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ORIGINAL ARTICLE

Observational Study

Needle-based confocal endomicroscopy in the discrimination of mucinous from non-mucinous pancreatic cystic lesions

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Abstract

BACKGROUND

Pancreatic cystic lesions (PCLs) are considered a precursor of pancreatic cancer. Needle-based confocal endomicroscopy (nCLE) is an imaging technique that enables visualization of the mucosal layer to a micron resolution. Its application has demonstrated promising results in the distinction of PCLs. This study evaluated the utility of nCLE in patients with indeterminate PCLs undergoing endoscopic ultrasound fine-needle aspiration (EUS-FNA) to distinguish mucinous from non-mucinous lesions.

AIM

To evaluate the accuracy of nCLE in indeterminate PCLs undergoing EUS-FNA to distinguish mucinous from non-mucinous lesions.

METHODS

Patients who required EUS-FNA between 2015 and 2017 were enrolled prospectively. During EUS-FNA, confocal imaging, analyses of the tumor markers carcinoembryonic antigen and amylase, and cytologic examination were

patient from the study.

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conducted. All patients were followed for at least 12 mo and underwent laboratory testing and computed tomography scanning or magnetic resonance imaging. nCLE videos were independently reviewed by 6 observers to reach a final diagnosis (mucinous *vs* non-mucinous) based on criteria derived from previous studies; if there was disagreement > 20%, a final diagnosis was discussed after consensus re-evaluation. The sensitivity, specificity, and accuracy of nCLE were calculated. Adverse events were recorded.

RESULTS

Fifty-nine patients were included in this study. Final diagnoses were derived from surgery in 10 patients, cytology in 13, and imaging and multidisciplinary team review in 36. Three patients were excluded from final diagnosis due to problems with nCLE acquisition. Fifty-six patients were included in the final analysis. The sensitivity, specificity, and accuracy of nCLE were 80% [95% confidence interval (CI): 65-90], 100% (95%CI: 72-100), and 84% (95%CI: 72-93), respectively. Post-procedure acute pancreatitis occurred in 5%.

CONCLUSION

EUS-nCLE performs better than standard EUS-FNA for the diagnosis of indeterminate PCL.

Key Words: Needle-based confocal endomicroscopy; Pancreatic cystic lesion; Pancreatic adenocarcinoma; Endoscopic ultrasound; Endoscopic ultrasound fine-needle aspiration; Intraductal papillary mucinous neoplasm; Serous cyst adenoma

Core Tip: Pancreatic cystic lesions are considered a precursor of pancreatic cancer. Needle-based confocal endomicroscopy is an imaging technique that enables visualization of the mucosal layer to a micron resolution. Endoscopic ultrasound with fine-needle aspiration is the most accurate procedure for identifying pancreatic cystic lesions, as it combines cytology with analysis of intracystic carcinoembryonic antigen level, although its accuracy is low. Needle-based confocal endomicroscopy has demonstrated promising results.

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INTRODUCTION

Pancreatic cancer is the 10th most common cancer in men and 9th most common cancer in women. Compared to other cancers, pancreatic cancer has the lowest survival, with a 5-year survival rate of 9% and an estimated 56000 new cases per year according to the Surveillance, Epidemiology, and End Results database[1]. Pancreatic cystic lesions (PCLs) are considered a precursor of pancreatic cancer, as some have malignant potential and therefore should be evaluated carefully. However, other PCLs exhibit benign behavior with no surveillance required[2-4].

Currently, endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) is the most accurate procedure for identifying the nature of a pancreatic cyst, as it combines cytology with analysis of intracystic carcinoembryonic antigen (CEA) level. The specificity, sensitivity, and overall accuracy of CEA in the discrimination of mucinous from non-mucinous is 98%, 48%, and 79%, respectively. However, in the absence of an associated solid component, pancreatic cyst fluid is frequently acellular or paucicellular, with resultant low diagnostic yield[5,6].

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Confocal laser endomicroscopy is an innovative imaging technique that enables visualization in real-time, to a micron resolution, of the mucosal layer. Luminal confocal exploration has demonstrated excellent results in distinguishing neoplastic from benign tissue. Needle-based confocal endomicroscopy (nCLE) is a subtype of confocal laser imaging, in which a mini-probe is inserted through a 19-gauge EUS-FNA needle under EUS guidance. The first three clinical trials (total of 126 patients) described the correlation between nCLE and histological features, and established the criteria for characterizing the most frequent type of cysts; however, they did not evaluate the performance of these criteria[7-9]. Moreover, some concerns were raised about the safety of the procedure and interobserver agreement (IOA)[10,11]. Recently, two papers were published evaluating the impact of nCLE on surgical outcome[12, 13]; the results were very promising, with some interesting economic consequences for follow-up costs[14].

We present the results of a multicenter prospective study evaluating the diagnostic accuracy of EUS-guided nCLE in differentiating mucinous from non-mucinous PCLs compared to standard of care, by analysis of intracystic CEA and amylase level and/or cytology *vs* surgical pathology.

MATERIALS AND METHODS

Study design and inclusion criteria

From November 2015 to December 2017, all consecutive patients referred for EUS-FNA for undetermined PCLs were prospectively enrolled and underwent EUS associated with both FNA and nCLE at four centers (AOU-Modena; Ospedale Le Molinette-Torino; Istituto Nazionale Tumori-Milano; Ospedale Maggiore, Crema, Italy). The inclusion criteria were as follows: age > 18 years; ability to provide informed consent; and, had a single undetermined pancreatic cyst > 20 mm without evidence of communication with the main pancreatic duct (PD) in previous imaging investigations. Exclusion criteria were as follows: Known fluorescein allergy; pregnancy; worrisome features or high-risk stigmata according to Fukuoka Guidelines [15]; or, any contraindication to performing EUS (Figure 1). The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Baggiovara Hospital in Modena (Prot. 16/11/2015 prat n 4327; Baggiovara, Italy).

Study aims

The primary goal of the study was to determine the accuracy of nCLE in discriminating mucinous from non-mucinous PCLs. The secondary goals were to determine the feasibility of nCLE by evaluating the rate of procedure completion and by rating the ease of the procedure as easy, moderate, or difficult, and to assess the safety of the procedure by recording the immediate and 30-d complication rates (bleeding, infection, perforation, or acute pancreatitis (AP) classified as mild, moderate, or severe according to the European Society of Gastrointestinal Endoscopy guidelines)[16].

Procedures

EUS and EUS-FNA: All EUS procedures were performed by five operators with experience in biliopancreatic EUS (> 200/year) and nCLE (> 15/per operator). Antibiotic prophylaxis was administered 1 h before the procedure and continued for 3 d after[3]. The procedures were performed under deep sedation using a linear array echoendoscope (Olympus®, Tokyo, Japan or Hitachi-Pentax®, Hamburg, Germany) to evaluate the following PCL characteristics: site; morphology; cyst diameter; diameter of the main PD; communication with a duct (main or branch); thickness of the cyst wall; presence of septa and/or wall nodules; and, contrast medium to evaluate the enhancement of any septa or nodule. Once the cyst was visualized, it was punctured from the stomach or duodenum with a 19-gauge needle (Expect™; Boston Scientific, Boston, MA, United States) that was preloaded with the AQ-flex 19 miniprobe (Mauna Kea Technologies®, Paris, France). Then 2.5 mL of 10% fluoresceine was intravenously injected, the probe was gently advanced in contact with the cyst wall, and nCLE imaging was performed. After nCLE imaging acquisition, the probe was retrieved from the EUS-FNA needle and the cyst was completely aspirated. The cyst fluid was sent for analysis of CEA and amylase, and cytologic examination.

nCLE classification and diagnosis: Before patient enrollment, 6 investigators received nCLE training to learn technical tips and agreement for imaging interpretation,

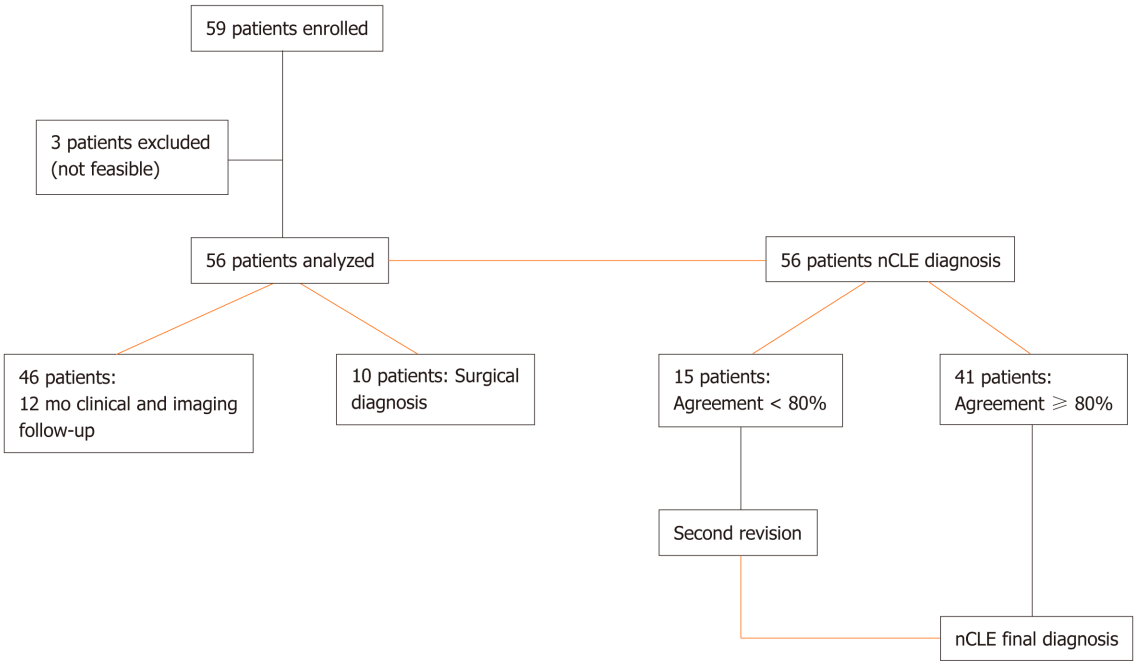

Figure 1 Flow chart. nCLE: Needle-based confocal endomicroscopy.

highlighting the high specificity of nCLE for the diagnosis of serous cystadenoma (SCA), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN) and for the differentiation of mucinous from non-mucinous lesions, with a 20-video review. The criteria used in this study were derived from previously validated criteria from publications by Napoleon *et al*[8,9] as well as studies on papillary projections in IPMN[7,17] (Figure 2A), the superficial vascular network in SCA[9] (Figure 2B), MCNs in which the epithelial cyst border appears as a gray band delineated by a thin dark line[9] (Figure 2C), pseudocysts identified by bright gray and black particles[9] (Figure 2D), and cystic pancreatic neuroendocrine tumors (PNETs) characterized by dark irregular clusters of cells surrounded by gray matter[9].

After the conclusion of follow-up, all nCLE videos were independently and blindly reviewed by the 6 observers; no clinical or imaging information was provided at this time. After video review, each investigator provided a final diagnosis of mucinous (mucinous cystadenoma or IPMN) or non-mucinous (SCA, pseudocyst, PNET) neoplasia, according to the criteria described above. In cases of disagreement between > 20% of observers, videos were discussed together to reach a final nCLE consensus diagnosis. In the event of persistent disagreement between the investigators, the videos were considered false negatives.

Final diagnosis: The final diagnosis was based on histological analyses of the surgical specimen and/or when FNA results were diagnostic on cell block sections or smears. Otherwise, all patients were followed up at 6 mo with magnetic resonance imaging (MRI) or computed tomography (CT) scan or EUS, and the final diagnosis was based on a consensus of EUS findings plus analysis of CEA level with at least 12 mo follow-up.

IOA

The extent of agreement among raters of nCLE diagnosis was performed with Gwet's agreement coefficient (AC) [95% confidence interval (CI)]. Gwet's AC provides a more stable interrater reliability coefficient than Cohen's kappa. It is also less affected by prevalence and marginal probability than Cohen's kappa, and therefore should be considered for use with interrater reliability analyses. For all measures of agreement, the following guideline provided by Landis and Koch[19] for the interpretation of kappa was used: < 0.00, poor; 0.00 to 0.20, slight; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; and 0.81 to 1.00, almost perfect[18,19].

Statistical analyses

The categorical variables are expressed as absolute numbers and percentages, while

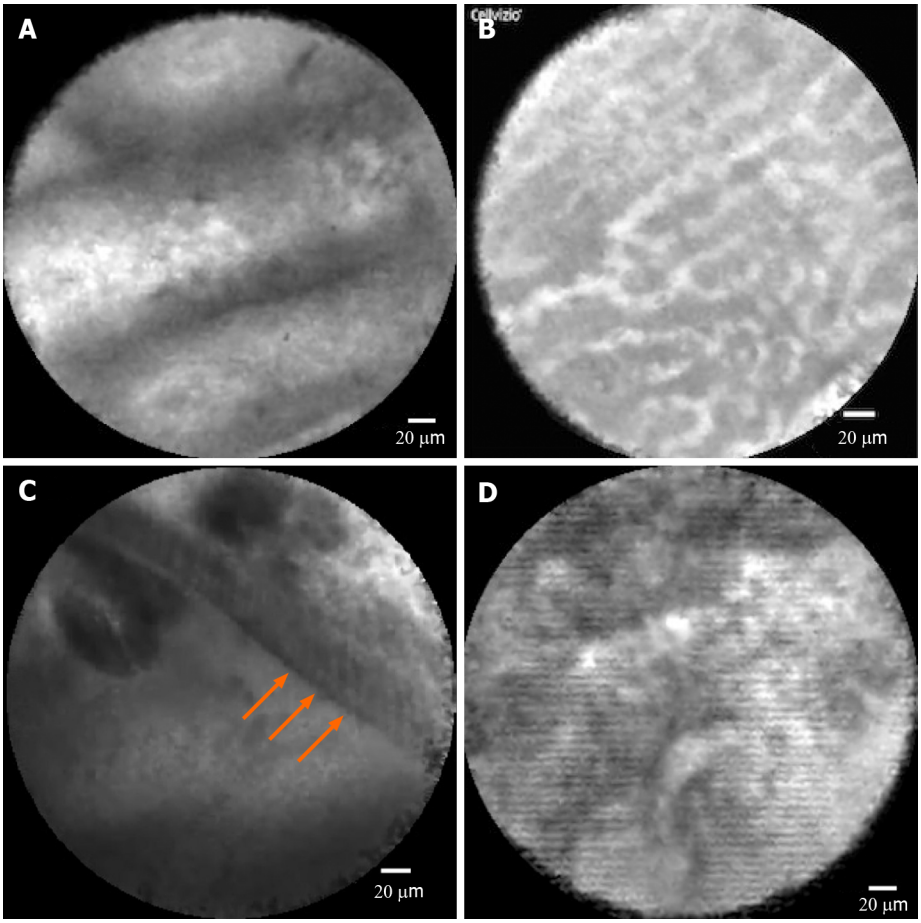

Figure 2 Confocal images of pancreatic cyst subtypes. A: Intraductal papillary mucinous neoplasm, showing papillary projections; B: Serous cystadenoma, showing superficial vascular network; C: Mucinous cystic neoplasm, in which the epithelial cyst border appears as a gray band delineated by a thin dark line; D: Pseudocyst, showing gray and black particles.

the continuous variables are expressed in the case of normal distribution as mean and standard deviation and relative 95%CI, or in the case of non-normal distribution, as median and interquartile range. The study was approved by the local Ethical Committee of Baggiovara Hospital in Modena (Prot. 4327/2016) and subsequently by the Ethical Committees of all centers involved.

RESULTS

Baseline patient characteristics

From November 2015 to December 2017 a total of 59 patients were referred for EUS-FNA of PCLs, and were prospectively enrolled in the study to undergo EUS-guided FNA and nCLE during the same session. Patient demographics and PCL features are listed in Table 1. The mean patient age was 64-year-old, and 41 patients were female (70%). The majority of patients at the time of EUS were asymptomatic (n = 45; 76%); a history of AP was identified in 3 (5%) and concurrent symptoms potentially attributable to PCL were reported in 11 (19%), all of whom had abdominal pain. Previous cross-sectional abdominal imaging reports for PCL evaluation were available in all cases (n = 33 CT, n = 43 MRI).

The PCLs were distributed as follows: head of pancreas in 13 patients (22%); uncinate process in 8 (13%); neck in 6 (10%); body in 26 (45%); and tail in 6 (10%). The median cyst size was 32 mm (range: 22-45 mm). The majority of lesions were multilocular (n = 27, 46%). The main PD communication was considered exclusion criteria if found during CT or MRI. However, in 1 case, a communication was detected by EUS. No PD dilation (≥ 5 mm) was identified. Solid components or intramural nodules were present in 3 patients (5%). Intracystic CEA was available in 53 cases (95%), with a level > 192 ng/mL in 28 patients (47%) and < 5 ng/mL in 14 cases (24%).

Table 1 Patients demographics and pancreatic cystic lesions features

Characteristic	Enrolled, *n* (%)
Patients, *n*	59
Age	64 ± 13
Sex, female	41 (70)
Clinical presentation	
Asymptomatic	45 (76)
Abdominal pain	11 (19)
Pancreatitis	3 (5)
Site of lesion	
Head	13 (22)
Uncinate process	8 (13)
Neck	6 (10)
Body	26 (45)
Tail	6 (10)
Cyst diameter mm	32 (22-45)
Morphology	
Unilocular macrocyst	31 (52)
Multilocular microcyst	27 (46)
Microcyst	1 (2)
Main pancreatic duct diameter > 3 mm	5 (8)
Communication with a duct	1 (2)
Cyst wall diameter > 1 mm	20 (34)
Septa and/or wall nodules	35 (59)
CEA > 192 ng/mL	21 (35)
Amylases ≥ 50 UI/L	53 (90)

CEA: Carcinoembryonic antigen.

Final diagnosis

Final diagnosis was made of 11 mucinous cystadenomas, 34 branch-duct IPMNs, 13 SCAs, and 1 cystadenocarcinoma (Table 2). Final diagnosis was derived from surgery in 10 patients (17%), cytology in 13 patients (22%), and a team discussion of the review of all CT/MRI/EUS images and intracystic CEA level in the remaining cases.

Feasibility

The procedure was technically feasible in 56 patients; therefore, the feasibility rate was 95%, with a rating of easy in 48 patients (82%), moderately difficult in 7 patients (11%), and difficult in 4 patients (7%). The median nCLE scanning time was 3 min and did not exceed 4 min in any case.

Comparison of CEA and nCLE

The analysis of "intention to treat" showed sensitivity, specificity, and accuracy for diagnosing mucinous lesions and intracystic CEA > 192 ng/mL of 58% (95%CI: 43-72), 100% (95%CI: 73-100), and 67% (95%CI: 53-78), respectively. The sensitivity, specificity, and accuracy of nCLE were 80% (95%CI: 65-90), 100% (95%CI: 72-100), and 84% (95%CI: 72-92), respectively, in distinguishing mucinous from non-mucinous lesions (Table 3).

Table 2 Final diagnosis

Final diagnosis	*n* (%)
Serous cystoadenoma	13 (22)
Cystoadenocarcinoma	1 (2)
Branch-duct IPMN	34 (58)
Mucinous cystoadenoma	11 (18)

IPMN: Intraductal papillary mucinous neoplasm.

Table 3 Diagnostic yield of carcinoembryonic antigen and needle-based confocal laser endomicroscopy in mucinous *vs* non-mucinous lesions

	Sensitivity (%)	Specificity (%)	Accuracy (%)
CEA > 192 ng/mL	58.0	100.0	67.0
nCLE mucinous *vs* non-mucinous	80.0	100.0	84.0

CEA: Carcinoembryonic antigen; nCLE: Needle-based confocal laser endomicroscopy.

IOA

IOA for nCLE diagnosis was 0.76 (range: 0.65-0.86). In 15 cases (26%), there was disagreement in more than 20% of the observers, so a second revision was necessary. After the second review, the sensitivity, specificity, and accuracy were calculated for 56 patients in whom nCLE was technically feasible.

Adverse events

Six adverse events (10%) were registered: 2 cases of self-limited intracystic bleeding (in 1 SCA and 1 IPMN); 3 cases of AP (in 3 IPMNs); and 1 case of abdominal pain (in 1 IPMN). AP was classified as interstitial edematous pancreatitis according to Atlanta classification[20] and required patient hospitalization; none developed infected pancreatic necrosis or walled-off necrosis.

DISCUSSION

PCLs are a heterogeneous family of lesions; some show benign behavior and others have unequivocal malignant potential and thus are considered a precursor of pancreatic cancer. The increased use of cross-sectional imaging, CT and MRI, has increased the reporting of incidental PCLs by up to 45%[2]. A key element of optimal clinical management of PCLs is identification of the small minority of cysts with early invasive cancer or high-grade dysplasia, and possibly the prediction of patients who will develop them in the future. A major challenge is that commonly used diagnostic tools, such as CT, MRI, and EUS-FNA cytology, and intracystic CEA analysis have suboptimal sensitivities and specificities for identifying patients at high risk, especially in cases of overlapping EUS features or borderline CEA intracystic level[5].

Recently a new technique, nCLE, has demonstrated promising results in visualization of the epithelial lining of the cyst wall, and consequently in the distinction of cyst type with accuracy and specificity that has not previously been described in PCLs. However, only limited studies on this technique with limited patients are available from three select centers: one from Europe[8] and two from the United States[7,11]. Consequently, optimal results could be related to the selected cases more than to the technique's performance.

The strength of our study was that the performance of nCLE was evaluated in four different centers with high EUS volume, by experts with previous experience in confocal endomicroscopy imaging, in a non-selected group of patients referred for EUS-FNA for undetermined PCLs without PD communication as determined by previous imaging. We also excluded worrisome features and high-risk stigmata as well as solid masses to avoid biased study results. The diagnostic yield of confocal

endomicroscopy in our study has been optimal with a specificity of 100%. In a clinical setting, these data confirm the potential of this technique to classify PCLs as high and low risk of progression, and consequently, to modulate the surveillance program for these patients.

The feasibility of EUS-guided nCLE has been a subject of debate due to the use of a large needle[7]. This study showed that the feasibility of the technique is excellent in experienced hands. Our study also confirmed the safety of nCLE; indeed, the rate of post-procedure AP was slightly higher (5%) than that described by Palazzo *et al*[14] but was lower than that in another report[15]. The cases of AP were mild, and none evolved to walled-off necrosis. We postulated that prolonged examination of the cyst wall could be related to an increased risk of bleeding or debris that could enhance the risk of AP; however, this was not statistically significant.

At the time of study onset, data derived from the two recently published papers by Napoleon *et al*[12] and Krishna *et al*[13] were not available; therefore, the performance of this technique is still considered under investigation. Our results support the recently published data, showing the potential of nCLE to be used in selected patients in a clinical setting as proposed by Napoleon *et al*[12], to evaluate multiple PCLs before surgery in order to guide partial *vs* total pancreatectomy, or to assess single lesions in young women where, in case of SCA, surveillance could be discontinued.

The limitation of our study was that it was conducted in a limited study population; thus, only small numbers of final surgical diagnoses were available. This has been frequently described in PCL studies due to the surveillance approach suggested by various international guidelines, even in lesions with a high risk of progression (mucinous cystadenoma and IPMN > 3 cm)[21].

CONCLUSION

In conclusion, a few years after the first publication on nCLE in PCLs[7], this study confirms that the diagnostic yield of EUS-guided nCLE is higher than any available technique for PCL characterization, and as such is a valuable tool in PCL management.

ARTICLE HIGHLIGHTS

Research background

Some pancreatic cystic lesions (PCLs) have unequivocal malignant potential, but the precise determination of the risk of progression with endoscopic ultrasound (EUS), fine-needle aspiration (FNA), analysis of carcinoembryonic antigen (CEA) level, and cytology is still challenging. Among the novel tools for assessing PCLs, needle-based confocal endomicroscopy (nCLE) has been identified as one of the most sensitive, but some concerns have been raised about its safety and reproducibility.

Research motivation

The first clinical trials published described a correlation between nCLE and histological features, and established the criteria for characterizing the most frequent type of cysts. However, no multicenter prospective studies have been performed at the time of study conception to evaluate the safety of the procedure and interobserver agreement (IOA).

Research objectives

The purpose of this multicenter prospective study was to evaluate the diagnostic accuracy of EUS-guided nCLE to differentiate mucinous from non-mucinous in PCLs compared to standard of care, by analysis of intracystic CEA and amylase level and/or cytology *vs* surgical pathology.

Research methods

The strength of the study is its observational design in high-volume centers compared to the single-center studies previously published. All nCLE videos were independently reviewed by 6 observers blind to clinical or imaging information; each investigator provided a final diagnosis, and if the disagreement between reviewers was > 20%, videos were discussed together in order to reach a final nCLE consensus diagnosis. In the event of persistent disagreement among investigators, the videos were considered

false negatives.

Research results

A total of 59 patients were enrolled in this study to receive EUS-FNA and nCLE. The procedure was technically feasible in 95% of patients; nCLE sensitivity, specificity, and accuracy for the diagnosis of mucinous lesions were 80% [95% confidence interval (CI): 65-90], 100% (95%CI: 72-100), and 84% (95%CI: 72-92), respectively, and for distinguishing mucinous from non-mucinous lesions compared to intracystic CEA > 192 ng/mL were 58% (95%CI: 43-72), 100% (95%CI: 73-100), and 67% (95%CI: 53-78), respectively. IOA for nCLE diagnosis was 0.76, and 10% of adverse events were recorded.

Research conclusions

Our study confirmed the feasibility of nCLE and its excellent performance in the discrimination of mucinous *vs* non-mucinous lesions. This new finding confirms the possibility of an accurate pre-operative diagnosis. The strength of the study was the multicenter, prospective observational design and the selection of a study group of real undetermined pancreatic cysts without pancreatic duct communication and free of worrisome features; this was also a weakness due to the low number of cases with surgical/histological diagnosis. The excellent performance of nCLE opens various possible scenarios for the management of undetermined PCLs.

Research perspectives

Future research should include fine-needle biopsies with biopsy forceps to improve pathological diagnosis without surgery.

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CASE REPORT

Acute upper gastrointestinal bleeding caused by esophageal right bronchial artery fistula: A case report

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Abstract

BACKGROUND

Fistula between the esophagus and bronchial artery is an extremely rare and potentially life-threatening cause of acute upper gastrointestinal bleeding. Here, we report a case of fistula formation between the esophagus and a nonaneurysmal right bronchial artery (RBA).

CASE SUMMARY

An 80-year-old woman with previous left pneumonectomy and recent placement of an uncovered self-expandable metallic stent for esophageal adenocarcinoma was admitted due to hematemesis. Emergent computed tomography showed indirect signs of fistulization between the esophagus and a nonaneurysmal RBA, in the absence of active bleeding. Endoscopy revealed the esophageal stent correctly placed and a moderate amount of red blood within the stomach, in the absence of active bleeding or tumor ingrowth/overgrowth. After prompt multidisciplinary evaluation, a step-up approach was planned. The bleeding was successfully controlled by esophageal restenting followed by RBA embolization. No signs of rebleeding were observed and the patient was discharged home with stable hemoglobin level on postoperative day 7.

CONCLUSION

This was a previously unreported case of an esophageal RBA fistula successfully managed by esophageal restenting followed by RBA embolization.

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Core Tip: Esophageal bronchial artery fistula is an extremely rare cause of upper gastrointestinal bleeding. Here, we describe a previously unreported case of fistula formation between the esophagus and a nonaneurysmal right bronchial artery (RBA), in the setting of palliative esophageal metallic stenting and previous left pneumonectomy. Hemostasis was achieved by the use of esophageal restenting followed by RBA embolization.

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INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is a potentially life-threatening emergency with a reported incidence of about 100 per 100000 persons per year[1,2]. Its etiology has been divided into variceal and nonvariceal bleeding. The most common causes of acute UGIB include peptic ulcer disease and esophageal varices, followed by Mallory–Weiss syndrome and neoplasms[1-3]. Acute UGIB caused by esophageal bronchial artery fistula is extremely rare. To date, only a few cases of fistula formation between the esophagus and the right bronchial artery (RBA) have been reported worldwide. Here, we describe a previously unreported case of a fistula between the esophagus and a nonaneurysmal RBA, in the setting of palliative esophageal metallic stenting and previous left pneumonectomy.

CASE PRESENTATION

Chief complaints

An 80-year-old woman was admitted to our bleeding unit due to severe anemia (hemoglobin 7.1 g/dL) and hematemesis with signs of hemodynamic instability.

History of present illness

One episode of hematemesis with presyncope occurred 1 h prior to hospital admission.

History of past illness

The patient underwent left pneumonectomy with adjuvant chemoradiotherapy for lung cancer 6 years before. An uncovered self-expandable metallic stent (SEMS) had been placed 3 mo prior at another institution for the palliation of a locally advanced esophageal adenocarcinoma.

Personal and family history

The patient denied further medical history. There was no family history of GI cancer.

Physical examination

On presentation, the patient was hemodynamically unstable (pulse 115 bpm, blood pressure 90/60 mmHg). She was afebrile, with respiratory rate 17 breaths/min and oxygen saturation 94%. On general physical examination, she looked pale and dehydrated. Abdominal examination revealed nondistended, nontender abdomen

with normal bowel sounds. The rectal examination exhibited melena.

Laboratory examinations

Complete blood count analysis was notable for hemoglobin of 7.1 g/dL and hematocrit of 23.6%. All remaining laboratory examinations, including liver enzymes, coagulation studies and renal function tests, were within normal limits.

Imaging examinations

After blood transfusion and hemodynamic stabilization, emergent computed tomography (CT) angiography was performed showing no active GI bleeding with the esophageal stent correctly placed. The RBA appeared tortuous, dilated and tightly adherent to the thickened middle esophagus wall. Although no contrast extravasation was noted, the tissue planes between the RBA and the esophagus appeared obliterated (Figure 1).

MULTIDISCIPLINARY EXPERT CONSULTATION

After prompt multidisciplinary evaluation, involving a GI endoscopist, surgeon, and a diagnostic and interventional radiologist, a minimally invasive step-up approach with esophageal restenting followed, if necessary, by RBA embolization was planned.

FINAL DIAGNOSIS

Fistula formation between the esophagus and a nonaneurysmal RBA, in the setting of palliative esophageal metallic stenting and previous left pneumonectomy.

TREATMENT

Under fluoroscopic and direct endoscopic guidance, an over-the-guidewire partially covered SEMS was placed through the previously inserted uncovered SEMS. Immediately thereafter, diffuse esophageal bleeding controlled by the partially covered SEMS was endoscopically noted (Figure 2). On postoperative day (POD) 1, hematemesis with severe anemization (hemoglobin 5.7 g/dL) and hemodynamic instability occurred. After blood transfusion and hemodynamic stabilization, emergent CT angiography was repeated, showing the esophageal stents correctly placed with unmodified previous findings and no GI active bleeding. Esophagogastroduodenoscopy (EGD) revealed fresh blood within the esophagus and a large amount of dark blood under the partially covered SEMS, in the absence of identifiable active bleeding sites (Figure 3). Thus, operative angiography was performed. Selective RBA arteriography showed contrast extravasation within the esophagus and RBA was successfully embolized with microcoils (Figure 4).

OUTCOME AND FOLLOW-UP

Postoperative stay was complicated by the occurrence of pulmonary edema responsive to medical therapy. No rebleeding was observed and the patient was discharged home with stable hemoglobin level (9.1 g/dL) on POD 7. The patient died at home 1 mo postoperatively, in the absence of overt GI rebleeding or anemization.

DISCUSSION

Arterioesophageal fistulas (AEFs) are pathological communications between an arterial system and the esophagus, which may lead to exsanguination from massive UGIB if not recognized promptly. They develop most commonly due to aortic fistulization caused by foreign bodies, aortic aneurysm, or esophageal neoplasms[4-6]. Nonaortic AEFs have been less frequently reported, with the bronchial artery being the most commonly involved vessel. Etiology includes foreign bodies, vascular surgery and thoracic arterial malformations, and chemoradiotherapy in esophageal cancer

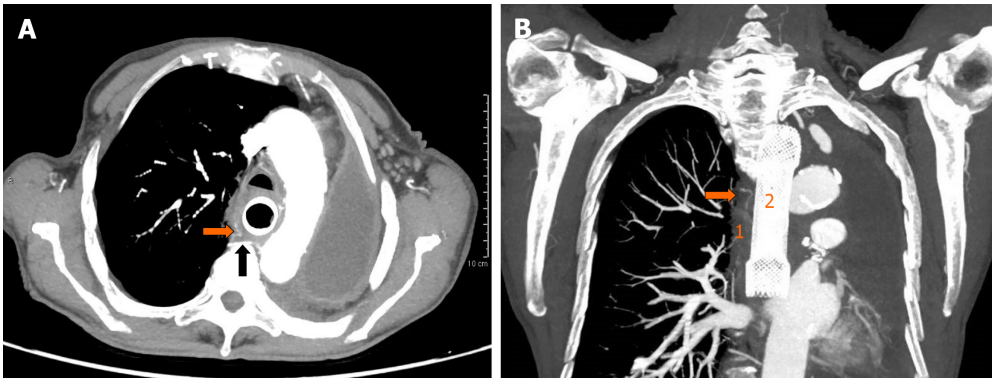

Figure 1 Arterial phase contrast-enhanced computed tomography. A: Axial view showing the tortuous and dilated right bronchial artery (orange arrow) originating from the right third posterior intercostal artery (black arrow); B: Coronal view showing delation of the tissue planes between the right bronchial artery (orange arrow) and the thickened middle esophageal wall (1), with correct placement of the esophageal metal stent (2).

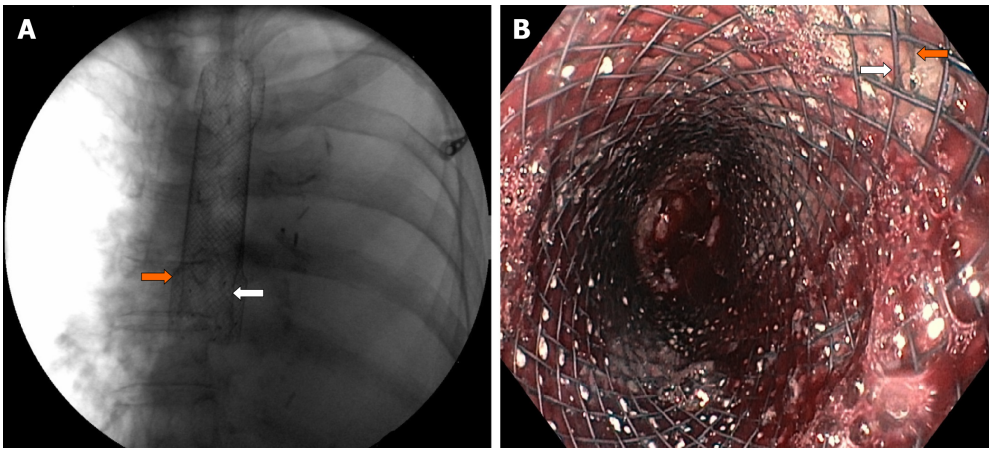

Figure 2 Placement of partially covered self-expandable metal stent (white arrow) through the previously inserted uncovered metal stent (orange arrow). A: fluoroscopic view; B: Endoscopic view showing esophageal bleeding controlled by the partially covered metal stent.

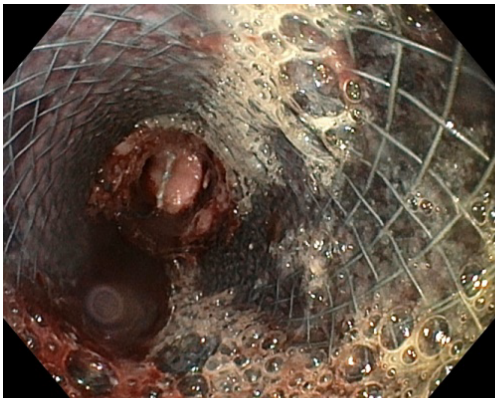

Figure 3 Second upper endoscopy showing fresh blood within the esophageal lumen and a diffuse amount of dark blood under the partially covered metal stent, in the absence of active bleeding sites.

patients with invasion of the aorta[7,8].

Although extremely rare, an esophageal RBA fistula is a potentially life-threatening condition. To date, only a few cases of fistula formation between the esophagus and a bronchial artery aneurysm have been reported. Shaer and Bashist[9] first reported a fatal case of massive UGIB due to a bronchial artery aneurysm with an esophageal fistula (BAAEF). Later on, two cases of BAAEFs successfully treated with RBA coil embolization have been reported[10,11]. In 2018, Nakada *et al*[12] reported a case of

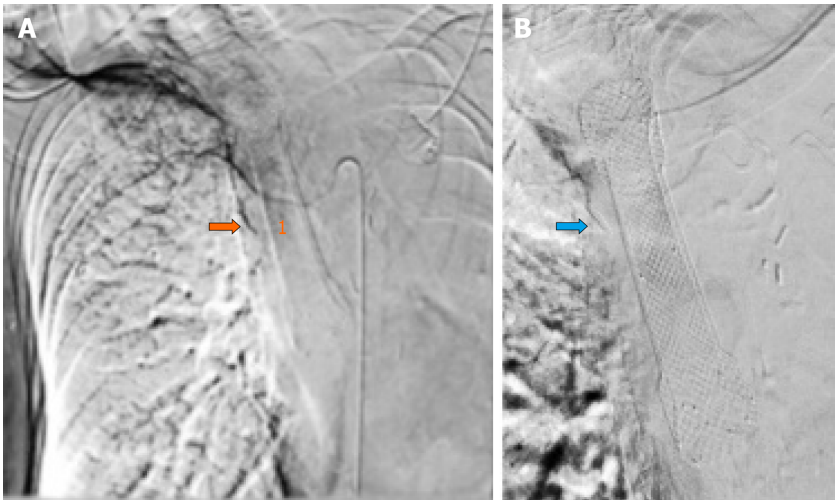

Figure 4 Operative angiography. A: Selective arteriogram of the right bronchial artery (orange arrow) showing contrast extravasation within the esophageal lumen (1); B: Right bronchial artery coil embolization (blue arrow).

BAAEF caused by bronchial arterial embolization. Due to the unfeasibility of transcatheter coil embolization, hemostasis was achieved by emergent thoracic endovascular aortic repair. Subsequently, aneurysmotomy, debridement and pedicled omental flap repair were successfully performed. Finally, a case of fistula between the esophagus and a RBA pseudoaneurysm secondary to an endobronchial ultrasound-guided transbronchial needle aspiration has been recently reported. This was successfully managed by endoscopic clipping followed by transcatheter coil embolization[13].

Moreover, only four cases of esophageal fistulas with a nonaneurysmal RBA have been reported, including three patients with locally advanced esophageal cancer and one with Mallory–Weiss tear refractory to endoscopic hemostasis. In all cases, the esophageal bleeding was successfully controlled by means of transcatheter arterial embolization[14-16].

However, to our knowledge, this is the first reported case of a fistula between the esophagus and a nonaneurysmal RBA, in the setting of palliative esophageal metallic stenting and previous left pneumonectomy.

In our case, emergent CT showed no active GI bleeding with the esophageal stent correctly placed. Although no direct signs of fistulization were observed, the RBA appeared tortuous, dilated and tightly adherent to the thickened middle esophagus wall, with obliteration of the tissue planes between the RBA and the esophagus. Subsequent emergent EGD confirmed the absence of active bleeding without identifiable bleeding sources. After prompt multidisciplinary evaluation, a minimally invasive step-up approach with esophageal restenting followed, if necessary, by RBA embolization was planned. However, after esophageal restenting, rebleeding occurred. Thus, operative angiography was performed. Selective RBA arteriography showed contrast extravasation within the esophageal lumen and RBA embolization was performed.

CONCLUSION

Digestive endoscopists should be aware of this critical, albeit extremely rare, cause of UGIB, in order to provide prompt diagnosis and treatment. In our opinion, early diagnosis, multidisciplinary evaluation and prompt tailored treatment seem to be crucial for the proper management of an esophageal RBA fistula.

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