Acute esophageal necrosis as a complication of diabetic ketoacidosis: A case report

Kasey Moss, Tahrin Mahmood, Robert Spaziani

ORCID number: Kasey Moss 0000-0002-5468-1476; Tahrin Mahmood 0000-0001-9013-8166; Robert Spaziani 0000-0002-0764-770X.

Author contributions: Moss K was the primary author who wrote and revised the paper; Mahmood T contributed to the writing and revising process heavily; Spaziani R provided his expertise and assistance in editing the paper and was the primary physician involved in the patient encounter; all authors have read and approve the final manuscript.

Informed consent statement: The patient whom the case report was written about provided verbal consent to have their case written and submitted for publication prior to the commencement of the case report being written.

Conflict-of-interest statement: None of the authors has any conflicts of interest.

CARE Checklist (2016) statement: The authors have submitted and followed the guidelines within the CARE checklist (2016) statement.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative

Abstract

BACKGROUND

Acute esophageal necrosis (AEN) is a rare condition that has been associated with low volume states, microvascular disease, gastrointestinal (GI) mucosal damage, and impaired GI motility. It has been linked in case reports with diabetic ketoacidosis (DKA) and is commonly associated with GI bleeding (GIB).

CASE SUMMARY

We report a case of endoscopy confirmed AEN as a complication of DKA in a 63-year-old Caucasian male without any overt GIB and a chief complaint of epigastric pain. Interestingly, there was no apparent trigger for DKA other than a newly started ketogenic diet two days prior to symptom onset. A possible potentiating factor for AEN beyond DKA is the recent start of a Glucagon-like peptide-1 receptor agonist (GLP-1 RA), though they have not been previously connected to DKA or AEN. The patient was subsequently treated with high dose proton pump inhibitors, GLP-1 RA was discontinued, and an insulin regimen was instituted. The patient’s symptoms improved over the course of several weeks following discharge and repeat endoscopy showed well healing esophageal mucosa.

CONCLUSION

This report highlights AEN in the absence of overt GIB, emphasizing the importance of early consideration of EGD.

Key Words: Acute esophageal necrosis; Gurvits syndrome; Acute necrotizing esophagitis; Black Esophagus; Diabetic Ketoacidosis; Glucagon-like peptide-1 receptor agonists

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.
Core Tip: Acute esophageal necrosis (AEN) is a rare condition with a mortality rate greater than 30%. It has been linked to low volume states including diabetic ketoacidosis in case reports but is usually associated with overt gastrointestinal bleeding (GIB). This report provides an important description of a patient presenting with AEN and no overt GIB. Interestingly, the apparent trigger for ketoacidosis appears to be a ketogenic diet. The case explores Glucagon-like peptide-1 receptor agonists as a possible AEN precipitant, which is not a finding previously described in the existing literature.

INTRODUCTION

Acute esophageal necrosis (AEN), also known as Black Esophagus or Gurvits Syndrome, is a rare entity distinguished by circumferential necrosis of the distal esophageal tissue that does not progress beyond the gastroesophageal junction (GEJ) [1]. The purported mechanisms of injury leading to AEN include ischemic injury, malnutrition, and acute gastric outlet obstruction or slowed peristalsis leading to increased gastric contents[2]. AEN has been linked with disease states that result in hemodynamic compromise, hypoperfusion, low volume states, and corrosive injuries [1]. One such possible disease state is diabetic ketoacidosis (DKA), a condition associated with hypoperfusion and transient hyperglycemic induced gastric dysmotility[3,4]. The treatment is high dose PPI, correction of causative condition, and monitoring for complications that may include esophageal strictures, perforations and abscess formation[2]. AEN is typically associated with gastrointestinal bleeding (GIB) [2], and only one of the previous 13 reported cases, see Table 1 [5-15] of AEN in DKA did not present with overt GIB. We report a case of AEN as a complication of DKA in a patient without any overt GIB.

CASE PRESENTATION

Chief complaints

A 63-year-old retired Caucasian male presented to Emergency with severe epigastric pain and dysphagia and odynophagia to both solids and liquids leading to several days of anorexia. He also complained of nausea and non-bloody, non-bilious emesis. There was no evidence of overt GIB.

History of present illness

The patient noted that due to his hypertension and type 2 diabetes mellitus (T2DM) he was attempting to lose weight. To do this, his primary care provider switched him from his previous liraglutide which he had received for one year, to a trial of semaglutide one week prior to symptom onset. Additionally, he began a ketogenic diet to help with his weight loss goals and 2 d later, when performing manual labour, he became acutely unwell. He did not have a history of reflux disease or dysphagia prior to this episode and attempted to alleviate the discomfort with bed rest and ceasing oral intake. When the pain and nausea peaked 5 d following symptom onset, see Figure 1 for timeline, he presented to the hospital.

History of past illness

The patient had a several-year history of hypertension, dyslipidemia and T2DM with no known microvascular complications. His glycemic control had been poor with a most recent HbA1c of 8.4%. His medications included metformin 500 mg twice daily, ramipril 5 mg daily, ezetimibe 10 mg daily, duloxetine 60 mg daily, pravastatin 40 mg daily, and semaglutide 0.5 mg weekly.
Table 1 A summary of the presenting symptoms and demographics of both our case and the 13 other patient presentations of diabetic ketoacidosis complicated by acute esophageal necrosis

| Ref.                  | Presenting symptoms                                                                 | GI bleeding | Age  | Gender | Diabetes type 1 or 2 |
|-----------------------|--------------------------------------------------------------------------------------|-------------|------|--------|----------------------|
| Our case              | Nausea, emesis, epigastric pain, dysphagia, odynophagia, anorexia                    | None        | 63   | Male   | 2                    |
| Rigolon et al[5]      | Nausea, emesis, epigastric pain, polyuria, polydipsia, fever                         | None        | 50   | Male   | 2                    |
| Talebi-Bakhshayesh et al[6] | Altered mental status, abdominal pain, nausea, emesis, fatigue                    | Yes         | 34   | Male   | Unknown              |
| Mccarthy et al[7]     | Death                                                                                | Unknown     | 67   | Female | 2                    |
| Uhlenhopp et al[8]    | Encephalopathy, hypoxic respiratory failure                                         | Yes         | 56   | Male   | 2                    |
| Ghoneim et al[9]      | Nausea, emesis, aphasia, gait difficulty                                             | Yes         | 67   | Female | Unknown              |
| Ghoneim et al[9]      | Nausea, emesis, right upper quadrant and epigastric abdominal pain                   | Yes         | 78   | Female | 2                    |
| Ghoneim et al[9]      | Melena, malaise, chills, cough, anorexia                                             | Yes         | 35   | Male   | 1                    |
| Choksi et al[10]      | Altered mental status                                                               | Yes         | 65   | Male   | Unknown              |
| Vien and Yeung[11]    | Lethargy, nausea, emesis, anorexia, odynophagia, cough                               | Yes         | 37   | Female | 2                    |
| Field et al[12]       | Nausea, emesis, epigastric pain, anorexia                                            | Yes         | 37   | Female | 1                    |
| Shah et al[13]        | Melena, sepsis, fever, anorexia, syncope                                             | Yes         | 34   | Male   | Unknown              |
| Haghbeyan et al[14]   | Emesis, anorexia                                                                      | Yes         | 55   | Female | Unknown              |
| Buckshaw et al[15]    | Nausea, emesis, epigastric pain                                                      | Yes         | 50   | Male   | 1                    |

Figure 1 Timeline of illness from symptom onset to resolution of esophageal damage in 63 year old Caucasian man with diabetic ketoacidosis and acute esophageal necrosis.

**Personal and family history**
The patient did not have any pertinent personal or family history. He did not have a significant alcohol intake, nor did he smoke or use recreational drugs.

**Physical examination**
The patient was 94 kg, 1.778 m tall, with a body mass index of 31.14 kg/m². Vital signs on presentation were notable for tachycardia (125 beats per minute), tachypnea (respiratory rate of 40) and blood pressure of 136/81. On physical exam he was noted to be in distress with Kussmaul respirations, lying in lateral decubitus position with voluntary abdominal guarding and frequent painful belching.

**Laboratory examinations**
Admission blood work revealed hemoglobin of 165 g/L, leukocytes of 17.9 × 10⁹/L and an anion gap of 25 with bicarbonate of 5 mmol/L. Venous blood gas showed acidemia (pH = 7.02) and a B-hydroxybutyrate level of 10.2 mmol/L (normal < 0.25 mmol/L). His glucose was initially 17 mmol/L and peaked at 82 mmol/L. Urinalysis was negative for leukocytes or nitrites.

**Imaging examinations**
An abdominal CT ruled out bowel obstruction or intra-abdominal infection/abscess as the source of his discomfort but demonstrated circumferential wall thickening of the distal esophagus.
FINAL DIAGNOSIS

Following investigations, he was admitted to the hospital for first presentation DKA. No triggers were identified except perhaps his recently started ketogenic diet and dehydration. To rule out latent autoimmune diabetes in adults, C-peptides were ordered and were within normal limits, 1087pmol/L (normal 370-1470pmol/L). After the resolution of DKA, he continued to experience out of proportion epigastric pain, reflux symptoms, and dysphagia. To investigate, an esophagogastroduodenoscopy (EGD) was performed. This showed severe class D esophagitis involving the entire esophagus. There were circumferential black, necrotic inflammatory changes in the mid to distal esophagus that stopped abruptly at the GEJ. This was thought to represent AEN which can be seen in Figure 2. Biopsies were not taken of the necrotic tissue. Erosions were seen in the body and antrum of the stomach, and multiple clean based ulcers were seen in the duodenum. Biopsies were taken of the gastric and duodenal mucosa, and histology report showed chronic gastroduodenitis with no sign of H. pylori or infectious organisms as well as no evidence of neoplasia.

TREATMENT

Following the EGD the patient was given pantoprazole 40 mg intravenously twice daily, sucralfate suspension of 1 g PO four times daily, and instructions to slowly increase from nil per os to clear and then full fluid diet.

OUTCOME AND FOLLOW-UP

He was discharged home in a stable condition on a liquid diet, sucralfate 2 g with meals and nightly for two weeks, and pantoprazole 40 mg twice daily. At discharge metformin and GLP-1 RA were discontinued and insulin aspart 5 units three times daily and insulin glargine 15 units nightly was prescribed.

A repeat EGD 8 wk post-discharge showed a healed esophagus with one polyp. Biopsies showed healed gastric and duodenal mucosa and mild inflammatory changes to the removed polyp. Follow up was arranged to ensure no return of symptoms and the patient’s follow up HbA1c was improved from the previous 8.4 to 7.2.

DISCUSSION

DKA has been previously associated with AEN in several case reports: A rare complication of a common presentation. As mentioned earlier, 13 cases to date have been reported, most of which have been associated with GIB. In fact, AEN, in general, is associated with overt GIB in 88% of presentations, and also often associated with non-specific symptoms such as GI upset, dysphagia, and hypotension[2,16].

It is critical to recognize AEN as it is associated with a mortality of 32%[2]. This case highlights the importance of considering AEN despite a lack of GIB when other concerning features are present, such as dysphagia. AEN is especially important to consider in patients such as males over 60 or those with increased risk of microvascular disease or hemodynamic compromise[1,16,17].

Interestingly, our case highlights two triggers that may have led to DKA in this patient and put him at greater risk for AEN. First, ketogenic diets, especially in conjunction with other triggers like dehydration or physiologic stress, have been linked to ketoacidosis in multiple case reports in diabetic and non-diabetic patients[18-20]. Ketogenic diets deplete the body’s glucose reserve and shift the metabolism into ketogenesis primarily by hepatic oxidation of fatty acids, making ketones an alternative to glucose[18]. In a patient with type two diabetes mellitus, who already has insulin resistance, the body’s ability to regulate ketogenesis is reduced, making them more prone to ketoacidosis. Moreover, the introduction of GLP-1 RA increases lipolysis and ketogenesis[21]. The combination of these factors may have been sufficient to tip this patient into ketoacidosis.

After the development of DKA, the development of AEN is largely thought to be multifactorial. First, DKA is a low volume state that predisposes the esophagus to necrotic injury[22,23]. Second, the hyperglycemia in DKA decreases gastric motility which increases acid reflux to the esophagus and therefore renders the esophagus
Figure 2 Endoscopic images. A: Endoscopic image of the presented patient’s mid-distal esophagus with circumferential black discolouration of the mucosa likely to be necrotic tissue; B: Distal esophagus with circumferential black discolouration of the mucosa with clear demarcation at the gastroesophageal junction in keeping with acute esophageal necrosis.

prone to injury\([3,24]\). Besides the direct impact of DKA, it is important to consider the risk factors associated with diabetes such as microvascular disease, which may have been underlying, which render the esophagus unable to withstand the hemodynamic changes associated with DKA. Furthermore, semaglutide is associated with adverse GI effects including gastritis, minor delays in gastric emptying, and GERD\([23]\). The delay in gastric emptying is caused by an inhibition of stomach peristalsis in combination with increased pylorus contraction\([25]\). A meta-analysis of adverse GI events in patients with T2DM using GLP-1 RAs showed that there is a dose-dependent increase in GI events, and GLP-1 RAs were more likely to cause adverse GI events in comparison to placebo\([24]\) or insulin\([25]\). Severe GI adverse reactions occurred in 1.7% of patients at our patient’s newly started dose of 0.5 mg\([23]\). The GERD and gastroparesis associated with GLP-1 RA could cause caustic injury which is a known contributor to AEN.

CONCLUSION
In conclusion, this case reiterates the association between AEN and DKA. With the evolving era of medicine, where diet and oral hypoglycemics are combined, AEN in the context of DKA may become more prevalent given the various mechanisms of actions involved. This case serves as a reminder for clinicians to keep a low threshold to proceed with EGD even despite a lack of overt GIB.

REFERENCES
1 Gurvits GE. Black esophagus: acute esophageal necrosis syndrome. World J Gastroenterol 2010; 16: 3219-3225 [PMID: 20614476 DOI: 10.3748/wjg.v16.i26.3219]
2 Gurvits GE, Shapsis A, Lau N, Gualtieri N, Robilotti JG. Acute esophageal necrosis: a rare syndrome. J Gastroenterol 2007; 42: 29-38 [PMID: 17322991 DOI: 10.1007/s00535-006-1974-z]
3 Krishnasamy S, Abell TL. Diabetic Gastroparesis: Principles and Current Trends in Management. Diabetes Ther 2018; 9: 1-42 [PMID: 29934758 DOI: 10.1007/s13300-018-0454-9]
4 Ebert EC. Gastrointestinal complications of diabetes mellitus. Dis Mon 2005; 51: 620-663 [PMID: 16458726 DOI: 10.1016/j.disamonth.2005.11.002]
5 Rigolon R, Fossa I, Rodella L, Targher G. Black esophagus syndrome associated with diabetic ketoacidosis. World J Clin Cases 2016; 4: 56-59 [PMID: 26881192 DOI: 10.12998/wjcc.v4.i2.56]
6 Talebi-Bakhshayesh M, Samice-Rad F, Zohrenia H, Zargar A. Acute Esophageal Necrosis: A Case of Black Esophagus with DKA. Arch Iran Med 2015; 18: 384-385 [PMID: 26058936]
7 McCarthy S, Garland J, Hensby-Bennett S, Philcox W, Keshar K, Stables S, Tse R. Black Esophagus (Acute Necrotizing Esophagitis) and Wischnewsky Lesions in a Death From Diabetic Ketoacidosis: A Possible Underlying Mechanism. Am J Forensic Med Pathol 2019; 40: 192-195 [PMID: 30676335 DOI: 10.1097/PAF.0000000000000463]
8 Uhlenhopp DJ, Pagnotta G, Sunkara T. Acute esophageal necrosis: A rare case of upper gastrointestinal bleeding from diabetic ketoacidosis. Clin Pract 2020; 10: 1254 [PMID: 32670536]
Moss K et al. AEN in a DKA patient

DOI: 10.4081/cp.2020.1254

9 Ghoneim S, Shah A, Dalal S, Landsman M, Kyprianou A. Black Esophagus in the Setting of Diabetic Ketoacidosis: A Rare Finding from Our Institution. Case Rep Gastroenterol 2019; 13: 475-480 [PMID: 31824236 DOI: 10.1159/000504434]

10 Choksi V, Dave K, Cantayne R, Shaharyar S, Joseph J, Shankar U, Kaplan S, Feiz H. "Black Esophagus" or Gurvits Syndrome: A Rare Complication of Diabetic Ketoacidosis. Case Rep Gastrointest Med 2017; 2017 [DOI: 10.1155/2017/4815752]

11 Vien LP, Yeung HM. Acute Esophageal Necrosis (Gurvits Syndrome): A Rare Complication of Diabetic Ketoacidosis in a Critically Ill Patient. Case Rep Med 2020; 2020: 5795847 [PMID: 32180810 DOI: 10.1155/2020/5795847]

12 Field Z, Kropf J, Lytle M, Castaneira G, Madruga M, Carlan SJ. Black Esophagus: A Rare Case of Acute Esophageal Necrosis Induced by Diabetic Ketoacidosis in a Young Adult Female. Case Rep Gastrointest Med 2018; 2018: 7363406 [PMID: 30631610 DOI: 10.1155/2018/7363406]

13 Shah AR, Landsman M, Waghary N. A Dire Presentation of Diabetic Ketoacidosis with "Black Esophagus. Cureus 2019; 11: e4761 [DOI: 10.7759/cureus.4761]

14 Haghbayan H, Sarker AK, Coones EA. Black esophagus: acute esophageal necrosis complicating diabetic ketoacidosis. CMAJ 2018; 190: E1049 [PMID: 30181152 DOI: 10.1503/cmaj.180378]

15 Buckshaw R, Stern ES, Andrews R, Stelzer F. Esophageal Necrosis: A Rare Complication of Diabetic Ketoacidosis – A Case Report. Poster Presented at: The American College of Physicians-Nationals, Philadelphia, PA [DOI: 10.1007/s10620-014-3382-1]

16 Gurvits GE, Cheriyan K, Shami MN, Korabathina R, El-Nader EM, Rayapudi K, Gandolfo FJ, Alshumrany M, Patel H, Chowdhury DN, Tsikos A. Black esophagus: new insights and multicenter international experience in 2014. Dig Dis Sci 2015; 60: 444-453 [PMID: 25297468 DOI: 10.1007/s10620-014-3382-1]

17 Day A, Sayegh M. Acute oesophageal necrosis: a case report and review of the literature. Int J Surg 2010, 8: 6-14 [PMID: 19800431 DOI: 10.1016/j.ijsu.2009.09.014]

18 White-Cotsmire AJ, Healy AM. Ketogenic Diet as a Trigger for Diabetic Ketoacidosis in a Misdiagnosis of Diabetes: A Case Report. Clin Diabetes 2020; 38: 318-321 [PMID: 32699486 DOI: 10.2337/cd20-0001]

19 von Geijer L, Ekelund M. Ketoacidosis associated with low-carbohydrate diet in a non-diabetic lactating woman: a case report. J Med Case Rep 2015; 9: 224 [PMID: 26428083 DOI: 10.1186/s13256-015-0709-2]

20 MacDonald PE, El-Kholy W, Riedel MJ, Salapatek AM, Light PE, Wheeler MB. The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. Diabetes 2002; 51 Suppl 3: S434-S442 [PMID: 12475787 DOI: 10.2337/diabetes.51.2007.s434]

21 Nakatani Y, Maeda M, Matsumura M, Shimizu R, Banba N, Aso Y, Yasu T, Harasawa H. Effect of GLP-1 receptor agonist on gastrointestinal tract motility and residue rates as evaluated by capsule endoscopy. Diabetes Metab 2017; 43: 430-437 [PMID: 28648835 DOI: 10.1016/j.diabet.2017.05.009]

22 Burtally A, Gregoire P. Acute esophageal necrosis and low-flow state. Can J Gastroenterol 2007; 21: 245-247 [PMID: 17431514 DOI: 10.1155/2007/920716]

23 Novo Nordisk Canada. Product Monograph Ozempic [Internet]. Mississauga, 2020. [cited 2020 December 21]. Available from: https://www.novonordisk.ca/content/dam/Canada/AFFILIATE/www-novonordisk-ca/OurProducts/PDF/ozempic-product-monograph.pdf

24 Blanco JC, Khatri A, Kifayat A, Cho R, Aronow WS. Starvation Ketoacidosis due to the Ketogenic Diet and Prolonged Fasting - A Possibly Dangerous Diet Trend. Am J Case Rep 2019; 20: 1728-1731 [PMID: 31756175 DOI: 10.7759/cureus.917226]

25 Li WX, Gou JF, Tian JH, Yan X, Yang L. Glucagon-like peptide-1 receptor agonists versus insulin glargine for type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. Curr Ther Res Clin Exp 2010; 71: 211-238 [PMID: 24688145 DOI: 10.1016/j.curtheres.2010.08.003]
