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Acute pancreatitis – An immune mediated injury of rheumatic fever

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ABSTRACT

Acute pancreatitis is an acute inflammatory disease of the pancreas that may also involve surrounding tissues since the pancreas lacks a capsule, the pancreatic enzymes access to adjacent area and digest the fascial layers. It is observed as an initial manifestation of group A beta hemolytic streptococcal infection in a 32 years young, obese male in this tropical region where Rheumatic fever is endemic. He was admitted with acute abdominal pain and supported with intravenous fluids and pain not relieved by any medications and blood analysis showed an elevated amylase and lipase levels, raised ESR and a positive ASO titer and CT abdomen revealed interstitial edematous pancreatitis (IEP). Patient was treated with intravenous antibiotics and the pain subsided immediately and blood parameters returned to normal levels at 4 weeks and follow up CT revealed no abnormal findings and symptom free thereafter.

KEY WORDS

Acute abdominal pain; Pancreatitis; ASO titer; Antibiotics; Preventive measures; Mucosal vaccine

ARTICLE HISTORY

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Introduction

Acute pancreatitis is a condition in which the pancreas becomes inflamed (swollen) and most people feel better within a week in mild cases (80%) and it is sometimes associated with a systemic inflammatory response leading to serious consequences and 15-20% risk of death if the patients have organ failure during the first few weeks of disease [1-4].

Acute pancreatitis is a condition in which the pancreas becomes inflamed (swollen) and most people feel better within a week in mild cases (80%) and it is sometimes associated with a systemic inflammatory response leading to serious consequences and 15-20% risk of death if the patients have organ failure during the first few weeks of disease [5].

Immune cells are crucial mediators, which determine the pathophysiology and the balance between pro- and anti-inflammatory events predict the severity of disease [6] and a significant proportion of patients progress to recurrent disease. Some studies suggested that the prophylactic antibiotics reduces the risk of pancreatic necrosis when becoming infected [7]. Abdominal pain is the presenting manifestation of acute rheumatic fever [8], usually precedes the other rheumatic signs and it is the consequence of rheumatic inflammatory process affecting the pancreas and autoimmune response may develop due to the body's immune response after a bacterial infection and molecular mimicry in the setting of genetic risk factors. T-regulatory cells mediated immune reaction and the shift of peripheral blood T lymphocytes towards T helper 2 response could also contribute to the recruitment of cytokines and interleukins that subsequently induce inflammation [9] and often relapse.

Case Report

Presentation

A 32 years old male was admitted with sudden onset of severe upper abdominal pain and he was in toxic state of tachycardia (pulse rate 114 bpm), hypotension (blood pressure 90/60 mmHg), fever (temperature 100.4°F) with distended abdomenand tenderness in the epigastric region. He had a history of alcoholic drinks occasionally. taking anticonvulsants (phenytoin sodium 100mg twice daily) for the past 4 years as he suffered 2 to 3 episodes of seizure attacks and his CT brain was normal earlier.

Investigations

On admission, his serum amylase was 548 IU/L (normal 10 to 96 IU/L). The total leukocyte counts 7190 cells/cumm blood (normal 4000 to 10000/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) 1.2mg/dl (normal 0.4 to 1.2mg/dl). Random blood glucose 98mg/dl (normal 60 to 125 mg/dl). Total cholesterol 180mg/dl (normal 150 to 220 mg/dl), serum triglycerides 270mg/dl (normal 50 to 150 mg/dl). Serum SGOT (Serum Glutamic-Oxaloacetic Transaminase) (AST- aspartate aminotransferase) 88 IU/L (normal 5 to 4 1 IU/L, SGPT (Serum Glutamate Pyruvate Transaminase) (ALT- alanine aminotransferase) 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, > 40 IU/L with normal amylase at the onset of abdominal pain in standing or sitting posture with a relief on lying down which is significant of acute pancreatitis). ASO (ant streptolysin O) titer was 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 negative. 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.

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Treatment

He was 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.

Progress

Plain CT done on 3rd day revealed mild peripancreatic fat strandings as shown in Figure 1 with normal pancreatic parenchyma and no significant ductal dilatation or calcification and fluid collections. Theabdominal distension subsided on 4th day and the patient was advised to resume semisolid liquid diet, tender coconut water, fruits and smashed vegetables without chilies slowly. The milk products were avoided. His condition began to improve thereafter. At 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 was 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 and symptom free and healthy on one year follow up. He was advised lifelong penicillin prophylaxis with oral penicillin V 250mg twice daily to prevent recurrent attacks of pancreatitis. Since he is obese with body mass index (BMI 32%), regular exercise and diet control were advised for weight reduction with periodic medical check-up. The treatment schedule is summarized in Table 1.

Table 1. Showing the treatment schedule and improvement in laboratory (Lab) parameters.

Day	Lab parameters	CT findings	Treatment schedule
1	Amylase 548 IU/L Lipase 1476 IU/L AST 88 IU/L ALT 78 IU/L ASO Titer 440 IU/ml		Antibiotics with IV fluids
3		Peripancreatic fat strandings	
3rd week	Amylase 148 IU/L Lipase 115 IU/L AST 36 IU/L ALT 51 IU/L ASO Titer 288.5 IU/ml		Antibiotics with semisolid liquid diet
4th week	Amylase 69 IU/L Lipase 31 IU/L ASO negative	normal	Discharged with lifelong penicillin prophylaxis

Relapse

He developed another episode after 6 months period which is mild to moderate and responded to same line of treatment for one week at Morning star hospital at Martha dam and thereafter went to Gulf countries for his professional work as a biomedical engineer. After one year, he returned to home at Martha dam in India at Kanyakumari district of Tamil Nadu state and in good health. He skipped the rheumatic fever prophylaxis and succumbed with another episode with severe abdominal pain and he was taken to major hospitals in Trivandrum district of Kerala state by his relatives and given deep sedation to relieve the abdominal pain and went down with respiratory arrest and shifted to another hospital and was on ventilator for more than one month. ASO titer remained as negative.

Outcome

He developed hypoxic encephalopathy with neurological deficits due to prolonged ventilatory support and now bedridden in 'locked-in-state' at home for the past 4 years.

The RT PCR for COVID 19 infection (reverse transcriptase polymerase chain reaction test) was negative and later COVID 19 antibodies remain elevated due to vaccination (Figure 1).

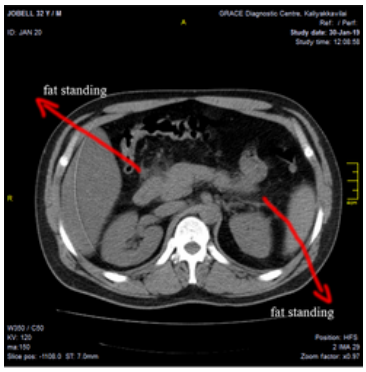

Figure 1. Showing 'fat stranding' as 'mistiness' or 'hazy streaky densities' due to inflammatory changes in the peripancreatic fat around the uncinate process of pancreas. extending towards tail region and perinephric area suggesting "acute interstitial edematous pancreatitis (IEP)".

Demographics

Day

Streptococcus pyogenes (S. pyogenes) can affect at any age and severe infections are more common in infants and elderly and usually affect younger adults (25 to 44 years).

Sex

Males shown to have higher rates of invasive S. pyogenes infections and its incidence in India is shown in Table 2.

Table 2. Showing sex wise and sample wise incidences of streptococcus pyogenes in India [10].

Sex	Incidence (%)
Male	48. 31
Female	20
	Different samples
Pus	50
Sputum	60
Throat swab	48
Cervical swab	10
Ear discharge	11

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Ethnicity

Higher rates of infections in individuals of non-white European descent and in tropical nations and United States have shown that between 2005 to 2012, there were an estimated 1136–1607 deaths each year due to GAS infections and in 2019 as 2250 deaths [11]. Furthermore, Canada's GAS infection rate in 2017 was more than tenfold that of 2003 [12]. Therefore, it is evident that diseases associated with GAS (Group A Streptococcus) infections are rapidly increasing.

Socioeconomic status

S. pyogenes (or GAS) infections and their associated sequelae are more prevalent in areas of socioeconomic disadvantage as over crowing and poor living standards.

Discussion

Etiopathogenesis

Normally, digestive enzymes released from the pancreas are not activated to break down fats and proteins until they reach the small intestine. Acute inflammation due to the activation of pancreatic enzymes prematurely in the pancreas by multiple triggers, which can lead to local damage as 'acinar cell destruction' and systemic inflammatory reactions. Neutrophils and macrophages infiltrate the pancreas and release their own proteases, free radicals, and cytokines which cause further tissue damage and inflammation, inducing an 'acute systemic inflammatory response syndrome (SIRS)' and organ damage. The patient may become dehydrated and in severe cases, pancreatitis can result in bleeding into the gland, leading to shock, serious tissue damage, infection, fluid collections and death due to multiorgan failure with high mortality [13].

The onset of acute pancreatitis is sudden with epigastric pain, vomiting and collapse due to massive release of toxic agents from the inflamed pancreas. The condition has to be differentiated from other diseases producing acute abdomen such as acute appendicitis, perforated peptic ulcer, acute cholecystitis and infarction of intestine following sudden occlusion of the mesenteric vessels.

Acute pancreatitis is associated with multiple infections and in most reports, bacteria are considered important only in late stage and not as a primary etiological agent. Salmonella infection significantly increases the serum activity of amylase in 6.7% and lipase in 16.7%. Serum lipase activity was significantly higher in gastroenteritis patients infected by Salmonella enterica serovar Typhimurium than in those infected by Salmonella enterica serovar enteritidis and ultrasonography did not show any pancreatic abnormalities [14].

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 and alcohol induced 'microcirculatory impairment' potentiated by smoking. When pancreatic ischemia occurs, its tissues begin to die as necrosis leading to acute necrotizing pancreatitis.

Streptococcus pyogenes (Lancefield 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. During bacterial invasion, the M1 protein (Matrix protein) is shed from its surface into the blood stream and causing widespread activation of host innate immune cells as shown in Figure 2. 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, The activation of the NLRP3 (Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing) inflammasome, a crucial part of the innate immune system, requires two distinct signals: a priming signal and an activation signal. The priming signal, often provided by microbial components or endogenous cytokines, leading to upregulation of NLRP3 and pro-IL-1β through NF-κB activation. The activation signal triggers inflammasome complex assembly, ultimately leading to caspase-1 activation and IL-1β production as shown in Figure 3 [15]. After recruitment to an inflammasome, caspase-1 is activated through proximity-induced autocatalytic activation that helps in cleaving pro-IL-1β and pro-IL-18 to its active biological form. The active IL-1β then facilitates the introduction of immune cells to the site of tissue damage or infections [16] and expression of TNF-α (tumor necrosis factor alpha) 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 and shock in susceptible individuals [17].

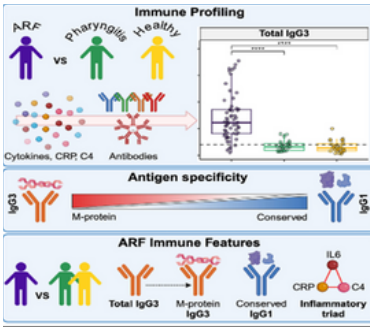

Figure 2. Showing the immune profile of streptococcus pyogenes [18].

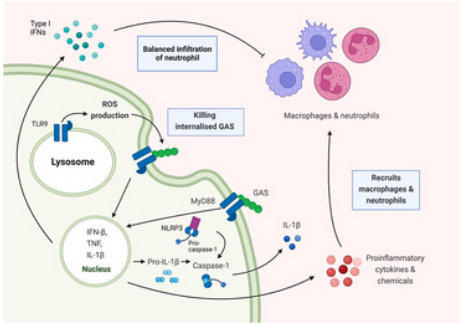

Figure 3. TLR and MyD88 signaling cascades stimulate the expression of IFN- and pro-inflammatory cytokines such as TNF and IL-6. TNF encourages macrophage recruitment to the infection. Type I IFN signaling induced by IFN- and other type I IFNs initiates unidentified responses that end in balanced neutrophil infiltration and protective immune responses against GAS. TLR9 promotes GAS killing by ROS production. GAS induces IL-1β in an NLRP3-dependent manner [19].

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Systemic inflammatory response syndrome (SIRS) is an exaggerated defense mechanism to noxious triggers like infection, acute inflammation, toxins, or ischemia. The dysregulation of proinflammatory and anti-inflammatory pathway homeostasis release acute phase reactants, which are direct mediators of widespread immunological alterations. Inflammation triggered by an infectious or noninfectious stimuli sets a complex interplay of the humoral and cellular immune response, cytokines, and complement pathway and an endotoxin or exotoxin produced by the infection activates neutrophils, macrophages, mast cells, platelets, and endothelial cells stimulate the activation of IL-1 and TNF alfa, which are the early mediators within the first hour and tilting the cascade towards a proinflammatory overdrive and results in the dissociation of nuclear factor-kB (NF-kB) from its inhibitory action to induce mass release of other proinflammatory cytokines including IL-6, IL-8, and Interferon-gamma. IL-6 induces the release of acute-phase reactants including procalcitonin and C reactive protein. Infections produce a greater surge of TNF-alpha and thus IL-6 and IL-8. Another potent proinflammatory cytokine is High mobility group box 1 (HMGB1) protein which is involved in the delayed cytotoxic response of SIRS and sepsis and it is an independent predictor of 1-year mortality [20]. The criteria to diagnose SIRS is shown in Table 3 and the emerging biomarkers to distinguish septic and non-septic etiology of SIRS include TREM 1 (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) [21]. Among them, suPAR correlated well with disease severity and the identification of no survivors in the sepsis group.

Table 3. Showing the criteria of SIRS (systemic inflammatory response syndrome) [22].

Physiological Parameter	SIRS Criterion
Heart rate	> 90 bpm
Core Temperature	< 36°C or > 38°C
White Blood Cell Count	< 4,000/mm³ or > 12,000/mm³
Respiratory Rate	> 20 breaths per minute

Imaging studies

Imaging studies may be normal in mild cases and ultrasonography show an increased pancreatic volume, quantified as a pancreatic body exceeding 2.4 cm in diameter with marked anterior bowing and surface irregularity with displacement of the adjacent transverse colon and/or stomach secondary to pancreatic volume expansion.

CT (computed tomography) findings of acute pancreatitis depend on the severity and extend of the inflammatory process. In Interstitial pancreatitis, inflammation of the tissue only and in necrotizing pancreatitis, pancreatic tissue loses its blood flow and begin to die. Three common imaging findings to look for acute interstitial pancreatitis are pancreatic enlargement, Inflammation and reactive inflammation as seen in nearby structures such as duodenal c-sweep. The inflammatory reaction can produce increased attenuation of the peripancreatic fat tissue commonly described as "stranding" [23] as shown in Figure 1 and localized in the head part in 18% of cases [24] and usually expands towards the left of tail and the left pararenal space. A relative decrease in the density of the perirenal fat tissue due to an increase in the density of Gerota fascia and pararenal space by the inflammatory process leads to "renal halo" sign [25]. The peripancreatic inflammatory changes are the most common CT findings in 88% of cases of acute pancreatitis, seen in my sentry, greater omentum and transverse mesocolon. Pancreatic parenchymal necrosis alone is seen in < 5% of cases and appears as lack of parenchymal enhancement on contrast-enhanced CT [26].

ERCP (Endoscopic Retrograde Cholangiopancreatography) is recommended in the setting of acute pancreatitis to rule out autoimmune etiology which shows 'diffuse or segmental irregular narrowing of the main pancreatic duct' as a characteristic feature [27] and to diagnose choledochocele , a cystic dilation of the bile duct, The papilla, the opening of the bile and pancreatic ducts into the duodenum, will appear enlarged and rounded and when the catheter tip is used to gently probe the area, it will feel soft and compressible, like a pillow (pillow sign) [28] when pressure is applied with the catheter tip. Routine ERCP is considered in presence of persistently abnormal liver function tests (particularly serum ALT > 150 IU/L suggests biliary obstruction) [29] to visualize bile ducts and to remove any obstructions if identified. Procedure related complications including acute pancreatitis, hemorrhage, perforation, sepsis, stricture and bile leakage can occur in 6% of cases. ERCP with manometry is the gold standard test for Sphincter of Oddi dysfunction (SOD) and basal sphincter pressures of more than 35 to 40 mmHg is consistent with its diagnosis [30], especially in recurrent acute pancreatitis [31].

Therapeutic Strategies

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 treatment includes 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 hours and dilaudid (hydromorphone) is preferred over morphine or fentanyl in the non-intubated patient [32] and it is 5-7 times more potent than morphine, smaller (usually 0.5-1mg IV every 4 hours) doses are needed for faster relief with potentially fewer side effects and also in patients with kidney problems since it produces fewer active metabolites than morphine [33]. 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 necessitates EUS-guided celiac plexus block.

NSAIDs (non-steroidal anti-inflammatory drugs) are the most promising group to attenuate the inflammatory response in acute pancreatitis. Rectal suppositories of 100 mg diclofenac or 100 mg indomethacin can reduce the incidence of post ERCP pancreatitis [34].

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Chronic use of opioids causes spasm and dryness of pancreatic ducts, which in turn increases the inflammation and producing more pain. The "non validated" 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.

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 [35]. Several studies have shown that early oral feeding decreases the mortality and infectious complications and it may begin as low- residue, low fat, soft diet when the patient appears to be improving as no tummy (abdominal) pain and found to be safe in mild acute pancreatitis [36]. In mild pancreatitis, oral feeding can be restarted, once abdominal pain diminishes with improvement of inflammatory markers, without waiting for the complete resolution of pain or laboratory abnormalities [37]. The American Gastroenterological Association recommends starting oral feeding within 24 h for patients with mild acute pancreatitis [38]. Around 80% of patients can initiate an oral refeeding within 7 days of hospitalization [39].

Intravenous hydration

The microangiopathic effects and edema of inflamed 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 [40]. 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 [41], to prevent severe complications such as pancreatic necrosis [42] 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 is advisable and the lactated Ringer's solution (20ml/kg bolus, followed by 3 ml/kg/hour improve outcome within 36 hours) appears to be more beneficial with anti-inflammatory effect, resulting less SIRS compared to normal (0.9%) saline [43] 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 non-anion gap, hyperchloremic metabolic acidosis.

Continuous use of aggressive hydration over 48 hours seems to be associated with increased morbidity and mortality [44,45] 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 [46]. 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 [47]. It should be monitored with transvacuolar bladder measurements in those patients on mechanical ventilation and managed with ultrafiltration [48].

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 [49] with a decrease in organ failure and mortality [50].

Enteral feeding maintains the gut mucosal barrier and prevents its disruption and translocation of bacteria that seed pancreatic necrosis. The safety of nasogastric feeding, which eases the administration of enteral nutrients in the clinical setting, is likely equal to Naso jejunal feeding. Jejunal feeding is advocated if gastric feeding fails [51] 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. The latest meta-analyses suggest that enteral nutrition significantly reduces the mortality rate of severe acute pancreatitis and it should be commenced within the first 24 h of hospital admission [52].

Total parenteral nutrition (TPN) should be considered only for patients who do not tolerate enteral feeding [53] because of severe ileus (intestinal failure) since it is associated with infection and line-related complications.

Case analysis

The pancreas produces elevated levels of enzymes, the amylase, lipase and trypsinogen, all derived from pancreatic acinar cells during acute pancreatitis. Serum amylase usually rises within 6 to 24 hours, peaks at 48 hours, and return to normal within 3 to 7 days [54] and lipase rises within 4-8 hours, peaks at 24 hours and decreases to normal in 8 to 14 days [55]. 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.

A laboratory "acute pancreatic screen" to determine the etiology should also include serum ASO titer [56]. Streptococcus pyogenes produces various exotoxins such as streptolysin O that can acts 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.

This 32 years old male was presented with acute abdomen as an initial manifestation of rheumatic fever due to Lancefield group A beta hemolytic streptococci [57] as evidenced by raised ASO titer and ESR . Elevated

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amylase and lipase with CT features of peripancreatic inflammatory changes as 'mistiness' (fat strandings) suggesting acute interstitial edematous pancreatitis (IEP) as in Figure 1 which constitute in vast majority of cases of acute pancreatitis as 90-95 % [58] 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 [59].

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 predisposes to further infection and so penicillin prophylaxis is indicated.

Preventive measures

A healthy lifestyle can reduce the chances of developing acute pancreatitis

Mild to moderate elevations in triglycerides (2-10 mmol/L) (150 to 499mg/dl) are extremely common in the early phase of acute pancreatitis of any etiology. and more likely to be an epiphenomenon of the acute pancreatitis rather than a true causal precipitant. Triglyceride (TG) levels remained mildly elevated for up to 15 days, probably reflecting an underlying lipid disorder. It is also stated that mild to moderate hypertriglyceridemia is causally related to increased risk of acute pancreatitis [60].

It is commonly accepted that a fasting TG level >1.7 mmol/L (> 150 mg/dl) constitutes hypertriglyceridemia (HTG) and alcohol itself increases the triglyceride level in a dose dependent manner and so avoidance of alcohol and reduction of triglyceride level are mandatory. In some cases, serum amylase levels may not be significantly elevated due to the interference from the triglycerides with certain amylase assays. Persistence of hyperlipidemia on a fat-reduced diet should prompt the institution of lipid-lowering agents when serum TG levels are >5.6 mmol/L (> 500mg/dl) [61] since there is a high risk of developing pancreatitis (lipemic pancreatitis) [62]. The fibric acid derivatives (fibrates), such as gemfibrozil, fenofibrate or bezafibrate, are the drugs of first choice and Omega-3 fatty-acid products in refractory cases [63].

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, household surroundings, streets, cinema theatres, roadsides, toilets in public places, smoke emitting and dust spreading vehicles on the roads) may prone to harbor the infections and the exposure of the mucosal surfaces (oral cavity, throat, nasopharynx, genitals) favor the entry of the organism into the body. Establishment of "public health units" in these places are advisable to identify symptomatic cases and to implement preventive measures.

Moreover, the patients may not adhere the lifelong penicillin prophylaxis to prevent its occurrence. The one-week course of "Pulse Therapy" [64] as oral penicillin V (or penicillin G potassium tablets 400 mg daily), macrolides, cephalosporins and amoxycillin (amoxycillin should not be combined with penicillin's) is advisable for each episode 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.

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.

Lately, the COVID-19 vaccine (Pfizer/BioNTech COVID-19 mRNA vaccine) has been implicated in cases of acute pancreatitis [65] similar to other vaccines such as MMR and hepatitis A and B vaccine and other serious adverse effects such as anaphylaxis, myocarditis or pericarditis, Guillain-Barre syndrome, and facial palsy, have been reported [66]. The exact cause of COVID-19 vaccine-induced pancreatitis remains uncertain and similarities between vaccine components and body antigens might trigger an autoimmune response, akin to COVID-19 and Immunologic injury may be caused by a cytotoxic antibody system that has a heterophilic reactivity to acinar cells, the exocrine unit of pancreas. Boskabadi reported that a healthy 28-year-old female experienced abdominal pain within three days following the second dose of the COVID-19 vaccine and three months after the last vaccination, she was again hospitalized with recurrent abdominal pain due to acute pancreatitis [67].

This patient had not taken mRNA vaccine (vaccinated with Indian made Covishield) and also remain symptom free for one year and so COVID 19 vaccinations may not be the cause of relapse even though having raised COVID 19 antibodies due to vaccination.

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 pyogenic infection in susceptible patients.

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 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 was 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 [68].

Prophage encoding combination of streptococcal superantigens (SSA) and Spe (Streptococcal pyrogenic exotoxin) C, and Spd1 (streptococcal phage-encoded DNase), appear to play an important role in the evolutionary pathway that leads to emergence of more virulent strains [69-74]. GAS

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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 (SpeA) [75], and Spe C and DNase Spd1 function synergistically to mediate nasopharyngeal colonization [76].

The superantigen, the most potent T cell mitogen known to date and recent studies suggest that such T cell activation contributes to the establishment of GAS infection at mucosal surfaces [77,78]. The exotoxin genes SSa (streptococcal superantigen), 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 mechanism is unknown.

The GAS cell surface bears M proteins as shown in Figure 4 that form short hairlike 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 strains may have 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 [79], 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.

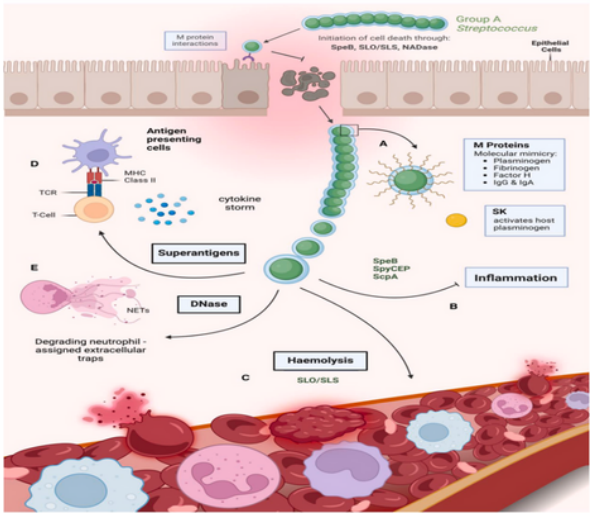

Figure 4. The role of M protein (The M proteins that are surface expressed helps in initial attachment of GAS to epithelial cells. Secretory toxins such as SpeB, SLS/SLO and NADase helps in breaking the epithelial barriers thereby helping in the translocation of GAS to host cells [80].

GAS can be transmitted by direct or indirect contact and by droplets [81]. Droplet transmission happens when an infected person coughs or sneezes, releasing respiratory droplets that can be inhaled by others. 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. Topical antibiotics (erythromycin) given to the eyes of a newborn within 1 h of birth can prevent the infection.

The persons > 65 years are at increased risk of sporadic cases or mortality due to GAS infection. For asymptomatic group A streptococcal colonized health care workers, benzathine penicillin G 12 lakhs IM + rifampin 300 mg twice daily for 4 days, clindamycin 300mg 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 and oral therapy with vancomycin and rifampin has been recommended and Clindamycin is the preferred agent (orally with a capsule (75 mg, 150 mg, 300 mg) or in solution (75 mg/5 mL) in such cases since it has documented effects on intestinal flora.

Future Directions

Immunoneutralization

In GAS infection, M-protein reactive T cells enter through the surface endothelium by binding to cell adhesion molecules such as VCAM 1(vascular cell adhesion molecule 1), causing leukocyte activation and compromise blood oxygenation by massive release of cytokines.

Immune neutralization of these specific adhesion molecules (ICAM 1 (intercellular adhesion molecule1), Mac 1 (macrophage-1 antigen), LFA 1(lymphocyte function–associated antigen 1) and PSGL 1(P-selectin glycoprotein ligand-1)) decrease the neutrophil infiltration and ameliorate the endotoxemia, acute lung damage and pancreatic inflammation.

Immunomodulation

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

PCR test

Identification of serum opacity factor (sof) gene which 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. 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.

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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).

Conclusions

GAS pharyngitis 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. Mucosal hygiene (nasal, oral cavity and genitals) is an important measure to prevent it. Vaccine development remains as a challenge for both conditions since seroconversions occurring frequently. Live attenuated vaccine similar to oral polio vaccine as “drops” at the exposed mucosal surfaces of the body (mucosal vaccine) to induce immunity (both ‘humoral’ or serum immunity and local immune response) is a better option to control the outbreaks and serum ASO titer screening and PCR tests are advised to identify these infections.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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