JOP. J Pancreas (Online) 2004; 5(5):384-387.

CASE REPORT

Coxsackievirus Infection Associated with Acute Pancreatitis

George Chrysos[1], Stelios Kokkoris[1], John Protopsaltis[1], Panagiotis Korantzopoulos[2], Gregory Giannoulis[1]

[1]Second Department of Internal Medicine, "Tzanio" General Hospital of Piraeus. Piraeus, Greece.
[2]Department of Internal Medicine, "G. Hatzikosta" General Hospital of Ioannina. Ioannina, Greece

ABSTRACT

Context A variety of infectious agents have been reported as rare causes of acute pancreatitis.

Case report We briefly describe a 36-year-old man who presented with acute pancreatitis and a maculopapular rash. The marked elevation in antibody titer against coxsackievirus B, as well as the skin biopsy, was compatible with acute coxsackievirus B viral infection.

Conclusion This case highlights the fact that an appropriate investigation for viral infections should be performed in patients having acute pancreatitis and no classical risk factors.

INTRODUCTION

While alcohol abuse and biliary disease are thought to be the main etiological factors in the development of pancreatitis, idiopathic acute and chronic pancreatitis represent a fairly high percentage of the total number of cases. Evidence supporting the concept of a viral etiology derives from serological studies, case reports and animal studies. We report a case of acute pancreatitis associated with coxsackievirus B infection.

CASE REPORT

A 36-year-old man presented to the Emergency Department of our hospital with severe acute abdominal pain radiating to the back, nausea, and vomiting of a 5-hour duration. Moreover, five days earlier, a maculopapular rash had erupted on both legs, with the exception of the plantar surfaces. Abdominal examination revealed only mild abdominal tenderness. The rest of the physical examination was normal. Overt salivary gland disease was also absent. His past medical history was unremarkable. Furthermore, he was not receiving any medication, and he did not drink alcoholic beverages. On admission, his vital signs were as follows: blood pressure 130/70 mmHg, heart rate 110 min^{-1}, respiration rate 21 min^{-1} and rectal temperature 37˚C. Chest and abdominal X-rays were all normal. Blood gas analysis revealed a mild respiratory alkalosis. An electrocardiogram revealed sinus tachycardia. A complete blood count, erythrocyte sedimentation rate, and blood biochemical tests including troponin-I, C-reactive protein, glucose, aspartate aminotransferase (AST), bilirubin, triglycerides and calcium, were all within reference limits. Alanine aminotransferase (ALT) was slightly elevated (71 IU/L; reference range: 10-35 IU/L), while serum amylase (750 IU/L; reference range: 25-125 IU/L) and urine amylase (2,545 IU/L;

reference range: 0-400 IU/L) were both elevated. Serological tests for various infectious agents including herpes simplex viruses I and II, varicella zoster virus, cytomegalovirus, mumps, Epstein-Barr virus, HIV I and II, hepatitis A, B and C viruses, echoviruses, toxoplasma, mycoplasma, *Leptospira* and *Legionella* were all negative. Tumor markers were also negative. However, antibody titer against coxsackievirus B was markedly elevated and it was quadrupled four weeks later. Autoantibody screening was negative. An ultrasonographic examination of the abdomen revealed neither gallstones nor biliary sludge. A subsequent abdominal computed tomography scan revealed a mild swelling of the pancreas without revealing any additional abnormality. Ranson's criteria number on admission, as well as during the first 48 hours, was 0. The patient was treated conservatively with nasogastric suction, intravenous fluids, and analgesics with progressive improvement of his clinical status. On the second day after admission, biopsies were taken from the skin lesions. Histological examination revealed lymphocytic infiltrations of the dermis. Taking into consideration the aforementioned examinations, a diagnosis of coxsackievirus infection-induced acute pancreatitis was made. The patient recovered uneventfully and was discharged in apparently good physical condition 9 days after admission. Serum amylase activity was within reference limits immediately before his discharge. He was re-examined 3 months later and was found to be in excellent physical condition. All laboratory values were within reference limits and the rash had disappeared.

DISCUSSION

Acute pancreatitis may have diverse etiologies such as alcohol ingestion (acute or chronic), gallstones, drugs and toxins, metabolic disorders (hypertriglyceridemia, hypercalcaemia, and others), connective tissue diseases, infections, and others. The most common infectious causes are mumps, viral hepatitis, coxsackieviruses, echoviruses, and mycoplasma [1]. Our patient was not an alcoholic, did not take any drugs at all, did not have gallstones, his triglyceride and calcium levels were both within reference limits and the serological tests for many infectious agents were all negative except for coxsackievirus B. The marked elevation in antibody titer against coxsackievirus B, the characteristic rash on both lower limbs, and the histological results of the skin lesions, were compatible with acute coxsackievirus infection. Therefore, we considered that coxsackievirus B-associated acute pancreatitis was the most plausible diagnosis.

Coxsackieviruses are enteroviruses belonging to the *Picornaviridae* family. The first reported coxsackievirus isolate came from the town of Coxsackie in upstate New York [2]. These enteroviruses are further subdivided into two serogroups, A and B, which comprise 24 and 6 serotypes, respectively [3]. Of the two serogroups, the group A viruses are associated with less severe clinical syndromes than the group B viruses. Hence, coxsackievirus research has focused predominantly on the group B viruses. The group B viruses have been implicated in a variety of human diseases such as pancreatitis, type 1 (insulin-dependent) diabetes mellitus, myocarditis, myositis, severe systemic disease in infants, aseptic meningitis and respiratory illnesses [4, 5, 6, 7, 8, 9, 10]. Gooby Toedt *et al*. [11] reported a case of coxsackievirus-associated acute pancreatitis mimicking metastatic carcinoma. In addition to that, coxsackievirus-induced acute pancreatitis has been reported in a long term dialysis patient [12] as well as in a three-year-old girl with alpha 1-antitrypsin deficiency [13]. Although alcohol abuse and biliary disease are thought to be the main etiological factors in the development of acute pancreatitis, idiopathic acute pancreatitis represents a fairly high percentage of the total cases. In a retrospective study of 602 patients with acute pancreatitis, the etiology was biliary tract disease in 227 (37.7%), alcohol abuse in 177 (29.4%), unknown in 133 (22.1%) and other causes in 65 (10.8%) [14]. The incidence of pancreatitis of unknown

etiology may even be higher since the diagnosis of acute pancreatitis can be difficult and may go undetected. The reported incidence of acute pancreatitis that is not detected until postmortem examination ranges from 6.6% to 86% [15]. Idiopathic acute pancreatitis probably includes cases of viral etiology. A review of the literature revealed only a few cases of established coxsackievirus-induced acute pancreatitis. The correlation between coxsackievirus infection and pancreatitis has been primarily established by serologic conversion. Coxsackievirus B, as a possible cause of pancreatitis, was first reported in 1958 [16]. In this report, the relationship between the infection and pancreatitis was documented from the isolation of a B4 variant in a child who died from systemic infection and whose pancreas showed focal necrosis and inflammation [16]. Imrie *et al*. [17] carried out a prospective study on 116 patients with acute pancreatitis. The incidence of idiopathic pancreatitis in this study was 5.2% (six patients). Among them, five patients (all female) exhibited significant rising antibody titers to coxsackievirus B or mumpsvirus, while none of the remaining 111 patients showed this. Capner *et al*. [18] subsequently reported a higher incidence of elevated antibody titers against the group B coxsackieviruses in patients with acute pancreatitis. In addition, Arnesjo *et al*. [19] detected evidence of enteroviral infection in 18 of 91 patients with acute pancreatitis. The etiological agents were group B coxsackieviruses and echoviruses. Notably, in a study of patients with acute and relapsing chronic pancreatitis, 34% (40 out of 118) showed significant elevation in coxsackievirus B antibody titers [20]. Of these 40 patients, 14 had acute pancreatitis, 5 had relapsing acute pancreatitis and 21 had chronic pancreatitis while B4 and B3 were the most frequently detected serotypes. On the other hand, Laszik *et al*. [21] studied the presence of mumpsvirus and enterovirus RNA by in situ hybridization in 15 surgical biopsy specimens from patients with advanced acute pancreatitis. Neither the mumpsvirus nor the enteroviruses tested were present in the pancreatic tissue of these patients.

The relationship between coxsackieviral infection and pancreatic diseases is obviously extremely complex. The development of the disease is the result of the intricate interplay between the infecting viral strain and the genetic predisposition of the host and, therefore, a multi-disciplinary approach is required to increase our understanding of this complex relationship.

Finally, the differential diagnosis of acute pancreatitis in combination with a maculopapular rash includes systemic lupus erythematosus [22], Marburg virus [23], West Nile virus [24] and pharmaceutical agents such as azathioprine [25] and some antiretroviral drugs (stavudine, didanosine) [26].

CONCLUSION

In conclusion, acute pancreatitis may be due to a coxsackievirus infection and thus this type of infection should always be included in the differential diagnosis, especially in idiopathic cases of this disease. Screening patients with acute pancreatitis for coxsackievirus B infections is worthwhile and may minimise protracted biliary investigations.

Received July 7th, 2004 - Accepted July 20th, 2004

Keywords Coxsackievirus B; Exanthema; Pancreatitis; Virus Diseases

Correspondence
Stelios Kokkoris
30 Ermou st
Korydallos 18122
Greece
Phone: +30-694.618.2837/+30-210.496.6459
Fax: +30-210.459.2563
E-mail address: skokkoris2003@yahoo.gr

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