International Journal of Celiac Disease, 2018, Vol. 6, No. 2, 58-61
Available online at http://pubs.sciepub.com/ijcd/6/2/4

DOI:10.12691/ijcd-6-2-4

A Rare Association of Silent Celiac Disease, Acute Hepatitis and Aplastic Anemia: Case Report and Review of Literature

Amel Tej[1,*], Imene Akari[2], Raoudha Kbaili[1], Fehmi Ferhi[3], Ibtissem Ghdira[4], Samia Tilouche[1], Kahloul Najoua[1], Jihene Bouguila[1], Lamia Boughamoura[1]

[1]Department of pediatrics, Farhat Hached University hospital, Ibn Eljazar street 4000 Sousse, Tunisia
[2]Department of internal medicine, Farhat Hached University hospital, Ibn Eljazar street 4000 Sousse, Tunisia
[3]Department of reanimation and surgical resuscitation Farhat Hached University hospital, Ibn Eljazar street 4000, Tunisia
[4]Department of Immunology, Farhat Hached University hospital, Ibn Eljazar street 4000 Sousse, Tunisia
*Corresponding author: ameltej@yahoo.fr

Abstract Liver abnormalities are common extra-intestinal manifestations of celiac disease (CD). However, aplastic anemia had been rarely described in this disorder. Here, we report an exceptional case suggesting a rare association between asymptomatic CD, acute hepatitis and aplastic anemia: A Nine-year old girl presented with jaundice of 3 weeks duration and hepatosplenomegaly on physical exam. Investigations revealed an acute liver disorder with high serum transaminases levels. Extensive investigations excluded infectious, metabolic and auto immune as cause of acute liver disease. A celiac disease was diagnosed according to the histological exam of small bowel biopsy. A reversal of hepatic disorder was observed within 2 months after the initiation of Gluten free diet. However, the child developed aplastic anemia, which dramatically worsened despite immunosuppressive therapy. The etiological assessment of aplastic anemia was negative suggesting an association with hepatitis and silent celiac disease that could be explained by a common underlying immune pathological mechanism. Therefore, a screening of CD in acute liver disorder and AA should been considered by clinicians.

Keywords: *celiac disease, hepatitis, aplastic anemia, gluten free diet*

Cite This Article: Amel Tej, Imene Akari, Raoudha Kbaili, Fehmi Ferhi, Ibtissem Ghdira, Samia Tilouche, Kahloul Najoua, Jihene Bouguila, and Lamia Boughamoura, "A Rare Association of Silent Celiac Disease, Acute Hepatitis and Aplastic Anemia: Case Report and Review of Literature." *International Journal of Celiac Disease*, vol. 6, no. 2 (2018): 58-61. doi: 10.12691/ijcd-6-2-4.

1. Introduction

Celiac disease (CD) is considered as an autoimmune systemic disorder that affects the small bowel, the main target of the disease, and several others organs [1]. The spectrum of liver involvement in CD is particularly wide and liver blood tests abnormalities may be the sole presentation of atypical CD [2]. However, an association between CD and Aplastic anemia (AA) had been, rarely, described in published literature [3]. We here present the first case report of an exceptional association of silent atypical CD, acute hepatitis and AA in a child.

2. Case Report

A previously healthy nine-year old girl was admitted to explore jaundice. She had developed increasing abdominal distension with jaundice three weeks prior to admission, without fever, toxins or drug ingestion. Her family history revealed autoimmune diseases. Physical exam revealed normal weight and height, hepatomegaly, with splenomegaly. There was no lymphadenopathy. Cardiovascular, respiratory and neurologic examinations were normal.

On laboratory investigations, there were no hematologic abnormalities, the total protein was 63g/l. Liver functions tests revealed 60-fold-elevated serum levels of transaminases, cholestasis (BT/BC: 354/253UI/L; ALK/GGT: 210/68UI/l), without hepatic failure (prothrombin time and international normalized ratio was normal). Abdominal ultra-sonographic doppler examination showed splenomegaly and hepatomegaly with fine bile ducts.

Serological tests for alphabetic hepatitis (A, B, C and E), Epstein-Barr virus, cytomegalovirus, Parvovirus B19, Herpes, VZV, and HIV were negative. To explain this acute liver disorder, further investigations were realized: cupric tests, antinuclear antibodies, smooth muscle antibodies, anti-liver/kidney microsomal antibodies and perinuclear antineutrophilic cytoplasmic antibodies, the results were negative. The child did not also fulfill the criteria for autoimmune liver disease according to the International Association for the study of the liver (IASL) [4].

As the liver abnormalities tests remained unexplained, serological screening of CD had been performed even in the absence of clinical and biological features of malabsorption.

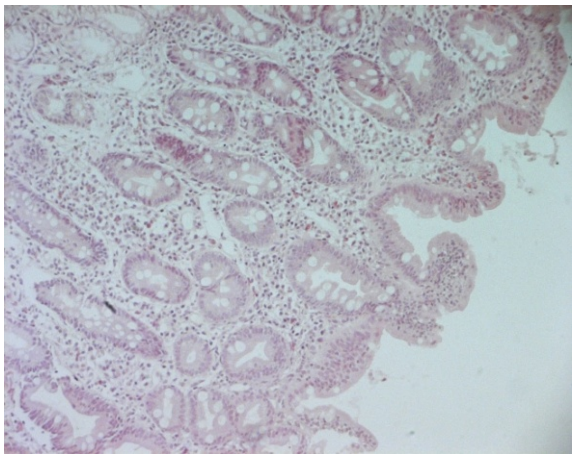

Figure 1. H.E x 100: Duodenal biopsy displaying subtotal atrophy of villi,

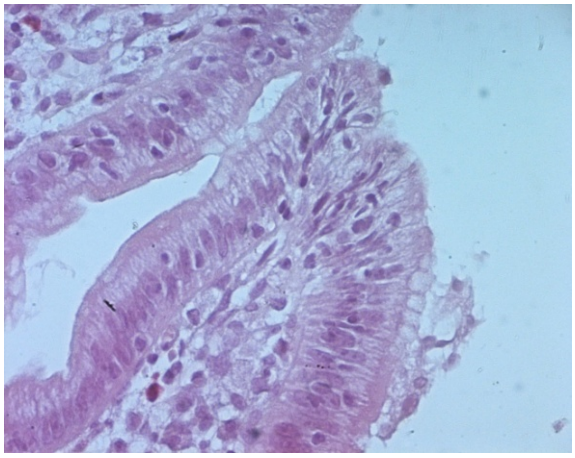

Figure 2. H.E x 400 crypt hypertrophy and a lymphocyte infiltration of the epithelium

Interestingly, we found increased IgA anti- tissue transglutaminase antibodies with histopathological examination of small bowel biopsy consistent with celiac disease: subtotal villous atrophy classified MARSH 3b (Figure 1, Figure 2).

A gluten-free diet (GFD) was started. Jaundice, hepatomegaly and splenomegaly were relieved. Liver tests were normalized at two months follow up on GFD.

However, 49 days after the onset of symptoms (Table 1), laboratory tests revealed hemolytic anemia with elevated lactate dehydrogenase (LDH). Peripheral smear was normal. Direct Coomb's test was negative. There was no deficiency in vitamin B12 or folates (374pg/ml/17ng/ml respectively). Bone marrow aspiration showed there were no signs of fibrosis or malignancy. As we suspected an autoimmune disorder, we started Prednisone (2mg/Kg/J). Clinical situation worsened with purpuric rashes and infectious complications due to severe thrombocytopenia 3000/ mm^3 and leukopenia 600/ mm^3 with profound neutropenia 0/ mm^3. Bone marrow biopsy was performed and revealed hypo cellular fatty marrow with depression of all three cell lines that confirmed the diagnosis of aplastic anemia. Cytogenetic examination of the aspired bone marrow was normal and peripheral blood flow cytometry showed the absence of paroxysmal nocturnal hemoglobinuria (PNH). Mitomycine-induced breakage in peripheral blood excluded Fanconi's anemia. His brother was suitable human leucocyte antigen (HLA) donor but he was only 9 months old. Prednisone was stopped and we started cyclosporine without any improvement. The patient died due to sepsis and cerebral bleeding. The immunity exploration showed a decreased level of CD4, IgA (0.26g/l) and IgM (0.35g/l) with normal IgG level at 9.8g/l. These results had been analyzed after the death of the child.

Table 1. Timeline of patient's medical history

	06/04	08/05	06/07	13/07	30/07	27/08
Therapy		3 weeks after GFD	7weeks after GFD	**First day Prednisone 8 weeks GFD**	**Withdrawal of prdenisone** GFD	GFD Cyclosporine
Hb (g/dl)	12.1	9.6	**8.3**	7.4	5.1	6.7
VGM (fl)	75.20	96.5	**102.8**	102.8	103	83.8
GB (/mm^3)	6300	1800	**1700**	1700	1900	600
PNN (/mm3)	3528	1206	**697**	799	475	
Lcytes(/mm3)	1764	558	**867**	884	1387	
Platelets (/mm3)	301000	39000	**11000**	59400	35100	
Réticulocytes(/mm3)		103400	**70100**	10000		3000
TP (%)	**75**					96
BT (µmol/L)	**354**	19.47	13.8	6	10.10	
BC (µmol/L)	**253**	3.10	3.10	0	1.10	
AST (UI/L)	**2522**	381.12	94			10
ALT (UI/L)	**1142**	77.50	142			8
GGT (UI/L)	**68**		32			22
ALK (UI/L)	210					115
LDH (UI/L)			**912**	222		

3. Discussion

Hepatitis associated aplastic anemia (HAAA) is a well recognized and distinct variant of aplastic anemia in which pancytopenia follows an acute attack of hepatitis [5,6]. However, association between aplastic anemia (AA) and celiac disease has rarely been reported [3]. The combination of these three entities in the same patient and the type of liver disorder associated to CD are very particular.

An unexplained hypertransaminasemia is a classical association between CD and liver disorders that generally normalized after 6-12 months of GFD adherence [7], this cryptogenic liver disorders is also known as celiac hepatitis [7,8].

However, an acute liver disorder is not common in CD. Thomas and al [8], reported six cases of severe liver damage, four of them had an acute liver failure. The investigations could not find any alternative pathogenetic cause and thus the association with CD had been suggested.

In our case, the child presented with an acute liver damage for which clinical, immunological, metabolic and biochemical work up was negative. A screening of CD was realized even in the absence of clinical and biological signs. The diagnosis had been confirmed by histopathological exam of small bowel biopsy. A liver biopsy was discussed but delayed if no improvement on GFD would be noted.

Liver injury can be presented as two clinical forms (cryptogenic and autoimmune liver disease) [9,10]. The response of liver disease to GFD depends in part, on whether CD accompanies or causes liver dysfunction [9].

In the present case our case, clinical and biological abnormalities were normalized at 2 months follow up. This good response to GFD was in favor of celiac disease causality and suggested a cryptogenic form of hepatic disorder.

However, hematological parameters revealed a pancytopenia that was installed 49 days after the onset of symptoms. The second question revealed by this case report was if this aplastic anemia was related to the acute hepatitis, to celiac disease or a simple coincidence.

Most studies report that Hepatitis associated aplastic anemia (HAAA) accounts for 0,1-0,2% of hepatitis cases, the interval between these two disorders varies between studies from less than 1 year to less than 3 months. It most frequently affects young male children and is often fatal if untreated [11]. The standard therapy employed for the treatment of HAAA is bone marrow transplantation with immunosuppressive therapy [5].

On the other hand, only 8 cases of celiac disease associated aplastic anemia (CDAAA) have been published [12,13]. The diagnosis of celiac disease was done simultaneously with aplastic anemia in five patients. While, in the other three cases, celiac disease had previously been diagnosed and despite GFD, these patients developed aplastic anemia as in our case [12,13].

Maheshwari.A et al [14] published the first case report suggesting an association of celiac disease with aplastic anemia in children. The patient was a 13-year-old boy without celiac disease history who presented with petechiae all over the body associated to hematochezia. Investigations revealed an aplastic anemia. Long term follow-up of this patient revealed a persistent improvement of hematologic disorders on GFD.

According to Maheshwari. A et al [14], the management of CDAAA is different in adults and required with GFD a treatment with anti thymocyte globulin (ATG) and cyclosporine. This difference might be due to the longstanding immune dysregulation in undiagnosed adults in comparison to children.

A second case of a rare association of CD and AA in a child was published on 2014 by Badyal et al [15], and as in our case, AA developed after a previous diagnosis of CD.

In the present case, an immunosuppressive therapy has been introduced but the situation worsened and the patient dead because of pancytopenia complications. Unfortunately, we could'nt afford bone marrow transplantation or ATG therapy.

The mechanism of cause and effect regarding this CD and AA association is unclear. The onset of AA despite the good adherence to GFD might be explained by other possible and intricate causes such as autoimmunity or systemic inflammation… an underlying immune mechanism, with auto-reactive T-cells mediating tissue-specific destruction is shared between CD and AA [13,14].

On the other hand, the absence of response to immune suppressive therapy is rather in favor of an HAAA since the prognosis of this disorder is thought to be fatal without bone marrow transplantation. Further studies to explain the underlying pathological mechanism of theses three disorders are necessary.

To conclude, Silent CD represents a diagnostic challenge. Patients with hepatitis or aplastic anemia should undergo serological screening for CD. A gluten-free dietary regimen can produce the amelioration of symptoms associated even with advanced liver disease, but immunosuppressive therapy and even bone marrow transplantation or ATG therapy are required for AA.

Abbreviations

AIH: autoimmune hepatitis
AA: aplastic anemia
CD: celiac disease
GFD: Gluten free diet
AST: aspartate aminotransferase
ALT: alanine aminotransferase
TB: total biluribin
CB: conjugated biluribin
ALK: Alkaline Phosphatase
GGT: Gamma Glutamyl Transferase
ATG: anti thymocyte globulin

Acknowledgements

No specific acknowledgement.

Conflict of Interest

Authors disclose no conflict of interest.

References

[1] Tovoli F, De Giorgio R, Caio G, and al. Autoimmune Hepatitis and Celiac Disease: Case Report Showing an Entero-Hepatic Link. Case Rep Gastroenterol 2010; 4: 469-475.

[2] Emami MH, Hashemi M, Kouhestani S and al. Should We Look for Celiac Disease among all Patients with Liver Function Test Abnormalities? Int J Prev Med. 2012 Mar; 3(3): 167-172.

[3] Basu. A, Ray. Y, Bowmik.P and al. Rare association of coeliac disease with aplastic anaemia: report of a case from India. Indian J Hematol Blood Transfus (Sept 2014) 30 (Suppl1): S208-S211.

[4] Liberal R, Grant CR, Longhi MS, Mieli-Vergani G, Vergani D. Diagnostic criteria of autoimmune hepatitis. Autoimmun Rev. 2014 Apr-May; 13(4-5): 435-40.

[5] Rauff.R, Idrees.M, Amjad Riaz Shah S and al. IU and Ali.M. Hepatitis associated aplastic anemia: a review. Virology Journal 2011, 8: 87.

[6] Amjad Riaz Shah.S, Idrees.M and Hussain.A. Hepatitis G virus associated aplastic anemia: a recent case from Pakistan. Virology Journal 2011, 8: 30.

[7] Marciano F, Savoia M, Vajro P. Celiac disease-related hepatic injury: Insights into associated conditions and underlying pathomechanisms. Digestive and Liver Disease, 2016, 48: 112-119.

[8] Casswall TH, Papadogiannakis N, Ghazi S, Németh. Severe liver damage associated with celiac disease: findings in six toddler-aged girls. A Eur J Gastroenterol Hepatol. 2009 Apr; 21(4): 452-9.

[9] Al- Hussaini.A, Bsheer.A and Czaja.AJ. Liver failure unmasks celiac disease in a child. Annals of hepatology. Vol.12, 2013: 501-505.

[10] Bonamico.M, Pitzalis.G, Culasso.F et al. Hepatic damage during celiac disease in childhood. Minerva Pediatr 1986; 38: 959-63.

[11] Wang H, Tu M, Fu R, Wu Y, Liu H, Xing L, Shao Z.The clinical and immune characteristics of patients with hepatitis-associated aplastic anemia in China. PLoS One. 2014 May 20; 9(5): e98142

[12] Salmeron.G, Patey.N, De Latour RP. Celiac disease and aplastic anemia: a specific entity. Br J Hematol. 2009; 146: 113-24.

[13] Grey-Davies.E, How.JM, Marsh JCW. Aplastic anemia in association with coeliac disease: series of 3 cases. Br J Hematol. 2008; 82996-1000.

[14] Maheshwari.A, Nirupam.N, Aneja.S, and al.Association of celiac disease with aplastic anemia. Indian J Pediatr (October 2012) 79 (10): 1372-1373.

[15] 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 Nov-Dec; 17 (6): 470-3.