

# Hemophagocytic Lymphohistiocytic Syndrome and Enteropathy-Associated T-cell Lymphoma in a Patient with Refractory Celiac Disease

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## Abstract

A 70-year-old woman with celiac disease presented with weight loss and diarrhea unresponsive to gluten-free diet (GFD) and prednisone. Diagnosis of type 2 refractory celiac disease (RCD) was made by small intestinal biopsies showing severe villous blunting and intraepithelial lymphocytosis. She was diagnosed with hemophagocytic lymphohistiocytic syndrome (HLH) after developing fever, pancytopenia, hypofibrinogenemia, elevated ferritin, and demonstration of hemophagocytosis on her bone marrow biopsy. An expert pathologist on lymphoma reviewed her biopsies and revised the final diagnosis to type 1 enteropathy-associated T-cell lymphoma (EATL) based on large T-cells infiltrating the lamina propria. We describe the first case of HLH associated with localized EATL and RCD.

## Introduction

Hemophagocytic lymphohistiocytic syndrome (HLH) is a rare, rapidly progressive and potentially fatal syndrome characterized by overactive histiocytes. HLH has been described in advanced enteropathy-associated T-cell lymphoma (EATL), a type of non-Hodgkin's T-cell lymphoma associated with celiac disease. We report the first case of HLH associated with localized EATL in the context of refractory celiac disease (RCD).

## Case Report

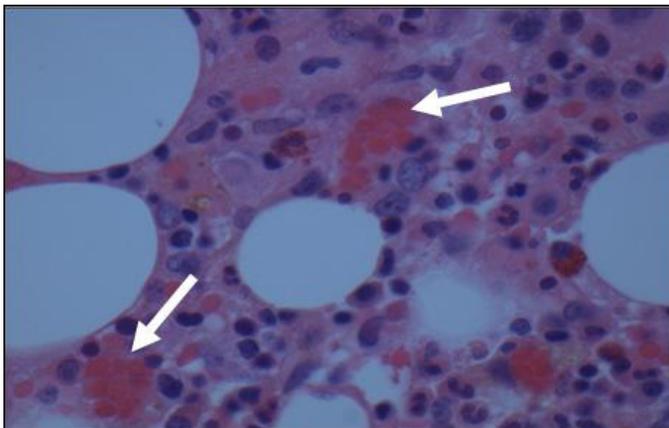
A 70-year-old woman with a 4-year history of celiac disease was referred for RCD unresponsive to strict gluten-free diet (GFD) and 1 month of treatment with prednisone. She initially presented with a 25-lb weight loss over 4 months, non-bloody diarrhea, and abdominal bloating, and had been diagnosed via duodenal biopsies showing villous atrophy. Since then, she had followed a strict GFD.

Prior to referral, she had negative evaluations for metabolic and infectious causes of diarrhea. Her blood work showed increased anti-tissue transglutaminase IgA, antigliadin antibody IgG, and antigliadin IgA, with normal total IgA levels. An abdominal computed tomography (CT) showed inflammation in the small bowel with loss of the normal jejunal mucosa. Five days into her admission, she developed melena; esophagogastroduodenoscopy (EGD), colonoscopy, and push enteroscopy did not identify a source of bleeding. She was diagnosed with type 2 RCD based on duodenal and jejunal biopsies, which demonstrated severe villous blunting, intraepithelial lymphocytosis, and lymphoplasmacytic infiltration. Her diarrhea persisted despite a strict GFD and prednisone. Cyclosporine 60 mg IV was started but discontinued due to drug-related fever. She was treated empirically with piperacillin/tazobactam and transferred to our center.

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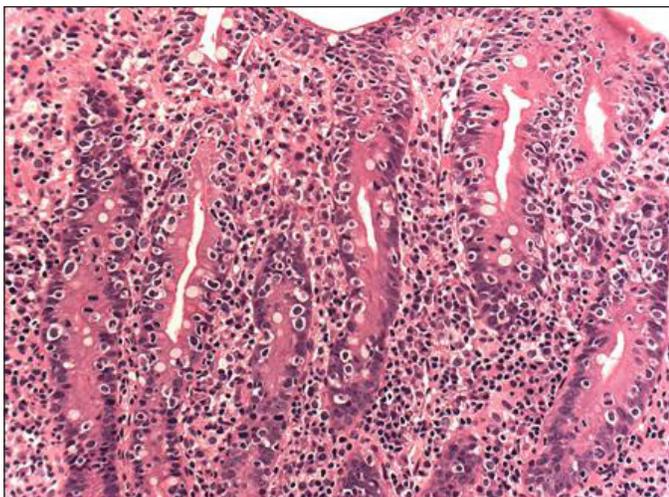
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**Figure 1.** Bone marrow biopsy showing digested red blood cell debris in cytoplasm of macrophages as indicated by the arrows (200x power).

On referral, the patient was cachectic, tachycardic, and hypotensive with evidence of ongoing gastrointestinal bleeding. A repeat abdominal CT showed no small bowel abnormality, hepatosplenomegaly, or lymphadenopathy. HLH was suspected after the patient developed pancytopenia, hypofibrinogenemia, elevated liver enzymes, and hyperferritinemia (19,574 ug/L; normal: 51–400 ug/L) in the context of ongoing fever. Bone marrow biopsy confirmed the diagnosis, revealing prominent hemophagocytosis (Figure 1). An HLH treatment protocol was initiated with dexamethasone 10 mg IV twice daily, cyclosporine 100 mg IV twice daily, anakinra 100 mg subcutaneously daily, 1 dose of etoposide 100 mg IV, and intravenous immunoglobulin (IVIG), along with transfusions of blood products. She was unresponsive to treatment and remained pancytopenic while her ferritin increased to 60,552 ug/L.

Persistent diarrhea and GI bleeding were suspicious for a small bowel EATL. A pathologist experienced in lymphoma reviewed her previous small intestinal biopsies and revised the final diagnosis to include type 1 EATL based on the high proportion of



**Figure 2.** Endoscopic small intestinal biopsy showing prominent infiltration of epithelium and lamina propria by medium-to-large mononuclear cells (20x power).

large T-cells with prominent nucleoli infiltrating the lamina propria and the abnormal T-cell marker profile (Figure 2). Unfortunately, on the day of the diagnosis, the patient passed away from a small intestinal bleeding.

## Discussion

We describe a rare case of EATL-associated with RCD and subsequent development of HLH, of which there are very few reported cases.<sup>1,2</sup> RCD is a diagnosis of exclusion defined by ongoing symptoms and persistent villous atrophy despite a strict GFD for 1 year.<sup>3</sup> RCD is classified into type 1 (normal intraepithelial lymphocyte morphology) and type 2 (abnormal intraepithelial lymphocyte morphology).<sup>3</sup> Type 2 RCD, often diagnosed in elderly women, is more commonly associated with serious complications, with 60–80% of patients developing EATL within 5 years.<sup>3</sup> It carries a 5-year survival rate of 40–58%.<sup>4</sup> HLA-DQ2 haplotype is present in up to 98% of cases.<sup>5</sup>

EATL is a rare form of non-Hodgkin's T-cell lymphoma that is associated with celiac disease in up to 70% of cases.<sup>6</sup> EATL usually develops in the jejunum or ileum, but can arise in any part of the gastrointestinal tract. Two types of EATL exist. Type 1 EATL is strongly linked to celiac disease and RCD<sup>7</sup> and is characterized by large cells or non-monomorphic cytology with negative CD56 and positive CD30 T-cell marker expression. Type 2 EATL has a monomorphic cytology with CD56 expression. The prognosis of EATL is poor. Median progression-free survival ranges between 3 and 6 months, with 5-year progression-free survival of 3.2–18%.<sup>8</sup> Mortality typically results from perforation, bleeding, and malabsorption.

EATL may not be identified on standard imaging. CT enteroclysis may detect tumors as small as 5 mm, with sensitivity and specificity of 95–100%.<sup>9</sup> Positron emission tomography (PET) scans may be more sensitive than CT for detecting EATL, but experience with magnetic resonance imaging (MRI) for diagnosing EATL is limited.<sup>10</sup> Validated magnetic resonance (MR) enteroclysis scores have been developed for identification of type 2 RCD and CD-related small bowel non-Hodgkin's lymphoma (NHL). The presence of less than 10 folds per 5 cm of jejunum, mesenteric fat infiltration, and bowel wall thickening are associated with type 2 RCD.<sup>11,12</sup> The diagnosis of EATL relies primarily on histology. Treatment options for EATL include surgical resection and anthracycline-based chemotherapy with modest survival benefits.<sup>8</sup> Emerging therapies utilizing high-dose induction chemotherapy and autologous stem cell transplantation have demonstrated improved survival.<sup>8,11</sup>

HLH is characterized by the activation, proliferation, and abnormal function of histiocytes.<sup>12</sup> It requires at least 5 of the following 8 criteria: fever, splenomegaly, peripheral cytopenia of 2 lineages, hypertriglyceridemia and/or hypofibrinogenemia, hyperferritinemia, elevated soluble CD25, absent natural killer cell activity, and histological hemophagocytosis in the bone marrow, lymph nodes, or spleen.<sup>13</sup> Primary HLH is an autosomal recessive genetic disorder.<sup>12</sup> Secondary HLH is associ-

ated with disorders that induce immune overactivation, such as viral infections, autoimmune diseases, or malignancies. In acquired HLH, the course is rapidly progressive with multi-organ dysfunction within weeks. Treatment includes addressing the underlying cause and chemotherapy with etoposide, high-dose corticosteroids, and cyclosporine A.<sup>12,14</sup> Early administration of etoposide (<4 weeks from onset) has demonstrated improved survival in Epstein-Barr virus-associated HLH.<sup>14,15</sup> IVIG has helped to decrease HLH inflammatory response.<sup>14</sup> Anakinra has shown limited success as a salvage therapy.<sup>16</sup> Malignancy-associated HLH is rare, and no specific recommendation has been made regarding its treatment. In case reports of EATL-associated HLH, none of the patients received HLH-specific therapy.

There is no published case report of RCD associated with HLH. Only 7 cases have been reported of EATL-associated HLH, of which all patients had metastatic EATL before development of HLH and died within 3 months.<sup>1</sup> Our patient rapidly declined after developing HLH and died shortly after a confirmed diagnosis of HLH.

This is the first case of EATL-associated HLH treated with HLH-specific therapy. Since vinblastine resulted in temporary improvement in a previous case report,<sup>1</sup> perhaps these patients should be treated more aggressively for their underlying EATL as opposed to HLH-directed therapy. Our patient did not receive EATL-specific therapy because the diagnosis of EATL was delayed. Our case demonstrates that HLH can develop with RCD and early-stage EATL. Gastroenterologists should consider screening patients with RCD and EATL for HLH. Prompt referral is crucial for early diagnosis and treatment of EATL and HLH. When suspicion is high and EATL is not apparent on standard imaging, clinicians should remember that EATL requires histological diagnosis by an experienced pathologist.

## Disclosures

Author contributions: L. Lu and S. Ning drafted the manuscript. Z. Kassam, R. Hunt, and M. Puglia reviewed and edited the manuscript. All authors approved the final manuscript. M. Puglia is the article guarantor.

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