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ORIGINAL ARTICLE

Retrospective Study

Polymyxin B hemoperfusion as a feasible therapy after source control in abdominal septic shock

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Author contributions: All authors helped to perform the research; Kim JJ is the lead investigator, collected the data, designed the study, performed literature search and wrote the manuscript; Park YJ performed literature search and the statistical analysis; Moon KY, Park JH and Jeong YK collected the data and revised manuscript; Kim EY revised the manuscript.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Seoul St. Mary's hospital.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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Abstract

BACKGROUND

Polymyxin B hemoperfusion (PMX-HP) has been used as a treatment for intra-abdominal septic shock by absorbing and removing endotoxins of gram-negative bacilli.

AIM

To investigate the clinical efficacy of PMX-HP in patients with gram-negative septic shock who underwent abdominal surgery.

METHODS

From January 2012 to December 2018, patients who had septic shock secondary to peritonitis were enrolled. They were classified into PMX-HP treated and control groups based on postopreative intervention using PMX-HP. The clinical outcomes were compared using 1:1 propensity score matching methods to balance the overall distribution between the two groups.

RESULTS

After propensity score matching, 40 patients were analyzed (20 patients in the PMX group and 20 patients in the control group). The scores of total Sequential Organ Failure Assessment (SOFA) score, renal SOFA and coagulation SOFA were significantly improved in the PMX group but not in the control group. (from 11.2 ± 5.8 to 4.7 ± 3.5 in PMX group *vs* 10.0 ± 4.0 to 8.7 ± 7.3 in control group, $P = 0.047$ from 2.6 ± 1.0 to 0.7 ± 1.0 in PMX group *vs* 2.6 ± 1.5 to 2.8 ± 1.6 in control group, $P = 0.000$, from 1.6 ± 1.5 to 1.3 ± 1.3 in PMX group *vs* 1.2 ± 1.2 to 2.8 ± 1.8 in control group, $P = 0.014$, respectively). Further, the length of intensive care unit (ICU)

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stay was significantly shorter in PMX group. However, no statistically significant difference was found in ICU mortality (50% in PMX group *vs* 50% in control group).

CONCLUSION
PMX-HP is a feasible adjunct treatment for peritonitis in ICU patients with peritonitis for improved organ impairment and to stabilize hemodynamics. It would be helpful to enhance clinical outcomes especially in patients with complete elimination of the source of gram-negative bacilli infection by surgical procedure accompanied with conventional treatment of sepsis.

Key words: Intraabdominal septic shock; Panperitonitis; Polymyxin B hemoperfusion; Sepsis; Toraymyxin

Core tip: Polymyxin B hemoperfusion (PMX-HP) has been proposed as a treatment for intra-abdominal septic shock by eliminating endotoxins of gram-negative bacilli. The aim of this study was to investigate the clinical efficacy of PMX-HP using propensity score matching in patients with gram-negative septic shock who underwent abdominal surgery. Forty patients were analyzed (20 patients in the PMX group and 20 patients in the control group) and there were significant improvement for total Sequential Organ Failure Assessment (SOFA) score, renal SOFA and coagulation SOFA were significantly improved in the PMX group. Furthermore, the length of intensive care unit stay was significantly shorter in PMX group.

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INTRODUCTION

Intra-abdominal infection is one of the common causes of sepsis or septic shock and is associated with a high mortality rate of 19.5%[1,2]. Because of the inherent bacterial colonization in abdomen, gram-negative bacilli (GNB) are probably the major source of infection[3,4]. Lipopolisaccharide (LPS) is the core lipid portion of the endotoxin in gram-negative microorganisms, and has been considered as one of the important triggers of sepis or septic shock[5]. It induces a systemic inflammatory response syndrome resulting in the release of cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and nitrous oxide, and also activates the coagulation and complement system of the host[1,6]. Moreover, LPS translocation into the blood stream when the intestinal mucosa is impaired in sepsis, results in multiorgan failure[3].

Polymyxin B (PMX) is an antibiotic, which binds to LPS of GNB and inactivates the endotoxin with increased affinity. Hemofiltration with PMX hemoperfusion (PMX-HP, Toraymyxin, Toray Industries, Tokyo, Japan) immobilized to a polysterene-derived fiber was developed in Japan in the 1990s, to selectively adsor and remove the endotoxin of GNB in the blood stream[5,7-9]. Since 2017, our institution have used the PMX-HP in selected patients who underwent surgery for the treatment of septic shock originated from abdominal peritonitis. However, there is still lack of a comparative study of the effectiveness of PMX-HP treatment after abdominal surgery, and PMX-HP is not routinely used to manage post-operative patients with peritonitis.

Herein, we evaluated the clinical efficacy of PMX-HP treatment *via* propensity score matching in patients undergoing abdominal surgery due to peritonitis with gram-negative sepsis.

MATERIALS AND METHODS

Study design and participants

This study was approved by the Institutional Review Board of our institution (No. IRB; KC18RESIO782). Patients who manifested septic shock secondary to peritonitis between January 2012 and December 2018 were enrolled. All the patients were diagnosed with abdominal septic shock due to suspected or established GNB infection, and they underwent surgical control of the source of infection. Subsequently, the patients received standard management based on Survival Sepsis Campaign (SSC) guidelines for sepsis[10,11]. The diagnosis of severe sepsis and septic shock was defined according to the SSC criteria[12]. Patients were treated according to SSC bundle with appropriate volume resuscitation, the culture prior to administration of antibiotics and usage of vasopressor. In addition, the culturing multiple sites including blood, sputum, drain or urine were performed during the intensive care unit (ICU) stay[6]. Gram-negative etiology of sepsis was strongly suspected according to the source of infection or based on microbiological tests[3]. All participants were classified into postoperative PMX-treated and untreated control group. Since 2016, patients at our institution have been treated with PMX-HP in the surgical intenstive care unit after source control following a diagnosis of intra-abdominal infection with septic shock. Based on the Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock (EUPHAS) 1 trial, we adopted PMX-HP treatment based on our own guidelines. The indications for PMX-HP were same as follows: (1) Age over 18 years; (2) Clinical signs of sepsis or septic shock originating in the abdominal cavity with a Sequential Organ Failure Assessment (SOFA) score > 2; (3) Persistence or worsening of septic shock despite appropriate antibiotic treatments and effective source control; (4) Need for high dose of vasopressor within 12 h from diagnosis; and (5) Suspected or confirmed gram-negative infection traced to a recognized source of sepsis[1,8,13-15]. PMX-HP was not used to treat cases with the following contraindications: (1) Age less than 18 years; (2) Incomplete source control due to poor condition of patients; (3) Pregnancy; (4) Previous history of hypersensitivity to PMX; (5) Uncontrolled hemorrhage within 24 h; (6) Severe thrombocytopenia (platelet count < 30000 × 10^9/L); (7) Severe leukocytopenia (leucocyte count < 500 μL/L); (8) Hematologic malignancy; or (9) Immunosuppressive therapy[6,15,16]. The control group was treated using standard intensive therapy according to guidelines recommended by SSC after surgical source control[10,11].

In this study, the source control was defined as any surgical procedure or intervention, which eliminates the focus of ongoing infection and also corrects the anatomical derangements involving intra-abdominal viscera in order to restore normal physiologic function[17]. According to Solomkin *et al*[18], the successful source control was defined as the case obtaines these findings after surgery or intervention; resolution of fever (oral temperature < 37.5 °C), improvement in leukocytosis [white blood cell (WBC) < 12000 μL/L], resolution of physical findings of tenderness and rigidity, restoration of enteric function and no further need for operative or other intervention[18]. However, the failure of source control was defined by a strong clinical suspicion of infection in the abdomen based on the color change of the drain, the result of imaging study such as computed tomography scan or clinical progression to septic condition despite operation or intervention. Patients manifesting any of these findings were excluded from the analysis; previously signed "do not resuscitate" orders, those with documented treatment limitations such as prohibition of further organ support or initiation of renal replacement therapy, as stated in the medical records.

Study protocol: Polymyxin B hemoperfusion group vs control group

The study protocol is summarized in Figure 1. In case of PMX group, the first PMX-HP session was initiated within 12 h after surgical source control followed by a second PMX-HP session within 24 h after completion of the first session. A dual-lumen catheter (12Fr Arrow International, Reading, PA, United States) was inserted into the internal jugular vein or femoral vein guided by ultrasound. Subsequently, two sessions of PMX-HP were performed using toraymyxin cartridge (Toraymyxin, Toray industries, Tokyo, Japan) in the continuous renal replacement therapy (CRRT) machine. The blood flow rate varied between 80 to 120 mL/min, and Nafamostat mesylate (Futhan, Torii Pharmaceuticals, Tokyo, Japan) was used as anticoagulant for the circuit at a dose of 20-30 mg/h[3,19]. Based on the study of Kawazoe *et al*[20], each session was conducted for 6 h except in cases indicated for PMX-HP therapy discontinuation. To reduce the risk of postoperative bleeding, nafamostat was also used for patients with CRRT in the control group according to our institution's policy.

Data collection and study endpoint

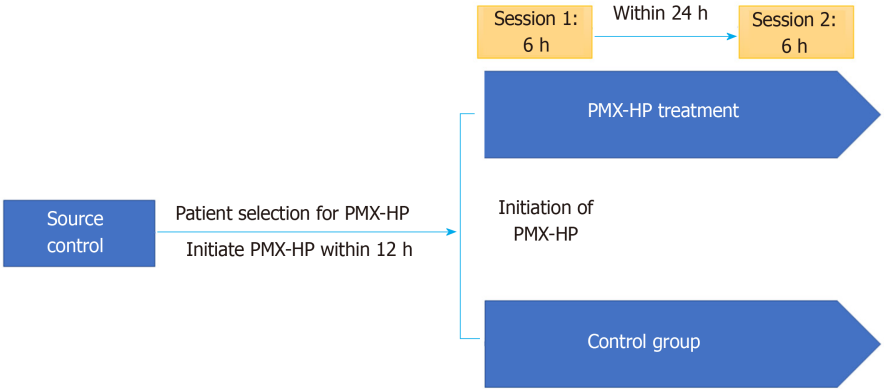

Figure 1 Design of the study protocol from the operation until second session of polymyxin B hemoperfusion. PMX-HP: Polymyxin B hemoperfusion.

For each patient, the data were prospectively collected from medical records and vital chart at baseline, at 48 h and at 72 h. In terms of hemodynamic status, it was assessed according to their mean arterial pressure (MAP), blood lactate concentration, and vasopressor load represented by the inotropic score [Inotropic score = (dopamine dose × 1) + (dobutamine dose × 1) + (adrenaline dose × 100) + (noradrenaline dose × 100) + (phenylephrine dose × 100)].

All doses were expressed as μg/kg/min. Because the vasopressor dose was titrated to maintain MAP of 65 mmHg, a dose-response relationship between MAP and vasopressor dose was expressed as the vasopressor dependency index (VDI) (VDI = Inotropic score/MAP).

On the aspect of PMX-HP, the duration, and the frequency and, the time to initiation of PMX-HP were recorded. The degree of organ dysfunction was expressed using the SOFA score[21]. Adverse events related to PMX-HP were defined by tachycardia (heart rate > 100 bpm) or heart rate increase greater than 10% at the beginning of PMX-HP, hypotension (MAP < 70 mmHg), and any type of hemorrhagic complication[3]. The primary endpoints were 28-d mortality and changes in hemodynamic parameters such as VDI and inotropic score within the first 3 d. The secondary endpoint was the 7-day mortality and the variation in the SOFA score within the first 3 d[4,16].

Statistical analysis

SPSS for Windows (version 21.0, SPSS Inc., Chicago, IL, United States) was used for statistical analysis. The *P* value of less than 0.05 was considered statistically significant. Continuous variables were analyzed using Student's *t*-test and expressed as the mean standard de*via*tion. Categorical variables were presented as proportions, and were analyzed *via* χ^2 test or Fisher's exact test. The variations in SOFA score were analyzed using Wilcoxon rank sum test. We used propensity-score matching in order to minimize the lead-time bias and selection bias. Propensity-score matching was conducted to adjust for confounding of baseline characteristics and the severity of clinical conditions. To estimate the propensity score, a logistic regression analysis of clinical factors including age, sex, body weight, underlying malignancy, APACHE II score, pre-existing organ dysfunction, initial SOFA score, microorganism responsible for sepsis, and the initial values of lab including the count of WBC, platelet count, hemoglobin and the level of prothrombin time or international normalized ratio, was performed in patients who underwent PMX-HP treatment. In the propensity score-matched population, we compared the continuous variables using a paired *t* test or the Wilcoxon rank test and categorical variables with the McNemar's or Bowker's test in the same group. Also one-way ANOVA was used to compare two groups. The C-statistics were estimated to evaluate the goodness of fit. We used 1:1 matching and a caliper width equal to 0.01 of the standard de*via*tion of the logit of the propensity score was used.

RESULTS

A total of 308 eligible patients including the PMX group (n = 20) and control group (n = 288) were finally enrolled, and 20 propensity-score-matched pairs were generated.

Figure 2 demonstrates the study profile. Table 1 presents a comparative analysis of the baseline characteristics of the PMX and the control groups after propensity-score matching. Patient characteristics were adequately balanced between the two groups after propensity-score matching in terms of mean age, gender, underlying malignancy, pre-existing organ dysfunction, use of vasoactive agents and disease severity. Table 2 presents a comparative analysis of etiology and treatment for sepsis between the two groups. The leading primary infection site was lower gastrointestinal tract in both groups. (14 cases, 70.0% in PMX group *vs* 10 cases, 50% in control group, $P = 0.166$) Microbiological evidence of infection was confirmed in 28 (70.0%) patients, based on the bacterial cultures obtained before the operation or intervention. Multiple microorganisms were isolated in 12 (30.0%) patients. Gram-negative species were the predominant pathogen isolated in both groups (11 cases, 55.0% in PMX group *vs* 10 cases, 50% in control group, $P = 0.752$). The majority of patients (95.0%) received surgical treatment, and two patients underwent radiological intervention such as percutaneous trans-hepatic gallbladder drainage. There was no significant difference in the proportion of patients receiving CRRT or mechanical ventilation in both groups, and both groups had comparable clinical and laboratory parameters as described in Table 2.

Regarding the clinical effects of PMX-HP, there was a significant improvement in the SOFA score at 72 h in patients included in the PMX-HP group compared with the control group (from 11.2 ± 5.8 to 4.7 ± 3.5 in PMX group *vs* 10.0 ± 4.0 to 8.7 ± 7.3 in control group, $P = 0.047$). Especially, the renal and coagulation SOFA scores were significantly improved in PMX group (from 2.6 ± 1.0 to 0.7 ± 1.0 in PMX group *vs* 2.6 ± 1.5 to 2.8 ± 1.6 in control group, $P = 0.000$, from 1.6 ± 1.5 to 1.3 ± 1.3 in PMX group *vs* 1.2 ± 1.2 to 2.8 ± 1.8 in control group, $P = 0.014$, respectively). Furthermore, the inotropic score and VDI were significantly decreased in PMX group (from 163.7 ± 302.1 to 8.9 ± 19.1 of inotropic score in PMX group *vs* 90.8 ± 181.7 to 1.4 ± 4.2 in control group, $P = 0.006$, and from 2.4 ± 3.4 to 0.1 ± 0.3 of VDI in PMX group *vs* 1.0 ± 2.0 to 0.0 ± 0.1 in control group, $P = 0.001$, respectively) (Table 3). The PMX group showed a greater reduction compared to the control group in terms of renal SOFA (mean delta SOFA score, -1.9 *vs* 0, $P = 0.007$) and coagulation SOFA (mean delta SOFA score, -0.36 *vs* 1.93, $P = 0.013$). However, the two groups were similar in term of total SOFA (mean delta SOFA score, -6.13 *vs* -1.28, $P = 0.121$), cardiovascular SOFA (mean delta SOFA score, -2.12 *vs* -1.43, $P = 0.315$) respiratory SOFA (mean delta SOFA score,-1.0 *vs* -0.65, $P = 0.613$) (Figure 3). The length of ICU stay was significantly shorter in the PMX group than the control group (10.9 ± 3.9 d in PMX group *vs* 14.6 ± 6.4 d in control group, $P = 0.036$). The ICU mortality rate was lower in the PMX group ($n = 4$, 20%) than in the control group ($n = 8$, 40%) without any statistically significant difference. Similarly, there was no significant difference between the two groups in the in-hospital mortality and duration of mechanical ventilation (Table 4).

DISCUSSION

In the current study, PMX-HP treatment significantly improved the hemodynamic parameters such as inotropic score and VDI, and the degree of organ failure represented by the renal, coagulation or total SOFA score, and the length of ICU stay, for patients whose infection focus were successfully removed by surgical intervention.

In terms of hemodynamic aspects, the inotropic score and VDI decreased significantly in the PMX group consistent with previous studies that showed a significantly increment in arterial pressure and decreased need for vasopressor after PMX-HP treatment[4,14]. PMX is a lipopeptide antibiotics isolated from *Bacillus polymyxa*. It disrupts the outer membrane of GNB and binds to the lipid A portion of LPS selectively[19]. Circulating LPS activates the inflammatory reaction, complement or coagulation system of the hosts. Nakamura *et al*[22,23]. reported that circulating monocyte and neutrophils were removed through the PMX cartridge, and PMX-HP reduced the levels of TNF-α, IL-6, IL-10, plasminogen activator inhibitor 1, metalloproteinase and anandamide. These mechanisms of PMX-HP improved tissue oxygenation and hemodynamic status, and contributed to the improvement of hemodynamics in patients with abdominal septic shock.

Moreover, PMX-HP treatment improved the cardiac function *via* elimination of myocardial depressant mediator such as anandamide of 2-arachidonoylglycerol. Therefore, it reduces the dosage of catecholamine drugs and enhances the hemodynamic outcome[24]. We propose that this mechanism decreases the adverse cardiovascular effects of high-dose catecholamines such as arrhythmia, decreased cardiac output, ischemic change of mesentery caused by potent vasoconstriction. Maynar *et al*[14]. reported that 28-d mortality rates were significantly decreased in

Table 1 Baseline patient characteristics in propensity-matched groups

	PMX-HP (*n* = 20)	Control (*n* = 20)	*P* value
Age, yr	66.7 ± 9.9	67.8 ± 10.2	0.719
Sex, Male, *n* (%)	12 (60.0)	12 (60.0)	1.000
Underlying malignancy, *n* (%)	11 (55.0)	12 (60.0)	0.749
Pre-existing organ dysfunction, *n* (%)	13 (65.0)	13 (65.0)	1.000
Liver insufficiency	1 (5.0)	0 (0.0)	0.311
Chronic respiratory disorder	1 (5.0)	5 (25.0)	0.077
Chronic heart failure	0 (0.0)	2 (10.0)	0.147
Chronic hemodialysis	3 (15.0)	1 (5.0)	0.292
Immunocompromised	3 (15.0)	0 (0.0)	0.072
Use of vasoactive agents			
Norepinephrine	18 (90.0)	16 (80.0)	0.376
Dopamine	3 (15.0)	9 (45.0)	0.038
Dobutamine	2 (10.0)	0 (0.0)	0.147
Vasopressin	10 (50.0)	1 (5.0)	0.001
Epinephrine	6 (30.0)	5 (26.3)	0.798
Disease severity			
SOFA score	11.2 ± 5.8	10.0 ± 4.0	0.446
APACHE II	19.1 ± 6.5	18.0 ± 4.4	0.534

Results are expressed in mean ± standard de*via*tion; PMX-HP: Polymyxin B hemoperfusion; APACHE II: Acute physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment.

patients who reduced their norepinephrine dose by more than half within 24 h after PMX-HP. Our study also revealed a significant improvement in the inotropic score and VDI of the PMX group and suggested that PMX-HP treatment in reduced the levels of myocardial depressant mediator in cardiac function.

The role of PMX-HP in septic shock would also affect the pulmonary function by absorbing various inflammatory mediators including endotoxins and proinflammatory cytokines. The improvement in hypercytokinemia and inflammation prevented the damage to pulmonary endothelium consequently[1,25,26]. Pulmonary complications are common in septic shock, and rapidly increased due to fluid resuscitation or compromised respiratory function triggered by anesthesia after major surgery, and therefore PMX-HP might improve and protect pulmonary functions in patients after emergency abdominal surgery who has high risk of pulmonary complications such as acute respiratory distress syndrome[27]. However, we failed to detect a statistically significant improvement in pulmonary function probably due to its small sample size, and a further study with a large sample size should be needed.

In addition, one of the most common complications of septic shock is acute kidney injury (AKI) and it occurs in more than 20% of patients with sepsis that is related to higher mortality rate[28]. Ebihara *et al*[29] suggested that PMX-HP restored the angiopoietin-1 levels and diminished the levels of angiopoietin-2 in septic AKI, thereby preventing the apoptosis of renal tubular cells resulting in a protective effect against AKI[19]. Our results demonstrated a dramatic decrease in renal SOFA score, and considering the high mortality of septic AKI, authors expect that the removal of endotoxin or cytokines might protect the renal function in abdominal septic shock. Our study also showed a significant reduction in the length of ICU stay and SOFA score at 72 h indicating improvement in overall organ function. PMX-HP therapy may have improved the prognosis in the early phases of intraabdominal septic shock and promoted organ preservation, ultimately.

Despite these interesting results of the PMX-HP, our study has some limitations inherent to its retrospective design and small sample size. Since it covers a period of more than six years, the evolution of intensive care may have affected the survival. However, a single intensivist performed the treatment according to the standard protocol, and no major changes in SSC guidelines have occurred. In addition, we could not exclude the impact of renal replacement therapy such as CRRT for clinical outcomes. For next study, we will fully consider this limitation and we will perform additional subgroup analysis on modified SOFA scores to completely exclude the impact of renal replacement therapy such as CRRT for clinical outcomes. In fact, in order to overcome these limitations, we performed a propensity score matching to

Table 2 Characteristics of patients, laboratory findings, and treatment of sepsis in propensity-matched groups

	PMX-HP (*n* = 20)	Control (*n* = 20)	*P* value
Primary infection site, *n* (%)			0.166
Upper GI tract	0 (0.0)	3 (15.0)	
Small bowel	4 (20.0)	7 (35.0)	
Lower GI tract	14 (70.0)	10 (50.0)	
Hepatobiliary system	1 (5.0)	0 (0.0)	
Soft tissue infection	1 (5.0)	0 (0.0)	
Microorganisms, *n* (%)			
Gram-negative species	11 (55.0)	10 (50.0)	0.752
Gram-positive species	6 (30.0)	7 (35.0)	0.736
Fungus	4 (20.0)	3 (15.0)	0.677
No growth	5 (25.0)	7 (35.0)	0.490
Number of microorganisms, *n* (%)			0.747
Single microorganism	9 (45.0)	7 (35.0)	
Multiple microorganisms	6 (30.0)	6 (30.0)	
Laboratory test on admission			
WBC, 10^9/L	87.6 ± 64.9	94.0 ± 49.1	0.731
Platelet counts, 10^9/L	130.0 ± 102.0	163.7 ± 133.5	0.375
Hb, g/L	9.6 ± 2.0	10.5 ± 2.2	0.178
PT, %	45.7 ± 24.4	55.0 ± 16.5	0.168
Lactate, mmol/L	7.8 ± 6.9	7.2 ± 3.1	0.738
Methods of infection control, *n* (%)			1.000
Surgical intervention	19 (95.0)	19 (95.0)	
Radiologic intervention	1 (5.0)	1 (5.0)	
Other therapeutic management, *n* (%)			
pRBC transfusion, *n* (%)	11 (55.0)	19 (95.0)	0.006
Mechanical ventilator	14 (70.0)	16 (80.0)	0.537
Re-intubation	3 (15.0)	2 (10.0)	0.633
RRT	9 (45.0)	8 (40.0)	0.749

GI: Gastrointestinal system; Hb: Hemoglobin; pRBC: Packed red blood cells; PT: Prothrombin tine; RRT: Renal replacement therapy; WBC: White blood cell count; PMX-HP: Polymyxin B hemoperfusion.

correct for disease severity and baseline characteristics. Moreover, we believe that the bias might be minimized because the PMX-HP treatment was indicated to only patients with abdominal sepsis who underwent source control for the infectious foci. Additionally, the detection of further statistically significant differences in parameters such as 28-d mortality or ICU mortality was precluded due to the small sample size. A prospective multicenter randomized trial with a large sample size is needed in the near future to confirm our study results.

Actually, there have been studies to identify the effect of PMX-HP in various randomized controlled trials in the meantime. In the EUPHAS I trial of 2009[4], PMX-HP significantly reduced the 28-d mortality and improved SOFA score in patients with septic shock associated with gram-negative infeciton. In the EUPHAS 2 trial of 2014, there was a significant decrease in SOFA score in patients with only abdominal sepsis[13]. We agree that PMX-HP is more effective in patients with abdominal sepsis following surgical elimination of infection foci. In case of other gram-negative infections, such as infection of the lower respiratory tract, the control of infectious source should be accomplished *via* using antibiotics, and this limitation might be implicated in a resistance to antibiotics or drug toxicity. On the other hand, in patients with abdominal sepsis, PMX-HP may be used after complete elimination of infection focus *via* surgical control, resulting in clearance of the residual circulating endotoxin more effectively compared with other sites of infection[7]. We expect that this study, which involved only patients with abdominal sepsis controlled surgically, would be useful in establishing treatment guidelines for PMX-HP intervention.

In conclusion, PMX-HP would be a feasible treatment modality in ICU patients with peritonitis to restore organ function and improve hemodynamics. It is expected

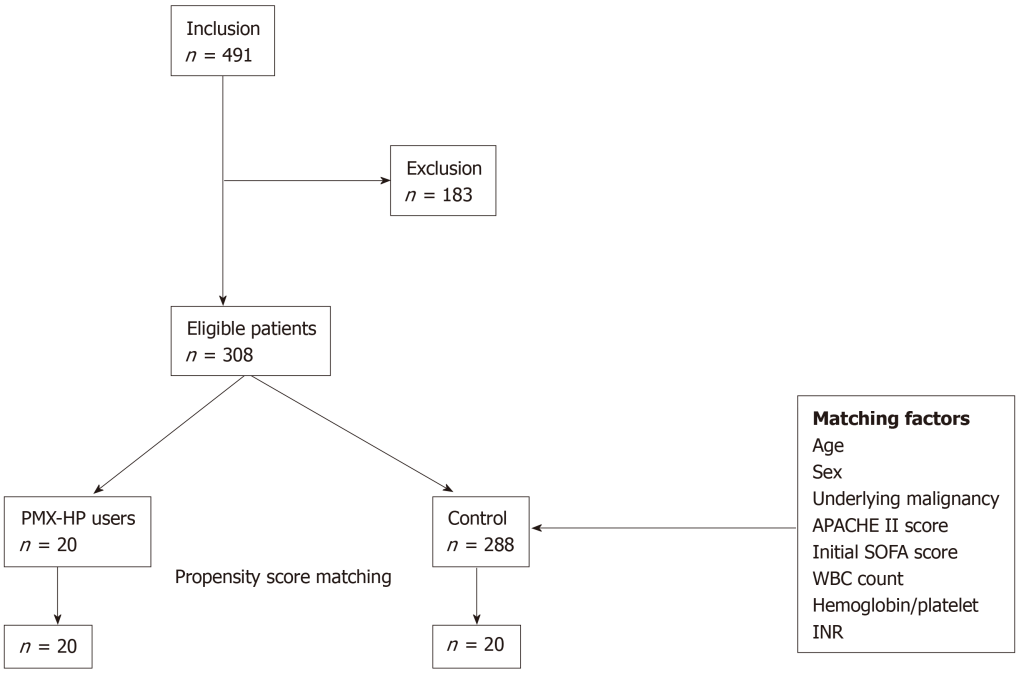

Figure 2 Outline of patient selection and propensity score matching. PMX-HP: Polymyxin B hemoperfusion; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; WBC: White blood cell; INR: International normalized ratio.

to facilitate clinical outcomes especially in patients with complete elimination of the source of GNB infection *via* surgical procedures. A further prospective study with large samples is needed to establish the precise guidelines for PMX-HP therapy.

Table 3 Comparative analysis of variables changes between baseline and 72 h after treatment

Patients	PMX-HP (*n* = 20)		Control (*n* = 20)		*P* value
	T_o[1]	T_{72}[2]	T_o[3]	T_{72}[4]	
SOFA score	11.2 ± 5.8	4.7 ± 3.5	10.0 ± 4.0	8.7 ± 7.3	0.047[a]
Respiratory SOFA	2.6 ± 1.0	1.9 ± 1.0	2.6 ± 1.5	1.8 ± 1.0	0.799
Cardiovascular SOFA	3.4 ± 1.2	0.4 ± 0.9	2.3 ± 1.8	1.2 ± 1.3	0.072
Liver SOFA	0.7 ± 0.9	1.1 ± 1.5	0.7 ± 1.3	1.4 ± 1.3	0.683
Renal SOFA	2.6 ± 1.0	0.7 ± 1.0	2.6 ± 1.5	2.8 ± 1.6	0.000[a]
Coagulation SOFA	1.6 ± 1.5	1.3 ± 1.3	1.2 ± 1.2	2.8 ± 1.8	0.014[a]
WBC, 10^9/L	87.7 ± 65.0	102.5 ± 62.7	94.0 ± 49.1	115.6 ± 59.0	0.552
Hb, g/L	9.6 ± 2.0	9.0 ± 0.9	10.5 ± 2.2	9.7 ± 1.0	0.024[a]
Inotropic score	163.7 ± 302.1	8.9 ± 19.1	90.8 ± 181.7	1.4 ± 4.2	0.006[a]
VDI	2.4 ± 3.4	0.1 ± 0.3	1.0 ± 2.0	0.0 ± 0.1	0.001[a]

[1]Immediately after completion of two session of polymyxin B hemoperfusion (PMX-HP);
[2]Seventy-two hours after completion of two session of PMX-HP;
[3]Immediately after surgical control;
[4]Seventy-two hours after conventional standard therapy according to survival sepsis campaign.
[a]$P < 0.05$, compared with variables between just before initiating treatment and 72 h after initiating the treatment in PMX-HP group and control group.
SOFA: Sequential organ failure assessment; WBC: White blood cell; Hb: Hemoglobin; VDI: Vasopressor dependency index; PMX-HP: Polymyxin B hemoperfusion.

Table 4 Mortality, length of Intensive care unit stay and ventilator free days in polymyxin B hemoperfusion and control groups

	PMX-HP (*n* = 20)	Control (*n* = 20)	*P* value
ICU mortality (%)	4 (20)	8 (40)	0.168
28-d mortality (%)	9 (45)	8 (40)	0.749
In hospital mortality (%)	10 (50)	10 (50)	1.000
Length of ICU stay (d)	10.9 ± 3.9 (5-19)	14.6 ± 6.4 (5-23)	0.036
Mechanical ventilator days (d)	5.1 ± 4.7 (0-16)	4.9 ± 5.4 (0-18)	0.926

ICU: Intensive care unit; PMX-HP: Polymyxin B hemoperfusion.

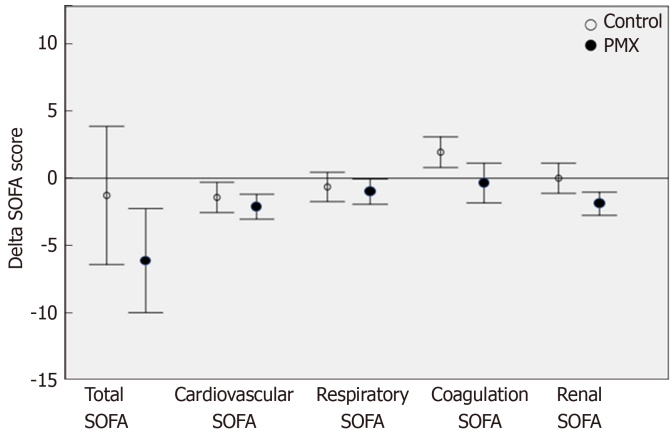

Figure 3 Comparison of the Sequential Organ Failure Assessment score at 72 h between polymyxin B hemoperfusion and control groups. Error bars represent 95% confidence intervals. Negative values of delta Sequential Organ Failure Assessment scores indicate improvement of organ function. SOFA: Sequential Organ Failure Assessment; PMX: Polymyxin B.

ARTICLE HIGHLIGHTS

Research background

Polymyxin B hemoperfusion (PMX-HP) has been used as a treatment for intra-abdominal septic

shock by absorbing and removing endotoxins of gram-negative bacilli.

Research motivation
Intra-abdominal infection is one of the common causes of septic shock and is associated with a high mortality rate despite the treatment under survival sepsis guidelines. Previous studies demonstrate the favorable results of extracorporeal removal of endotoxin.

Research objectives
The objectives of this study is to investigate the clinical efficacy of PMX-HP in patients with gram-negative septic shock who underwent abdominal surgery.

Research methodes
From January 2012 to December 2018, patients who had septic shock secondary to peritonitis were enrolled. They were classified into PMX-HP treated and control groups based on postopreative intervention using PMX-HP. The clinical outcomes were compared using 1:1 propensity score matching methods to balance the overall distribution between the two groups.

Research results
After propensity score matching, 40 patients were analyzed (20 patients in the PMX group and 20 patients in the control group). The scores of total Sequential Organ Failure Assessment (SOFA) score, renal SOFA and coagulation SOFA were significantly improved in the PMX group but not in the control group. (from 11.2 ± 5.8 to 4.7 ± 3.5 in PMX group *vs* 10.0 ± 4.0 to 8.7 ± 7.3 in control group, $P = 0.047$ from 2.6 ± 1.0 to 0.7 ± 1.0 in PMX group *vs* 2.6 ± 1.5 to 2.8 ± 1.6 in control group, $P = 0.000$, from 1.6 ± 1.5 to 1.3 ± 1.3 in PMX group *vs* 1.2 ± 1.2 to 2.8 ± 1.8 in control group, $P = 0.014$, respectively). Further, the length of intensive care unit (ICU) stay was significantly shorter in PMX group. However, no statistically significant difference was found in ICU mortality.

Research conclusions
PMX-HP is a feasible adjunct treatment for peritonitis in ICU patients with peritonitis for improved organ impairment and to stabilize hemodynamics. It would be helpful to enhance clinical outcomes especially in patients with complete elimination of the source of gram-negative bacilli infection by surgical procedure accompanied with conventional treatment of sepsis.

Research perspectives
Our study is limited by its retrospective nature and small sample size. Also, since it covers a period of more than six years, the evolution of intensive care may have affected the survival. Further studies especially prospective multicenter randomized trial with a large sample size should be conducted to confirm our study results.

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CASE REPORT

Atraumatic splenic rupture after cocaine use and acute Epstein-Barr virus infection: A case report and review of literature

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Author contributions: Kwok AMF was the primary treating surgeon, performed the literature review and composed and reviewed the manuscript.

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Abstract

BACKGROUND

Atraumatic splenic rupture (ASR) accounts for just over 3% of all cases of splenic rupture and is associated with a high mortality rate. The most common culprit is acute infection with Epstein-Barr virus (EBV) but other documented aetiologies include neoplasia, other viral/bacterial infections, acute and chronic pancreatitis, amyloidosis and anticoagulant medications. There are four previous reports of cocaine-associated ASR but never before has it been documented in combination with concurrent acute EBV infection.

CASE SUMMARY

A 21-year-old man presented to hospital with acute left shoulder pain which radiated to the right shoulder and upper abdomen. He denied any history of recent trauma and had no relevant past medical history. He took no regular prescription medications but had used cocaine within the previous 24 h. Investigations revealed splenomegaly, a Grade 3 subcapsular splenic haematoma, moderate haemoperitoneum and an incidental 9 mm splenic artery pseudoaneurysm. There was also serological evidence of acute EBV infection. Prophylactic endovascular embolisation of the pseudoaneurysm was performed and the splenic rupture was managed non-operatively. The patient remained admitted in hospital for seven days and did not require any transfusion of blood products. Serial imaging showed complete resolution of the haemoperitoneum after 5 wk. The importance of abstinence from illicit drug use was emphasised to the patient but it is unknown whether or not he remains compliant.

CONCLUSION

This case demonstrates that ASR is a rare condition that can result from acute EBV infection and cocaine ingestion and requires a high index of suspicion to diagnose clinically.

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Key words: Atraumatic; Spontaneous; Splenic rupture; Cocaine; Epstein-Barr virus; Splenic artery pseudoaneurysm; Case report

Core tip: Atraumatic splenic rupture (ASR) is an uncommon condition that carries a high mortality rate if not recognised early. We describe the case of a 21-year-old man who suffered ASR as a result of a both acute Epstein-Barr virus (EBV) infection and recent cocaine ingestion. An incidental splenic artery pseudoaneurysm was also discovered on imaging which required endovascular embolisation. An association between ASR, acute EBV infection, cocaine use and splenic artery pseudoaneurysm has never been described previously in the literature. ASR requires a high index of suspicion to diagnose clinically and requires prompt, appropriate management to reduce morbidity and mortality.

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INTRODUCTION

Splenic rupture is traditionally observed in the context of trauma to the upper abdomen or lower left thoracic region. Increasingly there are reports of atraumatic splenic rupture (ASR) occurring in the absence of an obvious precipitant and a number of mechanisms have been proposed in the literature. The overall incidence of ASR is poorly defined but is thought to represent around 3% of all splenic ruptures[1]. Infectious mononucleosis, caused by acute infection with Epstein-Barr virus (EBV), has been implicated as the single largest contributor to this phenomenon[2]. A number of cases have also been observed in patients taking newer oral anticoagulant medications, such as the direct Factor Xa inhibitors apixaban and rivaroxaban[3,4]. Irrespective of the underlying cause mortality from ASR is high at 12.2%, but had approached 30% in earlier reports[2,5].

We aim to raise awareness of this diagnosis to facilitate its prompt recognition in a patient with acute abdominal pain and clinical evidence of bleeding without a history of trauma or anticoagulant use. This is essential to arranging early management and to ensure optimal patient outcomes.

We present the case of a 21-year-old man who presented with haemoperitoneum secondary to an acute ASR. Closer questioning and further investigations revealed that he had two simultaneous risk factors for ASR as well as an incidental splenic artery pseudoaneurysm, which itself is another risk factor for spontaneous haemoperitoneum.

CASE PRESENTATION

Chief complaints

A 21-year-old man presented to our institution with sudden onset pain in the left trapezius and shoulder.

History of present illness

At the time of symptom onset he was engaged at work driving heavy machinery, but denied any recent history of injury or trauma. He had not been recently unwell and denied any constitutional symptoms such as weight loss or fever. Over the following five hours his pain began to also affect his right shoulder and there was associated generalised abdominal pain of increasing severity, most marked in the left and right upper quadrants.

History of past illness

The patient had no significant past medical history, specifically never having had an episode of pancreatitis before. He was not taking any regular prescription

medications but upon closer questioning admitted to occasional recreational cocaine use, the most recent ingestion of which was within 24 h of hospital admission.

Family history
The patient had no significant family history of medical illness.

Physical examination
Clinical examination revealed a well-looking man in no obvious distress. Although he was mildly tachypnoeic (20 breaths/min) his other vital signs were normal (heart rate 78 beats/min, blood pressure 129/84 mmHg, temperature 36.9 °C and oxygen saturations 99% on room air). His abdomen was not distended but there was generalised percussion tenderness most profound in the left and right upper quadrants. Examination of his shoulders revealed no focal tenderness and full active and passive ranges of motion with preserved motor and sensory function.

Laboratory examinations
Initial biochemical findings included a haemoglobin of 138 g/L, leucocyte count 4.74 × 10^9/L, platelets 197 × 10^9/L and international normalised ratio of 1.1. Plain chest X-ray was unremarkable. Repeat blood tests were performed after five hours due to the increasing severity of his symptoms which revealed a haemoglobin of 99 g/L, indicating a significant decrease from the initial value.

Imaging examinations
The combination of worsening abdominal pain and a falling haemoglobin prompted a computed tomography (CT) scan of his abdomen and pelvis which was conducted with both oral and IV contrast in the portal venous phase. It revealed a large amount of high-density fluid within the abdominal cavity, consistent with haemoperitoneum. Moderate splenomegaly (16.4 cm × 9.9 cm × 7.4 cm) and an overlying Grade 3 subcapsular splenic haematoma[6] were also noted (Figure 1).

A repeat CT with IV contrast in the arterial phase (CT angiogram) was then performed to exclude the presence of active arterial bleeding. Although no active extravasation was observed on this study, an incidental splenic artery pseudoaneurysm measuring 9.1 mm × 8.3 mm × 8.1 mm was discovered near the superolateral aspect of the spleen (Figures 2 and 3).

Further diagnostic work-up
In the search for an underlying precipitant, viral serological testing was ordered despite the absence of typical prodromal symptoms. Both IgM and IgG antibodies against EBV viral capsid antigen were detected 24 h later.

FINAL DIAGNOSIS
The final diagnosis of the presented case is ASR due to a combination of recent cocaine ingestion and acute EBV infection. There was also an incidental finding of a 9.1 mm non-bleeding splenic artery pseudoaneurysm at the superolateral aspect of the spleen.

TREATMENT
The patient was resuscitated with intravenous crystalloid fluids and, despite his haemodynamic stability, a precautionary intensive care review was requested due to the degree of haemoperitoneum demonstrated on CT and his falling haemoglobin level. Transfusion of blood products was not performed due to his stable clinical status and lack of any underlying coagulopathy.

Upon incidental discovery of a splenic artery pseudoaneurysm, it was decided that prophylactic intervention would be appropriate to reduce the chance of spontaneous rupture. After discussion with the consultant radiologist, formal catheter angiography was performed *via* a right common femoral artery puncture and a 8 mm × 13.5 mm Amplatzer Vascular Plug (St. Jude Medical™, Minnesota, United States) was deployed within the splenic artery between the dorsal pancreatic artery and the pancreatic magna artery (Figure 4). Subsequent angiography demonstrated successful occlusion of the proximal splenic artery and an absence of distal flow (Figures 5 and 6).

The patient was allowed to mobilise gently around the ward and given a normal diet. He remained clinically stable throughout the remainder of his admission with haemoglobin levels being maintained at or above 105 g/L without the need for blood transfusion. His abdominal pain gradually subsided and there was no clinical

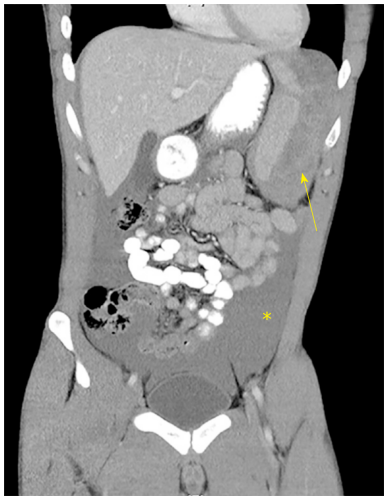

Figure 1 Coronal slice of abdominal computed tomography with intravenous contrast in the portal venous phase demonstrating haemoperitoneum (asterisk) and splenic subcapsular haematoma (arrow).

evidence of rebleeding. Progress CT on day 5 demonstrated a marked reduction in the size of the splenic haematoma and the amount of free intraperitoneal blood (Figure 7). No splenic infarction was noted on this repeat scan, likely owing to the presence of a rich collateral arterial supply.

OUTCOME AND FOLLOW-UP

The patient was discharged uneventfully on day 7 of admission with advice to avoid exertional activity or contact sports for 4 wk and to cease illicit drug use indefinitely.

At initial 3-wk follow-up he remained well and there was no evidence of post-procedural complications. Advice to cease cocaine was re-emphasised to the patient. A progress CT performed 2 wk after the initial review demonstrated complete resolution of haemoperitoneum and almost-complete resolution of the splenic subcapsular haematoma. The patient has not re-presented to hospital with abdominal pain or any other complaint in the following five months. It is unknown whether or not he continues to use recreational cocaine.

DISCUSSION

ASR is a potentially life-threatening condition which affects males twice as frequently as females and predominantly occurs in middle age (mean age 45 years)[2]. Due to the of lack an internationally-recognised consensus regarding classification, the literature consists of sporadic case reports which attribute various causes to making the spleen vulnerable to spontaneous bleeding in the absence of trauma. Although acute EBV infection is cited as the most common cause of ASR[2], less common causes include cytomegalovirus infection[7], tuberculosis[8], meliodosis (infection with *Burkholderia pseudomallei*)[9], amyloidosis[10], systemic lupus erythematosus[11] and splenic vein thrombosis due to prothrombin gene mutation[12]. There are even reports of ASR being caused by an ectopic pregnancy[13] and splenic metastases of melanoma[14].

In an attempt to bring together the plethora of known or suspected aetiologies, Renzulli *et al*[2] performed a systematic review of ASR and devised a classification system comprising of six main groups: Neoplastic disorders, infectious disorders, inflammatory disorders, iatrogenic (pharmacological) causes, mechanical disorders and idiopathic (those involving a normal spleen). As a group, neoplasia is the most common aetiology (30.3%) and consists mainly of haematological conditions such as lymphoma, leukaemia and myeloproliferative disorders. Infectious disorders are the 2nd most common cause as a group (27.3%) although EBV was the single most common cause of ASR overall (11.0%). Anticoagulants are the main cause within the pharmacological group, with one review attributing up to 33% of cases of ASR to medications such as apixaban and rivaroxaban[3]. Interestingly, only 7% of cases of ASR were found to be truly idiopathic where no other predisposing factors could be identified and where the spleen was found to be normal following pathological examination, indicating that the vast majority of cases (93%) are associated with

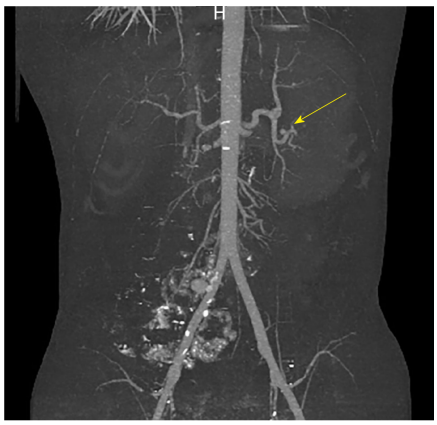

Figure 2 Coronal slice of computed tomography angiogram demonstrating splenic artery pseudoaneurysm (arrow) with no evidence of active bleeding (measurements 9.1 × 8.3 × 8.1 mm).

underlying systemic conditions or histological abnormalities of the spleen. Splenomegaly was noted to be a common feature in ASR and is found in 55% of cases.

With respect to operative rates and mortality, Renzulli *et al*[2] found that 85.3% of patients had surgery within 24 h of diagnosis (with an associated mortality rate of 7.4%), while the remaining 14.7% of patients who were managed conservatively had a mortality rate of 4.4%. Non-operative management was successful in up to 80% of those who were initially managed conservatively, yielding overall splenic salvage rates of 13.7%. Overall mortality was 12.2% but was found to be higher in patients over 40 years of age. No sex-based difference was found.

Splenic rupture is the leading cause of death in infectious mononucleosis and should be considered in any patient with abdominal pain and known or suspected acute EBV infection[15,16]. The presence of left shoulder pain in this setting is known as Kehr's sign and is present in 17% of patients with ASR[17]. Diagnosis of infectious mononucleosis consists of appropriate clinical findings (the "classical triad" of fever, pharyngitis and lymphadenopathy) and serological evidence (detection of anti-viral capsid antigen IgM antibodies)[18]. Approximately 0.5% of these patients will suffer from ASR with an associated mortality rate of 9%-30%[5,19,20]. Rupture is most common within the first 3 wk but may present as late as 8 wk after acute infection. Predisposition to ASR in this setting is thought to arise from mononuclear cell proliferation causing splenomegaly, vasculitis of the larger follicular veins and parenchymal and capsular stretch and inflammation[5,20].

Cocaine is a potent sympathomimetic and causes vasoconstriction and elevation of blood pressure by blocking noradrenaline reuptake at the synaptic level. The resultant hypertension can be severe enough to precipitate haemorrhagic cerebral infarction while vasospasm can result in ischaemic strokes and impaired mucosal blood flow to the gastrointestinal organs. Increased expression of platelet-derived growth factor after cocaine ingestion increases vascular permeability which may also increase the likelihood of haemorrhagic transformation in ischaemic strokes. Cases of gastroduodenal perforation and bowel ischaemia have also been attributed to cocaine use[21]. In cases of ASR associated with recent cocaine ingestion, it has been postulated that the initiating event is the development of splenic infarctions as a result of profound vasospasm. Increased vascular permeability and hypertension then result in haemorrhagic transformation and eventual capsular rupture[22]. To our knowledge there are only four previous reports of cocaine-associated ASR[21-23], making this quite a rare phenomenon.

Following splenic rupture, autotransplantation of splenic tissue into the peritoneal cavity is a well-known phenomenon and was named "splenosis" by Buchbinder and Lipkoff in 1939[24]. It is usually described in the setting of previous traumatic rupture but its occurrence following ASR is highly plausible. Splenosis is present in up to 76% of patients who have undergone splenectomy for trauma and is most commonly found in the pelvis but has also been described on the greater and lesser omenta, the diaphragm, small and large bowel, in subcutaneous tissue beneath a surgical scar, within the parenchyma of the liver and even within the thorax[25]. It can be distinguished from congenital splenunculi by the lack of a true hilum and by its blood supply being derived from multiple peripheral feeding vessels penetrating capsular tissue[26].

The clinical significance of splenosis is twofold: Firstly, awareness and recognition of this condition is required to differentiate it from carcinomatosis or endometriosis if

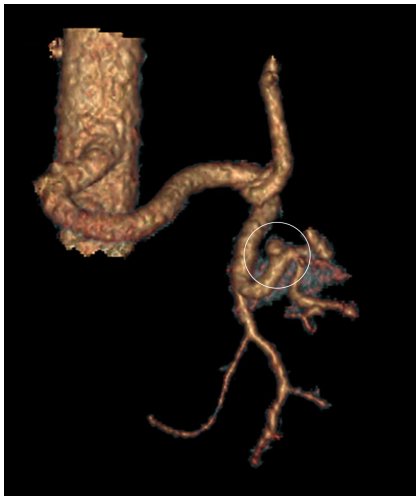

Figure 3 3D reconstruction of computed tomography angiogram demonstrating splenic artery pseudoaneurysm (circled).

it is encountered intra-operatively[24]. Secondly, it must be considered when there is recurrence of haematological conditions (such as idiopathic thrombocytopenia purpura, ITP) following splenectomy[25]. Splenosis is usually asymptomatic and may even provide some degree of immunological function in the absence of the spleen[27]. If the condition is suspected (for example, recurrent ITP after splenectomy), a ^{99}Tc scintigram using heat-damaged erythrocytes is the most sensitive and specific investigation to detect residual splenic tissue and is the imaging modality of choice[27].

Another possible sequela of splenic rupture is the development of splenic pseudocysts. Although they are asymptomatic in up to 60% of cases, patients may present with pseudocyst rupture or infection or with compression of surrounding structures when significant enlargement has occurred[28]. Diagnosis is made based on imaging and a history of prior splenic injury, but they must be differentiated from true splenic cysts such as those found in hydatid disease. Intervention is indicated when pseudocysts become symptomatic. Total splenectomy was traditionally performed but the theoretical risk of overwhelming post-splenectomy infection has increased enthusiasm for spleen-preserving approaches such as cystectomy and partial splenectomy. Laparoscopic approaches have been performed successfully[29] and one report described the use of indocyanine green in the resection of a large pseudocyst in order to help differentiate it from normal parenchyma and hence maximise preservation of normal splenic tissue[28]. Percutaneous drainage and surgical deroofing are less invasive but are associated with high recurrence rates of up to 40%[29].

Splenic artery pseudoaneurysms (SAPA) are the most common form of all visceral artery pseudoaneurysms and account for 46%[30]. Unlike true visceral artery aneurysms, pseudoaneurysms are more commonly encountered in males and are much more prone to rupture (76% *vs* 3%)[31,32]. SAPA are seen almost exclusively in patients with chronic pancreatitis, which causes long-standing inflammation and erosion of the vessel wall that compromises its integrity, although a small number are iatrogenic from surgical or radiological procedures[33]. Between 4.5%-17% of all patients with chronic pancreatitis have SAPA and although most are asymptomatic, rupture is fatal in 90% of cases[32,34,35]. The most common site of rupture is into a pancreatic pseudocyst which causes bleeding into the pancreatic duct and subsequently the gastrointestinal tract[33]. Only 10% of SAPA rupture freely into the peritoneal cavity[32]. Risk of rupture does not correlate with size and hence all SAPA should be treated when discovered. Endovascular plugs, coils or thrombin embolisation are the usual methods[32-34], but other options include splenic artery ligation and splenic artery stent grafting[30,33]. Splenectomy is reserved for cases in which more conservative measures have failed, are inappropriate (due to clinical instability) or are not available. Possible complications after endovascular management of SAPA occur in 12.5% and include splenic infarction, coil/stent migration, rebleeding and puncture-site haematoma[31].

Our patient had two known risk factors for ASR as well as an incidental splenic artery pseudoaneurysm which itself is a risk factor for spontaneous rupture and acute haemorrhage. The timing of the recent cocaine ingestion makes it a likely contributing factor to the development of ASR along with acute EBV infection. Our patient had

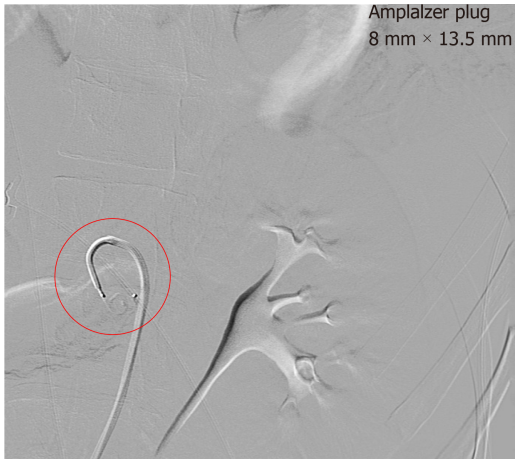

Figure 4 Still image from formal angiogram demonstrating intra-arterial catheter and deployment of endovascular plug (circled, visible beyond the tip of the catheter).

both splenomegaly and Kehr's sign, which are found in 55% and 17% of cases respectively, but unlike previous cases the acute EBV infection was subclinical and otherwise asymptomatic. In keeping with the literature, our patient had pre-emptive embolisation of an incidentally-detected SAPA owing to its high risk of rupture.

In summary, this combination of acute EBV infection and recent cocaine use causing ASR, in association with an incidental splenic artery pseudoaneurysm, is an interesting variant of a recognised phenomenon that has not been previously reported in the literature. Opportunities for further research in this area are numerous, given that non-operative management is being employed with increasing frequency and that the wide availability of CT scanning is likely to see an increase in the number of cases of ASR being diagnosed. Nevertheless, since only 7% are considered idiopathic, this implies that a large number of cases are associated with an underlying abnormality of the spleen. A longitudinal cohort study may be employed to ascertain the long-term incidence of primary splenic disorders in patients who undergo operative and non-operative management for ASR. Additionally, routine questioning of patients with ASR regarding illicit drug use may be helpful in ascertaining their role in its pathogenesis.

CONCLUSION

ASR is an uncommon event and accounts for 3% of all splenic ruptures. It can be classified as pathological (93%) or idiopathic (7%), with pathological causes including neoplasia, infections, inflammation and iatrogenic injury. Infectious mononucleosis is the largest single cause of ASR worldwide, even when otherwise asymptomatic as in our patient. This case highlights the importance of early recognition of ASR, the possibility of success with a non-operative approach (depending on the Grade of injury) and the need for prompt intervention for visceral artery pseudoaneurysms due to their high risk of rupture, independent of size. The combination of ASR, acute EBV infection, recent cocaine use and the presence of a splenic artery pseudoaneurysm has not been previously described in the literature.

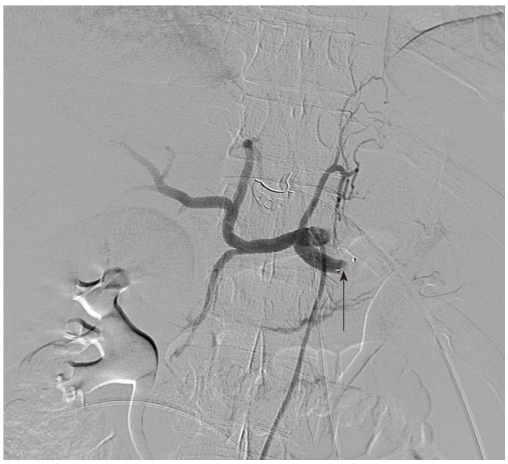

Figure 5 Coeliac angiography after deployment of endovascular plug. Note the abrupt cessation of blood flow in the proximal splenic artery (arrow).

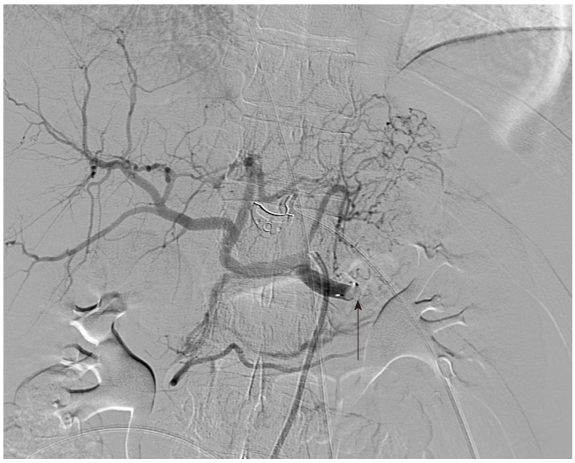

Figure 6 Delayed still image from coeliac angiogram confirming complete occlusion of the proximal splenic artery by endovascular plug (arrow).

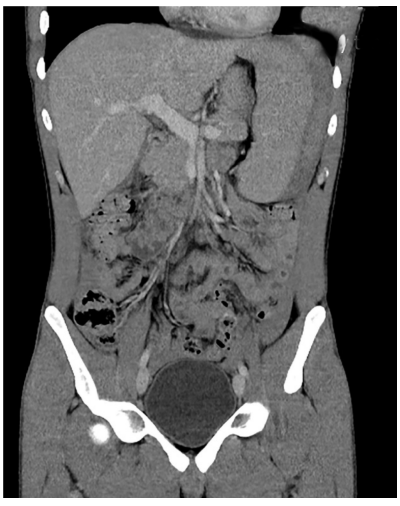

Figure 7 Coronal slice of abdominal computed tomography on day 5 of admission, demonstrating reduction in size of both haemoperitoneum and splenic subcapsular haematoma.

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CASE REPORT

Early pancreatic cancer in IgG4-related pancreatic mass: A case report

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Author contributions: Glinka J and Calderón F designed the report; Calderón F collected the patient's clinical data; Spina J, Mullen E and Pol M provided relevant figures; Glinka J, Calderón F, Hyon SH, Gadano A, de Santibañes M and de Santibañes E analyzed the data and wrote the paper.

Informed consent statement: Consent was obtained from the patient for publication.

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Abstract

BACKGROUND

IgG4-related disease can manifest diversely, including autoimmune pancreatitis and IgG4-related cholangiopathy. We are reporting a very unusual cause of pancreatic cancer triggered in a previously unknown IgG4-related disease.

CASE SUMMARY

A 75-year-old man was diagnosed with a 43 mm × 33 mm pancreatic head tumor after consulting for abdominal pain and jaundice. A pancreaticoduodenectomy was carried out uneventfully, and the histopathology report showed an early stage of acinar-cell pancreatic cancer. The patient reconsulted on the 30th postoperative day with fever, jaundice and asthenia. Magnetic resonance cholangiopancreatography evidenced an extense bile duct stricture. A percutaneous biliary drainage proved to be ineffective, even after exchanging it with larger bore drainage. Reviewing the surgical specimen, features compatible with IgG4-related disease were observed. Consequently, empiric treatment with steroids was initiated achieving excellent results.

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CONCLUSION
IgG4-related disease may cause chronic inflammation of the pancreas and can condition pancreatic malignancies.

Key words: Autoimmune pancreatitis; Pancreatic adenocarcinoma; Pancreatic cancer; IgG4; IgG4-related disease; Case report

Core tip: Until today, the relationship between autoimmune pancreatitis and pancreatic cancer was not clear, and there are no studies in this regard. We are reporting a very unusual cause of pancreatic cancer triggered in a previously unknown IgG4-related disease and conducted an up-to-date literature review.

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INTRODUCTION

IgG4-mediated disease is a systemic condition that can manifest in various clinical forms, including autoimmune pancreatitis (AIP type 1) and IgG4-related cholangiopathy[1-3]. It is well known that chronic pancreatitis is a physiopathological model for pancreatic adenocarcinoma (PAC), but there is no firm evidence that AIP can serve as a pathway for pancreatic neoplasm[4]. We are reporting a very unusual cause of pancreatic cancer (PC) triggered in a previously unknown IgG4-related disease.

CASE PRESENTATION

Chief complaints
Upper abdominal pain, pruritus and jaundice.

History of past illness
The patient had history of smoking, ischemic cardiomyopathy and type 2 diabetes mellitus.

History of present illness
A Caucasian 75-year-old man was diagnosed with pancreatic tumor in another center. Upon endoscopic retrograde cholangiopancreatography and plastic biliary stenting (7-Fr × 10 cm), the patient was referred to our institution for further treatment. Upon discussion in a multidisciplinary oncology meeting, surgical exploration was decided under the presumption of a potentially resectable PAC of the head and uncinate process. No preoperative biopsy was performed.

Physical examination
Physical examination was relevant for jaundice, minor skin lesions due to scratching and a mild upper abdominal tenderness without peritoneal signs.

Laboratory testing
Plasma laboratory was positive for total bilirubin: 7.6 mg/dL; direct bilirubin: 4.0 mg/dL; alkaline phosphatase: 900 IU; and plasma CA 19-9: 1380 IU.

Imaging examination
Abdominal computed tomography scan revealed a 43 mm × 33 mm mass embracing the pancreatic head and uncinate process with an uncertain superior mesenteric vein abutment. No metastatic disease was found in the routine work-up (Figure 1).

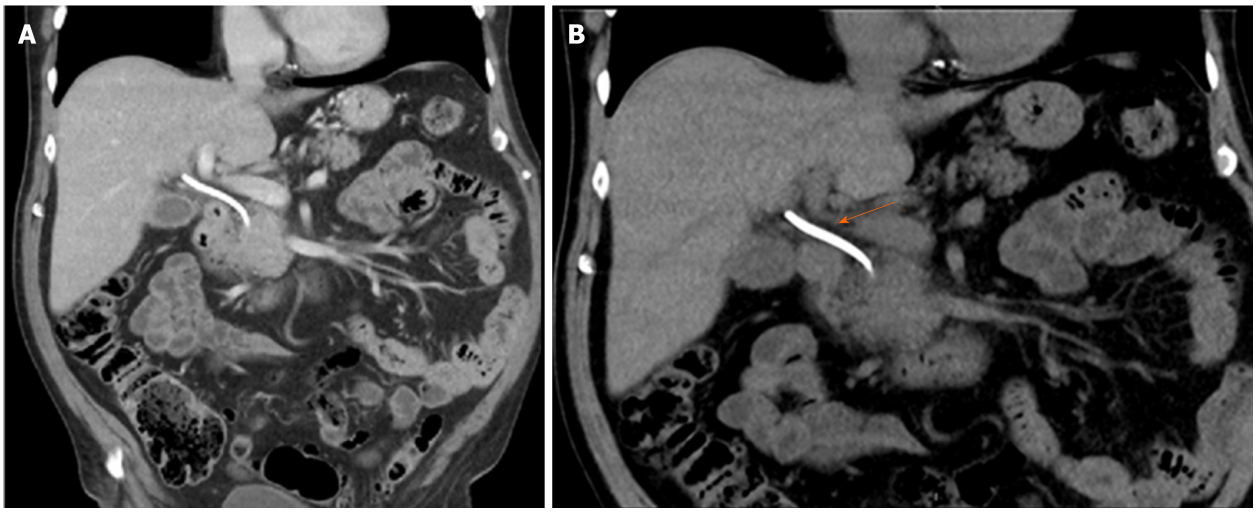

Figure 1 Coronal projection of the preoperative abdominal computed tomography scan. A: The pancreatic head tumor can be appreciated; B: Orange arrow showing the plastic stent placed in the bile duct before referral.

FINAL DIAGNOSIS

Early PC within a probable IgG4-related disease pancreatic mass.

TREATMENT

A pancreaticoduodenectomy (Whipple procedure) was performed.

OUTCOME AND FOLLOW-UP

Surgery was carried out uneventfully, and the patient was discharged on the 7th day after surgery. Histopathology of the surgical specimen revealed a well differentiated acinar cell PC with negative margins. No perivascular or perineural invasion was observed, and none of the fourteen resected lymph nodes were positive for malignancy. Thirty days after surgery, the patient presented at the Emergency Department with fever, jaundice and a noteworthy asthenia. Laboratory exams revealed total bilirubin: 14.0 mg/dL; direct bilirubin: 8.6 mg/dL; alkaline phosphatase: 950 IU; aspartate aminotransferase: 147 IU; and alanine aminotransferase: 56 IU.

A magnetic resonance cholangiopancreatography showed intrahepatic bile duct dilation with a biliary stenosis extending from the hepatic carrefour to the hepatojejunostomy. Presuming an anastomotic stricture, a percutaneous transhepatic cholangiography was done, followed by insertion of an internal/external, 8.5-Fr biliary drainage with the pigtail locked into the jejunal loop. Plasma bilirubin worsened, reaching levels of total bilirubin: 20 mg/dL and direct bilirubin: 11 mg/dL at 7 d post procedure. The 8.5-Fr drain was replaced by a 10.2-Fr drain, but no improvement occurred.

A new magnetic resonance cholangiopancreatography revealed persistent intrahepatic bile duct dilation and a common bile duct stricture from the biliary confluence to the anastomosis with an eccentric parietal growth from the common bile duct (Figure 2). On histopathological revision of the resected specimen and surrounding the neoplastic lesion, pathologic characteristics of IgG4-related disease could be recognized. There was an intense lymphoplasmacytic infiltrate predominantly on a periductal fashion, a trabecular fibrotic pattern and focal vascular structures with obliterative phlebitis.

After immunohistochemical evaluation, most of the plasma cells were IgG positive with more than 50 IgG4 positive plasma cells/high power field and an IgG4/IgG ratio greater than 40% (Figure 3). Because the lesion met most of the Honolulu Criteria a diagnosis of acinar cell pancreatic cancer in a context of a probable IgG4-related disease was made[5]. The clinical context in addition to the histopathology and immunohistochemistry allowed inferring a systemic IgG4-related disease. Autoimmune cholangiopathy was then presumed, which mandated starting steroid

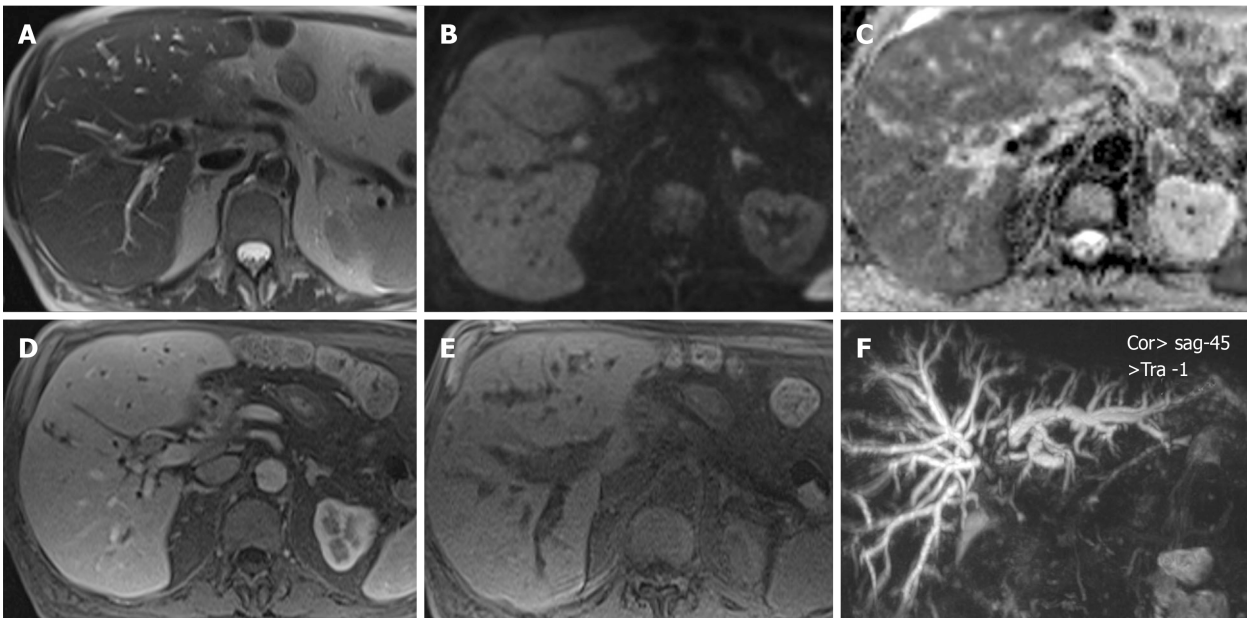

Figure 2 Magnetic resonance cholangio-pancreatography showing parietal concentric ingrowth of the main bile duct with stenosis from the hepatic carrefour up to the hepaticojejunostomy with dilatation of intrahepatic bile ducts. A: Axial T2 with concentric parietal growth; B: Diffusion-weighted imaging b800. Hyperintensity; C: Apparent diffusion coefficient with hyperintensity; D: Axial T1 without contrast; E: Axial in a portal phase; F: Three dimensional cholangiography showing dilation of intrahepatic ducts superior to the hepatic carrefour with stenosis from the carrefour up to the anastomosis.

therapy with 0.6 mg/kg-body-weight of meprednisone daily (40 mg daily). Upon 7 d of treatment, liver function tests normalized, and all symptoms disappeared allowing gradual reduction in meprednisone dosage up to 8 mg daily.

DISCUSSION

The IgG4-related disease is considered a systemic condition, which has clinical manifestations in diverse organs. AIP and cholangiopathy are two of the many manifestations of this rare disorder[6]. Patients with AIP can often manifest a pancreatic mass simulating a PC. In this setting, the differential diagnosis is usually challenging and often confirmed after surgical resection[7,8].

In certain cases, determination of IgG4 serum level and the presence of a characteristic radiology may serve to differentiate between AIP and PC[9,10]. Even so, in the study reported by Pak *et al*[11], up to 9% of pancreatic masses due to PC have high serum IgG4. Therefore, overconfidence in this marker and the assumption that a pancreatic mass is an AIP may lead to dangerously misdiagnosing a PAC and consequently missing a curative chance. In the study by Macinga *et al*[12], their histopathology specimens of resected PAC were retrospectively analyzed. They found an impressive 40% of AIP coexisting with PAC. As the patient reported here presented with jaundice, weight loss, a pancreatic mass in the imaging studies and high CA 19-9 serum marker, a PC was assumed as the main diagnosis and neither specific autoimmunity studies nor a biopsy prior to surgery was performed.

After surgical resection of the mass and a confirmatory histopathology of acinar-cell PC, early jaundice occurred, which raised the suspicion of stricture of the biliodigestive anastomosis. However, the lack of response to effective biliary drainage as well as the development of new intrahepatic bile duct strictures led us to review the specific immunohistochemistry of the surgical specimen. Subsequent steroid therapy resulted in a spectacular improvement of cholestasis, confirming the diagnosis. Until today, the relationship between AIP and PC was not clear, and there are no studies in this regard[13].

Furthermore, in a recent review by Okamoto *et al*[4], not only the correlation between these entities is refused, but also AIP is considered as a paraneoplastic syndrome of PC and not its determinant. There is agreement that chronic inflammation is a major determinant of biliopancreatic malignancies due to chronic pancreatitis and autoimmune cholangiopathy being well recognized risk factors[14]. Therefore, it may not be surprising that a causal association in the natural history of AIP can be established with precision in the future.

An unsettled issue is how to differentiate patients who are in an intermediate stage;

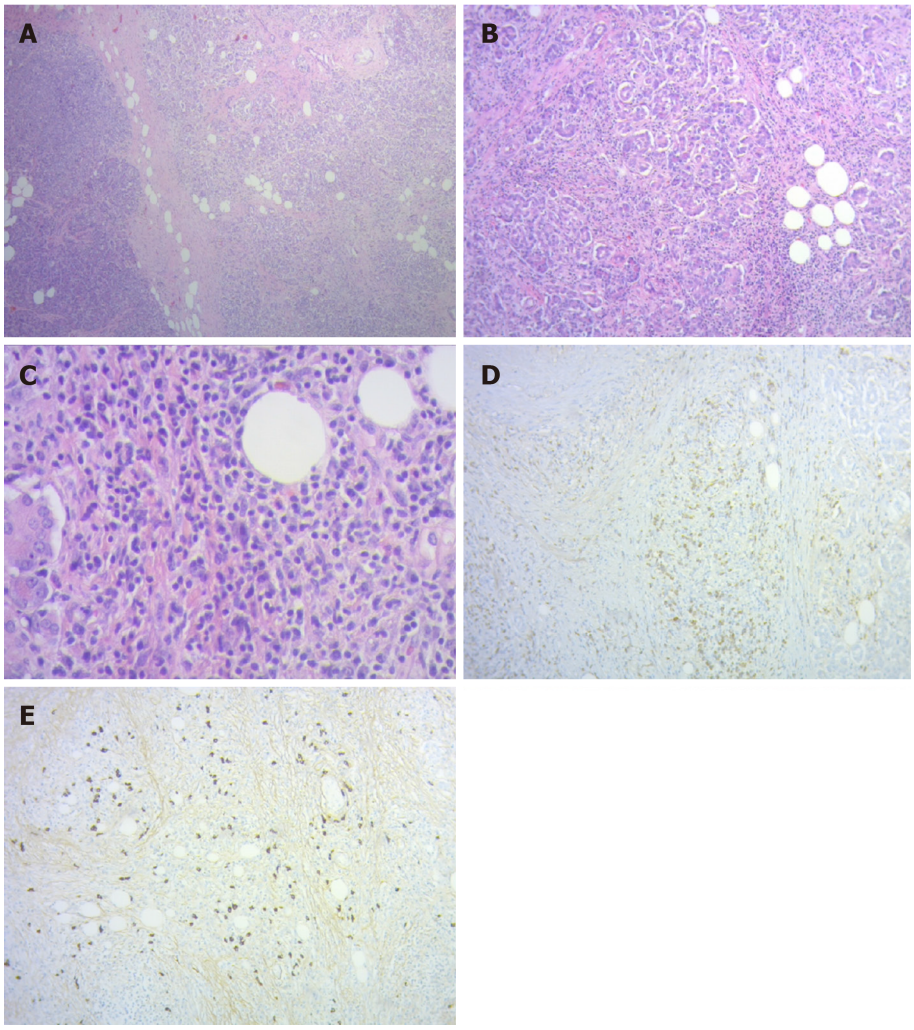

Figure 3 Histopathological analysis of the surgical specimen. A: Limits between normal pancreatic tissue and carcinoma (hematoxylin and eosin 40 ×); B: Lymphoplasmacytic peritumoral infiltration (hematoxylin and eosin 100 ×); C: Plasmacytic peritumoral infiltration (hematoxylin and eosin 400 ×); D: Immunohistochemistry with IgG positive plasma cells; E: Immunohistochemistry with frequent IgG4 positive plasma cells.

that is, determining who carries a pancreatic mass or a biliary stricture that will progress to malignancy. This is mandatory to provide each patient the best available treatment. Improving knowledge on this unusual disease may result in an earlier diagnosis and a timely therapy.

CONCLUSION

All efforts must be addressed to correctly diagnose patients with suspected IgG4-related disease so as to offer them the most appropriate and timely treatment. Misdiagnosing an AIP with a mass and a PC could be catastrophic. On the other hand, performing a pancreaticoduodenectomy in a patient with a pancreatitis is not harmless, even in specialized centers. Thus, further studies to determine a precise causal correlation between AIP and PC are needed.

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