症例報告

著明な胆嚢壁肥厚を呈したA型肝炎の1例

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Hepatitis A Complicated by a Thickened Gallbladder Wall

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Abstract　We describe a 9-year-old Japanese boy with hepatitis A. Acute hepatitis A in our patient was characterized by jaundice, an increase in AST and ALT, a positive serologic test for the IgM antibody to HAV, and negative serologic test for hepatitis B, C, infectious mononucleosis, cytomegalovirus infection, and mycoplasmal infection. Ultrasonography showed a thickened gallbladder wall without pericholecystic fluid in transverse projection. Computed tomography indicated a gallbladder wall of more than 10 mm thickness. Gallbladder wall thickening appears as a thin rim of enhancing mucosa, surrounded by a thicker zone of near-water attenuation, representing submucosal edema. We also studied a viral strain collected from a serum sample of our patient. The nucleotide variation within a 168 base region encoding the putative VP1/2A was not detected and the viral strain was classified as subgenotype IA.

While epidemics of hepatitis A have not occurred recently in Japan, cases of hepatitis A are not infrequent. We should still pay attention to hepatitis A.

Keywords　*Hepatitis A, Genotype, Pediatric case, Epidemic, Thickened gallbladder wall*

Introduction

Hepatitis A virus (HAV) is a member of the Picornavirus family. HAV infections occur throughout the world but are most prevalent in developing countries. In addition to the liver, other organ systems can be affected by HAV infection. For example, regional lymph nodes and the spleen may be enlarged ; even acute pancreatitis or myocarditis has been reported, although rarely[1)].

This study reports a child with hepatitis A whose gallbladder wall was remarkably thickened during the acute phase of the disease. We also investigated the HAV genotype in serum from the patient.

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Case report

On March 22, 2002, a 9-year-old Japanese boy was taken by his mother to a physician because of fever. The patient was diagnosed as tonsillitis. On March 31, he ate sushi and by April 2, began feeling easily tired. Then, on April 4, he ate sushi again. The day after, he lost his appetite. On April 8, he became nauseated and vomited once. Then, on April 12, he vomited again and began to have right upper quadrant pain and systemic itching. The urine was noted to be dark-colored. He was taken by his mother to a physician again. Because his blood chemistry revealed high levels of total bilirubin at 4.0 mg/dl, aspartate aminotransferase 1119 IU/l and alanine aminotransferase 1668 IU/l, he was referred to our hospital.

On admission, his body weight was 44 kg, height was 143 cm, body temperature was 36.4℃, pulse was 96 per minute, respiration was 20 per minute, blood pressure was 110 mmHg systolic and 68 mmHg diastolic, bulbar conjunctiva was slightly icteric, heart examination was within normal limits on ausculation, the liver was palpable 3 cm below the costal margin, smooth and of normal consistency, and the gallbladder region was slightly tender on pressure. The laboratory test results are shown in Table 1 and 2. Hepatitis studies were negative for hepatitis B, C, infectious mononucleosis, cytomegalovirus infection, and mycoplasmal infection. However, acute HAV infection was diagnosed by detecting immunoglobulin M (IgM) antibodies (anti-HAV) by enzyme immunoassay. Urinalysis showed bilirubinuria.

Abdominal ultrasound of the gallbladder revealed a thickened wall without stones (Fig.1). A contrast-enhanced computed tomography (CT) scan of the abdomen also indicated a thickened gallbladder wall (Fig.2).

Although antibiotics were administered because of signs of cholecystitis, the patient mainly rested and displayed symptomatic improvement.

Table 1. Hematological values on admission

Red-cell count	$456\times10^4/\mu\ell$
Hemoglobin	13.0 g/dl
Hematocrit	37.5 %
White-cell count	$5.8\times10^3/\mu\ell$
Differential count	
Neutrophils	52.0 %
Lymphocytes	39.0 %
Monocytes	8.0 %
Eosinophils	1.0 %
Platelet count	$30.3\times10^4/\mu\ell$

Table 2. Blood chemistry values, coagulation tests, and serological data on admission

Total protein	7.6 g/dl
Albumin	3.7 g/dl
Thymol turbidity test	35.0 U
Zinc sulfate turbidity test	20.5 U
Total bilirubin	4.4 mg/dl
Direct bilirubin	3.1 mg/dl
Urea nitrogen	4.5 mg/dl
Creatinine	0.4 mg/dl
Sodium	137.2 mEq/l
Potassium	4.5 mEq/l
Chloride	103.2 mEq/l
Aspartate aminotransferase	425 IU/l
Alanine aminotransferase	1105 IU/l
Lactic dehydrogenase	1450 IU/l
Alkaline phosphatase	1027 IU/l
γ-glutamyl transpeptidase	171 IU/l
Leucin aminopeptidase	1450 IU/l
Calcium	8.9 mg/dl
Glucose	107 mg/dl
Ammonia	43 μg/dl
C-reactive protein	$<$0.2 mg/dl
IgM anti-HAV (EIA)	4.9 (positive)
Prothrombin time	90 %
Activated partial thromboplastin time	30.9 seconds
Fibrinogen	226 mg/dl

HAV, hepatitis A virus ; EIA, enzyme immunoassay

Now, the patient is well and free from hepatitis A.

We also investigated a viral strain. To analyze the sequence, viral RNA from serum was extracted. The semi-nested PCR targeting the VP1-P2a regions followed by sequence analysis was performed[2]. Primer sequences BR-5, BR-9 and BR-

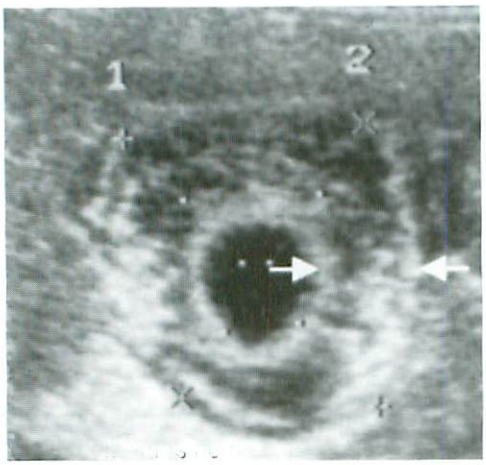

Fig.1
Ultrasonography showed a thickened gallbladder wall without pericholecystic fluid in transverse projection (arrows). A minor axis of the gallbladder measured approximately 4 cm. Partly hypoechoic gallbladder wall and no gallstones were detected.

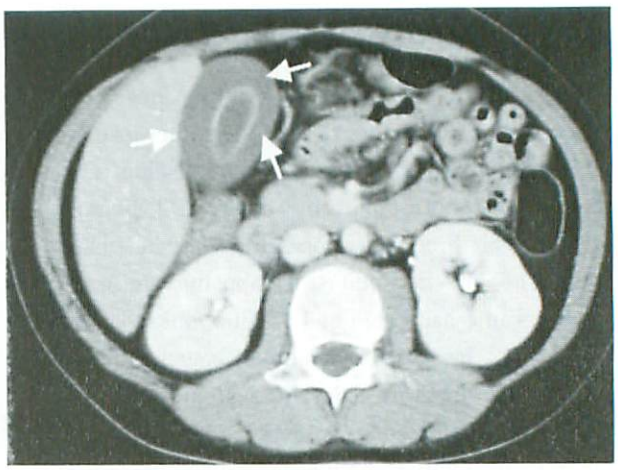

Fig.2
Computed tomography indicated a gallbladder wall of more than 10 mm thickness. Gallbladder wall thickening appears as a thin rim of enhancing mucosa, surrounded by a thicker zone of near-water attenuation, representing submucosal edema. The presence of small structures was enhanced within the wall (arrows). Ascitic fluid was not elicited.

6 were derived from published sequences[2]. BR-9 was used for reverse transcription. Outer primer sets were BR-5 and BR-9 for the VP1-P2a region. The inner primer set was BR-6 for the VP1-P2a region. The nucleotide variation within a 168 base region encoding the putative VP1/2A was not detected and the viral strain was IA subgenotype.

Discussion

In our case, the right upper quadrant pain and jaundice were suggestive of cholestasis. Furthermore, contrast enhanced CT scan showed apparent pericholecystic fluid. However, his acute infection was diagnosed by accepted methods, indicating that the jaundice was induced as not cholestasis but a secondary condition from injury in viral hepatitis. Goldstein et al. suggested three clues that allow CT to distinguish a pericholecystic fluid collection from a gallbladder wall thickening[3]. The first clue is detection of two concentric enhancing rims with intervening low density material. The second clue is to identify small enhancing punctate structures within the apparent fluid. The final clue is recognition that an inflammatory pericholecystic fluid collection is typically focal whereas gallbladder wall thickening is typically diffuse. The first and second clues were consistent with our patient.

A normal gallbladder wall is no more than 3 mm thick[4~6]. CT revealed a remarkably thickened gallbladder wall, maximum measurement of which was 14 mm in our case. There are a few reports of gallbladder wall thickening associated with hepatitis A infection[7,8]. As in these reports, pathogenesis of the thickened gallbladder wall in our patient was not clear. Jüttner et al. reported that thickening of the gallbladder wall may be secondary to the inflammatory process in the adjacent liver[9]. Yamada et al. discussed associations with mononucleosis syndrome in which immunologic reactions might cause gallbladder wall thickening[6]. Furthermore, they also reported that hypoproteinemia and hypoalbuminemia were pathogenic mechanisms. However, our data were not consistent with their report. As another possibility, Sharma et al.

reported direct invasion by the hepatitis virus[4]. We had too few patients to attempt any correlation between the etiological agent and gallbladder wall thickening. Clarification of the pathogenesis of gallbladder wall thickening due to hepatitis A requires further study.

CT revealed a remarkably thickened gallbladder wall in our case. However, CT radiation dose optimization is an important issue. The benefit to the patient of an accurate diagnosis should always be balanced against radiation risk and thereby, if possible, we should reduce radiation dose due to CT[10].

Robertson et al. reported a comprehensive analysis of sequence data derived from the VP1/2A junction region, resulting in the definition of seven unique genotypes (I to VII)[11]. Four of these genotypes (I, II, III, and VII) have been associated with human disease[11].

According to the investigation of the public health center from March 25 to April 19, 22 patients including our patient and his mother were also suffering from hepatitis A. Of the total 22 patients, 19 were male and 3 were female. Our patient was the only pediatric case. They all ate sushi at the same sushi shop. Individual viral isolates were assembled from clinical specimens containing HAV (stools or serum). Of the total 22 patients, 17 patients who included 15 males and 2 females were investigated for the viral strain. The viral strain from the specimens of all these patients was classified as IA subgenotype. Therefore, there was an epidemic of hepatitis A. Our findings that the majority of HAV in our patients is of subgenotype IA is consistent with the previous report[11].

To our knowledge, there are no reports that genomic differences of HAV are responsible for the gallbladder wall thickening. Fujiwara et al. suggested that viral factors might be involved in determining the severity of the disease. However, they reported that disease severity was not associated with the HAV genotype-determining region[12, 13]. It was not clear whether genotypes would correlate to the pathogenesis of gallbladder wall thickening in this case. Therefore further analysis is required.

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