

INTESTINAL TUBERCULOSIS ON TOP OF CROHN'S DISEASE: A NEVER-ENDING DILEMMA

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ABSTRACT

Significance: The global trend indicating rising incidence of inflammatory bowel disease in newly industrialized countries like the Philippines will add up to the major health problem of tuberculosis disease burden. Addressing this looming concern requires adequate data to develop good clinical practice for better delivery of health care. Availability of clinical information will help clinicians develop comprehensive approach in dealing with possible coexistence of crohn's disease and intestinal tuberculosis.

Clinical Presentation: We present a case of 33-year-old, Filipino, male diagnosed with crohn's disease with coexisting intestinal tuberculosis.

Management: Judicious approach to distinguish crohn's disease from intestinal tuberculosis is the initial step for management. Treatment of intestinal tuberculosis must take precedence over crohn's disease. In cases of complications, like stricture formation leading to obstruction and perforation, surgical intervention must be considered.

Recommendation: A thorough clinical evaluation, including comprehensive history and complete physical examination in addition to endoscopic, histopathologic and biochemical investigations must be seek out prior to any attempts to start definite treatment. Ensure to rule out other diseases especially infectious etiology, most particularly intestinal tuberculosis because medications use to treat crohn's disease has the potential to induce flare of tuberculosis leading to complications.

Keywords: Inflammatory bowel disease, Crohn's disease, Intestinal tuberculosis

INTRODUCTION

In recent years, the impact of inflammatory bowel disease has become global with accelerating incidence in newly industrialized countries in Africa, Asia, South America while incidence in the western world stabilized, its prevalence remains high.¹ If this epidemiological trend continues people affected with inflammatory bowel disease in these developing countries is forecasted to approximate or even surpass that of cases in the western world in the year 2025.^{2,3}

In high tuberculosis burden countries like the Philippines, emergence of this disease will add up to the already major public health concern. Presentation of intestinal tuberculosis (ITB) will confront clinicians in making distinction from inflammatory bowel disease as this two-distinct disease entity both present as chronic granulomatous disorder with overlapping clinical, endoscopic as well as histopathologic features.⁴

Here we report an unusual case of inflammatory bowel disease, crohn's type with concomitant intestinal tuberculosis. During treatment, the patient developed small bowel obstruction which subsequently underwent surgery.

CASE PRESENTATION

A 33-year-old, Filipino, male newly diagnosed case of crohn's disease (**Figure 1**), currently on Mesalamine 1.5g TID and recently started on Prednisone 20mg BID presented with five-day history of progressive crampy abdominal pain initially generalized but localized afterwards at the left lower quadrant. This was associated bloatedness and fever. He had previous pulmonary tuberculosis with complete 6-month treatment. Patient was admitted and underwent whole abdominal CT-Scan with IV contrast

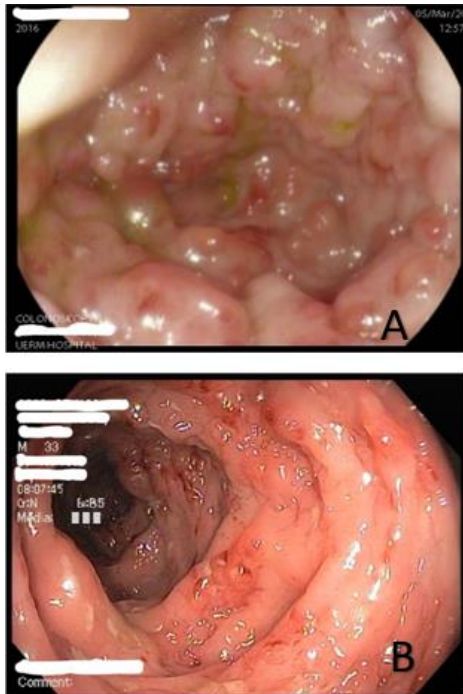


Figure 1: Endoscopic Findings

- A. (Cecum) Congested and hyperemic mucosa
- B. (Descending colon) Patchy areas of erosions with surrounding erythematous and congested mucosa

revealing, “Partial small bowel obstruction and gastroesophageal reflux, secondary to the diffuse thickening of the terminal ileum, ileocecal region, and ascending colon, most likely due to crohn’s disease. Intestinal tuberculosis is also a consideration.” (Figure 2) He was referred to surgery and subsequently underwent exploratory laparotomy with right hemicolectomy with end ileostomy and distal mucous fistula. Intraoperatively findings showed, “thickened ileocecal area with noted fibrous band impinging the terminal ileum causing the obstruction; small bowels were dilated with moderate accumulation of seropurulent peritoneal fluids, mesentery of the small bowels was noted to be studded with

matted necrotic tissue with findings of fistula formation in hepatic flexure to the proximal transverse colon.”

Tissue for histopathologic examination was submitted showing, “Inflammatory bowel disease, crohn’s type, involving the ileum, cecum, ascending and transverse colon with the following features: fissuring ulceration of the mucosa, transmural inflammation, non-caseating epithelioid granulomas; associated transmural necrosis with perforation, abscess formation and peritonitis; acute suppurative lymphadenitis; caseating granulomatous lymphadenitis consistent with tuberculosis, transverse colon.” (Figure 3 A-D).



Figure 2: Abdominal CT-Scan

- A. Axial View: Thickening of the terminal ileum
- B. Coronal View: Persistent collapse and diffuse wall thickening of the terminal ileum, extending to the ileocecal region, and ascending bowel segments.

Specimen for MTB Gene Xpert was likewise submitted showing, “MTB detected – Medium; Rif resistance – not detected.” Mesalamine was discontinued and patient was referred to infectious disease specialist and was started on quadruple anti-tuberculous (HRZE) medications. Patient clinically improved with no noted post-operative complications. He was discharged on his 19th hospital day.

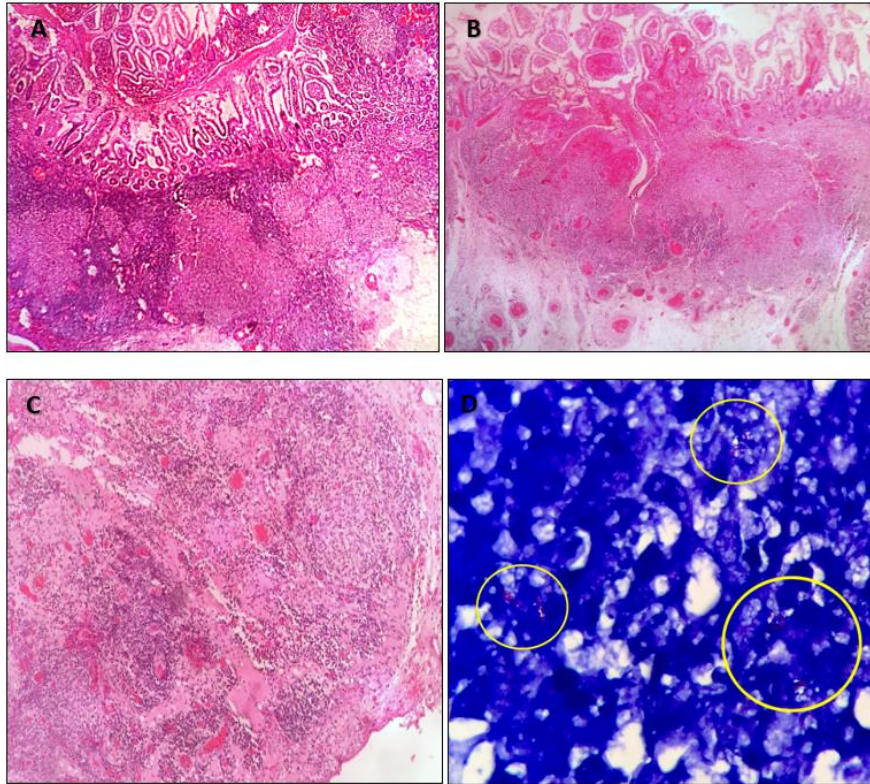


Figure 3 A-D Histopathologic Findings

- A. Transmurular lymphoplasmacytic inflammation with granuloma formation
- B. Mucosal tissue with transmural inflammation
- C. Lymph node with granuloma formation
- D. Acid fast bacilli in the lymph node

DISCUSSION

The rapid socioeconomic development and westernization of the low to middle income countries is associated with increasing epidemiological trend of inflammatory bowel disease as a global health burden.^{2,3-5} While these countries still battling infection as a public health concern the looming rise of this chronic disease will add up to the economic incumbrance. In the Philippines, wherein the burden of illness of tuberculosis remains high, clinicians were confronted with major dilemma for distinguishing inflammatory bowel disease from the other mimickers of the disease especially intestinal tuberculosis.

Crohn's disease (CD) and intestinal tuberculosis (ITB) are both chronic granulomatous condition that share overlapping clinical, endoscopic, radiologic, and histopathologic features.^{7,8,9,10} More challenging is that, there is no single gold standard for diagnosis of crohn's disease.^{14,15} This make differentiation with intestinal tuberculosis difficult. Distinguishing these two -

disease entity though is important because they have distinct natural course. Intestinal tuberculosis is curable when appropriate therapy is started while crohn's disease is progressive and relapsing illness.¹¹

Ileocolonoscopy plays a central part in the diagnosis, management, surveillance as well as differentiation of crohn's disease.¹² Two factors can be considered endoscopically to aid in the differentiation of CD and ITB – that is, area of distribution and endoscopic appearance.¹² Features suggestive of crohn's disease includes involvement of more than or equal to 4 segments of the colon especially the terminal ileum and ileocecal valve, presence of longitudinal ulcers, aphthous ulcers, cobblestone appearance and findings of perianal lesions.^{12,13} Intestinal tuberculosis on the other hand, usually involved less than 4 segments of the colon with findings of transverse ulcers and patulous ileocecal valve.^{12,13}

Mucosal biopsy during endoscopic examination is usually part of the first line investigation for the diagnosis of CD.¹⁶ Both the Asia-Pacific consensus on Crohn's disease and the 3rd European Evidence-based consensus on the diagnosis and management of Chron's disease recommends multiple biopsies (at least 2) from five sites in the colon including the rectum.^{14,15} In a retrospective study by Ye, Z. et al.,¹⁷ granulomas were present in 81.3% of ITB cases and in 67.3% of CD cases (P = 0.36). Features favoring ITB granuloma includes confluent, large size (mean widest diameter, 508±314mm; range, 100–1100mm), in contrast to CD granuloma showing small size (mean widest diameter, 253±197mm; range, 50–800mm) not confluent.¹⁷ While basal cell plasmacytosis, lymphoid aggregate, and lymphangiectasia were commonly seen in CD than ITB.¹⁷ Other microscopic favoring features CD includes focal (discontinuous) chronic (lymphocytes and plasma cells) inflammation and patchy chronic inflammation, focal crypt irregularity (discontinuous crypt distortion).¹⁴

Employing imaging to differentiate CD from ITB has been studied using CT enterography technique. The presence of wall stratification, comb sign, and fibrofatty proliferation significantly favored CD, while short segmental involvement significantly supported the diagnosis of ITB.¹⁸ Inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin did not show statistical significance in differentiating CD from ITB, so is serum biomarker anti-Saccharomyces cerevisiae antibody (ASCA).^{18,19-20}

Taking into consideration all aspects in diagnosis of crohn's and its differentiation, several scoring systems were developed. Lee, YJ et al., uses 8 specific endoscopic indicators to establish a scoring system with aim to differentiate CD from ITB.²¹ Huang X, et al., also developed a scoring system with 12 high specificity indicators including clinical, endoscopic and histopathological features with PPD and T-SPOT.TB.²² These scoring systems may aid in differentiating CD from ITB, but validation studies should be employed for it to be use in general.

In cases where it is not possible to confidently differentiate ITB from CD, Asia-Pacific consensus on Crohn's disease recommended 8-12 weeks therapeutic trial of anti-TB therapy (ATT) with repeat colonoscopy at 8-12 weeks to document treatment response.¹²

The goals of treatment for crohn's disease includes induction and maintenance of remission, improving quality of life, as well as prevention of complications.¹² But recent advances in treatment armamentarium has shifted the paradigm to deeper remission, that is pointing towards clinical remission with associated mucosal healing.^{23, 24}

Inflammatory bowel disease independently, is not associated with increased risk for active tuberculosis but in association with immunosuppressants used for treatment increases risk for active tuberculosis.²⁵ In the case presented the crohn's disease is complicated by activation of intestinal tuberculosis leading to small bowel obstruction. Surgical intervention was done. Tissue biopsy with noted positive Acid-fast bacilli as well as PCR-TB test confirmed diagnosis of TB. Treatment with intestinal tuberculosis follows the basic principle of treatment with pulmonary tuberculosis employing a 6 to 9-month regimen consisting of 2 months isoniazid, rifampicin, pyrazinamide and ethambutol in the initial phase followed by 4-7 months of isoniazid and rifampicin in the continuation phase.²⁶

CONCLUSION

In the Philippines where burden of tuberculosis remains high, increase incidence of inflammatory bowel disease will add up to present health burden. Inevitably this rapid change will occur in the coming years but with careful planning through innovations in the utilization and delivery of health care curtailed to this anticipatory change will somehow reduce the looming problem. Compendium of scientific information and clinical data will help clinicians to develop strategies and clinical pathways to address possible dilemma due to close association of these two diseases.

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REFERENCES

1. Siew C Ng, et.al., Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*, The, Copyright 2017 Elsevier Ltd
2. Kaplan GG., The global burden of IBD: from 2015 to 2025. *Nat Rev Gastroenterol Hepatol*. 2015 Dec;12(12):720-7. [PMID: 26323879]
3. Kaplan GG, Ng SC, Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. *Gastroenterology* February 1, 2017; 152 (2); 313-321.e2 [PMID: 27793607]
4. Ye Z, Lin Y, Cao Q, He Y, et.al., Granulomas as the Most Useful Histopathological Feature in Distinguishing between Crohn's Disease and Intestinal Tuberculosis in Endoscopic Biopsy Specimens. *Medicine (Baltimore)*. 2015 Dec;94(49):e2157. [PMID: 26656343]
5. Kaplan GG, Ng SC, Globalisation of inflammatory bowel disease: perspectives from the evolution of inflammatory bowel disease in the UK and China. *Lancet Gastroenterol Hepatol*. 2016 Dec;1(4):307-316. [PMID: 28404201]
6. Bernstein CN, Eliakim A, et. Al., World Gastroenterology Organisation Global Guidelines Inflammatory Bowel Disease: Update August 2015. *J Clin Gastroenterol*. 2016 Nov/Dec;50(10):803-818. [PMID: 27741097]
7. Maitra RK, Bowling T, Venkatesan P, Maxwell-Armstrong C., Crohn's disease or TB – the perennial question and diagnostic pitfalls. *BMJ Case Rep*. 2012 Apr 2;2012. pii: bcr0120125620. [PMID: 22602826]
8. Constantinos Chatzicostas, Ioannis E Koutroubakis, et.al., Colonic tuberculosis mimicking Crohn's disease: case report. *BMC Gastroenterol*. 2002 May 13;2:10. [PMID: 12019037]
9. Madunil A. Niriella, S. Kuleesha Kodisinghe, Arjuna, et.al., Intestinal tuberculosis masquerading as difficult to treat Crohn disease: a case report. *BMC Res Notes*. 2016 Aug 24;9(1):417. [PMID: 27557645]
10. Steven DiLauro, MD; Ileitis: When It Is Not Crohn's Disease. *Curr Gastroenterol Rep*. 2010 Aug;12(4):249-58. [PMID: 20532706]
11. Weng MT, Wei SC, et.al., Seminar Report From the 2014 Taiwan Society of Inflammatory Bowel Disease (TSIBD) Spring Forum (May 24th, 2014): Crohn's Disease Versus Intestinal Tuberculosis Infection. *Intest Res*. 2015 Jan;13(1):6-10 [PMID: 25691838]
12. Grace Chan, MRCPI, MRCP(UK), David S. Fefferman, MDRichard J. Farrell, MD, FRCPI, Endoscopic Assessment of Inflammatory Bowel Disease: Colonoscopy/Esophagogastroduodenoscopy. *Gastroenterology Clinics of North America*, 2012-06-01, Volume 41, Issue 2, Pages 271-290
13. Ji Min Lee and Kang-Moon Lee, Endoscopic Diagnosis and Differentiation of Inflammatory Bowel Disease. *Clin Endosc*. 2016 Jul;49(4):370-5. [PMID: 27484813]
14. Gomollón F, et.al., 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis*. 2017 Jan;11(1):3-25 [PMID: 27660341]
15. Ooi CJ, Makharia GK, et.al., Asia Pacific Consensus Statements on Crohn's disease. Part 1: Definition, diagnosis, and epidemiology (Asia Pacific Crohn's Disease Consensus—Part 1). *J Gastroenterol Hepatol*. 2016 Jan;31(1):45-55. [PMID: 25819140]
16. Coremans G, Rutgeerts P, Geboes K, Van den Oord J, Ponette E, Vantrappen G. The value of ileoscopy with biopsy in the diagnosis of intestinal Crohn's disease. *Gastrointest. Endosc*. 1984; 30: 167–72.
17. Ziyin Ye, MD, Yuan Lin, MD, PhD, Qinghua Cao, MD, Yao He, MD, PhD, and Ling Xue, MD, PhD , Granulomas as the Most Useful Histopathological Feature in Distinguishing between Crohn's Disease and Intestinal Tuberculosis in Endoscopic Biopsy Specimens. *Medicine (Baltimore)*. 2015 Dec;94(49):e2157. [PMID: 26656343]
18. Julajak Limsrivilai, MD, Andrew B. Shreiner, MD, PhD, et.al., Meta-Analytic Bayesian Model For Differentiating Intestinal Tuberculosis from Crohn's Disease. *Am J Gastroenterol*. 2017 Mar;112(3):415-427. [PMID: 28045023]

19. Ghoshal UC, Ghoshal U, Singh H, et al. AntiSaccharomyces cerevisiae antibody is not useful to differentiate between Crohn's disease and intestinal tuberculosis in India. *J Postgrad Med.* 2007; 53:166–70. [PubMed: 17699989]
20. Makharia GK, Sachdev V, Gupta R, et al. AntiSaccharomyces cerevisiae antibody does not differentiate between Crohn's disease and intestinal tuberculosis. *Dig Dis Sci.* 2007; 52:33–9. [PubMed: 171604]
21. Lee YJ, Yang SK, Byeon JS, Myung SJ, Chang HS, Hong SS, Kim KJ, Lee GH, Jung HY, Hong WS, Kim JH, Min YI, Chang SJ, Yu CS ., Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. *Endoscopy*, June 1, 2006; 38 (6); 592-7
22. Xin Huang, Wang-Di Liao, Chen Yu, Yi Tu, Xiao-Lin Pan, You-Xiang Chen, Nong-Hua Lv, Xuan Zh, Differences in clinical features of Crohn's disease and intestinal tuberculosis., *World J Gastroenterol.* 2015 Mar 28;21(12):3650-6 [PMID: 25834333]
23. Iacucci M, Ghosh S Looking beyond symptom relief: evolution of mucosal healing in inflammatory bowel disease. *Therap. Adv.Gastroenterol.* 2011; 4: 129–43. [PMID: 21694814]
24. Ambrogio Orlando, Francesco William Guglielmib, et.al., Clinical implications of mucosal healing in the management of patients with inflammatory bowel disease. *Digestive and Liver Disease*, 2013-12-01, Volume 45, Issue 12, Pages 986-991
25. Faten N. Aberra, Nicolas Stettler, Risk for Active Tuberculosis in Inflammatory Bowel Disease Patients. *Clinical gastroenterology and hepatology* 2007;5:1070–1075
26. Clinical Practice Guidelines for the Diagnosis, Treatment, Prevention and Control of Tuberculosis in Adult Filipinos: 2006 UPDATE