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ORIGINAL ARTICLE

Non-occlusive Mesenteric Ischemia as a Fatal Complication in Acute Pancreatitis: A Case Series

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Abstract

Background Vascular complications of severe acute pancreatitis are well known and largely described unlike non-occlusive mesenteric ischemia, which is a rare and potentially fatal complication. Non-occlusive mesenteric ischemia is an acute mesenteric ischemia without thrombotic occlusion of blood vessels, poorly described as a complication of acute pancreatitis.

Methods We retrospectively reviewed a prospectively maintained registry of all pancreatic diseases referred to our center from 2013 to 2018, in order to determine the causes of early death. We identified three patients who died within 48 h after hospital admission from severe acute pancreatitis complicated by irreversible non-occlusive mesenteric ischemia. Their clinical presentation, management, and outcomes were herein reported.

Results Three consecutive patients with severe acute pancreatitis developed non-occlusive mesenteric ischemia within the first 5 days after onset of symptoms and died 48 h after non-occlusive mesenteric ischemia diagnosis despite optimal intensive care management and surgery, giving a prevalence of 3/609 (0.5%). Symptoms were unspecific with consequently potential delayed diagnosis and management. High doses of norepinephrine required for hemodynamic support ($n=3$) potentially leading to splanchnic vessels vasoconstriction, transient hypotension ($n=3$), and previous severe ischemic cardiomyopathy ($n=1$) could be involved as precipitating factors of non-occlusive mesenteric ischemia.

Conclusion Non-occlusive mesenteric ischemia can be a fatal complication of acute pancreatitis but is also challenging to diagnose. Priority is to reestablish a splanchno-mesenteric perfusion flow. Surgery should be offered in case of treatment failure or deterioration but is still under debate in early stage, to interrupt the vicious circle of intestinal hypoperfusion and ischemia.

Keywords Acute necrotizing pancreatitis · Non-occlusive mesenteric ischemia · Fatal outcome · Acute abdomen · Peritonitis · Second-look surgery

Abbreviations

AMI	Acute mesenteric ischemia
AP	Acute pancreatitis
ARDS	Acute respiratory distress syndrome
CK	Creatine kinase
CRP	C-reactive protein
ERCP	Endoscopic retrograde cholangiopancreatography
IAP	Intraabdominal pressure
ICU	Intensive care unit
KDIGO	Kidney Disease Improving Global Outcomes
LDH	Lactate dehydrogenase
mCTSI	Modified computed tomography severity index
MDCT	Multi-detector computed tomography
MOF	Multiple organ failure
NOMI	Non-occlusive mesenteric ischemia
SAPS 3	Simplified Acute Physiology Score 3
SOFA	Sepsis-related Organ Failure Assessment
VAC	Vacuum-assisted closure
VV-ECMO	Veno-venous extracorporeal membrane oxygenation

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Introduction

Acute pancreatitis (AP) is a potentially lethal disease, with an annual incidence of 13–45 cases per 100,000 inhabitants [1]. Gallstones and alcohol misuse are the main risk factors for AP [2, 3]. Approximately 20% of AP are moderate to severe with pancreatic necrosis and/or organ failure. The overall mortality of patients with AP is 5%; but it reaches 30% in case of severe AP with persistent organ failure [4, 5].

Most common vascular complications of AP include thrombosis of the spleno-porto-mesenteric venous axis, arterial thrombotic occlusion, pseudoaneurysms, and direct erosion of an artery causing hemorrhage [6, 7]. Non-occlusive mesenteric ischemia (NOMI), defined as an acute mesenteric ischemia (AMI) without thrombotic occlusion of blood vessels, could involve all abdominal organs and the whole gastrointestinal tract (from the esophagus to the rectum) but is underreported as a complication of AP [8]. NOMI represents only 20% of all AMI cases [9] but has a very high mortality rate of 70 to 90% [10], mainly because of delayed diagnosis or misdiagnosis.

In this case series, we aimed to identify all patients with acute pancreatitis complicated by NOMI, present their clinical characteristics, and describe their outcomes.

Materials and Methods

Data regarding adult patients suffering from a first episode of moderate-to-severe AP and admitted at Erasme Hospital, Brussels, Belgium, between January 2013 and December 2018 were retrospectively retrieved from a prospectively maintained registry of all pancreatic diseases referred to our institution. Moderate-to-severe AP was defined as at least one of the following criteria: pancreatic parenchymal necrosis $\geq 30\%$, intensive care unit (ICU) admission, and total hospital stays ≥ 10 days. Time 0 (T0) was considered as the day at onset of AP symptoms (typical abdominal pain with back irradiation). Early death was defined as death occurring ≤ 7 days after T0 and late death as death occurring > 7 days after T0.

Patients with acute recurrent pancreatitis, acute on chronic pancreatitis or neoplasia-related acute pancreatitis, were excluded as well as patients younger than 18 years old, pregnant women, and patients admitted to our center later than 7 days after the onset of symptoms.

AP severity was graded according to Balthazar classification [11] and modified computed tomography severity index (mCTSI) [12]. Acute kidney injury was staged for severity according to the Kidney Disease Improving Global Outcomes (KDIGO) recommendations [13].

Mesenteric ischemia was proven by macroscopic evaluation during exploratory surgery or was strongly suspected on the basis of clinical and biological manifestations combined to contrast-enhanced abdominal multi-detector computed tomography (MDCT) findings. The MDCT early features of NOMI were mainly distended bowel segments with paper thinned wall showing reduced or absent enhancement in venous phase, in the absence of any mesenteric fat abnormality or vascular occlusion. CT angiography reconstructions could show irregularity in caliber and reduced conspicuity of arterial mesenteric distal branches of the affected bowel segments. In the late phase, bowel wall pneumatosis, portal venous gas, ascites, and pneumoperitoneum could appear as signs of transmural necrosis [14].

The study was approved by the Ethic Committee of the Erasme University Hospital (Brussels, Belgium) (A2019/016, 22/01/2019). Since this is a retrospective study collecting an anonymized dataset, applicable Belgium law does not require written, informed consent. The study conforms to the ethical guidelines of the 1964 Helsinki Declaration and its later amendments.

Results

Among 1771 patients included in the pancreatic diseases registry, 609 (34.4%) were diagnosed with an AP. A total of 63 patients (10.3%) fulfilled inclusion and exclusion criteria and were classified as moderate-to-severe AP. Among them, 9 patients died early (≤ 7 days after T0) and 3 (4.8% of moderate-to-severe AP patients) of them presented a NOMI (Fig. 1). The remaining causes of early deaths in our study were sudden cardiac arrest/post-anoxic encephalopathy ($n=2$), septic shock secondary to post-endoscopic retrograde cholangiopancreatography (ERCP) duodenal perforation ($n=1$), brain death following intracerebral hemorrhage ($n=2$), and hypoxic respiratory arrest post-bronchial inhalation ($n=1$).

Case Presentations

Case 1

A 71-year-old man presented to the emergency department of another institution, 8 h after the onset of intense persistent epigastric pain, radiating to the back. Pain visual analogue scale was 8/10. Severe biliary AP was diagnosed based on laboratory data (lipasemia > 3000 IU/L), imaging as MDCT demonstrated a grade E AP according to Balthazar classification with extended necrosis (mCTSI at 10/10) and abdominal ultrasound revealed gallbladder stones. The patient was transferred to our hospital on day 2 after onset

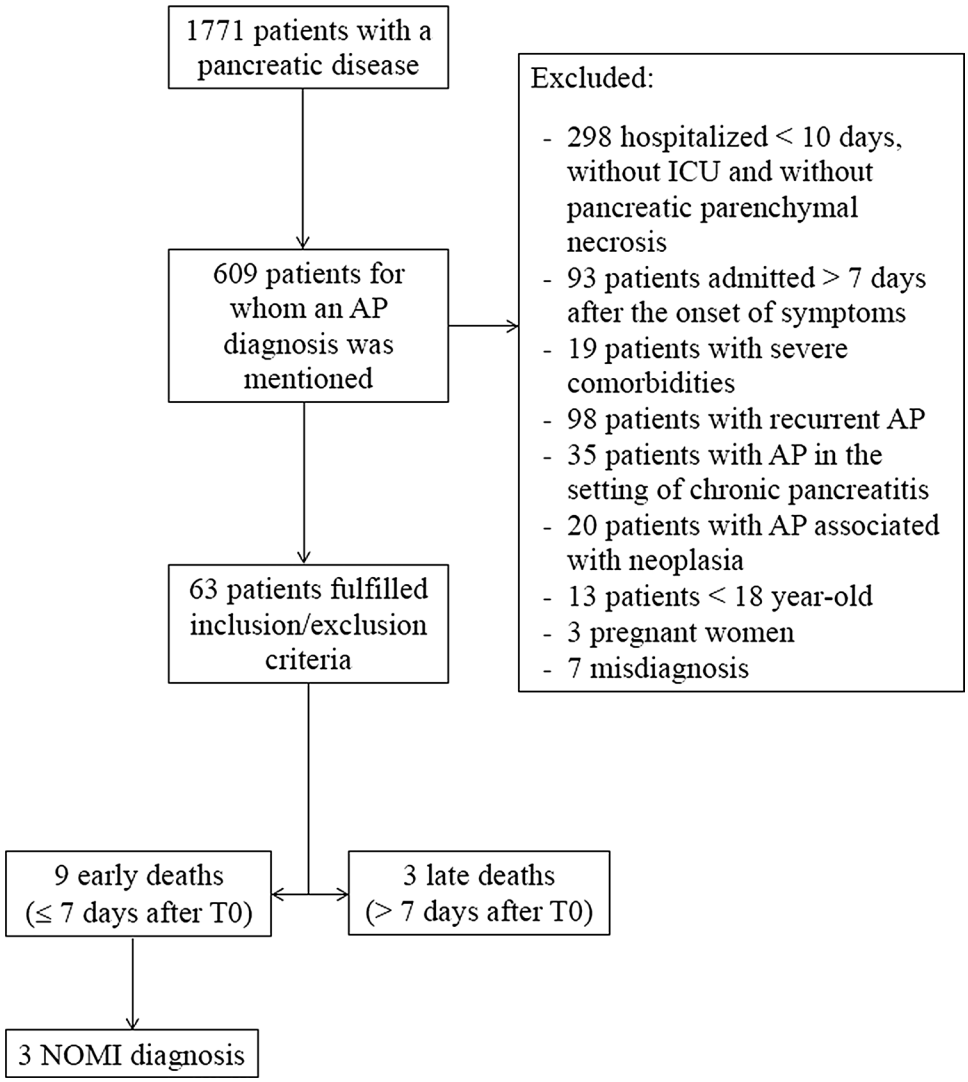

Fig. 1 Flowchart of our study. From 1771 patients admitted for a pancreatic disease, 609 patients had an acute pancreatitis (AP) mentioned in the pancreatic diseases registry (01.01.2013–31.12.2018). Sixty-three patients fulfilled inclusion and exclusion criteria among whom 9 died within 7 days after T0. Three patients died 48 h after Non-Occlusive Mesenteric Ischemia (NOMI) diagnosis

of pain, following ERCP and biliary sphincterotomy failure. Soon after his admission, the patient presented rapid clinical deterioration with hypoxemia and arterial hypotension. He was transferred to the ICU. At this time, laboratory investigation revealed a C-reactive protein (CRP) at 360 mg/L (normal value < 10 mg/L), creatine kinase (CK) at 463 U/L (normal values 39–308 U/L), lactate dehydrogenase (LDH) at 1756 U/L (normal value < 225 U/L), and arterial lactatemia at 6.7 mmol/L (normal value < 2 mmol/L). Hypernatremia (148 mmol/L; reference range 135–145 mmol/L) and increased hematocrit (47.9%; reference range 39.5–52.1%) suggested significant dehydration.

Sepsis-related Organ Failure Assessment (SOFA) score [15] (reference range 0–24) and Simplified Acute Physiology Score 3 (SAPS 3) [16] (reference range 0–217) were at 16 and at 70, respectively. Intraabdominal pressure (IAP) was not measured. Antibiotics (amoxicillin–clavulanic acid and amikacin) were started urgently. Circulatory shock was refractory to best hemodynamic optimization (volemic expansion with crystalloid solutions) and required increasing dose of norepinephrine up to 80 mcg/min (1 mcg/kg/min) to maintain a mean arterial pressure above 65 mmHg. The ongoing clinical deterioration prompted us to perform a second abdominal contrast-enhanced MDCT, which confirmed the severe AP with necrosis of more than 80% of the pancreatic parenchyma with the presence of several peripancreatic fluid collections (Fig. 2a). Moreover, it was suggestive of NOMI with reduced enhancement of several small bowel loops and reduced transverse, left and sigmoid colon enhancement, associated with a parietal thinning (Fig. 2b). Neither parietal pneumatosis nor hepatic portal vein gas, or sign of venous or arterial thrombosis was present, but there were ischemic loci in the left lobe of the liver, reinforcing the hypothesis of a generalized perfusion deficit. After multidisciplinary meeting, the patient underwent an exploratory laparotomy on the morning of day 3. The small bowel was judged viable, and no intestinal resection was performed. The abdomen was temporarily closed

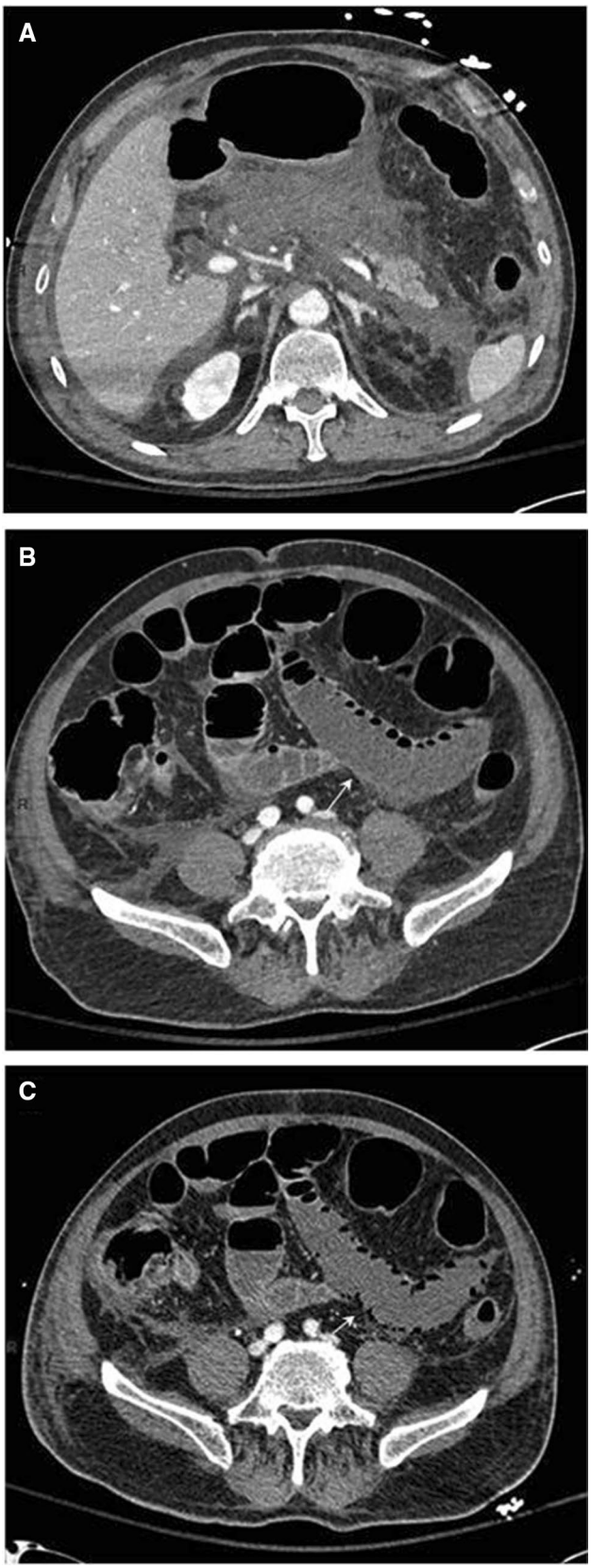

Fig. 2 **a** Case 1. MDCT in portal venous phase showing signs of severe AP with necrosis of more than half of the gland and peripancreatic fat necrosis. **b** Case 1. Same examination as (**a**) showing thinning ileal wall in the left hemiabdomen with reduced enhancement (arrow) compared to the adjacent loop. **c** Case 1. Repeated MDCT scan 8 h later showing the absence of parietal enhancement in the affected ileal loop and the appearance of wall pneumatosis (arrow)

with a vacuum-assisted closure (VAC) system to prevent abdominal compartmental syndrome. Despite optimal ICU management including veno-venous extracorporeal membrane oxygenation (VV-ECMO) therapy for severe acute respiratory distress syndrome (ARDS) and refractory hypoxemia, the patient's condition further deteriorated. MDCT was repeated, showing an aggravation of the NOMI features with the absence of parietal enhancement of ileal and colonic loops and parietal pneumatosis of the affected ileum (Fig. 2c). A second-look laparotomy performed 12 h after the first surgical exploration showed severe intestinal ischemia with necrosis of the small bowel and total colonic necrosis. Major resections were performed: 20 cm of necrotic small intestine and total colectomy with terminal ileostomy. Abdominal closure was not feasible, and again a VAC device was placed. Despite surgical treatment, multiorgan failure worsened and the patient died on day 4 from pain onset and < 48 h after his admission in our hospital.

Pathological examination reported acute focal transmural ischemia of the colon and the proximal ileal segment with signs of acute peritonitis. Small bowel examination displayed acute ischemia localized to the mucosa and the submucosa associated with features of acute peritonitis (Fig. 3a).

Autopsy confirmed AP with steatonecrosis and acute peritonitis. Moreover, calcified atherosclerosis of abdominal aorta was observed in addition to atheromatosis of the coronary arteries.

Case 2

A 68-year-old woman was admitted to the emergency department of our hospital with acute retrosternal pain evolving for a couple of hours and appearing after eating a normal breakfast. Progressively, the patient reported nausea and vomiting, while the pain was localized on the epigastrium radiating to the right hypochondrium. The diagnosis of AP (lipasemia > 3000 IU/L) of biliary origin (gallbladder microlithiasis visualized at abdominal ultrasonography) was established. Standard management of AP with fluid resuscitation, painkillers, and fasting was initiated in the ward, but the patient had to be transferred to the ICU on day 2 because of abdominal defense and acute renal failure. SOFA and SAPS 3 scores were at 9 and at 68, respectively.

At her arrival in the ICU, the patient suffered from lactic acidosis (pH 7.28, pCO_2 33 mmHg, lactates 6.0 mmol/L)

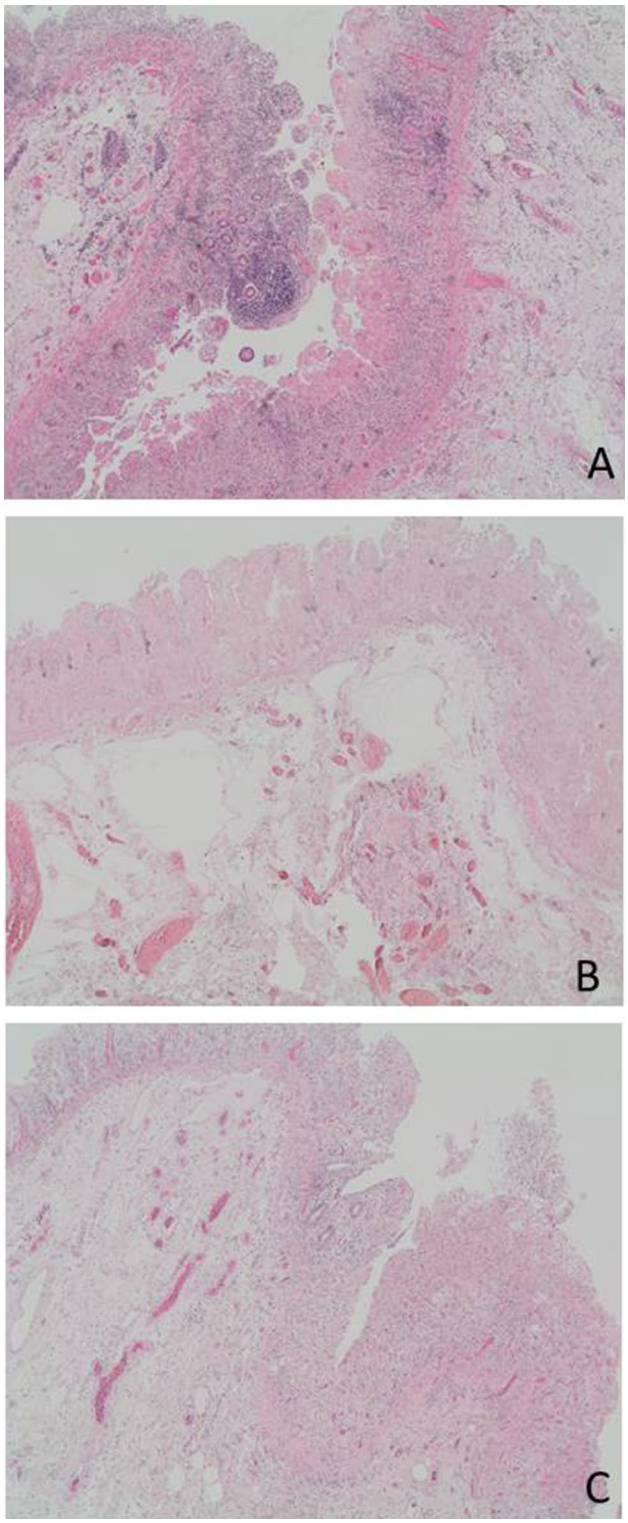

Fig. 3 Pathological examination of the intestinal resections specimen showed similar changes for the 3 cases (**a**–**c**), characterized by a ghost aspect of the mucosa and necrosis (Hematoxylin–Eosin, original magnification × 4)

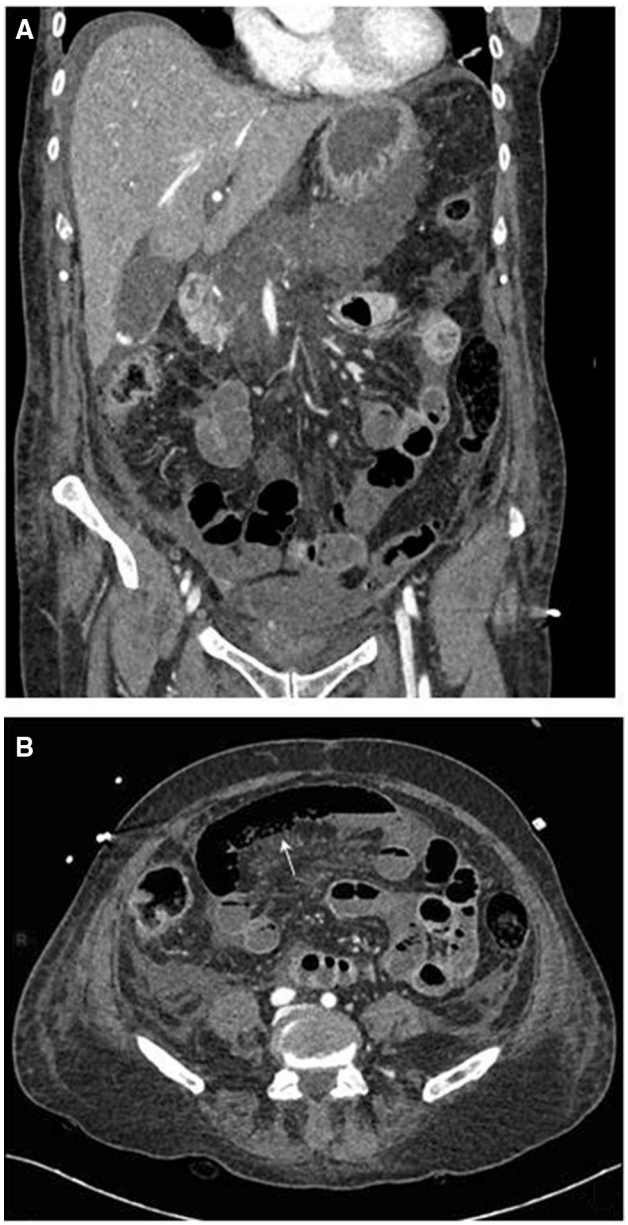

Fig. 4 **a** Case 2. MDCT in portal venous phase showing signs of severe acute pancreatitis with nearly total necrosis of the gland. **b** Case 2. Same MDCT examination showing signs of small bowel ischemia with paper thinned wall, no enhancement, and wall pneumatosis (arrow)

and acute renal failure (KDIGO stage 1). CRP and LDH were at 260 mg/L and at 746 U/L, respectively.

Hematocrit and natremia were within normal range (38.5% and 142 mmol/L, respectively).

The abdominal contrast-enhanced MDCT demonstrated severe AP (mCTSI at 10/10) with peripancreatic mesenteric collections and peritoneal effusion (Fig. 4a). Based on lack of wall enhancement of several ileal loops and the presence of bowel wall pneumatosis, AMI was suspected, with no

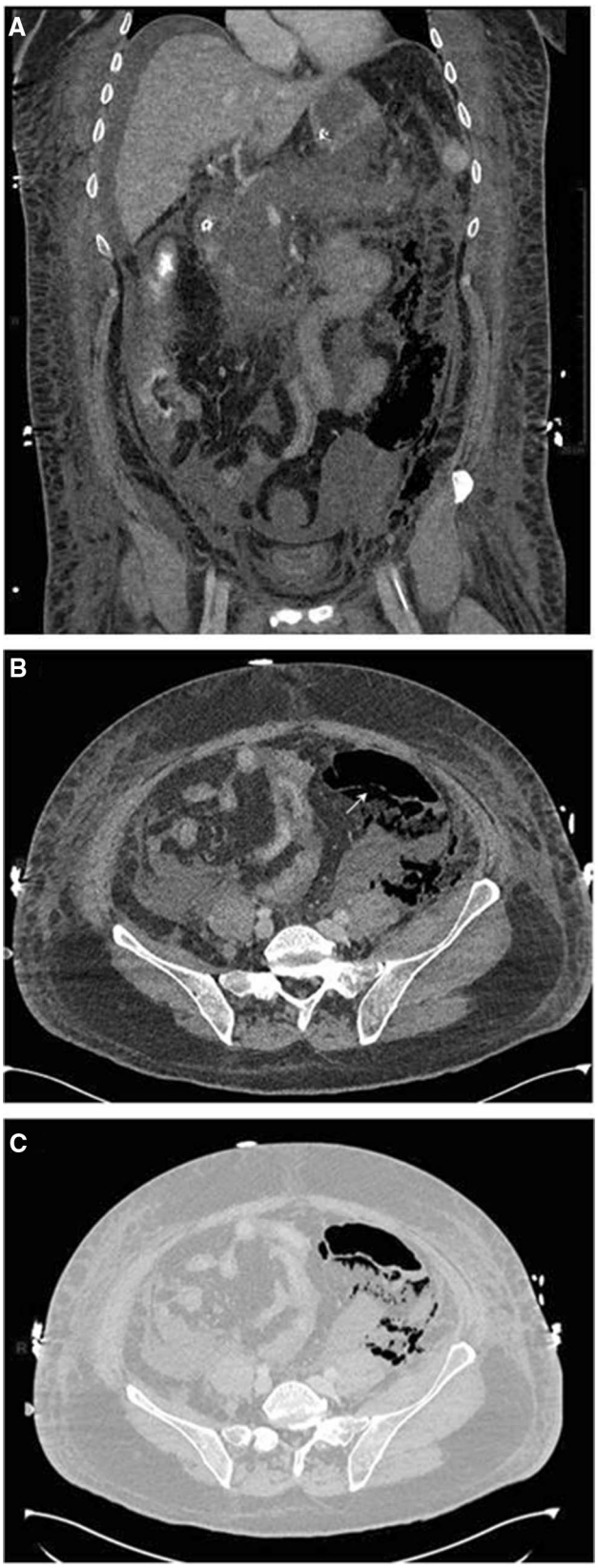

Fig. 5 **a** Case 3. Coronal view of MDCT in portal venous phase ▶ showing signs of acute necrotic pancreatitis with periglandular infiltration, ascites, and free intraperitoneal air in the left flank. **b** Case 3. Same examination in the axial plane showing extremely thinned sigmoid wall (arrow) with pneumatosis and adjacent pneumoperitoneum. **c** Case 3. Same image as in (**b**) with window setting enhancing low density structures such as air, better displaying distribution of the pneumoperitoneum

sign of venous or arterial thrombosis (Fig. 4b). IAP was not measured. Despite antibiotic therapy based on amoxicillin–clavulanic acid, the patient developed a circulatory shock needing an initial dose of norepinephrine 34 mcg/min (0.4 mcg/kg/min) and rapidly deteriorating, which prompted surgical exploration on day-3. Laparotomy confirmed the presence of extensive mesenteric ischemia, requiring resection of more than one meter of small bowel and part of the colon. Within the first 12 postoperative hours, a second-look surgery was required because of further clinical deterioration; the remaining intestine was found necrotic and beyond therapeutic possibilities. The patient died on day-4 after the symptoms onset. On histopathological examination, the ileocaecal resection specimen revealed focal transmural ischemia of both small bowel and colon associated with acute peritonitis (Fig. 3b).

Case 3

A 59-year-old man was admitted in another institution for AP of undetermined etiology. The patient had undergone cholecystectomy 6 years previously and did not consume any alcohol, while serum calcium and triglycerides levels were normal. His past medical history included ischemic heart disease treated by four coronary stents several years before. Five days after pain onset, he was transferred to the ICU of our hospital because of the development of a refractory ARDS requiring VV-ECMO support and severe circulatory shock with high rate (75 mcg/min, 0.8 mcg/kg/min) of norepinephrine. Antibiotic therapy with piperacillin–tazobactam, started 4 days before in the other hospital, was continued. IAP was measured at 24 mmHg, while further physical examination revealed ecchymosis of the flanks (Grey Turner's sign). SOFA and SAPS 3 scores were at 20 and at 107, respectively. Laboratory tests revealed increased levels of CRP (390 mg/L), CK (12,920 U/L), LDH (1929 U/L), lactates (3.5 mmol/L), and acute renal failure (KDIGO Stage 2).

The contrast-enhanced abdominal MDCT confirmed the presence of an AP (grade E according to Balthazar, mCTSI at 10/10) (Fig. 5a) complicated by non-occlusive ischemia of the sigmoid colon with the concomitant presence of extra-visceral gas (Fig. 5b, c). The patient underwent urgently left colectomy, loop ileostomy, and VAC therapy. Unfortunately, mesenteric ischemia progressed

to ileostomy necrosis and persisting distributive shock leading to a new laparoscopic exploration revealing diffuse toneless small bowel with multiple ischemic areas. Despite the supportive treatment, the patient died the day after, from multi-organ failure. Pathological analysis of the left colectomy specimen displayed multiple perforation sites with focal transmural ischemic colitis (Fig. 3c). Autopsy revealed a complete necrosis of the pancreas with steatonecrosis and a diffuse necrotic bowel.

Discussion

In this study, we present three cases of severe AP complicated by irreversible NOMI. Some common characteristics regarding initial clinical presentation can be underlined: NOMI seems to appear very early after the diagnosis of pancreatitis, 48 to 120 h after symptoms onset. In all cases, pancreatitis was severe with a mCTSI at 10/10 score and a grade E according to Balthazar classification. Intensive care management and surgery were provided to all patients; however, their evolution was unfavorable with fatal outcome (Table 1).

Table 1 Characteristics of patients with NOMI

	Case 1	Case 2	Case 3
Age/gender	71/M	68/F	59/M
Etiology	Biliary	Biliary	Idiopathic
mCTSI	10/10	10/10	10/10
Balthazar score	E	E	E
SOFA/SAPS 3	16/70	9/68	20/107
Cardiovascular risk factors	Yes Active smoking	Yes Weaned smoking Dyslipidemia	Yes Arterial hypertension Ischemic heart disease with stents Dyslipidemia
Duration of symptoms at Erasme admission	2 days	0 day	5 days
Primary versus transfer admission	Transfer	Primary	Transfer
CK at NOMI diagnosis (U/L)	463	Normal	12,920
LDH at NOMI diagnosis (U/L)	1756	746	1926
Lactates at NOMI diagnosis (mmol/L)	6,7	5,9	3,5
IAP (mmhg)	NA	NA	24
Part of intestinal necrosis 1st laparotomy	No necrosis	Necrosis of a part of small bowel and colon	Sigmoid colon perforation
Second-look	20 cm of small bowel and total colon	Necrosis areas extended to the remaining bowel	Diffuse toneless small bowel with multiple ischemic areas
First surgery	No resection	110 cm of small bowel and 20 cm of right colon resection	Left colon resection and ileostomy
Second-look surgery	Resection of necrotic small bowel and total colectomy with terminal ileostomy	No further resection	No further resection
Antibiotherapy	Amoxicillin–clavulanic acid and amikacin	Amoxicillin–clavulanic acid	Piperacillin–tazobactam
Vasopressive drugs	Norepinephrine from 26 to 80 mcg/min (1 mcg/kg/min)	Norepinephrine 34 mcg/min (0.4 mcg/kg/min)	Norepinephrine 75mcg/min (0.8 mcg/kg/min)
MOF	Yes	Yes	Yes
Hemodynamic	+	+	+
Renal	+	+	+
Respiratory	+	-	+
Outcome (time from onset)	Died of MOF (at 4th day)	Died of MOF (at 4th day)	Died of MOF (at 7th day)

mCTSI modified computed tomography severity index, *SOFA* Sepsis-related Organ Failure Assessment, *SAPS3* Simplified Acute Physiology Score 3, *CK* creatine kinase, *NOMI* non-occlusive mesenteric ischemia, *LDH* lactate dehydrogenase, *IAP* intraabdominal pressure, *MOF* multiple organ failure

Moreover, we assume a posteriori that some warning signs should have led to early suspicion of NOMI, such as the need to increase norepinephrine doses, biological signs suggestive of AMI such as high levels of LDH and metabolic acidosis, and the occurrence of intraabdominal hypertension (formally assessed only in case 3), and that could be also related to severe AP.

NOMI is a rare condition, concerning 0.5% of patients with AP in our study and 4.8% of patients in our selected subgroup of patients with moderate and severe AP. Early diagnosis is difficult, often leading to delayed treatment because symptoms are unspecific: abdominal pain, nausea, vomiting, and gastrointestinal bleeding [17–19]. Unlike AMI due to embolic or thrombotic events, NOMI may have a more vague and milder clinical presentation [20].

To the best of our knowledge, we have found only one study, published in 2003, and reporting cases of AP complicated by NOMI [8]. In a retrospective Japanese study, including 120 consecutive patients with AP (60 with severe AP), the authors have diagnosed NOMI in 8 of them with a mortality rate of 100% for the 5 patients who developed intestinal gangrene [8]. The 3 patients who were treated with continuous regional arterial infusion of nafamostat mesilate (a protease inhibitor previously investigated in acute necrotizing pancreatitis [21]) via the celiac artery and the superior mesenteric artery survived.

The pathophysiology of NOMI seems to be a consequence of a low splanchnic blood flow due to a superior mesenteric artery vasoconstriction and/or a low cardiac output. Indeed, hypovolemia and the use of vasoconstrictive agents may precipitate NOMI [22, 23]. This early injury affects the intestinal mucosa and submucosa and potentially impairs mechanisms that prevent the translocation of bacteria from the intestinal lumen [24]. This sequence of events can result in worsened vasospasm, and more extensive injury to the bowel wall, that can progress to transmural infarction and death [25, 26].

Currently, different risk factors for NOMI have been identified in non AP patients and included: age >50 years, ischemic heart disease, congestive heart failure, cardiac arrhythmias, aortic insufficiency, cardiopulmonary bypass, renal or hepatic disease, major abdominal or cardiovascular surgery, or prior episodes of hypotension [20, 27, 28]. To the best of our knowledge, there is no established relationship between AP etiology and NOMI. Regarding underlying risk factors, all 3 patients were over 50 years old, one patient (case 3) had a history of myocardial infarction, and autopsy revealed calcified atherosclerosis of abdominal aorta and atheromatosis of the coronary arteries in another one (case 1). Of note, patient 2 had undergone a complete unremarkable cardiac evaluation just a few days before AP development.

Despite surgical intervention, the mortality rate was 100% in our case series, identical to the one reported in the Japanese study [8]. It is likely that the decision to intervene surgically was based on the suspected diagnosis of NOMI by imaging associated with a worsening of the patient's condition. Unfortunately, the mortality of NOMI, at this (too late) stage of surgical resection of frankly necrotic bowel, is very high (50–80%) even in the absence of AP [23]. All 3 cases needed high dose of norepinephrine for hemodynamic support, which certainly hampered splanchnic perfusion through local vasoconstriction. Moreover, 2 of them had signs of dehydration, pointing out the potential role of hypovolemia as a precipitant factor of NOMI.

In NOMI, early diagnosis and multidisciplinary immediate therapy are essential for a successful outcome. Angiography was previously considered as the gold standard diagnostic technique of NOMI [29], but MDCT has the advantages to be more accessible, less invasive, and less expensive and offers the possibility to explore bowel wall abnormalities and peritoneal cavity [14, 30]. Moreover, the post-processing of the early arterial phase images can easily provide angiographic-like reconstruction of the mesenteric arteries, to enable early diagnosis of NOMI similarly to a conventional angiographic procedure. Finally, MDCT allows the differential diagnosis with other painful acute abdominal conditions and could be repeated within few hours to follow the changes in the enhancement of the bowel. Unfortunately, it somehow lacks sensitivity [19] and underestimates the bowel perfusion impairment, NOMI being clearly evident only once transmural necrosis had already occurred with pneumatosis intestinalis (as in cases 1 and 2), bowel perforation (as in case 3), or portal venous gas seen at the MDCT (Table 1).

Management of NOMI aims to treat the underlying precipitating pathology and, to reestablish a splanchnomesenteric perfusion flow [31, 32]. This latter is a hard, if not impossible, task once the vicious circle of NOMI is established. The mesenteric arteries have no properties of autoregulation, meaning that flow is directly proportional to pressure. Moreover, in case of shock, the renin–angiotensin axis promotes a relative increase in mesenteric vascular tone compared to other regional vessels [33]. Cardiac output should then be optimized mainly with fluid resuscitation except in case of cardiac failure. However, rapidly, the typical capillary leak that occurs in these patients will lead to overload syndrome, with an increase in IAP, decreasing the perfusion pressure (equal to mean arterial pressure minus IAP), and a gut edema that will increase tissular ischemia. Subsequently, maintaining a perfusion pressure in these vasoplegic patients requires the administration of vasopressors which increase the mesenteric vasoconstriction. With this regard, norepinephrine is less toxic than epinephrine or

vasopressin [34]. But finally, the systemic attempts to maintain the mesenteric flow will worsen the situation.

In this setting, two radical strategies may be considered although evidence is low for both:

- intramesenteric administration of vasodilators like papaverine hydrochloride has been proposed; an alternative could be the use of high dose of intravenous prostaglandin [35, 36];
- in parallel with hemodynamic optimization, an early radical surgery aiming to remove the ischemic bowel could interrupt the vicious circle. For instance, a German team has proposed the use of an intraoperative indocyanine green fluorescence imaging to assess intestinal perfusion in patients with NOMI. This technique may be useful in the surgical management of NOMI to define resection margins more accurately and support surgical decision [37]. Conversely, "late" surgery although mandatory in case of bowel perforation or peritonitis leads to poor results as highlighted in our report, where surgery did not stop the fatal process. In the specific case of NOMI occurring in AP patients, surgery is certainly even harder to decide considering the very high mortality associated with early emergency laparotomy in this setting [38].

In our patients, early death due to persistent and irreversible multi-organ failure could be ascribed mainly to NOMI-related complications (i.e., acute peritonitis due to diffuse necrotic bowel). Nevertheless, in this setting of critically severe AP, which can also induce multi-organ failure, the final causality of death is difficult to establish.

Some limitations of our study have to be acknowledged. First, we did not use validated criteria for AP severity according to the 2012 revised Atlanta classification [39], but arbitrary criteria (length of hospital stay, need for ICU, pancreatic necrosis) easy to identify retrospectively. Secondly, our 3 patients were observed within a short period of 2 months at the end of the year 2018, while no other similar case was diagnosed previously during a 6-year period. Due to the retrospective design of the study, we cannot exclude that a few less dramatic cases of intestinal ischemia associated with AP were not diagnosed and have survived to the AP episode.

Conclusion

NOMI is an extremely severe disease, difficult to diagnose at the early stage and for which multidisciplinary management is mandatory. It initially presents with atypical acute abdominal pain, increased demand of norepinephrine, or patient's clinical deterioration and can occur as a fatal complication of severe AP, as shown in our case series. Priority should be given to reestablish splanchno-mesenteric perfusion flow, while surgery could be offered in case of treatment failure or deterioration but is still under debate in early stage to interrupt the vicious circle of intestinal hypoperfusion and ischemia.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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