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EDITORIAL

Intestinal tuberculosis or Crohn's disease: Illusion or delusion or allusion

Tuberculosis (TB) has reveled in its ability at clever disguise, cunning deceit, and masquerading as any disease beyond any logic. Interestingly, these illusory presentations of TB have been more commonly and inexplicably linked to specific anatomical sites like the intestine, the central nervous system, or the eye compared to its native habitat, the lungs. Robert Koch isolated tubercle bacilli and formulated Koch's postulates based on this, yet it is ironic that Koch's bacillus at extrapulmonary sites is defiant and resists all attempts made to fulfil its own creator's postulates. However, what Koch's favorite bacillus in the intestine had not fathomed was that the 20th century would bring in a conquistador that would be the very imitation of itself. Crohn's disease (CD) was found, and it imitated the great masquerade of TB so closely that it baffled caregivers. So much so that, despite the knowledge of its illusory state, physicians and the diagnosticians remained deluded and hoped for an allusion to end their diagnostic misery.

North America and Europe, 'the Western world,' found TB to be one of the major killers in the 18th and early 19th centuries, where it spread explosively due to urban human crowding, a consequence of the Industrial Revolution.[1] This 'white plague epidemic' followed the Industrial Revolution, spreading to Eastern Europe, South Americas, East Asia, and Southeast Asia ('the developing world') in the 20th century.[2] While the incidence and mortality of TB waned in the Western world, even before the advent of antitubercular therapy (possibly due to improving hygiene and sanitation),[3] most of the developing world is still shackled with a high disease burden of TB. The disease process of extrapulmonary TB (EPTB) starts from the pulmonary focus, from where the bacterium disseminates to other areas, which could possibly account for the low bacterial load (paucibacillary) in extrapulmonary sites. The paucibacillary nature of EPTB makes it difficult to diagnose, more so if the Koch's postulates are followed, which has led to alternative diagnostic criteria depending upon the individual sites.[4] The problem is further compounded at the sites that are affected by phenotypically similar but etiologically different disease processes, with the intestine (CD), thoracic cavity (sarcoidosis), and eyes (Eale's disease) primarily being such sites.[5,6] The epidemic of these immune-mediated disorders, such as inflammatory bowel disease (IBD), has followed the decline of TB in the West,[2] marked by a rising incidence in the 20th century that has stabilized over the last decade,[7] while the developing world is following this pattern and is at the epidemiologic crossroads with a declining or stabilizing burden of TB[8,9] and a rising incidence of IBD and other such disorders.[10–13] Hence, the nontubercular etiologies at these extrapulmonary sites have largely replaced TB in the West, but the TB-endemic regions continue to be affected by both the etiologies, creating a diagnostic challenge for clinicians in these regions.

Over the last two decades, there have been several efforts by gastroenterologists to decipher the dilemma of CD and intestinal TB (ITB), and considerable progress has been made toward dissecting this diagnostic conundrum, but a perfect solution still remains.[14–16] The problem persists primarily due to two reasons: poor sensitivity of definite diagnostic tests for ITB (because of paucibacillary disease) and nonspecific diagnostic criteria for CD.[17] The microbiological (positive stain for acid-fast bacillus or culture for mycobacterium TB or positive Gene-Xpert) or pathological tests (caseation granuloma) do have 100% specificity but are limited by poor sensitivity.[18–20] The present study by Israrahmed et al. is another laudable effort in this direction.[21] The authors propose a computed tomography (CT)-based diagnostic algorithm for differentiating CD from ITB based on their findings on CT enteroclysis/enterography in a cohort of 61 patients with ITB and 24 patients with CD. Homogenous bowel wall thickening and confluent bowel involvement were significantly more common in ITB, while stratified bowel wall thickening with mucosal hyperenhancement, skip lesions, and comb sign were significantly more common in CD. Furthermore, stratified bowel wall enhancement with an intervening layer of fat was specific to CD, and necrotic lymph nodes were specific to ITB. The algorithm starts with the CT findings and incorporates endoscopy, histology and microbiology, and a therapeutic antitubercular therapy (ATT) trial when these tests are inconclusive. Although the study echoes previously reported findings,[15,22] it provides a useful direction. Although the addition of radiology in this and the previous studies (necrotic lymph nodes on CT abdomen or evidence of active pulmonary TB) has increased the sensitivity,[22] a large diagnostic gap still remains, and a similar situation exists for other etiologies such as sarcoidosis.

Hence, the most important step toward bridging this gap should involve a holistic effort (across involved specialties) targeting the root, that is, its paucibacillary nature. Xpert/MTB-RIF (Xpert/mycobacterium tuberculosis-rifampicin) was an important addition, but its poor sensitivity for EPTB specimens was an impediment to the resolution of the situation.[23] The cornerstone for global TB control involves the development of novel, rapid, and accurate diagnostic techniques for all forms of TB, and a global laboratory initiative (GLI) has been launched in this regard.[24,25] These efforts should also benefit the diagnostic uncertainties existing between EPTB and respective site-specific immune-mediated etiologies. Another approach would involve the development of biomarkers for accurate diagnosis of EPTB, and FOXP3 T-regulatory cell enumeration in peripheral blood has revealed reasonable diagnostic accuracy in differentiating CD

from ITB.[26] It has also been prospectively validated at the same center[27] but requires further validation at different centers and across other sites.

Pushing our boundaries of understanding through this maze have been the development of machine learning-based diagnostic algorithms incorporating multiple features (as very few are exclusive to CD or ITB, and those that are have very poor diagnostic sensitivity) on a platform through which these algorithms can be effortlessly applied. The Bayesian meta-analytical model by Limsrivilai et al. incorporated clinical, endoscopic, and histological features into a predictive model with good diagnostic accuracy to differentiate CD from ITB.[28] Furthermore, a nomogram based on seven parameters, including age, transverse ulcer, rectum involvement, skipped small bowel involvement, target sign, comb sign, and a QuantiFERON gold assay (for model 1) or Mantoux test (for model 2), also revealed good sensitivity and specificity for differentiating CD from ITB.[29]

Before we develop a perfect strategy for upfront diagnosis of EPTB or for upfront differentiation of CD from ITB, we need to rely on a therapeutic ATT trial. In addition to the concern of ATT-induced hepatotoxicity and steroid-induced flare of TB, the ATT trial has recently been associated with complicated disease course in patients with an eventual diagnosis of CD. The etiologies for this ATT-induced complication have been identified as ATT-induced diagnostic delay or the profibrotic effects of ATT (independent of the diagnostic delay) in two different studies from India.[30,31] Having realized this additional and significant side effect of ATT, more vigilance and early decisions are required in patients on a therapeutic ATT trial. Hence, the follow-up algorithm proposed earlier and endorsed by guidelines[32,33] requires a revisit with early (at 2–3 months of ATT) objective evaluation and possible shortening of ATT duration in patients with a higher suspicion of CD.

The TB–CD tale is reminiscent of Star Wars trilogy. The latest episode is "The Return of the Jedi." First, TB existed in the intestine; then, CD was found at the same site; and now, the 21st century brings a new permutation that is "TB on CD." This concern, specific to TB-endemic regions (or the regions where this diagnostic dilemma exists), regards the identification of definite evidence of TB in a patient with definite CD. The increasing disease burden of IBD and improving economy in the developing world have led to increased use of antitumor necrosis factor (TNF) therapy in IBD. TB reactivation is a major concern with anti-TNF use, and the local TB burden has been identified as a major risk factor for this association,[34] with the highest rates of reactivation being reported from high TB burden countries such as India.[35,36] TB that develops after anti-TNF therapy can be extrapulmonary in up to 50% and can also involve the intestine. Therefore, the clinicians in these areas need to be aware of this emerging perplexity of "TB on CD," which has further enhanced the diagnostic confusion with regard to "TB or CD".

The emergence of IBD (and other immune-mediated disorders) and persistence of TB in the developing world continue to perplex the clinicians. Although this illusion of diagnostic certainty (or uncertainty) delays the correct therapeutic approach, the progress is steady, and a joint effort toward global TB control through improved diagnostic techniques and the advent of big data features would certainly bring about a definite solution. As previously stated, the new religion is Dataism. Dataism is a word first used by David Brooks in the New York Times in 2013, underlining the emerging importance of big data.[37] He felt it would greatly influence human thinking as "in a world of increasing complexity, relying on data could reduce cognitive biases and illuminate patterns of behavior we haven't yet noticed." This new religion was propelled to the masses by Yuval Noah Harari is his landmark book "Homo Deus: A Brief History of Tomorrow" when he suggested "Forget about listening to ourselves.[38] In the age of data, algorithms have the answer." And this could very well be the gospel truth or the allusion for ending this deluded illusion of TB or CD.

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Declaration of conflict of interest

None.

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References

1 Stead WW. The origin and erratic global spread of tuberculosis. How the past explains the present and is the key to the future. *Clin. Chest Med.* 1997; **18**: 65–77.
2 Das K. Crohn's disease and the "white plague": a hypothesis. *Gut*. 2014; **63**: 1030–1.
3 Wilson LG. The historical decline of tuberculosis in Europe and America: its causes and significance. *J. Hist. Med. Allied Sci.* 1990; **45**: 366–96.
4 Sharma SK, Mohan A. Extrapulmonary tuberculosis. *Indian J. Med. Res.* 2004; **120**: 316–53.
5 Agrawal R, Kee AR, Ang L *et al*. Tuberculosis or sarcoidosis: opposite ends of the same disease spectrum? *Tuberculosis (Edinb.)*. 2016; **98**: 21–6.
6 Biswas J, Sharma T, Gopal L, Madhavan HN, Sulochana KN, Ramakrishnan S. Eales disease—an update. *Surv. Ophthalmol.* 2002; **47**: 197–214.
7 Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. *Nat. Rev. Gastroenterol. Hepatol.* 2021; **18**: 56–66.
8 Dhoble P, Desai D, Abraham P. Is the rise in Crohn's disease in India accompanied by a fall in intestinal tuberculosis? A single-center experience. *Indian J. Tuberc.* 2020 Cited 10 Jan 2021. Available from URL: http://www.sciencedirect.com/science/article/pii/S0019570720301396.
9 Tsironi E, Feakins RM, Probert CSJ, Roberts CSJ, Rampton DS, Phil D. Incidence of inflammatory bowel disease is rising and

abdominal tuberculosis is falling in Bangladeshis in East London, United Kingdom. *Am. J. Gastroenterol.* 2004; **99**: 1749–55.
10 Ahuja V, Tandon RK. Inflammatory bowel disease in the Asia-Pacific area: a comparison with developed countries and regional differences. *J. Dig. Dis.* 2010; **11**: 134–47.
11 Ahuja V, Tandon RK. Inflammatory bowel disease: the Indian augury. *Indian J. Gastroenterol.* 2012; **31**: 294–6.
12 Singh P, Ananthakrishnan A, Ahuja V. Pivot to Asia: inflammatory bowel disease burden. *Intest Res.* 2017; **15**: 138–41.
13 Kedia S, Ahuja V. Epidemiology of inflammatory bowel disease in India: the Great Shift East. *Inflamm Intest Dis.* 2017; **Nov 2** :102–115.
14 Makharia GK, Srivastava S, Das P *et al*. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. *Am. J. Gastroenterol.* 2010; **105**: 642–51.
15 Kedia S, Das P, Madhusudhan KS *et al*. Differentiating Crohn's disease from intestinal tuberculosis. *World J. Gastroenterol.* 2019; **25**: 418–32.
16 Amarapurkar DN, Patel ND, Rane PS. Diagnosis of Crohn's disease in India where tuberculosis is widely prevalent. *World J. Gastroenterol.* 2008; **14**: 741–6.
17 Gomollón F, Dignass A, Annese V *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; **11**: 3–25.
18 Kumar S, Bopanna S, Kedia S *et al*. Evaluation of Xpert MTB/RIF assay performance in the diagnosis of abdominal tuberculosis. *Intest Res.* 2017; **15**: 187–94.
19 Sharma V, Soni H, Kumar MP *et al*. Diagnostic accuracy of the Xpert MTB/RIF assay for abdominal tuberculosis: a systematic review and meta-analysis. *Expert Rev. Anti Infect. Ther.* 2020; **Sept 2020**.
20 Du J, Ma Y-Y, Xiang H, Li Y-M. Confluent granulomas and ulcers lined by epithelioid histiocytes: new ideal method for differentiation of ITB and CD? A meta analysis. *PLoS One.* 2014; **9**: e103303.
21 Israrahmed A, Yadav RR, Yadav G *et al*. Systematic reporting of CT enterography/enteroclysis, an aid to reduce diagnostic dilemma when differentiating between intestinal tuberculosis and Crohn's disease: A Prospective Study at A Tertiary Care Hospital. *JGH Open.* 2021; **5**: 180–9.
22 Kedia S, Sharma R, Sreenivas V *et al*. Accuracy of computed tomographic features in differentiating intestinal tuberculosis from Crohn's disease: a systematic review with meta-analysis. *Intest Res.* 2017; **15**: 149–59.
23 Penz E, Boffa J, Roberts DJ *et al*. Diagnostic accuracy of the Xpert® MTB/RIF assay for extra-pulmonary tuberculosis: a meta-analysis. *Int J Tuberc Lung Dis.* 2015; **19**: 278–84 i–iii.
24 Stop TB Partnership - Global Laboratory Initiative (GLI) [Internet]. Cited 10 Jan 2021. Available from URL: http://www.stoptb.org/wg/gli/
25 World Health Organization. Global tuberculosis control: key findings from the December 2009 WHO report. *Wkly Epidemiol Rec.* 2010; **85**: 69–80.
26 Tiwari V, Kedia S, Garg SK *et al*. CD4+ CD25+ FOXP3+ T cell frequency in the peripheral blood is a biomarker that distinguishes intestinal tuberculosis from Crohn's disease. *PLoS One.* 2018; **13**: e0193433.
27 Rampal R, Kedia S, Wari MN *et al*. Prospective validation of CD4 +CD25+FOXP3+ T-regulatory cells as an immunological marker to differentiate intestinal tuberculosis from Crohn's disease. *Intest Res.* 2020.
28 Limsrivilai J, Shreiner AB, Pongpaibul A *et al*. Meta-analytic Bayesian model For differentiating intestinal tuberculosis from Crohn's disease. *Am. J. Gastroenterol.* 2017; **112**: 415–27.
29 He Y, Zhu Z, Chen Y *et al*. Development and validation of a novel diagnostic nomogram to differentiate between intestinal tuberculosis and Crohn's disease: a 6-year prospective multicenter study. *Am. J. Gastroenterol.* 2019; **114**: 490–9.
30 Banerjee R, Pal P, Girish BG, Reddy DN. Risk factors for diagnostic delay in Crohn's disease and their impact on long-term complications: how do they differ in a tuberculosis endemic region? *Aliment. Pharmacol. Ther.* 2018; **47**: 1367–74.
31 Gupta A, Pratap Mouli V, Mohta S *et al*. Anti-tubercular therapy given to differentiate Crohn's disease from intestinal tuberculosis predisposes to stricture formation. *J. Crohns Colitis*. 2020; **14**: 1611–18.
32 Pratap Mouli V, Munot K, Ananthakrishnan A *et al*. Endoscopic and clinical responses to anti-tubercular therapy can differentiate intestinal tuberculosis from Crohn's disease. *Aliment. Pharmacol. Ther.* 2017; **45**: 27–36.
33 Ooi CJ, Makharia GK, Hilmi I *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; **31**: 45–55.
34 Kedia S, Mouli VP, Kamat N *et al*. Risk of tuberculosis in patients with inflammatory bowel disease on infliximab or adalimumab is dependent on the local disease burden of tuberculosis: a systematic review and meta-analysis. *Am. J. Gastroenterol.* 2020; **115**: 340–9.
35 Agarwal A, Kedia S, Jain S *et al*. Very high rate of tuberculosis complicating infliximab therapy for inflammatory bowel disease despite tuberculosis screening in India. *J. Crohns Colitis*. 2018; **12**: S486.
36 Puri AS, Desai D, Sood A, Sachdeva S. Infliximab-induced tuberculosis in patients with UC: Experience from India: a country with high prevalence of tuberculosis: Infliximab-induced tuberculosis: India. *J. Gastroenterol. Hepatol.* 2017; **32**: 1191–4.
37 Brooks D. *Opinion|The Philosophy of Data* 2013. The New York Times [Internet]. Cited 13 Jan 2021. Available from URL: https://www.nytimes.com/2013/02/05/opinion/brooks-the-philosophy-of-data.html
38 Harari YN. *Homo Deus: a brief history of tomorrow*. UK: Vintage Penguin Random House; 2016: 428.