Review of Infectious Etiology of Acute Pancreatitis

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Abstract

While gallstones and alcoholism are widely known to be the most common causative agents of acute pancreatitis, about 10% of cases are thought to be caused by infectious microorganisms. These microorganisms include viruses (e.g. mumps, Coxsackie B, and hepatitis), bacteria (e.g. \textit{Mycoplasma pneumoniae} and leptospirosis), and parasites (e.g. Ascaris lumbricoides, Fasciola hepatica, and hydatid disease). Each organism causes acute pancreatitis through diverse mechanisms. The review is primarily conducted in an attempt to provide a better understanding of the possibility of acute pancreatitis presenting as a complication relating to these organisms, and the aim is to guide future diagnoses, management, and predictions of complications.

Keywords: Infectious causes; Acute pancreatitis

Introduction

Acute pancreatitis (AP) is an inflammatory disease affecting the exocrine part of pancreatic parenchyma. It may range from a mild self-limiting form (acute interstitial pancreatitis) up to a more severe and rapidly fatal form (acute necrotizing pancreatitis). It may also extend beyond pancreatic tissue to the peripancreatic region and is usually associated with a systemic inflammatory response, which, if not treated properly, may end up in multi-organ failure [1].

Although life-threatening, AP is a reversible process of interstitial edema, inflammatory cell infiltration, as well as cellular apoptosis, necrosis, and hemorrhage. It mainly causes exocrine dysfunction; however, the repetitive process of inflammation and subsequent fibrosis can cause both exocrine and endocrine dysfunction [2].

Etiology of AP

Gallstones and alcoholism are two most common etiological factors of AP. Cholelithiasis is reported in 40-70% of cases while alcoholism is seen in 25-35% [3]. Other rare causes of AP include drugs such as azathioprine, 6-mercaptopurine, and DDI; however, these only account for 1-4% of cases, and further evidence is required to demonstrate their correlation to this condition [4]. In hypertriglyceridemia, serum triglycerides should rise above 1,000 mg/dL to be considered as a possible cause of AP. Benign or malignant strictures of the pancreatic duct are associated with AP in about 5-14% patients [5]. In a recent study on the different etiological factors of AP, 1,914 patients were considered for the causes of their AP, and this study revealed cholelithiasis to be the primary etiology, identified in 58.7% of cases. The second most common cause was idiopathic AP, identified in 543 patients (16.7%), followed by hyperlipidemia in 467 patients (14.3%) and alcohol in 148 patients (4.5%) [6].

Nevertheless, about 10% of AP cases are caused by other miscellaneous factors such as infection by parasites, bacteria, and viruses [7].

Infectious Etiology of AP

Various infectious microorganisms may cause infectious pancreatitis, and these include viruses (hepatotropic virus, Coxsackie virus, cytomegalovirus (CMV), human immunodeficiency virus (HIV), herpes simplex virus (HSV), mumps, varicella-zoster virus, and other viruses); bacteria (mycoplasma, legionella, salmonella, and leptospira); fungi (aspergillus); and parasites (toxoplasmosis, cryptosporidium, and ascaris) [8].

Precise investigations, however, should be performed to exclude other causes of AP and correlate the infectious agent to the disease so as to avoid false diagnoses and, subsequently, improper disease management as such instances can go as high as 10% of all AP cases [9].

Viral Causes of AP

The largest number of infectious pancreatitis incidents are caused by viruses including hepatotropic virus, Coxsackie virus, CMV, HIV, HSV, mumps, varicella-zoster virus, and other viruses.

Among all types of hepatitis viruses, hepatitis B virus is the one most commonly known to be associated with AP, typically occurring in post-transplantation patients. Immunosup-
The incidence of mumps among patients of AP was found to be about 5.1% of patients hospitalized for mumps in [6]. The incidence rate of mumps among patients of AP was found to be about 5.1% of patients hospitalized for mumps in [6]. The incidence rate of mumps among patients of AP was found to be about 5.1% of patients hospitalized for mumps in [6]. The incidence rate of mumps among patients of AP was found to be about 5.1% of patients hospitalized for mumps in [6].

Coxsackie virus type B virus is a single-stranded RNA picornavirus with six serotypes identified (serotypes 1-6). It typically causes self-limiting conditions involving the gastrointestinal and respiratory systems. Several retrospective and prospective studies in the literature have demonstrated the role of Coxsackie B virus in AP, where patients manifested symptoms of AP, and the virus was identified by immunohistochemistry methods and serologic tests (antibodies against viral antigens) [6]. Recently, different serotypes of Coxsackie virus B4, such as CB4-P and CB4-V, have been found to cause both acute and chronic pancreatitis, possibly due to different immune-mediated mechanisms [17].

CMV-associated pancreatitis is rare. In 2014, a case report by Chan et al describes an otherwise healthy individual with a history of acute viral prodrome who, then, developed hepatitis and pancreatitis. CMV infection was confirmed by a positive polymerase chain reaction, and the patient was put on ganciclovir, which caused clinical and laboratory recovery [18]. Salazar-Huayna et al also discussed two case reports of patients with AP who tested positive for CMV in reverse transcription PCR; both individuals were known HIV patients. As the case describes, the patients were prescribed ganciclovir, and they improved, both clinically and as indicated by laboratory findings [19].

Another case report by Baran et al reviews AP in a case of H1N1 viral infection and the case initiated a need for further studies to identify the relationship between influenza and AP [20].

In HIV infection, AP is a well-known complication. Its incidence rises to 40% among HIV-positive patients as compared to 2% in the general population [21]. It may be caused either by the direct effect of the virus on pancreatic tissue or, most commonly, by anti-retroviral drug regimens (HAART) such as a nucleoside reverse transcriptase inhibitor or protease inhibitors, which induce hypertriglyceridemia that, subsequently, causes AP [22].

There have been sporadic reports of HSV causing AP [23]. One particular case report was disseminated HSV causing AP. Notably, the HSV DNA was detected in the pancreas by using in situ hybridization [24].

The first reported case in the literature that identifies mumps as a causative organism for AP occurred in 1905 when Lemoine described a patient with an illness consistent with mumps and manifestations consistent with AP [8]. Mumps virus is a single-stranded DNA paramyxovirus that causes parotitis and orchitis in school-aged children and adolescents; it sometimes is complicated by meningocerebralitis and pancreatitis. When complicated by the latter, it manifests in abdominal pain and diarrhea, and the condition is usually self-limiting [6]. The incidence rate of mumps among patients of AP was found to be about 5.1% of patients hospitalized for mumps in the US [25]. It is worth noting that, following the use of the MMR vaccine, just a single case of mumps virus-associated AP has been described in the literature [26].

Varicella-zoster virus might be a probable cause of AP in children as it has been implicated in causing pancreatic pseudocyst and duodenal obstruction [27].

Other viruses that might cause AP include Epstein-Barr virus, rubella, and rubeola, but there is not yet sufficient evidence to link them directly to AP as causative agents [8].

Bacterial Causes of AP

Many studies in the extant literature have reported the association between bacterial pathogens and AP. In the mid-70s, Freeman first described the association between *Mycoplasma pneumonia* and AP in nine out of 27 patients (33%), and the diagnosis was confirmed by serological tests [28]. Although this association between *Mycoplasma pneumonia* and AP has been further enriched by Leinikki et al and McMahon, no evidence of infection in pancreatic cells by the organism was identified, drawing the organism as a potential etiology into question [6]. A more recent case report and review of the literature by Lacasa et al in March 2017 provided evidence for patients with AP who had a history of upper respiratory tract infection and positive serum serology for *Mycoplasma pneumonia* [29]. In his report, Lacasa depended on the rule by Parenti et al [8], formulated in his intensive review about infectious causes of AP, where Parenti states that serological tests alone are not enough and that patients must show characteristic symptoms of the causative organism to avoid false association with AP.

Only a few cases reported in the literature describe the association between leptospirosis and AP. Leptospirosis is commonly known as “yellow fever”. Possible complications due to leptospirosis include acute renal failure (95% of cases), acute hepatic failure (72% of cases), acute respiratory failure (38% of cases), acute cardiovascular failure (33% of cases) and AP (25%) [30]. A recent report of two cases by Kaya described AP with confirmed leptospirosis. However, for the diagnosis of AP in such a case, at least a four-fold increase in serum amylase and lipase is necessary to confirm AP as hyperamylasemia is exceedingly common in leptospirosis caused by factors other than AP (i.e. renal failure, reticuloendothelial system dysfunction). So, correlation with a four-fold serum amylase level elevation, as well as a CECT scan, was necessary to support the diagnosis of AP with leptospirosis [31].

*Mycobacterium tuberculosis* infection rarely causes AP [32]; however, a diagnosis can be made using biopsy or fine-needle aspiration followed by tissue culture or PCR to detect the microorganism in the pancreatic tissue [6].

Severe gastroenteritis and typhoid-like symptoms are the most common manifestations of *Paratyphoid salmonellosis*, but a causative relationship between the organism and AP is rarely reported in current literature. One case report that described a connection between *Salmonella paratyphi* and AP, and the presence of meningitis, was reported by Makhouli et al in 2015, though the authors did not mention how they verified the correlation among these conditions or whether or not the
organism was extracted from pancreatic tissue [33]. A prospective study carried out by Pezzilli et al in 2003 stated that, in 30 patients, hyperamylasemia and hyperlipasemia were reported in 6.7% and 16.7% of cases, respectively, without any clinical symptoms or signs suggestive of AP, which suggests a low risk of AP in Salmonella infections [34].

Sporadic cases of AP due to gastrointestinal bacteria like Campylobacter jejuni [35, 36], Yersinia enterocolitica [37, 38], Yersinia pseudotuberculosis [38], Brucella [39], and Nocardia [40] have been reported in the literature [6].

Parasitic Causes of AP

Ascaris lumbricoides is the most common parasite implicated in AP as mentioned by Parenti et al in their extensive review. The mechanism of pancreatitis involved in the adult worm’s obstruction of the pancreatic duct is shown in ultrasounds, surgery, endoscopy, or postmortem autopsies. As well, it is more common in children due to the smaller size of their pancreatic-biliary tree [8]. In a prospective study carried out in India, ascariasis was the leading cause of pancreatitis in 59 of 256 patients (23%) compared to 112 patients (44%) with gallstone pancreatitis [41].

The Chinese liver fluke, Clonorchis sinensis, was reported in some cases of AP due to the obstruction of the pancreatic duct [42].

Plasmodium falciparum is one of the most common protozoa, and it is known to cause malaria. In one 2016 case, a patient with malaria complicated by multi-organ affection was found to have AP as well. The diagnosis of Plasmodium malaria was made by a peripheral blood smear and a positive Paracheck rapid antigen test for Plasmodium falciparum. On ultrasound, the pancreas was found to be hypoechoic and bulky, and it was treated using anti-malarial agents that proved AP to be an atypical complication for malaria. Thus, it should be ruled out in patients presenting with AP with an unknown etiology [43].

Although infrequently associated with AP, taeniasis was also reported as one of the possible helminths that cause AP in a case published in 2005. In this instance, the patient presented with typical symptoms for AP and markedly elevated serum amylase and lipase, including a history of the passage of white worms with the stool for 4 years. The proglottids were extracted from the duodenal mucosa with ultrasound findings of dilated common bile duct and pancreatic duct, which provides possible evidence of a tapeworm passing through the biliary tree. The patient responded to anti-helminthic drugs, and the condition improved [44].

Other parasites implicated in AP include Opisthorchis species [45], Fasciola hepatica [46, 47], and Echinococcus granulosus [48], which may cause AP due to the compression of the pancreatic duct by the cyst [8].

Fungal Causes of AP

Despite the fact of lack of clear evidence in the literature, fungi have been at times implicated as causative agents for AP. In one case, fungus infection (aspergillus) was found to develop into AP, and a postmortem autopsy revealed the fungus invading pancreatic tissue causing infarction, necrosis, and inflammation [49].

A recent case-control study in 2007 reviewed patients with AP between 2003 and 2005 who tested positive for candida or gave signs of possible candida infection (candida in their fluids without evidence of candida in pancreatic necrotic tissue). The first group comprised about 21% of the participants while the second one comprised 19%. Most commonly, candida complicates acute necrotizing pancreatitis rather than causes it. Moreover, candida is also often responsible for a longer hospital stay and increased mortality rates [50].

Pathogenesis of AP Caused by Infectious Microorganisms

AP may manifest as a mild interstitial form, which constitutes 80% of cases and has a low morbidity and mortality rate (<1%); however, about 20% of patients with AP develop the more severe form (necrotizing pancreatitis). This form has an early vasoactive and toxic phase, and a late, more severe septic phase [51].

Many theories have been postulated to give us a better understanding of and describe the mechanism by which AP takes place. These theories include bile-pancreatic duct common pathway theory, pancreatic autodigestion theory, gallstone migration theory, enzyme activation theory, kinin and complement activation theory, microcirculation disturbance theory, leukocyte excessive activation theory, and pancreatic acinar cell apoptosis and necrosis theory, all of which are still currently under review [52].

Considering that infectious agents are responsible for about 10% of AP cases, the mechanism by which they cause AP is not so different from the ones previously mentioned. Each organism works in its peculiar way to cause AP.

Many theories have been created to explain viral pancreatitis, and one of these is the direct destruction of pancreatic acinar cells by inflammation and edema, a theory supported by autopsy findings that revealed HBV antigens in the cytoplasm of affected pancreatic acinar cells. There is the possibility of a causative relationship between the amount of affected pancreatic acinar cells and the severity of the disease. Another theory suggests that the damaging of pancreatic acinar cells by the virus leads to a leaking intracellular enzyme or precipitates a process of cell death similar to that occurring in hepatocytes affected in acute hepatitis [12]. Alternatively, another way of damaging pancreatic cells is by edema of the ampulla of Vater with obstruction to the outflow of pancreatic fluid [13].

Other mechanisms explain AP caused by Mycoplasma pneumoniae. One proposed mechanism is the production of cytokines triggered by bacterial lipoproteins, and another is the inflammatory response in different organs caused by the bacterial pathogen’s immune modulation. A third mechanism is the vascular occlusion mechanism in which both direct and indirect types are possible. The direct type is caused by bacteria in the blood stream triggering the release of local inflammatory
mediators, while the indirect one is the result of a systemic hypercoagulable state. The real pathological mechanism, however, is unknown [29].

Leptospirosis causes vasculitis and endothelial damage, and it most commonly affects the liver and kidneys though other tissues can be affected as well, such as the pancreas due to pancreatitis [31].

Parasites such as Ascaris lumbricoides cause AP from the adult worm obstructing either the pancreatic duct or the common bile duct as demonstrated by surgery, endoscopy, and autopsy findings. Alternatively, it may be caused by abscess formation if it has progressed to more distal parts of the pancreas [53]. While hydatid cysts do not cause pancreaticobiliary obstruction, the formation of cysts within the pancreas compresses the pancreatic duct, though such obstruction may also be caused by direct rupture of a hepatic hydatid cyst into the biliary tree, causing AP [8].

Conclusion and Future Perspectives

The current literature provides information about the types of organisms thought to be involved in causing AP as they are purported to coexist in patients with a concurrent clinical case of AP; however, much evidence is still lacking to determine them to be causative agents of AP. If such a correlation is proven to be true with enough evidence, then this will reflect on the different aspects of diagnosing and managing infectious causes of AP. Thus far, evidence in the literature is limited to multiple case reports and retrospective studies. Advanced diagnostic techniques like a biopsy or fine needle aspiration, along with tissue culture, PCR, or in situ hybridization, are required to give us a better understanding of the role played by infectious agents in causing AP. Whether treating the infectious process will lead to improved outcomes requires further investigation.

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Conflicts of Interest

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