Editorial

Distinguishing Between Crohn's Disease, Tuberculosis, and Lymphoma: Still in Murky Waters

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In recent years, a clear shift is observed in the epidemiology of numerous diseases owing to a multitude of factors such as improved sanitation, urbanization, better health care, as well as others. Nonetheless, underprivileged populations still lack access to food, sanitation, education, and health care; all of which contribute to the continuation of diseases that have decreased in other areas of the world. These variables coupled with the relative ease of relocation of individuals in various geographical areas of the world—either transiently through travel or permanently through immigration—make it a challenge for health care providers to keep an open mind to differential diagnoses, which are not limited to what they are used to in their geographical areas.

Although intestinal tuberculosis (ITB) is not frequent in North America or Western Europe, it still remains a significant public health issue in many parts of the world.[1] Furthermore, the incidence/diagnosis of Crohn's disease (CD) in areas of the world with previously known relatively lower rates is on the rise. Thus the overlap of symptoms, signs, and diagnostic tests becomes a challenge where both diseases are encountered. Misclassification of CD, ITB, or primary small intestinal lymphoma (PIL) would result in delayed therapy, possibly increased morbidity, impaired quality of life, and loss of productivity.[1]

To make things more complicated, the classical notion of "trial" of antituberculoses medications in these patients not only wastes valuable time if the diagnosis is not ITB, but may also deceive the clinician with a lack of response to the "trial" due to drug resistance even when ITB is the case.

Liu *et al*. attempted in their study to differentiate and distinguish these diseases that have overlapping clinical presentations, laboratory and radiological features.[2]

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The findings of the authors about clinical presentation of such patients, frequency and duration of presenting symptoms tend to concur with a number of other studies[3-6]; although these discrepancies might be true on a collective basis, any one of these findings do not help the clinician in making a diagnosis when faced by an individual patient, because none of these findings has a high enough likelihood ratio to make a definitive diagnosis.

Although Liu *et al*.[2] did not look into the use of interferon gamma (IFN-γ) release assays, it is important to mention that these have been implemented in the workup of patients presenting with overlapping features, with the results being far from perfect. A meta-analysis including five studies with a total of 616 patients found that the mean sensitivity of interferon-gamma release assays was 74%; the mean specificity 87%; and the area under the curve was 0.92.[7] Of note, there were two different assays used in the studies: One was the T-SPOT-TB test, whereas the other was the Quanti-FERON-TB Gold In-Tube (QFT-G-IT) test.[7] Moreover, none of the studies included in the analysis reported blinded interpretation of the IFN-γ release assays.[7] The authors of the meta analysis reported a positive likelihood ratio of 5.98, suggesting that patients with ITB have an approximately six fold higher chance of being IFN-γ assay positive compared with CD patients, and hence inferring that this probability would be considered insufficient to begin or continue anti TB treatment in ITB patients.[7] Similarly, a negative IFN-γ assay result should not be used alone as a justification to deny or to discontinue anti TB therapy.[7] Both aspects point out the limitations in these assays and should be a cautionary note prior to interpreting their results out of context.

Although there were differences reported in this study between groups with regard to findings on imaging, yet it was not clear whether all patients underwent imaging procedures, and if so, what procedures were specifically performed? A study by Park *et al*. from Korea demonstrated that a computed tomographic enterography showing a comb sign was highly suggestive of CD with a sensitivity of 74.1% and a specificity of 90.9% when compared with ITB.[8] A second group from China reported even higher accuracies for the findings of computed tomographic enterography in differentiating ITB from CD.[5] The same sign was also more frequently found in ITB when compared with PIL (63% vs. 11%; $P < 0.01$).[6] It is thus prudent to say that with such advances

in imaging we would probably get better at detecting subtle differences between these diseases, especially with the dissemination of computed tomographic enterography and the more recent use of magnetic resonance enterography.[9]

Histological examination of lesions sampled could yield the presence of granulomas, which on their own without further description would not aid the clinician.[10] In this study, none of the cases with PIL had granulomas but their presence, although infrequent, has been described in patients with PIL in at least one other study.[6] A key feature from this study as well as others is that the presence of granulomas with caseous necrosis almost only occurs in patients with ITB. A more recent marker that has been used histologically to differentiate ITB from CD granulomas, is the presence of mesenchymal cells bearing CD73 surface marker at the periphery of ITB granulomas.[4] *In situ* polymerase chain reaction (PCR) for ITB, although somewhat specific, still needs improvement in its sensitivity[10-12] prior to its widespread implementation.

It is prudent to point out the importance of communication with the pathologist at one's own institution prior to obtaining samples in such patients, as it would be worthwhile to obtain material for Ziehl-Neelsen stain, culture and sensitivity, PCR, and flow cytometry when lymphoma is suspected.

One of the strengths of the study by Liu *et al*.[2] is their use of clear definitions for each disease, which evades the issue of misclassification bias. But at the same time the method used for statistical analysis—hypothesis testing—detects differences between groups but does not quantify these differences, thus limiting its interpretation.

Where do we go from here? Well, the quote by Sir William Osler "Medicine is a science of uncertainty and an art of probability" fits this subject quite well. There remains to be identified a definitive single method in distinguishing these entities apart, but the art of medicine and the pre-test probability aided with the positive and negative likelihood ratios of clinical, laboratory, radiological, as well as endoscopic features should aid the clinician when faced with a patient with such a presentation. Finally, it would be wise to keep revisiting the possibility of a misclassification of the disease and reviewing the evidence available as time evolves.

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