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Single Case

Severe Hepatitis Complicating Olmesartan Enteropathy: A Case Report

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Keywords

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Abstract

Introduction: Olmesartan, an angiotensin II receptor antagonist, is associated with an uncommon complication of enteropathy that presents insidiously, usually months to years after initial commencement of anti-hypertensive therapy which can be dose-dependent. It has a variable spectrum of clinical presentation but commonly presents as a moderate to severe malabsorptive process with potential severe complications related to poor end-organ perfusion. Lymphocytic gastritis and microscopic colitis are often noted in patients presenting with olmesartan-induced enteropathy; however, hepatic involvement has been less frequently observed. ***Case Presentation:*** We illustrate a case of a 43-year-old female presenting with 2 weeks of profuse non-bloody diarrhea in the context of olmesartan enteropathy which was complicated by an acute severe ischemic and enteropathic hepatopathy. ***Conclusion:*** Our case prompts clinicians to maintain a high index of suspicion in cases presenting with a seronegative enteropathy and concurrent acute liver injury while on olmesartan therapy. Cessation of olmesartan therapy resulted in prompt resolution of diarrheal symptoms and normalization of the acute transaminitis on subsequent three-week follow-up.

Introduction

Olmesartan-induced enteropathy (OIE) is a rare entity first characterized in 2012 by Rubio-Tapia et al. [1] who described 2 patients that presented with 15 kg weight loss, nausea, vomiting and chronic diarrhea with small intestinal biopsies displaying features of intraepithelial hyperlymphocytosis and villous atrophy suggestive of a sprue-like enteropathy. OIE

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has the potential to involve the entire gastrointestinal tract with concurrent lymphocytic gastritis or microscopic colitis being frequently observed [1, 2]. Hepatic involvement however, has been significantly less common. A small number of studies have documented cases of an isolated acute hepatitis in the context of olmesartan therapy which were subsequently identified as a drug-induced liver injury [3, 4]. To our knowledge, there are only two other case-reports which have observed simultaneous enteropathy and acute hepatitis while on olmesartan [5, 6]. In contrast, our study highlights a case of OIE with concurrent severe mixed ischemic and enteropathic acute liver injury.

Case Report

We illustrate a case of a 43-year-old female presenting with a two-week history of large volume non-bloody diarrhea (up to 13 times per day). Her past medical history includes irritable bowel syndrome (diarrhea phenotype with up to four loose bowel motions a day), asthma and hypertension. Her daily medications were olmesartan-amlodipine which she was taking for 2 years, budesonide-formoterol via metered dose inhaler and cholecalciferol. Loperamide was utilized up to four times a week on an as-needed basis. Following an increase to her daily olmesartan-amlodipine from 20/5 mg to 40/5 mg by her general practitioner 2 weeks prior to presentation, she experienced diarrhea with up to 13 watery bowel motions daily. She had no significant travel history or sick contacts and denied recent consumption of any alternative herbal or wild mushroom preparations.

She was hypotensive on arrival with a blood pressure of 72/46 mm Hg and physical examination revealed a severely dehydrated state which improved with fluid resuscitation. A soft abdomen with no signs of peritonism or right upper quadrant tenderness were noted with no other stigmata of chronic liver disease found. Initial blood tests revealed a severe acute kidney injury with serum creatinine of 249 μmol/L (45–90 μmol/L). Liver function tests (LFT) demonstrated a predominant hepatocellular injury pattern with alanine transaminase (ALT) 1,337 U/L (5–35 U/L), aspartate aminotransferase (AST) 725 U/L (5–30 U/L), alkaline phosphatase (ALP) 343 U/L (30–110 U/L), gamma-glutamyl transferase (GGT) 408 U/L (5–35 U/L) and total bilirubin 87 μmol/L (0–20 μmol/L). LFT preceding her acute presentation demonstrated no significant abnormality. Her full blood examination was normal. Lactate dehydrogenase enzyme level on day 5 was elevated 285 U/L (120–250 U/L). Fecal pathogen polymerase chain reaction was negative. Serological testing for common infective etiologies such as Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus and hepatitis A, B and C were negative. Completion of the liver screen included testing for hereditary, autoimmune and vasculitic hepatopathies which were otherwise unremarkable. Anti-smooth muscle antibodies and serum γ-globulin levels were also normal including immunoglobulin G of 15.6 g/L (7.5–15.6 g/L). Paracetamol and alcohol levels were within normal range and a review of her regular medications did not reveal other significant hepatotoxic agents. A fecal calprotectin of 97.6 μg/g (0–50 μg/g) along with an absence of family and personal history of inflammatory bowel disease suggested this was not the likely cause. Pancreatic exocrine insufficiency was excluded following a normal pancreatic elastase result 379.9 μg/g (>200 μg/g). Computed tomography of the abdomen and pelvis with contrast on admission showed mild hepatic steatosis without other features of enteritis or colitis. Ultrasound evaluation demonstrated very minor steatosis without any other features of chronic liver disease. Testing for a neuroendocrine tumor with 5-hydroxyindoleacetic acid and chromogranin A levels were unremarkable.

She was commenced on loperamide and cholestyramine with minimal improvement in her diarrheal symptoms. Gastroduodenoscopy and colonoscopy were macroscopically

normal. Duodenal biopsies however, demonstrated duodenitis with intraepithelial lymphocytosis with marked villous atrophy (Fig. 1). Biopsies of the terminal ileum demonstrated mild ileal villous distortion with scattered intraepithelial lymphocytes (Fig. 2). Random colonic biopsies were otherwise unremarkable. Despite early restoration to a clinically euvolemic state and cessation of olmesartan-amlodipine on presentation (in the context of her volume-depletion and hypotension), her ALT levels continued to be considerably elevated 10 days into the admission at 441 U/L (5–35 U/L) which suggested a secondary pathological process. Coeliac serology returned negative and genetic testing utilizing a sequence-specific oligonucleotides method conferred the following genotype: Human Leukocyte Antigen (HLA) – DQB1*02- (DQ2), DQA1*05- and DQB1*03:02+ (DQ8). Her LFT on discharge (day 15) had improved with an ALT 290 U/L, GGT 364 U/L, ALP 255 U/L and total bilirubin 22 μmol/L with repeat testing 3 weeks later revealing only a mild elevation in ALP 123 U/L and GGT 78 U/L. Early gastroenterology outpatient clinic follow-up was arranged 1 month post-discharge where she reported a significant improvement in bowel habits with one to two formed motions daily. She had also noted an 8 kg weight gain during this time which suggested an improvement in the malabsorptive state associated with OIE. She was counseled on the risks associated with olmesartan use and recommended alternative anti-hypertensive therapy.

Discussion

Since the first documented cases of OIE in 2012, it has become an increasingly recognized disease entity generally presenting months to years following initiation of olmesartan therapy [2, 5]. OIE most commonly presents as a constellation of unintentional weight loss, persistent diarrhea, nausea and vomiting with rare cases of further complications such as ischemic colitis or bowel perforation [7, 8]. Despite the predominant presentation of OIE as a moderate to severe malabsorptive process, other areas in the gastrointestinal tract are frequently affected whereby lymphocytic gastritis and microscopic colitis have been observed, of which the clinical significance is to be determined [1, 2]. A review of the current literature reveals only a limited number of cases presenting with concurrent hepatic involvement and thus highlights an ongoing gap in the literature [5, 6].

The exact mechanism in which olmesartan induces a sprue-like enteropathy has not been clearly established, although there are several common theories regarding its immunopathogenesis. Immunohistochemistry analysis performed on biopsies of 26 patients with OIE found an increase in CD8+ cytotoxic T-cell infiltration and presence of granzyme B+ cells in duodenal mucosa, suggesting cytotoxic T-cell mediated damage [9]. Additionally, an overexpression of interleukin 15 receptor (IL-15R) which is also seen in refractory coeliac disease, was noted and could further potentiate cytotoxic T-cell mediated damage by disrupting regulatory T-cell function [9]. Involvement of the transforming growth factor-beta (TGF-β) pathway has been theorized where a disruption to normal regulatory T-cell function occurs via the inhibitory effect of olmesartan on angiotensin II receptor type 1 [1, 5]. Studies have found that up to 72% of patients with OIE were positive for HLA-DQ2 or DQ8 [1, 7]. It has been proposed that HLA-DQ2 and DQ8 may contribute to the disease process in OIE via inappropriate activation or upregulation of CD4+ T cells; however, an increase in CD4+ cells in villous crypts were not seen on biopsy in OIE [9]. Although our patient's genotype indicates a predisposition for coeliac disease, the absence of positive coeliac serology confers a high negative predictive value and thus, it was imperative to exclude other alternative causes of enteropathy [10]. Given the initial severe liver function derangement, we performed an autoimmune screen which was largely negative. We identified a non-specific positivity for

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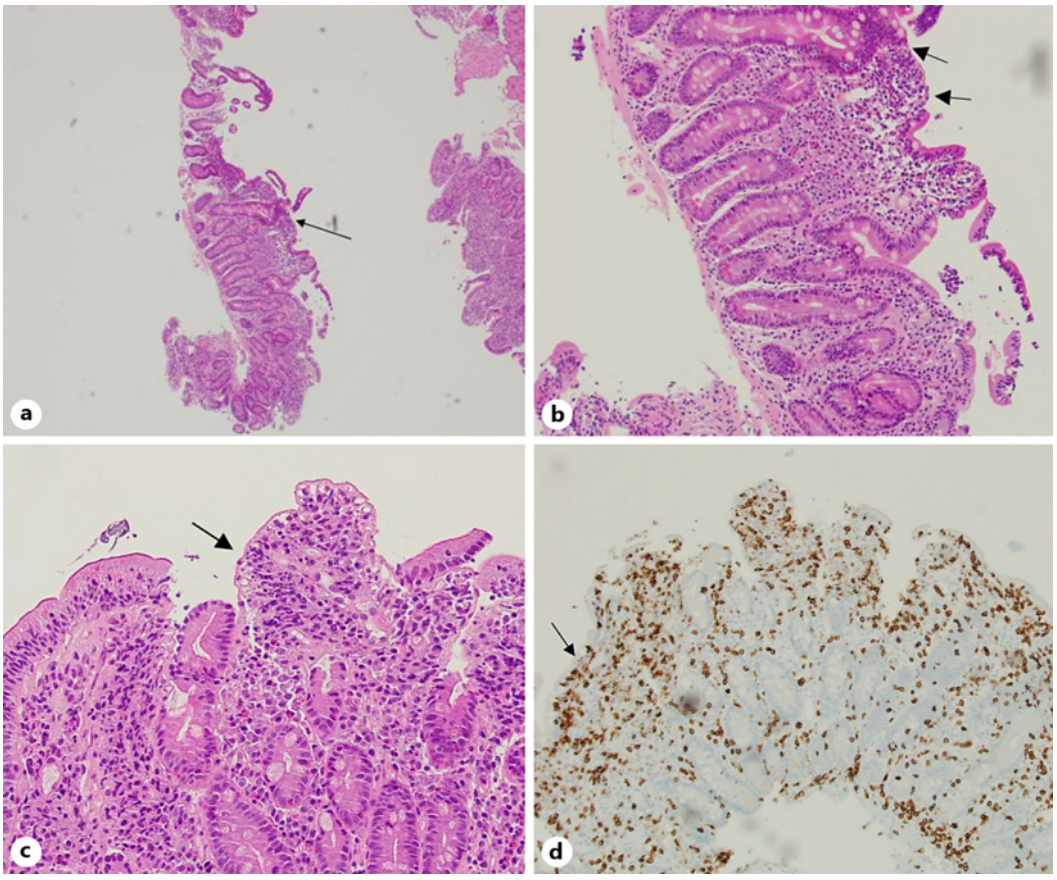

Fig. 1. Histopathology of biopsy. **a** Duodenal biopsy with marked villous blunting (arrow). **b**, **c** Duodenal surface epithelium shows increased intraepithelial lymphocytosis (arrows). **d** The CD3 highlights the presence of lymphocytes within the surface epithelium (arrow).

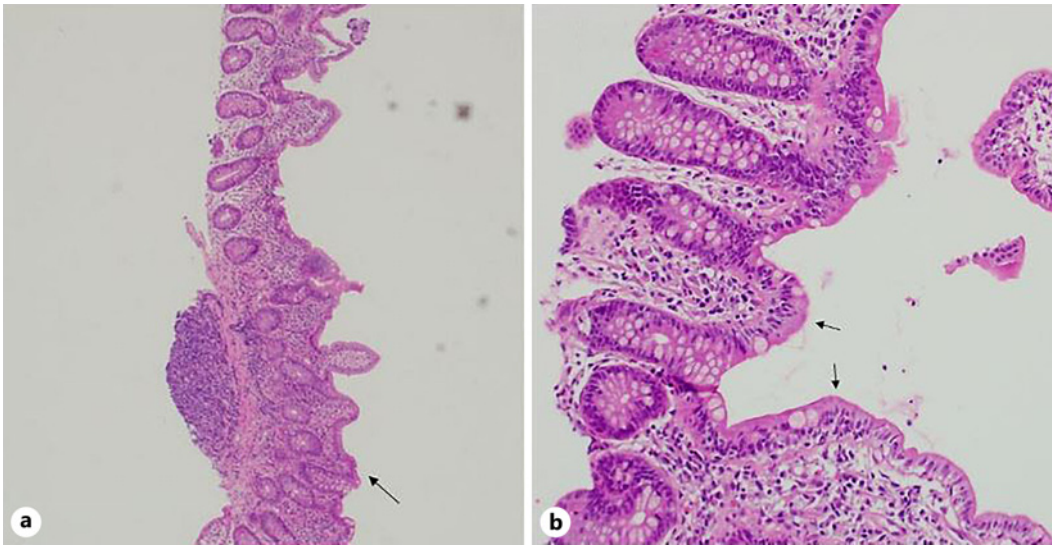

Fig. 2. Histopathology of biopsy. **a** Terminal ileum biopsy shows mild villous architectural distortion with blunting (arrow). **b** Terminal ileum biopsy shows scattered intraepithelial lymphocytes (arrow).

anti-nuclear antibody 1:1,280 (<1:160) in a homogenous pattern in the absence of other serological markers of autoimmune hepatitis, which is a noted occurrence in OIE [11, 12]. The liver screen was otherwise unremarkable for other infective or hereditary hepatopathies. The predominant hepatocellular injury pattern on LFT and the significant volume-depleted state on presentation were initially suggestive of an ischemic hepatitis secondary to hepatic hypoperfusion. Contrary to this, we observed only a very slow improvement with intravenous hydration without normalization of the transaminitis on follow-up 36 days later. This is uncharacteristic of an isolated ischemic hepatitis as complete normalization of the transaminitis is typically expected within 10–14 days, suggesting an additional element of liver injury [13, 14]. Transaminitis is common in untreated coeliac disease where it is suggested that increased intestinal permeability secondary to a chronic inflammatory state mediates the passage of hepatotoxic metabolites or substances into the portal circulation, resulting in transient liver injury [15]. This raises the possibility that a similar mechanism of liver injury occurs in OIE, but given the disease process is still poorly understood, further studies are warranted. A potential dose-related response has been suggested where OIE was not observed until it increased to 40 mg daily [5]. This relationship was reflected in our case where olmesartan therapy at a dose of 20 mg daily had been established for 2 years prior to the increase to 40 mg daily which coincided with the onset of clinical symptoms. Our case highlights an acute severe liver injury occurring secondary to an initial ischemic hepatitis with a superimposed enteropathic hepatopathy. As with OIE, cessation of olmesartan resulted in a gradual improvement in liver function during the admission with subsequent normalization of the transaminitis 3 weeks post-discharge. Following the exclusion of other autoimmune and infective causes of liver injury, a detailed review of the medication history is warranted to identify other potential agents which may contribute to a drug-induced liver injury in the evaluation of cases of acute hepatitis. Our case raises further awareness of a potential dose-response relationship in OIE and reinforces the importance of casting a wide differential in the assessment of a seronegative enteropathy with concurrent acute hepatitis. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538552).

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Author Contributions

R.T. and J.H.A. were responsible for the draft of the manuscript. R.T., J.H.A., H.D., C.C.K., T.W., and S.T. were responsible for critical revision for important intellectual content and editing of the manuscript and have given final approval of the article for publication. All authors have contributed to the manuscript in terms of concept, writing, and editing; were responsible for critical revision for important intellectual content and editing of the manuscript; and have read and given final approval of the article for publication.

Data Availability Statement

The participant of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research, supporting data is not available. All relevant data has been included in this article and further inquiries can be directed to the corresponding author.

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