Persistent Celiac Symptoms: What to Suspect Beyond Gluten Exposure

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Patients with celiac disease (CD) who adhere strictly to a gluten-free diet (GFD) expect symptom resolution. But for a subset, debilitating gastrointestinal symptoms persist, raising immediate questions about compliance, diagnosis, and the potential for more serious underlying pathology. This clinical conundrum demands a systematic diagnostic approach, moving beyond simple dietary adherence checks to identify refractory celiac disease (RCD) or other complications.1

KEY TAKEAWAYS

- The Pivot: Serum chromogranin A (CgA) and β2-microglobulin levels can accurately identify patients with refractory celiac disease.
- The Data: CgA at 90.2 ng/mL (sensitivity 83%, specificity 100%) and β2-microglobulin at 696 mcg/L (sensitivity 100%, specificity 100%) differentiate RCD from uncomplicated CD.
- The Action: Clinicians should consider these serological markers as a screening tool for RCD, guiding decisions for further endoscopic evaluation in patients with persistent symptoms on a GFD.

The persistence or recurrence of symptoms in patients diagnosed with celiac disease, despite rigorous adherence to a gluten-free diet, presents a significant diagnostic challenge. This scenario, often termed 'non-responsive celiac disease,' requires a thorough differential diagnosis to exclude continued gluten exposure, alternative diagnoses, or the development of complications such as refractory celiac disease (RCD). RCD, a rare but severe complication, carries a substantial risk of progression to enteropathy-associated T-cell lymphoma (EATL), particularly RCD type II.1

A study published in Cancers (Basel) investigated the utility of serum markers in predicting refractoriness in CD patients. The study included 72 patients followed at a single center, comprising 49 with uncomplicated CD (before and after GFD) and 23 with RCD. Investigators measured serum levels of chromogranin A (CgA) and β2-microglobulin at baseline and at a median follow-up of 13 months in both groups.1

Identifying Refractory Celiac Disease

Refractory celiac disease is defined by persistent villous atrophy and symptoms despite strict GFD for at least 6 to 12 months, in the absence of other causes. It is classified into two types: RCD type I, characterized by a normal intraepithelial lymphocyte (IEL) phenotype, and RCD type II, which involves an aberrant IEL population with clonal T-cell receptor rearrangements. The distinction is critical because RCD type II carries a much higher risk of progression to EATL, a highly aggressive lymphoma.1

The current diagnostic pathway for RCD typically involves repeated endoscopic biopsies and immunohistochemical

staining to characterize the IELs. This process is invasive, costly, and often delayed due to the need for specialist centers. A non-invasive screening tool could significantly streamline this work-up, allowing for earlier identification and management of RCD.1

The Diagnostic Utility of Serum Markers

The Cancers (Basel) study found that serum levels of CgA and β2-microglobulin were significantly higher in patients with RCD compared to those with uncomplicated CD ($p < 0.001$), both at baseline and at follow-up. The investigators observed no significant difference in marker levels between RCD type I and RCD type II, indicating their utility as general markers for refractoriness rather than for subtyping.1

The estimated cut-off point for CgA was 90.2 ng/mL, demonstrating a sensitivity of 83% and a specificity of 100% for differentiating RCD from uncomplicated CD. For β2-microglobulin, the estimated cut-off was 696 mcg/L, achieving a sensitivity of 100% and a specificity of 100%. These high specificity values suggest that elevated levels of these markers are highly indicative of RCD, reducing the likelihood of false positives.1

CgA is a neuroendocrine tumor marker, and its elevation in RCD patients may reflect increased neuroendocrine cell activity or damage in the inflamed small intestine. β2-microglobulin, a component of MHC class I molecules, is shed from cell surfaces and its elevated levels often indicate increased cell turnover or immune activation. Both mechanisms are plausible in the context of chronic intestinal inflammation and aberrant lymphocyte populations seen in RCD.1

Beyond Refractory Celiac Disease

But RCD is not the only explanation for persistent symptoms. Clinicians must systematically rule out other conditions. The initial step always involves a meticulous review of dietary adherence. Many patients inadvertently consume gluten through cross-contamination or hidden ingredients. A dietitian specializing in celiac disease can be invaluable here.1

Other conditions that mimic celiac symptoms include irritable bowel syndrome (IBS), microscopic colitis, small intestinal bacterial overgrowth (SIBO), and pancreatic exocrine insufficiency. Each of these requires specific diagnostic tests. For instance, hydrogen breath tests for SIBO or fecal elastase for pancreatic insufficiency.1

The presence of aberrant intraepithelial lymphocytes (IELs) is a hallmark of RCD type II. A study in the Journal of Immunology explored the mechanism of epithelial cell-specific cytotoxicity mediated by these aberrant IEL lines from RCD type II patients. They found that DNAM-1 (CD226) plays a significant role in this cytotoxicity, which contributes to the aggressive nature of RCD type II and its potential for severe mucosal damage.2

The aberrant IELs in RCD type II are characterized by a loss of surface CD3 and CD8 expression, and frequently express natural killer (NK) cell markers. These cells exhibit cytotoxic activity against epithelial cells, contributing to the persistent villous atrophy and inflammation. Understanding these cellular mechanisms helps explain why RCD type II is so resistant to standard treatments and carries a higher risk of malignancy.2

Rare Complications and Associated Conditions

In rare instances, persistent symptoms can signal severe complications. One such complication is cavitating mesenteric lymph node syndrome (CMLNS), a rare but serious condition associated with RCD. A case report in Z Gastroenterol described CMLNS as a complication of RCD. This syndrome involves cystic degeneration of mesenteric lymph nodes, leading to abdominal pain, malabsorption, and ascites.3

CMLNS is thought to be a consequence of chronic lymphatic obstruction and inflammation in the context of severe enteropathy. Its diagnosis often requires imaging studies, such as CT or MRI, and sometimes lymph node biopsy. Recognition of such rare complications is vital for clinicians managing complex CD cases.3

Other associated conditions can also complicate the clinical picture. These include autoimmune diseases (e.g., type 1 diabetes, autoimmune thyroid disease), lactose intolerance, and functional gastrointestinal disorders. The overlap with other inflammatory conditions can make diagnosis challenging, requiring a broad differential. Clinicians should consider these possibilities when initial investigations for RCD are negative.1

The Role of Endoscopy and Biopsy

While serum markers offer a valuable screening tool, upper gastrointestinal endoscopy with small bowel biopsies remains the gold standard for diagnosing RCD. Biopsies allow for histological assessment of villous atrophy and, importantly, immunohistochemical analysis of IELs to differentiate between RCD type I and RCD type II. This distinction guides prognosis and treatment decisions.1

The study's findings suggest that CgA and β2-microglobulin could serve as gatekeepers, identifying patients who truly require invasive endoscopic procedures. This could reduce unnecessary endoscopies in patients whose symptoms are due to other, less severe causes. The high specificity of these markers means that a positive result strongly points towards RCD, warranting further investigation.1

Limitations and Future Directions

The study's relatively small sample size, particularly for the RCD group (N=23), is an obvious caveat. Larger, multicenter studies are necessary to validate these cut-off points in diverse patient populations. The single-center nature of the study also limits the generalizability of the findings.1

The trial was not powered to detect differences in outcomes based on RCD subtypes, and that gap matters for clinical decision-making. While the markers differentiated RCD from uncomplicated CD, they did not distinguish between RCD type I and type II. This distinction is critical for risk stratification and therapeutic planning, especially given the EATL risk associated with RCD type II. Future research should focus on identifying markers that can reliably differentiate between these subtypes.1

The long-term prognostic value of these markers also remains to be fully elucidated. Do persistently elevated levels predict progression to EATL, or merely ongoing inflammation? This question requires longitudinal studies with extended follow-up periods. The Oxford Handbook of Gastroenterology & Hepatology provides further guidance on the management of complex GI conditions.

The utility of these markers in monitoring treatment response for RCD also warrants investigation. Can a decline in CgA or β2-microglobulin levels indicate successful therapeutic intervention, or predict mucosal healing? Such data would enhance their clinical applicability beyond initial diagnosis.1

The study did not explore the cost-effectiveness of incorporating these markers into routine clinical practice. While endoscopy is expensive, the cost of serial marker measurements and their impact on patient outcomes needs a formal economic analysis. This is particularly relevant in healthcare systems with constrained resources.1

The study also did not address the potential for false positives in conditions other than RCD that might elevate CgA or β2-microglobulin, such as renal impairment or other neuroendocrine tumors. A comprehensive diagnostic

algorithm would need to account for these confounding factors.1

The next trial needs to show how these markers perform in a real-world, heterogeneous patient population, accounting for various comorbidities and medication use. This would provide a more robust assessment of their clinical utility and help refine diagnostic algorithms for non-responsive celiac disease.1

CLINICAL IMPLICATIONS

The identification of reliable serological markers for refractory celiac disease is a practical step forward for gastroenterologists. Relying solely on repeated biopsies for every patient with persistent symptoms is inefficient and invasive, delaying definitive diagnosis and appropriate management. These markers offer a much-needed screening tool.

Clinicians can now consider CgA and β2-microglobulin as part of their initial work-up for non-responsive celiac disease. A positive result should prompt immediate referral for endoscopy and detailed histological assessment, streamlining the diagnostic pathway. This approach saves patient discomfort and healthcare resources.

But the markers do not differentiate between RCD type I and type II, a distinction critical for prognosis and treatment, especially given the EATL risk in type II. This means endoscopy and IEL phenotyping remain indispensable for definitive subtyping. The markers serve as a filter, not a replacement for biopsy.

For patients, earlier identification of RCD means potentially faster access to specialized treatments and closer monitoring for complications like EATL. This could significantly improve long-term outcomes, moving beyond the frustrating cycle of dietary compliance checks and symptomatic management.

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