GE Port J Gastroenterol. 2016;23(2):106–112

Portuguese Journal of Gastroenterology

www.elsevier.pt/ge

CLINICAL CASE

Refractory Celiac Disease Type II: A Case Report that Demonstrates the Diagnostic and Therapeutic Challenges

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Received 13 July 2015; accepted 18 August 2015
Available online 26 September 2015

KEYWORDS
Celiac Disease;
Cladribine;
Enteropathy-Associated T-Cell Lymphoma;
Hematopoietic Stem Cell Transplantation

Abstract Refractory celiac disease is an uncommon but serious complication of celiac disease. We describe a case of a severe refractory celiac disease type II, complicated with ulcerative jejunoileitis, in a 68 years old female, unresponsive to consecutive treatments with budesonide, prednisolone, cladribine and autologous stem cell transplantation. The patient maintained severe malnutrition, advanced osteoporosis, anaemia, vitamin deficiencies and hydro-electrolytic imbalances, necessitating consecutive hospitalizations for total parenteral nutrition. The patient also developed life-threatening complications, namely respiratory and urinary septic shock and also episodes of haemorrhagic shock secondary to ulcerative jejunoileitis. The progression to enteropathy associated T-cell lymphoma was never demonstrated, but the patient died 7 years after the diagnosis due to a septic shock secondary to a nosocomial pneumonia and osteomyelitis related to a spontaneous hip fracture. This case highlights the difficulties in the diagnostic process, therapeutic management and surveillance of this rare condition associated with very poor prognosis.

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http://dx.doi.org/10.1016/j.jpge.2015.08.001

PALAVRAS-CHAVE
Cladribina;
Doença Celíaca;
Transplante de Células Estaminais Hematopoiéticas;
Linfoma de Células T Associado a Enteropatia

Doença Celíaca Refratária Tipo II: Um Caso Clínico que Ilustra os Desafios Diagnósticos e Terapêuticos

Resumo A doença celíaca refratária é uma complicação rara mas muito severa da doença celíaca. Apresentamos o caso de uma doente de 68 anos, com doença celíaca refratária tipo II complicada de jejunoileíte ulcerativa, que não respondeu a tratamentos sucessivos com budesonido, prednisolona, cladribina e transplante autólogo de medula óssea. A doente manteve desnutrição e osteoporose severas, deficiências vitamínicas e desequilíbrios hidro-eletrolíticos, necessitando de múltiplas hospitalizações para receber nutrição parentérica total. Também desenvolveu diversas complicações potencialmente fatais nomeadamente sépsis com origem respiratória e urinária e choque hemorrágico secundário à jejunoileíte ulcerativa. Contudo, nunca se demonstrou a presença de um linfoma de células T. A doente faleceu 7 anos após o diagnóstico devido a choque sético secundário a pneumonia nosocomial e osteomielite relacionada com fratura espontânea da anca. Este caso ilustra as dificuldades sentidas no decurso do diagnóstico, terapêutica e vigilância desta entidade clínica rara, a qual está associada a um péssimo prognóstico.

1. Introduction

Celiac disease (CD) is a chronic immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals. It is a common autoimmune disease affecting around 1% of the general population.[1] The diagnosis is often easy in the presence of classic symptoms of malabsorption, positive celiac-specific antibodies and villous atrophy in duodenal biopsies. However, some patients, mainly those diagnosed in the adulthood, can only present atypical or extra intestinal manifestations (e.g. iron deficiency, fatigue, abnormal liver function tests, bone disease, skin disorders, peripheral neuropathy, depression), and the specific serology can be negative.[2,3] Strict life-long gluten free diet (GFD) is the only treatment available, leading to clinical and mucosal recovery in most patients, but a small minority does not show clinical improvement upon GFD.[1,4] Refractory CD (RCD) is a rare and severe condition, developing in 1–5% of the adult-onset CD patients, and is defined as persistent or recurrent symptoms and signs of malabsorption with small intestinal villous atrophy despite a strict GFD for more than 12 months in the absence of other causes of villous atrophy.[5,6] RCD is divided in two types based on the absence (Type I) or presence (Type II) of abnormal intraepithelial lymphocytes (IEL).[7] Type II RCD (RCD-II) has limited therapeutic options, often complicates with severe malnutrition, ulcerative jejunoileitis and enteropathy associated T-cell lymphoma (EATL).[7,8]

We report an unfavourable case of RCD-II, describing the difficulties in the initial diagnosis, the consecutive failures of distinct therapeutic options, and the multiple complications that finally led to the death of the patient.

2. Case report

We present the case of a 68 years old white female, diagnosed with CD in 2008, when she was 61 years old, and whom never become asymptomatic despite strict GFD. The diagnosis was made considering characteristic histologic features, despite negative specific-CD serology. She had no other comorbidities apart from chronic depression and there was no family history of CD or other autoimmune diseases. The patient presented to our department for the first time in February 2010 complaining of chronic diarrhoea, vomiting, anorexia, asthenia and weight loss, despite 2 years of GFD. She showed severe malnutrition (body mass index – BMI: 12 kg/m^2, extreme hypoalbuminemia), threatening hydroelectrolytic imbalances (hypomagnesaemia, hypokalaemia, hypophosphatemia, hypocalcaemia), normocytic anaemia (haemoglobin of 8.1 g/dL), coagulopathy (INR of 8.2), vitamin deficiencies and severe osteoporosis. The adherence to GFD was revised and ensured. Upper gastrointestinal (UGI) endoscopy with duodenal biopsies was repeated, showing endoscopic aspects compatible with CD (Fig. 1). A marked villous atrophy, with villous to crypt ratio of <1/1 and increased IEL were observed – Marsh-Oberhuber stage 3b (Fig. 2). These biopsies also allowed the diagnosis of giardiasis that was successfully treated with metronidazole (confirmed with repeated biopsies after treatment). Ileocolonoscopy was performed, and despite absence of mucosal changes random biopsies demonstrated the presence of lymphocytic colitis. Apart from these two parallel diagnoses that could contribute to the refractory symptoms, careful investigation and exclusion of other entities that could be the cause of symptoms and villous atrophy was made (Table 1). Specific-CD serology was repeated and it was negative once again. HLA typing was determined and revealed a DQ2/DQ8 compound heterozygote. Immunohistochemical analysis was performed in duodenal biopsies and revealed more than 50% of aberrant IELs, which were CD3+, but mostly CD8- and CD30- (Fig. 3), being compatible with a RCD-II, with no evidence of EATL. The aberrant pattern was confirmed by detection of T-cell receptor chains clonal rearrangement, performed at the Celiac Centre Amsterdam, VU University Medical Centre. A CT scan