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Distinguishing Intestinal Tuberculosis and Crohn's Disease: How Certain Are we of the Diagnosis?

Johanna Alba De Souza[1,] Muktha R. Pai[2,] Reba Philipose[3,] CK Nada[4]
(Department Of Pathology, A.J Institute Of Medical Sciences, Mangalore, Karnataka, India)

Background : *Intestinal tuberculosis (IT) and Crohn's disease (CD) are chronic granulomatous disorders that pose diagnostic challenge as they show an overlap in their histological features.*

Aim : *To evaluate distinctive clinical and histological parameters in colonic biopsy specimens for their ability to distinguish between CD and IT.*

Methods: *Thirty colonoscopic biopsies were studied, of which twenty cases were diagnosed as CD and ten cases were IT. Clinical history and colonoscopic findings were assessed in association with evaluation of histomorphology of biopsies.*

Results: *Clinical parameters useful in differentiating CD from IT included perianal fistulae, extraintestinal manifestations of CD and chest radiographic features of tuberculosis. Characteristic histological features of IT which showed statistical significance ($p<0.05$) were large confluent granulomas, caseation necrosis and ulcers lined by conglomerate epithelioid histiocytes. The features of CD which showed statistical significance were architectural alteration, microgranulomas and focal enhanced colitis even in endoscopically normal appearing areas. In the present study, 75% of patients with CD showed response to treatment, 5% of patients diagnosed as CD responded to antituberculous treatment (ATT) and 20% of patients diagnosed as IT failed ATT and resorted to CD therapy.*

Conclusion: *Thus a combined evaluation of clinical features, endoscopy, histology and response to treatment are most useful to differentiate CD from IT.*

Keywords: *Crohn's disease, tuberculosis, mucosal biopsy.*

I. Introduction

Discriminating between intestinal tuberculosis (IT) and Crohn's disease (CD) is a chief diagnostic task, notably in developing countries wherein IT remains common. [1,8,- 16] Jointly, IT and CD are chronic granulomatous conditions and exhibit an overlay with respect to their histological features. The eventual course and treatment of these two disorders is diverse. Simultaneously, with the growing incidence of TB, there has also been a comparable surge in the incidence of intestinal TB. CD is a progressive and relapsing illness, on the contrary, T.B is a completely curable disease. [2] Specimens retrieved through fibreoptic sigmoidoscopes or colonoscopes from the rectum, various areas of the colon, ileocaecal valve and terminal ileum aid in the histological validation of the diagnosis of Crohn's disease and IT even in suspected early cases.[1]

II. Materials And Methods

A retrospective study of 1 year duration , from June 2013 to June 2014 was carried out. A total of 30 colonoscopic biopsies were studied , out of which 20 were clinically diagnosed as Crohn's disease and 10 were of intestinal tuberculosis .Clinical history and colonoscopic findings were assessed in association with evaluation of histomorphology of biopsies. Biopsy specimens were fixed in 10% buffered formaldehyde and embedded in paraffin. Serial sections, 3-5 µ thick were prepared and stained with routine H & E stain. Additional sections were stained with Zeihl Neelson stain for detection of acid fast bacilli.

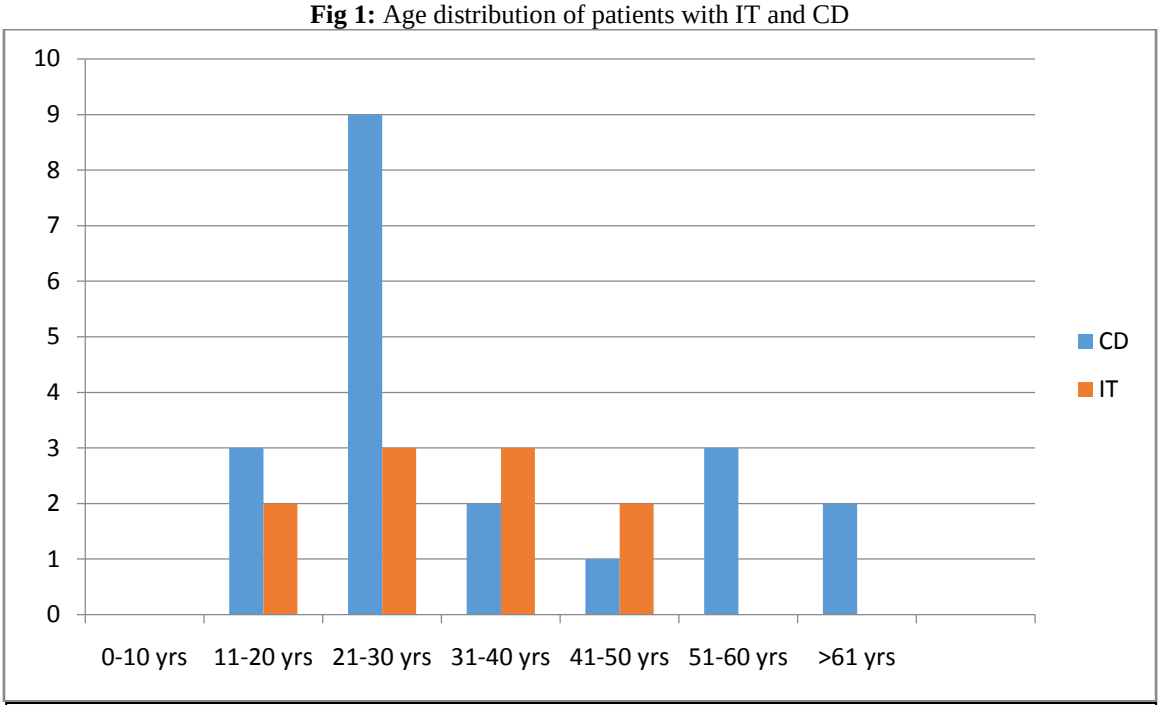
Granulomas are descibed as organised collections of epithelioid cells, Langhans giant cells, lymphocytes. On the other hand, microgranulomas were stated as small, poorly defined collections of epithelioid cells with absence of the other features of granulomas.[3] Aphthous ulcers are superficial erosions of the epithelium. When the mucosa is replaced by granulation tissue, a deep ulcer is noted. In deep ulcers, band of conglomerate epithelioid cells with scattered Langhans giant cells and lymphocytes were noted. Alteration in the architecture of the crypts and chronic inflammation were documented. Focally enhanced colitis is infiltration and of crypts by neutrophils, together with excess mononuclear cells in the adjacent lamina propria, without involving the full thickness of the mucosa. Focal activity was specified as focal cryptitis and crypt abscess formation without mononuclear infiltrate. [3]

The Fischer's exact probability test was used to evaluate differences in the frequency of the various histological parameters and a two tailed p value was computed to know if it was statistically significant.

III. Result

45% of patients with Crohn's disease were in the age group of 21-30 years however 60 % of patients of IT were in the age group of 21-40 years (Fig 1) . In reference to gender, A large majority of both these diseases occured in males. Mean age obtained in our study was 34.8 for C.D and 32.1 for I.T. With regard to age, the youngest patient in case of CD was 15 years, whereas in IT the youngest patient was 14 years. The oldest patient in Crohn's disease was 76 years, while in IT it was 50 years. 70% of patients with CD were males whereas 30 % were females. In IT 60% were males and 40% were females. The most prevalent site involved in case of CD was the left colon (33%) followed by terminal ileum (28%), right colon (23%) and caecum (16%) while in IT was the terminal ileum in 40% of the cases. Several clinical parameters (Table 1) that expressed statistical significance ($p<0.05$) in case of CD were perianal fistula 12 cases (60%), extraintestinal manifestations of crohn's disease (40%). The clinical parameters suggestive of IT ($p< 0.05$) were chest Xray findings of tuberculosis 3 cases (30%). Statistically significant histological parameters (Table 2) in case of Crohn's disease were architectural alteration (100%) , microranulomas(70%), focal enhanced colitis(50%). Histological parameters which were far more frequent in case of I.T were caseous necrosis (70%), Langhan's giant cell (80%), ulcers lined by epithelioid histiocytes (80%), and confluence of granulomas (80%). 75% of patients with Crohn's disease showed response to therapy, 5% responded to ATT (antituberculosis treatment) and failed CD therapy. In case of IT, 80% responded to ATT, 20% failed ATT & responded to CD therapy.

Fig 1: Age distribution of patients with IT and CD



X axis: Age in years. Y axis: Number of cases.

Table 1: Prevalence of selected clinical parameters in patients with IT and CD

Clinical Parameters	No. of cases C.D n= 20 n (%)	No of cases I.T n= 10 n (%)	P value
Perianal fistula	12 (60%)	0 (0%)	0.016
Extraintestinal manifestations	8(40%)	0 (0%)	0.02
Chest Xray features of tuberculosis	0 (0%)	3 (30%)	0.02

P< 0.05- statistically significant. Two tailed p value computed from a contingency table using Fischer's exact test

Table 2 : Prevalence of selected histological parameters in patients with IT and CD

Histological parameters	No. of cases C.D n= 20 n (%)	No of cases I.T n= 10 n (%)	P value
Architectural alteration	20 (100%)	5(50%)	0.0018
Microgranulomas	14 (70%)	2 (20%)	0.01
Focal enhanced colitis	10 (50%)	1 (10%)	0.04
Caseous necrosis	0 (0%)	7 (70%)	0.0001
Langhans giant cell	2 (10%)	8 (80%)	0.0001
Ulcers lined by epithelioid histiocytes	0 (0%)	8 (80%)	0.0001
Confluence of granulomas	0 (0%)	8 (80%)	0.0001

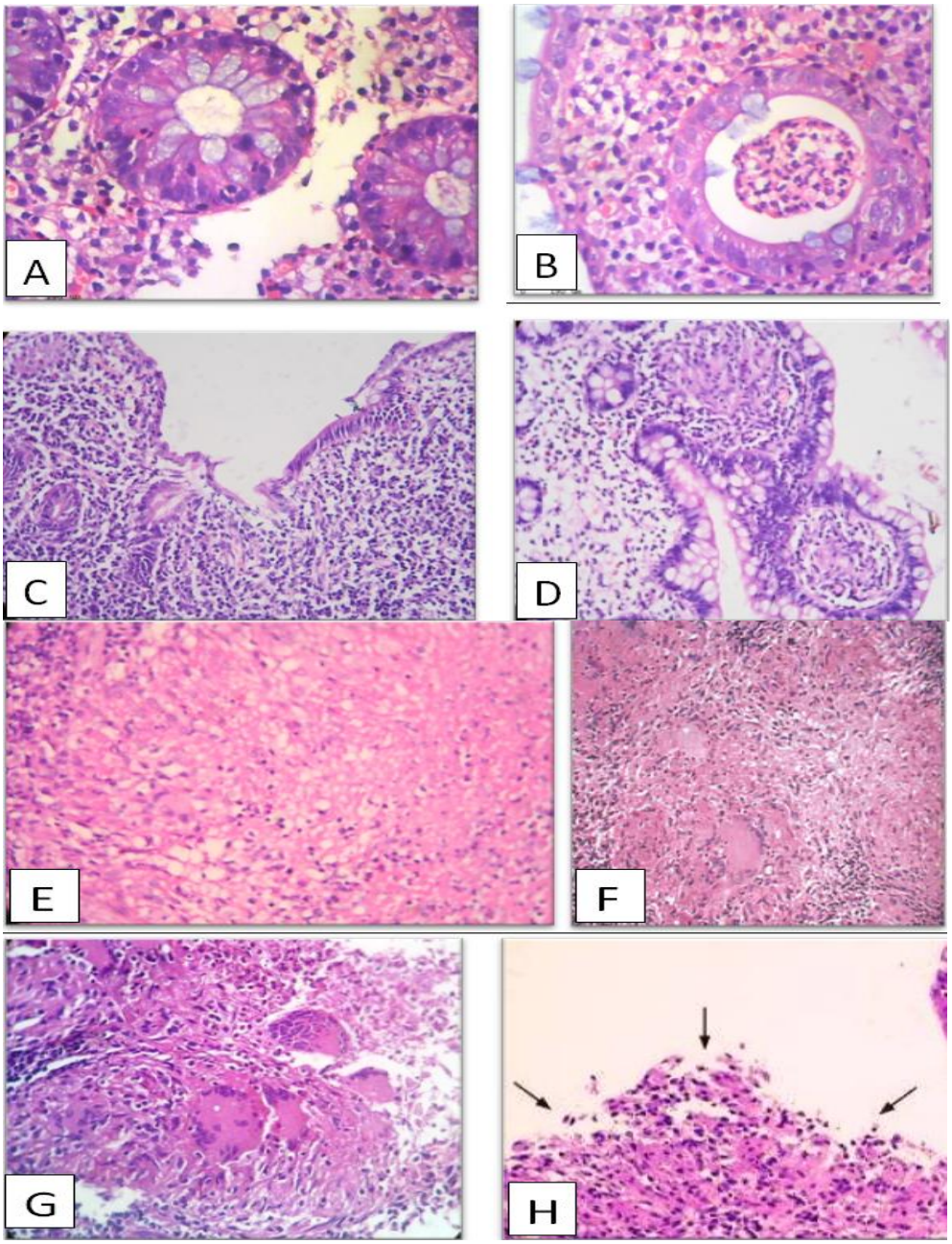


Figure 2: Colonic biopsy specimens from patients with disease, stained with H& E. Patients with CD showing (A) cryptitis 40x. (B) crypt abscess 40x. (C) aphthous ulcer 10x. (D) microgranulomas 10x. Patient with IT showing (E) caseous necrosis 40x. (F) confluence of granulomas 10x . (G) Langhan's giant cells 10x. (H) ulcers lined by epithelioid histiocytes 10x.

IV. Discussion

An enormous amount of patients with Crohn's disease to begin with are misclassified as having IT in regions where tuberculosis is endemic [2]. Around 35-45% of patients with CD in India are initially diagnosed to have ITB which aptly highlights the difficulty in differentiating between the two diseases. [4, 19] The escalating incidence of CD in India further augments this hindrance and appeals for development of suitable & successful tools to distinguish the two conditions. The eventual path of the two disorders is dissimilar. Endoscopy plays a crucial part in diagnosis.

Both these diseases are common in fourth decade of life & both show male prelidiction. Similar results were obtained in studies conducted by Kirsch et al [3, 4, 5]. In our study, the most prevalent site afflicted in C.D was left colon (33 %) followed by terminal ileum (28%) however in case of I.T, the terminal ileum (40%) was the predominantly affected site. This finding was consistent with studies conducted by Kirsch et al. Ileocaecal involvement was seen in both I.T & C.D in studies conducted by Pulimood et al[3, 5].

The ileo-caecal area has been stated to be the zone most commonly involved in IT. It owes to the evident affinity of the tubercle bacillus for lymphoid tissue and regions of physiologic stasis. Thus, accelerating prolonged contact between the bacilli and the mucosa[6, 20-28]

On mucosal biopsy, in adjunct to AFB detection, large granuloma, caseation, band of epitheloid histiocytes in ulcer base, granulomatous inflammation in cecum ,> four sites of granulomatous inflammation favour the diagnosis of TB; however non-caseating granuloma, , focal crypt-related inflammation, mucosal changes distant to sites with granuloma as well as granuloma in rectum or sigmoid colon favour of diagnosis of CD.[3, 29] In additional studies, occurrence of small, mucosal or submucosal distinct,mucosal granuloma lacking caseation are characteristics of CD, whereas dense, large confluent granuloma with caseation with or without AFB positivity favour TB [5, 30-32].

Presence of AFB in biopsy samples on histology or on culture is diagnostic of tuberculosis but was present only in a one case. Merely, 35–60% of cases can be promptly diagnosed by the finding of acid-fast rods, while there are reports showing no detection of tubercle bacilli in the biopsies [6, 33].

In contrast, a study by Gan et al, [7] found colonoscopic biopsy specimens to be ineffective in differentiating between IT and CD[1.] These differ from the findings derived in our study.

Our study documented, 75% patients with CD responded to treatment, 5% initially responded to CD therapy, later responded to ATT. In case of IT, 80% patients responded to ATT, 20% failed ATT & responded to CD therapy.

In an analogous study conducted by Amarapurkar et al, all patients with IT & CD showed complete response to treatment. With respect to a retrospective study governed by Navaneethan et al, the diagnosis changed from CD to IT in one case (5%) and from IT to CD in 14 cases (23%). Dutta et al pointed out 5 patients (17%) with CD had history of receiving ATT in the past.

Consequently, in a country wherein TB is endemic, the likelihood of missing a diagnosis of TB should be stabilised against incorrect use of ATT in patients incorrectly classified as TB instead of CD. . Nevertheless the discordance of histomorphological features in advanced active IT and CD may pose great challenge in concluding the diagnosis.

V. Conclusion

IT may simulate CD clinically, endoscopically and histologically. We ought to consider IT in the differential diagnosis of CD, specifically in regions where tuberculosis is endemic .Thus a collective assessment of clinical features, endoscopy, histology and response treatment are most useful to differentiate CD from IT. A regulatory-based method to a patient with granulomatous colitis with respect to both diagnosis and treatment would go a long way in preventing irrelevant unsuitable ATT for patients with CD and appropriate early treatment for a patient with TB. In cases of diagnostic dilemma, starting ATT would be more suitable especially in developing countries, where TB is endemic. [2]. In addition to caseous necrosis and acid-fast bacilli (which are present in a minority of biopsy specimens from patients with intestinal tuberculosis), size, number and confluence of granulomas, presence of ulcers lined by bands of epithelioid histiocytes and disproportionate submucosal inflammation may assist in differentiating intestinal tuberculosis from Crohn's disease.[1] Huger, prospective studies possibly will aid in recognition associations of histological and clinical features with a positive predictive value for intestinal tuberculosis satisfactory to value a trial of antituberculous treatment. . Nevertheless, the discordance of histomorphological features in advanced active IT and CD may pose great challenge in concluding the diagnosis.

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