Gastroenterology and Hepatology From Bed to Bench.
2023 **RIGLD**, Research Institute for Gastroenterology and Liver Diseases

REVIEW ARTICLE

p-ISSN: 2008-2258 e-ISSN: 2008-4234

The possible role of viral infections in acute pancreatitis: a review of literature

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ABSTRACT

Acute pancreatitis, a potentially fatal disease, with symptoms including nausea and/or vomiting, indigestion, and abdominal pain, is known to range from a mild self-limiting state up to a more severe and lethal form. This review aims to provide a clearer picture to improve understanding the role of viral agents in the development of acute pancreatitis. Common databases including PubMed, Google Scholar, and Scopus were used for the literature search. In this review search terms including virus, viral, infection, and specific descriptive terms for a virus were considered in different combinations. Various causative agents are recognized in the development of acute pancreatitis as one of the most frequent gastrointestinal diseases, such as gallstones, alcoholism, and hypertriglyceridemia. Microbial pathogens with about 10% of acute pancreatitis cases, mainly viruses, among other factors, are thought to play a role in this regard. Once the pancreatitis diagnosis has been made, depending on the causative agent, the management approach and specific interventions affect the final outcome. Virus-induced acute pancreatitis in patients should be considered. Advanced diagnostic tests such as PCR, in situ hybridization, and biopsy can help for a better understanding of the role of viruses in causing acute pancreatitis. Improvement in the tests will lead to timely diagnosis, treatment, and better management of pancreatitis.

Keywords: Acute pancreatitis, Virus, Gastrointestinal, Abdominal pain.

(Please cite as: **Sarshari B, Zareh-Khoshchehreh R, Keshavarz M, Dehghan Manshadi SA, SeyedAlinaghi S, Asadzadeh Aghdaei H, Mohebbi SR. The possible role of viral infections in acute pancreatitis: a review of literature. Gastroenterol Hepatol Bed Bench 2023;16(3):270-281. https://doi.org/10.22037/ghfbb.v16i2.2582).**

Introduction

Acute pancreatitis is one of the most frequent gastrointestinal diseases for admission to hospital, whose annual incidence has been reported at 34 per 100,000 person-years in developed countries, with no significant relationship with gender (1). Acute pancreatitis is caused by a series of inflammatory processes within the pancreas and is usually associated with abdominal pain, vomiting, and nausea. The clinical course of the disease is variable depending on the inflammatory response level, local or systemic. Mild acute pancreatitis, with a self-limiting course, is more common in patients and recovery is achieved within one week. Approximately 20 to 30% of patients indicate the moderate or

Received: 05 November 2022 *Accepted*: 02 January 2023
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severe acute pancreatitis form, a life-threatening condition. Although the overall mortality rate in acute pancreatitis is low and occurs in 1% of cases, the hospital mortality rate in the severe form is about 15% (2, 3).

Meanwhile, exposure to various risk factors and diagnostic practices can play an important role in these results. The main causes of acute pancreatitis in high-income countries are gallstones (45%), alcohol use (20%), and hypertriglyceridemia (10%). Additional causes such as infection, genetics, endoscopic retrograde cholangiopancreatography (ERCP), autoimmune diseases, hypercalcemia, and medication have also been reported (4).

According to the Atlanta Criteria, the diagnosis of acute pancreatitis is possible based on two of the following three criteria: upper abdominal pain, an elevated serum lipase or amylase level (or both) greater than three times the upper normal threshold, and abdominal imaging findings (3). Acute pancreatitis can progress to recurrent acute pancreatitis and eventually lead to chronic pancreatitis. Acute pancreatitis can relapse in 20% to 30% of people and in 10% of people, it can develop into chronic pancreatitis (5).

Since chronic pancreatitis is considered a factor in the development of pancreatic cancer, the role of pancreatitis-causing factors seems to be important in this cancer. Infectious agents such as viruses are among these causes (6). Also, since pancreatitis affects the patient's quality of life through abdominal pain, vomiting, exocrine and/or endocrine dysfunction, jaundice, and weight loss, understanding the etiologies, details of pathological mechanisms and influential factors of this disease is very crucial. About 10% of pancreatitis is thought to be caused by infectious agents, mainly viral, through direct viral injury or the immune-mediated inflammatory response to viral infection (7). The possible molecular mechanisms of viruses in pancreatic complications have not been elucidated. Nevertheless, inflammations and continuous immune responses to viral proteins, molecular mimicry, virus-host proteins interactions might be involved in the process. This research aims to explore the possible roles of viral agents in the development of pancreatitis through literature review.

Search Strategy

Common databases including PubMed, Google Scholar, and Scopus were used for the literature search. In this review search terms including virus, viral, infection, and specific descriptive terms for a virus such as "human immunodeficiency virus" or "HIV" with pancreatitis, pancreas, and pancreatic were considered in different combinations. The inclusion criteria were as follows: original articles, case reports, and case series. The exclusion criteria included reviews, duplicates, and articles whose full text was not available or were not in the English language. The search was limited to human studies published up to September 2021.

Pancreatitis: pathophysiology and etiology

Acute pancreatitis, one of the most common gastrointestinal diseases, is the result of a rapid inflammatory response to pancreatic damage. Injured pancreatic acinar cells trigger the activation of trypsinogen to trypsin and the initial neutrophils' recruitment into the pancreas. In turn, activated trypsin converts the other pancreatic digestive pro-enzymes to active enzymes. Ultimately, these enzymes result in the process of self-digestion of the pancreatic cells and the destruction of the pancreatic tissue. In most patients, this positive feedback loop usually stops spontaneously. However, in some persons, the disease progresses and causes a very serious illness, leading to widespread pancreatic necrosis (3).

Gallstones are the most common cause of acute pancreatitis in most high-income countries, accounting for approximately 40% of cases. Pancreatic duct obstruction caused by gallstones, raises pressure within the pancreatic duct, which causes the bile acid to return back into the pancreas and the activation of trypsinogen inside the pancreas, can lead to tissue injury (8). Excessive alcohol consumption causes 25% of acute pancreatitis cases around the world and is the second most common etiology of acute pancreatitis. Most commonly, alcoholic pancreatitis occurs in males, with the mean age of almost 40 years, with a range of alcohol consumption around 100 to 150 g/day equal to ~ 4-5 drinks daily) for over five years (9).

Despite the long-standing recognition of this association, the mechanisms by which ethanol influences acute pancreatitis development are poorly understood where both genetic and non-genetic associated factors can contribute to the progression of this disease. Ethanol through its direct toxic effects and metabolites sensitizes acinar cells to cholecystokinin, which leads to increased

trypsin production in the pancreas and reduced threshold for the development of pancreatitis (3).

Hypertriglyceridemia, the third most common etiology of pancreatitis, accounts for approximately 10% of all cases of pancreatitis in the world. A serum triglyceride level greater than 1000 mg/dL typically increases the risk of acute pancreatitis. Pancreatic lipase breaks down triglycerides into toxic free fatty acids (FFA) and leads to induction of inflammatory changes and tissue damage in the pancreas (10). Rare causes of acute pancreatitis include medications, autoimmune etiologies, genetic factors, toxins, and infectious microorganisms.

Viruses associated with acute pancreatitis

Among the infectious agents, viruses including SARS-CoV-2, hepatitis viruses, EBV, CMV, HSV, varicella-zoster virus, Coxsackie virus, mumps, measles, HIV, and other viruses play the most important role in the development of acute pancreatitis (Table 1). Tropism and the replication of viruses in pancreas tissue such as SARS-CoV-2 can infect the tissue through ACE2 and TMPRSS2 receptors, which are expressed on exocrine and endocrine cells in human pancreatic tissue (11). Some evidence suggests tropism of the IAV for the pancreas. The expression of human-like (α-2,6-linked) sialic acid (SA) receptor by the human pancreatic cancer cell line PANC-1 and the replication of IAV subtypes in vitro have been reported in a study (12). Additionally, persistent infections by coxsackieviruses-B (CV-B) have been previously established in vitro as well as in vivo (13). Nevertheless, in addition to direct viral infection in pancreas tissue, other indirect mechanisms have been mentioned in the development of virus-induced acute pancreatitis.

Table 1. Overall results of cases of acute pancreatitis associated with viral infections in case report and case-series studies

	Number; Male/female	Median age in years (range)	Method of diagnosis of infection	Therapy	Ref
HBV	6/2	44 (27-64)	PCR for HBV DNA	NR	(15, 16, 81, 84)
HCV	8/4	50 (38-65)	PCR for HCV RNA	Stopping use of Peginterferon	(17-19, 85)
HAV	27/14 13 NR	16 (2-81)	anti-HAV IgM & RNA	Conservative surgery, and hemodialysis	(86)
HEV	36/2 18 NR	28 (7-54)	anti-HEV IgM & RNA	Conservative, surgery, and hemodialysis	(82, 87)
SARS-CoV-2	28/34	42 (7-76)	PCR for SARS-CoV-2 RNA	NR	(30)
VZV	5/6	44 (2-86)	IgM antibodies & VZV DNA	Acyclovir	(32-39, 88-91)
CMV	6/3	45 (21-75)	IgM antibodies & CMV DNA	Ganciclovir	(40-44, 92, 93)
EBV	6/10	16 (3–39)	IgM antibody	Acyclovir & supportive	(48, 94, 95)
HSV	3/2	24 (21-73)	Cowdry type A Inclusions, IgM & DNA HSV	NR	(49-51, 96, 97)
HIV	6/2	37 (17-52)	p24 HIV-1 antigen and PCR for HIV RNA	Stopping use of antiretroviral	(98-104)
INFLUENZA	2/1	37 (19-42)	PCR for influenza RNA	Oseltamivir	(61-63)
COXSACKIE VIRUS	2/2 19 NR	56 (39-67)	IgM titer against CV A4, B1, B2, B4 and B5	NR	(64, 65, 105-107)
ROTAVIRUS	4/1	2 (1-10)	Stool examination with culture and Immuno-chromatography kit	Intravenous rehydration	(67)
MUMPS	2/3	46 (19-72)	IgM antibody	Symptomatic and supportive	(73, 75, 108, 109)
MEASLES	2/2	16 (2-22)	IgM antibody	Symptomatic and supportive	(76-79)

NR: not reported.

Hepatitis B virus (HBV)

HBV is one of the viruses infecting the pancreas. Several studies have shown the role of acute hepatitis B virus infection in the development of acute pancreatitis. In a study by Jain et al. on 54 patients with acute hepatitis B virus infection, after four weeks of follow-up, one (2%) of them showed signs of acute pancreatitis (14). Meanwhile, immunosuppressive therapy after organ transplantation in people with chronic HBV infection can result in acute pancreatitis. On the contrary, Ohshiro et al. reported acute pancreatitis in a patient with acute/non-fulminant HBV infection after reducing the dose of an immunosuppressive agent (15). Yuen et al. reported that 5.6% of acute pancreatitis cases (5 patients) in the Chinese were possibly induced by chronic HBV infection. The mortality rate in the HBV group (concomitantly chronic HBV infection and acute pancreatitis) was higher (4 out of 5, 80%) compared to the two control groups (85 non-HBV patients with acute pancreatitis and 406 patients with chronic HBV without acute pancreatitis), individuals with pancreatitis (13 out of 85, 15.3%), and those with only acute HBV exacerbation (9 out of 406, 2.2%) (16). So far, several case reports of acute pancreatitis in people with acute hepatitis have been published. In most cases, the development of pancreatitis has been associated with immunosuppressive therapy in transplant recipients with hepatitis B surface antigen (HBsAg) seropositivity.

Hepatitis C virus (HCV)

The first case of acute pancreatitis associated with HCV has been reported in a 70-year-old female with symptoms of abdominal pain, hyperamylasemia, and hyperlipasemia. Severe acute hepatitis was not observed, which may explain pancreatitis is the result of local function by HCV (17). Rarely, an association has been observed between the use of peginterferon and acute pancreatitis (18). Also, in a study, out of 1706 HCV-infected individuals who were treated with IFN alpha-2b and ribavirin (RBV), diagnosis of acute pancreatitis was confirmed in seven patients (0.4%). Pancreatitis was resolved in all seven patients after discontinuation of antiviral therapy, indicating a possible role of this therapy in the development of pancreatitis in patients with chronic HCV (19).

Hepatitis E virus (HEV)

The first documented case of acute pancreatitis related to acute hepatitis E (AHE) was reported by Mishra et al. in 1999 (20). Over the past few years, many case reports have also been published in this regard and are available in the literature. To date, the frequency of acute pancreatitis associated with AHE has estimated in two prospective cohort studies. Raj et al. reported 16 (2.1%) positive of acute hepatitis E cases of the seven hundred ninety patients with acute pancreatitis, with no other causes of pancreatitis (21). Bhagat et al. evaluated three hundred and thirty-four patients with acute pancreatitis admitted from 2004 to 2006 and reported 4 HEV-positive patients (22). Also, two other studies have investigated acute pancreatitis rate in acute hepatitis E patients including four cases of acute pancreatitis among 54 AHE patients by Jain et al, which was performed over a 2-year follow-up period (14); also within a 5-year prospective study, Sudhamshu et al. indicated 18 cases of acute pancreatitis among 286 AHE patients (6.2%) (23).

Hepatitis A virus (HAV)

There is a causal relationship between HAV and acute pancreatitis. To our knowledge, most cases of HAV-related acute pancreatitis have been published in the form of case reports, including four separate reports of the existence of an association between acute hepatitis A virus (HAV) infection and acute pancreatitis in patients. HAV infection was confirmed by the detection of IgM antibodies against HAV (24-26). Epidemiological data on the frequency of pancreatitis developing in HAV infection have been indicated in two articles. Sixteen patients with a positive test for IgM anti-HAV were followed up by Jain P et al., for acute viral hepatitis over three years. None of the patients had a history of pancreatitis signs before the infection. Pancreatitis was positive in two patients and finally, recovery was achieved through conservative management (14). Also, a cross-sectional study by Bhagat et al. reported three confirmed cases of hepatitis A virus-related acute viral hepatitis in 334 patients of acute pancreatitis (22).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Angiotensin-converting enzyme 2 (ACE-2), a receptor for SARS-CoV-2 viral entry, is highly expressed in the pancreatic gland and gastrointestinal epithelial cells. Studies have shown that gastrointestinal symptoms, including diarrhea, vomiting, nausea, and abdominal pain are present in up to 50% of COVID-19 cases (27). Brikman et al. reported a 61-year-old man with SARS-CoV-2 who had two of the three criteria for

acute pancreatitis, with no lipase level elevation (28). In another publication, Madhurantakam et al. reported two cases of SARS-CoV-2 infection in patients with acute pancreatitis (29). In a case report, Mazrouei et al. concluded that SARS-CoV-2 infection probably plays a role in acute pancreatitis. A few case series and multiple case reports (21 studies) of SARS-CoV-2 associated with acute pancreatitis were reported in 2020 (30). Inamdar et al. during the COVID-19 pandemic, in a cohort study of patients admitted to 12 hospitals in New York, reported 32 COVID-19 positive from 189 acute pancreatitis patients (17%). They suggested the possibility of a causative role of SARS-CoV-2 in association with acute pancreatitis (31).

Varicella-zoster virus (VZV)

The VZV infection occurs in early childhood and is usually a benign and self-limited illness in immunocompetent individuals. Its complications include moderate fever, headache, myalgia, malaise, and a typical skin rash with different developing stages. Other symptoms include pneumonia, hepatitis, encephalitis, myelitis, retinitis, and acute pancreatitis, which are more common in immunocompromised people. Acute pancreatitis is considered as one of the rare complications of VZV. VZV-induced pancreatitis has mostly been reported in children and immunocompromised adults (32-35). However, multiple cases of VZV-induced pancreatitis have been observed in adults with an immunocompetent system (36-39).

Human cytomegalovirus (HCMV)

Our search in the literature resulted in five case reports of pancreatitis associated with cytomegalovirus in immunocompetent individuals. Chan et al. described a case report of hepatitis and pancreatitis for HCMV in an immunocompetent individual. Liver histology and endoscopic ultrasound did not show other etiologies. After ganciclovir treatment, the viremia was cleared and recovery was achieved (40). Oku et al. reported a 55-year-old man with acute pancreatitis who had a high titer of CMV IgG antibody and without HCMV IgM, indicating reactivation of cytomegalovirus disease (41). In the study of Saeed et al., the patient was a 75-year-old woman with HCMV pancreatitis and gastric perforations. Clinical recovery was observed after the initiation of intravenous ganciclovir (42). Gastrointestinal complications including pancreatitis in immunocompromised patients are much more severe than in immunocompetent people. In a case report by Huayna et al., on two HIV-positive people, secondary pancreatitis associated with HCMV infection was observed. The patients were improved through treatment with ganciclovir (43). In other cases, HCMV pancreatitis has also been reported in AIDS patients who improved with ganciclovir (44, 45).

Epstein-Barr virus (EBV)

The first case of Epstein-Barr virus-associated acute pancreatitis was reported in 1966 (46), with 16 cases documented in the literature from then on, which is more common in young people, 8-35 years old. Although acute pancreatitis involved with acute hepatitis is observed commonly in hepatitis infections such as HAV, HBV, or HEV, in acute hepatitis concurrent with acute pancreatitis, the differential diagnosis of EBV needs to be considered. As an example, Kang et al. reported an 11-year-old female with cholestatic hepatitis and infected with EBV, who had symptoms of abdominal pain as well as vomiting and confirmed pancreatitis. Reactivated EBV infection was diagnosed by viral capsid antigen (VCA) IgM, IgG, and ultimately, recovery was reached with conservative management (47). Acute pancreatitis associated with Epstein-Barr virus infection is usually mild and recovers with conservative management (48).

Herpes simplex virus (HSV)

The results of our survey of the literature indicated five cases of herpes simplex acute pancreatitis. Shintaku et al., reported two acute pancreatitis patients, a 59-year-old woman and a 73-year-old man, with HSV-1 infection which was confirmed by the polymerase chain reaction (PCR) method in autopsy specimens. Also, intranuclear inclusions of Cowdry type A and the ground-glass opacity were observed in the nuclei of infected cells (49). Rand et al. isolated HSV-1 from the gastric contents of a young man with acute pancreatitis, with no evidence of primary infection (50). In the last case, a 13-year-old boy was reported with abdominal pain, vomiting, and an elevation in serum amylase and lipase. IgM antibody for HSV was positive and the patient improved after conservative treatment (51).

Human immunodeficiency virus (HIV)

Although the pancreatitis incidence is not very noticeable, 17 to 30 cases per 100 000 populations, the rate

observed is higher in people with HIV. In this regard, risk factors such as nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) consumption side effects, and CD4 cell counts have been observed in HIV-positive people receiving antiretroviral therapy (52). Several studies have shown that the use of NRTIs is associated with a high incidence of pancreatitis. It appears that treatment with didanosine, stavudine and or together is associated with a higher rate of pancreatitis (53-57). However, other studies have not found evidence of a link between didanosine or stavudine and the incidence of pancreatitis (58). Studies have shown that PI therapy in people infected with HIV can be associated with hypertriglyceridemia. Although this association has been observed, no significant increase appears to have occurred in the prevalence of hyperlipidemic pancreatitis in HIV-infected patients during those years following the use of PIs (59). Also, in studies conducted on HIV/AIDS individuals with low levels of CD4 cell counts (i.e., CD4<50 cells/mm^3), a higher risk of developing acute pancreatitis has been reported (52, 60).

Influenza

The first case of acute pancreatitis caused by influenza has been reported by Blum et al., a 37-year-old man with upper abdominal pain and high levels of amylase. The patient improved with combined antibiotic treatment and Tamiflu (61). In a few other case reports, a possible association of acute pancreatitis with H1N1 influenza has been described. In these patients, the symptoms including abdominal pain, vomiting, and elevated serum amylase or lipase resolved after oseltamivir (Tamiflu) treatment and influenza clearance, further supporting an association (62, 63).

Coxsackievirus

In several case reports, patients with myocarditis and pancreatitis associated with coxsackievirus infection have been observed by serotypes A4, B1, B2, B4, and B5 A (64). The serological findings of 118 patients with acute and chronic pancreatitis show that the Coxsackie-B virus, in addition to developing acute pancreatitis, can also cause relapse chronic pancreatitis in people (65). An interesting finding in the experimental study by Tracy S et al. revealed that pancreatitis and myocarditis can be induced by group B coxsackievirus in mice model (66).

Rotavirus

To date, several case reports have been published regarding acute pancreatitis and rotavirus. The literature search identified five case report publications, on children between the ages of 1 to 10 years (four boys and one girl). Abdominal pain was reported in two cases (67, 68). In three cases, abdominal imaging such as computed tomography (CT) scan showed a mildly enlarged edematous pancreas (69-71). By evaluating these studies, this does not infer that acute pancreatitis associated with rotavirus infection results in severe disease in patients (67).

Mumps

About 4% of mumps infections are linked to pancreatitis (72). The most common virus associated with acute pancreatitis in adults is the mumps virus (73). Also, according to the literature, case reports of mumps pancreatitis without parotitis have been described both in children and adults, although this form of pancreatitis being usually milder (74). Meanwhile, it can even occur in people who are vaccinated against mumps. Nevertheless, it does not seem to be very important and significant, as the incidence of mumps-induced pancreatitis has decreased after the mumps vaccine was introduced (75). Tagajdid et al. reported acute pancreatitis in a 49-year-old woman, with epigastric pain, vomiting, and fever. The IgG and IgM antibodies were positive for mumps, confirming an acute viral infection, and the serological tests were rejected for HIV, EBV, CMV, HBV, and HCV. Infection with mumps can be possible with regard to the patient's age, as vaccine-induced immune response drops over time (73).

Measles virus (MV)

Up to now, several case reports of acute measles-induced pancreatitis have been published. The symptoms of pancreatitis disappeared along with the clearance of the measles virus, indicating the etiological relationship between the measles virus and pancreatitis (76-79). Due to the reduction in the incidence of measles disease after the measles-mumps-rubella (MMR) vaccine immunization program in recent years, the measles-induced pancreatitis cases are expected to decline.

Mechanisms involved in viral-induced pancreatitis

To date, various hypotheses have been proposed to explain viral pancreatitis (Figure 1). A possible mechanism presented for developing HBV-induced acute pancreatitis is the direct cytotoxic effects of the HBV infection on the pancreatic cells. Cavallari et al. demonstrated the presence of HBV-DNA and HBsAg in the cytoplasm of pancreatic acinar cells, indicating the direct destruction of the pancreas by HBV (80).

Another possible mechanism may be an HBV-induced immune response which is directed against HBV-infected pancreatic hepatocytes (81). There are various mechanisms by which IFN α may be involved in the development of pancreatitis. Hypertriglyceridemia disorder, a well-known cause of acute pancreatitis, is a result of interferon treatment. From another path, interferon α by stimulating the immune response can lead to a pancreatic-specific autoimmune disease. Also, RBV by causing anemia and chronic hemolysis may lead to gallstones, which is one of the most common causes of acute pancreatitis (19). Development of pancreatitis in patients with HEV and/or acute viral hepatitis (AVH) may result from a multifactorial mechanism. Regarding AVH, one possible explanation is the development of edema of the Vater's ampulla due to viral infection, which leads to obstruction of the outflow of pancreatic fluid. A more probable mechanism is the virus's direct destruction of pancreatic acinar cells. The leakage and circulation of lysosomal enzymes from the damaged liver cells, which change pancreatic trypsinogen to trypsin, may be another possible mechanism of acute pancreatitis.

The exact mechanisms by which the Hepatitis A virus causes pancreatitis remain to be elucidated. These mechanisms are the same as those described for the HEV, including direct inflammation and cytotoxic effect of the virus on acinar pancreatic cells and or immune-mediated process against infected pancreatic cells (82). During the VZV infection, the virus may remain latent in the posterior sensory nerve roots, while it contains fibers from both the skin and visceral organs, such as the pancreas. It is assumed that VZV probably damages the membrane of the pancreatic acinar cell and leads to the release of intracellular enzymes. Another possible mechanism is that the patient's immune response causes the cytopathic effect (34). Rotavirus infection has been shown to activate nuclear factor-κB (NF-κB), a critical transcription factor for the up-regulation of interleukin-8 (IL-8) gene expression. IL-8 attracts neutrophils, monocytes,

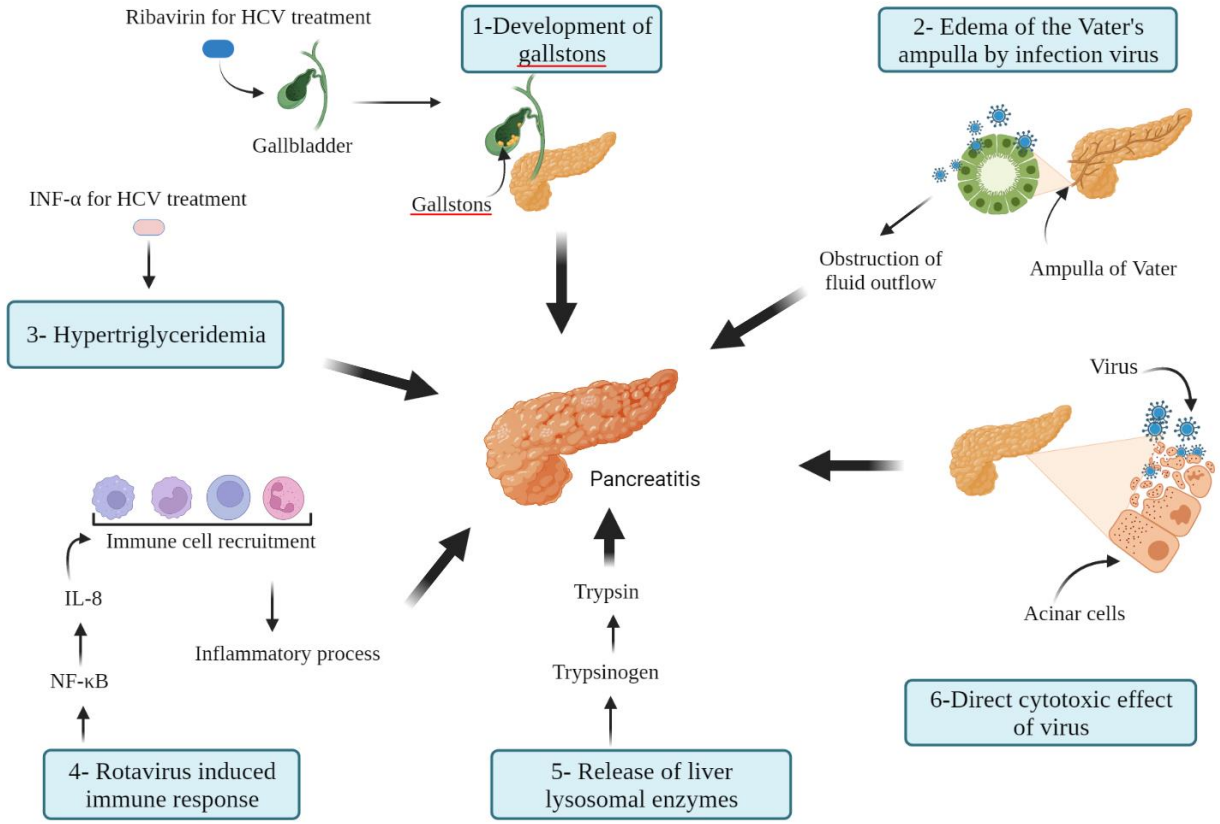

Figure 1. An overview of mechanisms involved in the development of acute pancreatitis caused by viral agents.

macrophages, and lymphocytes to an inflammatory site, and is involved in the initiation and development of inflammatory responses related to acute pancreatitis (83).

Conclusion

There is extensive information in the literature about the implication of various viral agents in acute pancreatitis and the probable involvement of viruses in the development of acute pancreatitis. However, due to the need for extensive laboratory evidence to determine them as the causative agents of acute pancreatitis, currently, many of these cases are thought to coexist with the occurrence of acute pancreatitis. Nonetheless, if proven that such an association is really true with sufficient evidence, then different aspects related to the diagnosis and treatment of virus-induced acute pancreatitis in patients should be considered. To date, most published studies in this regard have been limited to retrospective and case report studies. Since case reports cannot prove association causality, further studies are required. Also more accurate and advanced diagnostic tests such as PCR, in situ hybridization and biopsy can help us better understand the real role of viruses in causing acute pancreatitis. Future research should establish the most appropriate diagnostic and therapeutic strategies for improving virus-induced pancreatitis outcomes. Last but not least, it is definite that more extensive studies with proper design and precise diagnostic methods are necessary to elucidate the link between viral infections and pancreatic complications.

Conflict of interests

The authors declare that they have no conflicts of interest.

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