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Case Study

Post-ERCP acute infected necrotising pancreatitis in a patient with Cushing's disease

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Acute pancreatitis, ERCP, walled-off necrosis, post-ERCP pancreatitis, Cushing's syndrome, steroid-induced pancreatitis, endoscopic necrosectomy.

Key learning points

1. Despite extensive research and endoscopic experience, acute pancreatitis remains a significant complication of diagnostic and therapeutic ERCP.
2. Hypercortisolism in Cushing's syndrome constitutes a probable risk factor for development of acute pancreatitis following insults to the pancreas.
3. The complications of severe pancreatitis should be managed conservatively, with surgical or endoscopic debridement reserved for patients in whom collections become infected.
4. Several strategies can be used to reduce the risk of acute pancreatitis following ERCP but awareness of these among ERCP practitioners in the UK is currently limited.

Introduction

Acute pancreatitis (AP) is a well-documented complication of endoscopic retrograde cholangiopancreatography (ERCP), an important procedure in the diagnosis and treatment of pancreatobiliary disease[1]. Despite increasing endoscopic experience and development of prevention guidelines, post-ERCP pancreatitis (PEP) remains a significant cause of increased morbidity, mortality, hospitalisation length, and financial cost. This report discusses the case of a patient with Cushing's disease who developed acute necrotising pancreatitis following ERCP for treatment of common bile duct (CBD) calculi. After a discussion of current strategies to reduce the risk of PEP, evidence on the clinical intersection between hypercortisolism and AP is summarised. Finally, recent research on the management of severe pancreatitis is discussed to review the scientific basis for the current standard of care.

The case

KT is a 54-year-old woman, who works a senior manager for a toy company and lives with her husband and son. On 21st October 2020, she presented to the emergency department of the John Radcliffe Hospital in Oxford with a two-hour history of right upper quadrant (RUQ) pain and nausea. On examination, KT showed a Cushingoid habitus (moon face, malar flush, hirsutism) and RUQ tenderness with a positive Murphy's sign. Alongside a history of non-alcoholic fatty liver disease and focal nodular hyperplasia, KT had for several years struggled with diet resistant hypertension and obesity, which she attributed to Cushing's syndrome. KT was not on any prescribed medication, with no known drug allergies. She did not smoke and drank 5 units of alcohol per week. Blood tests revealed deranged liver function (bilirubin 58 mg/dl, ALT 1919 U/l). While ultrasonography showed no change in liver nodules, magnetic resonance cholangiopancreatography (MRCP) revealed multiple calculi in KT's gallbladder, as well as a 6 mm CBD stone and a 15 mm cystic lesion on her pancreas. KT was referred to the general surgery and gastroenterology teams for further investigations.

In November 2020, KT also received a provisional diagnosis of Cushing's syndrome following a failed overnight dexamethasone suppression test, elevated 24hr urinary cortisol levels and an elevated plasma ACTH. In parallel, she was discussed by the hepatobiliary MDT and scheduled for endoscopic ultrasound (EUS) and ERCP followed by cholecystectomy. EUS/ERCP was performed on 18th December: CBD stones were removed, and a stent placed in the pancreatic duct (PD) to reduce the risk of PEP following multiple cannulation attempts. While awaiting surgery, however, KT developed severe epigastric pain radiating to her back. She was also tachycardic, hypotensive and jaundiced (bilirubin 142 mg/dl, CRP 600 mg/l, amylase 2000 U/l). CT of her abdomen revealed extensive fat wrapping of the pancreas, suggesting AP. Since her Glasgow-Imrie score was of only 2 (albumin 28 g/l, calcium 1.95 mmol/l), KT was judged to be at low risk for severe pancreatitis and was managed conservatively with fluids, pancreatic enzymes and analgaesia. KT was stable in the following days but gradually developed a small left pleural effusion with statically raised inflammatory markers. A repeat CT revealed small non-drainable pancreatic collections with no evidence of necrosis. She was judged to be safe for outpatient management and discharged on 14th January 2021 with prophylactic dalteparin treatment due to the hypercoagulable state of Cushing's patients.

Despite regular follow-ups, KT was readmitted

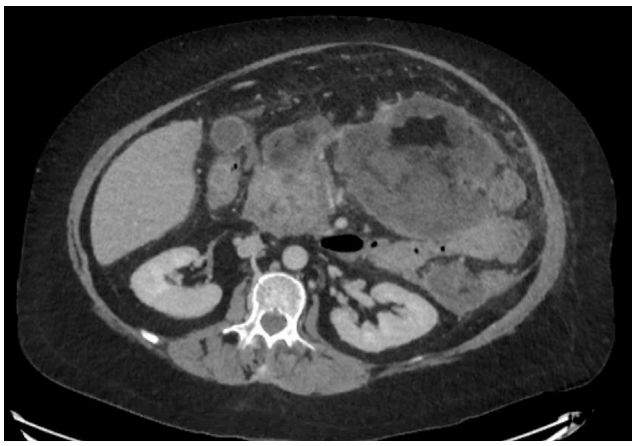

Figure 1: KT's axial abdominal CT scan (2nd February 2021). Radiological report described multiple areas of walled-off pancreatic necrosis, enlargement of peripancreatic collections, pseudocysts and a pancreaticopleural fistula.

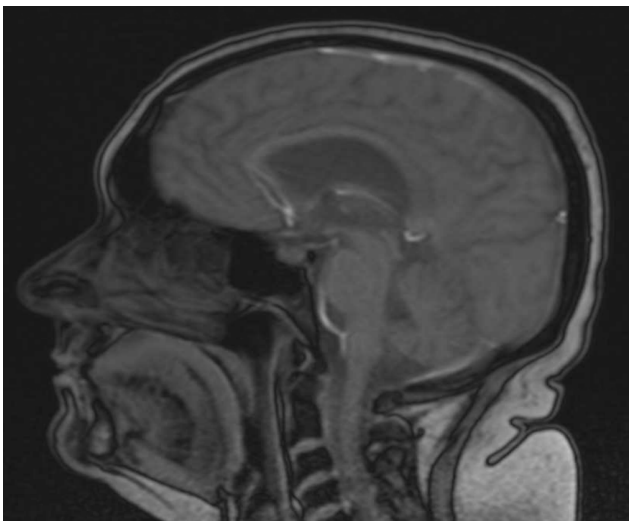

Figure 2: KT's pituitary MRI (10th October 2021). Radiological report described a 6x6 mm lesion in the right side of the pituitary gland with minor deviation of the pituitary stalk.

on 2nd February after presenting with worsening dyspnoea, retching and fatigue. Abdominal CT showed marked pancreatic pathology with large areas of walled-off necrosis, and significant enlargement of existing peripancreatic collections (Figure 1). Collections were drained by both EUS-guided cystogastrostomy and CT-guided percutaneous drainage – drained fluid grew E. *coli* and K. *pneumoniae* on culture.

KT continued deteriorating with severe abdominal pain and dyspnoea. On 25th February, she underwent a repeat cystogastrostomy with endoscopic necrosectomy through her transgastric stent. Post-operatively, KT then developed atelectasis and pulmonary oedema, followed by hypotension, tachycardia, and hypokalaemia. As a result, she was provided with total parenteral nutrition (TPN) and transferred to the intensive care unit (ICU). KT's ICU stay lasted two months, during which she faced several complications including sepsis, recurrent pulmonary embolisms, and fractures of vertebrae T7 and T8. Remarkably, KT survived this deterioration and was finally stepped down to ward care on 26th April. She was discharged from hospital on 5th June 2021 with referral to the physical and occupational therapy teams.

KT made a very positive recovery in the second half of 2021. She gradually regained normal mobility and was able to resume her endocrinological care. She was diagnosed with Cushing's disease after MRI of her pituitary, which revealed a small microadenoma, and inferior petrosal sinus sampling, which established a central cause for her elevated ACTH levels (Figure 2).

KT underwent transsphenoidal surgery to remove her pituitary adenoma on 17th December. This cured her Cushing's disease and secondary hypertension but also made her dependent on exogenous hydrocortisone treatment. Critically, she was still suffering from RUQ pain due to her remaining gallbladder calculi, which put her at risk of recurrent pancreatitis. Indeed, she presented to surgical triage on 20th April 2022 with RUQ pain radiating to her back. Her CRP was elevated at 53 mg/l and MRCP confirmed the presence of multiple gallstones, leading to a diagnosis of cholecystitis. KT was admitted for laparoscopic cholecystectomy, which took place under perioperative IV hydrocortisone cover after discussion with the endocrinology team. Despite extensive omental wrapping of Calot's triangle and multiple adhesions due to her past procedures, KT's surgery did not require conversion to open and had no complications. She was then treated with IV hydrocortisone (50 mg QDS) and stepped down to an increased oral dose (40 mg daily) once able to tolerate tablets. After being advised to return to her regular maintenance regimen (20 mg daily) only after feeling fully recovered, KT was finally discharged on 30th April, 15 months after her first presentation to the surgical team.

Post-ERCP acute pancreatitis: epidemiology and prevention strategies

In contrast to solely diagnostic procedures like MRCP or EUS, ERCP plays an important role in treating pancreatobiliary disease. It is associated with several complications, most commonly acute pancreatitis (AP) followed by infection, bleeding and perforation[2]. The incidence of AP in the UK is estimated as 56 cases per 100,000 people per year. About 75% of cases are due to gallstones and alcohol abuse, with ERCP belonging to a rarer group of causes (viral infection, hyperlipidaemia, steroids, etc.)[3]. Based on the revised Atlanta classification (2012), AP is classed into three grades of severity (mild, moderate, severe) ranging from self limiting inflammation to infected necrosis of pancreatic parenchyma and surrounding tissue with multi-system organ failure[4-6]. About 25% of AP cases are classed as severe and these have an estimated mortality of 25%, on the background of a 5% mortality for AP overall[5].

According to the European Society for Gastrointestinal Endoscopy (ESGE), PEP has a frequency of 3.5% among unselected ERCP patients[4,7]. However, estimates of incidence in the literature range from 1% to 40%, largely due to heterogeneity in inclusion criteria and AP definitions across studies[2,8]. Consensus from prospective studies is that diagnostic ERCP is associated with a lower risk of PEP (1-3%) compared to therapeutic ERCP (4-5%)[8, 9]. PEP is mild or moderate in about 90% of cases, with the remaining 10% being the cause of most ERCP-related morbidity and mortality. The risk of PEP among ERCP patients is shaped by the synergy of patient- and procedure-related factors[4,7]. Established patient-related risk factors include female sex, previous pancreatitis, and sphincter of Oddi dysfunction, whilst the possible contributions of young age and eubilirubinaemia remain unclear[7,10]. Procedure related risk factors include

endoscopic balloon dilation of the sphincter of Oddi, repeated PD contrast injections and multiple cannulation attempts[4,11,12]. Inadvertent cannulation of the PD may have contributed to development of PEP in KT's case.

Research in the last two decades has focussed on devising strategies to prevent the development of PEP in ERCP patients as well as on perfecting stratification algorithms aimed at identifying patients at high risk of complications. However, progress on this latter front has been limited. Imaging-based scoring systems, such as the CT severity index (CTSI), have remained the gold standard for grading AP severity, due to their ability to assess local necrosis, peripancreatic inflammation and extrapancreatic complications (e.g. mesenteric oedema)[13-15]. Moreover, comparative studies have shown that CT-based scoring systems have similar predictive values for severe AP to commonly used clinical ones (e.g. Glasgow-Imrie score, Ranson's criteria). Routine use of CT for severity prognostication in AP patients is therefore not indicated[16].

Overall, prediction accuracy for severe disease in AP patients remains at around 80%[16-19]. For example, meta-analyses have estimated the positive predictive value and sensitivity of the Glasgow-Imrie score as respectively 40-50% and 60-70%[8,17]. Therefore, about half of patients with predicted severe AP do not develop complications and roughly a third of patients with a score suggesting mild AP instead do, as was the case for KT. Without discounting the desire for reliable predictive tools, clinical recognition of signs of organ dysfunction remains the most useful strategy to prognosticate clinical course and severity in AP patients.

By contrast, some modifications to the delivery of ERCP have been clearly shown to reduce the risk of PEP. Current ESGE guidelines recommend routine rectal administration of NSAIDs (diclofenac or indomethacin) before or after ERCP and placement of a prophylactic stent in the pancreatic duct, as well as limiting cannulation attempts and using PD guidewires rather than contrast-assisted methods for deep biliary cannulation[7]. Meta-analyses have consistently concluded that PD stents and rectal diclofenac or indomethacin lead to an approximately 50% reduction in PEP rates[20-25]. A network meta-analysis also found that rectal NSAIDs alone were superior to PD stents, with no added benefit from combining the two[26]. Nonetheless, a 2014 UK-wide survey of ERCP practitioners, including gastroenterologists, gastrointestinal surgeons, and radiologists, found that less than 53% of respondents used PD stents or NSAIDs and that only 6% routinely measured amylase after ERCP[27]. This suggests that increasing awareness of existing prevention guidelines may be the most effective strategy to reduce the burden of post-ERCP pancreatitis in the UK.

Acute pancreatitis and Cushing's syndrome: the role of dual pathology in KT's case

The association between AP and Cushing's syndrome is uncommon. Little basic research has been dedicated to the possible interaction between the pathophysiologies of the two diseases and clinical evidence is limited to a small number of case reports[28]. Clague *et al*. described the case of a 53-year-old man with ectopic ACTH production due to bronchial carcinoma who died after developing AP and postulated that endogenous steroid excess may contribute to the pathogenesis of AP[29]. This was also suggested by Hiramatsu *et al*. after observing a similar case in a 64-year-old woman with Cushing's disease[30]. Cougard *et al.* described two cases of necrotising AP occurring after bilateral laparoscopic adrenalectomy for ectopic ACTH secretion and suggested that hypercortisolism may exert a specific contribution to an increased risk of AP in these patients, independently of intraoperative trauma to the pancreas[31].

Treatment with exogenous steroids is a well-established risk factor for the development of AP. A nationwide nested case-control study in Sweden concluded that current oral glucocorticoid use was associated with an increased risk of developing AP between 4 and 14 days of drug dispensation[32]. While the mechanism by which glucocorticoids may propitiate AP remains unknown, this latency suggests that effects of glucocorticoids are likely to be mainly mediated by changes in gene transcription. Previous studies in rodents have indeed described a critical influence of adrenocortical steroids on the exocrine function of the pancreas: adrenalectomy was found to selectively inhibit amylase synthesis in acinar cells and to decrease the density of zymogen granules[33,34]. A study in the caerulin-induced animal model of AP observed that rats treated with hydrocortisone experienced a significant increase in pancreatic weight because of increased protein synthesis and storage. Administration of caerulin in these animals led to severe interstitial oedema of the pancreas and increases in serum amylase values to triple the level observed in control animals[35]. This suggests that high levels of corticosteroids may be associated with increased density of zymogen granules and high sensitivity to secretagogues, which would increase the likelihood of developing AP following a pancreatic insult. While studies in humans are lacking, this hypothesis is consistent with the observation that the local features of AP in KT's case were particularly severe, with amylase levels exceeding 1000 U/l.

Another poorly understood aspect of the dual pathology between Cushing's syndrome and AP is how hypercortisolism may influence the systemic sequelae of pancreatic inflammation. On the one hand, serum levels of CRP and inflammatory cytokines (TNFa, IL-6, IL-8) have been shown to be elevated in AP patients, although none have sufficient sensitivity or specificity for use in severity prognostication[36]. On the other hand, several studies support the notion that peripherally generated cytokines stimulate activation of the HPA axis to mitigate the systemic consequences of inflammation through the anti-inflammatory effect of glucocorticoids[37]. Animal models suggest that this mechanism may be relevant to AP progression. For example, a study in the caerulin-induced and closed duodenal loop (CDL) rat models observed that experimental induction of AP led to significant elevation of both IL-8 and corticosterone levels. Critically, adrenalectomy increased the severity of AP and mortality among CDL rats, while exogenous hydrocortisone replacement suppressed IL-8 elevation in adrenalectomised rats and reduced both AP severity and mortality[38]. If this counter-regulatory effect of corticosteroids were to play a significant role in the development of systemic complications, AP patients with hypercortisolism would be expected to be relatively protected from inflammatory sequelae, at the expense of increased infection risk. KT's clinical course is consistent with this speculative hypothesis since she did develop local and distant infective complications but was nonetheless able to withstand multiple deterioration episodes. Evidence thus suggests that hypercortisolism may act as a risk factor for the development of AP but a mitigating factor in its progression.

Clearly, no suggestion of a change to the normal management of AP in Cushing's patients can be made based on such a limited number of studies. However, considering

that outcomes in AP strongly depend on clinical acumen and early diagnosis, keeping a high index of suspicion and thus a low threshold for investigations (i.e. serum amylase, CT) constitutes an important piece of advice to medical professionals faced with Cushing's patients presenting with AP symptoms.

Severe necrotising pancreatitis: recent trends in diagnosis, management, and prevention

According to the Atlanta classification, severe AP is characterised by the presence of persistent (>48hr) single-organ or multi-organ (i.e. cardiovascular, respiratory or renal) failure, which has been shown to act as the main determinant of AP-related mortality[6,39,40]. Most patients with severe AP display radiological evidence of local complications, which include interstitial pancreatitis (i.e. peripancreatic fluid collections, pancreatic pseudocysts and fistulas) and necrotising pancreatitis (i.e. necrotic collections and walled-off necrosis)[41]. Moderate AP, which is characterised by local complications without infected necrosis or organ failure, instead leads to prolonged and complicated hospital stays but only carries a 1-2% mortality[6,42].

The management of pseudocysts and necrotic collections in severe AP is matter of contention in the surgical literature since the 1920s but has been majorly informed by research in the last decade[18,43]. The treatment options are percutaneous drainage, endoscopic cystenterostomy with or without necrosectomy, and video-assisted or open retroperitoneal debridement. The surgical mortality rate for these procedures is still between 10 and 20% despite improvements in fluid therapy and antibiotics[18,43]. The main conclusion of trials since the 1990s has hence been that sterile interstitial or necrotising pancreatitis should be managed conservatively, with invasive treatment reserved for patients in whom collections become infected or cause pain or other symptoms (e.g. gastric outlet obstruction)[44]. Observational studies also suggest that optimising conditions for debridement by waiting for collections to demarcate leads to lower morbidity and mortality[45]. ESGE guidelines advise that patients who develop infected necroses early in their disease course should be managed with IV antibiotics and percutaneous drainage, with endoscopic or surgical interventions only considered beyond 4 weeks from the onset of AP[46]. This indication is supported by findings from a recent study in patients with walled-off pancreatic necrosis (WOPN), which observed that in 40% of cases percutaneous drainage led to resolution without the need for later endoscopic necrosectomy[47].

The standard of care followed in KT's case is based on an 'endoscopic step-up approach' which was validated by two recent landmark RCTs. The PANTER trial in 2010 first concluded that a graded approach to patients with infected WOPN, starting with percutaneous or transluminal drainage followed by minimally invasive retroperitoneal necrosectomy if necessary, led to a 29% reduction in the absolute risk of major complication (i.e. new-onset multiple organ failure, perforation, enterocutaneous fistula) or death compared to primary open necrosectomy[48]. In 2018, the TENSION trial compared this surgical step-up approach (i.e. percutaneous drainage followed by minimally invasive debridement) with an endoscopic step-up approach in which EUS-guided transluminal drainage was followed by endoscopic necrosectomy. While rates of major complication or death were found to not significantly differ between the two, endoscopic treatment was shown to result in a lower rate of pancreaticocutaneous fistulas and a reduced need for reinterventions at initial (6 months) and long-term (mean 7 years) follow-up[49,50].

Concluding remarks

The case of KT illustrates how, even with adherence to clinical guidelines (e.g. PD stents, endoscopic step-up), ERCP is still associated to an important risk of acute pancreatitis, which can have catastrophic complications if severe. In 2002, a panel of the National Institutes of Health concluded that less invasive techniques like MRCP and EUS would 'soon eclipse ERCP's status as tool for diagnosing pancreatobiliary disease'[51]. Two decades later, this forecast has proven to be overoptimistic. While efforts to limit its diagnostic use are commendable, ERCP will remain a cornerstone of pancreatobiliary disease management for the foreseeable future. Therefore, closer adherence to guidelines and more extensive studies on candidate agents for PEP prophylaxis will remain essential strategies to reduce the incidence, morbidity, and mortality of post-ERCP pancreatitis in coming years.

Funding

None.

Consent

The patient has consented to the publication of this case study.

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