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Celiac disease in older persons: A case of seronegative disease

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Abstract

A 68-year-old man with a history of smoking (former smoker of 40 cigarettes per day), euthyroid goiter, deep vein thrombosis and depression, came to our attention for weakness, cachexia, abdominal bloating and diarrhea lasting for almost six months. Furthermore, he had lost about 25 kilograms of weight in the last year and was bedridden for three months. Combining the results of serological, histopathological and genetic tests, he was diagnosed with a seronegative celiac disease. Gluten-free diet, combined with nutritional supplements and physical therapy, improved his clinical condition and allowed the recovery of weight and the walking ability. Celiac disease might be suspected in elderly patients with diarrhea, malabsorption, malnutrition and cachexia, but also with other symptoms such as anemia, micronutrients' deficiency, fragility fractures and neurological symptoms.

Keywords

celiac disease; cachexia; malnutrition; gluten-free diet; elderly

Case Report

A 68-year-old man came to our attention for weakness, cachexia, abdominal pain and diarrhea lasting for almost six months. Furthermore, he reported also a weight loss of 25 kilograms over the last year and was bedridden for three months. The patient was a former smoker of about 40 cigarettes per day and without history of alcohol's abuse. His medical history included a euthyroid goiter, deep vein thrombosis, depression and cholecystectomy for gallbladder's lithiasis. Finally, it is noteworthy that he had not been taking any medication at home.

During the medical exam he appeared in poor clinical conditions; he was alert, oriented in time and space, apathetic, cachectic, markedly sarcopenic, with abdominal bloating and intestine protruding through the abdominal wall (intestine's hypermotility was visible to the naked eye), and with a second stage bedsore on the sacrum. He had hypotension (85/50 mmHg), with regular cardiac frequency, remarkable peripheral edema and mild tachypnea. The patient complained of legs muscle cramps and peripheral paresthesia, and he had hyporeflexia. Laboratory tests showed macrocytic anemia (Hb 7,6 gr/dl, MCV 100 fl) associated with very low plasmatic levels of folic acid, cobalamin, iron and ferritin. There were also mild hypertransaminasemia, hypoalbuminemia, hypogammaglobulinemia, hypokaliema, hypocalcemia, hypomagnesemia, and hypovitaminosis D, while plasmatic levels of thyroid's hormones, calcitonin, anti-thyroglobulin and anti-peroxidase antibodies were normal. None of

the tumor markers (CA 15.3, CA 19.9, CEA, NSE, S100, α-fetoprotein, PSA) was elevated and the search of auto-antibodies did not give positive results, except for a mild positivity of anti-smooth muscle antibody. A total-body Computerized Tomography disclosed bilateral pleural effusions with a parenchymal inflammatory densification in the middle lobe of the right lung and intraperitoneal supra- and sub-mesocolic effusion without any intra-abdominal organ alteration. Fecal occult blood test, performed on three stool samples, resulted negative. Moreover, the microbiological and cultural test of feces, colonoscopy and searching for *Helicobacter pylori*'s antigen were negative as well. Fecal chemical-physical test showed the presence of steatorrhea.

Meanwhile, we treated the patient with intravenous infusion of albumin, electrolytes, enteral and parenteral nutritional supplements and with antibiotics, in order to manage pneumonia. We underwent blood tests for gluten autoantibodies - anti-endomysial (EMA), IgA and IgG anti-tissue transglutaminase (TTG) for a suspected celiac disease. Our laboratory test panel also included IgA anti-gliadin antibodies to determine if the patient produced sufficient IgA antibodies for the EMA and TTG to be reliable, however he did not have an IgA deficiency. The search of antibodies was negative (Tab. I), nevertheless the result did not prove to be reliable considering the patient's remarkable hypogammaglobulinemia. Indeed, there was still clinical suspicion of celiac disease.

Therefore, the patient underwent an esophagogastroduodenoscopy. The exam showed a plentiful lake of bile in the stomach as a result of duodenum-gastric reflux, diffuse gastric and duodenal mucosal hyperemia and tubulization of the second portion of duodenum with scalloping of folds (Fig. 1). Histopathological examination of duodenal bioptic specimens reported mild atrophy of villi, a proportion between intraepithelial CD3+-T lymphocytes and epithelial cells (IEL/EC) greater than 25 on 100 cells, and an increase of lymphocytes in the context of *lamina propria*, a morphological image compatible with type 3a celiac disease according to Marsh-Oberhuber histological classification. The exam discovered also a mild superficial chronic inactive gastritis, negative for *H. pylori*. (Table II and Fig. 2).

In order to better define the diagnosis, HLA-typing test was performed to evaluate patient's genetic susceptibility. Our patient was DQB1*02-positive, but DQA1*05-negative, a condition that can be found in 5% of patients with celiac disease. When the diagnosis of celiac disease was confirmed histologically, the patient started gluten-free diet. He was adequately informed about food he totally might remove and received a daily dietary plan adjusted for his caloric need.

After gluten restriction, the patient gradually started to show a remarkable improvement of general condition with a decrease of abdominal pain, intestinal bloating and diarrhea. We also observed an improvement in albuminemia and plasmatic electrolytes levels, a reduction of anasarca, and a resolution of anemia (although slowly). The patient started physical and rehabilitative therapy, first during the recovery in our geriatric ward, and following at home, by means of home assistance. The physical therapy enabled the patient to recover the upright position and then the walking capacity, first using aids (walker, canes and crutches), and afterward independently.

Six months after hospital discharge, the patient came to our geriatric ambulatory clinic. The general clinical conditions were remarkably improved with the only aid of a cane while walking. He had gained six kilograms of weight compared to body weight at hospital discharge and his laboratory tests

were normal. We decided to evaluate patient's bone mass density and evaluate his risk of fragility fractures. The dual energy x-ray absorptiometry showed a T-score of -3.0 SD at lumbar spine and a T-score of -2.5 SD at femoral neck. The vertebral column X-ray put in evidence two mild thoracic vertebral fractures (T9 and T10) according to Genant's morphometry. Consequently, according to national Italian guidelines, he started treatment with IV zoledronic acid. The endoscopic control one year after the diagnosis and the beginning of gluten restriction showed an improvement of duodenal morphological image both at macroscopic examination (with no more scalloping and *restituito ad integrum* of duodenal folds) as well as at microscopic analysis.

The patient appeared in good clinical conditions, he walked with no aid, with recovery of performance in basic and instrumental activities of daily living (ADL and IADL). He had no symptoms of cognitive decline (Mini Mental State Examination was normal), and did not show symptoms of depression when tested with Geriatric Depression Scale (GDS).

Discussion

Celiac disease has been traditionally recognized as a disorder of children and young adults. However, recently, there has been an increase in the diagnosis of the disease in older populations [1, 2]. In the 80's, Swinson et al. demonstrated that the diagnosis of celiac disease in adults has a bimodal distribution for age with a peak in the fourth decade (mostly women) and a second peak in the sixth and seventh decades (mostly men) [3]. Nevertheless, celiac disease is underdiagnosed in late life at present.

A low index of suspicion by physicians for celiac disease in older adults may be due to a different clinical presentation when compared to that in young people. Typical symptoms and signs of celiac disease, expression of impaired intestinal absorption, such as diarrhea and weight loss, while common, are less prominent than in younger patients. Older patients often present with mild symptoms, such as abdominal discomfort and bloating, instead of clear abdominal pain and this may be due to a limited mucosal extension of the disease in duodenum and jejunum [1]. Our patient presented with abdominal bloating and chronic diarrhea associated with weight loss and other signs of malabsorption. Moreover, he had a remarkable steatorrhea, of which celiac disease can be considered the most common cause in over 50-year-old people and the second most common cause in those aged 65 years [4].

Malabsorption may present with a spectrum of manifestations going from symptoms and signs of isolated deficiencies of specific nutrients (such as iron, folic acid and other vitamins) until severe malnutrition and cachexia. Micronutrient deficiencies often are not recognized or lead to the suspicion of other disorders. For example, iron deficiency anemia often leads physicians to undergo studies in order to exclude colon cancer [1]. Anemia is very common in older adults with celiac disease and Hankey et al. reported that more than 80% of celiac older people in a British series had anemia [5]. Iron deficiency is the most frequent cause of anemia in these patients, but it is common to find a dimorphic peripheral blood smear when iron deficiency combines with cobalamin and/or folic acid deficit. In our patient, the dimorphic anemia was the result of a sideropenic anemia (due to iron and ferritin's deficiency) combined with a macrocytic anemia (due to cobalamin's malabsorption resulting from chronic gastritis).

Other abnormal laboratory tests in celiac older patients include hypomagnesemia - which could justify some neuropsychiatric symptoms such as muscular cramps, apathy and depression,

hypertransaminasemia and other liver chemistry changes [6] - a condition called *celiac* hepatitis [7] - and hypoalbuminemia, which additionally may lead to hypomagnesemia and hypocalcemia [8,9]. The remarkable hypoalbuminemia in our patient caused the development of peripheral edemas, ascites and bilateral pleural effusions, which slowly regressed after the starting of the gluten-free diet and the normalization of albuminemia. In addition, plasmatic levels of transaminases were normalized after gluten restriction and the restoration of normal magnesium concentrations contributed to the resolution of muscular cramps and apathy.

Another interesting aspect of our case is represented by the peripheral neurological symptoms: peripheral paresthesia and hyporeflexia at patella and Achilles tendon. According to Hadjivassiliou et al., ataxia and peripheral neuropathy are the most common neurological manifestation of celiac disease [10], while myopathy and hyporeflexia have also been described [11]. Muscle impairment in our patient was most probably due to the malabsorption associated with celiac disease and to the progressive reduction of muscular exercise and use until the forced bed rest of the patient. The combination of gluten free diet and physical therapy allowed the recovery of muscular tone, trophism and function.

Deficiency of calcium and vitamin D is another clinical feature of celiac disease in late life, leading to a reduction of bone mineral mass and increasing the risk of fragility fractures [9,12]. In addition to hypocalcemia and hypovitaminosis D (that we have initially corrected with IM cholecalciferol) and with them interrelated, our patient presented osteoporosis complicated by two vertebral fragility fractures. Although celiac people may improve their bone mineral density with gluten restriction, the bone mass increment is limited in older adults with celiac disease [1]. According to national Italian guidelines, our patient started therapy with an IV bisphosphonate.

None of the most important autoimmune disorders frequently associated with celiac disease were observed in our patient. Among them, the most common is dermatitis herpetiformis, which can be the first manifestation of gluten-sensitivity also in celiac older patients, presenting with extremely pruritic papulo-vescicular lesions on extensor surfaces such as elbows, knees, scalp and buttocks [13]. Other common autoimmune disorders associated with celiac disease are thyroid autoimmune diseases, which are frequent in celiac older patients, presenting with hypothyroidism [1].

During the follow-up visits at six months and one year after the diagnosis of celiac disease, we had the first confirmation – not completely exhaustive, but certainly important – that the patient had not developed a refractory disease and had clearly understood the features of his disease and the correct approach to avoid its complications. In fact, in an older celiac patient, several serious disorders may complicate the clinical course of the disease [14], such as refractory disease, collagenous sprue and small bowel lymphoma. In most, the persistence of symptoms is due to limited compliance to the gluten restriction or inadvertent consumption of gluten [1], which in older patients may be a consequence of cognitive decline, depression, loss in ADL and IADL, or poor quality of caregiving. Our patient was a "young old" without cognitive decline, with no need of caregiver and with cultural and social condition well enough to understand and respect the gluten-free diet. In other patients, the persistence of symptoms, like diarrhea or weight loss, may be related to other causes with no relationship with celiac disease (e.g., infectious diarrhea and ischemic bowel disease), to superimposed diseases of small intestine, to associated causes (e.g., pancreatic exocrine insufficiency), or to complications like

lymphomas (mostly of T-cell type) and malignant tumors of small bowel and other parts of the gastro-intestinal system [1].

In some cases serological tests are not useful to diagnose celiac disease. In fact, seronegative patients represent 5% of all celiac patients. This means – as the case of our patient demonstrates – that the absence of EMA and TTG does not consent to rule out the diagnosis of the disease. A recent retrospective Italian study [15], conducted in a group of 810 celiac patients, defined the clinical, histological and laboratory features of seronegative compared to seropositive celiac disease. In particular, seronegative disease showed a higher prevalence of classic clinical manifestation, with gastro-intestinal symptoms and severe atrophy of villi. It resulted as a late onset form of celiac disease: the median age at diagnosis was significantly higher than in seropositive disease. Moreover, seronegative celiac disease was described as the most frequent cause of seronegative flat duodenal mucosa (45%), followed by Giardiasis, common variable immunodeficiency and autoimmune enteropathy.

It is reasonable to conclude that celiac disease is a disorder in which physicians might think about in old patients, considering that it is common not only in the young, but also in the older adults. It may not be apparent for many years causing only subtle and non-specific symptoms and then it may present for the first time with complete malabsorption, severe weight loss and serious complications. Physicians must elevate their index of suspicion on the possible presence of celiac disease and become more conscious of its incidence and clinical presentation in the older people, in order to reduce the delay in the diagnosis. A comprehensive and multidisciplinary approach is essential to face the challenges that the management of the disease may present in late life.

Tables

Table 1: Celiac disease antibodies tests results in our patient

TEST	RESULT	Normal
EMA IgA	NEGATIVE	Negative
TTG IgA	2,5	<20 UR/ml
TTG IgG	<1	<1 UR/ml

Table 2: Marsh-Oberhuber classification of histologic findings in celiac disease.

Type	0	1	2	3a	3b	3c
IEL	<25	>25	>25	>25	>25	>25
Cript hyperplasia	Normal	Normal	Increased	Increased	Increased	Increased
Villi	Normal	Normal	Increased	Mild atrophy	Marked atrophy	Marked atrophy

Figures

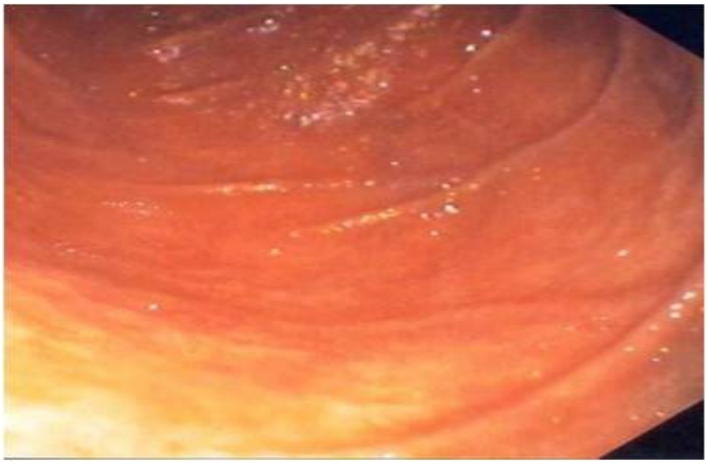

Figure 1: Endoscopic image: *scalloping* of duodenum.

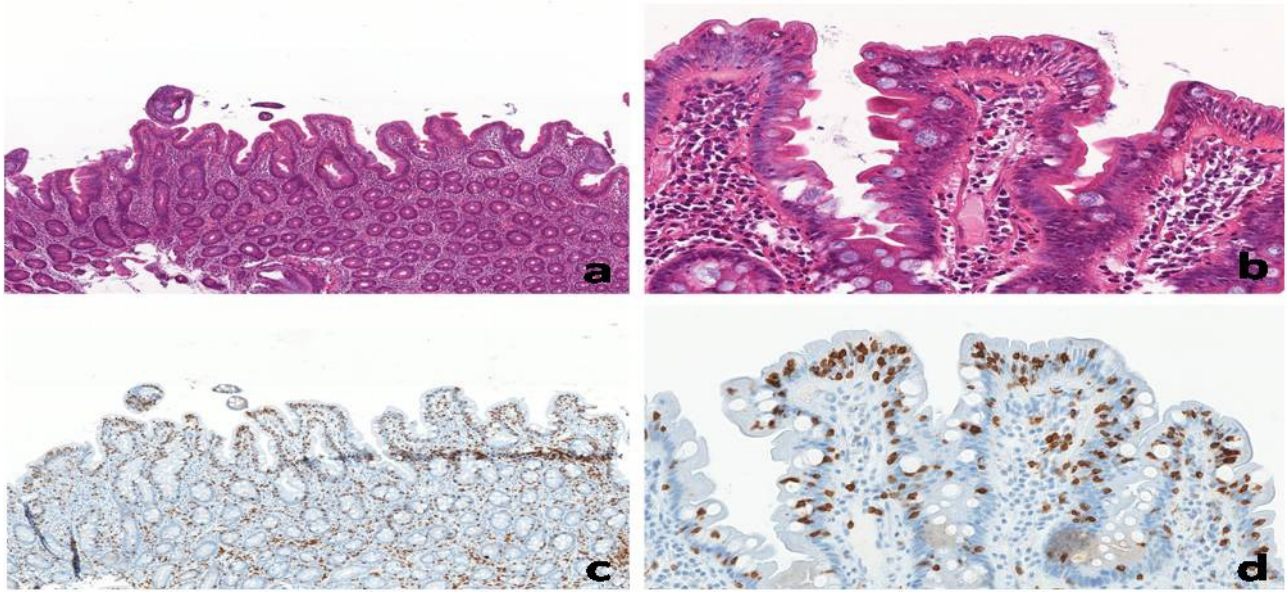

Figure 2: a,b) Mild atrophy of duodenal villi; c,d) The immunohistochemical stain for CD3 shows a pathological intraepithelial T lymphocytosis (>25/100)

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