Case Report

Type II Refractory Celiac Disease in Two Siblings: One with Myoclonic Ataxia

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Abstract

Refractory celiac disease (RCD) is defined as a clinical complicated variant of celiac disease (CD), characterized by the persistence of recurrent malabsorption symptoms and villous atrophy, despite a strict adherence to a gluten-free diet (GFD) for at least 6-12 months, in the absence of other causes of non-response and overt associated any type of cancer. The prognosis is dismal and fortunately its prevalence is very rare, being estimated, in less than 5% of CD diagnosed total population. We describe the onset of this complication in the same family, affecting two siblings, a man of 59 years with a progressive myoclonic ataxia and a woman of 50 years, with a jejunal localization of an Enteropathy Associated T-cell Lymphoma (EATL). Both died within a few months after the onset of their RCD, as a consequence of the associated complications of the illness. For establishing a firm diagnosis it is necessary to confirm the presence of abnormal changes in the intraepithelial lymphocyte population. These patients did not express the surface receptors (CD3 and CD8) and had a positive monoclonal detection of T receptor chains confirmed in both siblings, as positive markers of immunological diagnosis of RCD-2 type in these patients, according to an aggressive clinical course and a poor prognosis. The family association of this important complication (RCD-type II) is remarkable and the neuropathological complication of a myoclonic ataxia is very uncommon.

ABBREVIATIONS

RCD: Refractory Celiac Disease; CD: Celiac Disease; GFD: Gluten Free Diet; EATL: Enteropathy Associated T-Cell Lymphoma; TTG: Anti-Tissue Transglutaminase Antibodies; EMA: Anti-endomysium antibodies; VA: Villous atrophy; CSF: Cerebro-Spinal Fluid

INTRODUCTION

Celiac disease (CD) is an autoimmune process, defined as a permanent intolerance to gluten, which appears in genetically predisposed individuals. Following the introduction of a gluten-free diet (GFD), generally in a few weeks, it is produced a significant clinical improvement, while the histological lesions recover more slowly, may even persist in more than one third of cases for two years, in the absence of a clear symptomatology [1,2].

Refractory Celiac disease (RCD) was originally described by Trier et al. in 1978 [3] and was applied to some celiac patients presenting with continuous symptoms, together with duodenal villous atrophy and persistent diarrhea and unresponsive to GFD, at least for 6 months. The AGA (American Gastroenterology Association) has recently defined this entity, as patients who do not respond to a GFD, either primarily or secondarily [4]. This situation may initially appear without presenting some may not respond to the GFD from the initial diagnosis (primary) and other patients already diagnosed with CD, after a variable time may stop responding to the GFD (secondary). The presence of compliant data such as typical CD serology, positivity of HLA-DQ2 or family history, support the diagnosis of RCD, while the absence of any of these findings, require us to make a differential diagnosis with other diseases [5]. Fortunately the frequency of RCD is low, being less than 5% of all CD patients. In one reference center in Boston, the prevalence of RCD was 4% [6], while in some studies does not exceed, to 1% of the adult celiac population [7]. Its presentation in people less than 30 years is considered exceptional. Most cases occur in persons greater than 50 years, and with a slight prevalence in females [8]. In recent years there has been a major advance in the understanding of the disease pathogenesis, but nevertheless, the RCD type 11 has a poor prognosis with decreased survival of 50% at 5 years [9,10].

Although there is a high familial incidence of CD, the familial association of RCD type II is very unusual [11]. We describe two brothers with RCD type II, with different associated conditions.
one with a severe neurologic complication (Myoclonic Ataxia) and the other with a progressive enteropathy-associated T-cell lymphoma (EATL). Both died in short-term, as a consequence of the onset of these complications without response to the GFD.

**CASE PRESENTATION**

**Case 1**

Fifty nine years old man, presented with a three months history of abdominal discomfort with persistent and prominent bloating, frequent diarrhea and with moderate weight loss. The physical examination was unremarked. His anti-Transglutaminase antibody was positive (120 U / l) as was his anti-endomysium (EMA) at1/80. Genetic typing was positive for the marker HLA-DQ2 (HLA-DQA1 * 0502 and DQB1 * 0201) homozygosis. The histological examination of duodenal biopsies showed complete villous atrophy (Marsh grade 3c) with a large submucosal inflammatory infiltrate consisting of lymphocytes. The patient was diagnosed with CD and treated with gluten-free diet (GFD). Clinically responded, with total disappearance of the diarrhea and significant weight gain usual standard. After 2 years of strictly following the GFD, he redeveloped diarrhea and weight loss, along with the emergence of a major difficulty in walking, secondary to abnormal movements of the right leg. When he moved or touched the right foot, there was sudden involuntary jerking, which caused loss of balance with frequent falls (in one of them, he fractured their both wrists). These movements did not occur being at rest, or during the night at sleeping time. A cerebral CT scan was reported as normal and a brain and spinal MRI, showed a slight atrophy of the cerebellum, leading to a diagnosis of Myoclonic Ataxia.

The neurological condition worsened, presenting with frequent shocks of the right leg, with progressively increasing difficulty walking and increased clumsiness in his right hand accompanied by tremors. It was not accompanied by sensory disturbances, or sphincter disruption. Gradually he presented with progressive dysarthria, with clear language disorder and associated memory impairment.

The neurological examination confirmed hypertonia and hyperreflexia in the lower extremities, being more pronounced in the right leg. The Romberg sign, was positive. The electrophysiological studies showed clear evidence of cortical myoclonus. Given the progressive worsening of the neurological disease the patient was treated with five plasmapheresis sessions, which slightly improved the dysphasia, but the motor myoclonic movements persisted. Somato-sensory evoked potentials showed increased responses that were most striking in the right hemisphere. The cerebrospinal fluid (CSF) analysis, including determination of oligoclonal bands and multiple serological tests were negative. A repeated gastroscopy with duodenal biopsies was performed and confirmed the persistence of severe villous atrophy (Marsh stage 3c) associated with a dense and diffuse lymphocytic infiltrate and the immunoclonal cytoplasmic staining for CD3 lymphocytes was positive in the duodenal biopsies (Figure 1). The patient was treated with azathioprine and steroids during 6 months without a response, and remained in a wheelchair after a year of the onset of ataxia with severe and progressive neurologic and general deterioration. Finally, the patient died within 2 years after the onset of myoclonic ataxia, secondary to aspiration pneumonia, followed by an uncontrolled severe sepsis.

**Case 2**

A fifty years old woman, (sister of the previously described patient), diagnosed with celiac disease (CD) five years ago, presented initially with a history of chronic diarrhea, weight loss and abdominal pain. She had positive serology for CD, with a very high anti-tissue transglutaminase titer (85 U / l), a positive genetic marker for HLA-DQ2 homozygous and duodenal biopsies revealed the presence of marked villous atrophy (Marsh 3c) with remarkable lymphocytic infiltrate associated. She started on a strict GFD and within a few weeks had resolution of her symptoms. The clinical, serologic, genetic and histologic duodenal findings at the moment of CD diagnosis in both siblings are shown (Table 1). Following 3 months, of strictly following the GFD she developed anintense epigastric pain as well as anorexia, frequent nausea, intermittent vomiting, persistent diarrhea, loss
of about 7 Kg. of weight and high fever with peaks up to 40° C. Her body mass index (BMI) was very low (18 Kg/m2) and had decreased levels of total proteins (5.1 g/dl) and serum albumin (2.0 g/dl). A new gastroscopy was reported as normal. Endoscopically duodenal biopsies confirmed the presence of severe villous atrophy (Marsh-3c with plenty lymphocytic infiltrate. The transglutaminase was highly positive (130 U/l). (Normal less than 200U/l). She underwent a colonoscopy that was normal and an abdominal CT scan confirming an area of stenosis at the proximal jejunum. An endoscopic confirmed the presence of a jejunal stenosis of about 5 cm. in length, accompanied by several ulcerations and protruding areas. The patient was operated on and it revealed the presence of a jejunal tumor located about 20cm from below of the Treitz angle with multiple mesenteric lymph nodes necessitating a partial resection of the jejunum with eipioplasty. The microscopic sections showed a marked villous atrophy with a dense lymphocytic infiltration of the submcosa with T cells predominant. Staining of lymphocyte immunophenotyping showed an absence of CD3, CD4 and CD8 at the intraepithelial level. CD3 was only positive intraepithelially but not at the membranes. Also a high activity of Ki67 was confirmed and a positive monodonal proliferation of gamma T-cell receptor chains rearrangement was identified by specific polymerase chain reaction (Figure 2). After a full evaluation of the small bowel it was confirmed that the tumor was restricted to that location of the jejunum and was finally diagnosed as a primary enteric- associated T cell lymphoma (EATL), of non-Hodgkin type (stage IV-B, IPI). The patient followed a difficult postoperative course with fever peaks and purulent drainage. An abdominal CT scan showed two collections at the left colic gutter with suspected perforation of the colon necessitating another operation leading to are section of the transverse colon with colostomy. Subsequent chemotherapy was initiated as CHOP rate, broad-spectrum antibiotic coverage associated, receiving 2 full cycles. He developed severe malnutrition, sepsis and multi-organ failure and died at 8 months following his diagnosis of EATL. The clinical characteristics, complications at the moment of diagnosis of RCD-type 2 and their evolution of the two siblings are described in (Table 2). Subsequently the family tree was analyzed and 2 more cases of celiac disease among first degree members was found revealing a familial incidence of 4/29 (13.8%).

**DISCUSSION**

Refractory celiac disease (RCD) is a rare complication of the celiac disease (CD) that involves malabsorption and villous atrophy, despite continuous adherence to a strict gluten-free diet (GFD) for at least 12 months, in the absence of another known cause. RCD may be classified as primary or secondary, based on the time of onset. Primary RCD, is described when an individual with CD was never responsive to a GFD, whereas secondary RCD appears in patients who had been previously responsive to a GFD during several months, years, or even decades. RCD is better classified according with the immunophenotyping studies performed in the duodenal biopsies based on the T-cells determinations in the intra-epithelial lymphocyte (IEL). Type 1 RCD type 1 has normal IEL populations whereas RCD type 2 has aberrant IEL clonal proliferation, measured by PCR (polymerase chain reaction) for T cell receptors (TCR) at the β /γ loci. This classification is important, as the prognosis and treatment is significantly different. RCD type 2 carries a very poor prognosis, with a five-year mortality of about 55%. RCD type 1 carries a much better prognosis with a mortality rate of around 7%, with aggressive treatment involving strict adherence to a GFD, nutritional support and pharmacologic intervention [12]. The first patient described developed an extra-intestinal manifestation of RCD, a special form of cerebellar ataxia, called “myoclonic ataxia”. This unusual neurologic complication is the less common ataxic manifestation, associated with CD. A recent publication of a series of nine patients with this phenotype, described that all of them, presented asymmetrical irregular

**Table 1:** Clinical, serological, genetic and duodenal biopsy findings at CD diagnosis, in the two siblings.

<table>
<thead>
<tr>
<th>Case number</th>
<th>Gender</th>
<th>Age</th>
<th>Clinical symptoms</th>
<th>Serology</th>
<th>Genetics HLA-II</th>
<th>Duodenal Biopsy findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>M / 56</td>
<td></td>
<td>Chronic diarrhea</td>
<td>tTG2 = 120 U/l</td>
<td>DQ2 (+)</td>
<td>Marked VA Marsh 3c</td>
</tr>
<tr>
<td>Case 2</td>
<td>F / 45</td>
<td></td>
<td>Abdominal pain</td>
<td>tTG2 = 85 U/l EMa = 1/40</td>
<td>DQ2 (+)</td>
<td>Marked VA Marsh 3c</td>
</tr>
</tbody>
</table>

**Abbreviations:** M: Male; F: Female; tTG: Anti-Tissue Transglutaminase-2 Antibodies; EMA: Anti-Endomysium Antibodies; VA: Villous Atrophy; Marsh: Marsh classification of duodenal biopsies for CD

**Table 2:** Clinical characteristics and evolution at the RCD-type 2 diagnosis, in the two siblings.

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Gender</th>
<th>Age</th>
<th>Clinical Symptoms</th>
<th>RCD-Type 2 diagnosis</th>
<th>Clinical Complication</th>
<th>Evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>M / 59</td>
<td></td>
<td>Difficulty in walking intermittent jerking attacks in left leg Frequent falls and secondary fractures</td>
<td>Staining of subpopulations of lymphocytes in the duodenal mucosa</td>
<td>Myoclonic Ataxia</td>
<td>Death After 2yrs. of onset</td>
</tr>
<tr>
<td>Case 2</td>
<td>F / 50</td>
<td></td>
<td>Continuous and diffuse abdominal pain Anorexia, vomiting and persistent diarrhea High fever Marked and quick weight of loss</td>
<td>Staining of subpopulations of lymphocytes in the jejunal mucosa</td>
<td>jejunal EATL</td>
<td>Death After 8-months of onset</td>
</tr>
</tbody>
</table>

**Abbreviations:** M: Male; F: Female; EATL: Enteropathy Associated T cell lymphoma
myoclonus preferentially involving one or more limbs, similar to the clinical presentation of our patient, and sometimes including also the face [13]. The myoclonus was often stimulus sensitive and became widespread over time. Five of these patients (55.5%) had a history of at least one secondarily generalized seizure. Despite the fact that all patients adhered to a strict gluten-free diet, all had ongoing intestinal inflammation, suggestive of refractory CD. Two patients of this series (22.2%) died as a consequence of the association with an enteropathy-associated lymphoma (EATL). Experimental evidence suggests that there is antibody cross-reactivity between antigenic epitopes on Purkinje and other cerebellar cells (granular layer) and gluten peptides. For example, anti-gliadin antibodies have been shown to react with human and rat cerebellar Purkinje cells in vitro probably playing a pathogenic role causing these lesions [14]. Even with the use of vigorous immunosuppression, usually in the form of mycophenolate, these patients remained disabled, primarily due to the troublesome myoclonus which proved to be resistant to all medication used. When encountering such neurologic complications, it is essential to monitor closely with repeated duodenal biopsies and take a low threshold or even better to stop completely the immunosuppressive therapy. The prognosis remains ominous in the great majority of these patients. CD is characterized by an increased mortality [15]. It is well known that this fact is mainly the result of the complications of CD itself, represented by refractory CD (RCD) and enteropathy-associated T-cell lymphoma (EATL) [16]. This is a rare complication (<1% of lymphomas) and as a poor prognosis [17]. RCD type 1 (RCD1) is characterized by persisting villous atrophy despite a strict GFD associated with increased but still phenotypically normal IELs. Conversely, a clonal expansion of abnormal IELs lacking surface CD3, CD8, and TCR markers, but expressing intracellular CD3, indicates RCD type 2 (RCD2), a condition that frequently evolves into EATL, the most serious complication of CD. Nevertheless, the RCD prevalence is low, being estimated to appear in around 1% of CD patients [18]. For RCD the 5-years survival rate is reported to be between 70% and 85% in patients with RCD1, but is only between 40% and 58% in patients with RCD2. Five-year survival dropped to between 8% and 20% in RCD2 patients who developed EATL [19,20]. Although the incidence of EATL was reported to be rare in the general population. (1 per 106 person-year), it was shown that it occurs in 60% to 80% of patients with RCD2 within 5 years [21,22]. The description of EATL arising in patients with RCD1 seems to be exceptional. Recent evidence suggests that non-EATLs, including intestinal B-cell and extraintestinal T-cell lymphomas, may rarely occur in celiac patients [23]. EATL in the western world generally appears in adult patients with previously diagnosed CD, successfully treated until then with a strict GFD (secondary EATL), as an exacerbation of the classic symptoms of CD, such as abdominal pain, diarrhea, and unexplained weight loss. The concomitant presence of fever and night sweating, together with laboratory parameters indicative for hypoaalbuminemia, anemia, and increased lactate dehydrogenase (LDH), and marked weight loss and overt clinical malabsorption, should alert physicians to this complication. The median age at diagnosis of EATL is 60 years, with similar frequency between men and women. On the other hand, EATL may also arise in patients without a known history of CD and on a gluten-containing diet (primary EATL), and in these cases, the diagnosis is more difficult and delayed because of the low specificity of symptoms and the very low index of clinical suspicion. In the subjects with EATL identified before CD has been diagnosed, the link between CD and EATL may be suggested by the detection of CD-specific antibodies (e.g., EMAs or anti-tTG), although the latter often disappears once the refractory state is fully developed [15]. Because EATL may be complicated by gastrointestinal perforation, obstruction, or hemorrhage, many EATLs are diagnosed at laparotomy. At gross examination, EATL appears as a massive tumor infiltration, which may be transparietal with ulcerations and induration of the intestinal wall. Up to 25% of cases have a multifocal presentation, and the proximal small bowel, particularly the jejunum, is a more common localization than the large bowel or rectum [24, 25]. There are reports of an association between EATL and peripheral eosinophilia, mesenteric lymph node cavitation, or splenic atrophy, the latter of which may increase susceptibility to severe infections or sepsis [26]. Malnutrition is a common feature, especially when EATL has an insidious and chronic presentation or manifests after a long-standing RCD. Extraintestinal presentations of EATL is rare, and there is a lack of data on the precise characteristics of its cutaneous, neuromeningeal, or pulmonary manifestations. Systemic or B symptoms, such as fever of no evident cause, night sweats, and weight loss of more than 10% of body weight, should be taken as signs of clinical progression, although they occur in less than 30% of EATLs. A high level of clinical suspicion for an overt lymphoma should lead to an extensive workup, including abdominal imaging, endoscopy, and histologic examination of gut biopsies. Laparotomy with collection of full-thickness biopsy specimens may be necessary in some cases.

We have described the clinical presentation of a rare form of familial RCD2 in two brothers with different associated complications. This highlights the need to screen first degree relatives of patients diagnosed with CD in order to begin early a GFD in order to prevent these possible complications.

REFERENCES