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# Pancreatolithiasis: Does Management Depend on Clinical Manifestations?

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
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Literature Search F  
Funds Collection G

ABDE 1 **Daniel Paramythiotis**  
ABEF 2 **Eleni Karlafti**  
BEF 1 **Angeliki Sevasti Kollatou**  
BEF 1 **Theodora Simou**  
BD 3 **Xanthippi Mavropoulou**   
B 3 **Elisavet Psoma**  
BD 3 **Vasileios Rafailidis**   
B 3 **Angeliki Papachristodoulou**  
B 3 **Nikoletta Pyrrou**  
BF 1 **Aristeidis Ioannidis**  
BF 1 **Stavros Panidis**  
D 1 **Antonios Michalopoulos**

1 1<sup>st</sup> Department of Propaedeutic Surgery, AHEPA University General Hospital of Thessaloniki, Aristotle University of Thessaloniki, Thessaloniki, Greece  
2 Department of Emergency, AHEPA University General Hospital of Thessaloniki, Aristotle University of Thessaloniki, Thessaloniki, Greece  
3 Department of Clinical Radiology, AHEPA University General Hospital of Thessaloniki, Aristotle University of Thessaloniki, Thessaloniki, Greece

**Corresponding Author:** Angeliki Sevasti Kollatou, e-mail: kollatoua@auth.gr  
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**Case series**  
**Patients:**  
**Final Diagnosis:**  
**Symptoms:**  
**Clinical Procedure:**  
**Specialty:**  
**Objective:**  
**Background:**

**Male, 78-year-old • Female, 27-year-old**

**Pancreatic duct stones**

**Abdominal pain**

—

**Surgery**

**Rare disease**

Pancreatic calculi (PC) or pancreatolithiasis refers to the presence of stones in the main pancreatic duct (MPD), side branches, or parenchyma of the pancreas. It is highly associated with chronic pancreatitis (CP), and is present in 50-90% of those patients. The stone formation can be attributed to a diversity of factors, all of them leading to obstruction in the duct, hypertension of its distal part, increased intraductal and parenchymal pressure, and inflammation, causing the standard symptom, epigastric pain. Immediate restoration of pancreatic secretion flow is of utmost importance and can be achieved with both endoscopic and surgical techniques. Endoscopic techniques include endoscopic retrograde cholangiopancreatography (ERCP) combined, if possible, with extracorporeal shock wave lithotripsy (ESWL), while surgical techniques consist of drainage and resection procedures. The choice of treatment for PC depends on the location, size, and number of stones, and the existence of other complications.

**Case Reports:** We present 2 cases that were diagnosed with PC, in which clinical symptoms, laboratory results, and imaging examinations were different, suggesting the variety of manifestations pancreatolithiasis can cause. Each patient was treated differently, according to their clinical situation and the presence or absence of complications. Both patients were discharged and fully recovered.

**Conclusions:** The management of pancreatolithiasis can be demanding in some cases, mostly when there are complications. The purpose of this case report is to indicate the importance of personalized treatment for each patient, as different approaches to the same medical condition should be easily identified and successfully treated.

**Keywords:** **Pancreatic Ducts • Endoscopy, Digestive System • Cholangiopancreatography, Endoscopic Retrograde • Lithotripsy • Pancreatic Pseudocyst**

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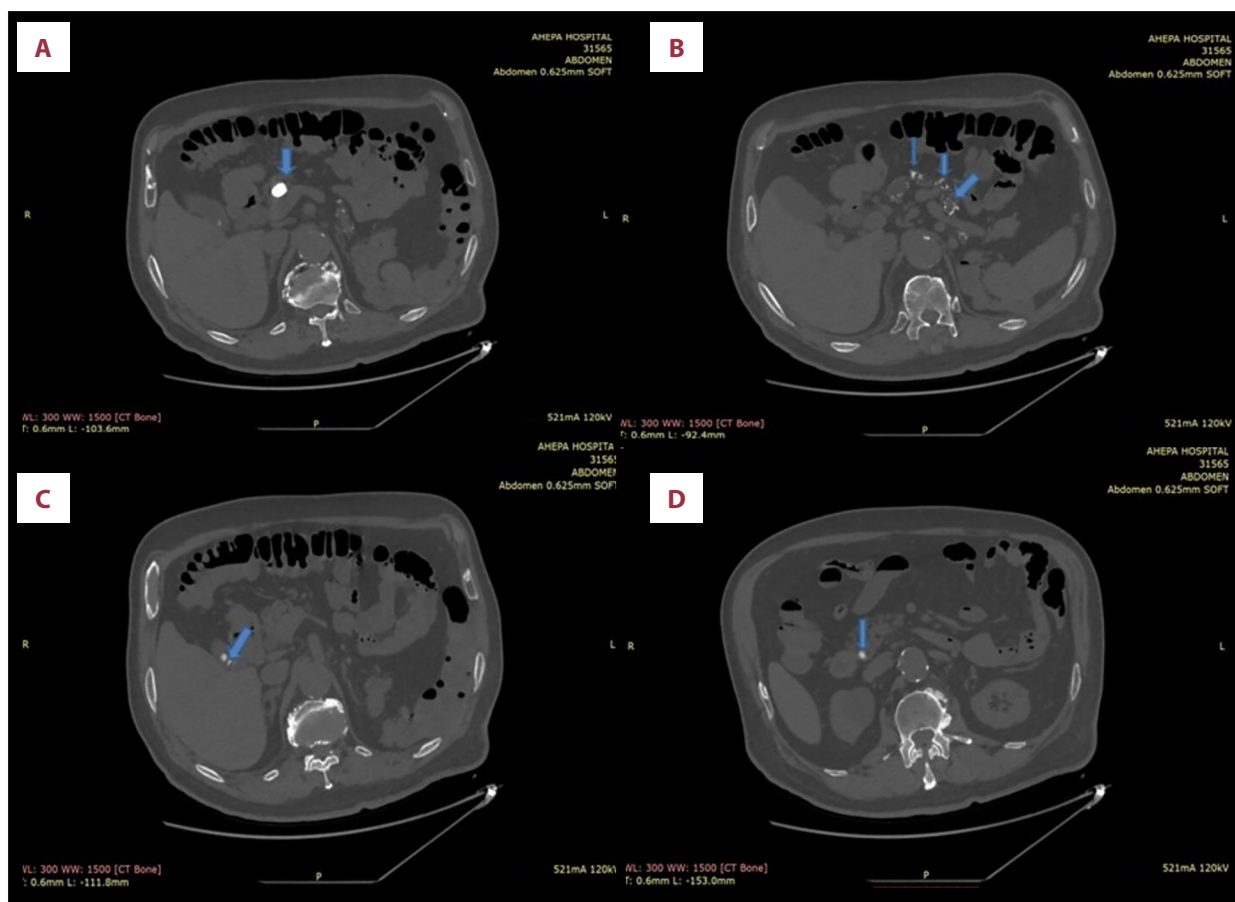
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## Introduction

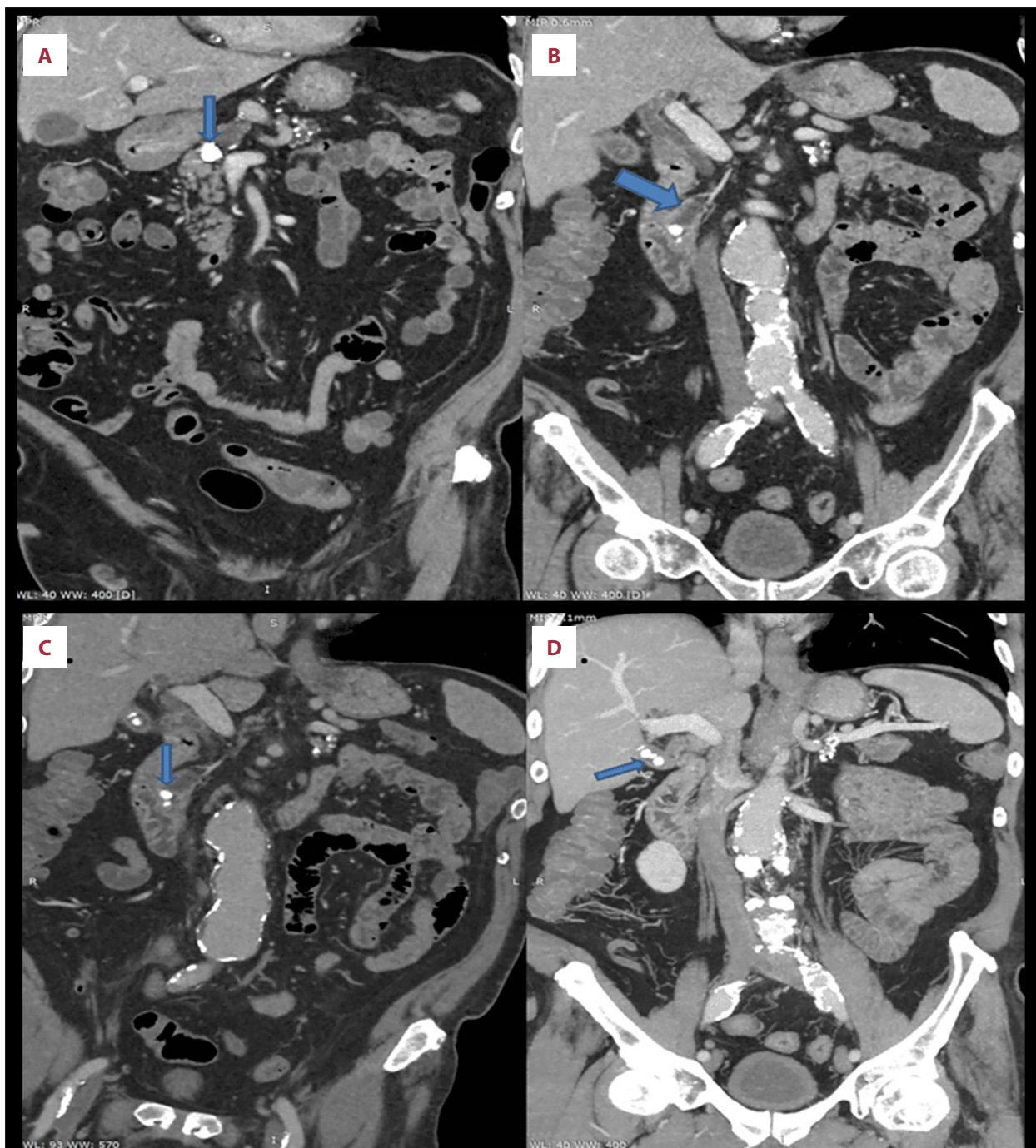
Pancreatic calculi (PC), also known as pancreatolithiasis, is to the presence of stones in the main pancreatic duct (MPD), side branches, or parenchyma of the pancreas [1]. Depending upon the stones' type and number, they can be considered radio-opaque, radiolucent, or mixed, and also as single or multiple [2,3]. Importantly, there is a strong association with chronic pancreatitis (CP), which is present in 50-90% of these patients [4]. However, CP in the long term can be associated with a variety of complications affecting both the pancreas (pancreatic pseudocyst, pancreatitis and pancreatic adenocarcinoma) and the adjacent anatomical structures, causing biliary and duodenal obstruction [3,5,6]. Moreover, PC is found in less than 1% of a random sample of the population, mainly in older people, but also in younger people and rarely in children [7,8]. While the exact cause of pancreatic stone formation remains unclear, it is related to a decreased level of pancreatic stone protein (PSP) followed by supersaturation of pancreatic juice with calcium carbonate [9]. Pancreatic duct stones (PDSs) typically cause obstruction, and, consequently, hypertension of the distal part of the duct, elevated parenchymal

pressure, ischemia, and inflammation of the pancreatic nerves, which can cause abdominal pain, insufficient exocrine pancreatic function, and other complications such as obstructive jaundice, diabetes, and steatorrhea [10,11]. Pancreatic pain is associated with a reduced quality of life, as it is sometimes combined with weight loss and low work productivity, and is regularly treated with opiates, which can cause dependence and hospitalization [11,12]. Consequently, it is essential to restore pancreatic duct flow, either with medical, endoscopic, or surgical therapy [9]. In endoscopic techniques, endoscopic retrograde cholangiopancreatography (ERCP) is conducted, accompanied by sphincterotomy and insertion of stents, or extraction of stones with balloons or baskets [1,13]. During the last 30 years, extracorporeal shock wave lithotripsy (ESWL) has been increasingly applied to fragment larger stones that cannot be extracted by ERCP, and it is considered an excellent method with minimal complications [14]. Surgery is performed when PDSs are extensive and endoscopic procedures are not effective or when other complications exist [1,15].

Here, we present 2 cases of PDS, in a 78-year-old man and a 27-year-old woman, whose clinical manifestations were



**Figure 1.** CT (axial): (A) Large pancreatic duct stone. (B) Duct dilatation and parenchymal atrophy. Diffuse pancreatic calcifications. (C) Calcified stones in the gallbladder. (D) Stone in the ampulla of Vater.



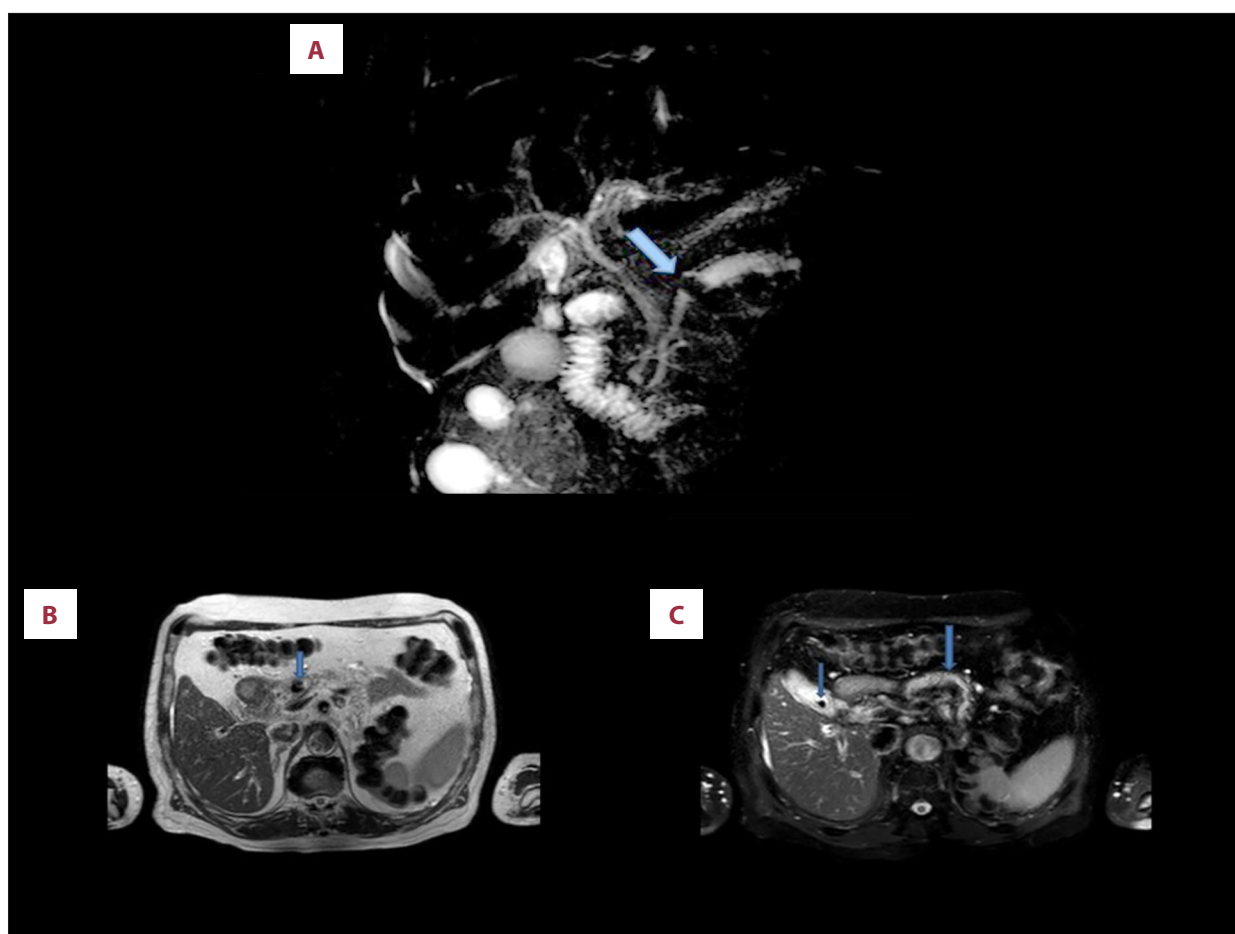
**Figure 2.** CT, MIP (coronal): (A) A large pancreatic duct stone. (B) Peripheral duct dilation. (C) Calcified gallstones in the ampulla of Vater. (D) Calcified stones in the gallbladder.

different, indicating the diverse clinical picture PDS can create. We also emphasize the importance of choosing the most appropriate treatment for each patient based on clinical, laboratory, and imaging examinations.

## Case Reports

### Case Report 1

The first patient was a 78-year-old White man who was admitted to our surgical department to investigate jaundice with symptoms of abdominal pain. He reported having dark



**Figure 3.** (A) Large pancreatic duct stone and stone dilation in MRCP. (B) Large pancreatic duct stone in MRI. (C) Calcified stone in gallbladder and dilated pancreatic duct in MRI.

urine and pale-colored stools, whereas other symptoms, such as nausea, vomiting, or fever, were not present. His medical history included bronchial asthma and an aneurysm of an abdominal aorta, for which he received per os formoterol 12 mg and acetylsalicylic acid 100 mg at home. He was a long-term smoker, a social alcohol user, and had no previous surgery or allergy history. A recent abdominal computed tomography (CT) scan revealed stones in the neck of the gallbladder and pancreatic atrophy, with multiple calcifications in the parenchyma and the pancreatic duct, in the context of chronic pancreatitis (**Figures 1, 2**).

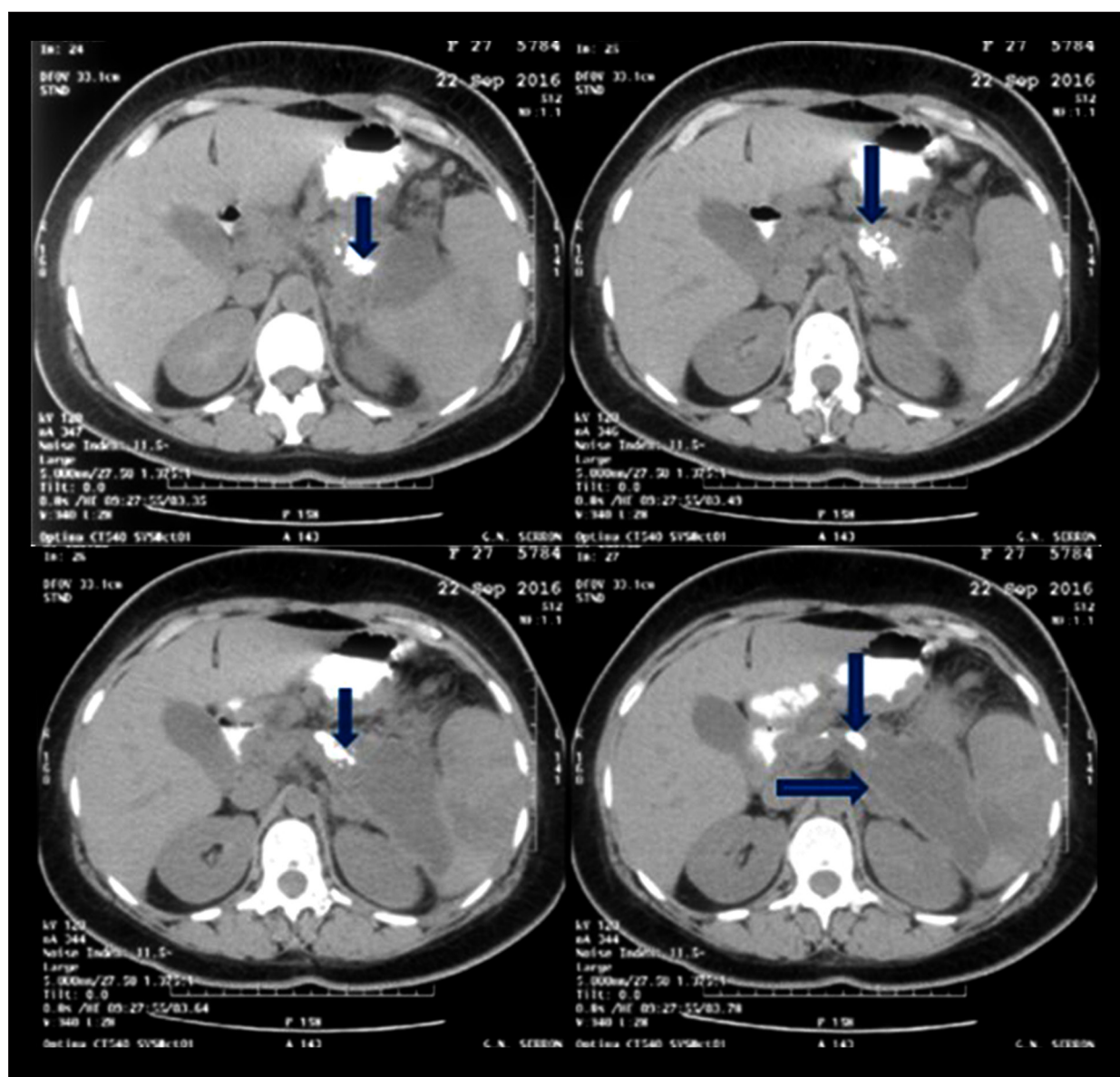
Physical examination revealed a soft abdomen with mild pain in the right upper quadrant, jaundiced conjunctiva and sclera of the eye, and a positive Murphy's sign. His vital signs were normal: blood pressure: 128/76 mmHg, pulse: 80 beats per minute (bpm), SpO<sub>2</sub>: 97%, and temperature 36.7°C. His blood and biochemical laboratory examinations disclosed elevated liver and bile duct function indicators as follows: total bilirubin: 8.41 mg/dl, direct bilirubin: 7.84, aspartate transaminase (AST): 72 U/l, alanine transaminase (ALT): 89 U/l, gamma-glutamyl

transferase (GGT): 685 U/l, and amylase: 225 U/l. Regarding serum tumor markers, carbohydrate antigen 19-9 (CA 19-9) was elevated (15.833 U/ml) and carcinoembryonic antigen (CEA) was slightly raised (5.36 ng/ml).

The patient was scheduled for magnetic resonance cholangiopancreatography (MRCP) for the upper abdomen, which showed stones in the neck of the gallbladder up to 7 mm with accompanying swelling of the wall, normal range of extrahepatic bile duct, and a pancreatic duct stone 10 mm at the neck of the pancreas, with dilation of the distal part of the main pancreatic duct (MPD) at 15 mm, as well as pancreatic atrophy (**Figure 3**).

Accordingly, an ERCP was conducted, in which the catheterization and outline of the MPD showed a constriction point. A pancreatic sphincterotomy was performed and a plastic stent was placed to allow the stone to drop out. Catheterization of the common bile duct showed a normal range without filling deficits. However, multiple filling deficits that corresponded to gallstones were recognized in the cystic duct. The ERCP





**Figure 4.** CT: multiple stones in the pancreatic duct and in the parenchyma. Severe dilation of the duct peripherally.

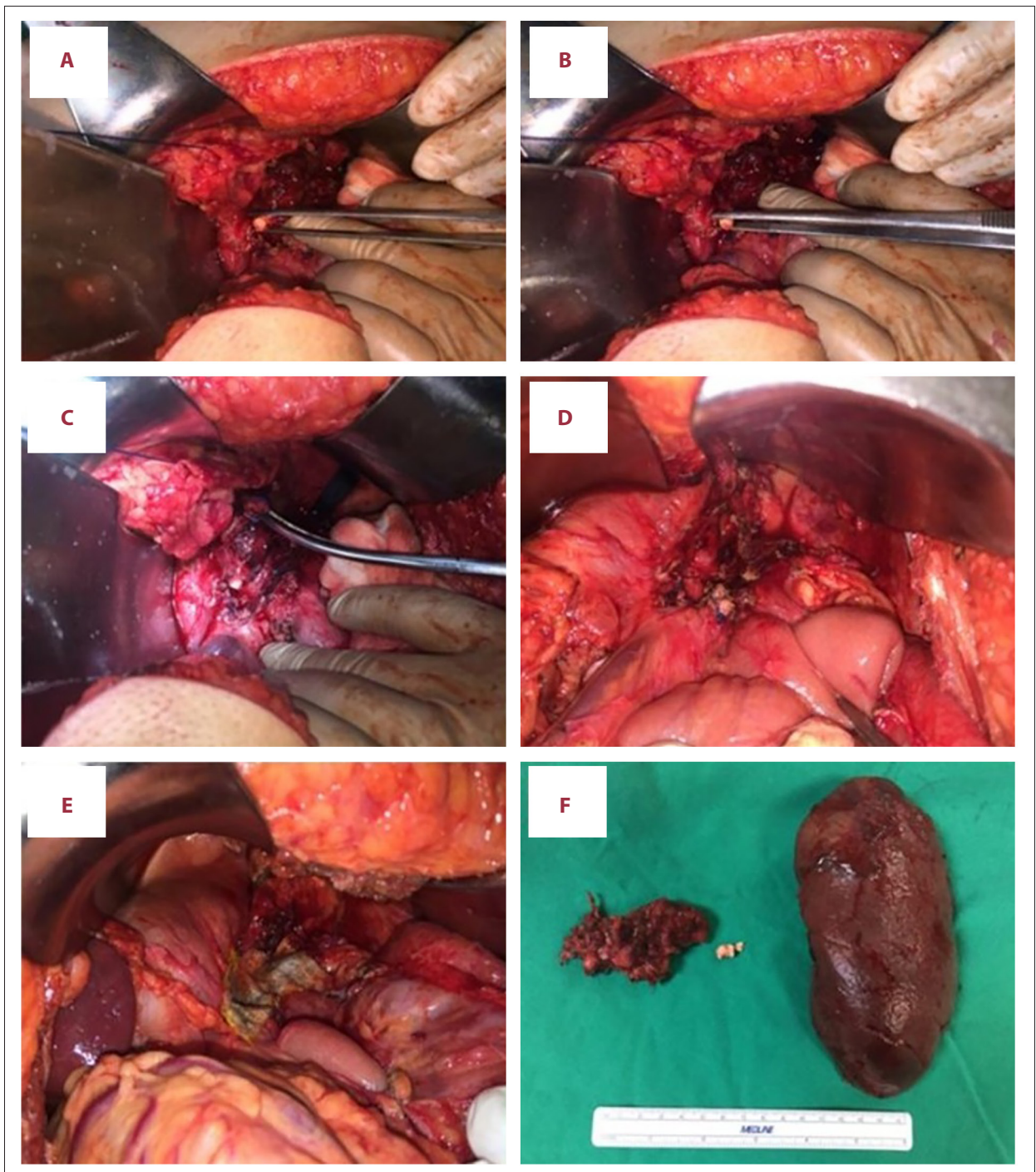
was completed with no complications and the reduction of the jaundice was visible beginning on the next day. Five days later the patient underwent an open cholecystectomy, with a normal postoperative course.

The laboratory examination of the patient showed improvement, with a reduction in all his previously elevated indicators. As his recuperation was uneventful, he was discharged from the hospital on the 4<sup>th</sup> postoperative day.

## Case Report 2

The second patient was a 27-year-old White woman who was admitted to our surgical department as she reported intense

and continuous pain detected in the left upper abdomen radiating in the lumbar region during the past 7 days, which was alleviated only after taking paracetamol. Other symptoms, such as nausea, vomiting, or fever, were not reported. However, her history included a gynecological examination 2 years previously, in which a cyst was incidentally found in the left lateral region of the abdomen, which was then investigated with an abdomen CT scan. The scan revealed mild dilation of some of the pancreatic duct, especially in the tail of the pancreas, a cystic lesion in the body and tail of the pancreas, and an enlarged spleen. As she was asymptomatic, she declined further investigations, despite the recommendation for a magnetic resonance imaging (MRI) scan. Her medical history also included diabetes mellitus type I, for which she received



**Figure 5.** (A, B) Removal of the stone from the pancreatic duct. (C) Pancreatic duct ligation. (D, E) Suture and hemostatic sponge placement. (F) Pancreatic pseudocyst, stone, and spleen.

insulin glargine 50 units, insulin as part 10-12 units 3 times a day, and metformin 850 mg, appendicectomy, and C-section. She reported no alcohol abuse.

During the clinical examination in our department, the following findings were observed. The abdominal examination

revealed mild tenderness in the left hypochondriac region; however, the abdomen was soft with no palpable masses and with normal sounds. Auscultation of the heart revealed no pathological findings, but auscultation of the lungs indicated decreased respiratory sounds in the bases of both lungs, especially the left. Her vital signs were normal, with blood pressure:



125/79 mmHg, pulse: 82 beats per minute (bpm), SpO<sub>2</sub>: 98%, and temperature 36.4°C, and her laboratory test results were normal except for hematocrit (HCT) 32.4% and hemoglobin (HGb) 10.6 g/dL. PT and INR were slightly elevated, and her amylase was low (20 U/l).

A chest X-ray was also performed and revealed mild elevation of the left hemidiaphragm. Then an abdomen CT scan was conducted, which detected a large pancreatic pseudocyst with uneven margins in the body and tail of the pancreas, and multiple splenic infarcts (**Figure 4**). An MRCP was also performed, which revealed pancreatic stones and pancreatic duct dilatation.

After the necessary assessment of the patient with the appropriate examinations, the findings were considered suspicious for the existence of cystadenoma or cystadenocarcinoma, as due to the size of the lesion the possibility of a benign or a malignant neoplasm could not be excluded, so distal pancreatectomy and splenectomy were performed (**Figure 5**).

A histopathological examination was conducted in the excised pancreatic tissue and the excised spleen. Macroscopically, the extracted pancreatic tissue was a fibroelastic specimen measuring 5.7×2.2×0.8 cm. An intraoperative consultation was requested, and a routine histopathology examination followed. Microscopically, a sample of 10 lymph nodes was prepared, indicating lesions of reactive lymphadenopathy. Moreover, severe-grade lesions of CP, suggesting low-grade pancreatic intraepithelial neoplasia (PanIN-1B), were detected. Microscopical examination of the spleen revealed extended subcapsular hemorrhagic necrosis. Malignant lesions were not found.

Postoperative complications were not observed and the patient was discharged from the hospital in good condition on the 6<sup>th</sup> postoperative day.

## Discussion

Pancreatic calculi (PC) or pancreatolithiasis can occur during the natural development of CP due to its pathophysiology of increased parenchymal pressures and repeated episodes of severe epigastric pain [11,16]. However, pain in PDSs can originate from ischemia, nerve compression, and central hypersensitivity, explaining its perseverance in a few cases, even with full clearance of the duct [2]. Although the formation of pancreatolithiasis is incompletely understood, it is clearly associated with low levels of PSP, owing to different factors, including gene expression, alcohol use, and CP [1,17]. Insufficiency of factors such as intraductal bicarbonate and citrate that prevent calcium condensation may also play a role [9]. As a result, crystallization and supersaturation of calcium carbonate create stones in the pancreatic juice [17]. Moreover, pancreatic

stones can be the outcome of hypercalcemia in patients with hyperparathyroidism [17]. PC can coexist with a variety of complications such as pancreatic carcinoma and pancreatic pseudocyst [3,18]. The relationship of PDSs with pancreatic cancer is of utmost importance, with a 27-fold higher risk of carcinoma in patients with PC [11]. Pseudocysts can be present in up to 20% of the patients with pancreatitis, and they communicate with the MPD in 40-60% of cases [19]. Diagnosis of PDSs can be challenging, as PDSs in abdominal X-ray cannot be easily differentiated from parenchymal calcification, so ultrasound is conducted, which can detect the dilated pancreatic duct [20]. CT can show other manifestations such as pseudocysts or pathological pancreatic lesions [5]. However, direct visualization of the MPD can be accomplished only by ERCP or MRCP [21]. Moreover, endoscopic ultrasonography (EUS) can be performed, with the maximum levels of sensitivity [14].

For management of pancreatolithiasis, the removal of stones and the reinstatement of the pancreatic duct flow through medical, endoscopic, and/or surgical therapy are crucial [10]. Medical management can include pancreatic enzyme replacement therapy (PERT), a low-fat diet, and analgesics, usually opiates [17]. The aim of these therapies is the reduction of pancreatic juice and intraductal pressure through inhibition of cholecystokinin release and repression of the exocrine parenchymal stimulation, and not decomposition of the stones [17]. Although trimethadione has been used for dissolution of PDSs, because of its hepatic toxicity, it is rarely used [1,17].

The first endoscopic pancreatic sphincterotomy was performed about 160 years ago to extract PDSs with a basket [22]. Endoscopic techniques for PDSs include ERCP with pancreatic sphincterotomy, balloon sphincteroplasty, extraction baskets or rat tooth forceps, stent placement, stone fragmentation with ESWL, and per-oral pancreatoscopy (POP) with laser lithotripsy (LL) or electrohydraulic lithotripsy (EHL) [5,23]. Small stones (<5 mm) can be withdrawn using traditional ERCP with pancreatic sphincterotomy, followed by balloon or basket extraction [1,5]. Stent placement after sphincterotomy is also an option, as in our first case, which can alleviate intraductal hypertension and pain, and can restore patency of the duct [19]. Use of pancreatic stents can minimize the risk of symptoms relapse and treat post-ERCP pancreatitis [24]. However, some complications can occur, such as stent occlusion, inward or outward migration, and anatomic changes in the pancreatic duct [19,25].

ESWL was first used in the 1980s for the treatment of renal and ureteric calculi and was also soon applied to large biliary and pancreatic stones [14]. Based on shock wave energy, this technique overcomes the challenging extraction of larger (>5 mm) or impacted stones with ERCP alone, by fragmenting the PDSs before endoscopic removal and, as a result, increasing the clearance rates up to 60-90% [2,3,17]. As a result, ESWL

is suggested as the first-line treatment for the management of PDSs >5 mm [12]. The shock waves produce compressive stress, which reduces the size of the stones into fragments of <3 mm, as it overcomes their tensile strength [14]. Despite its huge contribution to PDSs treatment, ESWL is not applied in all centers because it is expensive, needs general or intravenous anesthesia, and requires multiple sessions [22,26]. Moreover, indications of ESWL do not include cases with extensive head, body, and tail stones or cases with isolated tail stones, as there is a greater risk of collateral spleen damage [14]. Contraindications also include pseudocysts, pancreatic ascites, multiple strictures, and head mass, as well as cholangitis or coagulopathy, because biliary strictures must heal before ESWL is performed [14]. ESWL may be accompanied by rare complications, such as necrotizing pancreatitis, skin erythema and tenderness, fever, abdominal pain, biliary obstruction, asymptomatic hyperamylasemia, perirenal hematoma, bleeding, splenic rupture, bowel perforation, and liver trauma [3,27]. The American Society for Gastrointestinal Endoscopy (ASGE) suggests as first-line treatment of PC endoscopic techniques followed by ESWL, while the European Society for Gastrointestinal Endoscopy (ESGE) suggests ESWL as the first treatment, mainly when PDSs are >5 mm [5].

If ESWL fails, POP with intraductal lithotripsy, including EHL or LL, may be considered [23]. The stone fragmentation in EHL is a result of absorption of energy from high-frequency hydraulic pressure waves, whereas, in LL, infrared light energy enters the stones, composing a cloud of electrons, which in an aqueous medium produces a strong shock wave [3,22,28]. After POP, balloons and/or baskets are used for stone removal from the pancreatic duct [29]. POP has to be repeated if the duct is not fully cleared [30]. Contingent benefits of POP are that it enables direct calculi visualization and segmentation throughout the same ERCP session using pancreatoscopes, as well as detecting PDSs missed by high-resolution imaging [23,26]. Its drawbacks are the cost and the requirement for experience with the device, adequate diameter of the pancreatic duct, the diameter of the pancreatoscope, the long duration of the process, and the mediocre success rates of standard methods [23]. Pain aggravation is considered the most common adverse event (AE), whereas cholangitis, cholecystitis, and duodenoscope-related infection transmissions are rarely encountered [12].

In our first case, the detected stone was approximately 10 mm and it was located at the neck of the pancreas. To avoid the limitations of other techniques such as ESWL, which, compared with endoscopic removal, has a higher cost, may demand multiple sessions, and is not practicable in all centers, we chose the traditional ERCP with insertion of a stent, restoring the normal pancreatic fluid's flow. The pancreatic stent eliminated the patient's intraductal hypertension and pain, but unfortunately,

due to the peripheral location of the stone, the endoscopic removal was not successful.

Surgery in patients with PC is now less commonly performed, mainly when PC is accompanied by other pancreatic manifestations, such as pseudocysts or a possible malignant lesion, when endoscopic treatment fails, when there is a stricture in the duodenum, or when extensive calculi or multiple strictures are present [1,5]. Surgical techniques include drainage, pancreatic resection, and combined methods if necessary [15]. In patients with masses of inflammation in the head of the pancreas caused by PDSs, decompression endoscopic techniques do not relieve pain, so surgery is performed (extraction of the head of the pancreas), which alleviates pain symptoms in 90-95% of patients [31]. However, although surgery has the best long-term results in pain relief, it is associated with many complications and high rates of morbidity (20-47%) and mortality (1-5%) [3,15,32]. A characteristic example is the Puestow surgery technique, which was conducted for more than 40 years as a drainage method in CP, until it was realized that 30-40% of patients experienced after-surgery episodes of recurrent pain [15,33]. Also, even after duodenum-preserving resection, which has proven to be the ideal surgical procedure for CP, 12.5% of patients have recurrent episodes of pain [34].

Pseudocysts, which can occur during pancreatolithiasis, resolve without treatment in a small percentage of patients [29]. However, some criteria demonstrate the possibility of its perseverance, such as the thick wall of the pseudocyst, the proven CP, an anomaly of the pancreatic duct, and persistence for over 6 weeks [29]. Treatment indications are large-vessel compression, stomach or duodenum obstruction, MPD stenosis, pseudocyst infection, pleural pancreatic fistula, and symptoms such as nausea, vomiting, pain, early satiety, and upper gastrointestinal bleeding [29]. These can be managed by resection or with internal or external drainage [6]. In internal drainage, communication is created between the pseudocyst and the stomach (cystogastroanastomosis), jejunum (cystojejunostomy), or duodenum (cystoduodenostomy) [35]. The choice of anastomosis depends mainly on the location of the cyst [35]. Surgical drainage has a 9.5% rate of recurrence and a 16.7% rate of complications [36]. In our second case, the pseudocyst was considered suspicious for malignancy, so we conducted a distal pancreatectomy and splenectomy. ESWL was not a choice, since pseudocyst is a contraindication of this procedure.

Personalization of PC treatment is of utmost importance. Although we chose the conservative approach in our first patient, with endoscopic technique and placement of a stent, we decided on a surgical approach for our second patient due to the coexisting complications (pseudocyst) and the suspected cystadenocarcinoma.



## Conclusions

Management of pancreatolithiasis can be challenging, as it can present with a variety of clinical symptoms, mainly abdominal pain. Selection of the most suitable therapy for PDSs is determined by the location, size, and number of stones, complications, and the current situation of the patient. Although ERCP can extract small stones, many cases with larger stones require highly developed curative techniques, such as ESWL or POP with intraductal lithotripsy. In our first case, the implementation of ERCP, even though challenging for larger PDSs, contributed to the patient's recovery and clinical and laboratory

improvement. However, when endoscopic treatment has failed, malignancy is questionable, or a duodenal stricture is present, surgery is the treatment of choice. In our second case, the distal pancreatectomy constituted a comprehensive approach, and the patient fully recovered. Personalized treatment, based on a clear diagnosis, is essential.

## Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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