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Hematologic Manifestations of Celiac Disease

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1. Introduction

Celiac disease is a systemic disease, which is associated with a number of hematologic manifestations. Individuals can present with hematological abnormalities even prior to the diagnosis of celiac disease. Anemia secondary to iron, folic acid and vitamin B12 malabsorption is a common complication of celiac disease. Patients can also present with thrombocytosis, thrombocytopenia, leukopenia, venous thromboembolism, hyposplenism and IgA deficiency. Celiac disease also predisposes to lymphoma development. The highest risk is for enteropathy associated T-cell lymphoma (EATL), an aggressive lymphoma with poor prognosis, however an increased risk for B-cell lymphomas and extraintestinal lymphomas has been described. Strict adherence to a gluten-free diet is known to decrease the risk of lymphomas.

2. Anemia

Anemia is a frequent finding in patients with celiac disease (CD) and may be the presenting feature. It may also be the only abnormality identified. Anemia was particularly common in patients with untreated CD in the past, but it is still frequently encountered in undiagnosed adults.1,2,3,4 The etiology of anemia in celiac disease is multifactorial. The anemia is usually hypoproliferative, reflecting impaired absorption of essential nutrients like iron and various vitamins. In prior studies, the overall prevalence of anemia at the time of diagnosis of celiac disease has been estimated between 12 and 69%. 5,6,7 Anemias caused by hemolysis are very rarely reported in celiac disease patients. Ivanovski et al. reported an 11-year old girl with untreated celiac disease who had hemolytic anemia and suggested that CD should be serologically screened in patient's with Coombs negative "immune" hemolytic anemia. As in this case the anemia improved after initiating a gluten free diet. 8

2.1 Mechanisms of anemia in celiac disease

A number of causative factors deserve consideration for explaining the mechanism of anemia in celiac disease.

2.1.1 Abnormal iron absorption

The most obvious cause of anemia in celiac disease is impaired absorption of iron and other nutrients including folate and cobalamin. Iron is absorbed in the proximal small intestine and the absorption is dependent upon several factors, including an intact mucosal surface and intestinal acidity.9 Villous atrophy of the intestinal mucosa is an important cause of abnormal iron absorption, which is reflected as laboratory evidence of iron deficiency anemia (IDA) in most anemic patients with celiac diasease. Abnormal iron absorption is also supported by the failure to increase serum iron levels following oral iron loading and refractoriness to oral iron treatment. 1,2,3

2.1.2 Increased blood loss

Occult gastrointestinal blood loss was detected in about half the patients with celiac disease in one study, and this finding appeared to correlate with the severity of villous atrophy. 16 An important limitation of that study was the use of an indirect (guaiac) test for detecting bleeding. In a subsequent study employing 51 Cr radiolabeled red blood cells, a daily blood loss exceeding 1.5 mL was detected in only one of 18 subjects studied. Others have also found that the rate of positive occult blood tests in celiac disease is low and does not exceed that in the general population. Thus, the evidence supporting increased fecal blood loss in celiac disease remains controversial, and although abnormal intestinal bleeding may occur in some celiac patients, it does not appear to play a significant role in the causation of anemia. 1,16

2.1.3 Abnormal vitamin absorption

The anemia seen in celiac disease can also result from malabsorption of various micronutrients necessary for normal hematopoiesis. Sideropenia, vitamine B12 and folat acide deficiency has been described in patients with celiac disease. 1, 39, 52 Copper deficiency has been described in adults and children with CD and may result in anemia and thrombocytopenia. 17, 18 Deficiencies in vitamin B6, pantothenic acid, and riboflavin have also been suggested as etiologic factors in patients with CD but recent data are lacking.1

2.1.4 Inflammation

Pro-inflammatory cytokines play an essential role in the inflammatory and cytotoxic mechanisms involved in the pathogenesis of celiac disease. Such cytokines, in particular interferon- γ (IFN-γ), and IL6, are powerful mediators of hypoferremia in inflammation inducing the synthesis of the iron regulatory hormone hepcidin.15, 19, 20, 22 Increased hepcidin synthesis in turn is responsible for increased ferroportin degradation and the inhibition of iron release from macrophages and enterocytes leading to the well known abnormalities in iron homeostasis associated with anemia of chronic disease (ACD). 19

2.2 Iron-deficiency anemia

Iron-deficiency anemia (IDA) is the most commonly encountered anemia in humans and is usually due to either increased iron loss or impaired absorption of iron.23 Iron-deficiency anemia is frequently seen in patients with celiac disease and can be found even in the absence of diarrhea or steatorrhea. IDA has been reported in up to 46% of cases of subclinical CD, with a higher prevalence in adults than children.3, 9 Iron deficiency has also

been reported in patients with dermatitis herpetiformis. 10 IDA usually manifests as microcytic, hypochromic anemia and patients characteristically have low serum iron levels, elevated total iron-binding capacity, and low ferritin levels. 9, 11 Measurements of soluble transferrin receptors (sTfRs) can also be valuable in the evaluation of IDA, and the ratio of sTfR to ferritin may indicate CD in children with refractory IDA.12 Iron deficiency that is refractory to therapy can be the sole manifestation of CD, especially in pediatric patients and the prevalence of CD in patients with refractory IDA may be as high as 20%13, 14, 15. Fayed et al. reported that refractory IDA may be due to clinically unapparent CD in children. They recommended treatment with a gluten-free diet rich in iron and suggested that early detection and treatment of IDA with prophylactic iron and folic acid supplementation would go a long way in preserving good mental and psychological functions. 35 Patients with anemia had low levels of erythropoietin for the degree of anemia and increased serum interferon-gamma.This study supported the hypothesis that anemia in celiac disease is multifactorial in etiology and suppression of intestinal inflammatory changes as a result of a gluten-free diet improves anemia by correcting iron and vitamin malabsorption as well as mechanisms contributing to anemia of chronic disease. 19, 20

The prevalence of celiac disease in patients presenting with iron-deficiency anemia ranges from 0 to 8.7%. 23, 24, 25, 26, 27, 28 In a study conducted in Italy, anemic patients were screened for celiac disease using antigliadin and antiendomysial antibodies. 14 Jejunal biopsies were obtained from patients with positive serology. The prevalence of celiac disease was 5% in all patients with anemia and 8.5% in those with iron-deficiency anemia. 23 In a study conducted in the United Kingdom, 115 patients with iron deficiency anemia were assessed with esophagogastroduodenoscopy, flexible sigmoidoscopy, and barium enema; 2.6% of these patients had celiac disease. However, fewer than half of the patients underwent a small bowel biopsy, and hence the true prevalence of celiac disease might have been underestimated. Of interest, however, the three patients with celiac disease had normal appearing mucosa on small bowel endoscopy. 25 In two studies, biopsies were performed on the patients with positive serology, and the prevalence of biopsy-proven CD was 2.3% to 4.7%. 25, 27 Iron deficiency in celiac disease primarily results from impaired absorption of iron but there may also be occult blood loss in the gastrointestinal (GI) tract. 31, 32 Occult gastrointestinal bleeding was detected in 25% to 54% of patients with CD, depending on the degree of villous atrophy, in 1 study. 16 Occult GI blood loss was seen in 26.7% of children with CD that appeared to respond to treatment with a gluten-free diet (GFD), according to another study. 33 More-recent studies have, however, suggested that occult GI bleeding in patients with CD may be much less common. 34, 35 Biopsy-proven CD was reported in 2.6% to 5% of patients. 23, 28 Three other studies included patients with anemia other than IDA but the vast majority in all 3 studies suffered from IDA. 25, 29, 30 Serologic evidence of CD was observed in 2.3% to 10.9% of these anemic patients. In 2 of the studies, biopsies were performed on the patients with positive serology, and the prevalence of biopsy-proven CD was 2.3% to 4.7%. 25, 30 One of the studies suggested that history of chronic diarrhea predicted CD as the cause for the anemia. 36 Clinicians should consider CD as a possible cause of anemia in all subjects with unexplained IDA, including menstruating women. Endoscopic markers of CD in patients with IDA have been shown to lack sensitivity for diagnosis and have limited utility in selecting patients for a small-bowel biopsy. 38 biopsies should be performed even if the duodenal mucosa appears normal to the endoscopist. One recent study has shown that many patients undergoing an endoscopy for anemia do in fact not have a small-bowel biopsy performed.39 In conclusion, IDA is common in CD, and CD

is frequently found in patients presenting with IDA. The treatment of IDA associated with CD is primarily a GFD and iron supplementation until the iron stores have been restored.

2.2.1 Folate deficiency

Folic acid is an element essential for amino acid and nucleic acid metabolism. Adequate folic acid is required for normal hematopoiesis and development of the nervous system. 40 Folic acid is primarily absorbed in the jejunum, and malabsorption is frequent in diseases of the small intestine. 40, 41 Deficiency of folic acid usually presents as macrocytic or megaloblastic anemia, but abnormalities of other cell lineages are common. Concomitant iron deficiency as seen in CD can result in atypical findings on the blood smear, and patients with deficiencies of folate and vitamin B12 may not present with the characteristic macrocytosis. Examination of the blood smear may reveal a dimorphic picture reflecting the effects of both deficiencies. Severe folic-acid deficiency can result in a decrease in both leukocytes and platelets and even manifest as severe pancytopenia. The diagnosis is usually made by measuring serum folate and red-cell folate levels. Serum folate is highly dependent on folate intake and is frequently increased in patients with deficiency of vitamin B12. Red-cell folate is not specific for folate deficiency, as it can be decreased in patients with vitamin B12 deficiency, but red-cell folate is less subject to transient changes secondary to variations in folate intake. 41 Elevated serum homocysteine levels can be helpful in diagnosing folate deficiency but the sensitivity of serum homocysteine is somewhat less for vitamin B12 deficiency. 43, 44 Previous studies have shown that many untreated patients with CD are folate deficient. 45Two small studies found that folate deficiency is a common finding in children, but it does not usually result in anemia. 46, 47 More-recent studies have confirmed that folic-acid deficiency continues to be a frequent finding in subjects with newly diagnosed CD and can be observed even in adolescents and young adults with CD detected by screening. 30, 48, 49 Folate deficiency has also been reported in association with dermatitis herpetiformis. 50, 51 Homocysteine levels are commonly elevated in CD patients at the time of diagnosis and may serve as a diagnostic clue. 52

2.2.2 Vitamin B12 deficiency

Vitamin B12 is an essential cofactor and a coenzyme in multiple biochemical pathways, including the pathways of DNA and methionine synthesis. While the main site of vitamin B12 absorption is the distal ileum (where it is absorbed bound to intrinsic factor), a small proportion is also absorbed passively along the entire small bowel. 53 Although celiac disease has been considered a disorder of the proximal small bowel, associated vitamin B12 deficiency has been reported. Deficiency of vitamin B12 is common in CD and frequently results in anemia. Malabsorption of vitamin B12 resulting in anemia has also been described in patients with dermatitis herpetiformis (DH). 54 Dickey et al. in their study reported, that of 159 patients, 13 had low serum B12 at diagnosis. A further six had been receiving B12 replacement therapy for 3-37 years before diagnosis, giving an overall prevalence of 12% (19 patients). Only 2 of 19 patients had gastric corpus atrophy, one with intrinsic factor antibodies and the other with hypergastrinaemia. There was no relationship between low B12 levels and clinical characteristics. 55 The cause of vitamin B12 deficiency in CD is unclear. It may include decreased gastric acid, bacterial overgrowth, autoimmune gastritis, decreased efficiency of mixing with transfer factors in the intestine, or perhaps dysfunction (inflammation) of the distal small intestine. 56, 57 Recent studies suggested that 8% to 41% of previously untreated

subjects with CD were deficient in vitamin B12. 58, 59 Bode et al. In their study reported an 11% incidence of vitamin B12 deficiency in 50 consecutively diagnosed patients with CD. 60

Measurements of vitamin B12 levels can be misleading and difficult to interpret, especially if the results fall within the lower range of normal or if there is a coexisting deficiency of folic acid. 61 Patients with vitamin B12 deficiency should receive therapy with parenteral vitamin B12. Even though studies have suggested that oral vitamin B12 may be as effective as parenteral vitamin B12, no such studies have been performed in patients with vitamin B12 deficiency secondary to CD. 62

2.2.3 Anemia of chronic disease

In a study focusing on the clinical features of anemia in celiac disease, Harper et al. noted that although serum ferritin levels were indicative of iron deficiency in the majority of anemic subjects, unexpectedly, in 13% of patients ferritin levels were increased. Because a gluten-free diet resulted in increased serum ferritin in iron-deficient patients, but decreased ferritin levels in those with previously high ferritins, they concluded that nutritional deficiencies alone do not explain anemia in all cases, and that inflammation appears to contribute in some individuals, as evidenced by the presence of anemia of chronic disease (ACD). In a recent study, Bergamaschi et al. decided to focus on the role of anemia of chronic disease in the development of anemia among patients with celiac disease. A peculiar feature in the design of this study was the use of refined precision instruments to identify anemia of inflammation. At the outset, and in a follow-up period of one year on a gluten-free diet, they collected data on serum iron, transferrin, serum ferritin, soluble transferrin receptor (sTfRc), endogenous erythropoietin (Epo) and IFN-γ. Among 65 anemic celiac patients, 45 had uncomplicated iron deficiency anemia, and 2 had cobalamin or folate deficiency. In 11 subjects, anemia of chronic disease alone or in combination with iron deficiency was identified, a prevalence of 17%. To increase the sensitivity and specificity of these blood tests, Bergamaschi et al. employed not only primary data but a combination of findings: (a) the sTfRc/log (ferritin) ratio that increases in iron deficiency and decreases in ACD, (b) the ferritin/transferrin ratio that decreases in iron deficiency and increases in ACD, and (c) the log(Epo) O/P ratio that describes the increase in endogenous serum EPO in proportion to the severity of anemia, a response known to be normal in iron deficiency anemia but blunted in the anemia of chronic disease. Compared with a group of 30 non-anemic celiac subjects, 45 of the celiac patients had findings typical of iron deficiency anemia. However, in 11 the findings indicated anemia of chronic disease with decreased sTfRc/log(ferritin), increased ferritin/transferrin ratio, and a decreased log(Epo) O/P ratio implying a blunted EPO response. Remarkably, serum IFN-γ levels in ACD were 12-fold higher than controls, but even in the iron deficient group they were increased 3-fold, indicating that some degree of inflammation might have been present in all anemic celiac patients. Hepcidin is an important indicator of ACD. By contrast, correlation of iron status with hepcidin is limited. The use of a pro-hepcidin assay instead of direct hepcidin measurements could explain the failure to demonstrate significant differences in prohepcidin levels among the three groups in the above study. In the Bergamaschi et al. study the response to a gluten free diet after one year was favorable in both, the IDA and ACD subjects, indicating that the suppression of intestinal inflammation by a gluten-free diet can improve anemia both

by correcting iron and vitamin malabsorption as well as by abolishing the mechanisms responsible for anemia attributable to inflammation. 15, 19, 20, 22

3. Leukopenia

Fisgin et al. reported leukopenia and anemia in a few children with celiac disease as the first sign of disease. 63 Deficiencies of both folate and copper have been implicated as the possible etiology of leukopenia. The data on treatment of these patients are extremely limited but initiating a GFD and dietary supplementation with oral copper sulfate if there is evidence of copper deficiency, can improve the white blood count. 64, 65, 66

4. Thrombocytopenia and thrombocytosis

Thrombocytopenia has rarely been reported in patients with CD and it may have an autoimmune etiology. It has been reported in case reports in association with with keratoconjunctivitis and choroidopathy, suggesting an autoimmune pathophysiology. 67 Therapy for thrombocytopenia in association with CD is unclear, but GFD may result in normalization of the platelet count in some cases. 67-69 Thrombocytosis in association with CD appears to be more common than thrombocytopenia, occurring in up to 60% ofpatients. 70-72 The etiology of thrombocytosis associated with celiac disease is unknown, but it may be secondary to elevations in inflammatory mediators, autoimmune processes or, in some cases, secondary to iron-deficiency anemia or functional hyposplenism. 71, 72 Dupond et al. reported that in 14 of 23 patients with celiac disease thrombocytosis was present and it was unrelated to iron deficiency or an inflammatory syndrome. Among patients with thrombocytosis, 6 had an associated autoimmune disease, but this association was absent in patients without thrombocytosis. 73

Thrombocytosis might probably be useful in the assessment of patients with celiac disease and reflect enhanced disease activity. Moreover, the presence of thrombocytes in these patients' blood may indicate an associated autoimmune disease. Thrombocytosis may resolve after institution of a GFD. 71, 74 Caroccio et al., described an elderly woman hospitalized for extreme thrombocytosis associated with severe anaemia who was diagnosed with celiac disease. 72 They suggested, that celiac disease should be considered in addition to myeloproliferative disorders or other neoplastic conditions in an elderly patient when extreme thrombocytosis and severe anaemia is detected.

5. Venous and arterial thromboembolism

Ramagopalan et al. postulated in their study that men with celiac disease have a higher risk of thromboembolism. 82 Ludvigsson et al. in their study found a significant association between celiac disease and venous thromboembolism and they reported that venous thromboembolism may be the first clinical sign of celiac disease 83 Though celiac disease is not classically thought to predispose to thrombosis, there are several pathophysiological mechanisms that have been noted in celiac disease that may contribute to the development of a potentially prothrombotic state. 83 Cassela et al. in their study showed that hyperhomocysteinemia is relatively frequent in patients with CD, being present in about 20% of the patients in their series. 84 Hyperhomocysteinemia might represent a link between undiagnosed celiac disease and thromboembolism. Hyperhomocysteinemia may be

due to genetic factors, with cystathionine beta synthetasis deficiency being considered the most common genetic cause, or from acquired folate and vitamine B12 deficiencies (83, 84). Homozygous deficiency of N5-N10-methyl tetrahydrofolate reductase, the vitamin B12 dependent enzyme required for remethylation of homocysteine to methionine, may cause hyperhomocysteinemia, and this condition is more problematic to manage compared to cystathionine beta synthetasis deficiency, as there is currently no effective therapy 81. Moreover, treatment with a gluten-free diet and folic acid in patients with celiac disease and N5-N10-methyl tetrahydrofolate reductase variants does not consistently improve hyperhomocysteinemia. Thus, celiac disease might lead to increased cardiovascular events due to secondary hyperhomocysteinemia, further aggravated by the possible presence of genetic abnormalities responsible for hyperhomocysteinemia. 81, 84 Hypofibrinolysis has been proposed as another possible cause of thrombosis in patients with celiac disease. Thrombin-activatable fibrinolysis inhibitor (TAFI) is a major inhibitor of fibrinolysis. Increased plasma TAFI levels are associated with a risk for venous thromboembolism. TAFI plasma levels are increased in patients with celiac disease and might contribute to the risk of thromboembolism in these patients. 75, 76, 78, 80 Decreased levels of the K vitamin–dependent anticoagulant proteins, protein S and C, have recently been suggested as a causative factor of thrombosis associated with celiac disease too. 77 Antiphospholipid syndrome is characterized by arterial and venous thrombosis, and its association with celiac disease has been described in a few cases. 85 The clinical spectrum of thromboembolism observed in patients with celiac disease is variable, but most cases appear to involve the venous circulation and resulting in deep vein thrombosis, pulmonary embolism, Budd-Chiari syndrome or splenic thrombosis. 79, 80, 81 Only a few case reports have described patients with arterial thrombosis, and in those cases the role of CD in predisposing to thrombosis is uncertain. 86, 87, 88 Moutawakil et al. Reported a case of a young male lacking typical gastrointestinal symptoms who presented with neurologic signs suggestive of an ischemic stroke. The mechanisms of vascular damage involving the CNS in celiac disease are controversial. The most widely incriminated factor is autoimmune vasculitis due to autoantibodies targeting tissue transglutaminase. Other mechanisms for e.g. vitamin deficiency are still debated,. 89

6. Coagulopathy

Untreated celiac disease may induce malabsorption of many nutrients, which may also induce vitamin K deficiency. CD can be associated with abnormalities in coagulation factors resulting in a bleeding diathesis. A decrease in K vitamin–dependent coagulation factors results in prolongation of coagulation assays or parameters such as the prothrombin time (PT), international normalized ratio (INR), and the activated partial thromboplastin time (aPTT). 90, 91 Cavalloro et al. found that the prevalence of prolonged PT is about 20% in a large series of untreated adult celiac patients, but a prolonged prothrombin time was only found in a few patients with subclinical celiac disease (0.9%). Symptomatic patients were also more likely to present with a prolonged PT. 92 Patients with CD occasionally present with a hemorrhagic disorder as their first symptom. The resulting hemorrhage can be minimal to severe. 95 Granel et al. described an interesting case of bilateral adrenal haemorrage in a patient with an hypocoagulable state due to untreated celiac disease. 93 Therapy is initially with parenteral vitamin K, but occasionally plasma products may be needed in actively bleeding patients. Malabsorption of vitamin K is uncommon in CD

patients who do not have evidence of malabsorption of other nutrients. The treatment primarily consists of initiating a GFD and correcting the vitamin K deficiency. 90, 92, 94

7. IgA deficiency

Selective IgA deficiency, as defined by the total or severe deficiency of the IgA class of immunoglobulins in serum and secretions, is the most common immunodeficiency disorder. Studies suggest that 1 in every 500 people may have selective IgA deficiency. Even though a large number of individuals with selective IgA deficiency are relatively healthy, there are many affected with variety of disorders. These include recurrent sinopulmonary and gastronintestinal infections, allergies, and autoimmune disorders. 97, 99 The prevalence of IgA deficiency in patients with CD is 10 to 15 times higher than that in the general population. Approximately 2% to 3% of CD patients have IgA deficiency, and up to 8% of IgA-deficient individuals may have CD. 96, 97, 98 Patients with selective immunoglobulin (Ig) A deficiency have a 10- to 20-fold increased risk of celiac disease 99. Cataldo et al. reported that the clinical presentation of CD patients with selective IgA deficiency is different from that of patients with CD who have normal IgA levels, demonstrating a greater incidence of the silent form in the former. Because of the mild form of clinical presentation in IgA-deficient patients with CD, there may be a delay in recognizing such cases before appropriate GFD therapy can be instituted.96 The serum antibody markers that are currently used in the diagnosis of celiac disease are anti-AGA, ARA, EMA, and tTG antibodies. These serologic markers are highly sensitive and specific markers for CD, especially for IgA-based antibody tests. Because of the high prevalence of IgA deficiency in patients with CD, attention has been focused on the problem of diagnosing such individuals and the optimal testing strategy. IgA deficiency can lead to false-negative serology, as most of the existing serologic methods detect only IgA antibodies. The basic serologic test that can detect IgG antibodies related to CD is the AGA test. However, as the AGA IgG antibody test has limited specificity (76-80%), this test alone may not reliably establish a definitive diagnosis 99. Evaluating EMA IgG antibodies and anti-transglutaminase antibodies can be helpful for diagnosis of celiac disease with IgA deficiency. 99, 100, 101 Celiac disease patients with IgA-deficiency are prone to other enteric conditions such as inflammatory bowel disease or chronic parasitic infections, especially giardiasis, which could mimic CD. Secondly, patients with IgA deficiency are also at risk of developing anaphylactic transfusion reactions that may be life threatening if the recipient has anti-IgA antibodies. 96, 97, 99

8. Lymphoma

The association of CD and intestinal lymphoma is well known. 102 This association was first described in 1937 by Fairley and Mackie.116 Initially it was thought that the enteropathy and malabsorption that occurred was secondary to the lymphoma itself, a concept that persisted for many decades until it became apparent that CD often preceded the development of lymphoma. Later reports suggested that lymphomas involving the GI tract were relatively more common in CD patients and were a major cause of death. 100-105 Multiple studies now support the association of CD and lymphomas. 106-118

Patients with celiac disease have a 50- to a 100-fold increased risk of developing lymphoma compared with the general population Catassi et al. in their study found that celiac disease

was diagnosed in 6 (0.92%) of 653 patients with lymphoma. The odds ratio (adjusted for age and sex) for non-Hodgkin lymphoma of any primary site associated with celiac disease was 3.1 for gut lymphoma, and 19.2 for T-cell lymphoma, respectively. The risk for non-Hodgkin lymphoma in this study was 0.63%. 102 The risk of developing an NHL as a complication of CD is not fully known, but recent epidemiologic studies suggest a relative risk ranging from 2.1 to 6.6.112, 113, 116, 117, 132, 133 The risk of contracting lymphoma in the setting of DH appears to be increased to a similar degree. 133, 134 Other studies have indicated that there may be a much higher risk, ranging from a 15-fold up to 100-fold increase. A recently published 30-year population-based study from Finland followed 1147 patients diagnosed with celiac disease or DH at a single medical center over 17 245 person-years. This study reported an standarized incidence ratio of 3.2 and 6.0 for developing NHL in patients diagnosed with CD or DH, respectively. This study provided further support to the theory that compliance with a GFD protects against the development of lymphoma in patients with CD. 131 Smedby et al. reported that celiac disease is associated with a doubled risk of NHL overall that was mainly attributed to a nearly 20-fold increased risk for T-cell lymphoma and to a nearly 3-fold increased risk for diffuse large B-cell lymphoma. There was a substantial and statistically significant, increased risk of gastrointestinal NHL and there was weak evidence for an increased risk for nongastrointestinal lymphoma. 116 A large population-based case-control study undertaken in both Denmark and Sweden assessed the risk of NHL in patients with a variety of autoimmune disorders, including CD. Participants including 3055 patients with NHL identified through a national hospital and tumor registries and 3187 matched controls were surveyed regarding a history of autoimmune disorders. Nineteen patients with NHL and 9 controls reported a previous diagnosis of CD. CD was associated with a doubled risk of NHL with an OR of 2.1. The odds ratio (OR) for diffuse large B-cell lymphoma (DLBCL) was 2.8 in contrast to an OR of 17 for T-cell lymphoma. Ten lymphomas were extranodal, including 5 involving the GI tract. The OR for gastrointestinal NHL was estimated to be 12 in comparison with an OR of 1.7 for non-gastrointestinal NHL.116 Many studies suggest that there may be a reduction of risk with long-term adherence to a GFD.106,107,110,111,113, 115 A GFD may also reduce the risk in patients with DH.135, 136 The benefit of a GFD may be slow in accruing in those who are diagnosed later in life.

In a study by Holmes et al. a two-fold relative risk (RR) of cancer was found, including an increased risk of cancer of the mouth and pharynx, oesophagus, and of non-Hodgkin lymphoma. 110 The risk was increased, however, in those taking a gluten containing diet and when celiac disease was diagnosed late in adulthood. A significant decreasing trend in the excess morbidity rate over increasing use of a gluten freed diet and early diagnosis was found. The findings of Holmes et al. are suggestive of a protective role for a GFD against malignancy in coeliac disease and give further support for advising all patients to adhere to a strict GFD for life. 110

8.1 Enteropathy-associated T-cell lymphoma

The association between CD and a specific type of intestinal T-cell non-Hodgkin lymphoma (NHL), called enteropathy-associated T-cell lymphoma (EATL), appears to be particularly strong, but overall these aggressive lymphomas are rare. EATLs are rare lymphomas accounting for less than 1% of all NHL.153 EATL appears to be more frequent in Europe, where it represents 9.4% of all peripheral T cell lymphomas. An sssociation between EATL

and celiac disease is consistently demonstrated in only 30% of patients. The global incidence of this lymphoma is rare, being about 0.5 to 1 per million 119. EATL frequently presents as multifocal lymphoma with ulcerative lesions and commonly results in bowel perforation or other abdominal emergencies. 119, 120, 121 The neoplastic cells of EATL are thought to derive from clonal proliferations of phenotypically abnormal intraepithelial lymphocytes (IELs). 122, 123 In gluten-sensitive individuals with EATL, 68% are homozygotes for the DQB1*02 allele. Constant over-stimulation of intraepithelial T-cells eventually results in neoplastic growth. 129 Loss of CD8 expression by IELs is characteristic for early EATL also refereed to as refractory celiac disease type II. Cellier et al. reported that an immunophenotypically aberrant clonal intraepithelial T-cell population, similar to that observed in most cases of enteropathy-associated T-cell lymphoma, can be found in up to 75% of patients with refractory coeliac sprue. They suggested that refractory sprue associated with an aberrant clonal IEL population may be the missing link between celiac disease and EATL. 127 The IELs seen in refractory CD type II have been shown to express cytosolic CD3 (cCD3) and are monoclonal on analysis for T-cell receptor gene-rearrangements. 126, 127 Interleukin-15 is considered an important signaling molecule in driving the expansion of IELs. 128 The apperance of phenotypically aberrant monoclonal IELs seems to be the first step in the pathogenesis of ETL.123 The etiology of this increase in monoclonal IELs remains unknown, but it may be secondary to chromosomal gains or mutations of tumor-suppressor genes. EATL cells typically express CD3, CD7, and CD103, they may also express CD30, but are usually negative for CD4, CD5, and CD8. Sometimes the EATL cells lack CD3 expression. 123, 126 Immunostaining for CD3, CD8, and CD4 may be helpful for initial screening, but molecular-clonality analysis is required for confirmation in the cases suspected to have early, evolving or cryptic EATL.

EATL originates most often in the jejunum. A single or multiple sites within the jejunum may be involved with lymphoma. The large intestine and stomach are affected much less frequently. EATL rarely causes swollen peripheral lymph nodes that patients can feel. Patients will complain of abdominal pain, diarrhea, vomiting and gastronintestinal hemorrhage. Weight loss is also commonly reported. This is due to decreased absorption of nutrients, especially protein, in the small intestine. Fatigue may also be present due to anemia. As many as 40% of patients will present with acute abdominal symptoms, including lymphoma-mediated intestinal obstruction or perforation. This is a potentially life-threatening complication of EATL, requiring immediate surgery. Late in the course of EATL, the disease may spread to the liver, spleen and other organs. 136, 137, 138 Diagnosis of EATL can be complicated, as many more common disorders can cause abdominal symptoms. Most patients will be diagnosed while undergoing exploratory abdominal surgery, with a biopsy of the affected lymph nodes. Once the diagnosis of EATL is established, patients should undergo diagnostic tests to determine the extent of disease. This should include gastrofibroscopy, colonoscopy and enteroscopy, CT scans of the chest, abdomen and pelvis, a complete blood count, serum chemistries (including liver function tests, lactate dehydrogenase (LDH) and serum albumin) and a HIV test. Hepatitis B testing is also recommended due to reports of hepatitis reactivation during chemotherapy. A bone marrow biopsy is optional, as less than 10% of patients with EATL have involvement of this organ, but this may be an underestimate due to failure to recognize minimal disease. It is clear from recent studies, that the neoplastic cells are widespread even in the early stage of disease pathogenesis. 127 Finally, a baseline echocardiogram to evaluate heart function should be done prior to chemotherapy, as some drugs can damage the heart. The essentials

for diagnosis of EATL include histopathology and immunochemical staining analysis. Therefore mentioned tests enhance the diagnostic yield and establish the stage of EATL for each patient. 136, 137, 139 Staging of EATL is as follows 139, 141:

- Stage I: One involved lymph node group
- Stage II: Two or more involved lymph node groups on the same side of the diaphragm
- Stage III: Multiple lymph node groups involved on both sides of the diaphragm
- Stage IV: Disseminated involvement of other extra-nodal sites, such as the liver or spleen

Therapy for CD-associated lymphoma is not different from the therapy used in similar lymphomas in patients without CD. However, the presence of CD may raise issues of malnutrition, an increased risk of infection due to concomitant hyposplenism, and increased likelihood of diarrhea or other consequences of CD 143. Combination chemotherapy is most frequently used, and the choice of regimen depends on the lineage of the lymphoma. B-cell lymphomas are usually treated with combinations such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab. T-cell–derived lymphomas have been more challenging to treat. Therapy of ETL currently remains unsatisfactory, with a 5-year survival ranging from 11% to 20% in 2 studies and a 2-year survival of 28% according to another study. 142, 143, 144 Survival of patients with T-cell intestinal lymphoma appears to be inferior to the survival of patients with intestinal B-cell lymphoma and patients with other types of peripheral T-cell lymphomas.140, 141, 142 A recent study reported stem cell transplantation in patients with EATL. Results suggested, that patients with novel therapy with IVE/MTX (ifosfamide, etoposide, epirubicin/methotrexate) and autologous stem cell transplantation had longer survival like patients with standard therapy withou stem cell transplantation. 145

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