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Review Article

Celiac Disease: What about Hematological Manifestations?

Adel Alhabbal [1,*], Hossam Murad [2], Imad AbouKhamis [1]

[1] Department of Microbiology & Biochemistry, Faculty of Pharmacy, University of Damascus, Damascus, Syria
[2] Molecular Biology and Biotechnology Department, Human Genetics Division, Atomic Energy Commission of Syria, Damascus, Syria

ABSTRACT

Celiac disease (CD) is a systemic disease that is triggered by gluten consumption in genetically susceptible patients, with a predominance approximating nearly 1% of the overall community. Although CD primarily involves the small intestine, it may also affect other bodily systems and present as a disease outside of the gastrointestinal tract. Therefore, individuals who have CD might visit a physician for appraisal of several hematological issues before reaching the diagnosis of CD. Secondary anemia due to vitamin B12 and folic acid deficiency or due to malabsorption of iron are frequent problems in CD. In addition, individuals may reveal thrombocytopenia, leukopenia, venous thromboembolism, hyposplenism, and thrombocytosis. These hematological changes may represent the distinctive features of the disease and should cue the physician to test for CD in a suggestive clinical setting. Identification of non-typical extraintestinal manifestations, including hematologic ones, could provide a significant chance to increase the rate of CD diagnosis, as this disease is grouped with the most underdiagnosed chronic intestinal disorders throughout the world.

This review summarizes new evidence concerning the hematological manifestations of CD, and concentrates on applicable recommendations for physicians.

Keywords: Celiac disease, Anemia, Neutropenia, Thrombocytopenia, Thrombocytosis, Hyposplenism

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INTRODUCTION

In genetically predisposed people, celiac disease (CD) is a chronic, autoimmune disorder caused by sensitivity to gluten consumption. It may occur at any time in the life of persons with the haplotype DQ2 / DQ8 that renders carriers susceptible to this specific ailment and results in gluten- dependent small bowel inflammation, composed of villous atrophy and crypt hyperplasia. Because gluten is the offending agent triggering the autoimmune-mediated villous atrophy, its elimination from diet of patients with CD relieves their symptoms, reconstructs the mucosa of the small bowel, and prevents the development of adverse outcomes. The general prevalence of CD is around 1% globally, with higher rates reported in countries in Northern Europe (1,2). As many people diagnosed with CD have extraintestinal symptoms, CD is acknowledged worldwide as a disease involving multiple organs and not restricted to the small bowel alone. In addition, the typical manifestations of malabsorption syndrome are often seen in children but rarely so in adults, who mostly present with digestive symptoms of moderate, sporadic, and low severity and a wide range of extraintestinal findings (3-6). A wide variety of rheumatological, neurological, hematological, endocrinological,

Corresponding author:
Adel Alhabbal, MD
Syrian Arab Republic, Damascus, Almazzah, 17th April, Damascus University, Faculty of Pharmacy
Tel: + 963 966732802
E-mail: Dr.a.habbal@gmail.com
adel.alhabbal@damascusuniversity.edu.sy

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dermatological, and metabolic manifestations are included in the extraintestinal features of CD (6-9). Hematological manifestations, in particular, are one of the most common presentations and may often be the only abnormality found (10). In this context, a high CD suspicion index is required in individuals with uninterpretable isolated hematological anomalies. This demands improved awareness among physicians from different specialties of general medicine (11). The hematological manifestations of CD comprise a diverse set of disorders, including anemia, alternation in platelet count (thrombocytopenia/thrombocytosis), hemorrhagic or thrombotic incidents, IgA deficiency, hyposplenia, and most frighteningly, lymphoma (12,13). Hematological changes in patients with CD had been recorded in high incidence (84%) throughout the past years (14). Even so, there is still a good chance of missing a diagnosis of CD while dealing with common medical conditions like chronic unresponsive iron deficiency anemia, which results in a significant diagnostic delay. Better identification of the hematological presentations may provide a new tool to raise the diagnostic value of CD, which is considered to be gravely underdiagnosed (15), despite the fact that current guidelines from the American College of Gastroenterology (ACG), the British Society of Gastroenterology (BSG), the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), and the European Society for the Study of Coeliac Disease (ESsCD)(16-19) approach some of these hematological manifestations of CD, but other manifestations are not reported. For this reason, our purpose was to carry out an assessment of new literature information concerning hematological features of CD and their management. In this review, we summed up modernized information concerning hematological features of CD conforming with updated facts published in the literature.

Anemia

Anemia is defined as a lower number of red blood cells or a lower hemoglobin concentration than normal. It is a recurrent finding in individuals with CD and could be considered the main characteristic of CD.

Furthermore, anemia could be the only identified abnormality. Anemia has always been common in the past, especially in patients receiving no treatments. Furthermore, anemia is constantly found in adults who are not diagnosed (20-23). The etiology of anemia is multi-factorial in CD. Anemia is commonly hypo proliferative, and it usually reflects the impaired absorption of basic nutrients such as iron and different kinds of vitamins. Previous studies showed that the total prevalence of anemia has been appraised around 12% to 69% (24-26). However, hemolysis is considered a rare cause of anemia among patients with CD. A case of an untreated 11-year-old girl with CD and hemolytic anemia, published by Ivanovski and colleagues suggested that it was essential to use serological methods in the diagnosis of CD in individuals with negative Coombs "immune" hemolytic anemia. Thus, anemia is getting better following the start of a gluten-free diet (27).

Mechanisms of anemia in CD

Different responsible elements are worthy of paying attention to while discussing the mechanisms implicated in anemia in patients with CD.

Abnormal iron absorption

Impaired iron absorption is clearly the main cause of anemia in CD in addition to malabsorption of other nutritional elements like cobalamin and folate. The absorption of iron in the duodenum is widely based on many factors, including undamaged mucosal surface and intestinal acidity. The chief reason for irregular iron absorption is villous atrophy of the bowel mucosa that is considered laboratory proof of anemia (iron deficiency) in individuals suffering from anemia with CD. Abnormalities of iron absorption are further supported by oral iron therapy and oral iron loading failure in elevating serum levels of iron (20-22).

Increased blood loss

A study has revealed that occult blood loss from the gastrointestinal tract was detected in approximately 50% of individuals affected by CD. This finding correlated with the severity of villous atrophy (28). However, the use of indirect guaiac examination for determining the presence of bleeding proved an important limitation to the study. Daily blood loss surpassing 1.5 mL in succeeding research utilizing 51 Cr radiolabeled red blood cells was found in just one patient from 18 studied individuals. Nevertheless,

few studies discovered that the frequency of positive occult blood results rate in CD was very low and did not exceed that in the overall community. Therefore, although some patients with CD may suffer from abnormal intestinal bleeding, it does not seem to have a key role in causing anemia, and this finding is still controversial due to the supporting evidence of increased fecal blood in CD (20, 28).

Abnormal vitamins absorption

Several micronutrients, essential for normal hematopoiesis, are malabsorped in CD and thus may lead to anemia. Patients with CD have been described to have sideropenia, vitamin B12, and folic acid deficiency (20-30). Moreover, adults and children with CD have also been shown to have copper deficiency, which can result in thrombocytopenia and anemia (31,32). Other causative factors such as a decrease in the levels of pyridoxine, vitamin B5, and Vitamin B2 have been reported in individuals with CD; however, new details are missing (20).

Inflammation

Pro-inflammatory cytokines have a fundamental part in the cytotoxic mechanisms and inflammation engaged in the pathogenicity of CD. Some cytokines, especially interleukin 6 and interferon-gamma, are potent mediators of hypoferremia in inflammation including their influence on the production of iron regulatory hormone (Hepcidin) (33, 34, 35, 36). In the case of increased hepcidin synthesis, ferroportin degradation is increased, and the release of iron from macrophage & enterocytes is inhibited as well. This leads up to marked instability in iron homeostasis that relates to anemia pertaining to chronic disease (34).

Iron deficiency anemia (IDA)

An observational and retrospective study by Jones and colleagues revealed that IDA was the most frequent problem in 32 patients with CD (37). A mean corpuscular volume (MCV) beneath 80 fL, low serum iron, in addition to low ferritin, are the most common laboratory findings in IDA (38). However, IDA is commonly subsequent to improper absorption of iron (39), and conceivably to gastrointestinal bleeding (28).

The ambiguous part of gastrointestinal bleeding in iron deficiency anemia was studied in 1996. 50% of the participants were examined using guaiac in order to determine the presence of bleeding. Apparently, bleeding was associated with the severity of villous atrophy (28). An additional investigation has proposed that bleeding is not common in CD by using 51 Cr radiolabeled red cells (40). Therefore, the proof that supports the increased rate of fecal blood loss in CD remains in question, and the possibility of bleeding as an important cause of iron deficiency in these subjects is weakly entertained. IDA is mostly explained by malabsorption as iron absorption takes place in the proximal duodenum, which is substantially implicated in CD (38). Furthermore, the distinctive aspect of iron deficiency anemia related to CD manifests in the refractoriness to iron administrated orally, which strongly points toward iron malabsorption (41). Hence, in the absence of clear proof for bleeding from the gastrointestinal tract and in the presence of refractory anemia despite oral iron supplements, CD diagnosis must be taken into consideration in all patients having IDA.

After endoscopy and biopsy, a gluten-free diet must be started immediately. The cause behind the individual's recuperation from anemia in 180 to 360 days is the gluten-free diet and its implication in restoring the normal histological architecture of the intestinal mucosa (38). Awaiting histological normalization, it is sensible to require serum iron, serum ferritin, and total iron binding capacity (TIBC) besides regular CBCD and a peripheral smear. However, iron can be substituted if the anemia is symptomatic, TIBC > 380 mg/dL, or serum iron < 50 mg/dL.

Vitamin B12 (cobalamin) deficiency

Vitamin B12 is basically found in animals' sources such as eggs, milk, and meat (42), and its deficiency is linked to neurological, hematological, and psychiatric presentations. Hematological features include megaloblastic anemia and pancytopenia (43). Because serum vitamin B12 and folate measurements are lacking in sensitivity and specificity, methylmalonic acid (MMA) and homocysteine (Hcy) measurement in serum and urine is used in increased frequency (42). Patients who have B12 deficiency record a high level of both previously mentioned metabolites. However, patients who have folate deficiency are expected to show increased levels of homocysteine only (42).

Cobalamin deficiency is believed to be less common in CD than folate and iron deficiencies since the absorption of cobalamin takes place in the terminal ileum, and the latter is commonly spared in most cases of CD (44). Three suppositions attempted to figure out the causes of vitamin B12 deficiency in CD: extreme ileal villus atrophy subsequent to elevated amounts of consumed gluten (45), duodenal disease causing declining pancreatic excretion of protein R, which may result in malabsorption of cobalamin (46), and lastly gastric intrinsic factor deficiency linked to autoimmunity (47). Many experts illustrate that the deficiency of vitamin B12 is consequent to overconsumption of folate (44) or to the excessive growth of bacteria in advanced stages of the disease (47). Nevertheless, 56% of patients with CD and anemia and 30% of such patients without anemia suffer from vitamin B12 deficiency (48), as shown in a study conducted by Dahele and colleagues. Due to the hypothetical peril of precipitating subacute combined deterioration of the spinal cord in case of sole folate substitution in cobalamin-deficient individuals, it is still wise to look for vitamin B12 deficiency in every anemic individual before initiating folate or iron treatment.

Folate deficiency

Vitamin B9 (folic acid) is a pivotal component of nucleic acid and amino acids metabolism and regulation (49). In regard to the relationship between normal hematopoiesis and central nervous system development, sufficient vitamin B9 is required. However, malabsorption of folic acid is common in diseases of the small intestine, including the jejunum (49,50). In relation to cobalamin deficiency, folate can be reduced along with vitamin B12 in individuals affected by the latter deficiency. But in contrast to cobalamin, red blood cell folate undergoes less transient alterations secondary to changes in folate consumption.

Folic acid deficiency commonly presents with megaloblastic and macrocytic anemia. However, different abnormalities in cell lines are prevalent. As noted in CD, accompanying iron deficiency may cause irregular results in the blood smear, and the characteristics findings of macrocytosis might not be present in persons deficient in both folate and vitamin B12. Blood smears can show a dimorphic picture reflecting both deficiencies' effects. The severe deficiency of folic acid can cause a reduced leukocytes and platelets count, even revealing severe pancytopenia. Normally, diagnosis can be made by evaluating the levels of red cell folate and serum folate; serum folate is constantly increased in patients who have a vitamin B12 deficiency, and it depends largely on folate intake (51).

The raised level of serum homocysteine may aid the diagnose of folate deficiency, but its sensitivity is slightly lower for the deficiency of vitamin B12 (52,42). Earlier studies have shown that numerous untreated patients with CD have folate deficiency (53,54). Folate deficiency is frequent among kids, but it does not cause anemia as demonstrated by two small studies (55,56). Modern studies have assured that the deficiency of folic acid continues to be a familiar result with new CD diagnosis in both teenagers and young adults who have CD seen by screening (57-59). Moreover, folate deficiency is reported in relation to dermatitis herpetiformis (60,61). The levels of homocysteine are prevalently high in individuals with CD during the meantime of diagnosis, which functions as a diagnostic clue (62). Folate supplementation is advised along with a gluten-free diet in the treatment of these patients.

Anemia of chronic disease

Harper and others have reported in an investigation concentrating on clinical characteristics of anemia in CD that despite low ferritin levels in the serum, an indicator of iron deficiency, in most of the anemic participants, ferritin levels were surprisingly elevated 13% of the patients. As gluten-free regimen increased serum ferritin in patients with iron deficiency but decreased ferritin levels in patients with high ferritin in the past, authors deduced that nutritional deficiencies could not clarify anemia in every single case. However, inflammation seems to affect some patients, and this has been verified by the existence of anemia of chronic disease. Bergamaschi and colleagues concentrated in their study on how anemia of chronic disease affected anemia progression among patients with CD. The utilization of refined accuracy tools to determine the presence of anemia of inflammation constituted a distinct feature of designing this study.

Following up patients on a gluten-free diet for one year helped to gather various information on serum ferritin, iron, transferrin, soluble transferrin receptor (sTfRc), interferon-gamma, and endogenous erythropoietin (EPO).

However, Out of 65 anemic patients with CD, 45 experienced iron deficiency anemia that was not complicated and only two patients had folate deficiency.

Regardless of the coexistence of iron deficiency anemia or its absence, anemia of chronic disease was determined in 11 subjects with a prevalence of 17%. Bergamaschi utilized not only prime information but also many other findings in order to improve the sensitivity and specificity of the hematological tests including: (a) the sTfRc/log (ferritin) ratio, which increases in iron deficiency anemia and decreases in anemia of chronic disease, (b) the ferritin/transferrin ratio that decreases in iron deficiency and increases in ACD, and (c) the log(Epo) O/P ratio that depicts the enlargement of endogenous serum EPO compatible with the gravity of anemia, a reaction recognized to be regular in iron deficiency anemia but blunted in the case of anemia of chronic disease.

For the reason of comparison, a cohort of 39 non-anemic patients with CD was evaluated, in whom 45 persons had results compatible with IDA. On the other hand, the results of 11 patients revealed anemia of chronic disease with low STFRC/log (ferritin), high ferritin/transferrin ratio, and a declining log(Epo) O/P ratio implying a blunted EPO response. Notably, serum interferon-gamma levels in anemia of chronic disease were higher by 12-fold than in controls, despite their elevation by 3-fold in the iron-deficient group, demonstrating that a low level of inflammation may exist in all patients with CD suffering from anemia. Hepcidin is considered a significant indicator of ACD.

Contrarily, the connection between iron levels and hepcidin is restricted. Usage of a prohepcidin testing in place of direct hepcidin assays can elucidate the failure to exhibit meaningful distinctions in prohepcidin levels between the three groups in the previously mentioned research. Similar to the study of Bergamaschi, this study revealed that the reaction to a gluten-free regimen in patients with iron deficiency anemia and anemia of chronic disease was favorable after one year with hematological improvement. This suggests that the repression of bowel inflammation through gluten-free nourishment can improve anemia by correcting iron levels and vitamin malabsorption, in addition to terminating the mechanisms that are responsible for anemia imputable to inflammation (33, 34, 35, 36).

Refractory anemia to the gluten-free diet

The etiological factors of refractory anemia are diverse. Poor compliance with a gluten-free diet (GFD) must be excluded before declaring refractory anemia. Other reasons for refractory anemia include chronic inflammation or anemia due to chronic diseases, and refractory CD (RCD). The prevalence of the disease is higher than anticipated due to the involvement of other sections of the bowel or the appearance of other comorbidities (63). The first proposed result is that it is fake refractoriness or continuous anemia due to the adherence to the therapy is not being carried out in a correct manner.

GFD is not a simple choice to consent, nor is it usually performed well (64). The conventional techniques used to observe the illness have low performance, since, for instance, with serological procedures, transgression will be observed in only one of them for every six examinations (65), in addition, it provides little association with villous atrophy (66).

In feces, the immunogenic gluten peptide is assumed to be a better tool to assess commitment to diet (67). In most individuals, CD responds to GFD within few weeks. Unfortunately, in some patients, villous atrophy, malabsorption, and chronic intestinal inflammation persist for 12 months, in spite of good adherence to a GFD, suggesting a diagnosis of RCD (68-70). The latter could result in protraction of signs and symptoms, as well as anemia. RCD is considered uncommon in the pediatric age group, and its precise prevalence and occurrence in adulthood are undisclosed (71). Because of the poor response to therapy and the poorer prognosis in this case, it is necessary to reach a correct diagnosis (72), which is made by exclusion. To confirm the diagnosis of refractoriness or complications, full histological assessment of the whole small intestine is required (73). In a new study (74), the comparison of mucosal involvement between individuals with RCD and

individuals with uncomplicated CD showed that mucosal involvement was more extensive in the refractory group signifying that the greater extent of the disease is one of the direct causes of the persistence of symptoms. In a study (75) performed on adult patients with CD and persistent IDA, 23% of individuals revealed lesions of the small intestine found by video capsule endoscopy (VCE).

In a different new study on the pediatric CD group, (76) anemic patients showed substantially larger histological lesions than non-anemic patients with CD; 92% recuperated from anemia after one year of adherence to GFD.

The performance of VCE is advised in patients with suspected RCD, particularly type II (77). VCE is a proportionately safe method for detecting villous atrophy with high sensitivity (89% approximately) and specificity (95% approximately) (78), and it may assist in distinguishing between type I and type II RCD (74). Additionally, due to the risk of developing complications, like enteropathy associated with T-cell lymphoma (EATL), adenocarcinoma, jejunoileitis, and B-cell lymphoma, it is essential to differentiate individuals with uncomplicated CD from those with RCD (79, 80). If left untreated, CD poses an increased risk for developing tumors, particularly those of EATL and small intestinal adenocarcinoma (81) compared with the general population. Enteropathy associated with T-cell lymphoma is occasionally diagnosed as a result of signs and symptoms like perforation, intestinal obstruction or bleeding, and persisting anemia, which may be an indicator of it. In addition, one of the phenotypic expressions of RCD is ulcerative jejunoileitis. Abdominal pain, in relation to sub-occlusive symptoms, is the hallmark symptom of this complication, although it can manifest with hemorrhagic symptoms, perforation, or protein loss enteropathy because of the existence of inflammatory ulcers and constrictions in the small intestine.

Furthermore, jejunoileitis is associated with an increased risk of EATL (82). The existence of other comorbidities, not always associated with CD itself, is related to continuation of symptoms once adherence to the GFD has been confirmed, such as microscopic colitis, irritable bowel syndrome, food allergies, motility disorders, and collagen sprinkle. Collagen sprue manifests itself in the form of refractoriness, and its incidental association with EATL has also been depicted (83). Biopsy and pathological examination are used for diagnosis.

Aplastic anemia and celiac disease

CD has been related to numerous hematological disorders (12), like anemia, thrombopenia, thrombocytosis, leukopenia, splenic dysfunction, immunoglobulin A deficiency, and lymphoma. Anemia is the most common hematological abnormality of CD. In addition to the different etiologies of CD anemia (iron deficiency in consequence of micronutrient deficiency or chronic disorders), several cases of CD-related aplastic anemia have been depicted in the literature (84-89), both in pediatric and adult age groups. Although the underlying cause of this association is still unknown (84), it has been proposed that both conditions, mediated by autoreactive T cells involved in tissue destruction, may share a similar underlying pathophysiological mechanism (85).

In all cases, the patient displayed pancytopenia, and the diagnosis was made based on the biopsy of bone marrow. Pancytopenia was resolved with the GFD only in some affected individuals (86), whereas the response was only partial in other cases, and immunosuppressive treatment or even hematopoietic progenitor transplantation was required. Although uncommon, aplastic anemia may be an underdiagnosed entity. Thus, in the case of pancytopenia without obvious cause and in CD with pancytopenia, it is necessary to have a high level of diagnostic doubt. Anemia may be a consequence of various etiologies, such as autoimmunity or chronic inflammation caused by CD (89). On the basis of the reported cases in the past and until the present time, it appears that GFD is not sufficient to enhance pancytopenia, so most individuals need other treatments. Some researchers indicated that pediatric age had a better prognosis, probably since the duration of exposure to chronic inflammation is reduced, and the GFD is likely to reverse the process in that age group (86).

Leukopenia/Neutropenia:

It has been mentioned that a few children with chronic diseases have abnormally low white blood cell count (90). However, this finding is rare. The deficiency of copper and folate are probably the

causative element for leukopenia in these cases (91, 92, 93). Furthermore, information about the recovery of these patients is very limited, but in the case of copper deficiency in these patients, it is advisable to start a GFD and oral copper sulfate supplement.

Thrombocytopenia and thrombocytosis:

Thrombocytopenia could be encountered infrequently in patients with CD and like other hematological manifestations, it could have an autoimmune etiology as well. Additionally, it has been mentioned to suggest autoimmune pathophysiology in case reports associated with keratoconjunctivitis and choroidopathy (90). While in some cases, GFD can normalize platelet count, specific treatment for thrombocytopenia related to CD is still under study (90, 94).

Thrombocytosis tends to be more frequent than thrombocytopenia in association with CD, occurring in about 60% of affected individuals (95, 96). However, the etiology of celiac-related thrombocytosis remains unclear, but it can be attributed to autoimmune processes, and rise of inflammatory mediators. In some cases, it is ascribed to iron deficiency anemia or even functional hyposplenism (96, 97). Contrarily, Du pond and colleagues revealed that thrombocytosis was present in 14 patients with CD out of 23, and it was not associated with iron deficiency or inflammatory syndrome. Six of the patients with thrombocytosis had a related autoimmune disorder, but this correlation was not found in patients without thrombocytosis (98). Thrombocytosis can be helpful for evaluating patients with CD and may indicate increased development of the disease. Furthermore, existence of raised thrombocytes in the blood of these patients may point out an associated autoimmune disease. Thus, by following the GFD, thrombocytosis can be resolved (97, 99).

Caroccio and co-workers described an old woman who was admitted to the hospital for severe thrombocytosis in combination with severe anemia and who was diagnosed as having CD (96) They proposed that upon detection of extreme thrombocytosis and severe anemia, CD should be taken into consideration, in addition to myeloproliferative disorders or any other neoplastic conditions, especially in an elderly patient.

Hyposplenism and susceptibility to infections

Spleen dysfunction has been documented in patients with CD from early studies. Its basic mechanism appears to be associated with antibody deposits in the spleen (100). Some distinctive alterations like acanthocytes, Howell-Jolly bodies, and target cells can be seen on a peripheral blood smear (101). Estimating the spleen size is significant in case of doubted and approved CD, as some studies have linked splenic hypertrophy with CD, and others have revealed a relationship between small spleen mass and refractory CD (102, 103). Alongside the alterations in dimensions, functional hyposplenism is of significance in patients with CD, as it may prompt thrombocytosis and predispose to infections, especially with encapsulated bacteria like Streptococcus pneumonia, Haemophilus influenza, and Neisseria meningitides. That is why vaccinations against these microbes should be suggested in patients with CD (101, 104, 105). Malnourishment, vitamin D deficiency, changed mucosal penetrability, and modified gut microbiota can also result in susceptibility to infection, in addition to hyposplenism. The elevated rate of infections in patients with CD was attributed to influenza, herpes zoster, pneumonia, tuberculosis, and clostridium (106, 107). Nonetheless, the risk of infections demanding hospital admission does not appear to be affected by mucosal curing (108).

Thromboembolism and bleeding tendency

A few studies demonstrated uncommon cases of arterial thrombosis in individuals with CD; however, the pathophysiology remains indistinct (109, 110). Venous thrombosis appears to be more frequent, and it was presented in various case reports (111, 112). Miehsler and colleagues failed to detect an increased risk of venous thromboembolism (VTE) (113). Ludvigsson and others who carried out a large cohort study on the relationship between CD and thromboembolism, did not find any association between CD and subsequent venous thromboembolism. This risk was confined for patients with CD starting in adulthood (114), and they linked the discovery to a mix of surveillance bias and chronic information. The initial interpretation that comes to mind was hyperhomocysteinemia due to the lack of co-factors engaged with the enzymatic metabolism of Hcy (folate, vitamin B6 & B12) (115).

Magnesium deficiency has also been implicated in individuals with CD and vein thrombosis in the spleen (111, 116), however, the disruption of homeostasis in CD can likewise be ascribed to thrombocytosis, the inadequacy of protein S & C subsequent to vitamin K improper absorption, the existence of related autoimmune diseases or perhaps to hematologic malignancy (117), and a raised level of thrombin-activated fibrinolysis inhibitor that was discovered in individuals with inflammatory bowel disease (IBD) and CD (118-119). Nonetheless, a large portion of the revealed cases of venous thromboembolism co–existing with CD were from North Africa; hence, an ecological or a hereditary susceptibility may be proposed (120). Still, we propose that for each patient with CD presenting with thrombosis, Hcy levels should be checked and vitamin B12 and folate substitutions should be initiated in case of high levels. In addition to this, we recommend a proper workup for cancer detection. All patients

were managed firstly by GFD and sufficient anticoagulation with serial follow-up showing declined inflammation and normalization of cysteine levels.

CD has likewise been interrelated with an irregular bleeding tendency. This was initially observed by Wollaeger and Green in 1960 when they revealed that a prolonged prothrombin time might be encountered in up to 70% of untreated cases in grown-ups (121). After 40 years, because of the advancement in diagnostic and management tools, this percentage reached approximately 18.5% (122). Throughout the years, CD bleeding tendency has been presented as hematuria, hematomas, intestinal bleeding, hemarthrosis, retroperitoneal hemorrhage, intramuscular bleeding leading to compartment syndrome, and intracranial hemorrhage (123).

The bleeding tendency in patients with CD is probably less connected to impaired liver function (124-125). It may be a consequence of isolated thrombocytopenia (ITP). However, the main reason is still vitamin K malabsorption resulting in a defect in vitamin K-dependent coagulation agent along with subsequent prolongation of international normalized ratio (INR), prothrombin time, and activated partial thromboplastin time (aPTT) (126-127). Patients with CD who do not have improper absorption of other nutritious elements are less likely to have vitamin K malabsorption (122). Management of all manifestations of bleeding in patients with CD starts by using (transferring) blood or specific blood elements (when needed), consumption of vitamins, and exploring the reason for the bleeding. Prevention of bleeding can be achieved by gluten-free diet, which enhances absorption of vitamin K and other different nutritional supplements.

CONCLUSION

Although classical CD manifestations with characteristic malabsorption syndrome are becoming exceptional, extraintestinal manifestations are considered the prevalent ones. Hematological-related features are very frequent among the broad range of extraintestinal manifestations, and they may be the single presentation of the disease. The most common hematological features of CD is IDA, and screening for CD is ought not to be skipped in individuals with unexplained and refractory to iron-supplementation IDA. Earlier iron deficiency markers (changes of red blood cell hematological indices) and even alteration in platelet count should also prompt screening for CD in a suggestive clinical setting. Hemorrhagic or thrombotic incidents, though unexplained, can also be the presenting features of the CD. A diagnosis of CD should constantly be taken into account in the case of a patient with unexplained hematological disorders.

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Authors' contributions

AA wrote the first draft of manuscript. IA and HM, edited and commented on the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

None.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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