Microcytic anaemia as the clinical manifestation of coeliac disease in an adult patient: case report

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Abstract

Coeliac disease is a chronic inflammatory disorder of the small intestine caused by permanent gluten intolerance. It may develop in patients of any age with genetic predispositions. Advanced age in patients with undiagnosed and untreated coeliac disease increases difficulties in establishing a correct diagnosis, because symptoms in the gastrointestinal system become less pronounced than those in other organs. For example, hypoferric anaemia may be the only symptom of coeliac disease, or it may develop long before the fully symptomatic disease. This paper presents a case report on a 47-year-old female patient with anaemia, thrombocytopenia and weight loss, in which coeliac disease was diagnosed during hospitalization at the Clinic of Allergic Diseases, Clinical Immunology and Internal Diseases of L. Rydygier's *Collegium Medicum* in Bydgoszcz, Nicolaus Copernicus University, Toruń. The paper also presents a discussion on aetiopathogenesis, main symptoms, diagnostic criteria and management principles for coeliac disease.

Key words: coeliac disease, anaemia, adults.

Introduction

Coeliac disease, also known as gluten-dependent enteropathy, non-tropical sprue and coeliac sprue, is a chronic disease that develops as a consequence of immunological processes in the mucosa of the small intestine following exposure to gluten. The disease is underlain by permanent intolerance to gluten. It may be manifested at any age in genetically predisposed individuals. Classic, silent and latent forms of coeliac sprue can be identified by clinical manifestations. Detection of atypical forms of coeliac sprue has increased significantly in recent years, particularly in adults. As patients with undiagnosed and untreated coeliac sprue get older, proper diagnosis becomes increasingly difficult. Gastrointestinal symptoms become dominated by symptoms from other organs due to incessant autoimmune processes [1, 2]. For instance, haematological disorders, including the most common iron deficiency anaemia, may be the only symptoms of coeliac sprue or may precede the development of the full-blown disease by a considerable time [3].

Diagnosis of classic coeliac sprue is based on coincidence of clinical symptoms, positive serological tests, intestinal villous atrophy confirmed by a biopsy of small intestinal mucosa, and improvement in clinical status after the introduction of a gluten-free diet. Genomic tests may be decisive in difficult diagnoses of silent and latent forms of the disease [4].

Case report

A female patient, aged 47, was admitted to the Clinic of Allergology, Clinical Immunology and Internal Diseases of the *Collegium Medicum* in Bydgoszcz due to progressive weakness, worsening effort tolerance, significant drop in body weight (ca. 10 kg within 12 months) and generalized arthralgia. Other reported discomforts included painful cramps in the calves and abundant menstruation. Several years before, the patient had been treated in an outpatient setting with oral iron preparations due to microcytic anaemia. Family history data included a diagnosis of coeliac sprue in one of the patient's three daughters.

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The general condition of the patient upon admission was described as medium-severe. A physical examination revealed the following deviations from normal conditions: asthenic body, body mass deficiency (height 170 cm, body mass 51 kg, BMI 17.65 kg/m^2), facial and forearm skin discolorations, pale mucosa, accelerated heart rate of 100 bpm, systolic murmur above cardiac apex, radiating towards the left axilla. There were in addition deformations of the wrist bones and the interphalangeal joints of the hands and feet. Also notable were the disturbances in the mental condition of the patient, manifested as emotional lability, a depressed mood and an inclination to cry.

Laboratory tests revealed the following deviations from normal levels: significant microcytic hypochromic anaemia (HGB 4.5 g/dl, RBC 2.66 × 10^6/µl, HCT 19.0 %, MCV 71.8 fL, MCH 17.1 pg, MCHC 23.8 g/dl), thrombocytosis (PLT 1343 × 10^3/µl), reduced iron levels of 8 µg/dl and reduced ferritin levels of 2 ng/ml, iron absorption disorders identified in the serum iron curve. Also observed were an accelerated erythrocyte sedimentation rate of 22 mm/h, hyperkalaemia (5.8 mmol/l), and hypoalbuminemia (3.29 g/dl) with elevated α1 and α2-globulin levels in the protein profile. No abnormalities were observed in the leukocyte profile, haemostasis parameters, renal function, carbohydrate metabolism, hepatic enzymes, thyroid hormone activity, serum calcium levels, or in the levels of CRP and tumour markers.

Chronic gastric and duodenal mucositis was identified by panendoscopy of the upper gastrointestinal tract. The picture of the duodenum with swollen folds and no signs of bleeding suggested coeliac disease. A histopathological examination of mucosal specimens from the distal part of the duodenum revealed Marsh Grade 3c intestinal villous atrophy and endothelial lymphocytosis of 40/100 enterocytes, mononuclear cells and acidophils in the lamina propria, free intestinal crypts with a mitotic index of 4-3-3, and normal Paneth cells.

The immunological examination confirmed the presence of class IgA antiendomysial antibodies at high antibody titre (IgA-EmA 1 : 80). Other abnormalities observed in additional tests included a positive test for *Helicobacter pylori* and the presence of anti-HCV antibodies.

Due to the arthralgias and deformations observed in the physical examination, Latex-R reaction status was determined (negative) and radiological images of hands and feet were taken. The only abnormality observed in the radiogram consisted of geodes within the third metatarsal bone of the left foot. Following rheumatological consultation, suspicion of arthritis was proposed and the patient was referred to the Rheumatology Outpatient Clinic for further diagnosis.

On account of having a medical history of abundant menstruation, the patient was also consulted by a gynaecologist. The gynaecological examination revealed no abnormalities. The remaining additional examinations, including a chest X-ray and an abdominal ultrasound test, revealed no deviations from normal conditions. Due to significant anaemia, the patient was transfused with a total of 6 units of packed RBCs during the hospitalization period. This raised HGB levels to 10.1 g/dl. Parenteral iron preparations were also introduced.

Due to the overall clinical picture and the family history (first degree relative treated for coeliac disease), coeliac sprue was suspected. This suspicion was confirmed by additional studies (panendoscopy, histopathology and immune tests). The patient was instructed to follow a strict gluten-free diet and to report to the Gastroenterology Outpatient Clinic so that the disease could be monitored. The patient was also recommended to consider having screening tests performed on the remaining family members. Eradication treatment was introduced to fight *H. pylori* infection. Due to the presence of anti-HCV antibodies, a further diagnosis at the Hepatology Outpatient Clinic was recommended.

Discussion

Screening studies conducted in Europe and the U.S. show that coeliac disease occurs in 0.5-1% of the population [5, 6]. However, obtaining a complete epidemiological picture of the disease is difficult due to its complex clinical picture and the effect of local nutrition habits on its manifestations. For instance, the less common occurrence of the symptoms of coeliac disease in the Netherlands during World War II was attributed to a shortage of flour. The correlation was observed by Willem Dicke, who was the first to develop a gluten-free diet from his own studies [2].

For a long time, mostly paediatricians were interested in coeliac disease as it was mostly diagnosed in children. However, it should be kept in mind that the disease may be manifesteded at any age. Recent years have witnessed a drop in the incidence of classic coeliac sprue. This may be associated with nutritional changes. Environmental factors, such as the older age at which gluten is introduced into children's diets and the return to breastfeeding, are significant. At the same time, a steady increase in the silent and latent forms of the disease has been observed in adults with peak morbidity being observed in the fifth decade of life [7].

Studies conducted in Finland by Lohi *et al.* have shown that the increase in the number of diagnosed cases of coeliac disease observed in recent years reflects the actual increase in the incidence of the disease, not just improvements in detecting it [8]. In 1992, Logan compared the clinical picture of coeliac disease to an iceberg whose tip was the classic form with the atypical forms lying underwater [9].

Coeliac disease is more prevalent in women, who comprise 70% of all patients [7]. Coeliac disease is specific to the Caucasian race [9]. Coeliac disease is underlain by genomic, immune and environmental factors. Genetic pre-

disposition is due to the presence of specific tissue-typing antigens. Class II HLA genes (DQ2 and DR3) are identified in 80-90% of patients. Class I HLA genes (B8 and A1) are less common. The incidence of coeliac sprue in homozygotic twins and first degree relatives is higher than in the overall population, amounting to 70-75% and 5-10%, respectively.

In susceptible individuals, immunological processes are activated in the mucosa of the small intestine in response to gluten, a fraction of the prolamin proteins contained in the grains of European crops (gliadin in wheat, secalin in rye, hordein in barley), which leads to mucosal damage and intestinal villous atrophy [2].

Environmental factors which may have an impact on manifestation of coeliac disease include stress, pregnancy and infections (adenovirus 12E1A and rotavirus infections) [7, 10]. The clinical course and the symptoms of coeliac disease vary from the currently rare dramatic coeliac crisis to asymptomatic disease. Three forms of coeliac sprue have been identified: classic, silent and latent.

The classic form (full symptomatic, overt) is dominated by gastrointestinal symptoms such as stomach pains, flatulence, chronic fatty diarrhoea, malabsorption symptoms, and body weight loss. Intestinal villous atrophy and positive serology test results are observed [2, 4, 9, 11]. This clinical manifestation is mostly observed in children. However, it may also be encountered in adults. Some mention should be made of the similarities between gastrointestinal symptoms and those of the irritable bowel syndrome.

Silent coeliac disease is characterized by coincidence of autoantibodies and intestinal villous atrophy accompanied by little or no gastrointestinal symptoms [4]. Symptoms suggesting absorption disorders are predominant, iron deficiency anaemia being the most common, followed by vitamin B_{12} and folic acid deficiency anaemia. The characteristic features of this type of anaemia are that it is refractory to the treatment with oral iron preparations and that it improves following the introduction of a gluten-free diet. One of the possible manifestations of hyposplenism, often observed in coeliac disease, is significant thrombocytosis (above 1,000,000/µl), considered to be the determinant of disease activity. Sometimes, however, thrombocytopenia develops as a result of vitamin B_{12} and folic acid deficiency. The only clinical manifestation of coeliac sprue may consist of neurological disorders such as epilepsy, migraine, depression, ataxia, peripheral polyneuropathy, mental handicap, and/or dementive changes. Generalized weakness, growth deficiency, aching bones, early osteoporosis, enamel hypoplasia, and arthritis are frequently observed. In addition, recurrent oral afts and skin lesions in the form of intensively itching blister rashes, mostly around the buttocks, elbows and shoulders, are observed. The dermatological symptoms are described as dermatitis herpetiformis or Dühring's disease [2, 7]. Diagnosing for silent coeliac sprue and performing appropriate tests should be considered in reproduction disorders such as male or female infertility, and delayed adolescence [2].

The latent form of coeliac disease is characterized by its asymptomatic course, the normal condition of the small intestinal mucosa and the presence of antiendomysial antibodies. Intestinal villous atrophy may be observed in the future in this group of patients [4].

The literature contains a growing number of cases of refractory coeliac disease, in which atrophic lesions of small intestinal mucosa and clinical symptoms persist despite the introduction of a gluten-free diet [9]. Coeliac disease is accompanied by numerous abnormalities in laboratory test results, such as anaemia, thrombocytosis, leukocytosis, reduced levels of iron, vitamin B_{12}, folic acid, calcium, and vitamin D, and PT elongation. In addition, hypoalbuminemia, hypocholesterolemia and increased serum aminotransferase activity are observed [2, 3, 11].

Coeliac disease is often concurrent with selective IgA deficiency and autoimmune diseases such as type I diabetes, autoimmune thyroid diseases, rheumatoid arthritis, disseminated lupus erymathosus, autoimmune hepatitis, Addison's disease, Sjögren's syndrome, alopecia aroata etc. [2, 7]. Incidence of coeliac sprue is also higher in individuals with Down's syndrome, Turner's syndrome and Williams' syndrome.

The prognosis in coeliac disease is good and the risk of late complications is reduced if a gluten-free diet is adhered to. The most severe complications of untreated coeliac disease include tumours, particularly enteropathy-associated T-cell lymphoma (EATL). This disease develops in 5% of patients. Other reported tumours include oral, oesophageal, small intestinal and colon tumours [3, 7, 15].

Coeliac sprue was initially diagnosed using the "Budapest criteria" introduced in 1989. The diagnosis is made when the clinical symptoms are observed in association with the introduction of gluten into the diet or with suspected coeliac disease in high-risk groups, when specific serological markers are found in serum, when typical morphological lesions are found in histopathological examination of a specimen of small intestinal mucosa, when other diseases of similar clinical pictures are ruled out and when a gluten-free diet produces positive results [9, 11].

In clinical practice, histopathological methods are commonly used to diagnose coeliac sprue. Serological markers of coeliac disease include class IgA and IgG antiendomysial antibodies (EMA, first described in 1983 by Professor T. Chorzelski), class IgA anti-tissue transglutaminase ([TTG] antibodies) and class IgA and IgG antigliadin antibodies [4, 9, 11]. The highest specificity, up to 100% in both children and adults, was observed in the case of antiendomysial antibodies. Of somewhat lower specificity are anti-human tissue transglutaminase antibodies (98.2%). These are also characterized by high sensitivity (> 95%) [2, 11]. The presence of class A antiendomysial and anti-tissue transglutaminase antibodies is correlated with the degree of small intestinal mucosal lesions.

Screening tests confirmed the high usefulness of serological tests. It has to be borne in mind, however, that in ca. 2-3% of cases, coeliac disease is concurrent with isolated IgA deficiency, and therefore total IgA levels should be determined simultaneously [7]. Currently, determination of antigliadin antibodies is not recommended due to the low sensitivity and specificity of these markers [13]. The tests for serological markers should be carried out before a gluten-free diet is introduced [4].

None of the currently available serological tests is characterized by 100% sensitivity. Therefore, small intestinal biopsy remains the gold standard in diagnosing coeliac disease [9]. Specimens are collected in the second and third part of the duodenum, beyond the papilla of Vater, upon panendoscopy of the upper gastrointestinal tract or, less commonly, by aspiration biopsy using a Crosby capsule. Macroscopically, compression or complete atrophy of duodenal folds and translucency of blood vessels are observed in endoscopic examination [11]. Histological evaluation of lesions in the small intestinal mucosa specimens is based on the four-grade Marsh scale, accounting for the number of endoepithelial lymphocytes and the condition of intestinal crypts and villi [2]. Coeliac sprue is characterized by Marsh scale grade 3 (3a – partial, 3b – nearly complete, 3c – complete intestinal villous atrophy) and grade 4 histological lesions with crypt hypotrophy and endoepithelial lymphocytosis [1] .

A gluten-free diet is of highest importance in the treatment of coeliac disease, and must be observed for the rest of the patient's life. Wheat, rye and barley products must be eliminated from the menu. The role of oats in coeliac disease is still under study [7, 9]. Hidden sources of gluten, such as canned meat, concentrates, hot dogs, pâtés, powdered soups, sweets, some alcoholic drinks and medications [2], have to be eliminated too. Gluten-free products are marked with a crossed crop ear symbol. Eliminating gluten from the diet results in the resolution of inflammatory lesions in small intestinal mucosa in 85% of cases [11]. However, clinical improvement in adult patients requires more time than in the case of paediatric patients. Mood disorders are the first symptoms to be resolved, and an increase in body mass is observed [1].

Nutrient supplementation and prevention of dietary deficiencies is important. Supplementation of e.g. iron, calcium, or vitamins may be necessary [7]. In rare cases of diet-refractory coeliac disease, immunosuppressive medications (glucocorticoids, azathioprine, cyclosporine) are used [2, 14]. Monitoring the disease involves periodically determining anti-tissue transglutaminase and antiendomysial antibody levels, and screening for cancer diseases [1].

In light of current data, the age of the child when gluten is introduced into his/her diet may be important for the development of coeliac disease. The period between the fourth and the sixth month of life seems be associated with the highest risk in this respect [10].

In conclusion, it should be noted that in the light of population studies conducted in recent years, coeliac disease seems to be more prevalent than previously suspected, and its incidence may still be underestimated. Coeliac sprue is increasingly often manifested in middle-aged or even elderly individuals, and its course is usually atypical. Serological screening tests play an important role in the diagnostics of coeliac disease. These tests should be performed in high-risk groups, as they allow atypical forms of the disease to be diagnosed early. This in turn allows the appropriate treatment to be applied early. This makes it possible to avoid any late consequences or complications of coeliac disease. These pose a risk to patients with both full-blown and asymptomatic versions of the disease. Physicians should be made aware of the necessity for such tests in patients with refractory anaemia of unknown origin, body weight loss, chronic diarrhoea, depression, reproduction disorders and in genetically predisposed individuals, such as first degree relatives of coeliac disease patients.

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