A Case of Rubella Complicated by Hemolytic Anemia

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Introduction

Rubella is an acute viral infection characterized by rash, fever and lymphoadenopathy, and often affects school-age children in Japan. More than 80% of adults are considered to be immune to this disease. Encephalitis, meningitis, purpura and arthritis are well-known complications of rubella virus infection, while hemolytic anemia is rare1)~4). Here, we report an adult case with hemolytic anemia associated with rubella virus infection.

Case report

A 40-year-old Japanese man developed high fever of up to 40°C and small reddish eruptions on his chest and abdomen on June 15, 1997. The fever and eruptions disappeared within a day, however he noticed dark-colored urine on the following day. He had been in good health until then, and did not recall his past history of childhood diseases at the time. His height was 180cm, body weight 82kg, body temperature 36.5°C, pulse rate 84/min, and blood pressure 133/80mmHg. On physical examination, both the sclerae and skin were icteric. The conjunctiva showed slight pallor. Chest and abdominal examination revealed no abnormalities. The liver, Kidneys, spleen and superficial lymph nodes were not palpable. No pedal edema was observed. Neurological examination revealed no abnormalities. The laboratory data at presentation are shown in Table 1. Urine was strongly positive for urobilinogen. Hematological examination revealed slight anemia. The peripheral blood smear revealed fragmented red blood cells (RBCs) (Fig. 1). Blood chemistry showed elevation of the total bilirubin concentration, with predominance of indirect bilirubin. The serum levels of asparate aminotransferase, alanine aminotransferase, and lactate dehydrogenase were also increased. Serum haptoglobin level was significantly decreased. These data collectively suggested a diagnosis of hemolytic anemia. Serum anti-nuclear antibody was absent. Both the direct and indirect Coombs tests were negative. Ultrasonic scanning and computed tomography of the upper abdomen, performed on June 16, revealed no abnormality in the liver. Moreover, no splenomegaly was found.

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Hemolytic Anemia Following Rubella

Table 1 Laboratory data on admission

<table>
<thead>
<tr>
<th>Peripheral blood</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells: 3.660 (\mu l)</td>
<td>direct Coombs test (-)</td>
</tr>
<tr>
<td>Red blood cells: (413 \times 10^8\ \mu l)</td>
<td>indirect Coombs test (-)</td>
</tr>
<tr>
<td>Hemoglobin: 11.8 g/dl</td>
<td>Haptoglobin 5 mg/dl</td>
</tr>
<tr>
<td>Hematocrit: 37.0 %</td>
<td></td>
</tr>
<tr>
<td>Platelet: (16.3 \times 10^9\ \mu l)</td>
<td>Virus markers</td>
</tr>
<tr>
<td>Reticulocyte: 87 %</td>
<td>anti-HA IgM (-)</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>anti-HCV (3rd) (-)</td>
</tr>
<tr>
<td>Occult blood</td>
<td>HBs Ag (-)</td>
</tr>
<tr>
<td>Sugar</td>
<td>EBV</td>
</tr>
<tr>
<td>Protein</td>
<td>VCA IgG (+)</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>anti-EBNA (+)</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td>anti-CMV IgM (-)</td>
</tr>
<tr>
<td>Total bilirubin: 4.8 mg/dl</td>
<td>anti-rubella IgM (+)</td>
</tr>
<tr>
<td>Direct bilirubin: 1.1 mg/dl</td>
<td>anti-measles IgM (-)</td>
</tr>
<tr>
<td>Indirect bilirubin: 3.7 mg/dl</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase: 74 IU/l</td>
<td>Bone marrow*</td>
</tr>
<tr>
<td>Alanine aminotransferase: 72 IU/l</td>
<td>Nucleated cell counts (30 \times 10^4\ \mu l)</td>
</tr>
<tr>
<td>Lactate dehydrogenase: 1,823 IU/l</td>
<td>Myeloid/Erythroid 0.8</td>
</tr>
<tr>
<td>C-reactive protein: 7.6 mg/dl</td>
<td></td>
</tr>
</tbody>
</table>

* Erythroid hyperplasia was observed

A bone marrow aspiration, performed on June 19, showed hyperplasia of cells of erythroid lineage. Tests for hepatitis virus markers revealed that anti-hepatitis A IgM (anti-HA IgM), as well as hepatitis B virus surface antigen (HBsAg) and anti-hepatitis C antibody (anti-HCV), were all negative. The serum was positive for the Epstein Barr virus (EBV) anti-capsid antigen (VCA)-IgG, but negative for VCA-IgM. Anti-EBV nuclear antigen (anti-EBNA) was also found in the serum, while anti-cytomegalovirus IgM (anti-CMV IgM) was negative. He had small reddish eruptions and a high fever, which are characteristic features of some viral infections including rubella and measles infection, thus we performed further serological examinations for rubella and measles. The anti-rubella antibody IgM (anti-rubella IgM) was detected. In a later interview we asked him whether he had had rubella virus infection in his childhood. He disclosed that he had neither suffered from rubella nor received any vaccination for it. We thus diagnosed him as being infected with the rubella virus.

The patient’s hemoglobin value decreased to 8.6 g/dl, but blood transfusion was not indicated. The anemia slowly improved. The serum levels of total bilirubin and lactate dehydrogenase were nearly restored to normal within a week. The serum became negative for anti-rubella IgM, while anti-rubella anti-
body IgG (anti-rubella IgG) was detected. He was discharged on July 15 (30 days after admission). His hemoglobin value returned to normal by October, 1997 (Fig. 2).

Discussion

Hemolytic anemia is a rare hematological complication of rubella virus infection. More than twenty cases of rubella virus infection complicated with hemolytic anemia have been documented in literature in Japan. Before the present report, three adult cases had been reported in other Japanese proceedings, however, detailed descriptions of the cases are not available\(^5\)\(^6\)\(^7\). We believe ours to be the first documented case of hemolytic anemia following rubella virus infection in an adult.

Hemolytic anemia has been occasionally reported to complicate viral infection. Various viral infections, including rubella, measles\(^8\), Epstein Barr\(^9\) and cytomegalovirus infections\(^10\), have been reported to be complicated by hemolytic anemia\(^4\)\(^11\)\(^12\). Our patient had small reddish eruptions and a high fever prior to the diagnosis of hemolytic anemia, which are characteristic features of some viral infections. We performed serological investigation for several virus markers, and ruled out primary infection by measles virus, Epstein Barr virus and cytomegalovirus.

Although the mechanism of development of hemolytic anemia associated with rubella virus infection is not fully understood, direct destruction of RBCs by the rubella virus or the production of autoantibodies recognizing RBCs induced by rubella virus infection have been considered\(^11\)\(^12\). When hemolytic anemia is induced by this mechanism, a positive direct or indirect Coombs test and erythroid hyperplasia in the bone marrow may be observed. However, the Coombs tests were both negative in the present case, as is observed in many patients with hemolytic anemia. It might be reasoned that the amount of antibodies on the RBC surfaces or the fraction of specific antibodies in the serum recognizing RBCs was probably not enough to be detected by routine serological examinations\(^3\)\(^4\)\(^5\)\(^6\). A bone marrow examination in the present patient revealed erythroid hyperplasia, suggesting that the hemolytic anemia in this patient was probably caused by this mechanism.

It has been reported that a good outcome is obtained by advising rest alone in almost all patients suffering from hemolytic anemia, although patients with severe anemia require transfusion. According to a review of 23 cases of hemolytic anemia associated with rubella virus infection, there is no established indication for corticosteroid (CS) therapy\(^16\). Some patients had positive direct or indirect Coombs tests, but in some, both were negative. However, we believe that treatment with CS should be restricted to patients in whom an autoimmune mechanism is strongly suspected to be involved in the pathogenesis of hemolytic anemia. Our patient was not severely anemic, nor was he positive for anti-nuclear antibody or the direct and indirect Coombs tests. Therefore, we did not administer any specific treatment for the anemia in this patient. The hemoglobin level, which reached 8.6 g/dl at the lowest, returned to normal within a few months.

In Japan, a live attenuated vaccine was licensed for use in 13 to 15-year-old girls in 1977.

Fig. 2 Clinical course.
The vaccination was introduced as a strategy to prevent congenital rubella, by ensuring that very few pregnant women were susceptible. In 1989, a trivalent measles-mumps-rubella (MMR) vaccination program was introduced to immunize all infants, but this program was abolished due to the occurrence of mumps vaccine-related non-bacterial meningitis in 1994. Currently, monovalent rubella vaccine is used for infants and students in junior high school. We should be aware that adults who were born long before these vaccination programs were begun are still susceptible if they were not naturally infected with the rubella virus. This 40-year-old male patient had no past history of vaccination or rubella virus infection.

In summary, we report an adult case of rubella virus infection with the very rare complication of hemolytic anemia. To the best of our knowledge, this is the first documented adult case of hemolytic anemia following rubella virus infection in Japan.

**References**

溶血性貧血を合併した風疹の1例

米田 諭1） 吉川 正英2） 山根 佳子3）
西村 公男3） 福井 博1）

症例は40歳男性。発熱、四肢・体幹の米粒大の
赤色皮疹および黒色尿を認めたため当院を受診。
血液検査所見で、著明な網状赤血球の増加を伴う
貧血、間接ビリルビン値の黄疸、LDHの著明な
上昇を認めた。破砕赤血球も認め、溶血性貧血と
診断した。ウイルス学的検査で、抗風疹 IgM 抗体
は陽性であり、風疹と診断した。風疹に合併した
溶血性貧血の成人症例は稀であるため、文献的考
察を加え報告した。

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