EJCRIM
European Journal of Case Reports in Internal Medicine

CELIAC DISEASE AS A GASTROINTESTINAL MANIFESTATION IN A PATIENT WITH *CARMIL2* DEFICIENCY: REPORT AND REVIEW OF CURRENT LITERATURE

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Received: 24/07/2026
Accepted: 31/07/2026
Published: 04/09/2026

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent for participation and publication of clinical information and medical figures was acquired from the patient and his legal guardian and representative (his brother). Ethical approval was issued by the King Saud University Institutional Review Board on 05 November 2025 (Approval Reference: 25/0821/IRB).
Acknowledgements: The authors would like to sincerely thank Professor Maha Arafah from the Pathology Department for providing us with the histopathological figures, and to Dr. Ibraheem AlDeeri for his efforts and guidance throughout the writing of this manuscript.
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How to cite this article: AlHawamedeh AT, AlSunbul NF, Mubarak MF. Celiac disease as a gastrointestinal manifestation in a patient with CARMIL2 deficiency: report and review of current literature. EJCRIM 2026;13:doi:10.12890/2026_007371

ABSTRACT

CARMIL2 deficiency is a rarely occurring, autosomal recessive immunodeficiency disease, manifested as an impairment in CD28-mediated T-cell costimulation, actin cytoskeleton dysregulation and a broad immunological disturbance across T, B and NK cell lineages.

It has been strongly associated with an early onset of inflammatory bowel disease-like enteropathies, recurrent infections, dermatitis and eczema. While gastrointestinal involvement is well documented, celiac disease has not yet been reported in this context.

We present a case of a 23-year-old Saudi male with genetically confirmed *CARMIL2* deficiency who developed true celiac disease demonstrated through a comprehensive gastrointestinal evaluation, with an extensive diagnostic workup that included upper endoscopy with duodenal biopsies, histopathological examination and celiac serologies (tTG IgA, tTG IgG and DGP IgA/IgG).

KEYWORDS

Celiac disease, *CARMIL2* deficiency, Marsh score, autosomal recessive immunodeficiency

LEARNING POINTS

- Monogenic inflammatory bowel diseases have been extensively documented in association with diverse primary immunodeficiencies, but celiac disease has rarely been described in this context.
- This is a novel case of a young adult with a confirmed *CARMIL2* deficiency diagnosis who developed true celiac disease established by serology, duodenal biopsy and a response to a gluten-free diet.

EFIM
European Federation of Internal Medicine

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INTRODUCTION

CARMIL2 – capping protein regulator and myosin 1 linker 2 – deficiency is a rare autosomal recessive immunodeficiency, leading to an impairment in T-cell costimulation by CD28, actin cytoskeleton dysregulation and a broad immune dysregulation across T, B and NK cell lineages[1,2]. The protein encoded by *CARMIL2* has a key role in cytoskeletal remodelling, NF-κB signalling and the development of regulatory T cells (Tregs), placing it as a major node in both mucosal and systemic immune homeostasis[1,3,4].

Individuals with *CARMIL2* deficiency usually present early in life with symptoms such as recurrent infections, dermatitis, chronic eczema, viral warts, mucocutaneous candidiasis and gastrointestinal manifestations that range in severity[1,4-6].

Gastrointestinal manifestations of people with *CARMIL2* mutation are increasingly recognised. Recent case series have revealed that very early-onset inflammatory bowel disease, eosinophilic enterocolitis or chronic enteropathy occurred in patients affected[2,5,7]. Histologically, other findings may mimic Crohn's disease or ulcerative colitis, often characterised by lymphoplasmacytic infiltration and crypt architectural distortion[5,7,8]. Functional immunophenotyping of such patients shows a deficiency in FOXP3$^+$ Tregs and reduced CD45RO$^+$ memory T cells, correlating with impaired mucosal immune regulation and chronic gut inflammation[1,4,7].

In a multicentre cohort, Magg et al. described five patients from three unrelated families who developed IBD-like symptoms secondary to biallelic *CARMIL2* loss-of-function variants, all requiring immunosuppressive treatment and exhibiting poor response to traditional IBD therapy[2].

While monogenic IBDs have been extensively documented in association with diverse primary immunodeficiencies, celiac disease has rarely been described in this context. Celiac disease is an autoimmune enteropathy driven by gluten exposure in genetically susceptible individuals, characterised by both positive serological markers e.g. tTG IgA, and small intestinal mucosal damage, notably villous atrophy[9]. The clinical overlap between celiac disease and monogenic enteropathies such as persistent diarrhoea, malnutrition and villous flattening makes the diagnosis quite challenging in patients with primary immunodeficiencies[6,8]. Yet, to date there has been no definitive case illustrating a biopsy-proven celiac disease in a patient with genetically confirmed *CARMIL2* deficiency.

We present a novel case of a young adult with a confirmed *CARMIL2* deficiency diagnosis who developed a true celiac disease established by serology, duodenal biopsy and a response to a gluten-free diet.

CASE DESCRIPTION

A 23-year-old male first presented to our hospital at the age of 20, referred from another hospital as a case of progressive dysphagia due to severe reflux oesophagitis with distal oesophageal stricture. He was managed with the maximum proton pump inhibitor dose (esomeprazole 40 mg BID), needed for continuous serial endoscopic dilatations. Upon further investigations and examinations, pulmonology conditions were diagnosed to have recurrent sinopulmonary infections and bronchiectasis *(Fig. 1)*. Dermatologic manifestations were observed in the form of chronic eczema craquelé; a history of gastric outlet obstruction before being referred was reported in his transfer papers. Oesophagitis with ulceration and progressive stenosis, requiring periodic oesophageal dilatations, were also a finding *(Fig. 2)* in addition to a generalised lymphadenopathy with splenomegaly *(Fig. 3)* and a previously noted right atrial mass suspected to be a thrombus.

His condition was further complicated by a solitary functioning left kidney and persistent failure to thrive, and an inability to maintain growth, with multiple admissions due to malnutrition and micronutrient deficiencies since childhood.

Due to these conditions and the immunological state of the patient, a thorough molecular genetic testing was undertaken using a whole exome sequencing test, which demonstrated a homozygous frameshift indel in the

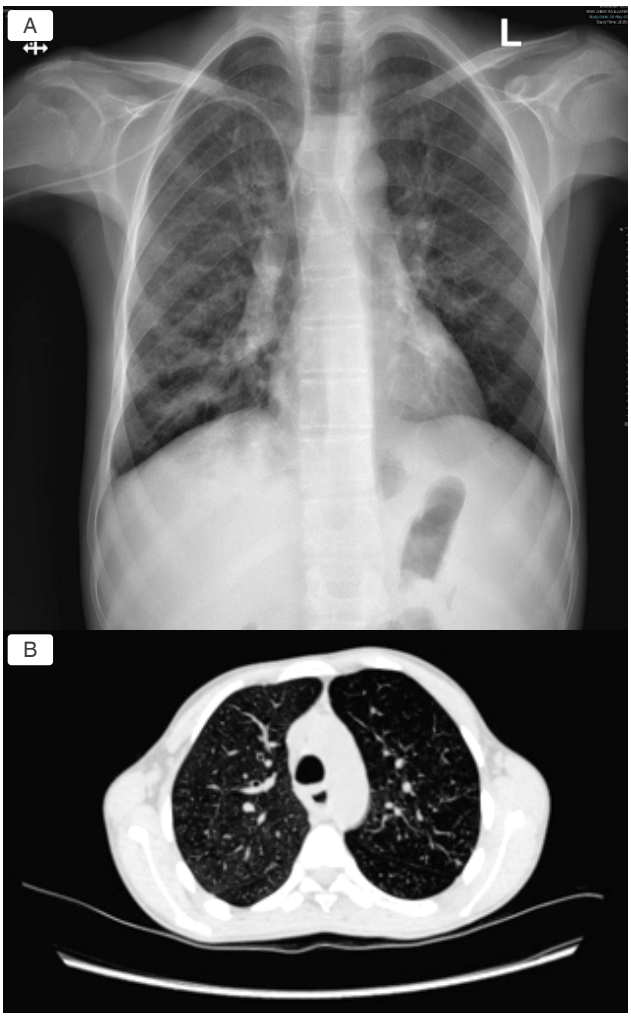


Figure 1. *A) Chest X-ray. B) CT scan showing chronic bronchiectasis.*

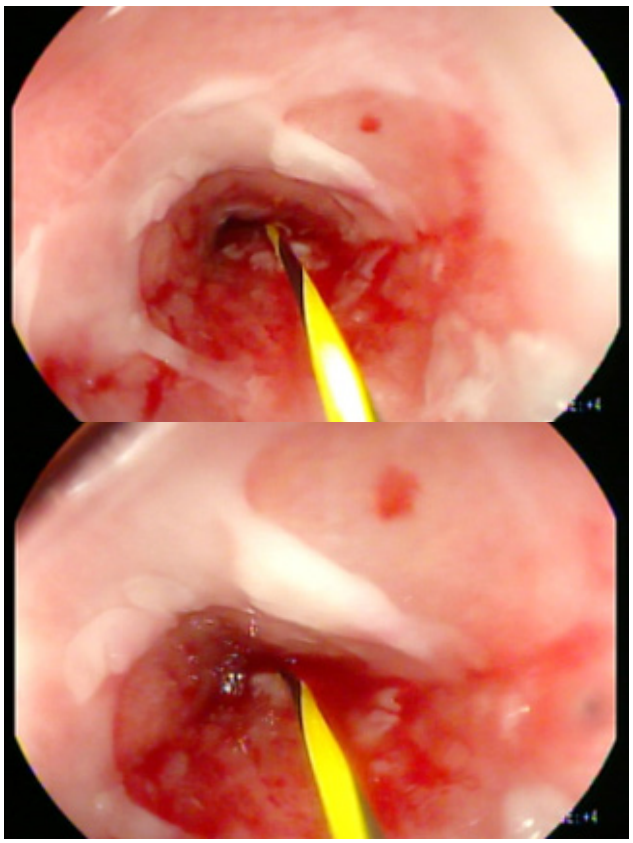


Figure 2. Distal oesophagus during one of the serial dilatations on the patient, showing reflux oesophagitis with ulceration and progressive luminal stenosis.



Figure 3. Noted splenomegaly in an abdominal CT scan.

CARMIL2 gene exhibiting *CARMIL2* deficiency, which explains most of the patient's clinical phenotype.

More recently, the patient had noted worsening gastrointestinal symptoms including abdominal discomfort, anaemia and episodes of rectal bleeding. Differential diagnoses were made for the patient for possible Crohn's disease and cytomegalovirus colitis. Colonoscopy was performed and histology was taken, which was negative for any IBD features; no viruses were detected, nor signs of malignancy.

A diagnostic endoscopy was undertaken *(Fig. 4)* that showed proximal small bowel villous atrophy and fissuring. A duodenal biopsy from D3 and D2 was taken, and the histopathological analysis displayed a partial villous atrophy and increased intraepithelial lymphocytosis representing type 3A on the Marsh score *(Fig. 5)*. These observations within the relevant clinical picture and serological profile align with celiac disease. There was no evidence of Helicobacter pylori, and no intestinal metaplasia or malignancy was detected. The duodenal specimens clearly showed mucosal changes typical of a gluten-sensitive intestinal change.

Laboratory testing also validated the diagnosis. The tTG IgG level was markedly elevated at 45.60 and 36.14 IU/ml on two separate occasions, along with mildly elevated anti-deamidated gliadin peptide (DGP IgA) at 4.16 and 5.89 and IgG at 1.12 and 0.96. While his tTG IgA remained within borderline ranges (0.84–1.02), the combination of biopsy findings and serology strongly confirmed the diagnosis of celiac disease. While gastrointestinal involvement has been previously noted, celiac-like enteropathy is rarely reported and remains underdiagnosed in many clinical settings.

The patient is currently managed with a gluten-free diet, proton pump inhibitors and supportive nutritional measures, and continues to receive a multidisciplinary follow-up in dermatology, immunology and gastroenterology services.

DISCUSSION

This case represents the first genetically confirmed *CARMIL2* deficiency patient, who developed true celiac disease, evidenced by a duodenal biopsy exhibiting partial villous atrophy, a positive anti-tTG IgG serology

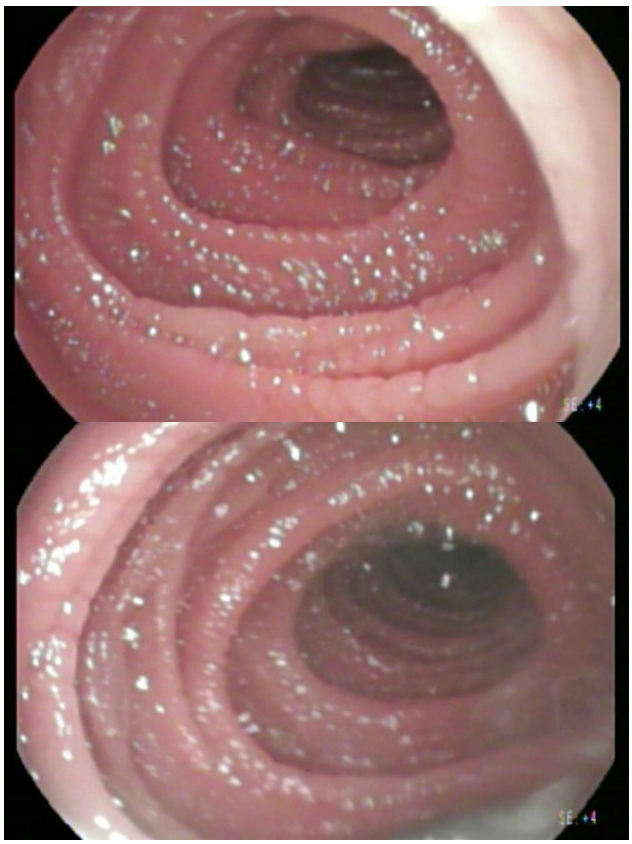


Figure 4. Diagnostic gastroduodenoscopy displays villus atrophy and fissuring.

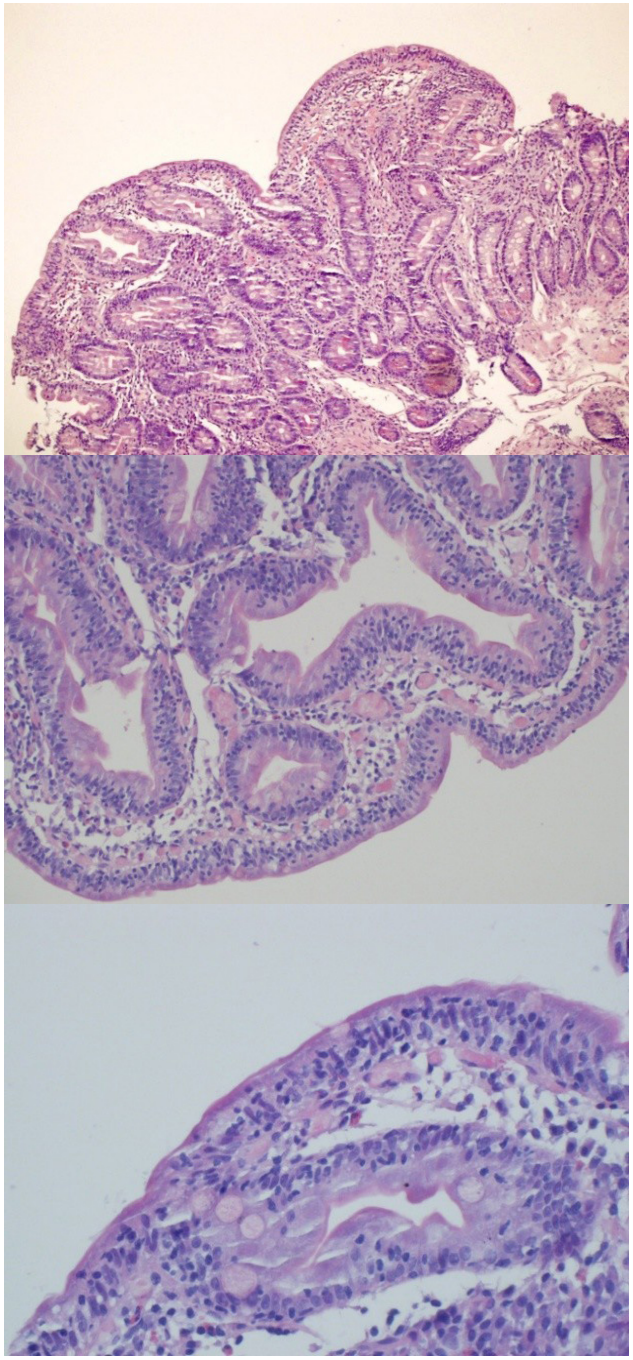


Figure 5. *Histopathological studies demonstrate a partial villous atrophy and increased intraepithelial lymphocytosis corresponding to 3A on the Marsh score.*

and a gluten-free diet clinical response. These findings expand the gastrointestinal phenotype associated with *CARMIL2* deficiency. In addition to celiac disease, the patient exhibited a range of clinical manifestations including chronic eczema, bronchiectasis and oesophageal strictures requiring serial dilatations, reflecting the multisystemic nature of this immunodeficiency[6,10].

Previous literature has consistently linked *CARMIL2* mutations to early-onset inflammatory bowel disease and chronic enteropathies. A previous study described the existence of biallelic *CARMIL2* variants in paediatric patients with Crohn-like or ulcerative colitis phenotypes, which is frequently associated with refractoriness to conventional therapeutic management[1,2]. These patients showed reduced regulatory T cells and impaired CD28-mediated T-cell activation, highlighting the immunologic mechanism underpinning intestinal inflammation[1,10]. Likewise, a patient with eosinophilic gastrointestinal disease and infantile colitis without any recurrent infections, reinforcing that intestinal manifestations may dominate the clinical picture even with a lack of any typical signs of a primary immunodeficiency[7]. In contrast, this case demonstrates a discrete, gluten-sensitive enteropathy, indicating a broader spectrum of intestinal immune dysregulation than previously recognised.

Despite the growing body of evidence on gastrointestinal involvement in *CARMIL2* deficiency, there are currently no prior reports of a biopsy-proven celiac disease in this population. While histologic features such as villous atrophy and lymphocytic infiltration have been represented in *CARMIL2*-related enteropathy[1,2], they have not yet been associated with gluten response.

Beyond intestinal disease, this case also highlights the sinopulmonary and dermatological spectrums associated with *CARMIL2* deficiency. Deficient patients commonly develop recurrent respiratory infections, bronchiectasis and chronic sinusitis due to impaired T-cell signalling and reduced Treg function, predisposing them to chronic inflammation and tissue remodelling.

There was a similar reported case of a child with recurrent pneumonias, hydropneumothorax and bronchopleural fistula as a rare complication, emphasising the fragility of lung tissue in these patients and the complexity of surgical management in immunodeficient states[11].

Chronic eczematous and psoriasiform dermatitis, allergic rhinitis and skin infections such as molluscum contagiosum are frequently reported, reflecting defective cytoskeletal regulation in keratinocytes and T cells[12].

Recurrent dysphagia and refractory oesophageal strictures have also been recorded in *CARMIL2* deficiency, which represent another therapeutic challenge as literature has reported recurrent oesophagitis, eosinophilic infiltration and even fungal colonisation in patients with a similar condition. This often requires serial endoscopic dilations and antifungal or anti-inflammatory therapy[12], corresponding to the patient's need for repeated dilations due to the relapsing nature of oesophageal involvement.

Furthermore, although studies such as that by Altay et al. identified celiac disease among patients with other autoimmune or auto-inflammatory diseases, for example familial Mediterranean fever and juvenile idiopathic arthritis[5], none of the *CARMIL2*-deficient patients in these cohorts were diagnosed with celiac disease. This suggests that the co-occurrence of celiac disease and *CARMIL2* deficiency in this patient is one of either an extremely rare association or a possibly underrecognized manifestation within the broader immune dysregulation.

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