CASE REPORT

Available from: http://www.jgld.ro/wp/archive/y2018/n1/a15
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.271.cld

Hemorrhagic Events in Adult Celiac Disease Patients. Case Report and Review of the Literature

Alina Dima[1], Ciprian Jurcut[2], Anca Manolache[2], Daniel Vasile Balaban[1,2], Alina Popp[1,3,4], Mariana Jinga[1,2]

1) Carol Davila University of Medicine and Pharmacy;
2) Dr. Carol Davila Central Military Emergency University Hospital;
3) Alessandrescu-Rusescu Institute for Mother and Child Health, Bucharest, Romania
4) Tampere Centre for Child Health Research, University of Tampere, Tampere University Hospital, Tampere, Finland

Address for correspondence:
Daniel Vasile Balaban, Internal Medicine and Gastroenterology Clinic, Carol Davila University of Medicine and Pharmacy, 010825 Bucharest, Romania
vbalaban@yahoo.com

Received: 23.10.2017
Accepted: 06.02.2018

ABSTRACT

Background & Aims: Celiac disease (CD) presents with a wide spectrum of extra-digestive symptoms, including hemorrhagic manifestations. The aim of this review was to conduct an extensive analysis of the hemorrhagic events reported in adult CD patients.

Methods: Case report and review of the literature. Pubmed (MEDLINE) database search from January 1970 onwards was performed using the medical subject headings [MeSH] terms "celiac disease" AND "blood coagulation disorders", "hemorrhage", "hematoma", "hematuria", "hemoptysis", "epistaxis", "hemosiderosis". Only case reports were identified on the search theme. Information on patients' characteristics, diagnostic features, coagulation parameters, symptomatology duration, and evolution under treatment were systematically collected and summarized.

Results: We present the case of a 40-year-old man hospitalized for spontaneous muscular hematomas, in whom CD was diagnosed. We performed a review of the literature and summarized the published case reports of 46 CD patients, aged between 19 and 74 years, 64% of male gender. In 25% of cases, the symptomatology was present for more than 5 years prior to CD diagnosis. The clinical hemorrhagic events were as follows: 15 patients had gastrointestinal bleeding, 9 hemoptysis, 4 epistaxis, 6 hematuria, 8 cutaneous hematoma, petechia or ecchymoses, and only in 1 case hemarthrosis, hemorrhagic vesicular dermatitis, subcortical hemorrhage, or adrenal hemorrhage. Sixty percent of the patients had digestive symptoms, while the rest had only extra-digestive CD involvement. The Lane Hamilton syndrome was defined in 15 patients. The evolution under a gluten-free diet was favorable in most cases.

Conclusion: This review of case reports aims to increase awareness to hemorrhagic events, rare but possible life-threatening conditions, as part of the CD clinical spectrum. To the best of our knowledge, this is the first review of all types of hemorrhagic events in adult CD patients.

Key words: celiac disease – Lane Hamilton syndrome – blood coagulation disorders – vitamin K.

Abbreviations: AGA: anti-gliadin antibodies; CD: celiac disease; DAH: diffuse alveolar hemorrhage; DIC: disseminated intravascular coagulation; DGP: anti-deamidated gliadin antibodies; EATL: enteropathy-associated T cell lymphoma; EMA: anti-endomysial antibodies; GFD: gluten-free diet; INR: international normalized ratio; IPH: idiopathic pulmonary hemosiderosis; LHS: Lane Hamilton syndrome; PLT: platelets; tTG: anti-tissue transglutaminase antibodies.

INTRODUCTION

Celiac disease (CD) is a multifaceted disorder that occurs in genetically susceptible individuals after gluten exposure. Now recognized as a relatively common condition in the general population, with a prevalence around 1%, CD is often difficult to diagnose mainly due to the pleomorphic clinical appearance. One third of the CD patients present with the classic digestive symptoms [1]; in the remaining two thirds, extra-digestive manifestations such as infertility [2], dermatitis herpetiformis [3], elevated aminotransferase levels [4], dyselectrolytemia [5], osteomalacia or myopathy [6, 7] can be found.

Furthermore, hemorrhagic events have been reported. The coagulation impairment in CD can be clinically reflected by a wide range of manifestations such as epistaxis [8-11], hemoptysis [12-18], hematochezia [19-22], melena [8, 22-26], muscular hematoma [9], or hematuria [8, 27-31].

The main pathogenic mechanism is related to the low vitamin K levels due to malabsorption [32]. Besides coagulopathy, diffuse alveolar hemorrhage with idiopathic pulmonary hemosiderosis (IPH) has been described in CD, an association also known as the Lane Hamilton syndrome (LHS) [14, 15, 17, 18, 33-40] and presenting with hemoptysis. Moreover, intestinal tumors [19, 21, 25, 41] or variceal bleeding [23] can determine digestive hemorrhage.

The oldest reports on hemorrhagic coagulopathy in celiac sprue are from 1948 [42] and 1956 [43]. However, even if this is a recognized feature in CD, to the best of our knowledge, the hemorrhagic manifestations encountered in adult CD patients have not been summarized before. The objective of this research was to extensively review the hemorrhagic clinical events reported in CD patients.

CASE REPORT

A 40-year-old man presented to the Emergency Room for a sudden onset of spontaneous ecchymoses and muscular hematomas. He denied recent trauma or at risk behaviors. For three days prior to presentation, he had been taking non-steroidal anti-inflammatory drugs for a renal colic. On physical examination, marked pallor was noted, multiple ecchymoses on the arms and large muscular hematomas on the thighs and left forearm (Fig. 1). Laboratory work-up revealed severe iron-deficiency anemia (hemoglobin 7.1 g/dl, serum iron 20 μg/dl), normal platelets count, incoagulable INR, marked inflammatory syndrome, low serum calcium and albumin. On imaging, thickened walls of several small bowel loops were observed, suggestive of intraparietal hemorrhage (Fig. 2). The patient denied any overt hemorrhage. He was admitted to the ICU, where extension of hematomas and the drop in hemoglobin levels (to 5 g/dl) were first noted, followed by a slow favorable recovery in the following 72 hours after blood transfusions (packed red blood cells, fresh frozen plasma) and nutritional support. Throughout the admission, a close surgical follow-up was set, for potential development of the compartment syndrome. A specific coagulation work-up ruled out a hematologic disease and concluded to hypocoagulability due to vitamin K deficiency. Upon careful history taking, the patient recalled some loose stools in the last few years, which, put together with other evidences of malabsorption (hypocalaemia, hypoalbuminemia), prompted us to test for CD antibodies, which were positive: IgA tissue transglutaminase antibodies (tTG) – 320 U, and anti-endomysial antibodies (EMA) – 1:500. Endoscopy revealed nodularity and fissures in both the duodenal bulb and distal duodenum (Fig. 3), and multiple biopsies were sampled. Histopathology revealed Marsh 3b lesion. On day 10 after admission, the patient was discharged (hemoglobin 10.1 g/dl). He started the gluten-free diet and at three months follow-up, the patient had normal complete blood count and INR, with tTG seroconversion. Later on, at two years follow-up, no recurrent hemorrhagic events were registered and the histological recovery of the duodenal mucosa was noted.

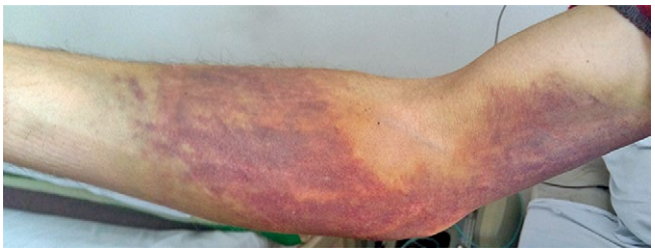

Fig. 1. Multiple cutaneous ecchymoses on the arms.

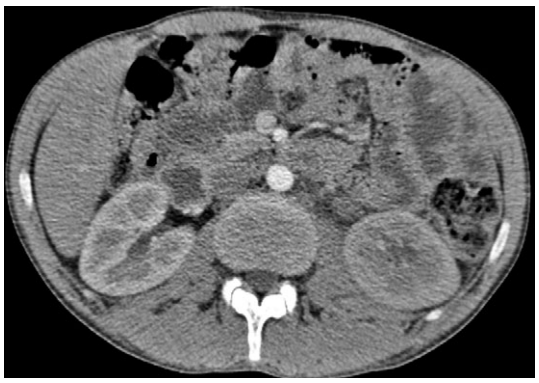

Fig. 2. Abdominal CT revealing thickened walls of several small bowel loops.

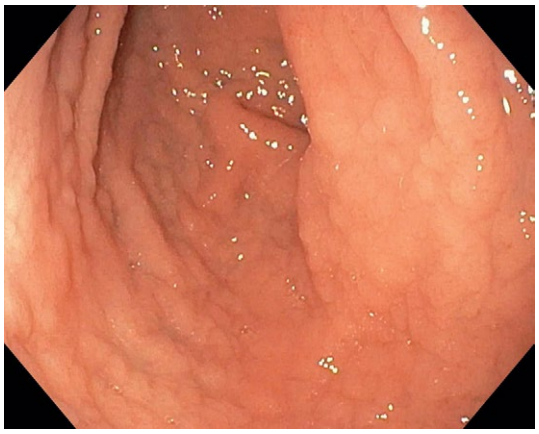

Fig. 3. Upper gastrointestinal endoscopy showing nodularity in the duodenal bulb.

REVIEW OF THE LITERATURE

We decided to realize an extensive literature search by the means of Pubmed (MEDLINE) database. The articles were identified using the medical subject headings [MeSH] terms: "celiac disease" (id 002446) and the following 1. "blood coagulation disorders" (id 001778), 2. "hemorrhage" (id 006470), 3. "hematoma" (id 006406), 4. "hematuria" (id 006417), 5. "hemoptysis" (id 006469), 6. "epistaxis" (id 004844), 7. "hemosiderosis" (id 006486).

The search was restricted to articles published from January 1970 onwards, articles with full text available in English or at least with access to the article abstract in English.

Reports on subjects younger than 18 years were excluded. Moreover, articles referring to a hypercoagulable state in CD were excluded, the search being focused on hemorrhagic events in adults. Also, a case series of previously published cases was not included as each case was noted only once. Cases presenting with cutaneous petechias in dermatitis herpetiformis context were excluded.

Further, the references of the identified articles were searched for additional published researches that were missed of the initially database search (Fig. 4).

RESULTS

Subjects' demographics

A number of 44 articles were identified, of which two presented more than one case. The main data systematically collected are presented in Supplementary Table I.

Among the 46 subjects described, the age range was between 19 and 74 years at the moment of the hemorrhagic event. Thirty nine percent of the subjects had less than 30 years, while 23% had ≥ 60 years. Almost two thirds (64%) were males. From 34 patients for whom the information was available, 32% were symptomatic for only a few months, while 25% presented symptomatology for more than 5 years before diagnosis; of them, 8 patients were symptomatic for more than 10 years.

Clinical forms of presentation

Among the 46 analyzed patients, in 9 hemoptysis was described, 4 epistaxis, 6 hematuria, 8 cutaneous hematoma, petechia or ecchymosis, and in 1 case haemarthrosis, hemorrhagic vesicular dermatitis, subcortical hemorrhage, or adrenal hemorrhage. Gastrointestinal bleeding was noted in 15 cases, but data on both clinical type of exteriorization and type of intestinal lesions were not described in all cases. Among cases with digestive bleeding, 4 patients presented hematochezia, 5 melena, 3 had intestinal ulcers, 2 intestinal hematoma and 1 variceal bleeding. In 15 patients, pulmonary involvement in LHS was defined. Troubles of coagulation were found in 31 patients. Only one patient presented both LHS and prolonged prothrombin time.

Regarding the clinical manifestation of the underlying disease, out of 30 patients for whom the information was available, 18 had digestive symptoms, while the rest had only extra-digestive CD involvement. In the LHS patients, digestive symptoms were present in 3 out of 8 cases.

Diagnostic approach

In 7 published cases [15, 20, 21, 23, 34, 44, 45], the CD diagnosis was already known before the hemorrhagic event, while in the rest, the CD diagnosis followed the hemorrhagic occurrence.

In 10 patients, the tTG antibodies, in 15 patients anti-gliadin (AGA) or anti-deamidated gliadin antibodies (DGP), and in 13 patients EMA were part of the diagnostic approach. Thirty four of the 46 cases reviewed had a biopsy-based diagnosis; in the remaining this information was lacking and it is possible that a histopathological confirmation was missing. The Marsh grading was reported only in three cases, Marsh grade 3b in 1 case [13], and 3c [8, 20] in another 2 cases. However, the positive serology and the favorable clinical response under a gluten-free diet (GFD) were observed in these cases, supporting the CD diagnosis.

Management and outcome

From the 31 case reports of the patients without LHS, prolonged prothrombin time was noted in 13 cases. In another 4 cases the hemorrhagic events were hematochezia in enteropathy-associated T cell lymphoma (EATL), variceal bleeding and hemorrhage following liver biopsy on nodular regenerative hyperplasia in patients with coagulation tests in normal ranges but with thrombocytopenia. In the remainder, data on coagulation tests were not available.

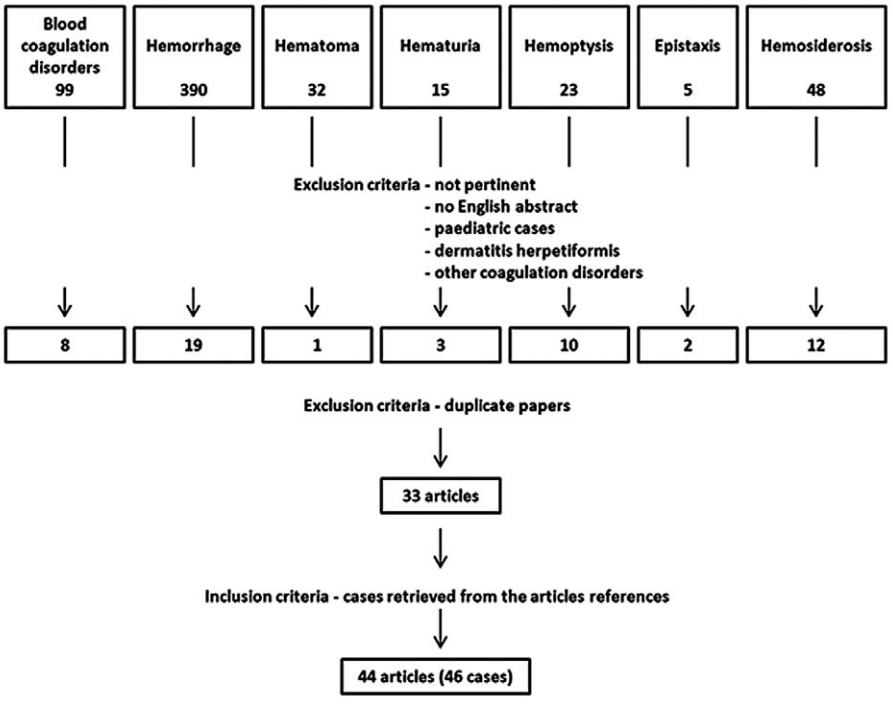

Fig. 4. Articles included in the review.

For the coagulopathy treatment, vitamin K [4, 9, 12, 28, 29, 32, 46-50], fresh frozen plasma [9,12] or coagulation factors [46] were administered.

For most of the cases reported, the evolution under GFD was favorable. Only in seven cases, the CD diagnosis had been established before the hemorrhagic event [15, 20, 21, 23, 34, 44, 45]. Therefore, in these cases, a GFD was already initiated, with various reported adherence, from suboptimal compliance [44] to strict adherence [23]. In the cases where a GFD had been initiated after the hemorrhagic event, a favorable outcome was generally observed. Also, in eight cases the improvement was established after biopsy, when histological amelioration/restoration under GFD was noted [9, 18, 26-28, 32, 49, 51]. In other cases, different parameters were described to support the favorable response under GFD, such as: clinical improvement [8, 10, 12-14, 17, 24, 35, 36, 47], increase in hemoglobin levels [12-14, 35, 36, 37, 52, 53], pulmonary recovery [12, 14, 36] and weight gain [13, 14, 46, 52-54].

DISCUSSION

In the cases reviewed, different clinical situations explained the development of hemorrhagic events, such as coagulopathy due to vitamin K malabsorption [4, 15, 20, 23, 32, 44, 45, 47], celiac crisis [8, 13], LHS [14, 15, 17, 18, 33-40], portal hypertension [23], or digestive tumors [19, 21, 25, 41].

Malabsorption of fat soluble vitamins (A, E, K) is encountered in bowel diseases such as ulcerative colitis or Crohn's disease [55]. In CD as well, low levels of vitamins A, E [47, 49] and K [56] are found due to intestinal absorption impairment. Vitamin K is important for the hepatic synthesis both for coagulation factors (factors II, VII, IX, and X) and for coagulation inhibitors (protein C and protein S). Therefore, hemorrhagic as well as thrombotic events could be related to its deficiency.

Celiac crisis is a severe CD form of presentation, possibly life-threatening, characterized by profuse diarrhea with secondary important malabsorption processes and hydro-electrolytic disturbances [57, 58]. It has been described mainly in young children [57], but celiac crisis might occur also in adults [58]. Hemorrhagic diathesis could be part of the celiac crisis features [8].

Rarely, hepatic impairment could lead to hemorrhagic events. Idiopathic non-cirrhotic portal hypertension, complicated with variceal development and bleeding, was described in CD patients. The pathogenic mechanism is only presumed, IgA anticardiolipin antibodies are produced during the gluten-induced enterocyte destruction. The veins of the affected intestine drain in the small portal veins and anticardiolipin antibodies might obstruct the portal venous microcirculation [23]. Austin et al. presented two cases of hepatic injury with hepatic nodular regenerative hyperplasia, which was complicated with disseminated intravascular coagulation and acute vein thrombosis in the presence of IgA anticardiolipin antibodies [44].

In up to 9% of the patients with iron deficiency anemia of unknown origin, CD might be identified [59]. Macroscopic bleeding is only rarely present, in 1 out of 18 patients [60]. On the contrary, a quarter of the patients with partial and half of those with total villous atrophy have positive Haemoccult tests [61].

Possibly by similar mechanisms as for the oral aphthous ulcers [24], gastric [22], small bowel ulcers [24], or ulcerative jejunitis have been described in CD [62] and could manifest as melena [24].

Rarely, CD complicates with EATL, an intestinal malignancy with poor prognosis, mainly occurring in the 6-7 decades [19, 41]. EATL could also be a cause of intestinal hemorrhage in CD [19, 41].

Idiopathic pulmonary hemosiderosis was described initially by Virchow in 1864 and characterized by the triad hemoptysis, iron deficiency anemia, and pulmonary infiltrates [35]. In 1971, the IPH presence was described in a 23-year-old man with idiopathic steatorrhea (LHS) [63]. The pulmonary symptomatology in LHS starts usually in childhood, and only 25% of all patients have an adult onset [14, 35]. Xi-Yuan et al. reviewed the literature for IPH and identified 37 patients (12 women, 24 men), out of whom 5 had CD [64]. In children with IPH, about 30% might have associated CD [65]. Celiac disease should be searched in patients with IPH as only half present gastrointestinal symptoms [14]. Furthermore, LHS associated with another rare syndrome, CEC (CD, epilepsy, and cerebral calcifications) syndrome, was reported in one case [34]. The origin of IPH in CD is not known, but it might be autoimmune mediated through autoantigens expressed on the alveolar basement membrane, such as antireticulin [66]. Interestingly, the pulmonary symptomatology responds to the GFD [18] independent of the evolution of intestinal histology [18].

Patients with CD also present an increased risk of idiopathic thrombocytopenic purpura (ITP) [67]. The occurrence of ITP in CD patients was described in patients with associated polyautoimmunity, such as inclusion body myositis [68], systemic sclerosis, autoimmune thyroiditis, and pernicious anemia [69], or Behcet disease [70].

Prolonged prothrombin time was found in only 1% of the asymptomatic CD patients, and in 19% of symptomatic non-treated adult CD patients [71]. Vitamin K deficiency might not be the only pathogenic link for hemorrhagic events occurrence in CD. Based on the factor XIII resemblance with the transglutaminase molecule, the hypothesis of anti-factor XIII antibodies production in CD was formulated. However, even if in one study anti-factor XIII antibodies were identified in 2 out of 20 CD patients, the susceptibility to hemorrhage was not proved [72]. In one case report, factor V deficiency due to protein malabsorption was presumed, as the genetic testing excluded a hereditary condition and the serum factor V levels corrected under GFD [26].

For the hemorrhagic events treatment, vitamin K administration was reported in many of the published cases. Taking into account the risk of hematoma, intramuscular administration of vitamin K is not recommended. Intravenous administration should be carefully followed for the risk of anaphylactic reactions [49]. Also, the risk of hemolytic adverse effects in patients with glucose-6 phosphate-dehydrogenase deficiency should be considered [68]. Further, oral vitamin K administration will continue the parenteral one [50]. Especially in patients with long-standing vitamin K deficiency, the rapid correction or administration after the

prothrombin time normalization is accompanied by a risk of ischemic events [74]. The hemorrhagic events are possible life-threatening conditions and might occur in the context of severe metabolic disturbances due to malabsorption [20, 22, 44, 75]; therefore, the patients' management should be rapidly and carefully established. Long term treatment is addressed to CD, having GFD as the gold standard. Generally, the evolution of the coagulation parameters under GFD is favorable.

In this review we focused only on the coagulopathy presenting as hemorrhagic events in CD. However, a pro-coagulant state might characterize the CD clinical appearance. The hepatic production of the proteins C and S is also vitamin K dependent [76-78]. Moreover, folate deficiency could be found in CD patients due to protein loss [39] with subsequent hyperhomocysteinaemia [76, 77]. Other authors described in CD changes such as endothelial dysfunction, platelets impairment, increased apoptosis and exposure of phospholipids [51]. Therefore, positive antiphospholipids antibodies could be found [77, 78, 80].

The present study has some limitations. The quality of the data collected is yielding a low degree of evidence as only case reports have been published so far. There is a need for prospective studies to better understand the risk factors for hemorrhagic events in CD patients. Also, in 5 cases we had access only to the article abstract. Even when the full text was available, not all the data were necessarily present. Moreover, we analyzed only the data of published case reports without any connection between them, as studies with more subjects are lacking. However, we conducted an extensive literature search regarding hemorrhagic events in CD, bringing interesting information to a less known subject.

CONCLUSION

Celiac disease testing should be considered in all patients with idiopathic hemorrhagic diathesis, coagulation troubles, or low levels of vitamin K of unknown origin. To the best of our knowledge, this is the first review focusing on overall hemorrhagic events in CD regardless of the clinical type of presentation (e.g. hemoptysis, melena, hematoma). We intended to draw attention and increase awareness to an important, possible life-threatening CD clinical feature.

Conflicts of interest: No conflict to declare. No funding was received for this study.

Authors' contributions: C.J.: concept of the manuscript; A.D.: literature search and concept of the review; A.D. and D.V.B.: manuscript drafting; A.M., C.J. and D.V.B.: patient management; A.P., M.J. and A.D.: summary of the relevant data in the table; A.P., C.J. and M.J.: critical review of the manuscript. All authors read and approved the final version of the manuscript.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://www.jgld.ro/wp/archive/ n1/a15 and http://dx.doi.org/10.15403/jgld.2014.1121.271.cld

REFERENCES

1. Murray JA, Van Dyke C, Plevak MF, Dierkhising RA, Zinsmeister AR, Melton LJ 3rd. Trends in the identification and clinical features of celiac disease in a North American community, 1950-2001. Clin Gastroenterol Hepatol 2003;1:19–27. doi:10.1053/jcgh.2003.50004
2. Ehsani-Ardakani MJ, Fallahian M, Rostami K, et al. Celiac disease and dysfunctional uterine bleeding; the efficiency of gluten free diet. Bratisl Lek Listy 2014;115:19–21. doi:10.4149/BLL_2014_004
3. Tu H, Parmentier L, Stieger M, et al. Acral purpura as leading clinical manifestation of dermatitis herpetiformis: report of two adult cases with a review of the literature. Dermatology 2013;227:1–4. doi:10.1159/000347108
4. McNicholas BA, Bell M. Coeliac disease causing symptomatic hypocalcaemia, osteomalacia and coagulapathy. BMJ Case Rep 2010;2010:bcr0920092262. doi:10.1136/bcr.09.2009.2262
5. Adhiyaman V, Adhiyaman S, Vaishnavi A. Life-threatening hypomagnesemic hypocalcemia and hypokalemia in celiac disease. Am J Gastroenterol 2001;96:3473. doi:10.1111/j.1572-0241.2001.05367.x
6. Oz B, Akan O, Kocyigit H, Gürgan HA. Proximal muscle weakness as a result of osteomalacia associated with celiac disease: a case report. Osteoporos Int 2016;27:837–840. doi:10.1007/s00198-015-3285-9
7. Kozanoglu E, Basaran S, Goncu MK. Proximal myopathy as an unusual presenting feature of celiac disease. Clin Rheumatol 2005;24:76–78. doi:10.1007/s10067-004-0977-5
8. Gutiérrez S, Toro M, Cassar A, et al. Celiac crisis: presentation as bleeding diathesis. Acta Gastroenterol Latinoam 2009;39:53–54.
9. Chen CS, Cumbler EU, Triebling AT. Coagulopathy due to celiac disease presenting as intramuscular hemorrhage. J Gen Intern Med 2007;22:1608–1612. doi:10.1007/s11606-007-0297-y
10. Medina-Banegas A, Pastor-Quirante FA, Osete-Albaladejo J, López-Meseguer E, López-Andreu F. Nasal septal perforation in a patient with subclinical celiac disease: a possible new association. Eur Arch Otorhinolaryngol 2005;262:928–931. doi:10.1007/s00405-004-0865-2
11. Laudage G, Schirp J. Life threatening epistaxis due to plasma coagulation disorder as a partial manifestation of gluten sensitive enteropathy. Leber Magen Darm 1995;25:94–96.
12. Popp A, Jurcuț C, Balaban DV, Șotcan M, Laurila K, Jinga M. Severe Alveolar Hemorrhage - What's in it for the Gastroenterologist? J Gastrointestin Liver Dis 2016;25:555–558. doi:10.15403/jgld.2014.1121.254.cut
13. Khilnani GC, Jain N, Tiwari P, Hadda V, Singh L. A young man with hemoptysis: Rare association of idiopathic pulmonary hemosiderosis, celiac disease and dilated cardiomyopathy. Lung India 2015;32:70–72. doi:10.4103/0970-2113.148457
14. Singhal KK, Janmeja AK, Sodhi R, Punia RS. Hemoptysis in patients of celiac disease with disproportionately severe anemia: tip of the iceberg? Multidiscip Respir Med 2013;8:25. doi:10.1186/2049-6958-8-25
15. Nishino M, Patrick JL, Connors JM. Case 155: Lane-Hamilton syndrome. Radiology 2010;254:985–988. doi:10.1148/radiol.09082062
16. Mayes DH, Guerrero ML. A few good men: a Marine with hemoptysis and diarrhea. Idiopathic pulmonary hemosiderosis and celiac sprue. Chest 2008;134:644–647. doi:10.1378/chest.07-2834
17. Bouros D, Panagou P, Rokkas T, Siafakas NM. Bronchoalveolar lavage findings in a young adult with idiopathic pulmonary haemosiderosis and coeliac disease. Eur Respir J 1994;7:1009–1012.
18. Pacheco A, Casanova C, Fogue L, Sueiro A. Long-term clinical follow-up of adult idiopathic pulmonary hemosiderosis and celiac disease. Chest 1991;99:1525–1526. doi:10.1378/chest.99.6.1525

19. Zhang JC, Wang Y, Wang XF, Zhang FX. Type I enteropathy-associated T-cell lymphoma in the colon of a 29-year-old patient and a brief literature review. Onco Targets Ther 2016;9:863–868. doi:10.2147/OTT.S96745
20. Van Domselaar F, Matoso MD, Piccioni HL, et al. Gastrointestinal bleeding and intestinal perforation due to polyarteritis nodosa in a patient with celiac disease. A case report. Acta Gastroenterol Latinoam 2011;41:312–316.
21. Gwiggner M, Patel P. An unusual case of obscure gastrointestinal bleeding in a patient with coeliac disease. Case Rep Gastrointest Med 2011;2011:634684. doi:10.1155/2011/634684
22. Weiss AA, Yoshida EM, Poulin M, Gascoyne RD, Owen DA. Massive bleeding from multiple gastric ulcerations in a patient with lymphocytic gastritis and celiac sprue. J Clin Gastroenterol 1997;25:354–357.
23. Musumba CO, Campbell F, Subramanian S, Richardson P, Smart HL. Acute variceal bleeding in a man with coeliac disease. Gut 2013;62:740–740. doi:10.1136/gutjnl-2012-303032
24. Rana SS, Sharma V, Rao C, Singh K, Bhasin DK. Obscure gastrointestinal bleeding persisting for a decade: A rare manifestation of a common disease. Ann Gastroenterol 2012;25:271–273.
25. Kimchi NA, Broide E, Zehavi S, Halevy A, Scapa E. Capsule endoscopy diagnosis of celiac disease and ileal tumors in a patient with melena of obscure origin. Isr Med Assoc J 2005;7:412–413.
26. Shanahan F, Aburajab A, Goodacre R, Blajchman MA. Factor V deficiency and its reversal with gluten restriction. In a patient with celiac disease. Arch Intern Med 1983;143:2009–2010. doi:10.1001/archinte.1983.00350100193038
27. Lubel JS, Burrell LM, Levidiotis V. An unexpected cause of macroscopic haematuria. Med J Aust 2005;183:321–323.
28. Moussa AM, Cavestro GM, Coruzzi P, Maino M, De Angelis GL, Di Mario F. Macrohematuria caused by a fall in prothrombin activity as a clinical presentation of celiac disease. J Clin Gastroenterol 2002;35:359–360.
29. Bhattacharyya A, Patel MK, Tymms DJ. Coeliac disease in adults: variations on a theme. J R Soc Med 1999;92:286–289.
30. Cabrera Chaves T, Gomollón García F, Simón Marco MA, Uribarrena Echevarría R, Alvarez Alegret R.Hemorrhagic diathesis as initial clinical manifestation of celiac disease. Rev Clin Esp 1996;196:28–31.
31. Gerson DE, Lewicki AM. Intramural small bowel hemorrhage: complication of sprue. Radiology 1973;108:521–522. doi:10.1148/108.3.521
32. Graham DR, Bellingham AJ, Alstead E, Krasner N, Martindale J. Coeliac disease presenting as acute bleeding disorders. Postgrad Med J 1982;58:178–179. doi:10.1136/pgmj.58.677.178
33. Lane DJ, Hamilton WS. Idiopathic Steatorrhoea and Idiopathic Pulmonary Hemosiderosis. Br Med J 1971;2:89–90. doi:10.1136/bmj.2.5753.89
34. Grover PJ, Jayaram R, Madder H. Management of cerebral venous thrombosis in a patient with Lane-Hamilton syndrome and coeliac disease, epilepsy and cerebral calcification syndrome. Br J Neurosurg 2010;24:684–685. doi:10.3109/02688697.2010.500412
35. Agarwal R, Aggarwal AN, Gupta D. Lane-Hamilton syndrome: Simultaneous occurrence of coeliac disease and idiopathic pulmonary haemosiderosis. Intern Med J 2007;37:65–67. doi:10.1111/j.1445-5994.2006.01226.x
36. Santos JW, Mello Neto AB, Marchiori RC, et al. Pulmonary hemosiderosis associated with celiac disease: improvement after a gluten-free diet. J Bras Pneumol 2012;38:412–414. doi:10.1590/S1806-37132012000300020
37. Malhotra P, Aggarwal R, Aggarwal AN, Jindal SK, Awasthi A, Radotra BD. Coeliac disease as a cause of unusually severe anaemia in a young man with idiopathic pulmonary haemosiderosis. Respir Med 2005;99:451–453. doi:10.1016/j.rmed.2004.09.007
38. Mah MW, Priel IE, Humen DP, Brown NE, Sproule BJ. Idiopathic pulmonary hemosiderosis, complete heart block and celiac disease. Can J Cardiol 1989;5:191–194.
39. Hemoptysis, pulmonary infiltrates, and diarrhea in a 36-year-old man. Am J Med 1986;80:930–938. doi:10.1016/0002-9343(86)90640-6
40. Wright PH, Menzies IS, Pounder RE, Keeling PW. Adult idiopathic pulmonary haemosiderosis and coeliac disease. Q J Med 1981;50:95–102.
41. Pun AH, Kasmeridis H, Rieger N, Loganathan A. Enteropathy associated T-cell lymphoma presenting with multiple episodes of small bowel haemorrhage and perforation. J Surg Case Rep 2014;2014: rju013. doi:10.1093/jscr/rju013
42. Bogaert R. Syndrome de diathèse hémorragique au cours de la sprue. Brux Med1948;28:2458.
43. Moore MJ, Strickland WH, Prichard RW. Sprue with bleeding from hypoprothrombinemia. AMA Arch Intern Med 1956;97:814–816.
44. Austin A, Campbell E, Lane P, Elias E. Nodular regenerative hyperplasia of the liver and coeliac disease: potential role of IgA anticardiolipin antibody. Gut 2004;53:1032–1034. doi:10.1136/GUT.2003.036806
45. Riestra S, Domínguez F, Rodrigo L. Nodular regenerative hyperplasia of the liver in a patient with celiac disease. J Clin Gastroenterol 2001;33:323–326.
46. Granel B, Rossi P, Frances Y, Henry JF. Bilateral massive adrenal haemorrhage revealing coeliac disease. QJM 2005;98:70–71. doi:10.1093/qjmed/hci011
47. Heiinger K, Kemkes-Matthes B, Matthes KJ, Franke F, Voss R, Heckers H. Endemic sprue: its first diagnosis based on bleeding complications. Dtsch Med Wochenschr 1995;120:1543–1546. doi:10.1055/s-2008-1055511
48. Kwolek S, Deming P. Warfarin hypersensitivity due to gluten-sensitive enteropathy: a case study. Clin Lab Sci 2012;25:78–80.
49. Hussaini SH, Ahmed S, Heatley RV. Celiac disease and hypoprothrombinemia. Nutrition 1999;15:389–391. doi:10.1016/S0899-9007(99)00028-3
50. Devignes J, Roche JF, de Maistre E, Goux A, Rieder D, Lecompte T. A case of celiac disease with late diagnosis by very long prothrombin and activated partial prothrombin times. Ann Biol Clin (Paris) 2004;62:597–600.
51. Cameron EA, Stewart JA, West KP, Rathbone BJ. Coeliac disease presenting with intraperitoneal haemorrhage. Eur J Gastroenterol Hepatol 1998;10:619–620.
52. Rajendra A, Perepletchikov A, Kopelman RI. Broadening the Differential Diagnosis. Am J Med 2006;119:410–412. doi:10.1016/j.amjmed.2006.03.006
53. Vaynshtein G, Rosenbaum H, Groisman GM, Markel A. Celiac sprue presenting as severe hemorrhagic diathesis due to vitamin K deficiency. Isr Med Assoc J 2004;6:781–783.
54. Avery RA, Duncan WE, Alving BM. Severe vitamin K deficiency induced by occult celiac disease BR96-026. Am J Hematol 1996;53:55. doi:10.1002/(SICI)1096-8652(199609)53:1<55::AID-AJH18>3.0.CO;2-2
55. Shaw S. Idiopathic steatorrhoea and haemorrhage due to iron-dextran injection. Br Med J 1960;2:647–648.
56. Mager DR, Qiao J, Turner J. Vitamin D and K status influences bone mineral density and bone accrual in children and adolescents with celiac disease. Eur J Clin Nutr 2012;66:488–495. doi:10.1038/ejcn.2011.176

57. Jamma S, Rubio–Tapia A, Kelly CP, et al. Celiac crisis is a rare but serious complication of celiac disease in adults. Clin Gastroenterol Hepatol 2010;8:587–590. doi:10.1016/j.cgh.2010.04.009
58. Mrad RA, Ghaddara HA, Green PH, El-Majzoub N, Barada KA. Celiac crisis in a 64-year-old woman: An unusual cause of severe diarrhea, acidosis, and malabsorption. ACG Case Rep J 2015;2:95–97. doi:10.14309/crj.2015.16
59. Grisolano SW, Oxentenko AS, Murray JA, Burgart LJ, Dierkhising RA, Alexander JA. The usefulness of routine small bowel biopsies in evaluation of iron deficiency anemia. J Clin Gastroenterol 2004;38:756–760.
60. Mant MJ, Bain VG, Maguire CG, Murland K, Yacyshyn BR. Prevalence of occult gastrointestinal bleeding in celiac disease. Clin Gastroenterol Hepatol 2006;4:451–454. doi:10.1016/j.cgh.2005.12.010
61. Fine KD. The prevalence of occult gastrointestinal bleeding in celiac sprue. N Engl J Med 1996;334:1163–1167. doi:10.1056/NEJM199605023341804
62. Green PH, Cellier C. Celiac Disease. N Engl J Med 2007;357:1731–43. doi:10.1056/NEJMra071600
63. Lane DJ, Hamilton WS. Idiopathic steatorrhoea and idiopathic pulmonary haemosiderosis. Br Med J 1971;2:89–90.
64. Chen XY, Sun JM, Huang XJ. Idiopathic pulmonary hemosiderosis in adults: Review of cases reported in the latest 15 years. Clin Respir J 2017;11:677-681. doi:10.1111/crj.12440
65. Taytard J, Nathan N, de Blic J, et al. New insights into pediatric idiopathic pulmonary hemosiderosis: the French RespiRare(®) cohort. Orphanet J Rare Dis 2013;8:161. doi:10.1186/1750-1172-8-161
66. Raj N, Cepeda J, Gottleib S. A Rare Case of Idiopathic Pulmonary Hemosiderosis in an Adult. J Pulm Respir Med 2014;4:193. doi:10.4172/2161-105X.1000193
67. Olén O, Montgomery SM, Elinder G, Ekbom A, Ludvigsson JF. Increased risk of immune thrombocytopenic purpura among inpatients with coeliac disease. Scand J Gastroenterol 2008;43:416–422. doi:10.1080/00365520701814028
68. Williams SF, Mincey BA, Calamia KT. Inclusion body myositis associated with celiac sprue and idiopathic thrombocytopenic purpura. South Med J 2003;96:721–723. doi:10.1097/01.SMJ.0000051148.97720.69
69. Sheehan NJ, Stanton-King K. Polyautoimmunity in a young woman. Br J Rheumatol 1993;32:254–256.
70. Yamout B, Usta J, Itani S, Yaghi S. Celiac disease, Behçet, and idiopathic thrombocytopenic purpura in siblings of a patient with multiple sclerosis. Mult Scler J 2009;15:1368–1371. doi:10.1177/1352458509345908
71. Cavallaro R, Iovino P, Castiglione F, et al. Prevalence and clinical associations of prolonged prothrombin time in adult untreated coeliac disease. Eur J Gastroenterol Hepatol 2004;16:219–223.
72. Sjöber K, Eriksson S, Tenngart B, Roth EB, Leffler H, Stenberg P. Factor XIII and tissue transglutaminase antibodies in coeliac and inflammatory bowel disease. Autoimmunity 2002;35:357–364.
73. Hosnut FO, Canan O, Özcay F, Özbek N. Awareness of glucose-6 phosphate-dehydrogenase deficiency in celiac disease. Acta Paediatr 2010;99:786–788. doi:10.1111/j.1651-2227.2009.01669.x
74. Florholmen J, Waldum H, Nordøy A. Cerebral thrombosis in two patients with malabsorption syndrome treated with vitamin K. Br Med J 1980;281:541.
75. Gheorghe L, Popescu I, Gheorghe C, Aposteanu G, Popescu C, Oproiu A. Fatal intestinal hemorrhage complicating ileal lymphoma after cyclosporine for unresponsive celiac disease. Hepatogastroenterology 1997;44:1342–1345.
76. Thorburn D, Stanley AJ, Foulis A, Campbell Tait R. Coeliac disease presenting as variceal haemorrhage. Gut 2003;52:758. doi:10.1136/gut.52.5.758
77. Berthoux E, Fabien N, Chayvialle JA, Ninet J, Durieu I. Adult celiac disease with thrombosis: a case series of seven patients. Role of thrombophilic factors. Rev Med Interne 2011;32:600–604. doi:10.1016/j.revmed.2011.02.025
78. Ghannouchi Jaafoura N, Atig A, Bouker A, et al. Thrombose intracardiaque au cours d'une maladie cœliaque. J Mal Vasc 2014;39:203–206. doi:10.1016/j.jmv.2013.12.002
79. Lerner A, Agmon-Levin N, Shapira Y, et al. The thrombophilic network of autoantibodies in celiac disease. BMC Med 2013;11:89. doi:10.1186/1741-7015-11-89
80. La Villa G, Pantaleo P, Tarquini R, et al. Multiple immune disorders in unrecognized celiac disease: A case report. World J Gastroenterol 2003;9:1377–1380. doi:10.3748/wjg.v9.i6.1377.

Supplementary Table I. Case reports of CD patients with hemorrhagic events

Index	Age (years)	Gender	Associated conditions	Coagulation parameters				Sympto-matology duration (years)	Digestive sympto-matology	Weight loss	Evolution under GFD	
				PT (s) or INR or activity (%)	aPTT (s)	PLT (x10^3/dl)	Coagulation factors					
1	29	M	intermittent hematochezia, severe anemia (4.5g/dl), EATL, liver metastasis, DIC	PT act - N (68.9%)	N (41.1)	-	-	0.5	yes	yes	-	[19]
2	48	F	severe hemoptysis, DAH - IPH (LHS), severe anemia (3.6g/dl)	INR - H	H	-	-	-	-	-	P	[12]
3	19	M	recurrent hemoptysis, IPH (LHS), anemia (7.8g/dl), dilated cardiomiopathy	N	N	H (540)	-	-	yes	no	P	[13]
4	60	M	recurrent rectal bleeding, bleeding intestinal, ulcers, EATL, bowel perforation	-	-	-	-	-	-	yes	-	[41]
5	27	M	hemoptysis, DAH - IPH (LHS), severe anemia (5g/dl)	N	N	N (210)	-	0.2	-	no	P	[14]
6	49	M	melena, variceal bleeding, splenomegaly, pancytopenia, idiopathic non-cirrhotic portal hypertension, anemia (6.2g/dl)	N	N	L (63)	-	> 1	-	-	N	[23]
7	60	F	melena, small intestine ulcers	-	-	-	-	12	-	-	P	[24]
8	29	M	IPH (LHS), anemia (5.5g/dl)	-	-	-	-	0.6	no	yes	P	[36]
9	66	M	hematochezia, intestinal ulcers with perforation, polyarterita nodosa (superior mesenteric artery)	-	-	-	-	8	yes	yes	-	[20]
10	72	M	hematochezia, warfarin anticoagulation for atrial fibrillation, jejunal adeno-carcinoma, anemia	-	-	-	-	-	-	-	-	[21]
11	50	F	hemoptysis, IPH (LHS), anemia (7.7g/dl), vitamin B12 deficiency	PT - N (14.6) INR – N (1.1)	N (34.2)	N (370)	-	> 10	-	-	-	[15]
12	26	F	IPH (LHS), cerebral venous thrombosis, epilepsy ceased under GFD, cerebral calcifications	-	-	-	-	-	-	yes	N	[34]
13	26	F	epistaxis, gingivorrhagia, hematuria, melena, limbs hematomas, hypoCa, celiac crisis	PT act – L (10%)	H (155)	-	-	> 2	yes	-	P	[8]
14	40	M	scant hemoptysis, IPH (LPH)	N	N	N	-	0.3	no	-	N	[16]
15	64	M	upper arm muscle hemorrhage, epistaxis, periorbital ecchymosis, hemorrhagic vesicular dermatitis, bruises, foot petechiae, hypoCa, hypoD, anemia (11-8.4g/dl)	PT - H (200)	H (143)	N	-	9	yes	-	P	[9]
16	38	M	IPH (LHS), anemia (8.3g/dl)	-	-	-	-	1	no	-	P	[35]
17	54	F	rectal bleeding, internal hemorrhoids, temporal lobe seizure disorder	-	-	N (460)	-	0	no	yes	P	[52]

Table I (continued)

18	35	F	recurrent epistaxis, nasal septal perforation, anemia	-	-	-	-	0	no	-	P	[10]
19	74	M	melena, two ileal tumors (carcinoid), anemia (7g/dl)	-	-	-	-	0.2	no	-	-	[25]
20	28	M	IPH (LHS), streaky hemoptysis, anemia (5.1g/dl)	-	-	-	-	0.1/4	no	no	P	[37]
21	43	F	bilateral massive adrenal hemorrhage, cachexia, hypoD, osteopenia	PT act - L (16%)	-	-	II – L, X – L, V – N	10	yes	yes	P	[46]
22	25	M	macroscopic hematuria, bilateral loin pain, low vitamin A, E, B12, folate	INR - H (> 10)	H (115)	H (727)	II – L, VII – L, IX – L, X – L	2	yes	-	P	[27]
23	41	M	multiple hematomas, easy bruising, anemia (6.4g/dl)	unclot-table	H (106)	L (122)	II – L, V – N, VII – L, VIII – N, IX – L, X – L	0.3	yes	yes	P	[53]
24	55	F	intractable hemorrhage following liver biopsy, liver nodular regenerative hyperplasia, ascites, thrombocytopenia	INR ≤ 1.3	-	-	-	24	-	yes	-	[44]
25	28	M	macrohematuria, lumbar pain, fever	PT act - L (0%)	-	-	-	0.1	yes	-	P	[28]
26	50	M	cerebral subcortical hemorrhage, liver nodular hyperplasia, esophageal varices, (history: hematuria), lymphocytic colitis	PT act - N (100%)	-	L (85)	-	14	yes	-	N	[45]
27	32	F	trunk and upper limbs bruising, watery diarrhea, low vitamin A and E, low normal vitamin D	PT - H (94)	H (86)	N (378)		0.5	yes	yes	P	[49]
28	65	F	hematuria, extensive bruising	INR – H (10)	-	N	-	0	-	-	P	[29]
29	42	M	hemorrhagic shock, spontaneous left mesocolonic hematoma, anemia (8.8g/dl)	INR – H (1.8)	H	-	-	-	-	-	P	[51]
30	-	M	massive intestinal bleeding after cyclosporine, EATL	-	-	-	-	-	-	-	N	[75] abs
31	73	M	severe melena and hematochezia, gastric and intestinal ulcerations, lymphocytic gastritis	-	-	-	-	1.2	yes	yes	-	[22]
32	-	-	hematuria, spontaneous cutaneous hemorrhage	-	-	-	-	-	no	no	-	[30] abs
33	68	F	limbs ecchymoses, hypoCa, low normal vitamin D, anemia	PT - H (45.5)	H (103)	L (173)	II – L, V – N, VII – L, IX – L, X – L	> 1	no	yes	P	[54]
34	47	M	legs hematomas, anemia (5.6g/dl), low levels vitamin A and E	PT act - L (5%)	H (180)	-	-	0	-	-	P	[47] abs
35	73	F	recurrent epistaxis, coagulopathy	-	-	-	-	12	yes	-	-	[11] abs
36	19	M	IPH (LHS), recurrent hemoptysis, anemia (7.1g/dl), vitamin B12 deficiency	-	-	-	-	1	-	yes	P	[17]

Table I (continued)

37	22	M	recurrent hemoptysis, IPH (LHS), anemia (12g/dl), blood transfusions since age of 7 years	N	N	N	-	15	no	-	P	[18]
38	24	M	IPH (LHS), complete heart block	-	-	-	-	-	-	-	-	[38] abs
39	36	M	IPH (LHS), anemia (8.4g/dl), low folate	PT - N (10.7)	N (38.6)	N (222)		2	yes	-		[39]
40	26	M	melena, widespread ecchymoses, spontaneous hematomas	PT - H (103)	H (110)	N	II – L, V – L, VII – L, IX – L, X - L	> 10	yes	-	P	[26]
41	27	F	limbs severe bruising, legs hematomas, hypoCa, anemia (9.5g/dl), low folate	PT - H (120s)	-	H (510)	II – L, VII – L, X – L	0.3	yes	yes	P	[32]
	21	F	spontaneous bruising, leg hematoma, knee haemarthrosis, amenorrhea, rectorragia, anemia (9.6-3.9g/dl)	PT - H (180s)	-			-	no	yes	P	
42	26	M	IPH (LHS)	-	-	-		-	-	-	P	[35] - abs,[40]
43	57	F	macrohematuria, subserosal intestinal hemorrhage, intramural intestinal hematoma, needle puncture hematoma	PT - H (10xN)	N	N	II - N V - N	5	yes	yes	-	[31]
44	23	M	IPH (description of LHS), anemia (6.9g/dl)	-	-	-	-	> 15	yes	-	-	[33]

abs: abstract; AGA: anti-gliadin antibodies; aPPT: activated partial thromboplastin time; CD: celiac disease; DAH: diffuse alveolar hemorrhage; DIC: disseminated intravascular coagulation; DGP: anti-deamidated gliadin antibodies; DIC: disseminated intravascular coagulation; EATL: enteropathy-associated T cell lymphoma; EMA: anti-endomysial antibodies; GFD: gluten-free diet; hypoCa: hypocalcemia; hypoD: hypovitamin D; INR: international normalized ratio; IPH: idiopathic pulmonary hemosiderosis; LHS: Lane Hamilton syndrome; PLT: platelets; PT: prothrombin time; tTG: anti-tissue transglutaminase antibodies; s: seconds.
F – feminin; H – high; L – low; M – male; N – normal; Neg – negative; P – positive; "-" – unknown.