



# Candidemia after endoscopic therapy with lumen-apposing metal stent for pancreatic walled-off necrosis

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## Abstract

Necrotizing pancreatitis remains a challenging and unpredictable condition accompanied by various complications. Endoscopic ultrasound-guided transmural drainage and necrosectomy have become the standard treatment for patients with walled-off necrosis (WON). Endoscopic therapy via lumen-apposing metal stents (LAMS) with large diameters has shown success in the management of pancreatic fluid collections, but there are few data on specific complications of that therapy. We report a case of infected WON and concomitant fungemia following LAMS placement and necrosectomy. In addition, a systematic literature review of current related studies has been provided.

**Keywords** Necrotizing pancreatitis · Walled-off necrosis · Endoscopic necrosectomy · Candida

## Introduction

Necrotizing pancreatitis is defined as necrosis of pancreatic and/or peripancreatic tissue that occurs in 5–10% of patients with acute pancreatitis [1]. The extent and natural history of resulting necrosis may vary from spontaneous resolution to liquefaction and formation of an acute necrotic collection (ANC) which can mature into a walled-off necrosis (WON). Secondary infection of such collections is reported to occur in 30–70% of cases with a high mortality burden of up to 32% or higher if accompanied by organ failure [2, 3]. The role of endoscopic interventions in the management of infected WON has been established in recent years with clear advantages over percutaneous and surgical methods [4, 5]. Direct endoscopic necrosectomy (DEN) is now increasingly used in light of reports showing favorable outcomes [6]. This technique allows drainage and endoscopic debridement of necrotic tissue through the gastric or duodenal wall. DEN has even shown to achieve higher rates of resolution compared with standard endoscopic drainage method [7]. The use of novel lumen-apposing metal stents (LAMS), specifically developed to facilitate

the performance of necrosectomy and drainage of necrotic debris is on the rise with contradicting results in several published reports on its efficacy and safety [8–13]. Most commonly described adverse events (AE) include infection, stent migration or occlusion and delayed bleeding [9]. Fungal infections of WON present an uncommon severe complication of necrotizing pancreatitis associated with increased morbidity and mortality and are particularly challenging to manage [14, 15]. Patients with concomitant fungemia have a significantly higher mortality in comparison to patients with fungal-infected necrosis only [16]. We present the case of a 56-year-old man with infected WON and concomitant fungemia following LAMS implantation.

## Case report

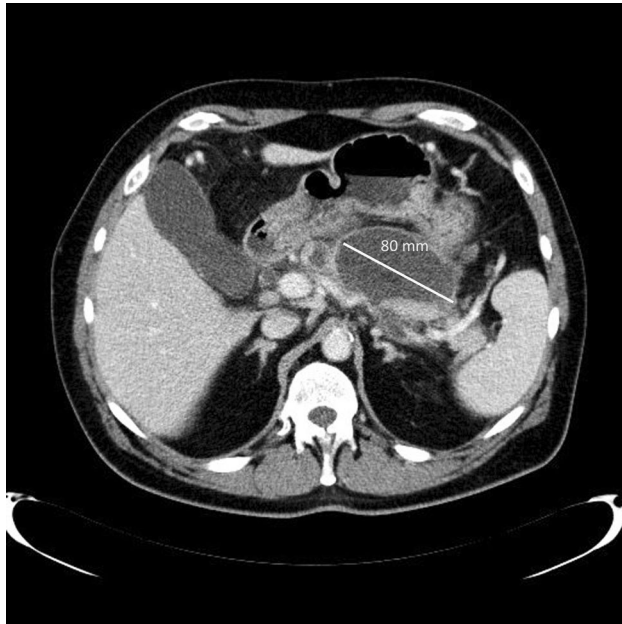
A 56-year-old white male was admitted to the emergency department presenting with abdominal pain and fever. Two months earlier he had been treated in our hospital for severe acute biliary pancreatitis complicated by the development of an ANC. After supportive and antibiotic treatment he had been discharged from the hospital in good clinical condition with a recommendation for an elective cholecystectomy. Three weeks prior to this hospitalization he had been readmitted for abdominal pain and fever. Computed tomography (CT) of the abdomen revealed the presence of the necrotic collection adjacent to the pancreatic body measuring 7.4 cm.

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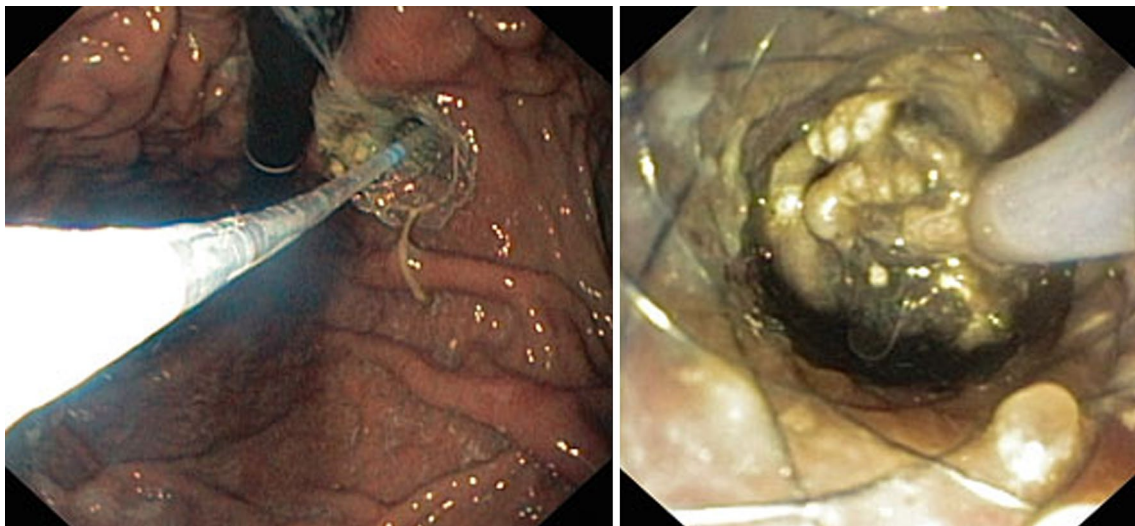
He had received supportive treatment, infection of the collection had not been established and he had been discharged after prompt clinical improvement.

Presently, laboratory parameters upon admission to the interventional gastroenterology unit revealed leukocytosis ( $22.7 \times 10^9/L$ ), elevated C-reactive protein (140 mg/L) and a serum lipase level of 190 U/L. The APACHE II score on admission was 10, SAPS II score 16. The CT scan of the abdomen revealed a WON in the area of the pancreatic body and tail to an extent of  $8 \times 6$  cm (Fig. 1). Blood cultures



**Fig. 1** CT scan of the abdomen showing walled-off necrosis in body and tail of the pancreas  $8 \times 6$  cm

were drawn and empiric antibiotic treatment (amoxicillin/clavulanic acid, metronidazole) was initiated. Due to clinical signs of ongoing sepsis and clinical suspicion of infected WON, the decision was made to attempt endoscopic drainage. Endoscopic ultrasound (EUS)-guided drainage was performed after the initial puncture of the collection with 19-gauge needle and aspiration of the content for microbiological, biochemical and cytological analysis. After leaving the guide wire in the collection, an 8-mm guide wire-guided balloon was used to dilate the cystogastrostomy fistula tract and a LAMS was advanced into the cyst cavity (Nagi™ Stent, Taewoong Medical Co., South Korea; 2 cm, 10 Fr). A sample of the necrotic collection revealed a contamination with *Candida* spp. and antimycotic treatment with fluconazole was initiated. Repeated blood cultures came back negative. Four days after stent placement no significant clinical improvement was noted with a persistent collection seen on transabdominal ultrasound. Following the step-up approach we then proceeded with endoscopic necrosectomy which was repeated three times over the following 8 days accompanied by repeated nasocystic lavage using saline, all of which led to a significant reduction of the necrotic collection on control transabdominal ultrasounds (Fig. 2). Despite antifungal treatment, antibiotics and interventional therapy the patient was still septic with intermittent fever relapses and elevated inflammation parameters. One week after endoscopic drainage paired blood cultures came back positive for coagulase negative *Staphylococcus* while a mixed flora was found in the necrotic material after first necrosectomy (*Candida albicans*, coagulase negative *Staphylococcus*, *S. viridans*, *Enterococcus* spp., *Bacteroides* spp., *Peptostreptococcus* spp., *Escherichia coli*, *Fusobacterium* and *Prevotella* spp.). Based on the antibiogram and



**Fig. 2** Endoscopic picture of necrosectomy procedure

after consulting a clinical pharmacologist, targeted therapy was continued with vancomycin, piperacillin and tazobactam, along with fluconazole. The central venous catheter (CVC) was replaced and the tip came positive for coagulase negative *Staphylococcus*. On the day the third necrosectomy was carried out paired blood cultures were taken from which *Candida parapsilosis* was successfully isolated, as well as from the tip of the subsequently extracted CVC. The follow-up CT scan (11 days after stent placement) confirmed a regression of the necrotic collection measuring now 3 cm in diameter and a splenic infarction with thrombosis of the lienal vein (Fig. 3). The regression of inflammation parameters was first observed 12 days after stent placement and 4 days after the last necrosectomy procedure. The disease course was additionally complicated by a right-sided pneumonia and acute congestive heart failure, but the patient's condition did not require ventilator support and cardiac ultrasound did not reveal signs of endocarditis. Sputum came back positive for *Candida* spp. Patient also suffered an acute gout attack which was treated with indomethacin. Three weeks after admission gradual clinical improvement was observed with inflammation parameters coming to normal levels and the patient was transferred to a gastroenterology ward for further observation and therapy. The final abdominal ultrasound before discharge revealed a small residual hypoechogenic area measuring 2 cm in diameter. Through a combination of enteral and parenteral nutrition the patient lost only 3 kg of body weight during the entire treatment period. One month after discharge the patient had normal laboratory values and



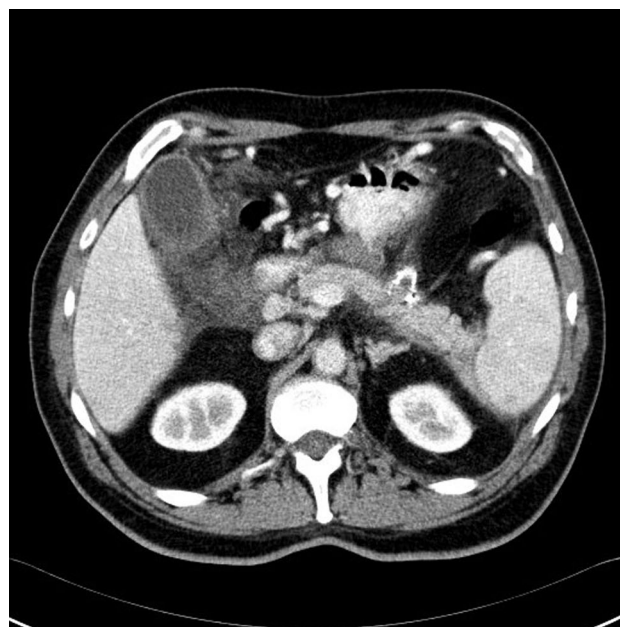
**Fig. 3** CT scan of the abdomen 11 days after stent placement showing regression of the necrotic collection in the pancreas, splenic infarction with thrombosis of the lienal vein

a CT scan revealed full regression of the necrotic collection (Fig. 4). LAMS extraction was planned, but the patient developed acute cholecystitis and laparoscopic cholecystectomy was performed. Postoperatively no further complications were observed, and 9 days later the stent was extracted without complications, 75 days after its placement. At 2 and 6 month follow-up visit the patient was in a good clinical condition, without abdominal pain or fever, with normal laboratory values and imaging procedures.

## Discussion

Data on complications of DEN using LAMS in fungal-infected pancreatic WON are scarce. This challenging clinical scenario with a complete recovery against unfavorable odds prompted us to research the available literature on the role of antibiotic treatment, microbiological culturing and advancements in interventional endoscopy in the management of WON infection.

Infection of WON is a severe complication of acute necrotizing pancreatitis associated with high mortality rate of 32% [3]. The presence of bacteraemia in these cases drives mortality rates even higher and is an independent risk factor for WON infection [17]. On the other hand, fungal infections in necrotizing pancreatitis are less common, ranging between 5% and almost 70%, with conflicting reports on its impact on mortality [18–20]. According to reports from some authors fungemia concomitant to fungal finding in necrosis occurs in approximately 26% of cases, and



**Fig. 4** CT scan of the abdomen prior to stent extraction revealing full regression of the necrotic collection

has been associated with a mortality rate of up to 50% [16, 18]. A group of authors from Denmark recently reported on their experience in managing fungal infections [16]. This retrospective study included 123 patients with WON treated with endoscopic drainage and necrosectomy during an 8-year period. Fungi in necrosis were found in 57 (46%) patients at some point of treatment of which 20 had fungi at index endoscopy. Ninety percent received prior antibiotic treatment. No significant difference in mortality, organ failure development, or need for intensive care unit treatment between patients with monofungal or multifungal (14%) or between primary or secondary fungal infection was found. Concomitant fungemia was found in 6 patients with a mortality rate of 50% vs. 14% in those with fungi in necrosis only. Local instillation of amphotericin B was used in 11 patients (6 concomitantly received systemic therapies) with no significant difference in mortality compared to those treated with systemic antifungals. The authors highlight the importance of repeated culturing in this group of patients for driving targeted antifungal treatment and question the role of antifungal prophylaxis advocated by some [21].

Several authors emphasize the importance of continuous microbiological culturing in infected WON because the rates of positive findings in subsequent endoscopic interventions tend to increase [16, 18]. Werge et al. found additional 24 positive fungal findings at second and 9 at third endoscopy [17]. In their study of the microbiological spectrum of infected WON in patients undergoing DEN, Schmidt et al. found fungi in 22% of cases and noted that polymicrobial finding were more common at second and third endoscopy. Same or additional microbes were found in the majority of patients despite targeted antibiotic treatment as well as a relatively high number of CVC positive cultures [18].

In our case *Candida* spp. was cultured from the initially obtained material as well as in all subsequent materials obtained during necrosectomies. Fungemia was detected in paired blood cultures taken on the day of the third DEN, with an additional finding of *Candida* spp. positive CVC culture, despite concomitant fluconazole treatment. The first study to evaluate the microbiological spectrum in patients with WON treated with DEN described fungemia in 8 out of 78 patients, and the presence of enterococci and fungi at the index endoscopy was significantly associated with in-hospital mortality (44% vs. 12%,  $p = 0.01$ ) [18]. Out of 12 patients diagnosed with fungi at index endoscopy, 10 patients received antifungals between the index and second endoscopy, and in only one patient fungi were identified at second endoscopy. Given the retrospective nature of that study, it was impossible to correlate the blood culture findings to necrosectomy procedures, as we have clearly proved in our case. The concept of DEN raises a concern of super infection due to the nature of intervention during which, in the attempt to remove

necrotic pancreatic tissue, small blood vessels may be exposed and pre-existent microorganisms introduced into the bloodstream. LAMS have allowed us to perform more aggressive direct approach on larger collections due to the ease of performing debridement. Siddiqui et al. recently in a retrospective study compared the efficacy of FCSEMS (fully coated self-expanding metal stents) and LAMS in WON and found no significant differences in early infection rates. There was, however, a marked difference in late infection rates (21.5 vs. 3.5%) resulting from the much higher rate of stent occlusion occurring in the FCSEMS treated group [13].

Current guidelines detract from antibiotic use in acute pancreatitis but the issue is not yet settled due to the lack of quality trials [1]. A clear association between the prior use of antibiotics and subsequent fungal infection has been established by multiple authors [18, 20, 22]. The patient in our case was started on empiric antibiotic treatment on admission, but failed to improve until targeted therapy (anti-microbial and endoscopic) was initiated. Furthermore, some studies raise a question of efficacy of systemic antibiotics in the treatment of infected WON since the majority of patients have the same or additional microorganisms in subsequent necrotic cultures despite targeted antibiotic treatment [18]. The clinical significance of candidemia detected while our patients was on antifungal therapy is unequivocal since we have proven *Candida* in his sputum while diagnosing pneumonia (there is also a possibility that splenic infarction described on CT scan was a consequence of septic embolus, not proven, however).

With an increased number of clinicians adopting the step-up approach to WON management, advocated by current guidelines which emphasize the role of endoscopic drainage and necrosectomy, the topic of AE arising from such procedures is self-imposing. The increased availability, relative ease of use, as well as novel deployment methods of LAMS are likely to drive their use and increase the volume of interventional procedures performed and accompanying associated complications. Even though the results of several author groups find the use of LAMS safe and effective, other authors question these findings. The AE events reported so far have included infections, stent migration/occlusion and bleeding. In a review by Patil et al. a high success rate and few adverse outcomes with the use of the AXIOS™ stent (Boston Scientific, USA) have been reported [8]. Sharaiha et al. in their retrospective multicenter study on the use of LAMS in 124 patients with WON noted generally low rates of AE with 4 cases of early and 3 cases of late super infection, respectively [9]. Bang et al. performed a retrospective case–control study in which they found no efficacy or safety advantages to LAMS over plastic stents in WON with an overall rate of 11.7% for post-procedural infections [10]. Table 1

**Table 1** Infectious adverse events in PFC drainage using LAMS

Study	N (WON/PC)	AE (%)	Infection (%)
Walter et al. [23]	46/15	9.0	6.5
Shah et al. [24]	11/22	15.2	3.3
Bang et al. [10]	13/7	20	10
Sharaiha et al. [9]	124/0	18.5	5.6
Rinninella et al. [25]	75/18	5.4	1.1
Vazquez-Sequeiros et al. [26]	99/112	21.0	11.0
Lakhtakia et al. [27]	205/0	3.9	–
Siddiqui et al. [13]	86/0	16.2	4.6
Han et al. [28]	608/204	10.1	3.6

PFC pancreatic fluid collections, LAMS lumen-apposing metal stents, WON walled-off necrosis, PC pseudocyst, AE adverse events

summarizes AE in pancreatic fluid collections (PFC) drainage using LAMS and highlights rates of infectious complications [9, 10, 13, 23–28].

The standardization and safety considerations of DEN in WON are of particular interest and a standardized management plan is yet to be defined. In a recent study by Thompson and co-workers involving 60 consecutive patients with WON undergoing a newly developed standardized care assessment and management plan (SCAMP) for DEN found lower rates of AE than reported in previous larger series. The authors used only balloon dilation and plastic stents with an 86% rate of clinical resolution and an excellent safety profile. This was a single-centre single-operator study based on an optimized patient selection which could limit the reproducibility of these very promising results, but could represent a great step forward in developing consistent recommendations for these procedures [29].

As the field of interventional endoscopy leaps forward embracing new technologies, based on their promise to facilitate management of this challenging group of patients, the need for a standardized approach based on quality randomized trials arises.

In conclusion, patients with infected WON require a focused and strategized management regarding supportive treatment, timing of drainage, decision to perform and repeat necrosectomy, accompanied by repeated microbiological culturing as well as timely and targeted antimicrobial and supportive therapy. The potential for fatal septic and bleeding complications following more “aggressive” endoscopic necrosectomy facilitated by LAMS is something to be aware of when deciding on the course of treatment.

### Compliance with ethical standards

**Conflict of interest** Tajana Pavic, Davor Hrabar, Dominik Kralj, Ivan Lerotic and Doris Ogresta declare that they have no conflict of interest.

**Human rights** All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Informed consent** Informed consent was obtained from all patients for being included in the study.

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