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Letter to the Editor

Letter to the Editor: Celiac Disease Diagnosis Pitfalls — Pediatric Pathways, Refractory Stratification, and Seronegative EATL Risk

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Dear Editors,

Diagnostic pitfalls in celiac disease (CD) extend beyond serologic variability and histologic heterogeneity in adults: clinically significant gaps remain in pediatric recognition, refractory disease stratification, and the detection of seronegative enteropathy-associated T-cell lymphoma (EATL). We read with interest the review by Majmudar *et al*.,[1] and we present complementary observations that extend their proposed framework across age groups and malignancy-risk phenotypes, focusing on three aspects that merit closer integration: the distinct diagnostic dynamics of pediatric CD, the biological and prognostic divergence of refractory celiac disease (RCD) subtypes, and the life-threatening but underrecognized phenotype of seronegative EATL.

First, pediatric CD exhibits diagnostic dynamics that differ substantially from those in adults, justifying age-stratified clinical pathways rather than a uniform framework. Children account for nearly one-third of global CD diagnoses and frequently present with transient seronegativity in early childhood (<5 years) and non-classical manifestations such as growth impairment or dental enamel defects.[2,3] These features reflect the developmental immaturity of the immune system rather than a fundamentally different disease entity, yet they carry distinct diagnostic implications: false-negative serology is more common, and serologic thresholds validated in adults cannot be directly transposed to pediatric practice.[3,4] Recent ESPGHAN updates document progression from potential to overt CD exceeding 45% at five years in children—substantially faster than adult trajectories—underscoring the need for active surveillance rather than watchful waiting.[5] Although ESPGHAN no-biopsy criteria have transformed the management of children with CD, their application remains conditional on strict threshold adherence (tissue transglutaminase immunoglobulin A (IgA) ≥10× ULN with endomysial antibodies positivity), and even within pediatric practice, concomitant infections and IgA deficiency constitute important sources of diagnostic error requiring systematic exclusion.[4,5] Furthermore, population-specific studies confirm that genetic susceptibility patterns (i.e., HLA-DQ2/DQ8) are globally conserved while phenotypic expression remains heterogeneous—reinforcing the need for context-adapted diagnostic awareness.[6]

Second, RCD represents a critical area where the proposed diagnostic framework could be further refined through explicit RCD subtype stratification: negative serology—observed in the majority of patients following gluten withdrawal—cannot exclude persistent immune-mediated enteropathy, and we build on this by emphasizing that failing to distinguish RCD-I from RCD-II has direct prognostic and therapeutic consequences. Specifically, RCD-II, defined by aberrant clonal intraepithelial lymphocytes (IELs) with a $CD3^{+}CD8^{-}$ phenotype (>30%) and interleukin-15–driven activation, carries an approximately 50% cumulative risk of progression to EATL within five years and substantially poorer survival compared to RCD-I.[7] IEL flow cytometry and T-cell receptor γ clonality analysis are therefore not merely confirmatory tools but essential components of the diagnostic workup in any patient with persistent villous atrophy on a strict gluten-free diet.[7,8] Thus, we propose that future iterations of the diagnostic framework include an explicit branching point at the diagnosis of RCD, prompting immunophenotypic subtyping as a mandatory rather than optional step (Fig. 1).[5,7] While seronegative CD is widely acknowledged as a diagnostic challenge, the specific danger of seronegative presentation in malignant enteropathy has received less systematic attention: up to 15% of RCD cases show negative tissue transglutaminase IgA and endomysial antibodies despite florid villous atrophy, creating false reassurance and delaying lymphoma diagnosis—with a reported median diagnostic delay of 12 months.[8,9] In clinical terms, a diagnosis of EATL, which carries a less than 20% five-year survival rate, may be postponed precisely because normal serology is misinterpreted as excluding severe pathology.[10] Although the strength of this alarm signal rests largely on tertiary-center case series rather than population-based epidemiological data, and future registry studies are needed to establish population-level estimates, the clinical consequence of diagnostic delay—transition from potentially treatable to advanced metastatic lymphoma—justifies heightened vigilance. We therefore propose that persistent malabsorption with normal serology should trigger early

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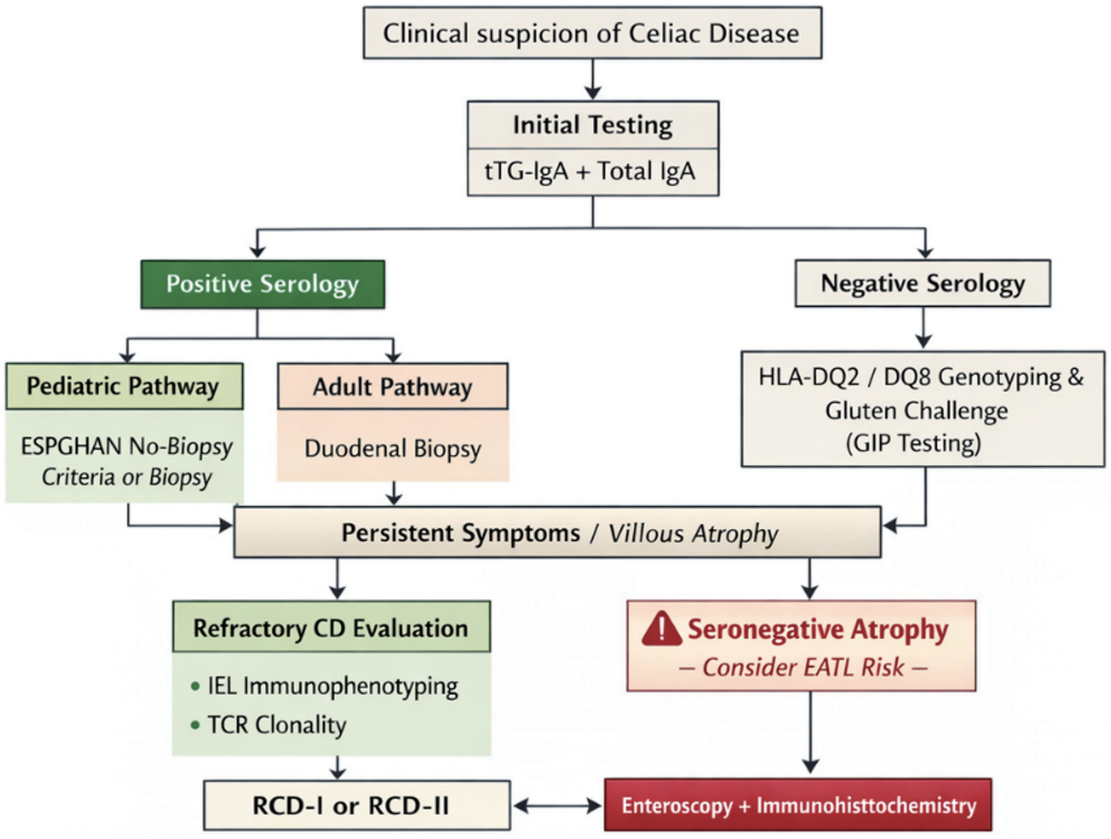

Fig. 1. Age-stratified CD diagnostic algorithm with EATL warning signal. Adapted from Mearin *et al*.[5] and van Gils *et al*.[7] CD, celiac disease; HLA-DQ2, human leukocyte antigen DQ2 haplotype; EATL, enteropathy-associated T-cell lymphoma; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; GIP, gluten immunogenic peptides; IEL, intraepithelial lymphocytes; IgA, immunoglobulin A; RCD-I, refractory celiac disease type I; RCD-II, refractory celiac disease type II; tTG-IgA, tissue transglutaminase IgA; TCR, T-cell receptor.

enteroscopic reassessment with IEL immunophenotyping, positron emission tomography–computed tomography staging, and biopsy, rather than clinical reassurance alone.[1,8,9]

Finally, objective monitoring of dietary gluten exposure using gluten immunogenic peptides (GIP) represents a translational advance with direct relevance to the scenarios above. Among apparently adherent patients, inadvertent gluten exposure rates detected by urinary or fecal GIP range from 25% to 97%, explaining a substantial proportion of apparently non-responsive CD.[11] GIP assays are particularly valuable in patients with seronegative or refractory disease, where conventional serology is uninformative, providing objective evidence of ongoing exposure before attributing mucosal injury to immune-mediated mechanisms. Incorporation of GIP monitoring into follow-up algorithms for non-responsive and RCD may help clinicians distinguish persistent exposure from true refractory disease—a distinction with major therapeutic implications. These additional diagnostic pitfalls are summarized in Table 1.[3,6–9,11]

In summary, we propose that integrating age-stratified pediatric pathways, mandatory RCD immunophenotypic subtyping, and a heightened index of suspicion for seronegative EATL would sub-

Table 1. Additional diagnostic pitfalls in celiac disease

Pitfall	Prevalence/Context	Prognostic impact	Actionable test(s)	Ref.
Pediatric seronegativity	5–10% in children <5 years; concurrent infections	Growth failure, developmental delay	HLA-DQ2/8 typing + serial tTG-IgA; IgA quantification	3,6
RCD-II misclassification	20–30% of refractory CD cases	Approximately 50% 5-year EATL risk; poor survival	IEL flow cytometry (CD3+CD8− >30%), TCRγ clonality	7,8
Seronegative EATL	4–15% of RCD cases (tertiary-center series)	<20% 5-year survival; median 12-month diagnostic delay	PET-CT, double-balloon enteroscopy, IEL immunophenotyping	8,9
Covert gluten exposure	25–97% of apparently adherent patients	Persistent villous atrophy; mimics RCD	Urine/stool gluten immunogenic peptides (GIP)	11

CD, celiac disease; EATL, enteropathy-associated T-cell lymphoma; HLA, human leukocyte antigen; IEL, intraepithelial lymphocytes; PET-CT, positron emission tomography–computed tomography; RCD, refractory celiac disease; TCR, T-cell receptor; tTG-IgA, tissue transglutaminase IgA.

stantively extend the diagnostic framework proposed by Majmudar *et al*.[1] The addition of GIP-based monitoring further addresses a practical gap in non-responsive disease surveillance. We believe such observations contribute constructively to ongoing refinements of CD diagnostic strategies.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Contributed to study concept and design (HR), data acquisition (HR), data analysis (HR), drafting of the manuscript (HR), critical revision of the manuscript (HR and NB), and supervision (NB). Both authors have made significant contributions to this study and have approved the final manuscript.

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