

Immune-mediated diarrhea with normal investigations: the importance of diagnostic stratification and small-bowel assessment

Steven Nicolaidēs^{a,b,c}, Zaid Ardalan^{b,c},
Alex Boussioutas^{b,c,d}

Western Health; The Alfred; Monash University;
University of Melbourne; Melbourne, Australia

We read with great interest the study by Shatila *et al*, describing immune-mediated diarrhea and colitis (IMDC) in patients with undetectable biochemical, endoscopic and histologic findings [1]. Recognition of this clinically important subgroup is highly relevant to current practice; however, several methodological considerations warrant discussion, as they materially influence interpretation of the reported outcomes.

First, incomplete exclusion of alternative immune-mediated enteropathies should be considered. Although autoimmune causes such as pancreatitis and thyroiditis were excluded by chart review, immune-mediated celiac disease is not specifically addressed. Celiac disease may present with diarrhea that mimics IMDC in patients receiving immune checkpoint inhibitors [2]. While such cases would often declare themselves clinically if untreated, targeted serologic testing and, where appropriate, small-bowel histologic assessment are particularly relevant in refractory or atypical presentations.

Second, the absence of stratification by diagnostic modality limits interpretation of the outcome signal. The “normal objective findings” cohort (n=131) pooled patients with normal endoscopy and histology together with those classified solely on the basis of a normal fecal calprotectin (n=72, 55%). These groups are biologically distinct. Patients with normal endoscopy and histology represent the clearest non-inflammatory phenotype, whereas those assessed by calprotectin alone may include early inflammatory IMDC, patchy disease, or microscopic colitis. Without stratified analyses, it is difficult to determine whether the favorable clinical course reflects a truly non-inflammatory entity, or dilution by less well-characterized disease.

Third, systematic small-bowel assessment was not performed, despite substantial treatment escalation; 23.7% of the cohort required selective immunosuppressive therapy. Small-bowel involvement, which is more likely to be steroid-refractory and require biologic escalation, was not excluded using cross-sectional or capsule-based imaging. Even a modest

proportion of unrecognized enteritis could meaningfully affect escalation rates and perceived response.

Intestinal ultrasound (IUS) could address several of these limitations. IUS offers a noninvasive, point-of-care method to assess colonic and small-bowel inflammation, including bowel-wall thickness and vascularity, and has shown utility in immune-mediated gastrointestinal toxicity [3]. Incorporating IUS into evaluation pathways for patients with suspected IMDC and normal initial investigations may better distinguish truly non-inflammatory phenotypes from occult disease, and guide decisions regarding steroid tapering versus escalation.

These considerations do not diminish the importance of recognizing IMDC with normal investigations but temper conclusions regarding disease biology and treatment responsiveness. Stratification by diagnostic certainty and systematic small-bowel assessment would strengthen future studies and clarify whether this represents a distinct non-inflammatory toxicity phenotype.

References

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^aDepartment of Gastroenterology, Western Health (Steven Nicolaidēs);

^bDepartment of Gastroenterology, The Alfred (Steven Nicolaidēs, Zaid Ardalan, Alex Boussioutas); ^cDepartment of Medicine, School of Translational Medicine, Monash University (Steven Nicolaidēs, Zaid Ardalan, Alex Boussioutas); ^dDepartment of Medicine, Royal Melbourne Hospital, University of Melbourne (Alex Boussioutas), Melbourne, Australia

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Correspondence to: Dr. Steven Nicolaidēs, Monash University, School of Translational Medicine, 99 Commercial Road, Melbourne, 3004, Australia, e-mail: steven.nicolaidēs1@monash.edu

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