Case Report

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Exploring the Multifactorial Aetiology of Gastric Emphysema in a complex case of Olmesartan-induced Enteropathy.

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ABSTRACT

A gentleman in his 70s presents with a subacute history of bloating, diarrhoea, nausea and vomiting, dysphagia, and anorexia over the course of several months. This led to significant weight loss, malnutrition, and deconditioning requiring a prolonged hospital admission. Differentials included malignant, infectious, and autoimmune aetiologies. A gastroscopy revealed active chronic gastritis with no evidence of Helicobacter pylori and duodenal biopsy showed mild villi blunting and no increased epithelial lymphocytes with mixed inflammatory infiltrate within the lamina propria. Coeliac serology was negative. Olmesartan-induced enteropathy was eventually suspected, and prompt improvement in symptoms ensued following cessation of the medication. On investigation of his symptoms, a CT scan showed gastric pneumatosis and air in the hepatic portal venous system (HPVS), consistent with previous reported cases of gastric emphysema (GE). This is a rare radiological diagnosis with uncertain mechanisms, likely multifaceted, which requires further explanation in the context of this complex case.

INTRODUCTION

Gastric emphysema (GE) is rare condition and various cases in the literature propose different aetiologies for this radiological diagnosis. This case represents a new iteration for this 'benign' condition, presenting in an unwell patient with a complex and protracted illness likely due to Olmesartan-induced enteropathy. Given its non-specific but alarming imaging, there was a clinical dilemma to distinguish GE from emphysematous gastritis, a potentially life-threatening condition (with chronic intestinal ischaemia being a possible contributing factor). This dilemma, as well as its recognition, diagnostic workup and management encompassed the challenges associated with this rare finding. To address this, we explored the potential mechanisms involved in this case as well as reported in others.

CASE PRESENTATION

A gentleman in his 70s developed unexplained bloating, nausea and weight loss and was first investigated with an outpatient CT scan of the chest, abdomen and pelvis, transabdominal ultrasonography and gastroscopy in early July, which were initially unremarkable. He also had a private gastroscopy in July which showed evidence of gastritis and duodenitis. The onset of these symptoms coincided with commencement of Olmesartan following a myocardial ischaemic (MI) event 5 months prior. Over a period of months, he progressively deteriorated and presented to hospital with severe diarrhoea (negative stool samples), anorexia and rapid weight loss. A repeat upper endoscopy in late July found oesophageal candidiasis and diffuse, mildly erythematous gastric mucosa. Biopsy showed changes consistent with acute on chronic gastritis with some loss of villi and blunting in the duodenum with negative coeliac serology as highlighted on **Figure 1 and 2**. There were no evidence of Helicobacter pylori or lymphocytic gastritis. An inpatient flexible sigmoidoscopy did not reveal any malignancy or endoscopic and histological evidence of colitis. He was commenced on fluconazole and nystatin for the fungal infection and a proton pump inhibitor. Repeat imaging with a CT abdomen was essentially normal apart from noting severe atherosclerosis of the coeliac trunk. The patient was discharged.

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He re-presented to hospital two months later in September, severely malnourished and deconditioned with a dramatic weight loss of 17kg, following persistent ongoing severe nausea and dysphagia resulting in loss of appetite. The ongoing diarrhoea was associated with hypotension and electrolyte disturbances. Despite this, he did not present with an acute abdomen or with symptoms of sepsis.

The patient's other medical history includes gastro-oesophageal reflux disease (GORD) with a small hiatus hernia, osteoarthritis, hypertension, dyslipidaemia, multiple renal calculi, chronic back pain, and atrial fibrillation. His medications included olmesartan 40mg daily, atorvastatin 40mg nocte, venlafaxine 75mg nocte, metoprolol 50mg twice a day (BD), rivaroxaban 20mg daily, pantoprazole 40mg daily and Burprenorphine patch. He is an ex-smoker and does not drink alcohol. His left ventricular ejection fraction was approximately 50% at the time of the acute ischemic event.

Figure 1

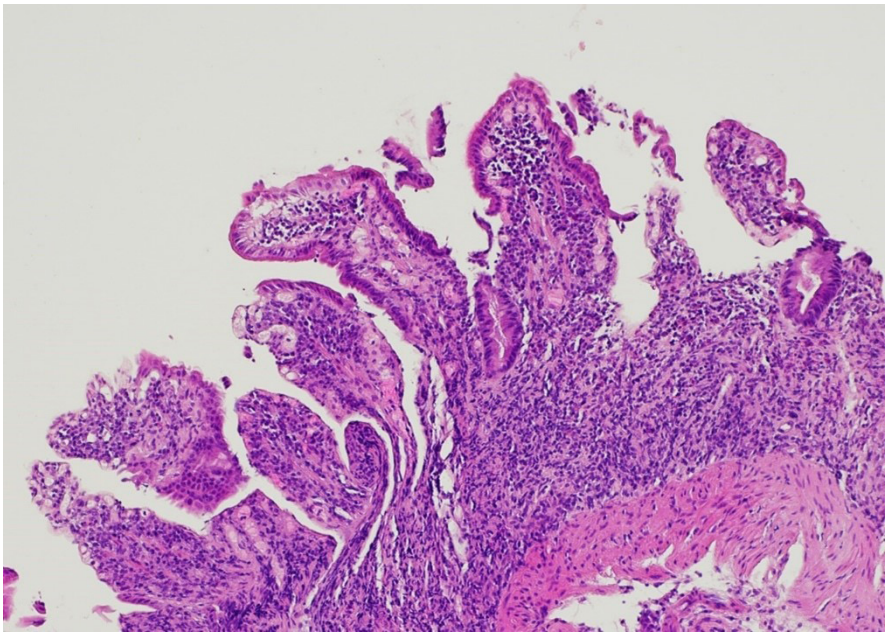

Figure 1: Biopsy of duodenum (x100) showing partial loss of surface epithelium, mild villous blunting and lamina propria is expanded by a mixed inflammatory infiltrate.

Figure 2

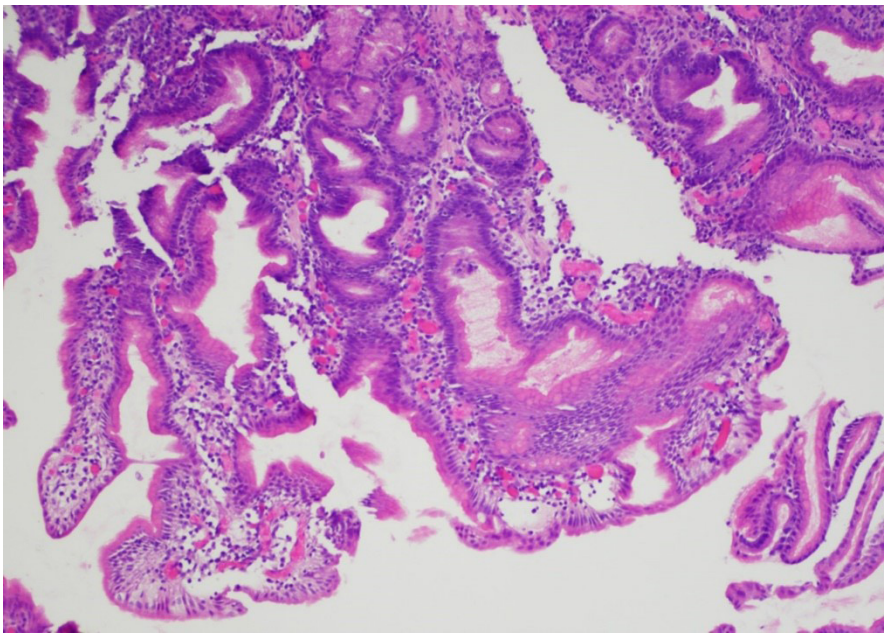

Figure 2: Biopsy of stomach body (x100) showing evidence of antral type gastric mucosa with foveolar hyperplasia and lamina propria being expanded by moderate active chronic inflammatory infiltrate.

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Investigations

Given the nonspecific symptomatology, a broad serological screen to exclude infectious, inflammatory, endocrinological and neoplastic causes were performed, of which was significant for a mildly elevated chromogranin A level. This was thought to be in the setting of proton pump inhibitor use. Faecal calprotectin level was elevated to 3600ug/g while faecal elastase level was low.

Multiple blood, urine and faecal cultures, clostridium difficile screen and viral PCR were negative. An urgent inpatient gastroscopy and flexi-sigmoidoscopy were performed during the first hospital admission with the aforementioned results.

In the second admission two months later, a gastric emptying study was performed and confirmed gastroparesis. Two weeks into his second admission, he developed coryzal symptoms and was tested positive for parainfluenza 3. However, his main gastrointestinal symptoms preceded this acute viral infection. A repeat CT chest, abdomen, and pelvis scan, which was performed for progressive weight loss and ongoing symptoms, showed new gastric pneumatosis involving the fundus and body with associated gas within the hepatic portal venous system (HPVS).

Aortic and coeliac arteries displayed findings of peripheral vascular disease which prompted concern for gastric ischemia (see Figure 3 and 4). His serum lactate was 1.3 with liver enzymes and inflammatory markers essentially normal. An urgent repeat gastroscopy revealed congested gastric and duodenal mucosa, however, no biopsies were performed due to recent anticoagulation use. He later had an outpatient colonoscopy which revealed multiple tubular adenomas but no evidence of malignancy or microscopic colitis.

Figure 3

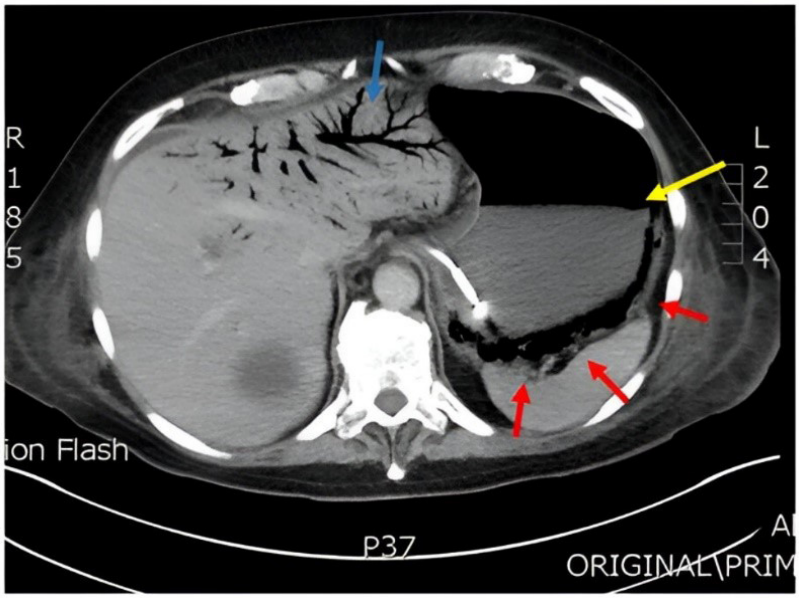

Figure 3: Axial section CT abdomen showing gastric pneumatosis (red arrows) and air in the intrahepatic portal venous system (blue arrow). Note the air fluid level in the lumen of the stomach (yellow arrow).

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Figure 4

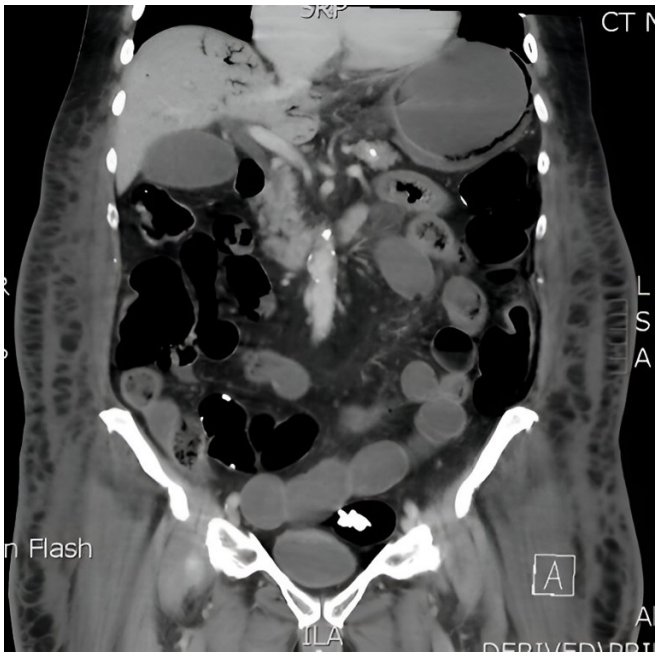

Figure 4: Coronal section of same CT scan.

Differential diagnoses

The patient's nonspecific symptomatology was a diagnostic dilemma with main differentials including neuroendocrine tumour, pancreatic insufficiency, coeliac disease, adrenal insufficiency. The duration of symptoms and progressive decline made infectious aetiologies less likely. Given the elevated chromogranin A level, a positron emission tomography (PET) whole body scan was organised to exclude neuroendocrine tumour, however it was not eventuated as patient's symptoms improved following cessation of Olmesartan. This was likely the result of his PPI therapy.

Coeliac disease was a strong consideration given the histological findings although he has negative coeliac serology and normal IgA levels. A provisional diagnosis of Olmesartan-induced enteropathy was suggestive given timeline of symptoms, histological findings and negative anti-tTG. Symptomatic improvement following cessation of olmesartan without any gluten restriction added weight to a plausible causal relationship between Olmesartan and the patient's presentation.

With regards to the radiological findings, the differential diagnosis included emphysematous gastritis, gastric emphysema with contributions from mesenteric ischaemia in view of his underlying peripheral vascular disease. Clinically, he did not exhibit signs of peritonism and had a normal lactate. He was also not septic and remained afebrile with multiple negative culture results. He was diagnosed with benign gastric emphysema (GE) and managed conservatively.

Treatment

His Olmesartan was ceased in the second week of his second hospital admission. Following the discovery of gastric emphysema a few days after cessation of Olmesartan, the patient's nasogastric tube was removed, and nasogastric feeding ceased. He was placed on a free fluid diet and upgraded slowly as tolerated. He was commenced on regular domperidone for gastroparesis. He was for clinical observation and conservative management and undertook inpatient rehabilitation for regain his functional and nutritional status from 15th October to 2nd November 2018.

Outcome

Ten days following cessation of Olmesartan, the patient's symptoms had significant improvement and he was able to slowly upgrade his diet. He required ongoing rehabilitation for deconditioning related to this protracted presentation of Olmesartan-induced enteropathy. A repeat CT scan showed complete resolution of GE.

DISCUSSION

Gastric emphysema (GE) is a benign radiological diagnosis and, in this case, could be multifactorial in aetiology due to

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gastroparesis, oesophageal candidiasis and Olmesartan enteropathy (1, 2). The patient's symptoms are consistent with Olmesartan-induced enteropathy which may present after 6 to 12 months as reported in a small case series (3). In our patient's case, his symptoms resolved in the span of a few months following cessation of Olmesartan, with almost immediate improvements at the time of stopping. This patient, therefore, was diagnosed with two rare clinical entities of which the link between them is unknown. We will focus on the differentials and pathogenesis former.

The radiological findings of gastric pneumatosis can be alarming, with emphysematous gastritis as the key differential for immediate exclusion (2, 4). In the context of our patient, he did not report abdominal pain at rest and had no clinical signs of peritonism. Several case reports propose varying aetiologies of GE and so is unclear regarding the exact mechanism. The aetiology in this case is likely multifactorial. Given its rarity and possibly incidental finding, it is difficult to verify anyone, however, we postulate the link between Olmesartan-induced enteropathy and gastric. By exploring the literature and the 2015 case review by Matsushima et al (2), we have proposed the broad mechanisms involved. This is illustrated in **Figure 5**.

Figure 5

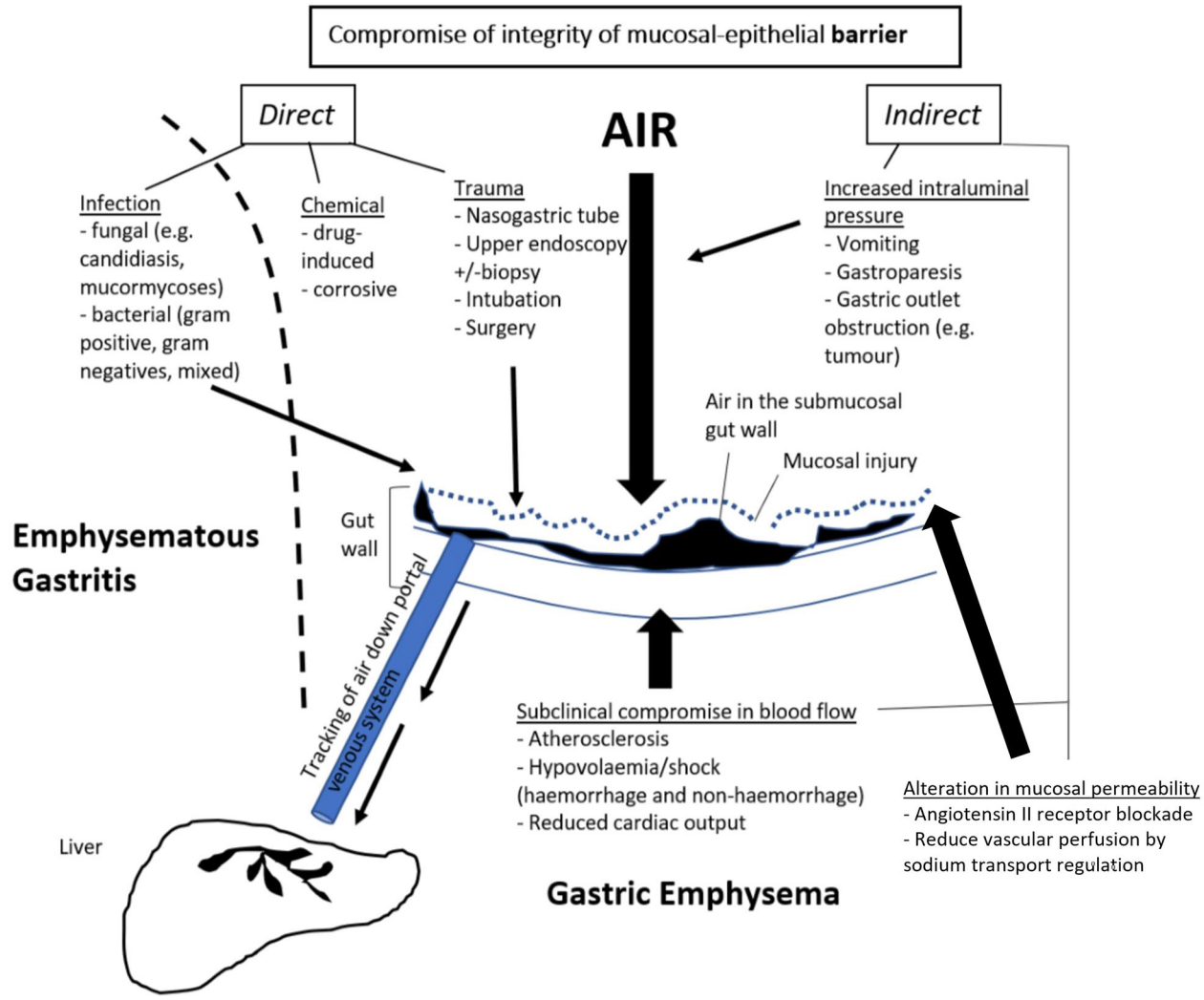

Figure 5 : Proposed mechanism of gastric emphysema (GE).

For air penetration into stomach wall to be radiographically evident, there must be a compromise in the integrity of the epithelial-mucosal-submucosal barrier of the stomach wall with possible air trapping. Air in the hepatic portal venous system suggests this emphysematous mechanism may extend to the submucosa where there is a rich network of portal vessels through diffusion and alteration of perfusion, to cause this significant tracking. The proposed aetiologies can be seen as 'insults' to the integrity of the mucosal barrier and can be classified as indirect and direct mechanisms.

Indirect mechanisms are factors which increase the intraluminal pressure in the stomach. As it is the development of intramural air is often preceded by gastric distension, mainly from gastric outlet obstruction (2, 5). Vomiting is also commonly reported

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(2, 4, 6). This acute change in pressure may force a large volume of air into a stomach lining where there is little time for dissolution, resulting in its 'trapping'. Indeed, our patient had demonstrated significant gastroparesis which may have led to an increase intraluminal pressure. Only one other case was associated with gastroparesis (7). The aetiology of gastroparesis is this instance is unknown. To the best of our knowledge, there has been no known association between Olmesartan-induced enteropathy and gastroparesis. He is a non-diabetic, and in terms of precipitating medications, he is on regular venlafaxine albeit for years.

Direct mechanisms include traumatic procedures which mechanically damage the mucosal lining. Cases reports list a number of these including upper endoscopy, nasogastric tube insertion, intubation, biliary stent perforation and post-surgery (2). In our case, the patient had nasogastric tube insertion for feeding purposes which might have resulted in direct mucosal damage. In addition, he also underwent two prior endoscopies within three months before the diagnosis on CT scan, although these happened quite some time prior and imaging between endoscopy and nasogastric tube insertion did not identify air.

Another direct cause of mucosal compromise is infection which in this context was oesophageal candidiasis. However, he did receive a course of treatment many weeks prior to the imaging findings. Patients presenting with sepsis are more likely to have emphysematous gastritis which has a mortality of 60% (1). Patients require intravenous antibiotics and bowel rest. In rare cases, this perforation, strictures, or uncontrolled sepsis occurs which may require total gastrectomy (5).

A direct chemical insult may also precipitate GE, from drug-induced gastritis to ingestion of corrosive material (8, 9). We propose that there might be a direct mucosal injury due to inflammatory changes secondary to Olmesartan-induced enteropathy. His gastroscopy revealed biopsy evidence of chronic duodenitis and gastritis (see Figure 1 and 2). This could compromise the integrity of the stomach wall. While the pathogenesis between Olmesartan-induced enteropathy is unclear, a small case series found that, histologically, the majority of Olmesartan-induced enteropathy demonstrated acute and chronic gastritis, like in our case (10). They proposed a delayed immune hypersensitivity reaction involving the inhibition of the transforming growth factor beta (TGF-β) signalling cascade by blocking the angiotensin I (ATI) receptor, which is the effect of Olmesartan. TGF-β is known to play an important role in the pathophysiology of inflammatory bowel disease through insufficient immune tolerance (11, 12)

In addition, alterations in mucosal/vasculature permeability that could be explained by Olmesartan enteropathy may have contributed. Angiotensin II receptors are expressed and functional in human esophageal and gastric mucosa (13,14). Within the gastric mucosa, expression is localised to surface epithelium, and glandular structures, mesenchymal cells and notably vessels in the lamina propria. Therefore, expression may influence blood perfusion by regulating sodium transport with therefore a plausible mechanism for air to efficiently translocate into the vasculature.

Another possible component to GE as well as EG is an underlying subclinical chronic mesenteric ischemia (1, 5). As it is, hypoperfusion of the gastric wall may predispose the stomach wall to injury and invasion of gas forming organisms. Our patient's CT scan had shown severe stenosis of celiac trunk from atherosclerotic disease, a finding similar to another case (1). Additionally, our patient had a myocardial ischaemic event with new onset atrial fibrillation six months prior, following which his bloating began. This may have led to chronic changes in the gut wall.

We postulate that the pathophysiological mechanism linking Olmesartan-induced enteropathy to gastric emphysema is multifaceted. The breach in the integrity of gastric epithelial-mucosal-submucosal barrier from chronic gastritis with increased permeability from perfusional changes likely function as predisposing factors. Increased intraluminal pressure resulting from vomiting and gastroparesis contribute to the pathogenesis of gastric emphysema.

In summary, this case illustrates the complex multifactorial aetiology of GE in this patient. We acknowledge that there are other factors not relating to olmesartan-induced enteropathy that could have contributed to the formation of gastric emphysema. This included oesophageal candidiasis, recent nasogastric tube insertion and potential subclinical chronic mesenteric ischemia. However, olmesartan induced enteropathy likely played a key role in this radiological diagnosis by resulting in mucosal inflammation, compromised the integrity of gastric epithelial-mucosal-submucosal barrier and altering the vascular permeability.

We have summarised postulated mechanisms based on reported case studies in the literature and our own limited experience. Identifying and addressing these mechanisms can be difficult and may remain unresolved. Nevertheless, efforts to address known causes cannot be understated to improving the quality of life and recovery of the patient.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Conflict of Interest

There are no conflicts of interest for all authors.

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The study did not receive any funding.

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