CASE REPORT

A 37-year-old woman with refractory coeliac disease type II disease treated by stem cell transplantation

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SUMMARY

This case study describes the disease course and treatment of a rare disorder, refractory coeliac disease. This disorder is associated with a marked increase in the risk of development of enteropathy-associated T-cell lymphoma. The patient in question developed coeliac symptoms despite strict adherence to a gluten-free diet, having been symptom-free for over 7 years. She presented with marked oedema of the legs and a distended abdomen. Investigations—laboratory, radiological and enteroscopy findings—were consistent with the development of refractory coeliac disease. This case illustrates the background and course of this disease, and the treatment options.

BACKGROUND

Coeliac disease is a T-cell-mediated enteropathy induced by ingestion of gluten with consequential intestinal injury. It is characterised by malabsorption and villous atrophy on small bowel biopsy and is typically reversed by withdrawal of gluten products from the diet.¹ It has an estimated prevalence of 1% in North America and Europe.² There is a subset of the disease, refractory coeliac disease (RCD), or refractory sprue, which does not respond to the gluten-free diet (GFD). This may present in three ways: (1) only partial improvement with GFD; (2) no beneficial response to GFD; or (3) good initial response to GFD, but relapse while still on a strict GFD.³

RCD is typically divided into two subgroups—RCD I and RCD II—differentiated by the presence or absence of abnormal intraepithelial T lymphocytes (IELs) on mucosal biopsy.⁴ Type I typically improves after treatment with immunosuppressants. The prognosis associated with type II is considerably poorer, with a high associated risk of developing enteropathy-associated T-cell lymphoma (EATL).²

CASE PRESENTATION

We present a case of a 37-year-old woman with a 9-year history of coeliac disease diagnosed in 2003. She was fully compliant with the GFD since diagnosis and was asymptomatic until 2011. Otherwise, her medical history was unremarkable. There was no history of coeliac disease in her immediate family.

In November/December 2011, the patient began to experience frequent, uncomfortable, abdominal bloating with associated diarrhoea and weight loss. This was despite strict adherence to a GFD, as confirmed by negative anti-tTG levels. These symptoms

progressively worsened and she developed drenching night sweats. In early February 2012, the abdominal pain became much more severe and she developed clay coloured and foul smelling stools. She presented to the emergency department with a history of 8–10 bowel motions a day and unintentional weight loss of 8 kg over the previous 3 months.

INVESTIGATIONS

Blood results showed low albumin of 18 g/L and an international normalised ratio of 3.2.

CT scan on admission showed abnormal thickening and distension of the small bowel, from the jejunum to the mid-ileum, with prominent lymph nodes.

An OGD did not show macroscopic changes associated with coeliac disease, but the duodenal biopsies showed total villous atrophy and markedly increased numbers of IELs.

Flow cytometry showed these IELs to be phenotypically abnormal with loss of cell surface expression of CD8.

A balloon enteroscopy revealed widespread ulcerative jejunitis with a non-specific inflammatory mucosal ulcer.

A positron emission tomography-computed tomography (PET/CT) scan showed diffuse inflammation and oedema of the small bowel, but focal metabolically active areas suggestive of lymphoma were not identified.

Bone marrow biopsy showed reactive features only, without evidence of lymphoid infiltration.

DIFFERENTIAL DIAGNOSIS

- Refractory coeliac disease
- EATL

TREATMENT

A trial of NG feeding was attempted, but was unsuccessful; the patient's albumin level dropped to 7 g/L. There was concurrent massive bipedal oedema and ascites. A peripherally inserted central catheter was inserted and a total parenteral nutrition regimen was initiated with concurrent albumin infusions; as the patient's albumin levels rose to normal, the oedema subsided. She was also started on budesonide with subsequent mild reduction in the frequency of diarrhoea and abdominal pain, but no sign of full recovery.

The haematology service was consulted for consideration of the role of autologous stem cell transplantation (ASCT). Based on the Mulder approach,^{5 6} treatment with the immunosuppressive

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purine analogue, cladribine, was started and after 5 days of therapy, the patient underwent a repeat double balloon enteroscopy and PET scan. The enteroscopic biopsies showed marked recovery in villi height, but there was still a significant increase in IELs. Albumin loss continued and the patient required weekly albumin infusions to maintain normal levels.

Based on the suboptimal response to cladribine, the patient underwent ASCT with fludarabine and melphalan conditioning in a tertiary centre. Stem cells had been harvested prior to commencing cladribine to prevent the risk of stem cell toxicity associated with this drug. Successful harvest occurred following administration of granulocyte-colony stimulating factor 10 µg/kg subcutaneously for 4 days. ASCT was complicated by ITU admission for neutropaenic sepsis, extensive enterocolitis and spontaneous small bowel perforation, in addition to global cardiac dysfunction and transient acute kidney injury.

OUTCOME AND FOLLOW-UP

Disease reassessment at 100 days post-transplant confirmed excellent response to treatment based on complete resolution of symptoms and signs of malabsorption (albumin, haemoglobin and body mass index), negative PET/CT scan and normal duodenal biopsy with IEL count within normal limits. T-cell receptor gene rearrangement studies showed persistent clonality of the delta component of the T-cell receptor, the most sensitive component of the test; however, the clonality in the β and γ chains demonstrated prior to transplant had become polyclonal. Subsequent clinical, endoscopic and histological follow-up at 6 and 12 months post-transplant showed continuing disease remission. Molecular studies at 12 months post-transplant were negative for T-cell receptor gene rearrangement.

DISCUSSION

We describe a case of RCD treated with ASCT. This patient is one of a very small number of patients in the UK and Ireland to have undergone ASCT for RCD II.

Non-responsive CD (NRCD) describes the continuing symptoms of coeliac disease despite GFD. There are a number of differentials to consider when this occurs, including slow response/mucosal, once a GFD diet is initiated; residual gluten in diet/poor dietary control (the leading cause of NRCD¹); other autoimmune diseases (inflammatory bowel disease); and functional causes, such as irritable bowel syndrome. RCD makes up only a small proportion of these cases.⁷

RCD is defined as symptomatic and persistent villous atrophy despite a strict GFD, and it is divided into type I and type II.⁴ RCD I demonstrates phenotypically normal IELs on intestinal biopsy; the hallmark of RCD II is the presence of aberrant IELs, which express cytoplasmic Cd3, but lack surface expression of T-cell markers, including CD3, CD4, CD8 and the T-cell receptor.⁸ Clonal expansion of aberrant IELs is believed to be responsible for the occurrence of EATL.⁹ It can thus be hypothesised that RCD II represents an early stage of EATL.⁵ Type II RCD is associated with a markedly worse 5-year survival rate than type I (43% vs 93%).¹⁰ Up to 60–80% of those with RCD II go on to develop EATL.¹¹

The risk factors for developing EATL include old age at presentation; male sex; ulcerative jejunitis; the presence of aberrant T-cells and DQ2 homozygosity.¹¹ The patient described in this case report was HLA-DQ2 homozygous.

Owing to the increased risk of development of EATL in patients with RCD II, close follow-up is warranted. Imaging by CT or PET scan is used to survey for possible lymphoma. Video endoscopy or balloon endoscopy can also be used for

surveillance. Survival rates for patients with EATL are low, between 11% and 20% at 5 years.¹¹

The treatment regimens recommended by the literature for RCD I include continued adherence to a gluten free diet and the introduction of immunosuppressive therapy, such as prednisolone/budesonide in combination with azathioprine or other steroid sparing agents⁹. These treatment strategies are successful in the majority of cases.

RCD II has proven to be more difficult to control. No curative treatment is currently available. Long-term immunosuppressive therapy is discouraged due to the risk of progression to EATL. Al Toma *et al* suggest that there may be a histological response to steroids in 76% of RCD II patients, but that this does not have concurrent impact on IEL levels.¹²

Chemotherapeutic agents, such as pentostatin and cladribine, both purine analogues, have been used in RCD II, with mixed results.¹¹ Greetje *et al*,⁸ treated RCD II patients with Cladribine and 50% of patients demonstrated a clinical improvement associated with an average 20% decrease in the number of IELs.

ASCT has shown benefit in controlling resistant autoimmune disease. In a study published in 2011, ASCT was trialled on those with RCD II who were unresponsive to cladribine, and resulted in a very promising 4-year survival rate of 66% with only one participant out of 13 involved in the trial developing EATL after 4 years.⁶

Further study with multi-centre collaboration and longer follow-up will be required to confirm the findings shown by Mulder *et al* regarding the efficacy of ASCT in RCD II. However, early results are encouraging and suggest that ASCT may reduce the risk of EATL developing in this patient population.

Learning points

- ▶ Refractory coeliac disease (RCD II) is a rare disorder and has a high rate of enteropathy-associated T-cell lymphoma development with a resultant high mortality.
- ▶ There have been no large scale studies on the treatment of RCD II. With the high risk of lymphoma development and poor 5-year survival rate, early aggressive intervention with autologous stem cell transplantation may be appropriate, based on single institution data.
- ▶ Owing to the rarity of the disorder, however, further large scale studies are needed, and multicentre cooperation will be essential to achieve meaningful results.

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Competing interests None declared.

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