

Immune-mediated diarrhea with normal investigations: future directions

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We appreciate the discussion raised by Nicolaidis *et al* [1], regarding our study on suspected immune-mediated diarrhea and colitis (IMDC) without evidence of inflammation [2]. We acknowledge the limitations inherent to our study's retrospective design and welcome the opportunity to clarify these issues.

The incidence of immune checkpoint inhibitor (ICI) enteritis is estimated at 0.1-0.5% [3] making it rare. Our study relied on colonoscopic evaluation with terminal ileal biopsy and fecal calprotectin (FC) to assess inflammation. FC has a high sensitivity and specificity for detecting endoscopic inflammation [4], including small bowel lesions [5]. It is therefore unlikely that a significant number of patients would have ICI-enteritis. Current guidelines do recommend esophagogastroduodenoscopy in cases with negative colonoscopy if there is clinical suspicion however [6].

One of the main limitations of our study was the inconsistency in the testing of included patients. Ideally, our sample would have both baseline and follow-up biomarker and endoscopic data to evaluate for inflammation. In clinical practice, this is difficult to achieve. For this reason, we grouped patients based on the information available.

The role of imaging in IMDC is currently limited; abdominal computed tomography has low sensitivity and negative predictive value for diagnosing IMDC [7]. Intestinal ultrasound (IUS) is a cost-effective alternative that is seeing increasing use in inflammatory bowel disease [8]. Only 3 studies have reported its use in IMDC, proving it effective at assessing endoscopic inflammation and therapeutic response [9-11]. More evidence supporting its use is needed before it can be incorporated into future guidelines.

To conclude, further studies will be important to determine the need for systemic immunosuppression and biologic agents for this disease. IUS is a readily available tool with a potential role in evaluating IMDC. However, more data on its use will be needed before recommendations can be made regarding its applications.

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