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Use of Steroids in Diagnostic Confusion between Intestinal Tuberculosis and Crohn's Disease: A Brief Experience

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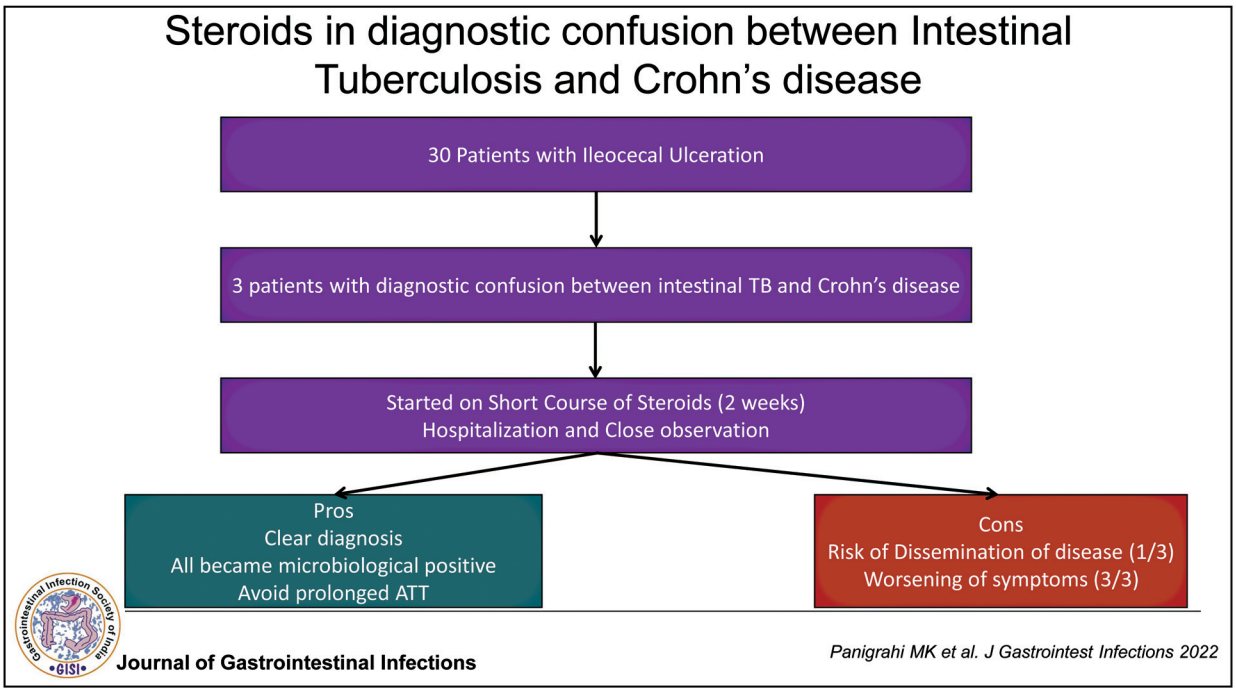

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Abstract

Background Differentiating intestinal tuberculosis (TB) from Crohn's disease (CD) is challenging. Even after complete workup, the underlying diagnosis can often remain unclear. Traditionally, trial of antitubercular therapy (ATT) is resorted to in such situations, but the use of ATT could increase stricturing complications in CD.

Methods We report findings from our cohort of patients with ileocecal ulcers. Among patients with a diagnostic confusion between intestinal TB and CD, steroids were started in an in-hospital setting under close observation. We report a brief series of patients with a close overlap in terms of disease presentation, behavior, laboratory, and histopathological findings. All the cases had skip lesions in the colon with inconclusive final diagnosis. We attempted to differentiate between the two by a short trial of steroids for 2 weeks.

Results Of the 30 patients with ileocecal ulceration, the diagnosis remained uncertain between intestinal TB and CD in three patients. All three patients received steroids for 2 weeks. Eventually, all were diagnosed to have TB. Administration of steroids helped increase microbiological yield with all three having a positive microbiological diagnosis at 2 weeks. However, one patient developed dissemination (pulmonary lesions).

Conclusion With a definitive risk of flare of TB with steroid, we encountered a positive diagnosis with repeat colonoscopy biopsy, positive result in bronchoalveolar lavage, and in third case positive report of cartridge-based nucleotide acid amplification test on repeat colonoscopy biopsy. In cases where differentiation of ileocecal TB from CD is not possible confidently, using a steroid-first approach increases the microbiological yield with a potential risk of dissemination.

Keywords
- Crohn's disease
- tuberculosis
- antitubercular therapy
- inflammatory bowel disease
- intestinal tuberculosis

Introduction

The emergence and increasing prevalence of Crohn's disease (CD) in India that is a tuberculosis endemic country have resulted in challenges in differentiating between the two closely similar conditions. The earliest possible description of CD dates back in 1761 by Giovanni Battista Morgagni (described CD in his treatise named "The seats and causes of diseases"),[1] while intestinal tuberculosis was possibly recognized as early as by Hippocrates. Both CD and ileocecal tuberculosis (ITB) are chronic inflammatory disorders with granuloma formation and have a great overlap in the disease behavior, histological, radiological, and endoscopic appearance.[2] ITB often complicates the diagnosis and management of CD and vice-versa; the story becomes more complicated in tubercular endemic areas like India where an initiation of empirical antitubercular therapy (ATT) could delay the diagnosis of CD. This may result in stricturing complications during the therapy.

We report here cases with great degree of overlap between these two similar entities and our observations after steroid therapy in these cases with strict in-hospital monitoring for clinical worsening and repeat endoscopy for histological and microbiology testing.

Methods

We are reporting retrospective case series with diagnostic confusion between ileocolonic tuberculosis and CD. Of the patients with ITB, we included those patients where the diagnosis was uncertain even after histopathological and microbiological evaluation. Instead of the usual approach in tuberculosis endemic region of ATT first, we started these patients on steroids. A short course of steroid trial (2 weeks) was administered in hospital and a repeat colonoscopy was performed with histopathology and microbiological evaluation.

Results

A total of 30 patients presented with ileocolonic ulceration during the last 2 years, of which three cases reported below had a close diagnostic confusion between tuberculosis and CD where we proceeded for treating with steroid first. The detailed description of case series with summary of relevant clinical features, radiology, and histopathology is precisely tabulated in ►**Table 1**.

Case 1

A 50-year-old male symptomatic with periumbilical colicky abdominal pain presented with anorexia and significant weight loss for 9 months. There was no history of fever, sweating, cough, joint pain, skin lesion, diarrhea, or bleeding per rectum. No family history of tuberculosis or inflammatory bowel disease was present. Rest laboratory parameters were normal including hemoglobin, white blood cells, platelet count, liver and renal function tests except for elevated

Table 1 Clinical characteristics, colonoscopic, radiological, and histopathological findings of cases

	Case 1	Case 2	Case 3
Age/sex	50/male	38 years/male	19 years/ female
Residence	West Bengal, India	Odisha, India	Odisha, India
Clinical presentation	1. Periumbilical colicky abdominal pain 2. Decreased appetite 3. Significant weight loss	1. Recurrent right lower abdominal pain 2. Intermittent small bowel diarrhea and constipation. 3. Decreased appetite 4. Weight loss of 10 kg	1. Chronic small bowel diarrhea with blood in stool 2. Swelling of face and lower limb 3. Periumbilical pain 4. Irregular menstruation and weight loss 5. Painful oral ulceration
Duration of symptom	9 months	2.5 years	2 months
Positive laboratory findings	ESR = 32 mm in 1st hour	ESR =35 mm/hr.	Hb =7.5 g/dl in-place of 7.5%g/dl (normochromic normocytic anemia) ESR = 72 mm/h, platelet = 10.8 lac/mm^3 Serum protein = 5.3 g/dL, serum albumin = 1.1 g/dL
Quantiferon Gold	Negative	Negative	Negative
Colonoscopic findings	–Ileocecal valve: deformed –Cecum: ulceronodular lesion Ascending colon and sigmoid colon: ulceration	–Ileocecal valve: deformed and patulous –Cecum: ulceration present –Proximal transverse colon: longitudinal ulcer	–Ileocecal valve: deformed with ulceration and gaping –Hepatic flexure and descending colon: deep longitudinal ulcers with normal intervening mucosa
Colonoscopic biopsy (before steroid therapy)	–Focal cryptitis, –Crypt abscess –No granuloma –Background of mixed cellular infiltrates of lymphocytes and occasional plasma cells	–Noncaseating small granuloma, –Crypt loss –Crypt irregularity –Background of lymphocytic predominant infiltration, No giant cell formation	–No granuloma –Crypt irregularity –Fusion and side branching, –Deep crypt lymphocytosis, –Scattered apoptosis
CECT abdomen	Skip lesions, multifocal symmetrical circumferential enhancing wall thickening (maximum of 1.2 cm) noted in distal ileum with intervening normal segment, mild ascites, and multiple subcentimetric lymph node	Ileocecal thickening skip lesion (intestinal thickening in cecum and splenic flexure area with normal mucosa in between area)	Chronic thrombosis of celiac axis at origin with inferior mesenteric collaterals, right pericolic, mesenteric, peripancreatic, aortocaval, pelvic necrotic lymph nodes with multiple splenic infarcts. Circumferential thickening involving ileocecal junction to proximal transverse colon with luminal narrowing
AFB staining and CBNAAT before steroid (in colonoscopy biopsy)	Negative	Negative	Negative
Definitive evidence of TB after steroid trial	AFB stain positive on colonoscopy biopsy after 2 weeks steroid therapy	Bronchoalveolar lavage fluid positive for AFB	CBNAAT positive on colonoscopic biopsy
ATT therapy: total 9 months of therapy	2HRZE +7 HRE H: Isoniazid R: Rifampicin Z: pyrazinamide E: Ethambutol	2HRZE + 7HRE	2HRZE+ 7HRE

Abbreviations: ATT, antitubercular therapy; AFB, acid fast bacilli; CBNAAT, cartridge-based nucleotide acid amplification test; ESR, erythrocyte sedimentation rate; TB, tuberculosis.

erythrocyte sedimentation rate (ESR) of 32mm/1st hour. Patient was negative for human immunodeficiency virus (HIV). Colonoscopy (►**Fig. 1A**) revealed deformed ileocecal valve with ulceronodular lesion in cecum and longitudinal ulcers in ascending colon and sigmoid colon. The colonoscopy biopsy showed focal cryptitis and crypt abscess without any granuloma and background of mixed cellular infiltrates of lymphocytes and occasional plasma cells. Contrast-enhanced computed tomography (CECT) of abdomen (►**Fig. 1B**) showed skip lesions, multifocal symmetrical circumferential enhancing wall thickening (maximum of 1.2 cm) noted in distal ileum with intervening normal segment, mild ascites, and multiple subcentimetric lymph node. Ascitic fluid was not amenable to diagnostic aspiration. Lung parenchyma was normal with no mediastinal lymphadenopathy on CECT chest. Mantoux test was negative. With inconclusive

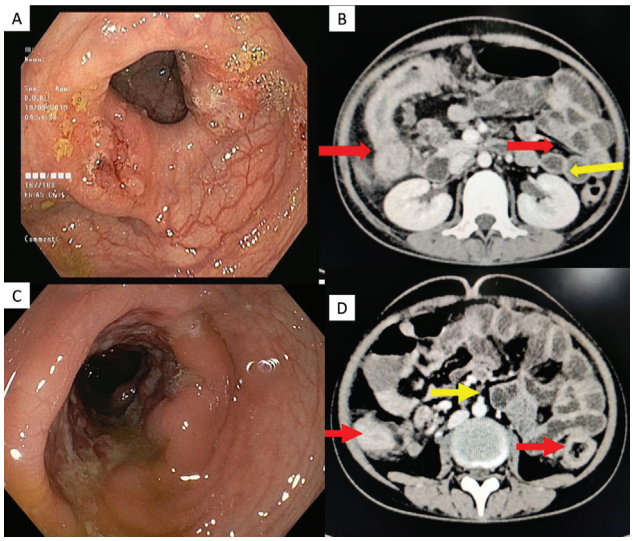

Fig. 1 (**A**) Ulceronodular lesion in cecum with deformed ileocecal valve. (**B**) Contrast-enhanced computed tomography (CECT) abdomen—red arrows showing thickened large intestine and ileocecal junction with normal intervening large intestine (yellow arrow). (**C**) Ulcerated mucosa in proximal transverse colon with normal appearing proximal mucosa. (**D**) CECT abdomen: thickened enhancing ileocecal region and large bowel (red arrow) with normal intervening mucosa; celiac axis thrombosis (yellow arrow).

histological and microbiological testing for tuberculosis and imaging suggestive of skip lesion, the diagnosis of CD was considered and treatment with tab. Prednisolone (40 mg once daily) therapy was initiated with close clinical, biochemical, and endoscopic monitoring in the hospital. Because of worsening of pain and clinical status on day 15 of immunosuppression, a decision to repeat colonoscopy and biopsy was taken and the same revealed granulomatous inflammation with acid fast bacilli (AFB) on staining that was not present in the previous colonoscopic biopsy sample. Patient was initiated with ATT with remarkable improvement of symptoms and attainment of normal weight on follow-up.

Case 2

A 38-year-old male presented with a history of recurrent right lower abdominal pain and altered bowel habits (intermittent small bowel diarrhea and constipation) for the last 2.5 years. The diarrheal episodes were lasting for 2 to 3 weeks in a month on an average. Stool was loose (Bristol stool scale 7), nonoily, with a frequency of five to six times a day with one to two nocturnal frequencies. No effect of fasting on stool frequency was appreciated by the patient. The above symptoms were associated with decreased appetite and 10 kg weight loss. No family history of colorectal malignancy or tuberculosis was present. Laboratory parameters were within normal limit except for ESR—35 mm/h. CECT abdomen revealed ileocecal thickening and skip lesion (intestinal thickening in cecum and splenic flexure area with normal mucosa in between area). Considering the above radiological findings, we proceeded for colonoscopy that revealed skip lesions, deformed and patulous ileocecal valve with ulceration in cecum, and longitudinal ulcer in proximal transverse colon (►**Fig. 1C**). Colonoscopy biopsy revealed noncaseating small granuloma, crypt loss, and irregularity with background of lymphocytic rich infiltration; AFB stain was negative as was the cartridge-based nucleotide acid amplification test (CBNAAT) in colonoscopy biopsy specimen. Chest X-ray was normal. Therapy was initiated with tab. Prednisolone (0.75 mg/kg once daily) was started. After 2 weeks of therapy, he developed fever with cough. CECT chest revealed suspicious upper zone consolidation in right lung and we proceeded for bronchoalveolar lavage (BAL) after negative sputum results and BAL fluid was positive for AFB stain. Patient started on ATT and responded well with remarkable recovery of clinical features. In this case, we did not proceed for repeat colonoscopy as we found microbiological evidence of tuberculosis in BAL fluid and both pulmonary and gastrointestinal complaints responded well with ATT. The patient remains well at 2 years of follow-up.

Case 3

A 19-year-old female presented with loose watery stools (4–6 times/day) with nocturnal symptoms without blood in stool with swelling of face and lower limb for 2 months. The above symptoms were associated with periumbilical cramps, easy fatigability, and irregular menstruation with weight loss of 8 kg. Two weeks prior to presentation, she noticed multiple painful oral ulcerations. During evaluation, she had hemoglobin—7.5g/dl in-place of 7.5% g/dl (normochromic normocytic anemia), ESR—72 mm/hr, platelet—10.8 lac/mm^3 (thrombocytosis), S. protein—5.3 g/dL, serum albumin—1.1 g/dL (hypoalbuminemia) and negative antinuclear antibody and HIV status. There was no proteinuria on urine routine examination. CECT abdomen (►**Fig. 1D**) revealed chronic thrombosis of celiac axis at origin with inferior mesenteric collaterals, small right pericolic, mesenteric, peripancreatic, aortocaval, pelvic lymph nodes with multiple splenic infarcts, and circumferential thickening involving ileocecal junction to proximal transverse colon with luminal narrowing. After consulting department of hematology, bone marrow biopsy was done because of thrombocytosis and celiac axis thrombosis and the result was negative for JAK-2 mutation (considering polycythemia vera as a hematological possibility). Colonoscopy findings include ileocecal valve that was deformed with ulceration and gaping, segmental deep ulcers with normal intervening mucosa. Segmental biopsy revealed crypt irregularity, fusion and side branching, deep crypt lymphocytosis, and scattered apoptosis without any granuloma. AFB as well as CBNAAT was negative in biopsy specimen. Upper gastrointestinal endoscopy was normal including biopsy. The features of marked thrombocytosis, recurrent oral ulceration, thrombosis of celiac axis, and segmental deep ulcers with no definitive evidence of tuberculosis led to a decision to start therapy with tab. Prednisolone and azathioprine was taken.

At 14 days of therapy, stool frequency increased with a new onset fever. Immunosuppressants were stopped and investigations for sepsis namely urine routine and microscopy, urine culture, and blood culture were negative including a

normal chest X-ray. Because of worsening clinical status, flare of underlying tuberculosis was suspected and we repeated colonoscopy and biopsy this time clinched the diagnosis with multiple granulomas with positive CBNAAT. ATT was started and after 6 months of completion of therapy, clinical symptoms and colonoscopic lesions resolved completely with persistence of celiac axis thrombosis. All laboratory parameters returned to normal.

Discussion

The differentiation of two closest entities that involves the ileocecal region is a long-time debate and we add our experience on from a tuberculosis endemic region. Even after complete workup with histology and microbiological armamentarium, the clinicians are often unable to resolve the diagnostic confusion in a substantial number of patients. We report our experience with a deviation from standard recommended approach of ATT first in differentiating these two entities.

Of total ITB, only 20 to 25% cases have concomitant active or latent pulmonary TB.[3,4] Ileocecal region is most common site involved in ITB and is reported to involve in 77% of ITB and 22 to 54% of CD cases.[5] Seo H et al have inferred that 17.9% of CD is initially misdiagnosed as ITB and 10.8% of ITB misdiagnosed as CD with increasing temporal trend of misdiagnosis of ITB as CD.[6] The classical features of caseating granuloma and AFB are present in less than 30% cases and culture positivity is reported in less than 20% of cases. Beside caseating granuloma, the presence of confluent granuloma, macrogranuloma (>200 µm), ulcers lined by bands of epithelioid histiocytes, and submucosal granuloma are other differentiating features.[7] In a recently published study with an exhaustive search for histological and microbiological proof for gastrointestinal TB, definite diagnosis could be established only in 66.5% of cases.[8]

In such difficult scenario, an empirical trial of ATT for 8 to 12 weeks has been recommended by Asian Pacific consensus statement on CD and diagnosis of CD should be considered after no response to empirical ATT.[2] The monitoring of patient with symptomatic improvement has its own shortcomings as CD may have symptomatic response to empirical ATT and patients with ITB with strictures may have persistence of symptoms.[9] The exact timing of repeat endoscopy for looking ulcer healing is still debated. While one group of clinicians is in favor of performing the endoscopy at end of therapy,[10] another group believes in performing endoscopy by 2 months to look for healing of mucosa thereby avoiding unnecessary longer empirical ATT before a concrete diagnosis is made.[11]

It is important to point that patients with CD who were diagnosed after empirical ATT trial (6 months) had high-rate stricture formation and less chance of remaining free from surgery on long-term follow-up.[12] In such diagnostic uncertainties, we attempted initiation of steroid therapy during hospitalization and repeated endoscopy at 2 weeks considering the basic pharmacological fact of hypothalamic-pituitary-axis suppression on steroid therapy occurs at 2 weeks of initiation of the therapy.[13]

The common similarity of the three cases described here was the segmental involvement of intestine, lack of concrete histopathology and microbiological evidence of tuberculosis at index presentation. The initiation of steroid therapy with presumptive diagnosis of CD led to flare of tuberculosis with positive AFB staining in colonoscopic biopsy specimen in case one, AFB staining in BAL in case two and worsening of symptoms with positive CBNAAT in case three. This approach could increase the risk of flare and add cost to the existing treatment due to hospitalization but may help by improving microbiological yield and possibly, stricturing complications. Use of steroids has previously been reported in peritoneal tuberculosis and reduces stricturing complications.[14]

To conclude, in cases with diagnostic confusion between intestinal tuberculosis and CD, using a steroid-first approach increases the microbiological yield with a potential risk of dissemination. A well-designed randomized controlled trial is required to support this approach of differentiation of ITB from CD.

Ethical Statement

Written informed consent was obtained from the patients. No ethical approval was sought because the work is a retrospective case series.

Author Contributions

M.K.P. conceptualized, designed, wrote, and edited the final version of manuscript. C.K. was involved in collection of the data and images, follow-up of patients, and writing the manuscript.

Data Availability Statement

All associated data are provided in the manuscript.

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None.

Conflict of Interest

None declared.

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