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Fecal Calprotectin as a Surrogate Marker for Mucosal Healing After Initiating the Therapeutic Anti-Tubercular Trial

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See "Value of Fecal Calprotectin Measurement During the Initial Period of Therapeutic Anti-Tubercular Trial" by Hyeong Ho Jo, Eun Young Kim, Jin Tae Jung, et al., on page 256-262. **Clin Endosc 2022;55:210-212**

Intestinal tuberculosis (ITB) and Crohn's disease (CD) are chronic granulomatous inflammatory diseases with similar presentations. According to expert recommendation, ITB should be excluded before CD diagnosis is made.[1] However, there is no single standard test for CD diagnosis. Approximately one-third of patients with negative ITB tests, including polymerase chain reaction for *Mycobacterium tuberculosis* using colon tissue biopsy specimens.[2] As a result, differentiating between the two diseases is challenging, especially in Asia where tuberculosis (TB) is prevalent. A physician must integrate clinical presentation, laboratory, endoscopy, radiology, and histology findings to make a probable diagnosis.

Diarrhea, abdominal pain, and weight loss are common in both conditions. Perianal involvement is often observed in patients with CD, while pulmonary involvement is usually observed in patients with ITB.[3] Erythrocyte sedimentation rate and C-reactive protein, hemoglobin, and albumin levels are not significantly different between ITB and CD.[4] Using serology, the tuberculosis interferon-gamma release assay (TB-IGRA) has a pooled sensitivity of 82–84% and a specificity of 86% for differentiating ITB from CD.[4,5] However, TB-IGRA positivity represents latent or active ITB. A high TB-IGRA level may help discriminate between ITB and CD.[6] A small study by Zhao Y et al.[6] reported a TB-IGRA cutoff value of ≥100 pg/ml for ITB diagnosis, with a sensitivity of 88% and a specificity of 74%. Patients with CD and a history of TB infection may show false-positive TB-IGRA results.

Ileocolonoscopic findings have shown that the ileum and cecum are the most commonly affected locations in both diseases.[4] Rectal, sigmoid, and multiple colonic involvements (≥4 segments) are more likely to be present in patients with CD than in those with ITB. A circular ulcer is significantly suggestive of ITB, while a longitudinal ulcer is suggestive of CD. An aphthous ulcer and pseudopolyps cannot be used to distinguish between the two diseases.[4] Regarding cross-sectional imaging findings, computed tomography enterography or magnetic resonance enterography shows comb, target, and adipose creeping signs that significantly favor CD. Concurrently, necrotic intra-abdominal lymph nodes greatly support ITB diagnosis. Regarding histopathological findings, patients with ITB are twice more likely to have granuloma than those with CD.[4] Some granuloma characteristics such as confluent, giant, and multiple granulomas significantly favor ITB.

Many diagnostic models have been proposed to combine all crucial factors differentiating between the two intestinal diseases.[7] A scoring system with more parameters available has a better than that with less parameters.[7] A multicenter retrospective study conducted in Asia validated various models for distinguishing between ITB and CD and showed that the

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clinical–endoscopy–pathology model was the best for ITB diagnosis, with a sensitivity of 90.9% and a specificity of 92.6%.[8] A recent study conducted in China developed a new algorithm comprising clinical, TB-IGRA, endoscopy, and radiology parameters and reported a sensitivity and specificity of 90.9% and 86.3%, respectively, for ITB diagnosis.[3]

Although these models help physicians make decisions with greater confidence in cases of diagnostic uncertainty, their application in clinical practice is limited due to the high rate of misdiagnosis between ITB and CD.[8] The most important factor for the definitive diagnosis of ITB and CD is treatment response. In this scenario, misdiagnosis of ITB as CD can result in harmful treatment with corticosteroids, immunomodulators, and anti-tumor necrosis factor agents in patients with ITB, leading to disseminated TB. In light of this risk, patients with uncertain differential diagnoses should receive a therapeutic anti-tubercular trial (TATT) according to the Asian Organization for Crohn's and Colitis and the Asia Pacific Association of Gastroenterology practice recommendations for managing inflammatory bowel disease (IBD).[1] In contrast, misdiagnosis of CD as ITB can also result in delayed treatment of CD for at least 2–6 months, risking structural bowel damage with stricturing, which may require bowel resection. There are still unmet needs for the two decision dilemmas.

The treat-to-target approach for managing IBD, which aims to achieve disease remission by regular monitoring and adjusting therapy according to treatment response targets, can be adopted. In clinical practice, patients with ITB show a clinical and endoscopic response after 8–12 weeks of TATT; however, treatment targets that are not achieved after a therapeutic trial of 12 weeks may indicate CD diagnosis. The initial treatment of ITB continues to resolve the target symptoms. Therefore, mucosal healing is recognized as a fundamental target of ITB therapy. Moreover, a non-invasive biomarker of fecal calprotectin (FC) helps monitor colonic inflammation. Therefore, the use of FC as a surrogate marker for endoscopic healing during anti-TB therapy trials is promising.

In the current issue of *Clinical Endoscopy*, Jo et al.[9] reported a retrospective review of the changing pattern of serial FC levels during the TATT in patients with possible ITB. In total, 33 patients were considered to have complete endoscopic healing after 2 months of the TATT. Among them, 30 patients were finally diagnosed with ITB, two patients were diagnosed with CD, and one patient was diagnosed with Bechet's disease. At baseline, the mean FC level was 170.2 μg/g (range, 11.5–646.5 μg/g). After initiating the TATT for 1 month and 2 months, the mean FC level significantly declined to 25.4 μg/g (range, 11.5–75.3 μg/g) and 23.3 μg/g (range, 11.5–172.2 μg/g), respectively. Three patients with non-ITB diagnosis showed no significant changes in FC levels at 1 month and 2 months after the TATT. In addition, the FC level in all patients with ITB was <100 μg/g at the 1-month follow-up. The authors concluded that the decreasing FC levels after only 1 month of the TATT were correlated with complete mucosal healing on the follow-up colonoscopy after 2 months of the TATT.[9] The findings of this study were consistent with those of a recent study by Sharma et al., which showed a statistically significant decrease in the FC level at 2 months and 6 months after the TATT in patients with ITB compared to that in patients without ITB.[10]

According to Jo et al.,[9] the usefulness of monitoring FC in assessing TATT response at 1 month in patients with suspected ITB is convincing. However, their study was limited by a small sample size and retrospective design, leading to selection bias. Further prospective studies in different regions are warranted to support FC as a surrogate marker for TATT response and determine the cutoff value for mucosal healing in patients with suspected ITB.

Conflicts of Interest

The author has no potential conflicts of interest.

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