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

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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], dysrythymia [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.
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, 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 antカードiolipin antibodies are produced during the gluten-induced enterocyte destruction. The veins of the affected intestine drain in the small portal veins and antカードiolipin 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 antカードiolipin 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 hemorata, 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 conditions [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

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

<table>
<thead>
<tr>
<th>Index</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Associated conditions</th>
<th>Coagulation parameters</th>
<th>Symptomatology duration (years)</th>
<th>Digestive symptomatology</th>
<th>Weight loss</th>
<th>Evolution under GFD</th>
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<td>M</td>
<td>intermittent hematochezia, severe anemia (4.5g/dl), EATL, liver metastasis, DIC</td>
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<td>-</td>
<td>-</td>
<td>P</td>
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<td>melena, varicose bleeding, splenomegaly, pancytopenia, idiopathic non-cirrhotic portal hypertension, anemia (6.2g/dl)</td>
<td>N N N L (63) &gt; 1</td>
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<td>IPH (LHS), streaky hemoptysis, anemia (5.1g/dl)</td>
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<td>bilateral massive adrenal hemorrhage, cachexia, hypoP3, osteopenia</td>
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<td>23</td>
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<td>multiple hematomas, easy bruising, anemia (6.4g/dl)</td>
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<td>L (122)</td>
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<td>INR ≤ 1.3</td>
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<td>macrohematuria, lumbar pain, fever</td>
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<td>- L (85)</td>
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<td>trunk and upper limbs bruising, watery diarrhea, low vitamin A and E, low normal vitamin D</td>
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<td>H (86)</td>
<td>N (378)</td>
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<td>INR - H (1.8)</td>
<td>H</td>
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<td>[51]</td>
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<td>-</td>
<td>M</td>
<td>massive intestinal bleeding after cyclosporine, EATL</td>
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<td></td>
<td>N</td>
<td>75 abs</td>
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<td>severe melena and hematochezia, gastric and intestinal ulcerations, lymphocytic gastritis</td>
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<td>1.2 yes yes</td>
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<td>limbs ecchymoses, hypoCa, low normal vitamin D, anemia</td>
<td>PT - H (45.5)</td>
<td>H (103)</td>
<td>L (173)</td>
<td>II - L, V - N, VII - L, IX - L, X = L</td>
<td>&gt; 1 no yes P</td>
</tr>
<tr>
<td>34</td>
<td>47</td>
<td>M</td>
<td>legs hematomas, anemia (5.6g/dl), low levels vitamin A and E</td>
<td>PT act - L (5%)</td>
<td>H (180)</td>
<td>- - 0 -</td>
<td>- P</td>
<td>[47]</td>
</tr>
<tr>
<td>35</td>
<td>73</td>
<td>F</td>
<td>recurrent epistaxis, coagulopathy</td>
<td>- - - 12</td>
<td></td>
<td>yes -</td>
<td>-</td>
<td>[11]</td>
</tr>
<tr>
<td>36</td>
<td>19</td>
<td>M</td>
<td>IPH (LHS), recurrent hemoptysis, anemia (7.1g/dl), vitamin B12 deficiency</td>
<td>- - - 1</td>
<td></td>
<td>yes</td>
<td>P</td>
<td>[17]</td>
</tr>
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Table 1 (continued)
<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Gender</th>
<th>Symptoms/Conditions</th>
<th>PT</th>
<th>Platelets</th>
<th>aPPT</th>
<th>Fibrinogen</th>
<th>Other Tests</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>22</td>
<td>M</td>
<td>recurrent hemoptysis, IPH (LHS), anemia (12g/dl), blood transfusions since age of 7 years</td>
<td>N</td>
<td>N</td>
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<td>38</td>
<td>24</td>
<td>M</td>
<td>IPH (LHS), complete heart block</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>39</td>
<td>36</td>
<td>M</td>
<td>IPH (LHS), anemia (8.4g/dl), low folate</td>
<td>PT - N (10.7)</td>
<td>N (38.6)</td>
<td>N (222)</td>
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<td>40</td>
<td>26</td>
<td>M</td>
<td>melena, widespread ecchymoses, spontaneous hematomas</td>
<td>PT - H (103)</td>
<td>H (110)</td>
<td>N</td>
<td>&gt; 10</td>
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<tr>
<td>41</td>
<td>27</td>
<td>F</td>
<td>limbs severe bruising, legs hematomas, hypoCa, anemia (9.5g/dl), low folate spontaneous bruising, leg hematomas, knee haemorrhosis, amenorrhrea, rectorragia, anemia (9.6-3.9g/dl)</td>
<td>PT - H (120s)</td>
<td>-</td>
<td>H (510)</td>
<td>0.3</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td>21</td>
<td>F</td>
<td></td>
<td>limbs severe bruising, legs hematomas, hypoCa, anemia (9.5g/dl), low folate spontaneous bruising, leg hematomas, knee haemorrhosis, amenorrhrea, rectorragia, anemia (9.6-3.9g/dl)</td>
<td>PT - H (180s)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>no</td>
<td>yes</td>
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<td>42</td>
<td>26</td>
<td>M</td>
<td>IPH (LHS)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>43</td>
<td>57</td>
<td>F</td>
<td>macrohematuria, subserosal intestinal hemorrhage, intramural intestinal hematomas, needle puncture hematomata</td>
<td>PT - H (10xN)</td>
<td>N</td>
<td>N</td>
<td>II - N</td>
<td>5</td>
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<td>44</td>
<td>23</td>
<td>M</td>
<td>IPH (description of LHS), anemia (6.9g/dl)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&gt; 15</td>
<td>yes</td>
</tr>
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</table>

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; 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.