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Clinical and endoscopic characteristics of acute esophageal necrosis and severe reflux esophagitis

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Abstract

The similarities and differences between acute esophageal necrosis and severe reflux esophagitis have not been elucidated. We compared Los Angeles classification Grade C reflux esophagitis, Grade D reflux esophagitis, and acute esophageal necrosis to consider the similarities and differences between acute esophageal necrosis and severe reflux esophagitis.

We retrospectively reviewed records of patients who underwent esophagogastroduodenoscopy at a tertiary referral center from January 2012 to December 2019. Data on patients diagnosed as Grade C reflux, Grade D reflux, or acute esophageal necrosis for the first time were extracted for analysis.

A total of 213 patients were enrolled in the study, composed of 130 Grade C reflux, 74 Grade D reflux, and 9 acute esophageal necrosis patients. Compared to Grade C reflux patients, Grade D reflux and acute esophageal necrosis patients were more likely to be transfused ($P = .013$ and $P = .011$, respectively), to have duodenal ulcers ($P = .025$ and $P = .049$, respectively), and to have psychiatric illnesses ($P = .022$ and $P = .018$, respectively). Compared to both Grade C and D reflux, acute esophageal necrosis patients were more likely to present with shock ($P = .003$ and $P < .001$, respectively), have type 1 diabetes ($P = .030$ and $P = .004$, respectively), and present in winter ($P < .001$ and $P < .001$, respectively). Significant step-wise differences (Grade C < Grade D < acute esophageal necrosis) were observed in the need for admission ($P < .001$ and $P = .009$), coffee ground emesis ($P < .001$ and $P = .022$), and stigmata of hemorrhage on endoscopy ($P = .002$ and $P < .001$). Admission ($P = .003$) and coffee ground emesis ($P = .003$) independently predicted either Grade D reflux or acute esophageal necrosis over Grade C reflux on multivariate analysis.

Shock, type 1 diabetes, and winter may predict acute esophageal necrosis, while the need for admission and coffee ground emesis may predict Grade D reflux or acute esophageal necrosis.

Abbreviations: AEML = acute esophageal mucosal lesion, AEN = acute esophageal necrosis, DKA = diabetic ketoacidosis, EGD = esophagogastroduodenoscopy, GERD = gastroesophageal reflux, PPI = proton pump inhibitor, RE = reflux esophagitis, RE-C = reflux esophagitis Grade C, RE-D = reflux esophagitis Grade D, SCJ = squamo-columnar junction.

Keywords: acute esophageal necrosis, endoscopy, gastroesophageal reflux disease, reflux esophagitis, upper gastrointestinal bleeding

1. Introduction

Gastroesophageal reflux (GERD) is a common gastrointestinal disorder characterized by the reflux of stomach contents into the esophagus. GERD classically causes heartburn and acid regurgitation and is observed in about 13% of the global population.[1] Endoscopic findings in reflux esophagitis (RE) are frequently categorized using the Los Angeles (LA) classification, which uses a scale from A to D to represent increasing severity.[2,3] While frequency and severity of symptoms are often associated with endoscopic severity, about 15% of both Grade C and D RE (RE-C and RE-D) patients are asymptomatic.[4]

Acute esophageal necrosis (AEN) is a rare esophageal disorder characterized by circumferential mucosal damage of the esophagus with a sharp demarcation at the squamo-columnar junction (SCJ).[5] Also known as black esophagus, at least 160 cases of AEN have been reported since the first report in 1990.[6,7] AEN is believed to result from multiple factors such as damage from reflux of gastric contents, ischemia, and weakened mucosal barriers secondary to other debilitating conditions. However, the precise pathogenesis is still under investigation. Despite the various similarities between AEN and severe RE, there is a clear discrepancy in reported risk factors and clinical courses of the 2 conditions.[5,7] It remains unclear whether AEN can be considered an extremely severe form of RE or a completely different entity.

We therefore conducted a three-way comparative analysis on RE-C, RE-D, and AEN patients at our institution. Specifically, we sought to identify factors which are observed in all 3 conditions to varying degrees as well as those which may be unique to AEN.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2. Materials and methods

2.1. Patients

We screened records of all patients who received at least 1 esophagogastroduodenoscopy (EGD) at St. Luke's International Hospital in Tokyo, Japan, between January 1, 2012, and December 1, 2019. A retrospective electronic chart review was conducted on all patients with endoscopic findings consistent with RE-C, RE-D, or AEN.

2.2. Definitions

In accordance with the revised LA classification for RE,[2,3] patients were diagnosed with RE-C if "1 (or more) mucosal break that is continuous between the tops of 2 or more mucosal folds but which involves less than 75% of the circumference" was observed at the SCJ. Similarly, patients were diagnosed with RE-D if "1 (or more) mucosal break which involves at least 75% of the esophageal circumference" was observed at the SCJ. AEN was defined as the circumferential mucosal damage of the esophagus with a sharp demarcation at the SCJ, at least involving the lower esophagus and extending proximally to various degrees[5] (Fig. 1). Diagnosis was based purely on endoscopic findings; pathology was not required for inclusion.

If multiple EGDs were performed on the same patient, only the first episode of the most severe disease (assuming RE-C < RE-D < AEN) was used for analysis. To correct for inter-observer variability[8] and to identify errors in electronic medical records, all endoscopic images of enrolled patients were confirmed by one of the authors (TO). If the reported severity differed from the definitions provided above, a second author (KF) was shown the endoscopic images asked to evaluate the severity of RE after being blinded to the report and the first author's opinion. Severity was changed only if both the first and second authors agreed that there was an error in the recorded RE grade. No exclusions were made for any particular cause of RE.

2.3. Statistical analysis

Data on demographics, clinical variables, endoscopic findings, and clinical outcomes were extracted for analysis. Denominators of proportional figures were adjusted for missing data. Statistical analyses were conducted using Pearson Chi-Squared test or Fisher exact test for categorical variables, as appropriate, and the Mann–Whitney *U* test for continuous variables. To evaluate significance in differences between the 3 groups, one-way analysis of variance was used for continuous variables and either the Pearson Chi–Squared test or Fisher exact test was used for categorical variables. Multiple comparisons were performed to calculate odds ratios and confidence intervals for statistically significant variables. Multiple regression analysis was performed to determine independent predictors of RE-D or RE-D/AEN relative to RE-C. Cramer's coefficient of association was calculated to determine correlation between dichotomous variables. *P* values <.05 were considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics ver. 25.0 (IBM Corp., Armonk, NY).

2.4. Ethical considerations

The study was approved by the ethics committee at St. Luke's International Hospital (20-R009). Patient consent was waived due to the retrospective study design. A summary of the study was publicized on the hospital website with an explicit statement that patients could opt-out of the study freely without any negative consequences relating to their care.

3. Results

3.1. Patient characteristics

A total of 49,789 EGDs were performed on 22,274 patients during the relevant period, of which 7079 patients were diagnosed with RE or AEN. The 6866 patients diagnosed with mild or moderate RE were excluded. A total of 213 patients were included in the study, with 130 RE-C patients (61.0%), 74 RE-D patients (34.7%), and 9 AEN patients (4.2%) (Fig. 2). Two of the AEN cases were subjects of previous publications from our institution.[9,10]

Patient characteristics of the 9 AEN patients are listed on Table 1. All had characteristic circumferential lesions with varying degrees of black areas. The median age was 69 years (range: 39–86 years) and 5 were male. All 9 patients presented after episodes of vomiting and all but 1 experienced hematemesis, coffee ground emesis, or melena. Five were in shock and 4 required transfusions. Only 3 had a history of RE. Notably, 2

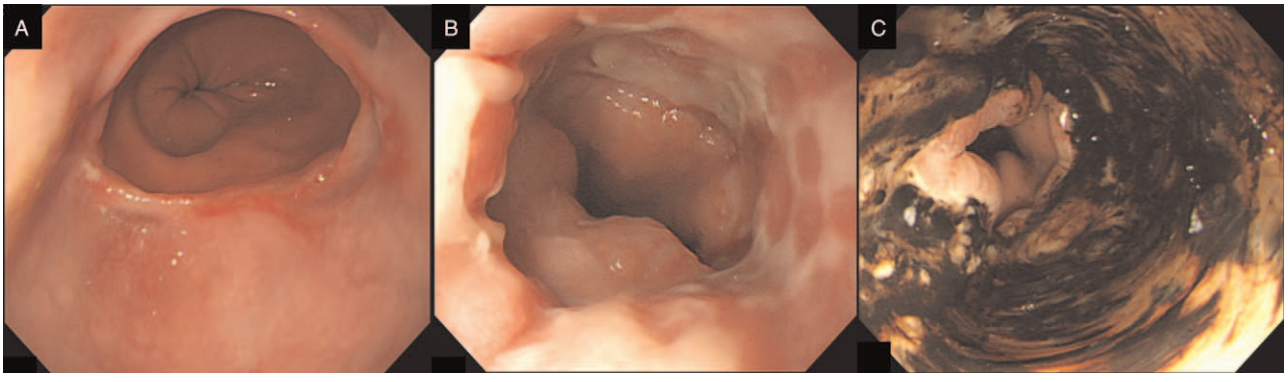

Figure 1. Typical endoscopic findings in Los Angeles classification Grade C reflux esophagitis (A), Grade D reflux esophagitis (B), and acute esophageal necrosis (C).

Table 1

Patient characteristics: acute esophageal necrosis.

							Medications before Admission									
Case	Age	Gender	Presentation	Shock	Transfusion	Medical History	PPI	NSAIDs	Antiplatelet/ Anticoagulants	BZ/Anti-psychotics	Alcohol	Smoking	Thickening of Esophageal Wall (CT)	Hospital Stay (Days)	Hemostatic Procedures	Endoscopies Performed
1	83	F	Vomiting 1 day PTA, followed by hematemesis and shock	+	+	Duodenal ulcer, RE, breast cancer, chronic kidney disease, Zollinger-Ellison syndrome, appendicitis	+	-	-	+	-	-	+	27	Duodenum	4
2	86	F	Vomiting from 10 days PTA, melena from 4 days PTA	+	+	None	+	-	-	+	-	-	+	25	Esophagus, duodenum	4
3	69	M	Melena from 5 days PTA, hematemesis from 2 days PTA	-	-	Type 2 DM, duodenal ulcer	-	-	-	-	+	-	+	5	-	1
4	52	M	Admitted for diabetic ketoacidosis; repeated episodes of vomiting	-	-	Type 1 DM	-	-	-	-	-	+	+	6	-	1
5	74	F	Melena from 3 days PTA, vomiting 1 day PTA	-	-	Gastric ulcer, alcoholic hepatitis	+	-	-	-	+	-	+	2	-	1
6	39	M	Coffee ground emesis	+	-	Type 1 DM, chronic kidney disease, depression, irritable bowel syndrome	-	-	-	+	-	+	NA	7	-	2
7	54	M	Repeated episodes of coffee ground emesis	+	+	Schizophrenia, RE, chronic hepatitis B infection	-	-	-	+	+	-	+	7	-	1
8	82	F	Frequent vomiting followed by coffee ground emesis	+	+	Breast cancer, paroxysmal atrial fibrillation, angina pectoris, ovarian cancer, RE, appendicitis	-	+	+	-	-	-	+	2	-	1
9	63	M	Hematemesis from 1 day PTA	-	-	Schizophrenia, type 2 DM	-	-	-	+	+	+	+	10	-	2
Proportion/ Median	69	55% male		56%	44%		33%	11%	11%	56%	44%	33%	100%	7	22%	1

BZ = benzodiazepines, CT = computed tomography, DM = diabetes mellitus, NA = not available, NSAIDs = non-steroidal anti-inflammatory drugs, PPI = proton pump inhibitors, PTA = prior to admission, RE = reflux esophagitis.

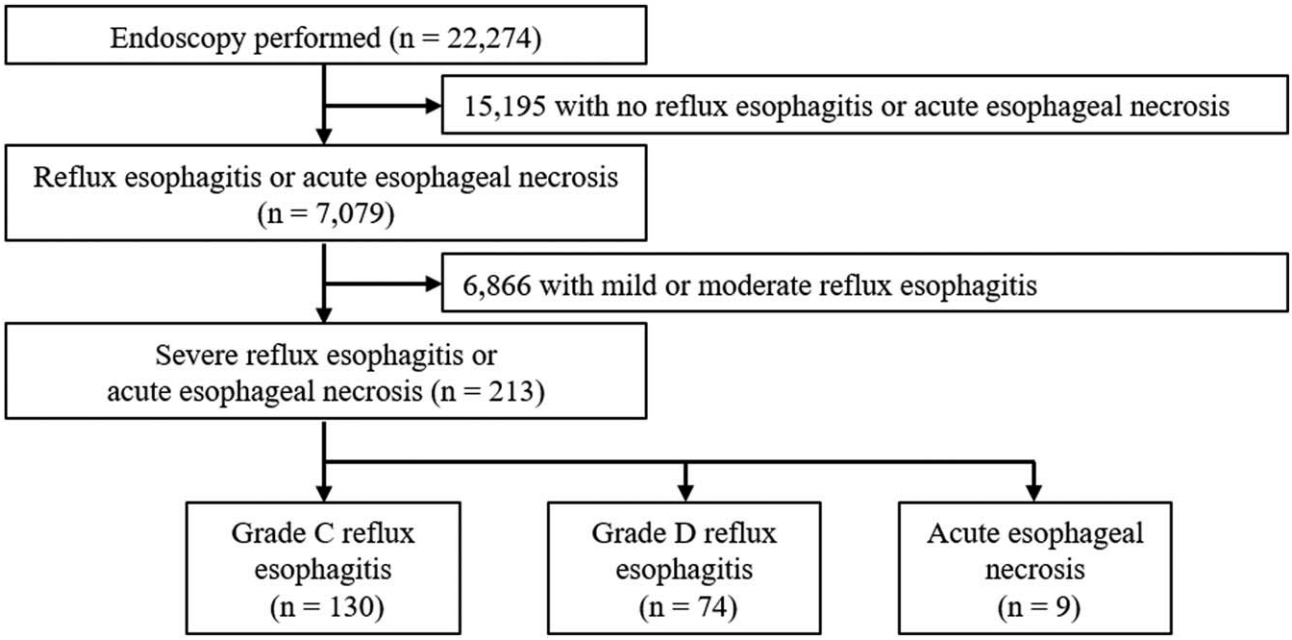

Figure 2. Study flow diagram.

relatively young patients had type 1 diabetes mellitus, while 2 others had schizophrenia. More than half were taking psychiatric drugs and/or benzodiazepines. All but 1 presented in winter (December, January, or February). Computed tomography was performed in 8cases, all of which showed a circumferential thickening of the lower esophageal wall. The median hospital stay was 7days (range: 2–27), and all patients survived. Endoscopy was repeated in 4 cases. Two cases requiring endoscopic hemostatic procedures each underwent endoscopy 4 times.

Initial laboratory data for the AEN patients are shown in Table 2. Seven had hypoalbuminemia, 6 had high blood urea nitrogen, and 5 had increased creatinine. Leukocytosis of varying degrees was observed in all cases, and 7 had increased C-reactive protein. Two patients had diabetic ketoacidosis (DKA), while one had severe hypoglycemia.

3.2. Comparison between acute esophageal necrosis and severe reflux esophagitis

A three-way comparison between the groups is provided on Table 3 and Table 4. There were no differences in age, gender, or body mass index between the 3 groups. Compared to RE-C patients, RE-D and AEN patients were more likely to be transfused ($P = .013$ and $P = .011$, respectively), to have duodenal ulcers ($P = .025$ and $P = .049$, respectively), and to have psychiatric illnesses ($P = .022$ and $P = .018$, respectively). Compared to both Grade C and D reflux, acute esophageal necrosis patients were more likely to present with shock ($P = .003$ and $P < .001$, respectively), have type 1 diabetes ($P = .030$ and $P = .004$, respectively), and present in winter ($P < .001$ and $P < .001$, respectively). Significant step-wise differences (Grade C < Grade D < acute esophageal necrosis) were observed in the need for admission ($P < .001$ and $P = .009$), coffee ground emesis

Table 2

Initial laboratory data: acute esophageal necrosis.

Case	Age	Gender	Albumin (g/dL)	BUN (mg/dL)	Creatinine (mg/dL)	White Blood Cells (/μL)	Hemoglobin (g/L)	Platelets (/μL)	CRP (mg/dL)	Glucose (mg/dL)	pH	Lactate (mmol/L)
1	83	F	3.1	52.6	2.01	19,200	10.1	360	12.5	148	7.586	2.3
2	86	F	2.1	27.5	0.88	25,400	6.1	327	6.5	96	7.574	4
3	69	M	3.3	14.5	0.88	8400	1.7	338	6.3	267	N/A	NA
4	52	M	4.6	40.5	1.55	17,800	17.0	297	18.1	1039	6.937	5
5	74	F	2.0	8.0	0.67	9300	10.0	164	0.5	163	7.39	4.8
6	39	M	3.6	51.7	2.93	26,200	11.5	28	1.7	1113	7.215	4.2
7	54	M	1.9	60.1	2.49	54,000	5.5	254	5.0	280	7.069	22
8	82	F	0.9	28.3	0.91	9000	6.0	102	15.0	15	7.501	2.8
9	63	M	4.8	15.8	0.76	13,100	13.7	249	0.2	180	NA	NA
Median	69		3.1	28.3	0.9	17,800	10.0	254	6.3	180	7.4	4.2

BUN = blood urea nitrogen, CRP = C-reactive protein, NA = not available.

Table 3

Patient characteristics.

	RE-C (n = 130)		RE-D (n = 74)		AEN (n = 9)		*P* value†
Age, median (interquartile range)	72	(62–81)	72	(60.3–85.8)	68	(53–81)	.643
Male, n (%)	81	62.3%	45	60.8%	5	55.6%	.912
Body mass index, median (interquartile range)	21.8	(19.1–24.5)	21.6	(18.7–24.4)	20.2	(19.1–23.4)	.653
Obese, n (%)	23	20.9%	11	17.2%	2	25.0%	.779
Symptoms, n (%)							
Admission	39	30.0%	43	58.1%	9	100.0%	<.001*
Shock	13	10.0%	12	16.2%	6	66.7%	<.001*
Death	0	0.0%	0	0.0%	0	0.0%	-
Transfusion	12	9.2%	16	21.6%	4	44.4%	.002*
Hematemesis	12	9.2%	13	17.6%	3	33.3%	.044*
Coffee ground emesis	15	11.5%	27	36.5%	7	77.8%	<.001*
Vomiting	26	20.0%	48	64.9%	9	100.0%	<.001*
Melena	14	10.8%	15	20.3%	4	44.4%	.010*
Abdominal pain	15	11.5%	12	16.2%	3	33.3%	.155
Bright red blood per rectum	0	0.0%	1	1.4%	0	0.0%	.389
Weight loss	5	3.8%	4	5.4%	0	0.0%	.705
Medical/Social History, n (%)							
Type 1 diabetes	0	0.0%	1	1.4%	2	22.2%	<.001*
Type 2 diabetes	24	18.5%	20	27.0%	2	22.2%	.360
Cardiovascular disease	27	20.8%	15	20.3%	1	11.1%	.784
Hypertension	44	33.8%	28	37.8%	0	0.0%	.077
Hyperlipidemia	14	10.8%	11	14.9%	0	0.0%	.365
Psychiatric disorders	7	5.4%	11	14.9%	3	33.3%	.005*
Chronic kidney disease	14	10.8%	10	13.5%	2	22.2%	.546
Cancer	14	10.8%	11	14.9%	1	11.1%	.688
Systemic sclerosis	7	5.4%	1	1.4%	0	0.0%	.288
Liver cirrhosis	4	3.1%	6	8.1%	0	0.0%	.209
Alcohol use (current or past history, >20 g of ethanol/day)	47	56.6%	28	48.3%	3	37.5%	.084
Smoking (current or past history)	31	39.2%	23	41.1%	2	28.6%	.222
Medications n, (%)							
Proton pump inhibitors	28	21.5%	22	29.7%	5	55.6%	.050*
Histamine 2 blockers	10	7.7%	4	5.4%	0	0.0%	.588
Bisphosphonates	4	3.1%	4	5.4%	0	0.0%	.584
Antithrombotic agents	23	17.7%	13	17.6%	1	11.1%	.879
Benzodiazepines/antipsychotics	20	15.4%	19	25.7%	4	44.4%	.038*
Non-steroidal anti-inflammatory drugs	14	10.8%	6	8.1%	0	0.0%	.505
Steroids	6	4.6%	3	4.1%	0	0.0%	.798
Diagnosis in winter (December–February)	32	24.6%	19	25.7%	8	88.9%	<.001*
Other endoscopic findings							
Hiatal hernia	86	66.2%	41	55.4%	4	44.4%	.178
Esophageal stricture	0	0.0%	2	2.7%	0	0.0%	.150
Atrophic gastritis	47	36.4%	22	29.7%	3	33.3%	.624
Gastric ulcer	6	4.7%	10	13.5%	0	0.0%	.046*
Gastric ulcer scar	6	4.7%	6	8.1%	1	11.1%	.501
Post-operative stomach	14	10.9%	5	6.8%	0	0.0%	.388
Duodenitis	8	6.2%	6	8.2%	1	11.1%	.773
Duodenal ulcer (all parts)	11	8.5%	16	21.9%	3	33.3%	.041*
Duodenal ulcer (1st part)	9	7.0%	15	20.5%	2	22.2%	.012*
Duodenal ulcer (2nd part)	6	4.7%	6	8.2%	3	33.3%	.005*
Duodenal ulcer scar	7	5.4%	12	16.4%	3	33.3%	.003*
Duodenal stricture	0	0.0%	10	13.5%	1	11.1%	<.001*
Stigmata of hemorrhage	20	15.4%	25	33.8%	9	100.0%	<.001*
Hemostatic intervention performed	8	6.2%	4	5.4%	2	22.2%	.150

AEN = acute esophageal necrosis, RE-C = reflux esophagitis Grade C, RE-D = reflux esophagitis Grade D * denotes statistical significance ($P < .05$).

† One-way analysis of variance used for continuous variables and Pearson Chi–Squared test or Fisher exact test used for categorical variables.

($P < .001$ and $P = .022$), and stigmata of hemorrhage on endoscopy ($P = .002$ and $P < .001$). Finally, AEN patients were more likely to present with melena ($P = .017$), to be taking proton pump inhibitors (PPI) ($P = .035$), benzodiazepines or antipsychotics ($P = .048$), or to have ulcers in the second part of the duodenum ($P = .0.013$) than RE-C patients, but the difference was not significant in relation to RE-D patients (Fig. 3). The difference in the frequency of admission and coffee ground emesis between RE-C and RE-D patients remained significant in multiple regression analysis ($P = .009$ and $P = .010$, respectively). The

Table 4

Multiple comparisons and multivariate analysis.

	% Observed			Multiple comparisons: Odds ratios (95% CI)			Multiple comparisons: *p*-value			Multivariate analysis: *P* value	
	RE-C	RE-D	AEN	RE-C vs RE-D	RE-D vs AEN	RE-C vs AEN	RE-C vs RE-D	RE-D vs AEN	RE-C vs AEN	RE-C vs RE-D	RE-C vs Re-D+AEN
Symptoms											
Admission	30%	57%	100%	3.1 (1.7–5.5)	1.8 (1.4–2.2)	3.3 (2.3–4.3)	<.001*	.009*	<.001*	.009*	.003*
Shock	10%	16%	67%		10.3 (2.3–47.1)	18.0 (4.0–80.7)	.193	.003*	<.001*		
Transfusion	9%	22%	44%	2.7 (1.2–6.1)		7.8 (1.9–33.3)	.013*	.137	.011*	.936	.755
Hematemesis	9%	18%	33%				.081	.235	.058		
Coffee ground emesis	12%	36%	78%	4.4 (2.2–9.0)	6.1 (1.2–31.4)	26.8 (5.1–141.3)	<.001*	.022*	<.001*	.010*	.003*
Vomiting	20%	65%	100%	7.4 (3.9–14.0)	1.5 (1.3–1.8)	5.0 (3.6–7.0)	<.001*	.027*	<.001*		
Melena	11%	20%	44%			6.6 (1.6–27.6)	.062	.116	.017*		
History											
Type 1 diabetes mellitus	0%	1%	22%		20.9 (1.7–259.9)	6.2 (1.9–20.0)	.363	.030*	.004*		
Psychiatric	5%	15%	33%	3.1 (1.1–8.3)		8.8 (1.8–42.7)	.022*	.173	.018*	.118	.096
Medications											
Proton pump inhibitors	22%	30%	56%			4.6 (1.1–18.1)	.191	.120	.035*		
BZ/antipsychotics	15%	26%	44%			4.4 (1.1–17.8)	.072	.209	.048*		
Diagnosis in winter	25%	26%	89%		22.2 (2.7–1039.3)	23.9 (3.0–1091.2)	0.868	<0.001*	<0.001*		
Endoscopic Findings											
Gastric ulcer	2%	14%	0%	3.2 (1.1–9.3)			.023*	.295	.664	.399	.553
Duodenal ulcer	9%	22%	33%	3.0 (1.3–6.9)		5.4 (1.2–24.5)	.025*	.345	.049*	.151	.094
Duodenal ulcer (1st part)	7%	20%	22%	3.4 (1.4–8.3)			.004*	.598	.153		
Duodenal ulcer (2nd part)	5%	8%	33%			10.2 (2.0–51.3)	.232	.056	.013*		
Duodenal ulcer scar	5%	16%	33%	3.4 (1.3–9.1)		8.7 (1.8–42.4)	.011*	.209	.019*		
Duodenal stricture	0%	14%	11%	1.2 (1.1–1.3)			<.001*	.659	.065		
Stigmata of hemorrhage	15%	34%	100%	2.8 (1.4–5.5)	3.0 (2.2–4.1)	6.5 (4.3–9.7)	.002*	<.001*	<.001*		

AEN = acute esophageal necrosis, BZ = benzodiazepines, CI = confidence interval, RE-C = reflux esophagitis Grade C, RE-D = reflux esophagitis Grade D.

* Denotes significance ($P < .05$).

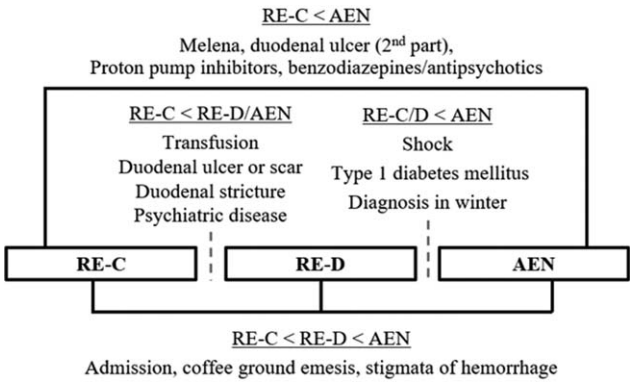

Figure 3. Significant differences between Los Angeles classification Grade C reflux esophagitis (RE-C), Grade D reflux esophagitis (RE-D), and acute esophageal necrosis (AEN).

differences in these 2 variables were more pronounced when AEN patients was added to the RE-D group ($P = .003$ and $P = .003$, respectively).

Seven RE-C patients, 11 RE-D patients, and 3 AEN patients were being treated for psychiatric disease at the time of diagnosis. Three RE-C patients, 5 RE-D patients, and 1 AEN patient had major depressive disorder, while 0, 3, and 2 had schizophrenia, respectively. Correlation analyses showed a significant association between psychiatric disease and vomiting (coefficient: 0.22, $P = .001$), coffee ground emesis (coefficient: 0.23, $P = .001$), and benzodiazepine or antipsychotic use (coefficient: 0.422, $P < .001$).

4. Discussion

4.1. Summary

In this study, we found that AEN patients were more likely to have type 1 diabetes mellitus, be in shock, present in winter, require admission, present with coffee ground emesis, and have stigmata of hemorrhage on endoscopy than both RE-C and RE-D patients. Compared to RE-C patients, AEN patients were also more likely to have a history of psychiatric illness, present with melena, be transfused, be taking PPIs, benzodiazepines or antipsychotics, and to have active or healed duodenal ulcers. Notably, there were no differences in age, gender, body mass index, use of antithrombotic agents, or the need for endoscopic hemostasis among the 3 groups.

4.2. Acute esophageal necrosis

In a pooled analysis on 114 AEN cases, 73% were male, with a mean age of 62.1 years.[6] Compared to this report, our 9 AEN patients had significantly higher rates of acute kidney injury (44% vs 8%, $P = .018$) and tended to present more frequently with shock (67% vs 29%, $P = .054$) based on a two-sided Fisher exact test, but all survived the episode of AEN (deaths: 0% vs 30%, $P = .062$). Recent case reports tend to describe patients with higher severity requiring surgery than older reports, possibly due to publication bias.

Reports from Japan which refer to AEN as acute esophageal mucosal lesion (AEML) tended to be missing from the pooled analysis. Tsumura et al[11] reported 12 cases of AEN, including 6 cases which were not black on the surface. They suggested use of the term AEML, as its acute and transient nature are similar to that of acute gastric and duodenal mucosal lesions. They found no differences in characteristics between 6 black and 6 non-black AEML cases. Only one case had a history of GERD, and only one case required acid suppression therapy after the acute phase.

4.3. Severe reflux esophagitis and acute esophageal necrosis

Sakata et al[12] conducted the only study to date which compared severe RE (RE-C and RE-D) to AEML cases. Comparing 39 RE cases with 32 AEML (6 black and 26 non-black esophagus) cases, they found male sex, hypertension, and renal dysfunction to be risk factors for AEML. Similar to our results, AEML patients tended to present with leukocytosis, high blood urea nitrogen, and hyperglycemia, and were more likely to need emergency endoscopy and to have concurrent duodenal lesions.

RE-D appears closer to AEN than mild RE in many respects. Coronary artery disease, congestive heart failure, and chronic obstructive pulmonary disorder are risk factors for RE-D, which may act through a mechanism similar to the way debilitating disease triggers AEN. RE-D patients are more likely to be older, admitted and/or required intensive care, and have more cardiopulmonary disorders and gastrointestinal bleeding compared to Grade A RE patients, but are less likely to be obese or have a history of alcohol use and tended to have less hiatal hernias.[13]

RE-C and RE-D patients experience more reflux at night than during the day, unlike their milder counterparts.[14] Healing occurs in only 70% and 58% of RE-C and RE-D patients after PPI therapy, respectively.[15] In contrast, most AEN patients achieve complete healing and are able to discontinue PPIs after the acute phase. Thus, AEN has some severe RE-like characteristics and some unique, AEN-specific characteristics. Our study also found that some factors are specific to severe RE or AEN, while others are common to both.

4.4. Seasonality

Eighty nine percent of our AEN patients presented in the winter. In contrast, no clear seasonality was observed in RE-C and RE-D patients. As an increase in ischemic heart disease and heart failure in the winter has been documented in various reports since 1937 and as necrosis is associated with compromised blood flow, a predilection for cold weather in AEN appears reasonable.[16,17] However, it must be noted that the timing of onset of RE in our RE-C and RE-D patients remains unclear, as many were diagnosed during routine endoscopies and/or without symptoms. The impact of seasonality in AEN has not been reported and may be a topic for further research.

4.5. Diabetic ketoacidosis

DKA has been associated with AEN in multiple reports, including 1 report with 4 cases among 16 AEN patients.[16–18] As there were only 29 DKA admissions during the relevant period in that report, AEN risk may be particularly high in this population.[18]

While gastric stasis and hypovolemia have been proposed as possible mechanisms in previous reports, the relationship and direction of causality between DKA and AEN remain unclear.[18,19] DKA is one of the most common diabetes-related

emergencies, which may result from various causes including concurrent conditions (such as infections) and poor adherence to medications.[20] Thus, a concurrent disease process may trigger both DKA and AEN.

Delayed gastric emptying in diabetics result from microvasculopathy, autonomic neuropathy, and enteric neuromuscular disturbances, all of which contribute to reduced contractility of the gastric antrum, spasm of the pylorus, and small bowel dysmotility.[21] Gastroparesis occurs in about 5% of type 1 diabetes mellitus patients and may lead to vomiting or reduced intake, both of which may precipitate AEN as well as DKA. Diabetic gastroparesis may also be associated with an infectious prodrome, which could also trigger DKA.[22]

DKA patients are inevitably hypovolemic due to osmotic diuresis which may be accompanied by poor intake, presenting a risk of hypoperfusion and ischemia. Increased lipase due to insulin deficiency leads to the accumulation of ketone bodies, resulting in high anion gap metabolic acidosis.[20] Hypovolemia and metabolic acidosis can both trigger hypercalcemia, which causes elevations in gastrin and acetylcholine.[23] This leads to an increase in gastric acid secretions and therefore predisposes affected patients to peptic ulcers, and possibly, to AEN.[24] Finally, DKA is associated with elevated proinflammatory cytokines such as interleukins and C-reactive protein, which may aggravate hypoperfusion via thrombus formation.[25]

4.6. Psychiatric disease

The relationship between psychiatric disorders and GERD is well-documented. The prevalence of GERD was higher in depressed patients than non-depressed patients in a population-based study, while other studies suggest that GERD is a risk factor for depression, anxiety disorder, sleep disorders, bipolar disorder, and schizophrenia.[26–29] The relationship between GERD and psychiatric disorders is most likely bidirectional and multifactorial.[30] Inflammatory cytokines produced from the esophageal mucosa in GERD can lead to depression or anxiety. Reduced quality of life due to GERD may also trigger or exacerbate psychiatric disease. Psychiatric disease has been reported to cause esophageal contraction abnormalities and alter sensory function. It may also alter health-related behavior which may induce GERD, including change in diet, alcohol consumption, smoking, compliance with medications, and frequency of hospital visits. Tricyclic antidepressants and benzodiazepines induce reflux by reducing the lower esophageal sphincter pressure.[31] Depression is also associated with the use of proton pump inhibitors in elderly patients.[32]

We found high rates of psychiatric disease in RE-D and AEN patients, particularly major depressive disorder and schizophrenia. In addition to the expected association with benzodiazepine or antipsychotic use, there was significant positive association between psychiatric disease and vomiting. While associations between psychiatric disease and AEN has not been reported in the existing literature, the abovementioned factors may predispose psychiatric patients to AEN. More research is required to elucidate the relationship between these 2 clinical entities.

4.7. Limitations

There are several limitations to this study. The study was a retrospective study at a single institution. Multivariate analyses could not be performed for AEN, owing to the small sample size. The same patient may fall in different categories of severity, depending on the timing of the EGD. No pathological evaluation was conducted. The period of PPI use prior to EGD could not be determined for patients taking PPIs. Long-term outcomes could not be evaluated in this study, as most AEN patients were lost to follow-up.

5. Conclusion

In conclusion, we present a three-way comparison of clinical and endoscopic characteristics in RE-C, RE-D, and AEN. AEN has some characteristics which are similar to severe RE, but has also some distinct features which set it apart as a separate clinical entity. Shock, type 1 diabetes, and winter may predict AEN, while the need for admission and coffee ground emesis may predict RE-D or AEN.

Author contributions

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