

# Atypical hematological manifestation of celiac disease: A case report of aplastic anemia in a 2-year-old child and review of the literature

Thea von Graffenried<sup>1</sup> | Mattia Rizzi<sup>2</sup> | Michel Russo<sup>3</sup> | Andreas Nydegger<sup>1</sup> | Simon Kayemba-Kay<sup>3,4</sup>

<sup>1</sup>Pediatric Gastroenterology Unit, Department of Pediatrics, University of Lausanne, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

<sup>2</sup>Hemato-Oncology Unit, Department of Pediatrics, University of Lausanne, Switzerland

<sup>3</sup>Department of Pediatrics, Centre Hospitalier du Valais Romand, Sion, Switzerland

<sup>4</sup>Department of Pediatrics, Centre Hospitalier des Pays de Morlaix, France

## Correspondence

Simon Kayemba-Kay's, Department of Pediatrics Centre Hospitalier des Pays de Morlaix, 15 Rue Kersaint Gilly, 29672 Morlaix, France

Email: [kkayembakays@ch-morlaix.fr](mailto:kkayembakays@ch-morlaix.fr)

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## ABSTRACT

**Introduction:** Celiac disease typically presents with symptoms of malabsorption, but extraintestinal manifestations are increasingly reported. Aplastic anemia as the mode of celiac disease presentation is extremely rare in children.

**Case presentation:** We report a 2-year-old boy who presented with loose stools, loss of appetite, and bicytopenia with severe aregenerative normocytic anemia. Investigations, including bone marrow aspirate and biopsy, revealed aplastic anemia. Screening for malabsorption showed increased plasma concentrations of anti-transglutaminase and anti-gliadin antibodies. A duodenal biopsy confirmed the histologic features of celiac disease. The child received a packed red cell transfusion and was started on a gluten-free diet, with a very good prognosis and normalization of both his blood and histological parameters. To the best of our knowledge, our report is the sixth pediatric case in the literature.

**Conclusion:** Screening for celiac disease should be performed in children with unexplained hematological abnormalities such as aplastic anemia with or without gastrointestinal symptoms.

## KEYWORDS

Aplastic anemia, Celiac disease, Child, Gluten-free diet

## INTRODUCTION

Celiac disease (CD) is a chronic systemic immune-mediated disease that is triggered following the ingestion of gluten protein in genetically susceptible individuals. The typical presentation of CD, in childhood, consists of malabsorption resulting from gluten-dependent small bowel mucosal inflammation and crypt hyperplasia along with typical mucosal villous atrophy.<sup>1</sup> Affected children, clinically present with well-known signs of malabsorption among which stunted growth, various abdominal embarrassment, and protruding belly with muscle wasting

are the commonest. CD is nowadays largely recognized as a multi-system disorder with both gastrointestinal and extra-intestinal features. In addition to its well-known gastrointestinal manifestations, CD has several other extra-intestinal features. It may even present with a clinical picture of rheumatologic, neurologic, endocrine, dermatologic, and metabolic affections. CD may also be associated with hematologic manifestations secondary to induced nutritional deficiencies (folate deficiency, anemia, thrombocytosis/thrombocytopenia, hyposplenism, IgA deficiency, etc.).<sup>2,3</sup> Even though cases of CD in association with aplastic anemia (AA) have been reported in the

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literature, especially in adult patients, this association remains extremely rare in children. To the best of our knowledge, only five pediatric cases have been published, before our case.<sup>4,5</sup>

We report a new case of AA which revealed CD, in a 2-year-old child. We aim to increase clinicians' awareness of this rare association and incite them to keep a high index of suspicion for CD in children presenting with AA of unclear etiology.

## CASE REPORT

A 2-year-old boy presented with a 6-week history of recurrent loose stools and loss of appetite. His feces were bulky, foul-smelling, and occurred 4–5 times/day, alternating with 1–2 episodes of consistent stools. There was an additional history of 3–4 daily bouts of vomiting lasting four days, associated with fever (peaks at 39°C) that had lasted three days, two weeks earlier. Parents also reported a loss of 10% body weight over a month. He weighed 12.7 kg (P25–50) on admission and his height was 95 cm (P>90). Upon clinical examination, the child was afebrile, looked pale with sunken eyes, his capillary refill time was immediate, heart rate was 125/min, respiratory rate, and blood pressure were within the normal range for age. Cardiopulmonary auscultation revealed a systolic murmur (2/6). The abdominal examination was unremarkable, with no hepatosplenomegaly, and no superficial adenopathies. There was no bone tenderness, no bruising, and no perianal lesions.

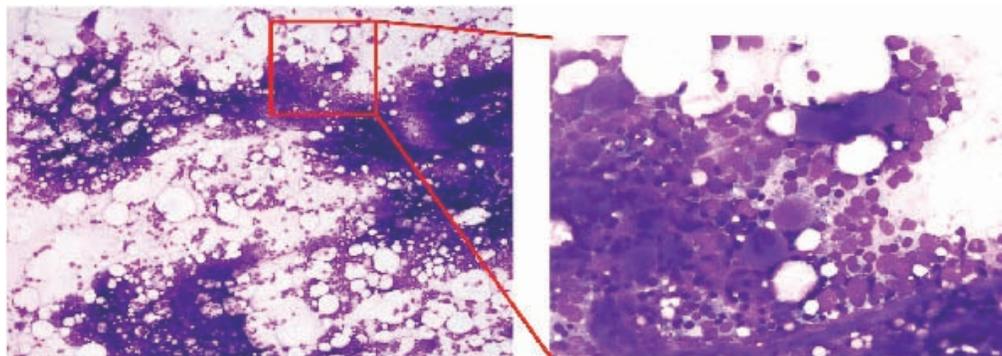
His initial laboratory workup showed bicytopenia with severe aregenerative normocytic anemia [hemoglobin 63 g/L, mean corpuscular volume 79 fl, reticulocyte 1%), leukopenia (white blood cell count  $3.9 \times 10^9$  /L) with severe neutropenia (absolute neutrophil count 500)], but normal platelet count ( $227 \times 10^9$ /L). There were no abnormal cells on the peripheral smear analysis. Workup for hemolysis, ferritinemia, plasma vitamins B9 and B12, liver, thyroid function, and renal tests were normal. Plasma adenosine deaminase and plasma proteins electrophoresis performed to rule out Blackfan-

Diamond syndrome were unremarkable. Hemoglobin electrophoresis was also normal. Epstein-Barr virus, cytomegalovirus, and parvovirus B19 serologies were all negative. The abdominal ultrasound showed insignificant infra-centimetric peri-umbilical adenopathies, and the chest X-ray was normal. Consequent to his febrile leukopenia, he was started on intravenous Ceftriaxone<sup>®</sup>. This was rapidly discontinued as C-reactive protein and blood cultures were negative. Due to the unexplained bicytopenia with a history of chronic diarrhea, bone marrow aspirate and biopsy were performed. Their analyses revealed a hypocellular marrow with decreased erythroid and myeloid precursors (25% hematopoietic cellularity) and increased megakaryopoiesis compatible with AA (Figure 1). There were no dysplasia or cytogenetic abnormalities.

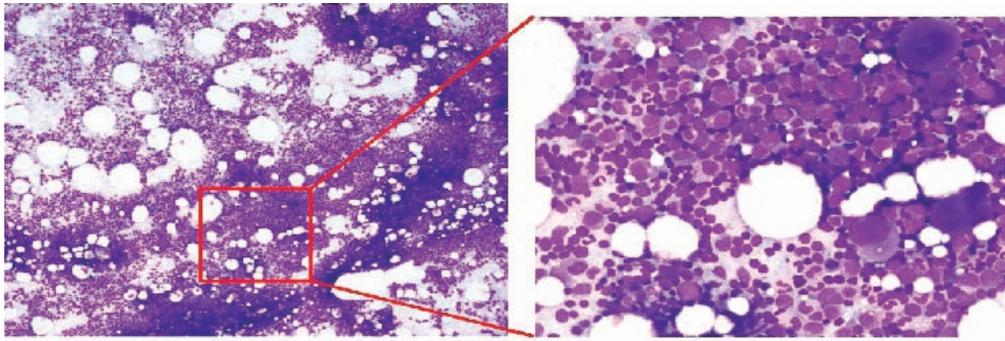
Screening for malabsorption showed elevated anti-transglutaminase (1330 IU/mL; normal < 20 IU/mL) and anti-gliadin antibodies (IgA 304 IU/mL and IgG 524 IU/mL; normal < 20 IU/mL). Upper gastrointestinal endoscopy with duodenal biopsy confirmed the pathologic features of fully developed CD. The patient received a packed red cell transfusion (180 mL) and was started on a gluten-free diet. At one-month post-hospitalization follow-up, the child was asymptomatic, his control tests showed anemia resolution, and normalized bone marrow (Figure 2).

## DISCUSSION

CD is nowadays widely recognized as a systemic disorder, rather than only a disease of the small bowel. It occurs as a consequence of autoimmune response resulting from exposure to gluten in predisposed individuals. The clinical presentation picture of CD is very variable, with only less than 50% of patients having gastrointestinal symptoms as inaugural features. Other modes of presentation include hematologic, neurologic, endocrine, dermatitis herpetiform, osteoporosis, iron-deficiency anemia, etc.<sup>6,7</sup> Among several extraintestinal manifestations, anemia is the most frequently reported hematological abnormality in association with CD; making it a diagnosis to look for



**FIGURE 1** Bone marrow aspirate: hypocellular marrow with decreased erythroid and myeloid precursors, and augmented megakaryopoiesis compatible with aplastic anemia (May-Grunwald-Gemsa stain,  $\times 200$  and  $\times 400$ ).



**FIGURE 2** Control bone marrow aspirate: normocellular marrow with trilineage hematopoiesis and normal differentiation (May-Grunwald-Gemsa stain,  $\times 200$  and  $\times 400$ ).

in case of iron-deficiency anemia of unclear origin.<sup>8-10</sup> The association of AA with CD is relatively rare, with most reported cases being adult patients. Our literature search for AA / CD association has yielded a total of only 13 reported cases, five of which were pediatric patients.<sup>4,5</sup> In three of the five cases in children, a CD was diagnosed simultaneously with AA,<sup>4,10,11</sup> in the remaining two, the diagnosis could not be confirmed in one child in whom the bone biopsy was not performed.<sup>12</sup> In the fifth patient, CD had initially presented as acute hepatitis, and was later complicated by AA despite the good observance of a gluten-free diet.<sup>5</sup> On the physiopathological standpoint, iron deficiency anemia, in patients with CD, results from malabsorption of micronutrients (iron, folates, and vitamin B12).

How CD induces AA remains, however, unclear and hypothetical. AA is regarded as an autoimmune disease in which there is active destruction of blood-forming cells by the lymphocytes. The physiopathological mechanisms involve T-cell-mediated organ-specific destruction of bone marrow hematopoietic cells with damage to DNA and subsequent apoptosis which occurs after gluten protein ingestion in genetically predisposed individuals. Moreover, a strong association between AA and human leukocyte antigen (HLA-DR2) has been reported by Khamaganova et al.<sup>13</sup> Acquired or secondary AA has several etiologies, among which, exposure to radiation, drugs, and chemicals (chloramphenicol, non-steroidal anti-inflammatory drugs, cytotoxic agents, antiepileptics, benzene, gold salts), Epstein-Barr virus, hepatitis virus, parvovirus, human immunodeficiency virus, immune diseases to which CD must be added, paroxysmal nocturnal hemoglobinuria, and pregnancy, are the most common. Cases with unknown etiologies are termed idiopathic.

AA in association with CD being rare, there are no evidence-based management guidelines. Therefore, gluten being the culprit in driving the autoimmune-mediated villous atrophy and the resulting bone-marrow suppression in some patients, it is reasonable to consider that its removal from the diet of CD patients could lead to symptom relief, restoration of the small bowel mucosa,

and avoidance of complications.<sup>3</sup> Our patient is the second pediatric case who has responded well to packed red blood cells (RBC) transfusion and a gluten-free diet alone. The reason could, probably, be our patient's shorter duration in exposure to immune processes. It is noteworthy that some patients, mostly adults, have been managed with immune suppressive drugs followed by hematopoietic stem cell transplantation.<sup>14,15</sup> A better understanding of hematologic abnormalities associated with CD is crucial for adequate patient follow-up after the initiation of a gluten-free diet and nutritional support when indicated. It will also lead to the avoidance of unnecessary hematological investigations, and most importantly, it will enable earlier diagnosis of deleterious comorbidities.<sup>9</sup>

We have reported the sixth pediatric case of AA in association with CD. This association is rare, the diagnosis requires a high index of clinical suspicion. We suggest that screening for CD should be performed in all children presenting with unexplained hematological abnormalities such as AA with or without gastrointestinal symptoms. Likewise, clinicians should be aware of the fact that AA may develop secondarily in patients with known CD on a gluten-free diet, especially if the observance is poor. Our patient positively responded to a gluten-free diet and packed RBC transfusion alone, probably because he was diagnosed in the early stage of his CD.

## CONSENT FOR PUBLICATION

Consent was obtained from the patient's parents.

## CONFLICT OF INTEREST

None.

## REFERENCES

1. Green PH, Cellier C. Celiac disease. *N Eng J Med.* 2007;357:1731-1743.
2. Halfdanarson TR, Litzow MR, Murray JA. Hematologic manifestations of celiac disease. *Blood.* 2007;109:412-421.
3. Balaban DV, Popp A, Ionita Radu F, Jinga M. Hematologic manifestations in celiac disease—A practical review. *Medicina (Kaunas).* 2019;55:373.

4. Irfan O, Mahmood S, Nand H, Billoo G. Celiac disease associated with aplastic anemia in a 6-year-old girl: a case report and review of the literature. *J Med Case Rep*. 2018;12:16.
5. Tej A, Akari I, Kbaili R, Ferhi F, Ghdira I, Tilouche S, et al. A rare association of silent celiac disease, acute hepatitis and aplastic anemia: Case report and review of literature. *Int J Celiac Dis*. 2018;6:58-61.
6. Hernandez L, Green PH. Extraintestinal manifestations of celiac disease. *Curr Gastroenterol Rep*. 2006;8:383-389.
7. Rodrigo L. Celiac disease. *World J Gastroenterol*. 2006;12:6585-6593.
8. Ludvigsson JF, Brandt L, Montgomery SM. Symptoms and signs in individuals with serology positive for celiac disease but normal mucosa. *BMC Gastroenterol*. 2009;9:57.
9. Baydoun A, Maakaron JE, Halawi H, Abou Rahal J, Taher AT. Hematological manifestations of celiac disease. *Scand J Gastroenterol*. 2012;47:1401-1411.
10. Maheshwari A, Nirupam N, Aneja S, Meena R, Chandra J, Kumar P. Association of celiac disease with aplastic anemia. *Indian J Pediatr*. 2012;79:1372-1373.
11. Badyal RK, Sachdeva MU, Varma N, Thapa BR. A rare association of celiac disease and aplastic anemia: case report of a child and review of literature. *Pediatr Dev Pathol*. 2014;17:470-473.
12. Kumar S, Suthar R, Thapa BR. Celiac disease presenting as pancytopenia. *JK Sci*. 2013;15:34-35.
13. Khamaganova EG, Murashova L, Zaretskaya Y. *HLA-DRB* and *DQB1* genes in predisposition to aplastic anemia. *Haematologica*. 2007;92:25.
14. Grey-Davies E, Hows JM, Marsh JC. Aplastic anaemia in association with coeliac disease: a series of three cases. *Br J Haematol*. 2008;143:258-260.
15. Salmeron G, Patey N, de Latour RP, Raffoux E, Gluckman E, Brousse N, et al. Coeliac disease and aplastic anaemia: a specific entity? *Br J Haematol*. 2009;146:122-124.

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