Fulminant Viral Hepatitis (Type B) in the Late Stage of Pregnancy Showing an Unusual Pattern of Serum Antigen and Antibody: Report of a case

Fukashi NAKAMURA1, Hiroshi SASAKI1, Masanori UEDA2, Michio YAMANOU2 and Hiroki KAJIHIRA3

1) Department of Internal Medicine, Hiroshima Memorial Hospital, 1-4-3, Honkawa-cho, Naka-ku, Hiroshima 730, Japan
2) Department of Obstetrics and Gynecology, Hiroshima Memorial Hospital, Hiroshima 730, Japan
3) Department of Internal Medicine, Tsuchiya Hospital, 3-30, Nakajima-cho, Naka-ku, Hiroshima 730, Japan
4) Department of Pathology, Hiroshima University School of Medicine, 1-2-3, Kasumi, Minami-ku, Hiroshima 734, Japan

ABSTRACT

A case of fulminant viral hepatitis type B in the late stage of pregnancy was successfully treated with glucagon-insulin therapy, corticosteroids and other drugs. A 26-year-old female (housewife and primipara) suddenly developed severe hepatic dysfunction and disturbance of consciousness at the 36th week of pregnancy. Sequential blood examinations revealed early response to HBs antibody and delayed response to HBC antibody but HBs antigen was not detectable. The two antibodies disappeared from the serum rapidly and anti-HBc IgM remained undetectable throughout the clinical course of the acute hepatitis. It is not rare for HBs antibody to appear and for HBs antigen to disappear rapidly in the early stage of the clinical course of fulminant viral hepatitis type B. Anti-HBc IgM is considered valuable in the diagnosis of viral hepatitis type B. However,! the present case demonstrated that anti-HBc IgM may be undetectable throughout the clinical course in some cases of viral hepatitis type B.

Key words: Fulminant hepatitis, Hepatitis virus type B, HBs antigen, HBs antibody, IgM HBc

Pregnancy is a physiological phenomenon. It has been said that development of hepatic injury by pregnancy is extremely rare. However, it has been repeatedly reported by many investigators that a pregnant woman is prone to develop viral hepatitis, which, when contracted during the late stage of pregnancy, readily becomes aggravated.

We recently experienced a case of fulminant viral hepatitis type B which developed at the terminal stage of pregnancy, but the life of the both the mother and infant was saved. The serum antigen and antibody titer of hepatitis virus of the case presented an interesting course. The findings of this case will be presented.

CASE REPORT

The case is a 26 year-old housewife and a primipara. She has no past history of diseases of the hepato-biliary system nor a history of alcohol intake or medical drug administration.

Last menstruation continued for one week from 7 June 1984 followed by amenorrhea. On 16 July she visited a local obstetric-gynecologic clinic for examination and diagnosis was made that she was in the sixth week of pregnancy with the expected date of delivery being 14 March 1985. Thereafter, her course was uneventful until the beginning of February 1985. Blood examination was normal and HBs antigen was negative. However, from about 10 February, general fatigue and loss of appetite developed, followed by somnolence on 15 February. On 18 February, hepatic injury GOT 160 U (normal, 8-40 U), GPT 127 U (normal, 5-35 U), T.Bil. 6.2 mg/dl (normal, 0.2-0.8 mg/dl), and r-GTP 67.6 mU/ml (normal, 0-40 mU/ml) was pointed out by a local physician and she was hospitalized. As there was no improvement of her disturbance of consciousness, on 20 February she was referred to the Department of Internal Medicine of our hospital (Hiroshima Memorial Hospital) and immediately admitted.

At the time of admission, she was in a state of somnolence or drowsiness. She responded to her name, but her speech was inarticulate. Flapping tremor could not be observed. Blood pressure was 130/90 mmHg and tachycardia of 136/min was ob-
served. Bulbar conjunctiva showed icterus. Percussion of the chest wall showed loss of hepatic dullness. Abdomen was distended and both the liver and spleen were not palpable. The uterine fundus was 32 cm from the pubic bone and abdominal girth was 85 cm.

Slight labor was evident at the time of admission and therefore she was admitted to the delivery room for observation of her course. As delivery did not proceed and pervaginal delivery was considered impossible, delivery by Caesarean section was performed for delivery of a baby girl weighing 2,675 g.

As for the results of the laboratory tests conducted at the time of admission, examination of the peripheral blood showed RBC of 429 x 10^4/mm^3, WBC of 15700/mm^3, Hb of 13.8 g/dl, and Ht of 42.8%, indicating leukocytosis (neutrophilia). Platelet was 84,000/mm^3, bleeding time 4 min, thromboplastin test 31%, PT 16.0 sec (cont. 10.2), APTT 62.8 sec (cont. 30.4), and fibrinogen 113 mg/dl. Serum FDP was 40 to 160 µg/ml and positive.

As for liver function tests, T.Bil. showed a high value of 12.82 mg/dl (direct Bil. 9.65 mg/dl), GOT 29 U, GPT 73 U, LDH 756 U (normal 50-400U), and remarkably elevated. As for test of hepatitis virus, HBs antibody was negative (RIA, cut off index, i.e., C.I. 0.4) and the evaluation of both HBs antibody (RIA, C.I. 1.2) and HBc antibody (RIA, 38%) was reserved. HBe antigen, HBe antibody, and IgM HBc antibody were negative. IgM HA antibody was negative and viral hepatitis type A was denied.

As for the course following admission, a state of somnolence continued even after delivery on the first hospital day. Even on the second hospital day, platelet was 87,000/mm^3, thromboplastin test 24%, PT 14.8 sec, APTT 58.8 sec, and FDP 40 to 160 µg/ml. As development of DIC was considered, glucagon-insulin therapy (G-I therapy), branched-chain amino acids infusion, administration of adrenocortical hormones, and frozen blood plasma transfusion were commenced. On the third hospital day, she opened her eyes when she was called and could respond and on the fifth hospital day, she could respond rather accurately to posed questions. On the eighth hospital day, her consciousness became clear and her general condition was restored to almost the normal level. As the results of the blood tests became almost normal, G-I therapy was suspended from the ninth hospital day.

Her subsequent course was satisfactory and on the 39th hospital day laparoscopic examination and liver biopsy were performed. Laparoscopic findings revealed the liver surface to be almost smooth but slight depressions could be seen in some sites. The color was strongly yellow and colonies of pale red spots could be seen at the margin. As for histological findings of the liver, hepatocytes showed scattered degeneration and destruction with focal inflammatory infiltration (Figs. 1 and 2). Acidophilic bodies (single cell necrosis) were also scatteringly

---

**Table 1. Changes of serum antigen and antibodies of our case**

<table>
<thead>
<tr>
<th>Time (hospital day)</th>
<th>HBs Ag</th>
<th>HBe Ag</th>
<th>IgMHBc</th>
<th>HBc Ab %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/20</td>
<td>-1</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2/21</td>
<td>0</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2/22</td>
<td>0.2</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2/23</td>
<td>0.4</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2/24</td>
<td>0.6</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2/25</td>
<td>0.8</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2/26</td>
<td>1.0</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2/27</td>
<td>1.2</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: +: present, -: absent, C.I.: cut off index.
Fulminant Viral Hepatitis in Pregnancy

Fig. 1. Histology of hepatic tissue obtained from our case. Single cell necrosis of hepatocytes (arrow) and focal inflammatory cell infiltration are scattered in the hepatic lobules. Inflammatory cell infiltration is also observed in Glisson's sheath. × 200 H-E stain

Fig. 2. Large magnification of hepatocytes of our case. Hydropic degeneration and swelling of the hepatocytes are well observed. H-E stain × 400

seen. Orcein stain was negative and fibrosis could not be seen.

Thereafter, on the 111th hospital day, T.Bil. became normal with a value of 1.00. On the 134th hospital day, the results of all the laboratory tests became normal with GOT of 35 U, GPT 48 U, and T.Bil. 0.96 mg/dl, and she was discharged.

Changes in serum antigen and antibody titer of hepatitis virus (Table 1): On the first hospital day, HBs antigen was negative (RIA, C.I. 0.4), evaluation of HBs antibody reserved (RIA, C.I. 1.2), HBe antigen negative (RIA, C.I. 0.4), HBe antibody negative (RIA, inhibition % 0), and evaluation of HBe antibody reserved (RIA, 38%). On the second hospital day, HBs antigen was slightly elevated with cut off index (C.I.) being 1.3, and though the evaluation had to be reserved, it was not positive. On the 6th hospital day, it became negative with C.I. being 0.4. HBs antibody was already positive on the 6th hospital day with C.I. being 5.1. On the 20th hospital day, C.I. elevated to 10.7, but thereafter it decreased gradually with the value being 3.1 on the 34th hospital day and 2.0 on the 55th hospital day. On the 90th hospital day, C.I. was 1.2 and evaluation had to be reserved. On the 115th hospital day, C.I. was 0.5 and negative. HBe antibody finally became positive on the 115th hospital day (RIA, inhibition % 74) and on the 151st hospital day it had already become negative with the inhibition % being 18. IgM HBe antibody was negative during the entire course. Viruses which bring rise to hepatitis such as herpes virus, EB virus, and cytomegalovirus were all negative.

DISCUSSION

It has been pointed out by many investigators that hepatitis is prone to aggravate during pregnancy. According to Mori, fulmination of hepatitis is evidently more common when onset of hepatitis is during the later stage of pregnancy or when the symptoms appear during the puerperal period. He has reported that this tendency becomes apparent from after the eighth month of pregnancy and that the cases of fulmination of hepatitis and death account for about 30% of the total when onset is at the ninth month of pregnancy, for about 50% at the 10th month of pregnancy, and for 75% at the puerperal period.

Onset of our case was at the 36th week of pregnancy, and it was assumed to be fulminant hepatitis type B. Furthermore, the changes of serum antigen and antibody titer presented very interesting findings. At the time of admission, HBs antigen, HBs antibody, HBe antibody, and IgM HBe antibody were all negative. On the second hospital day, only HBs antigen was slightly elevated, but the evaluation had to be reserved. Shortly thereafter, it became negative. Moreover, the appearance of HBs antibody was extremely early and on the sixth hospital day it has already become positive. After peaking on the 20th hospital day, the antibody titer decreased, evaluation had to be reserved on the 90th hospital day, and on the 115th hospital day it became negative. On the contrary, the appearance of HBs antibody was extremely delayed and only on the 115th hospital day did it finally become positive, but on the 151st hospital day it turned negative. IgM HBe antibody was negative throughout the clinical course.

Almedia et al [1] have pointed out that in fulminant hepatitis, antibody production is high in response to infection of hepatitis type B virus and that the large volume of immune complex produced by excessive antigen-antibody reaction can bring rise to massive hepatic cell necrosis. Furthermore, according to Gimson et al [5], due to the massive production of immune complex HBs antigen decreases early in the blood and frequently becomes negative. Trepo et al [23], in examining the temporal changes of HBs antigen titer, observed that the average positive period of HBs antigen among 17 cases of fulminant hepatitis was 5.2 days and extremely short when compared to 67 days in the...
hepatic injury in 26 cases (54.2%) out of 48 cases of fulminant hepatitis considered to be attributable to hepatitis virus type B, they have suggested the possibility that rapid immunologic HBs antigen exclusion mechanism by the early production of HBs antibody is involved in the pathogenesis of fulminant hepatitis. Woolf et al.24), in their electron microscopic study of HBs antigen-antibody complex in all the cases of fulminant hepatitis type B, but such aggregation could hardly be seen in nonfulminant cases. They reported the possibility of the involvement of accelerated production of HBs antibody in the fulmination of hepatitis.

On the other hand, McKay et al.29 made a pathomorphological study of various organs during toxemia of pregnancy and eclampsia and observed a similarity with Shwartzman reaction. It is well known that acute hemorrhagic necrosis can be induced experimentally in the liver by Shwartzman reaction. Mori et al.30, after producing Shwartzman’s preparatory state by the intradermal injection of endotoxin in the rabbit, were able to induce acute hepatic necrosis by injecting HBs antigen in the ear vein. This suggests in the fulmination of viral hepatitis the possibility of the involvement of not only viral infection of hepatitis but also Shwartzman reaction in its base. As pregnancy can be considered to be a preparatory state of Shwartzman toxemia of pregnancy and eclampsia and observed a similarity with Shwartzman reaction. In our other hand, McKay et al.29 made a pathomorphological study of various organs during toxemia of pregnancy and eclampsia and observed a similarity with Shwartzman reaction. It is well known that acute hemorrhagic necrosis can be induced experimentally in the liver by Shwartzman reaction. Mori et al.30, after producing Shwartzman’s preparatory state by the intradermal injection of endotoxin in the rabbit, were able to induce acute hepatic necrosis by injecting HBs antigen in the ear vein. This suggests in the fulmination of viral hepatitis the possibility of the involvement of not only viral infection of hepatitis but also Shwartzman reaction in its base. As pregnancy can be considered to be a preparatory state of Shwartzman reaction, it can well be assumed that hepatitis is the late stage of pregnancy is prone to fulminate.

It has become possible in recent years to make an early and accurate diagnosis of hepatitis type B by measuring IgM HBc antibody.2,4,9,16,19,21 Gerlich et al.22,23,24,25 have discovered that in acute hepatitis type B IgM HBc antibody appears at 3 to 6 weeks and detection becomes impossible from 6 months to 2 years. Even after HBs antigen disappears from the blood in transient infection due to hepatitis virus type B, IgM HBc antibody can be detected and thus measurement of IgM HBc antibody is regarded to be useful in the diagnosis of hepatitis type B. Shimizu et al.26 have also observed in fulminant hepatitis that HBs antigen sometimes disappears at the early stage and described in such a case the importance of measuring IgM HBc antibody for the diagnosis of hepatitis type B. However, in recent years interest has been focused to cases of primary infection of hepatitis virus B whose IgM HBc antibody has either a low value or is negative during the entire course.27,28 In our present case, though being considered to be definite acute hepatitis type B from the changes observed in the antigen-antibody titer of hepatitis virus type B and also from the histological findings, IgM HBc antibody remained negative from onset to the present 40 weeks thereafter. It should be borne in mind that among cases of acute hepatitis type B there are cases though small in number whose IgM HBc antibody reaction is low and whose IgM HBc antibody titer either low or negative.

(Received December 15, 1987)

REFERENCES