4% and 42.3%, respectively.

CONCLUSION: Simple clinical parameters like fever, bleeding P/R, diarrhoea and duration of symptoms have the highest accuracy in differentiating CD from GITB.

© 2008 WJG. All rights reserved.

Key words: Crohn's disease; Gastrointestinal tuberculosis; Differential diagnosis; Inflammatory bowel disease; Anti-neutrophil cytoplasmic antibody; Anti-*Saccharomyces Cerevisiae* antibody; Tissue polymerase chain reaction; *Mycobacterium Tuberculosis*; Acid-fast bacilli

Peer reviewers: Adrian G Cummins, Dr, Department of Gastroenterology and Hepatology, (DX 465384), 28 Woodville Road, Woodville South, 5011, South Australia, Australia; Ioannis E Koutroubakis, Assistant Professor, Ioannis Koutroubakis, Gastroenterology, University Hospital Heraklion, PO BOX: 1352 Heraklion, 71110 Crete, Greece

Amarapurkar DN, Patel ND, Rane PS. Diagnosis of Crohn's disease in India where tuberculosis is widely prevalent. *World J Gastroenterol* 2008; 14(5): 741-746 Available from: URL: <http://www.wjgnet.com/1007-9327/14/741.asp> DOI: <http://dx.doi.org/10.3748/wjg.14.741>

INTRODUCTION

In Western countries, the incidence of inflammatory bowel disease (IBD) has progressively increased since 1935^[1]. Ulcerative colitis (UC) has peaked earlier than Crohn's disease (CD)^[1,2]. Although CD has been increasing worldwide^[3], it is generally believed to be rare in developing countries like India^[4]. Indian migrants in Western countries have shown increased incidence of IBD, more so in the second generation of immigrants^[1,5]. In India, the incidence of UC has significantly increased over the last three decades, whereas the incidence of CD increased progressively in the last decade^[4,6-15]. Tuberculosis (TB) remains widely prevalent in developing countries such as India. Also, it is being increasingly encountered in industrialized nations due to

pandemic of human immunodeficiency virus infection and trans-global migration^[16-19].

There is a close resemblance in clinical, radiological, endoscopic, surgical and histological features of CD and gastrointestinal tuberculosis (GITB), thus differential diagnosis of these two conditions remains a major challenge to clinicians^[7-9,12,19-23]. In India, as more and more cases of CD are being recognized, the definite diagnosis of CD or GITB becomes increasingly important^[8,10]. In case of misdiagnosis of GITB, unnecessary anti-tuberculosis therapy (ATT) poses a risk of toxicity and treatment of the primary disease, i.e. CD is delayed. In contrast, treatment with steroids alone (for CD) can be disastrous, if diagnosis of GITB is missed. As response to empirical ATT is considered to be a favouring point for final diagnosis of TB, emergence of multi-drug resistant TB can further complicate the issue by decreasing the therapeutic response even in presence of TB. All these situations highlight the need to establish the diagnosis of either CD or GITB, before starting any form of empirical treatment.

In a recently published study with an exhaustive search for histological and microbiological proof for GITB, definite diagnosis could be established only in 66.5% of cases^[10]. In other previous series, attempts are made to differentiate CD and GITB on histopathology of endoscopic or surgical specimens^[7,12,22-24]; but no single feature can definitely exclude TB. Recent advances in armamentarium of diagnosis of CD and TB are serology tests, such as anti-neutrophil cytoplasmic antibody (ANCA) and anti-*Saccharomyces Cerevisiae* antibody (ASCA), and tissue polymerase chain reaction (PCR) for *Mycobacterium Tuberculosis* (TB PCR)^[25-27]. In one study by our centre, TB PCR was found highly specific for diagnosis of GITB, but lacked sensitivity^[11]. In another study at our centre, ASCA was not found useful in differentiating CD from GITB^[28].

Thus, it is very difficult to differentiate CD from GITB based on index evaluation of a patient. No single diagnostic criterion can define CD. Follow-up evaluations and treatment response are also important to reach the diagnosis. We have designed a study to define the accuracy of various parameters which can predict diagnosis of either CD or GITB at index evaluation.

MATERIALS AND METHODS

Study design

A prospective data analysis was performed in patients with definite diagnosis of CD and GITB. These data were collected prospectively during the study period.

Patient evaluation

During the study period from January 2002 to December 2004, all the patients with suspected diagnosis of CD and GITB were prospectively evaluated for the following parameters (details wide infra): demographic, clinical, laboratory, morphology, histology, microbiology, serology and treatment response at follow-up evaluation for next one year.

Demographic (age, sex and ethnicity), clinical (chronic diarrhoea, hematochezia, features of intestinal obstruction, fever, perianal involvement, extra-intestinal manifestations,

abdominal pain, ascites, weight loss, growth retardation, abdominal lump and duration of symptoms, long duration: > 1 year) and laboratory features (anaemia, hypoproteinemia and erythrocyte sedimentation rate) were noted in all the patients.

Morphological findings of intestine during endoscopy (endoscopic evaluation was done in all by the first author): skip lesions, deep ulcers, aphthous ulcers, fissures, fistula, cobble-stone appearance, stricture and site of involvement.

Histological findings were evaluated using paraffin-embedded tissue specimens after staining with hematoxylin and eosin. Histology of all the specimen was reported by an experienced gastrointestinal pathologist, who was completely unaware of clinical, morphological, microbiological and serological findings. The histological features were as follows: presence of granuloma, characteristics of granuloma (caseation or confluence), ulceration of surface epithelium, appearance of crypts, presence of lymphoid aggregates and site and type of inflammatory infiltrate. Presence of large, dense and confluent mucosal or submucosal caseating granuloma, > four sites of granulomatous inflammation, caseation, band of epithelioid histiocytes in ulcer base and granulomatous inflammation in cecum favoured histopathological diagnosis of TB; whereas presence of small, discrete and loose mucosal non-caseating granuloma, mucosal changes distant to sites with granuloma, focal crypt-related inflammation and granuloma in sigmoid or rectum favoured histopathological diagnosis of CD.

Biopsy specimens (endoscopic, at least 6 biopsy samples, or surgical) were subjected to Ziehl-Neelsen and fluorescence smear for AFB, Bactec culture for AFB and TB PCR. Paraffin-embedded biopsy specimens were tested for detection of *Mycobacterium Tuberculosis* complex by the Gen-Probe (USA) amplified *Mycobacterium Tuberculosis* direct test by PCR assay^[11]. The following serological tests were done in all the patients: IgG perinuclear-ANCA (p-ANCA), *in vitro* detection of IgG class of antibodies to myeloperoxidase using quantitative ELISA (MPO antibodies ELISA kit, Genesis diagnostics, UK); IgG cytoplasmic-ANCA (c-ANCA), *in vitro* detection of IgG class antibodies to serine protease-3 (PR3 antibodies ELISA kit, Genesis diagnostics, UK); IgA ASCA, detection of IgA anti-*Saccharomyces Cerevisiae* antibodies using quantitative ELISA (IgA ASCA ELISA kits, Genesis diagnostics, UK); IgG ASCA, detection of IgG anti-*Saccharomyces Cerevisiae* antibodies using quantitative ELISA (IgG ASCA ELISA kits, Genesis diagnostics, UK). Titres were considered positive if they were above the upper limit of normal range, i.e. for p-ANCA 0-4 μ /mL, for c-ANCA 0-4 μ /mL, IgA ASCA 0-10 μ /mL and for IgG ASCA 0-10 μ /mL.

All the surgical histological specimens of the patients who underwent intestinal surgeries in the past were re-examined using the above mentioned methods.

During the 1-year follow-up, all the patients were evaluated at regular interval with clinical, laboratory and imaging parameters. Endoscopic evaluations with histological and microbiological studies were performed at least twice (at 6 mo and at 1 year) during the follow-up.

Diagnostic criteria

In presence of demonstrable lesion in gastrointestinal tract,

diagnosis of GITB was established based on the following criteria: (1) presence of caseating granuloma on histology of diseased tissue (intestine, peritoneum or lymph nodes); (2) demonstration of acid-fast bacilli (AFB) on smear or on histological section; (3) positive culture for AFB; (4) histological or microbiological confirmed TB at extra-intestinal site; and (5) positive TB PCR. For the definite diagnosis of GITB, one or more of these criteria had to be fulfilled, except for complete response to treatment. Complete resolution of symptoms and morphological (endoscopic and histological/microbiological) features after completion of standard ATT-(HERZ)₂(HR)₁₀ (with or without surgery) was taken as criteria for successful treatment.

Diagnosis of CD was based on morphological (radiological, endoscopic or surgical findings) and pathological criteria suggesting focal, asymmetrical, transmural or granulomatous features: (1) morphological: (a) discontinuous/segmental and asymmetrical mucosal involvement, (b) deep mucosal longitudinal fissures/ulcers, (c) transmural inflammation, (d) rigid and strictured intestinal wall, (e) presence of entero-cutaneous/entero-enteric fistula and/or chronic perianal disease; (2) pathological: (a) normal mucus content in the goblet cells of the inflamed region, (b) lymphocyte aggregation in the mucosa and submucosa, (c) non-caseating granuloma, (d) longitudinal ulcers/fissures, (e) transmural inflammation or inflammation beyond mucosa. For definite diagnosis of CD, the following criteria were used: presence of at least 3 different criteria or presence of non-caseating granuloma on histology with at least 1 other criterion; exclusion of TB (by histology, microbiological and PCR studies) and complete resolution of symptoms and morphological (endoscopic and histological/microbiological) features after 1-year treatment of corticosteroid and 5-ASA preparations (with or without surgery).

Study population

During the study period, definite diagnosis of CD was achieved in 26 patients. In analysing data retrospectively, all these patients with CD and an equal number of consecutive age- and sex-matched patients with definite diagnosis of GITB were included.

Statistical analysis

Data were analyzed using SPSS (PC+version-6 statistical package) by medical statistician. Univariate Chi-square test (UCST) was applied to find out statistically significant variables which may be important in differentiating CD from GITB. $P < 0.05$ was considered statistically significant. These variables were taken for multiple logistic regression (MLR) statistical analysis to find out independent predictive variables for diagnosis of CD. Each significant parameter (clinical, morphological, histological, microbiological and treatment-related) individually or in combination, was further analyzed for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy in diagnosis of CD or GITB.

RESULTS

Demographic, clinical and laboratory features of both the

Table 1 Demographic, clinical and laboratory features

Characteristics	CD (n = 26)	GITB (n = 26)	P value
Demographic features			
Age (range), yr	36.6 ± 8.6 (6-79)	37.2 ± 9.6 (18-78)	NS
Sex (male:female) ratio	16:10	15:11	NS
Clinical features			
Duration of symptoms (range), mo	58.1 ± 9.8 (8-240)	7.2 ± 3.4 (2-24)	S
Chronic diarrhoea, n (%)	18 (69.2)	9 (34.6)	S
Hematochezia, n (%)	8 (30.7)	1 (3.8)	S
Fever, n (%)	6 (23.1)	18 (69.2)	S
Weight loss, n (%)	18 (69.2)	19 (73.1)	NS
Abdominal pain, n (%)	17 (65.4)	22 (84.6)	NS
Intestinal obstruction, n (%)	5 (19.2)	3 (11.5)	NS
Growth retardation, n (%)	2 (7.7)	0 (0)	NS
Ascites, n (%)	2 (7.7)	9 (34.6)	S
Abdominal lump, n (%)	2 (7.7)	4 (15.4)	NS
Extra-intestinal features, n (%)	16 (61.5)	6 (23.1)	S
Laboratory/radiological features			
Anaemia, n (%)	15 (57.7)	7 (26.9)	S
Hypoproteinaemia, n (%)	11 (42.3)	9 (34.6)	NS
ESR (range) mm at 1 h	54.7 ± 12.2 (10-104)	59.7 ± 13.6 (19-110)	NS
Pulmonary infiltration/fibrosis, n (%)	1 (3.8)	10 (38.4)	S
Abdominal lymphadenopathy, n (%)	3 (11.5)	11 (42.3)	S
Generalized lymphadenopathy, n (%)	0 (0)	2 (7.7)	NS

groups are demonstrated in Table 1. In CD and GITB groups, the following extra-intestinal features (%) were noted: (1) eye-related: episcleritis (3.8% and 0%), uveitis (0% and 0%); (2) skin and mucosa-related: erythema nodosum (7.7% and 3.8%), pyoderma gangrenosum (3.8% and 0%), vasculitis (7.7% and 0%), mouth ulcers (23.1% and 11.5%); (3) musculo-skeletal system related: ankylosing spondylitis (3.8% and 0%), arthritis (38.4% and 15.4%), osteopenia (15.4% and 0%); (4) hepatobiliary system-related: fatty liver (11.3% and 34.6%), autoimmune hepatitis (3.8% and 0%), primary sclerosing cholangitis (0% and 0%), gall stones (11.3% and 3.8%); (5) other system-related: thromboembolism (3.8% and 0%), renal stone (3.8% and 0%), amyloidosis (0% and 0%).

Morphological features including site and type of lesions, histological and microbiological features as well as serological features are described in Table 2.

Among 26 patients with CD, 7 patients had at least one surgical intervention for intestinal complications before index presentation to our centre. They were not diagnosed as having Crohn's disease at that time, were not on therapy, presented at our centre with recurrence of symptoms, and were included for index evaluation and review of previous surgical histological specimens. Two patients had surgical intervention for intestinal stricture while on therapy for recurrent intestinal obstruction. All patients with CD showed complete response to therapy during the 1-year follow-up.

In GITB group, none of the patients had received ATT before the index evaluation. During the follow-up, 4 patients required surgical interventions for intestinal stricture while on therapy for recurrent intestinal obstructions. All the patients with GITB showed complete response to therapy during follow-up.

On UCST analysis, significant clinical variables were: (a) duration of symptoms, (b) diarrhoea, (c) hematochezia,

Table 2 Morphological, histological, microbiological, serological and treatment-related features *n* (%)

Characteristics	CD (<i>n</i> = 26)	GITB (<i>n</i> = 26)	<i>P</i> value
Sites of involvement			
Oesophagus	0 (0)	1 (3.8)	NS
Stomach	0 (0)	2 (7.7)	NS
Duodenum	1 (3.8)	2 (7.7)	NS
Jejunum	2 (7.7)	1 (3.8)	NS
Ileum	16 (61.5)	20 (76.9)	NS
Ileo-cecal valve	20 (76.9)	21 (80.7)	NS
Right colon	18 (69.2)	21 (80.7)	NS
Left colon	10 (38.4)	5 (19.2)	NS
Rectum	8 (30.7)	5 (19.2)	NS
Anal and perianal region	2 (7.7)	1 (3.8)	NS
Endoscopic and/or surgical findings			
Skip lesions	6 (23.1)	2 (7.7)	NS
Deep linear/serpiginous ulcers	15 (57.7)	6 (23.1)	S
Aphthous ulcers	9 (34.6)	5 (19.2)	NS
Stricture	8 (30.7)	5 (19.2)	NS
Cobble-stone appearance	15 (57.7)	6 (23.1)	S
Pseudo polyps	9 (34.6)	5 (19.2)	NS
Neoplasm-like appearance	0 (0)	2 (7.7)	NS
Fistula	3 (11.5)	0 (0)	NS
Histological features			
Granuloma	8 (30.7)	15 (57.7)	NS
Caseation	0 (0)	9 (34.6)	S
Confluence	0 (0)	6 (23.1)	S
Interpreted as IBD by pathologist	10 (38.4)	3 (11.5)	S
Interpreted as TB by pathologist	0 (0)	13 (50)	S
Interpreted as non-specific chronic inflammation by pathologist	16 (61.6)	10 (38.4)	NS
AFB smear/culture positivity	0 (0)	6 (23.1)	S
TB PCR positivity	0 (0)	17 (65.4)	S
Serological features			
p-ANCA	1 (3.8)	1 (3.8)	NS
c-ANCA	1 (3.8)	0 (0)	NS
IgA ASCA	10 (38.4)	6 (23.1)	NS
IgG ASCA	10 (38.4)	11 (42.3)	NS
Treatment-related factors			
Recurrence after surgery, <i>n</i> /total patients underwent surgery (%)	7/9 (77.7)	0/4 (0)	S
Number of patients previously treated with ATT (without any response)	9 (34.6)	-	-
Complete response to ATT	-	26 (100)	-

(d) fever, (e) ascites, (f) extra-intestinal manifestations. Variables found to be significant for differentiating CD and GITB based on MLR were duration of symptoms, diarrhoea, hematochezia and fever.

In Table 3, sensitivity, specificity, PPV, NPV and accuracy are tabulated for various parameters, which were significant on UCST, either individually or in combination. Clinical score (absence of fever, presence of diarrhoea and hematochezia and long duration of symptoms) had an accuracy of 84.62% to predict CD, with high (> 80%) sensitivity, specificity, PPV and NPV. Parameters like recurrence of disease after surgery, pathological diagnosis of TB, positive TB PCR and positive AFB smear/culture had 100% specificity and PPV, but had low sensitivity and NPV. The accuracy of various parameters in descending order were: clinical score (84.62%); positive TB PCR (82.6%); pathologic diagnosis of TB (75%); extra-intestinal focus of disease (pulmonary lesions and abdominal lymphadenopathy) (73.1%); morphology features (deep linear/serpiginous ulcers and cobble-stone

appearance) (67.3%); pathologic diagnosis of IBD and granuloma (63.4%); positive AFB smear/culture (61.5%); and recurrence of disease after surgery (42.3%). Presence of caseating and/or confluent granuloma on histology, positive AFB smear and/or culture, positive TB PCR, histologic interpretation as TB, lack of response to ATT and recurrent disease after surgery were the only features which did not show any overlap between the two groups.

DISCUSSION

In spite of recent technical advances and better understating of pathophysiology, there is still no simple test for differentiating GITB from CD. There are many factors that lead to misdiagnosis. Both the diseases have marked overlap in demographic, clinical, radiological, endoscopic and surgical findings^[10,22,23]. They can involve any part of gastrointestinal tract. Both are granulomatous diseases, so inability to find caseating or confluent granuloma on histology can lead to erroneous or non-confident diagnosis by a pathologist. Routine tests for diagnosis of TB such as AFB smear examination, using conventional Ziehl-Neelsen stain, traditional AFB culture using egg-based or agar-based media or Guinea pig inoculation, lack sensitivity and/or are time-consuming^[29]. Smear examination using fluorescence technique and culture with Bactec technique are more rapid and more sensitive^[29]. As GITB is a paucibacillary disease, sensitivity for detecting mycobacterium in clinical specimens by any of the above methods remains poor. Although many serological tests for TB are commercially available, they are far from satisfactory in diagnostic dilemma^[29].

As we previously reported, features, which should alert a clinician for CD at presentation or on subsequent follow-up, were: (1) internal or cutaneous GI fistula; (2) perianal disease; (3) extra-intestinal manifestations, such as pyoderma gangrenosum, uveitis, primary sclerosing cholangitis, aphthous ulcers, arthralgia/arthritis or ankylosing spondylitis; (4) no caseating granuloma on histology and negative AFB smear or culture; (5) no involvement of the peritoneum, abdominal lymph node or site of extra-intestinal tuberculosis, such as extra-abdominal lymph node, lungs, pleura, mediastinum, liver, or kidney; and (6) no response to ATT^[10].

In the present study, prolonged duration of illness, diarrhoea, hematochezia and extra-intestinal manifestations were more common in CD as compared to GITB; while fever and ascites were common in GITB. About an 85% accuracy in predicting CD could be reached based on the history of hematochezia, diarrhoea and protracted duration of symptoms, and absence of fever. Endoscopic features or surgical finding of deep linear/serpiginous ulcers/fissures and cobble-stone appearance was more common in CD. None of the clinical or morphological features was exclusive for either of the diagnoses.

Recently, Pulimood *et al* have reported that on mucosal biopsy, in addition to AFB detection, large granuloma, > four sites of granulomatous inflammation, caseation, band of epithelioid histiocytes in ulcer base and granulomatous inflammation in cecum in favour of diagnosis of TB; whereas non-caseating granuloma, mucosal changes distant

Table 3 Sensitivity, specificity and accuracy in diagnosis of CD or GITB

Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Factors predicting CD					
Clinical score (fever, hematochezia, diarrhoea and duration of symptoms)	80.7	88.4	87.5	82.1	84.62
Co-existing deep linear/ serpiginous ulcers and/or Cobble-stone appearance	69.2	65.3	66.6	72	67.3
Pathologist reporting as IBD	38.4	88.4	76.9	58.9	63.4
Recurrence of disease after surgery	77.7	100	100	66.6	42.3
Factors predicting GITB					
Co-existing pulmonary lesions and/or abdominal lymphadenopathy	57.6	88.4	83.3	67.6	73.1
Pathologist reporting as TB	50	100	100	66.6	75
Granuloma on histology	57.6	69.2	65.2	62	63.4
TB PCR positive	65.3	100	100	74.2	82.6
Smear and/or culture positive for AFB	23	100	100	56.5	61.5
Complete response to ATT	100	100	100	100	100

to sites with granuloma, focal crypt-related inflammation and granuloma in sigmoid or rectum in favour of diagnosis of CD^[24]. In other studies, presence of small, discrete, loose mucosal granuloma without caseation are characteristics of CD, whereas large, dense, confluent granuloma with caseation with or without AFB positivity in mucosal or submucosal location favour TB^[8,23,24,30]. In the present study, pathological diagnosis of TB had higher sensitivity, specificity and accuracy in predicting GITB than pathological diagnosis of IBD in predicting CD. Histological feature of caseation and/or confluence in granuloma and pathological diagnosis of TB were present in GITB group exclusively and there was no overlap in these findings.

Serological test for IBD is being investigated as diagnostic markers for IBD. Sensitivity of positive ASCA for diagnosis of CD reaches up to 76%, whereas it is 98% in various trials^[27]. IgA ASCA and IgG ASCA are considered to be 95% specific for diagnosis of CD when individually tested, but 100% when tested in combination^[26,27]. These data come from countries where tuberculosis is uncommon and control population in these studies did not include patients with GITB. In the previous study, we found that (1) serological markers were not significantly different between CD and GITB; and (2) prevalence of positive ASCA was much lower in patients with CD than the reported incidence from Western countries^[28]. A recent study by another centre in India showed that ASCA was not helpful in differentiating CD from GITB^[31]. The present study confirms these results.

TB PCR was found to be highly specific for GITB, but had poor sensitivity; these results were in accordance with our previous study^[11]. TB PCR had accuracy of more than 80% in diagnosis of GITB. There was no false positive result in CD.

Since the sample size was small, patient groups were heterogenic (patients with involvement of both upper and/or lower GI tract were included) and conclusions are made based on prospective data analysis, a prospective study on all the patients with suspected CD or GITB with a larger sample size is needed to validate the clinical score.

In conclusion, simple clinical parameters like absence of fever, presence of hematochezia, presence of diarrhoea and long duration of symptoms have a highest pre-treatment accuracy in diagnosing Crohn's disease and differentiating it from intestinal tuberculosis. Microbiology

and histology are useful adjuncts, whereas serology is not useful in differentiating intestinal tuberculosis from Crohn's disease.

COMMENTS

Background

Differentiating Crohn's disease (CD) from gastrointestinal tuberculosis (GITB) is a major problem in the tropical countries, as there is a marked overlap in clinical, radiological, endoscopic and surgical findings. In case of misdiagnosis as GITB, unnecessary anti-tuberculosis therapy (ATT) is given and treatment of CD is delayed. In contrast, in case of misdiagnosis as CD, treatment with steroids alone can lead to fatal dissemination of tuberculosis.

Research frontiers

This study prospectively evaluates various parameters for accuracy in diagnosis of CD or GITB.

Innovations and breakthroughs

Simple clinical parameters (duration of symptoms, fever, diarrhoea and hematochezia) turn out to have maximum accuracy in diagnosis of CD as compared with various laboratory, imaging, pathological, microbiological or serological features.

Applications

A prospective multi-center study involving a large sample size should be planned to validate results of this study.

Peer review

The authors present a nicely conceived and analyzed study with very good clinical data. This study investigates the distinguishing features of intestinal TB and CD. Obviously this is of great importance because of the divergence of management. While of immediate importance in India, it is also of interest because of the increase in CD with affluence in India and because this problem is occasionally seen in Western countries.

REFERENCES

- 1 **Ekbom A.** Epidemiology of inflammatory bowel disease. In: Bistrian BR, Walker-Smith JA, editors. Inflammatory bowel disease. Nestle nutrition workshop series- clinical & performance programme. Nestle Ltd: Karger, Basel, 1999: 7-21
- 2 **Montgomery SM,** Morris DL, Pounder RE, Wakefield AJ. Asian ethnic origin and the risk of inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 1999; **11**: 543-546
- 3 **Loftus EV Jr.** Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004; **126**: 1504-1517
- 4 **Antia FP.** Crohn's conundrum in Indians. *Indian J Gastroenterol* 1986; **5**: 79-80

- 5 **Jayanthi V**, Probert CS, Pinder D, Wicks AC, Mayberry JF. Epidemiology of Crohn's disease in Indian migrants and the indigenous population in Leicestershire. *Q J Med* 1992; **82**: 125-138
- 6 **Probert CS**, Mayberry JF, Mann R. Inflammatory bowel disease in the rural Indian subcontinent: a survey of patients attending mission hospitals. *Digestion* 1990; **47**: 42-46
- 7 **Amarapurkar D**, Patel N. Crohn's disease in India. *Gastroenterol Today* 2002; **6**: 73-75
- 8 **Pulimood AB**, Ramakrishna BS, Kurian G, Peter S, Patra S, Mathan VI, Mathan MM. Endoscopic mucosal biopsies are useful in distinguishing granulomatous colitis due to Crohn's disease from tuberculosis. *Gut* 1999; **45**: 537-541
- 9 **Pai CG**, Khandige GK. Is Crohn's disease rare in India? *Indian J Gastroenterol* 2000; **19**: 17-20
- 10 **Patel N**, Amarapurkar D, Agal S, Baijal R, Kulshrestha P, Pramanik S, Gupte P. Gastrointestinal luminal tuberculosis: establishing the diagnosis. *J Gastroenterol Hepatol* 2004; **19**: 1240-1246
- 11 **Amarapurkar D**, Patel ND, Amarapurkar AD, Agal S, Baijal R, Gupte P. Tissue Polymerase Chain Reaction in Diagnosis of Intestinal Tuberculosis and Crohn's disease in India. *J Assoc Physicians India* 2004; **52**: 863-867
- 12 **Tandon HD**, Prakash A. Pathology of intestinal tuberculosis and its distinction from Crohn's disease. *Gut* 1972; **13**: 260-269
- 13 **Desai HG**, Gupte PA. Increasing incidence of Crohn's disease in India: is it related to improved sanitation? *Indian J Gastroenterol* 2005; **24**: 23-24
- 14 **Venkatkrishnan L**, Thakaran A, Francis J, Ramesh GN, Philip M, Augustine P. Crohn's disease-analysis of 26 cases. *Indian J Gastroenterol* 1995; **14**: A58
- 15 **Venogopalan S**, Radhakrishnan S, Rajachandrasekharan R. Crohn's disease (a study of 21 cases). *Indian J Surg* 1980; **42**: 388-396
- 16 **Guth AA**, Kim U. The reappearance of abdominal tuberculosis. *Surg Gynecol Obstet* 1991; **172**: 432-436
- 17 **Jain AK**. Current consensus in management of gastrointestinal tuberculosis. In: Gupta SB, editor. *Medicine Update*, Vol. 12. Mumbai: Association of Physicians of India, 2002; 730-737
- 18 **Fee MJ**, Oo MM, Gabayan AE, Radin DR, Barnes PF. Abdominal tuberculosis in patients infected with the human immunodeficiency virus. *Clin Infect Dis* 1995; **20**: 938-944
- 19 **Marshall JB**. Tuberculosis of the gastrointestinal tract and peritoneum. *Am J Gastroenterol* 1993; **88**: 989-999
- 20 **Ouyang Q**. Inflammatory bowel disease in China. *J Gastroenterol Hepatol* 2000; **15** Suppl: S25
- 21 **Das P**, Shukla HS. Clinical diagnosis of abdominal tuberculosis. *Br J Surg* 1976; **63**: 941-946
- 22 **Anand BS**. Distinguishing Crohn's disease from intestinal tuberculosis. *Nat Med J Ind* 1989; **2**: 172-175
- 23 **Chuttani HK**, Sarin SK. Intestinal tuberculosis. *Ind J Tuber* 1985; **32**: 117-125
- 24 **Pulimood AB**, Peter S, Ramakrishna B, Chacko A, Jeyamani R, Jeyaseelan L, Kurian G. Segmental colonoscopic biopsies in the differentiation of ileocolic tuberculosis from Crohn's disease. *J Gastroenterol Hepatol* 2005; **20**: 688-696
- 25 **Honore-Bouakline S**, Vincensini JP, Giacuzzo V, Lagrange PH, Herrmann JL. Rapid diagnosis of extrapulmonary tuberculosis by PCR: impact of sample preparation and DNA extraction. *J Clin Microbiol* 2003; **41**: 2323-2329
- 26 **Ruemmele FM**, Targan SR, Levy G, Dubinsky M, Braun J, Seidman EG. Diagnostic accuracy of serological assays in pediatric inflammatory bowel disease. *Gastroenterology* 1998; **115**: 822-829
- 27 **Amarapurkar DN**, Patel ND. Serology markers of inflammatory bowel disease. *Gastroenterol Today* 2005; **9**: 9-13
- 28 **Patel N**, Amarapurkar DN, Kulshrestha PP, Agal S, Baijal R, Pramanik, Gupte P. Utility of serological markers in inflammatory bowel disease. *Indian J Gastroenterol* 2002; **21**: A37
- 29 **Woods GL**. The mycobacteriology laboratory and new diagnostic techniques. *Infect Dis Clin North Am* 2002; **16**: 127-144
- 30 **Liu TH**, Pan GZ, Chen MZ. Crohn's disease. Clinicopathologic manifestations and differential diagnosis from enterocolonic tuberculosis. *Chin Med J (Engl)* 1981; **94**: 431-440
- 31 **Makharia GK**, Sachdev V, Gupta R, Lal S, Pandey RM. Anti-Saccharomyces cerevisiae antibody does not differentiate between Crohn's disease and intestinal tuberculosis. *Dig Dis Sci* 2007; **52**: 33-39

S- Editor Liu Y L- Editor Ma JY E- Editor Liu Y