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• *CASE REPORT* •

TT virus infection and pancreatic cancer: Relationship or accidental coexistence

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Abstract

TT virus (TTV) was first isolated in 1997 from the patient with acute post-transfusion hepatitis. This fact led to the conclusion that the virus was hepatotropic and could be one of the causative agents of acute hepatitis. Afterwards, however, the virus was found in other human tissues and serological studies revealed that it was widespread. Multiple tropisms of TTV and the fact of its high incidence in general population are considered to indicate no medical significance of TTV in human pathology. Here we present a report of two cases of TTV infection in patients who developed pancreas cancer. The patients were hospitalized at the Department of Infectious Diseases due to hepatitis of unknown origin. Since serological and virological markers of common primary and secondary hepatotropic viruses were negative, TTV-DNA was found in serum and was believed to be the only causative agent with probable hepatotropic action. The patients later developed pancreas cancer and they underwent operation. The relationship is difficult to confirm, however the cases we present should be treated as a preliminary report and a comment on the real role of TTV in human pathology.

Key words: TT virus; Hepatitis; Pancreas cancer; Hepatotropic viruses

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INTRODUCTION

The medical significance of TT virus (TTV) has not been completely explained. The virus was first isolated in 1997 in a Japanese patient with acute posttransfusion hepatitis and considered a transfusion-transmitted and hepatotropic one. The virus was named TT both due to initials of the first patient with detectable TTV-DNA in serum and as an abbreviation of the word "transfusion-transmitted".

The exact taxonomy of this unenveloped circular DNA virus has not been established. TTV is related to *Circoviridae*, although there are some opinions, that it should belong to a new family called *Circinovirida*[1].

The analysis of TTV infected patients with symptoms, signs and laboratory results characteristic of acute hepatitis have revealed that TTV is likely to be associated with human liver pathology. The fact that the virus was frequently found in the liver tissue of patients with hepatitis supports this thesis. However, the liver is probably not the only target of the virus. It was also identified in the bone marrow, lymph nodes, pulmonary tissue, spleen, kidney, muscles and pancreas. This indicates that the virus can replicate in these tissues and that the accurate assessment of the virus tropism is difficult[1].

The 10-300 times higher virus concentration in the liver than in the serum is one of the most evident indication of its hepatotropic nature[2]. However, TTV-DNA is likely to either integrate with a host genome or be present in hepatocytes in the episomal form[3-5].

Since the exact significance of TTV in human pathology has not been fully explained and its biological action probably involves integration with the human genome, some authors undertook studies on its possible role in the oncogenesis. Due to the association of TTV infection with liver diseases most of them focused on hepatocellular carcinoma.

We present here two case reports of patients infected with TTV who developed pancreas cancer. Since the coexistence of pancreatic cancer and TTV infection has not been reported to date, we found these cases interesting and worth investigating.

CASE REPORTS

Case 1

The patient, a 60-year-old male was admitted to our Department of Infectious Diseases of Medical University of Lublin due to moderate abdominal pain localized in the right upper quadrant and elevated aminotransferase levels. History revealed that he was hospitalized due to myocardial infarction 5 mo earlier, and therefore he did not travel abroad and stayed away from ill individuals, and refrained from the use of alcohol or drugs.

On the basis of epidemiological data and results of biochemical laboratory tests, infectious hepatitis was suspected. On admission the bilirubin level was 3.44 mg/dL, AST level - 222 UL and ALT - 372 UL (the normal level is up to 37 and 40 UL, respectively). Other routine biochemical serum examinations were normal. Morphology revealed no

pathology. Both chest X-ray and abdomen ultrasonography were normal.

Serological and virologic markers of common primary hepatotropic viruses A, B and C, including anti-HAV IgM, HBs Ag, HBe Ag, anti-HBe, anti-HBc, HBV-DNA, anti-HCV, and HCV-RNA, were negative. Moreover, negative results of serological tests excluded Epstein-Barr virus (EBV) and cytomegalovirus (CMV) infection. To find the cause of liver inflammation the test for autoantibodies was performed and no antinuclear (ANA), antimitochondrial antibodies (AMA) and anti smooth muscles antibodies (ASMA) were found. Finally markers of hepatitis G virus (HGV) and TTV infections were tested. The test for HGV was negative, however, using qualitative test based on polymerase chain reaction method, TTV-DNA was found in the patient's serum. The patient still had abdominal pain, and both alkaline phosphatase (AP) and gamma glutamyl transpeptydase (GGTP) increased to the alarming value, 516 UL (normal range 37-111 UL) and 1 223 UL (normal range 11-43 UL), respectively. CT scan was performed, first without and then using the radiographic contrast (Ultravist). The examination showed irregular enlargement of the pancreas head up to 4 cm in diameter, whereas CT density before contrast administration was 42-50 HU, and after it 80-104 HU. Simultaneously the widening of the common biliary tract and intrahepatic biliary tracts was visible. CT examination was done 2 wk after ultrasonography. The patient was sent to the Surgical Department, where pancreas cancer was diagnosed and the patient underwent operation. Unfortunately it was not possible to test TTV presence in pancreas tissue.

Case 2

The patient, a 44-year-old female, was admitted to the Department of Infectious Diseases of Medical University of Lublin due to dyspeptic symptoms and moderate pain in the right upper quadrant. The symptoms appeared two weeks before admission.

The history revealed no health problems and surgery or invasive diagnostic procedures in the past. In our opinion, the most important fact in the history was that the patient worked as a nurse in the surgical ward, so she was likely to be at risk of hepatotropic virus infection. On admission the biochemical parameters were as follows: bilirubin level -8.4 mg/dL, AST - 322 UL, ALT - 608 UL. An abdomen ultrasonography, performed on admission, revealed no pathology. Diagnostic procedures involved serological and virological markers of common primary hepatotropic viruses A, B and C. Anti-HAV IgM, HBs Ag, HBe Ag, anti-HBe, anti-HBc, HBV-DNA, anti-HCV, and HCV-RNA were negative. We also excluded EBV and CMV infections were also excluded.

The tests for autoantibodies were also negative. Antinuclear (ANA) and antimitochondrial antibodies (AMA) were absent. The only positive viral test was TTV-DNA, which was found using qualitative test based on the PCR method.

Although the hepatoprotective treatment had been introduced, the patient's condition aggravated. The bilirubin level reached 20.1 mg/dL whereas aminotransferase activity decreased (AST-178 and 310 UL). The level of serum cholestasis markers was continuously increasing (GGTP reached 1 174 UL). To find the cause of increasing jaundice, we repeated the abdomen ultrasonography. It showed the presence of widened intrahepatic biliary ducts and the hyperechogenic area in the lower zone of pancreas head, suggesting neoplasm. The patient was sent to the Surgical Department. The final diagnosis of pancreas cancer was based on the histological examination of the specimen obtained during operation.

DISCUSSION

The cases of TTV infection and pancreas cancer coexistence presented here should arouse special interest and provoke discussion about the question asked in the title of this paper. Is there any relationship between TTV infection and oncogenesis in the pancreas or is the coexistence completely accidental? We have not found any reports concerning that problem.

There are some reports mentioning the problem of correlation between TTV infection and the development of different neoplasm. Shiramizu *et al* carried out studies on the virus in the etiology of acute lymphoblastic leukemia (ALL). They performed the analysis of peripheral blood mononuclear cells and bone marrow cells, as well as cerebrospinal fluid and concluded that TTV was unlikely to be associated with ALL[6]. Because TTV is suspected of being a potentially hepatotropic virus, Liwen *et al* analyzed patients with chronic hepatitis, liver cirrhosis, and primary liver cancer, comparing the results in these study groups with a control group of healthy individuals. The frequency of TTV infection in hepatocellular carcinoma ranged from 8.1% to 100%. The authors suggested that such a great variability made explicit conclusions concerning the correlation between TTV infection and both chronic hepatitis and liver cancer impossible[7]. Similar results were obtained by Japanese[8,9] and Italian researchers[10]. Moriyama *et al*[11] demonstrated that the virus had no impact on clinical and serological profile of HBV and HCV infection. TTV did not change the results of chronic hepatitis B therapy with lamivudine. These conclusions were supported by the results of molecular research carried out by Yamamoto *et al*. They confirmed that the TTV genome was not integrated into the host hepatocyte DNA, which is probably necessary to initiate potential neoplasm development[12].

TTV co-infection was not associated with the presence of B-cell non-Hodgkin lymphoma. Cacoub *et al*[13] found TTV-DNA in only 7% of patients. On the other hand, according to Garbuglia *et al*[14], the significant prevalence of TTV DNA in lymphocytes circulating in the lymph nodes of both B-cell lymphomas and Hodgkin disease suggested TTV infection implication in the development of these lymphoproliferative disorders. Recently, Camci *et al*[15] has reported the high prevalence of TTV in patients with various malignancies. The viral load in cancer patients is extremely high. It might result from the impaired immune reaction[1,15]. Further studies are needed to explain whether the impairment is caused by neoplasm or by the virus itself.

The cases of coexistence of TTV infection and pancreas cancer presented above should be treated as a preliminary

report and the comment in the discussion about the real role of TTV in human pathology. Since the virus may infect the pancreatic tissue and the pathogenesis of pancreas cancer has not been completely cleared many factors, including infectious agent(s) should be considered in the oncogenesis study. Two case reports are not enough to draw any conclusions. We believe that further research on possible link between hepatitis or other pathology and TTV infection, is needed.

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