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Isolated Acute Rheumatic Pancreatitis—A Case Report

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Abstract

Aim: To emphasize the role of antibiotics in acute pancreatitis as prophylactic and therapeutic benefits. **Case Report**: A 32-year-old obese male was admitted with acute abdomen in the emergency room. He was supported with intravenous fluids and the blood chemistry revealed elevated amylase and lipase levels, raised ESR and a positive ASO titer test. CT abdomen suggested interstitial edematous pancreatitis (IEP) and no fluid collection. Patient was treated with IV cefotaxime and IV metronidazole, his condition remarkably improved with therapy, blood parameters returned normal at the end of 4 weeks, and follow-up CT revealed no abnormal findings and symptom free thereafter. **Conclusion**: Acute pancreatitis is usually a sterile inflammatory process caused by chemical autodigestion of pancreas. The edematous form of acute pancreatitis needs to correct its etiological factor to avoid recurrence. It is observed as an initial manifestation of group A beta hemolytic streptococcal infection in this patient and antibiotics play a role as curative and prophylactic in selected cases.

Keywords

Acute Abdomen, Pancreatitis, ASO Titer, Elevated Pancreatic Enzymes, Antibiotics

1. Introduction

Acute pancreatitis is a condition where the pancreas becomes inflamed (swollen) over a short period of time. Most people with acute pancreatitis start to feel better within about a week and have no further problems. It is sometimes associated with a systemic inflammatory response that can impair the functions of other organs, can go on to develop serious complications. The distant organ dysfunction may resolve or progress to organ failure. Thus, there is a wide spectrum of

disease from mild (80%), where patients recover within a few days, to severe (20%) with prolonged hospital stay, the need for critical care support, and 15% - 20% risk of death if patients have organ failure during the first few weeks of illness [1].

It occurs with an estimated incidence of 10 - 40 per 100,000 per year in the UK [2]. An increase in the annual incidence when acute pancreatitis has been observed worldwide varies between 4.9 and 73.4 cases per 100,000 [3] [4]. Every year, there are 275,000 hospitalisations for acute pancreatitis in the United States. In 2009, it is the most common gastroenterology discharge diagnosis with a cost of 2.6 billion dollars.

The evolving issues of antibiotics, nutrition, endoscopic, radiologic, surgical and other minimally invasive interventions will be addressed on early management to decrease morbidity and mortality.

Some studies have suggested that the administration of prophylactic antibiotics reduces the risk of pancreatic necrosis becoming infected [5]. Abdominal pain is the presenting manifestation of acute rheumatic fever [6], usually precedes the other rheumatic signs and it is the consequence of rheumatic inflammatory process affecting the pancreas in this patient, so this case had been reported.

2. Case Report

A 32 years old male was admitted with sudden onset of severe abdominal pain and he was found to be toxic and emaciated. His pulse rate was 114 bpm, blood pressure 90/60 mmHg and temperature 100.4˚F. Physical examination revealed distended abdomen with tenderness in the epigastric region. He had a history of alcoholic drinks occasionally. He was on anticonvulsants (phenytoin sodium 100 mg twice daily) for the past 4 years as he suffered 2 to 3 episodes of seizure attacks before and his CT brain revealed normal earlier. On admission, his serum amylase was 548 IU/L (normal 10 to 96 IU/L). The total leukocyte count 7190 cells/cumm blood (normal 4000 to 10,000/cumm of blood), neutrophils 65.8% (normal 40% to 75%), lymphocytes 26.3% (normal 25% to 35%), monocytes 4% (normal 3.5% to 11.5%), eosinophils 3.5% (normal 2% to 6%), basophils 0.4% (normal 0% to 1%). ESR (Erythrocyte sedimentation rate) 26 mm in one hour (normal 0 to 14 mm per hour). Serum bilirubin (total) 1.2 mg/dl (normal 0.4 to 1.2 mg/dl). Random blood glucose 98 mg/dl (normal 60 to 125 mg/dl). Total cholesterol 180 mg/dl (normal 150 to 220 mg/dl), serum triglycerides 270 mg/dl (normal 50 to 150 mg/dl). Serum SGOT (AST) 88 IU/L (normal 5 to 41 IU/L, SGPT (ALT) 78 IU/L (normal 5 to 50 IU/L). The renal parameters and serum electrolytes were within normal range. Serum lipase was highly raised as 1476 IU/L (normal < 60 IU/L). ASO (antistreptolysin O) titer was found to be positive 440 IU/ml (normal 0 to 150 IU/ml). The C reactive protein was 350 mg/dl (normal < 10 mg/dl). Tests for malarial parasites, dengue antibody, leptospira and HIV were normal. Urine analysis revealed normal results. X-ray chest PA

view, ECG and Echocardiography revealed normal. Ultrasonography of abdomen showed bulky pancreas with mild heterogenous echotexture and other organs were normal. He was diagnosed as "acute pancreatitis" and started with intravenous cefotaxime 1 g and metronidazole 500 mg twice daily, oral omeprazole 20 mg once daily and domperidone 10 mg twice daily with antacid gel 15 ml three times daily and maintained with IV fluids without any oral feedings. Pain subsided automatically without any medication to relieve pain. Plain CT done on 3rd day revealed mild peripancreatic fat strandings around the head, uncinate process, tail region and extending up to left perinephric region as shown in Figure 1 and Figure 2, with normal pancreatic parenchyma and no significant ductal dilatation and calcification. The liver and gall bladder appeared normal and no evidence of gallstones or fluid collections. The abdominal distension subsided

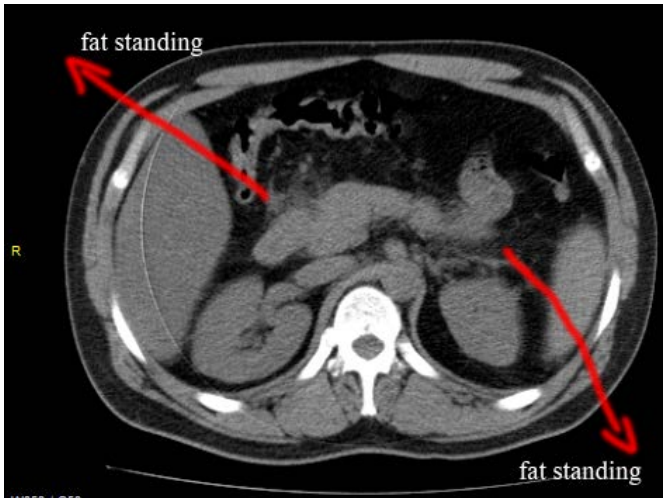

Figure 1. Showing the mild increase in densities of "fat stranding" as "mistiness" or "hazy streaky densities" representing the inflammatory changes in the peripancreatic fat near the uncinate process of pancreas, extending towards tail region and perinephric area suggesting "acute interstitial edematous pancreatitis (IEP)".

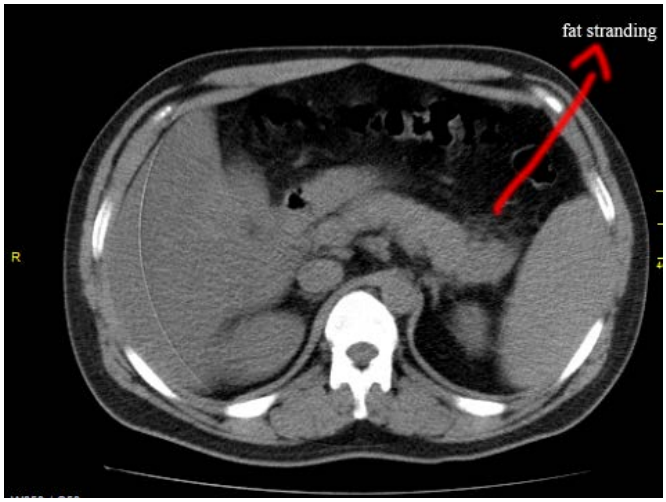

Figure 2. Showing the "mistiness" (fat stranding) in the tail region of the pancreas.

on 4th day and the patient was advised to resume semisolid liquid diet, tender (fresh) coconut water, fruits and smashed vegetables without chillies slowly. The milk products were avoided. His condition began to improve thereafter. After one week of treatment, the amylase level decreased to 303.1 IU/L and lipase level becoming 240.4 IU/L, AST 84 IU/L, ALT 80 IU/L. Then one week thereafter, the amylase level reduced to 151.2 IU/L, lipase level 128.4 IU/L, AST 49 IU/L and ALT remaining high as 89 IU/L. At 3rd week, AST 36 IU/L, ALT 51 IU/L, amylase 148 IU/L, lipase 115 IU/L and ASO titer 288.5 IU/ml.

The treatment continued and at the end of 4 weeks, the amylase 69 IU/L, lipase 31 IU/L and ASO titer became negative. The CT abdomen revealed no fat stranding and the pancreas appeared normal. The patient was discharged to home and advised to avoid alcohol and fatty foods thereafter. The patient was symptom free and healthy on one year follow up, advised lifelong penicillin prophylaxis with oral penicillin V 250 mg twice daily to prevent recurrent attacks of pancreatitis. Since he is obese with body mass index (BMI 32%), regular exercise programmes and diet control were advised for weight reduction with periodic medical check-up.

The RT PCR for COVID-19 infection (reverse transcriptase polymerase chain reaction test) was negative at present and it was not done initially since unknown at the time of presentation.

3. Discussion

Etiopathogenesis

The pancreas is a secretory organ with both endocrine and exocrine functions and the main functional unit is the acinar cell, which comprises the parenchyma of the gland. Exocrine products from the acinar cells are secreted into a tubular system and the digestive enzymes are released via the pancreatic duct into the small intestine where they are activated to break down the fats and proteins. The digestive hormones (insulin & glucagon) produced by the pancreas are released into the blood stream where they help to regulate the blood glucose level.

Normally, digestive enzymes released by the pancreas are not activated to break down fats and proteins until they reach the small intestine. Trypsin is a digestive enzyme produced in the pancreas in an inactive form and ethanol molecules affect the pancreatic cells, triggering them to activate trypsin prematurely. When the digestive enzymes are activated in the pancreas, inflammation and local damage as "acinar cell destruction" histologically occurs, leading to pancreatitis. Neutrophil polymorphs and macrophages infiltrate the pancreas and release their own proteases, free radicals, and cytokines which compound the vicious cycle of tissue damage and inflammation, inducing an "acute systemic inflammatory response syndrome (SIRS)" and organ damage. The patient may become dehydrated and then heart, lungs, kidney fail. In very severe cases, pancreatitis can result in bleeding into the gland, leading to shock, serious tissue damage, infection, fluid collections and sometimes death.

There are many causes of pancreatitis as obstruction of the secretory tree or direct parenchymal cell damage. The gallstones, infection and alcoholism are the most common causes of acute pancreatitis. In recurrent acute pancreatitis, Oddi sphincter manometry is performed and a basal sphincteric pressure > 40 mmHg [7] is the most common abnormal finding described in 30% - 40% of cases.

Acute pancreatitis is associated with multiple infections as shown in **Table 1**. In most reports, bacteria are considered important only in late stage of pancreatitis and not as a primary etiological agent. Pancreatic ischemia is rare due to its rich perfusion from superior and inferior pancreaticoduodenal arteries and ischemia may results from vasculitis due to rheumatic inflammation, atheromatous embolizatin of cholesterol plaques from aorta after angiography, after cardiopulmonary bypass, ergotamine overdose, cocaine use, hypercoagulable states (APL (antiphospholipid antibody) syndrome) and alcohol induced "microcirculatory impairment" potentiated by smoking.

When pancreatic ischemia occurs, its tissues begin to die as necrosis and when it happens, the pancreas can become infected and its spread into the blood causes "sepsis syndrome" mimicking SIRS in its early course of acute severe pancreatitis. The risk of infection is associated with degree of pancreatic necrosis. Patients with <30% necrosis have a 22.5% chance of infection, whereas >50% have 46.5% of risk of infection [8]. Infection of necrotic tissue by bacteria carries high morbidity and mortality [9].

Infections can result from a variety of sources

1) Bacterial translocation—from small bowel and colon through transmural colonic migration is a major source of infection in necrotizing pancreatitis [10]. Endotoxemia resulting from the release of components of gram negative bacteria from the gut is common in patients with acute pancreatitis. The bacterial translocation from the gut lumen to mesenteric lymph nodes and subsequent hematogenous dissemination could be a possible mechanism of the development of pancreatitis. Impaired body defences predispose to translocation of gastrointestinal organisms and toxins with subsequent secondary bacterial infection.

2) Hematogenous spread.

Table 1. Infectious agents causing pancreatitis.

Mumps	*E. coli*
Coxsackie B virus	candida
Hepatitis B	HIV
Varicella-zoster virus	Leptospirosis
Cytomegalo virus (CMV)	legionella (*L. pneomophila* found in plumbing, Shower heads, water storage tanks)
Shigella	salmonella
Parasites	Toxoplasma Ascariasis *Clonorchis sinensis*

3) Biliary sources—bile duct stone or gall bladder infection ascending from duodenum via the main pancreatic duct can lead to infected pancreatic necrosis.

Most pathogens in pancreatic necrosis are gastrointestinal gram negative bacteria (*Escherichia coli*, proteus, *Klebsiella pneumonia*), occur via disruption of intestinal flora and damage to bowel mucosa. However, gram positive bacteria (*Staphylococcus aureus*, *Streptococcus faecalis*, *Enterococcus*), anaerobes, occasionally fungi have also been found and 25% are polymicrobial infection [11].

Streptococcus pyogenes (Lancifield group A β hemolytic streptococci, a gram positive, non motile, non spore forming coccus is the causative organism of Rheumatic fever which is a systemic disease affecting the periarteriolar connective tissue. Acute pancreatitis is an abrupt inflammation of the pancreas and a potential pathway of inflammatory response induced by the cytokines TNF-α and IL-6 is responsible for the development of inflammation. During bacterial invasion, the M1 protein is shed from the surface of *Streptococcus pyogenes* into the blood stream causing widespread activation of host innate immune cells. The "superantigens" (streptococcal pyrogenic exotoxin (SPE)) mediate a non antigen specific binding between T cell receptors and major histocompatibility complex class II molecule on antigen presenting cells. Consequently, the monoclonal cells are activated to produce large amounts of cytokines, and expression of TNF-α in the pancreatic islets may induce an inflammatory response in the pancreas and also cause dilatation and altered permeability of blood vessels, leading to acute lung damage, hypoalbuminemia, ascites and shock in susceptible individuals [12].

Among immunocompetent individuals, mumps and coxsackie B virus are the most common cause of pancreatitis. Recently, gastrointestinal manifestations of COVID-19 (corona virus disease 2019), caused by SARS-CoV-2 (severe acute respiratory syndrome corona virus 2), a family of single-stranded RNA virus are increasingly being recognized and its pathogenesis is thought to be mediated by angiotensin converting enzyme (ACE2) receptor on the host cells, which are highly expressed in pancreatic islets [13]. Acute pancreatitis can occur due to direct cytopathic effects of local SARS-CoV-2 replication or indirectly by immune mediated inflammatory response induced by the virus [14]. It has been reported that there is 17% incidence of pancreatic damage occurred in COID 19 patients [15] [16] and CT revealed the changes of interstitial edematous pancreatitis in majority of cases rather than necrotizing pancreatitis [17]

In 1992, the Atlanta classification for acute pancreatitis was introduced to classify its various manifestations [18]. The revised classification described two distinct phases of acute pancreatitis, a first or early phase that occurs within the first week of onset of disease and a second or late phase that takes place after the first week of onset [19] and introduced a new terminology of fluid collections as acute peripancreatic fluid collection (APFC) and acute necrotic collections (ANC).

During the first week of acute pancreatitis, the pathologic condition in and around the pancreas progress from early inflammation with variable degrees of

peripancreatic edema and ischemia to resolution or to necrosis of pancreas or surrounding fatty tissue. Over the course of first week, organ failure either resolves or turns to more severe. The organ failure that resolves in 48 hours is considered to have mild pancreatitis without complications [20]. Severe acute pancreatitis in the first phase is defined as organ failure that lasts more than 48 hours or death. Expansion of systemic inflammatory response syndrome and ensuing multiorgan failure is responsible for many deaths during this phase. The late phase begins after the first week, may extend for weeks to months and is characterized by increasing necrosis, infection, and persistent multiorgan failure [21]. Local complications may manifest systemically with bacteremia and sepsis when necrotic tissue becomes infected.

Laboratory Parameters

The pancreas produces elevated levels of enzymes, the amylase, lipase and trypsinogen, all derived from pancreatic acinar cells during acute pancreatitis. Serum pancreatic enzyme measurement is the "gold standard" for the diagnosis of acute pancreatitis (AP) [22]. Serum amylase usually rises within 6 to 24 hours, peaks at 48 hours, and decreases to normal within 3 to 7 days [23] and lipase rises within 4 - 8 hours, peaks at 24 hours and decreases to normal in 8 to 14 days [24]. In this patient, both serum amylase and lipase persistently elevated up to 4 weeks with an early peak at 24 hours of onset of symptoms. The biochemical criteria are usually sensitive for detecting acute pancreatitis (55% to 100%) and its specificity is very high (93% to 99%). Amylase or lipase levels more than three times of the upper limits of normal (300 IU/litre^{-1} for amylase and 600 IU litre^{-1} for lipase) are diagnostic of acute pancreatitis and serum lipase has been recommended as assay of choice [25] since its concentrations are increased for up to 14 days after the onset of pancreatitis, and appears to be more sensitive and specific than amylase.

Trypsinogen is the zymogen of the pancreatic enzyme trypsin and in acute pancreatitis, its concentration in serum and urine rises to high levels within a few hours and decreases in 3 days. Urinary trypsinogen 2 dipstick test is a rapid and non-invasive bedside test with a reasonable sensitivity 82% and specificity 94% for acute pancreatitis [26] if positive (>50 ng/ml). In ERCP induced pancreatitis, serum trypsinogen concentration may rise within an hour of the onset.

Many clinicians consider the C reactive protein (CRP) as the gold standard for disease severity assessment [27], but its peak levels are reached only after 48 to 72 hours. The CRP at 24 hours ≥21 mg/dl (≥210 mg/l) indicates severe disease and its level on 3rd day ≥150 mg/l can be used as a prognostic factor for severe acute pancreatitis. Resistin is a newly identified peptide hormone, secreted by adipocytes that can cause obesity and hypertriglyceridemia, due to its association with insulin resistance. Resistin is an important cytokine in inflammatory reactions, in the regulation of other cytokines [28] and it is better to predict severe acute pancreatitis on day 3 and for the development of pancreatic necrosis than CRP or WBC levels. It has similar accuracy with Acute Physiology and chronic

health evaluation II (APACHE II) score in predicting persistent organ failure (POF) and leptin has a weak correlation with POF [29].

PCT (procalcitonin) may be valuable in predicting the risk of developing infected pancreatic necrosis. It is an inactive 116 amino acid propeptide of the biologically active hormone calcitonin, which was first described to have significantly increased concentrations in bacterial and fungal infections [30]. Procalcitonin is the most sensitive laboratory test for detection of pancreatic infections and low serum values appear to be strong negative predictor of infected necrosis. A procalcitonin value of 3.8 ng/ml or higher within 96 hours after the onset of symptoms indicates an infected pancreatic necrosis with sensitivity of 93% and a specificity 79% [31].

A laboratory "acute pancreatic screen" to determine the etiology also include the detection of viral antibodies, especially for corona virus. *Streptococcus pyogenes* produces various exotoxins such as streptolysin O that can act as antigens and the affected individuals produce specific antibodies against streptolysin O (antistreptolysin O (ASO)). Determination of these antibodies is very useful for the diagnosis of streptococcal infection and their relative effects. An elevated ASO titer > 200 IU/ml may indicate an acute streptococcal infection and in this patient the ASO titer was raised up to 440 IU/ml at the time of admission.

Advanced laboratory analysis for patients < 40 years of age includes the detection of α-1-antitrypsin phenotype, CFTR (cystic fibrosis transmembrane conductance regulator) gene analysis, a sweat chloride test, trypsin gene studies, and duodenal aspiration for microcrystals, the best indicator of bile duct stones is a serum total bilirubin > 1.35 mg/dl on the second day of admission [32]. The level of tumor marker, CA (cancer antigen) 19-9, should be measured in patients > 40 years of age.

Predictors of Severity

It is unable to predict which patients with acute pancreatitis will develop severe disease and different scoring systems showed similar predictive accuracy for the severity of acute pancreatitis, but the APACHE-II score demonstrated the highest accuracy [33].

It was able to identify patients at increased risk of mortality prior to the onset of organ failure [34]. The BISAP score of 2 was a statistically significant cutoff value for the diagnosis of severe acute pancreatitis, organ failure, and mortality as shown in **Table 2**.

The systemic inflammatory response syndrome (SIRS), originally adopted to predict the development of organ failure with sepsis, currently the most important predictor of prognosis and it requires at least two of the following criteria as shown in **Table 3**. It identifies the risk very early in the course of disease and can be assessed quickly in the emergency department.

The emerging biomarkers to distinguish septic and nonseptic etiology of SIRS include TREM1 (Triggering receptor expression on myeloid cells 1). DcR3 ("Decoy receptor 3" belongs to tumor necrosis factor family) and suPAR (Soluble urokinase type plasminogen activator receptor) [37].

Table 2. Showing the bedside index of severity of acute pancreatitis (BISAP) [35].

Blood urea nitrogen level > 25 mg/dl (89 mmol/l)
Impaired mental status (Glasgow coma score < 15)
Systemic inflammatory response syndrome
Age > 60 years
Pleural effusion

(A score of 3 points is associated with 5.3% rate of hospital death, 4 points with 12.7%, and 5 points with 22.5% of deaths.)

Table 3. Showing the criteria of SIRS (systemic inflammatory response syndrome) [36].

Heart rate > 90 bpm
Core temperature < 36˚C or > 38˚C
White blood cells < 4000 or >12,000/mm^3
Respirations > 20/mm

CT (Computed Tomography) Imaging

The peripancreatic inflammatory changes are the most common CT findings in 88% of cases of acute pancreatitis, seen in mysentry, greater omentum and transverse mesocolon as shown in **Figure 1** & **Figure 2** and the second most common finding is "pancreatic contour irregularity", seen in 80% of cases. Pancreatic parenchymal necrosis alone is seen in <5% of cases and appears as lack of parenchymal enhancement [38] on contrast-enhanced CT. The necrosis is seen as more homogeneous nonenhancing area of viable attenuation in the first week of necrotizing pancreatitis and later as more heterogeneous area.

The pancreatic parenchyma and peripancreatic fat begin to liquefy slowly and the extent of necrosis is categorized as >30%, 30% to 50%, >50% of gland involved [39]. The modified CT grading system described only two categories as <30% and >30% [40]. Areas of no or poor attenuation are edema rather than necrosis and estimate to be <30% [41].

Ultrasound Imaging (USG)

It can be used to look for gallstones and abnormalities of biliary system and it does not emit radiation. It may difficult to visualize pancreas in presence of clear and free peritoneal fluid. A combination of endoscopy and high frequency ultrasound (EUS) may be useful if CT fails to detect the CBD (common bile duct) stones and it is highly sensitive for the diagnosis of PD (pancreatic divisum) than CT [42] [43]. It is highly specific to diagnose pancreatic cancer and able to identify pancreatic masses as small as 2 to 3 cm [44].

MR (Magnetic Resonance) Imaging

It is helpful to visualize the distal common bile duct stones and also useful in patients with renal insufficiency to avoid contrast enhanced CT [45]. MR imaging or ultrasound may be used to determine the presence of nonliquefied material.

ERCP (Endoscopic Retrograde Cholangiopancreatography)

The endoscope, a thin flexible tube with a camera at the end can help to determine the exact location of gallstone. ERCP is recommended in the setting of acute pancreatitis with cholangitis, presence of jaundice and common bile duct obstruction. Autoimmune pancreatitis can be difficult to distinguish from pancreatic cancer on CT, but typically features "diffuse irregular narrowing of the main pancreatic duct" on ERCP. The diagnosis of choledochocele is usually confirmed by ERCP. Endoscopically, the papilla has a "bulging" appearance and feels soft (pillow sign) when pressure is applied with the catheter tip [46].

Routine ERCP is advised for all patients with acute gallstone pancreatitis. ERCP should be considered in presence of persistently abnormal liver function tests (serum ALT > 150 IU/litre^{-1} is predictive of gallstone pancreatitis) and it cannot be recommended without cholangitis or common bile duct obstruction due to procedure related complications including acute pancreatitis, hemorrhage, perforation, sepsis, stricture, bile leakage with mortality in 6% of cases. It does not allow the evaluation of pancreatic parenchyma and less sensitive to detect masses, chronic pancreatitis and microlithiasis [47]. Because of these reasons, ERCP is not advised in this patient.

MRCP (Magnetic Resonance Cholangiopancreatography)

It gives detailed information about the hepatobiliary and pancreatic systems [48], recommended for patients with recurrent acute pancreatitis of unknown cause to assess for pancreatic divism, choledochocele, anomalous pancreatobiliary junction or annular pancreas.

Secretin Stimulated MRCP (sMRCP)

Secretin is injected intravenously, causing the main pancreatic duct to secrete fluid, which improves the visualization of pancreatic ducts [49] and should be preferred for diagnosing pancreatic divisum.

4. Therapeutic Aspects

The treatment planning is based on severity of pancreatitis. IEP (interstitial edematous pancreatitis) is usually self limited and supportive measures alone suffice. Mild acute pancreatitis is moderately or severely painful. The first line treatments are bowel rest, IV fluids to prevent dehydration and pain medications.

Pain relieving agents

All patients with acute pancreatitis must receive some form of analgesics in the first 24 hrs and dilaudid (hydromorphone hydrochloride) is preferred over morphine or fentanyl in the non-intubated patient. Epidural analgesia may be considered in severe and acute critical care patients who require high doses of opioids for an extended period. Excessive sedation may worsen gut dysfunction with subsequent increase in intraabdominal pressure and intractable pain may need EUS-guided celiac plexes block.

NSAIDs (nonsteroidal antiinflammatory drugs) are the most promising group to attenuate the inflammatory response in acute pancreatitis. Rectal supposito-

ries of 100 mg diclofenac or 100 mg indomethacin can reduce the incidence of post ERCP pancreatitis.

Chronic use of opioids leads to spasm and dryness of pancreatic ducts, which in turn increases the inflammation and producing more pain. The "nonvalidated" medical therapies such as smooth muscle relaxers (calcium channel blockers or nitrates) may abort an attack if taken at the onset of symptoms. Oral pancreatic enzyme supplements which inhibit pancreatic enzyme secretion may be beneficial for pain control, especially in idiopathic chronic pancreatitis. Antioxidants (β-carotene, vitamin C, and vitamin E) are useful since they inhibit the release of oxygen-derived free radicals.

Bowel rest

Bowel rest is needed for a few days, so that not to take any food or drinks by mouth until their condition improves, resolution of pain, awaiting normalization of pancreatic enzymes and even imaging evidence of resolution of inflammation before resuming oral feeding [50]. Several studies have shown that early oral feeding decreases the morbidity, mortality and infectious complications and it may begin as low-residue, low-fat (<50 g/day), soft diet when the patient appears to be improving as no tummy (abdominal) pain and found to be safe in mild acute pancreatitis [51].

Intravenous hydration

The microangiopathic effects and edema of inflammed pancreas worsens the pancreatic hypoperfusion and decreases the blood flow, causes increased release of pancreatic enzymes, activating numerous cascades, leading to increased parenchymal necrosis and cell death [52]. Necrotizing pancreatitis is an ischemic event and the goal of volume resuscitation is to maintain pancreatic and intestinal microcirculation to prevent intestinal ischemia and subsequent bacterial translocation [53], to prevent severe complications such as pancreatic necrosis [54] and to minimize SIRS (systemic inflammatory response syndrome) to reduce the rate of organ failure, morbidity and death. So, early intravenous hydration during the first 12 to 24 hours with close monitoring is of paramount importance.

Hydration with isotonic crystalloid solutions are advisable and the lactated Ringer's solution (20 ml/kg bolus, followed by 3 ml/kg/hour within 36 hours) appears to be more beneficial with antiinflammatory effect, resulting less SIRS compared to normal (0.9%) saline [55] and a better electrolyte balance, improved outcomes and more pH balanced since low pH activates the trypsinogen, makes the acinar cells more susceptible to injury. The use of normal saline in large volumes may lead to nonanion gap, hyperchloremic metabolic acidosis.

Continuous use of aggressive hydration over 48 hours seems to be associated with increased morbidity and mortality [56] [57] and caution to avoid excessive resuscitation (>4 liters in 24 hours) due to complications such as volume overload, pulmonary edema (due to increased systemic permeability) and abdominal compartment syndrome [58]. Movement of fluid into the intracellular space ("third spacing") occurs in acute pancreatitis and fluid resuscitation exacerbates

it. The intraabdominal hypertension (sustained intraabdominal pressure > 12 mmHg) is associated with poor outcome. It should be monitored with transvascular bladder measurements in those patients on mechanical ventilation and managed with ultrafiltration.

Enteral feeding

Enteral nutrition is recommended to prevent gut failure and infectious complications. It is better to avoid solid foods for few days or longer since trying to digest solid foods could put too much strain on pancreas. When the solid foods need to be avoided, it may be given a special liquid food mixture through a tube as "enteral feeding". The enteral feeding is cheaper, safer, and associated with fewer infective complications and a better overall outcome [59] with a decrease in organ failure and mortality [60].

Enteral feeding maintains the gut mucosal barrier and prevents its disruption and translocation of bacteria that seed pancreatic necrosis. Jejunal feeding is advocated if gastric feeding fails [61] as a result of duodenal ileus or obstruction from inflammatory masses and there is some evidence of superiority of "distal jejunal feeding" in acute pancreatitis.

Total parenteral nutrition (TPN) should be considered only for patients who do not tolerate enteral feeding because of severe ileus since it is associated with infection and line-related complications.

Antibiotics

Prophylaxis refers to the administration of antibiotics in patients when no clinical infection is present with the intent to prevent pancreatic infection. Earlier trials suggested that prophylactic antibiotics might prevent infective complications in sterile necrosis [62], but subsequent trials failed to confirm this advantage and recent trials showed no decrease in mortality [63] and thus routine prophylactic antibiotics in acute pancreatitis may increase the incidence of infection with resistant bacteria or fungi and is no longer recommended [64].

CT rarely demonstrates gas in pancreas, lesser sac or retroperitoneum and it is only present in limited number of patients [65]. CT guided FNA (fine needle aspiration) for gram stain and cultures can guide to choose appropriate antibiotic regimen [66], but many centers abandoned the routine use of FNA because of high rate of false negative results. A more rational approach is to consider antibiotics if there is evidence of systemic sepsis or organ failure while recognizing the many signs of SIRS, especially with marked leukocytosis.

Since most infections in severe acute pancreatitis are caused by gram negative organisms, translocated from the gut, the carbapenems (imipenem and meropenem) have a good broad spectrum coverage, excellent pancreatic penetrance [67] and should be used only in critically ill patients due to spread of carbapenem resistant Klebsiella pneumonia. Aminoglycosides are poor penetrance to pancreas and are of little use [68].

Acylureidopenicillins (azlocillin, mezlocillin, piperacillin, and furazlocillin) have an intermediate penetrance into the pancreas and are effective against gram negative organisms [69]. Among these antibiotics, only Piperacillin/Tazobactam

is effective against gram positive bacteria and anaerobes. Quinolones (ciprofloxacin and moxifloxacin) have good tissue penetration into pancreas with an excellent anaerobic coverage [70], but discouraged due to high rate of resistance worldwide and used only in patients with allergy to beta-lactam agents. Metronidazole with its bactericidal spectrum focused almost exclusively against anaerobes, also shown good penetration into pancreas.

Fungal infection is a serious complication of acute pancreatitis and is associated with an increase in morbidity and mortality. When there is no clinical response to antibiotics, fungal infection can be suspected. Candida albicans is most frequent, followed by candida tropicalis and candida krusei. Fluconazole must be given if fungal isolates are identified.

Specific medical therapy

Insulin infusion (0.1 units/kg/hour in 24 hours until triglyceride level became <500 mg/dl by keeping blood glucose level in normal range with dextrose solution) is effective in decreasing triglyceride by increasing the lipoprotein lipase (LPL) activity which can degrade chylomicrons and thus reduces serum triglycerides in acute pancreatitis. Insulin will also rest pancreatic tissue and may improve immunoparalysis via upregulating the expression of human leukocyte antigen on monocytes and decreasing cell apoptosis [71].

In certain cases, a successful method of treatment relies on apheresis for lowering of triglyceride levels. Plasmapheresis (PEX) improves the outcome not only by lowering triglyceride but also by removing proinflammatory markers and cytokines to downregulate the inflammatory process [72].

CBPT (combined blood purification therapy) is a two-step approach for the management of acute severe pancreatitis involving plasmapheresis and continuous venovenous hemofiltration (CVVH) and shown to improve mortality and lowering of inflammatory markers in severe acute pancreatitis irrespective of its etiology [73].

HVHF (high volume hemofiltration) and hemoperfusion (HP) is considered when plasmapheresis is not available and it removes the proinflammatory cytokines in addition to lowering triglyceride level.

Steroids (prednisolone 0.6 mg/kg/day and maintenance dose over 3 to 6 months) are indicated in autoimmune pancreatitis, characterized by infiltration of IgG4-positive plasma cells [74]. The benefits of other agents such as antisecretory drugs (somatostatin, octreotide, lanreotide), N-acetyl cysteine and anti-inflammatory agent (lefipixant) are disappointing.

Surgical therapy

Surgical intervention is associated with high risk of death than medical therapy especially in sterile pancreatitis. Documented infection has been considered as a definite indication for debridgement and infected necrosis may also be treated successfully with antibiotics alone.

A single-stage surgical transgastric necrosectomy is a good option in patients with disconnected pancreatic duct syndrome since it causes peripancreatic collections in patients with lack of improvement [75] with a postoperative mortality

of 2% [76]. Routine intraoperative cholangiography is unnecessary in mild gallstone pancreatitis with normalizing bilirubin levels [77].

Interventional therapy

A catheter directed balloon tamponade, coil embolization or covered stent is preferable to control the massive hemorrhage occurring in 1% to 3% of cases of severe acute pancreatitis and late hemorrhage due to rupture of pseudoaneurysm of splenic artery. Pancreatic duct stent placement may decrease the post ERCP pancreatitis in those patients undergoing endoscopic procedures such as ampullectomy.

Outcome

The disease takes a mild course in most patients and the severe form carries a hospital mortality rate of 15%. Infection leads to 80% of deaths in acute pancreatitis [78] and is associated with worsening organ dysfunction in <5% of cases. The mortality rate in patients with infected necrosis without organ failure is 1.4%. The mortality rate of sterile necrosis remains relatively low as 5% to 10% and without necrosis, it is 0% mortality [79], but the superinfection of necrosis increases the mortality rate subsequently up to 20% to 30% [80]. The sterile necrosis with organ failure is associated with a mortality rate of 19.8%. The treatment of damages caused by systemic inflammation and better antibiotic treatment, nutritional support and learned surgical decisions decrease both early (< 6 days due to SIRS) and late mortality [81].

Case analysis

This 32 years old male was presented with acute abdomen as an initial manifestation of rheumatic fever due to Lancifield group A beta hemolytic streptococci [82] as evidenced by raised ASO titer and ESR. Elevated amylase and lipase with CT features of peripancreatic inflammatory changes as "mistiness" (fat strandings) suggesting acute interstitial edematous pancreatitis (IEP) as in **Figure 1** & **Figure 2** and these inflammatory changes are responded to antibiotic therapy. The patient improved dramatically within few days and resumed oral intake without any further complications. Cefotaxime showed good penetration into the pancreas to eradicate the infective process [83].

Presence of obesity, history of alcoholism, use of anticonvulsants and moderately raised triglyceride levels are the risk factors to trigger the pancreatic infection by streptococcus in this case. Periarteriolar connective tissue inflammation caused by the organism causes vasculitis and the resultant ischemia in the pancreas as an isolated event, may predispose to further infection and so penicillin prophylaxis is indicated.

Preventive measures

1) A healthy lifestyle can reduce the chances of developing acute pancreatitis.

Hypertriglyceridemia causes 2% to 5% of cases of pancreatitis and is associated with inherited disorders of lipoprotein metabolism, congenital type 1, II and V without a precipitating factor in children [84]. Serum triglycerides > 1000 mg/dl may precipitate the attacks of acute pancreatitis. The release of free fatty

acids by lipase may damage acinar cells or capillary endothelium and so reduction of triglyceride level is mandatory. Alcohol itself increases the triglyceride level in a dose dependent manner. In some cases, serum amylase levels may not be significantly elevated due to interference from triglycerides in certain amylase assays. Fibrates remain the drug of choice for long-term TG (triglyceride) control and omega-3-fatty acids as reasonable second choice.

2) Prevention of infectious episodes

Overcrowding, environmental pollution, poor sanitary hygiene in public places (airports, railway stations, bus stands, markets, hotels, shopping areas, hospital premises, schools, cinema theatres, household surroundings, streets, roadsides and toilets) may prone to harbour the infections and the exposure of mucosal surfaces (oral cavity, throat, nasopharynx, genitals) favour the entry of the organism into the body. "Public health units" are compulsory in these places to identify symptomatic cases and to implement preventive measures in these areas.

Moreover, the patients may not adhere lifelong penicillin prophylaxis to prevent its occurrence. The one week course of "Pulse Therapy" as oral penicillin V (or penicillin G potassium tablets 400 mg daily), macrolides, cephalosporins and amoxicillin (amoxicillin should not be combined with penicillins) is advisable for each episodes of attacks when the individual experiences sore throat, sneezing, running nose, febrile episodes with ASO titer positivity since silent and subclinical illness may cause organ damage via the immune mediated mechanisms [85].

Superinfection as Penicillin G potassium should not be used for extended periods since it can lead to the growth of dangerous organisms that are resistant or unresponsive to this medication.

New insights

The systemic inflammatory response syndrome as "cytokine storm" plays a major role in the occurrence of acute pancreatitis and lung damage in streptococcus pyogene infection in susceptible patients. The "cytokine" (bradykinin) storm is also responsible for "acute respiratory distress syndrome (ARDS)" in COVID-19 patients and pancreatic involvement occurs in small number of affected individuals.

A "superantigen" mediated acute infectious disease caused by human adapted pathogen group A streptococcus (GAS) and its large regional outbreaks emerged in North-East Asia in 2011, in the United Kingdom in 2014 and the potential trigger for these epidemics remain unclear. Detailed phylogenetic analysis of GAS outbreak isolates from Mainland China and Hong Kong proved that the increase in fever cases were neither *emm* type specific nor caused by a single clone and the multiclonal fever outbreak strains are commonly associated with the acquisition of related exotoxin carrying mobile genetic elements [86].

Prophage encoding combination of streptococcal superantigens SSA and Spe C, and the DNAase Spd1, appear to play an important role in the evolutionary

pathway that leads to emergence of more virulent strains [87] [88] [89] [90] [91]. GAS produces a cholesterol dependent cytolysin, the Streptolysin O (SLO), that perforates the host cell membrane and it directly damages the mucosa to allow the penetration of streptococcal pyrogenic exotoxin A [92], and Spe C and DNase Spd1 function synergistically to mediate nasopharyngeal colonization [93].

The superantigen, the most potent T cell mitogen known to date [94] and recent studies suggest that such T cell activation contributes to the establishment of GAS infection at mucosal surfaces [95] [96]. The exotoxin genes SSa, Spe C and spd1 and their impact on exotoxin driven enhanced colonization provides an evidence based hypothesis for the reemergence of infection globally similar to COVID-19 pandemic in which the pathogenic ACE 2 receptors are highly expressed in pancreatic islets although its clear pathogenesis is unknown.

The GAS cell surface bears M proteins that form short hair like fibrils. The key feature of M1 clone is its ability to switch rapidly to a hypervirulent phenotype during infection as a result of the CovR/S (*cov*, *control of virulence; csrRS*), two-component system, a global regulator of virulence gene expression in GAS. GAS posses a large battery of virulence factors, trigger the potent inflammatory response, leading to streptococcal toxic shock syndrome with multiorgan dysfunction, vascular collapse, and death in genetically susceptible individuals. GAS causes community acquired pneumonia in 2% to 5% of cases, most commonly after the outbreaks of viral illnesses such as influenza or measles. The current upsurge of invasive infection in developed countries is predominantly linked to the spread of clonal hypervirulent population of M1T1 serotype strain, also seen with M3 and M18 strain, which co-emerged with M1T1 clonal strain and M59 in Western provinces. The new clones evolve through the accumulation of point mutations or by acquisition of new genetic material through horizontal gene transfer events.

GAS can be transmitted by direct or indirect contact and by droplets similar to SARS-CoV-2. Health care workers may be the source of transmission to secondary nosocomial cases. Epidemiologically, specimens from mucosal surfaces, the nasopharynx, genitals (vagina) and anus for cultures, and the positive cases should be treated with antibiotics in order to eradicate the GAS infection.

The persons > 65 years are at increased risk of sporadic cases or mortality due to GAS infection [97]. For asymptomatic group A streptococcal colonized health care workers, benzathine penicillin G 12 lakhs IM + rifampin 300 mg twice daily for 4 days, clindamycin 300 mg orally three times a day for 10 days or azithromycin 500 mg orally daily for 5 days are advised. Rectal carriage of GAS is difficult to eradicate with penicillin based regimens. Oral therapy with vancomycin and rifampin has been recommended and Clindamycin is the preferred agent in such cases since it has documented effects on intestinal flora.

Future Directions

1) Immunoneutralization

In GAS infection, M-protein reactive T cells enter through the surface endothelium by binding to cell adhesion molecules such as VCAM 1, causing leukocyte activation and compromise blood oxygenation [98] by massive release of cytokines as noticed in COVID-19.

Immune neutralization of these specific adhesion molecules (ICAM 1, Mac 1, LFA 1 and PSGL 1) decreases the neutrophil infiltration and ameliorates the endotoxemia, acute lung damage and pancreatic inflammation [99] [100].

2) Immunomodulation

Stem cell therapy

Mesenchymal stem cell (or "stromal cell") therapy (MSCs) reduces the serum levels of proinflammatory cytokines (TNF-α, IFN-γ, IL-1β and IL-6) and decrease the acute inflammatory response via their immunomodulatory effect by secreting anti-inflammatory cytokines (IL-4, IL-10). Umbilical cord derived mesenchymal stem cells injection exerts the regenerative effect of damaged pancreatic cells via paracrine immunosuppressive effect rather than by directly differentiating into tissue-specific pancreatic cells, antiapoptotic effect by secreting the chemokine XCL 1, suppress CD4+ T cell proliferation [101] in the development of tissue injury during acute pancreatitis and enhancing angiogenesis. The SDF-1/CXCR 4 axis (CXC chemokine receptor 4) [102] regulates the migration of mesenchymal stem cells following acute pancreatitis by upregulating the SDF-1α (stromal cell derived factor-1α) in the injured pancreas when most intravenously infused MSCs become trapped in the lungs. MSCs (mesenchymal stromal cells) downregulate the expression of TGF-β_1, which is a major regulator of chronic inflammation and fibrosis and attenuate the local hypoxia and oxidative stress. It prevents T cell proliferation and B cell maturation and activates the regulatory T cells to further suppress the immune response. MSC transplantation along with granulocyte colony stimulating factor (G-CSF) therapy showed an improvement in pancreatic tissue damage. Since the first 24 hours after the onset of acute pancreatitis is critical for prognosis, only a few studies evaluated the outcome of MSCs [103], [104] as an attractive source of cell therapy. Within this time frame, it is a current conservative therapy to reduce mortality by ameliorating the acute process of pancreatic inflammation.

Icariin is a flavonoid with rhamnose as a ligand, a traditional Chinese medicine, extracted from potent Horny Goat Weed [105]. It acts as a natural anti-inflammatory drug which targets on proinflammatory cytokines (TNF-α, IL-6) and stimulates phosphoinositol 3-kinase (PI3K) protein kinase B (AKT) signaling pathway to ameliorate lipopolysaccharide (LPS)-induced acute inflammatory responses [106]. It has potent antioxidant activity and eliminates the reactive oxygen species (ROS). It preserves the proliferative power of MSCs and decreases their senescence and dysfunction. It acts as a preconditioning agent that increases the paracrine activity of MSCs. MSCs co-transplanted with Icariin improves the function of pancreatic stellate cells by enhancing the key β-cell markers PDX1 (pancreatic duodenal homeobox protein 1) and MafA (musculoaponeurotic fibrosarcoma oncogene homolog A).

C1 esterase inhibitor stabilizes the intravascular fluid status and prevents multiorgan failure caused by inflammatory chemokine MCP-1 (monocyte chemoattractant protein 1) and FKN (fractalkine) and prevents the development of acute pancreatitis following allogenic hematopoietic stem cell transplantation due to complement activation. Complement activation such as capillary leakage syndrome [107] plays a central role in mediating the systemic effects of acute pancreatitis. C1 esterase inhibitor reverses the cardiovascular instability and acute renal failure resulting from third spacing of fluids and resolution of serous effusion, but not significantly influences the local inflammation and autodigestive destruction of pancreas [108] due to self perpetuating activation of protease enzymes.

Aprotinin, a Kunitz protease inhibitor, has inhibitory activity against trypsin, chymotrypsin, kallikrein and when given intraperitoneally in high doses, it counteracts the development of necrosis in patients with severe acute pancreatitis [109] [110].

Use of immunomodulating agents such as IV polyspecific Immunoglobulin G (IV IG) that neutralize the toxins and pathological levels of pro-inflammatory cytokines are beneficial.

3) PCR test

Identification of serum opacity factor (SOF) gene serves as a marker for serotyping of *Streptococcus pyogenes*. Sof binds to fibulin 1 and fibrinogen present in the serum and it is a bifunctional cell surface protein expressed by 40% to 50% of group A streptococcal strain composed of C terminal domain that binds fibronectin and an N terminal domain that mediates opacification of mammalian sera. It exhibits N terminal sequence variation and is under the positive transcriptional variation of *mga* (multiple gene activator) and elicits type specific immune response [111]. Sof is a unique virulence gene of *Streptococcus pyogenes* and plays an important role in fibulin binding, opacifying the serum and adhesion of pathogen to the epithelial cells of the host [112].

PCR (polymerase chain reaction) is a powerful tool in detection of *Streptococcus pyogenes* in 1 hour without isolating genomic DNA from the pathogen. Sof is a virulence gene and does not have homology with other organisms and it can be used as a genetic marker for the detection of *Streptococcus pyogenes* causing pharyngitis, pancreatitis and ARDS (acute respiratory distress syndrome).

5. Conclusions

GAS epidemic pharyngitis as "sore throat" and invasive infections are more common as seasonal trends, "a wave of airborne infection" with close "person-to-person contacts" and predisposing to viral infections [113]. Mucosal hygiene (oral cavity and genitals) is an important measure to prevent it [114]. COVID-19 is similarly presenting and amenable to antibiotics in mild cases and vaccine development is a challenge for both conditions since seroconversions

occurring frequently as noticed in the United Kingdom due to new outbreaks of corona virus with different strains recently. Live attenuated vaccine similar to oral polio vaccine as "drops" at the exposed mucosal surfaces of the body to induce immunity (both "humoral" or serum immunity and local immune response) is a better option to control the outbreaks.

Acute abdomen, as pancreatitis and acute lung damage, as ARDS, are the presenting manifestations of both of these infections. Penicillin prophylaxis is indicated in epidemic areas to prevent its unexpected outbreaks and, serum ASO titer screening and PCR tests are advised to identify these infections.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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