Familial Cases of Severe Measles Pneumonia

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Abstract

We report two cases of severe measles pneumonia. Patient 1, a 17-year-old boy who contracted measles in the acute phase of infectious mononucleosis caused by Epstein-Barr virus (EBV), transmitted the disease to patient 2, his father. Both patients presented severe pneumonia with bilateral diffuse micronodular shadows. Diagnoses were established in both patients by antibody titers for measles and reverse transcriptase-polymerase chain reaction (RT-PCR) of blood and throat swab. Multinucleated giant cells with intranuclear inclusion bodies were revealed in the transbronchial lung biopsy (TBLB) specimen of patient 2. Both patients recovered with pulse steroid therapy.

Key words: Epstein-Barr virus, transmission, transbronchial lung biopsy, giant cell pneumonia, methylprednisolone

Introduction

Measles is a highly contagious viral disease which is currently drawing increasing attention worldwide. Although vaccination has dramatically reduced the incidence of this disease in industrialized countries, epidemics still periodically occur in hospital and school settings. In developing countries, measles remains a disease with high morbidity and an important cause of childhood mortality (1). Pneumonia caused by the measles virus itself is an uncommon complication which may develop into severe respiratory failure (2-4). We report two cases of measles that developed into severe bilateral diffuse pneumonia. The first case, a 17-year-old boy, transmitted the disease to the second case, his father.

Case Report

Case 1

A 17-year-old boy who had been previously healthy visited the outpatient clinic of the otolaryngology department in Kurashiki Central Hospital on June 8, 1998, after experiencing a persistent high-grade fever and sore throat for about ten days. He had never been vaccinated against measles. Enlarged cervical lymph nodes were palpable bilaterally. Complete blood count showed hemoglobin of 10.7 g/dl and a white blood cell count of 9,700/μl, with 38% segmented neutrophils, 15% band form neutrophils, 39% lymphocytes, 5% monocytes, 3% atypical lymphocytes, and a platelet count of 24.0x10⁴/μl. Serum chemistry revealed aspartate aminotransferase (AST) of 55 IU/l, alanine aminotransferase (ALT) of 85 IU/l, and lactic dehydrogenase (LDH) of 751 IU/l. Infectious mononucleosis was suspected. He had no direct contact with children in the febrile period.

Although his symptoms subsided spontaneously on June 17, high-grade fever recurred on June 20. He was admitted to the department of internal medicine with a face rash 2 days later and placed in a private room. He was seriously ill with a temperature of 39.6°C, pulse rate of 74/min with regular rhythm, and blood pressure of 140/78 mmHg. A few cervical lymph nodes on each side were enlarged up to 1 cm in diameter. Koplik’s spots were not seen on the buccal mucosa. Eruption emerged on the face on the admission day, and by the second day a pink eruption spread from the body trunk to the extremities. Small vesicles appeared over the patient’s entire body on June 30.

Chest radiograph taken on the admission day was normal. Complete blood count showed hemoglobin of 11.5 g/dl and a white blood cell count of 4,400/μl, with 28% segmented neutrophils, 35% band form neutrophils, 25.5% lymphocytes, 11.5% monocytes, and a platelet count of 16.7x10⁴/μl. Evaluation of serum chemistry was AST 35 IU/l, ALT 40 IU/l, and LDH 481 IU/l. The spun urinary sediments contained giant cells with intracytoplasmic inclusions (Fig. 1). We imputed the eruption and fever to either drug allergy or the recurrence of infectious mononucleosis. Despite nosotropic therapy, high-grade fever persisted. Seven days after admission, he complained of dyspnea at rest with tachypnea of 28/min, and chest radiograph revealed bilateral diffuse micronodular shadow (Fig. 2). Inspiratory fine crackles were heard on the back. A specimen of arterial blood gas showed a PaO₂ level of 58 mmHg and PaCO₂ of 41 mmHg. Serum retinol was measured at an abnormally low value of 34 IU/dl (normal range, 65 to 276 IU/
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Figure 1. Urinary spin sediments contained giant cells with intracytoplasmic inclusions (Sternheimer’s stain, ×200).

Figure 2. Chest radiograph of case 1 showed bilateral diffuse micronodular shadow.

Figure 3. Chest CT of case 1 demonstrated multiple ill-defined nodules which seemed to coalesce and form panlobular ground-glass opacities. Thickening of bronchovascular bundles was noted.

dl). Serum concentration of retinol-binding protein was 1.7 mg/dl (normal range, 2.5 to 8.0 mg/dl). The chest CT is shown in Fig. 3.

Viral infections, miliary tuberculosis, and drug-induced pneumonia were considered. Fiberoptic bronchoscopy performed to search for the cause of the pneumonia revealed yellowish pus adhering to the epiglottis and larynx, and red swelling of the bronchi. Culture of the pus yielded Staphylococcus aureus. The differential cell count of bronchoalveolar lavage fluid (BALF) from right S5 was 48.5% lymphocytes, 41.0% macrophages, 9.5% neutrophils, and 1.0% eosinophils. Histopathological examination of TBLB from right S8a revealed interstitial pneumonia with a slightly thickened alveolar wall with lymphocyte infiltration and swelling of type II pneumocytes. From June 30, 1 g of methylprednisolone was administered daily for 3 days by i.v. Three days after the last methylprednisolone administration, the patient’s clinical and radiographic recovery was noted. The micronodular shadows on the chest radiograph disappeared and he was discharged from the hospital on day 31.

The results of virological examination are shown in Table 1. Titers of VCA IgA and VCA IgM for EBV were elevated when he visited the otolaryngology department, so it was confirmed that he had acute EBV infection two weeks before admission. The diagnosis of measles was confirmed by the results of paired enzyme-linked immunosorbent assay (ELISA) antibody tests for measles. Measles antigen was detected in throat swab and blood by RT-PCR (SRL Inc., Japan). Cultures of throat swab, blood, and urinary samples did not yield measles virus.

Case 2

Patient 1’s 50-year-old father, a previously healthy person, was admitted to Kurashiki Central Hospital on July 6, 1998 with high-grade fever and systemic eruption. He was not sure whether he had been vaccinated against measles. He had been looking after patient 1 without any respiratory protection. At the time of admission he had been febrile for 5 days. Eruption first appeared on the face 4 days before admission and had spread over the entire body. Body temperature was 39.5°C, pulse rate was 104/min with regular rhythm, blood pressure was 110/52 mmHg, and respiratory rate was 24/min. Tonsils were swollen bilaterally, and Koplik’s spots were not seen on the buccal mucosa. Cervical lymph nodes were palpable bilaterally and measured 1 to 2 cm in diameter. A finely textured red skin rash was noted over the entire body. No rale was heard on auscultation.
Table 1. Antibody Titer of Case 1 for EBV and Measles

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<td>EA-IgG</td>
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<tr>
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<tr>
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<tr>
<td>IgG (mIU/ml)</td>
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<tr>
<td>IgM (index+)</td>
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<td>6.9</td>
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VCA: viral capsid antigen, EA: early antigen, EBNA: Epstein-Barr nuclear antigen. *Antibody titers for EBV were measured by the fluorescent antibody method and are expressed as inverses of serum dilution. **Antibody titers for measles virus were measured by enzyme immunoassay. +Indices were judged as follows: <0.8 negative, 0.8–1.2 suspended, 1.2< positive.

Complete blood count indicated a hemoglobin level of 17.8 g/dl and a white blood cell count of 9,800/μl with 32% segmented neutrophils, 55% band form neutrophils, 8% lymphocytes, 3.1% atypical lymphocytes, 1.3% monocytes, 0.7% metamyelocytes, and a platelet count of 13.1×10^9/μl. Blood chemistry on admission showed AST 72 IU/l, ALT 79 IU/l, and LDH 887 IU/l. Serological test revealed a C-reactive protein level of 13.1 mg/dl. Blood gas analysis indicated a PaO₂ level of 54 mmHg and PaCO₂ of 42 mmHg. The urine sediments showed giant cells with intracytoplasmic inclusions. Serum retinol and retinol-binding protein levels were both abnormally low, at 44 IU/dl and 1.2 mg/dl, respectively. Chest rontgenogram revealed diffuse micronodular shadow and faint infiltrate on the right lower lung field.

We suspected that a kind of viral disease had been transmitted from case 1 to case 2. Fiberoptic bronchoscopy was performed on the day after admission in order to detect the pathogen. The bronchi were reddish. Differential cell count of BALF from right S3a was 10.5% neutrophils, 11% lymphocytes, and 78.5% macrophages. Microscopic examination of TBLB specimens from right S3a and S8a showed interstitial pneumonia with multinucleated giant cells with intranuclear inclusions (Fig. 4). On hospital day 3, the diffuse shadows on chest radiograph became dense (Fig. 5). The chest CT revealed multiple micronodules and ground glass opacities (Fig. 6). From hospital days 3 to 5, the patient was treated with 1 g of methylprednisolone daily, and his fever remitted 3 days after the methylprednisolone therapy was started. Skin eruption subsided leaving only a slight pigmentation, and the shadows on the chest rontgenogram completely disappeared. He was discharged on day 23.

Serum antibody titers for measles and EBV were evaluated and are summarized in Table 2. ELISA antibody tests for measles were significantly elevated. Measles RNA was detected in throat swab and blood by RT-PCR. Cultures of the BALF, urine, throat swab, and blood samples did not yield the pathogen.

**Discussion**

The present two cases are interesting for two reasons. First, patient 1 presented serious measles pneumonia after infectious mononucleosis of EBV. Second, patient 2, the father of patient 1, also presented severe viral pneumonia after contracting the measles virus from his son.

In spite of the worldwide spread in the availability of measles vaccine since 1963, measles caused the death of approximately 1 million children in 1996 (1). Pneumonia is often a serious complication of measles and accounts for a major proportion of measles deaths. Mortality increases with young age (5), malnutrition (6), and other immune-suppressed statuses. Although pneumonia is a relatively benign complication in previously healthy adolescents, there are reports of fatalities due
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Table 2. Antibody Titers of Case 2 for EBV, Measles, and Parainfluenza Type 3

<table>
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<th>Jul. 7</th>
<th>Jul. 21</th>
<th>Aug. 19</th>
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<tr>
<td>EBV VCA-IgG</td>
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<td>VCA-IgA</td>
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<td>VCA-IgM</td>
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<tr>
<td>EA-IgG</td>
<td>&lt;10</td>
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<tr>
<td>EA-IgA</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>EBNA</td>
<td>40</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>Measles IgG (mIU/ml)</td>
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<td>1,700</td>
<td></td>
</tr>
<tr>
<td>IgM (index)</td>
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<tr>
<td>Parainfluenza type 3</td>
<td>64</td>
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</table>

Antibody titers for parainfluenza type 3 were measured by hemagglutination inhibition and are expressed as inverses of serum dilution.

to measles pneumonia among such cases (2, 3). Pneumonia is reported to complicate 3 to 50% of measles cases (7, 8). This considerable variation in the reported incidence may be due to biases in the methods physicians use to detect and care for pneumonia. Chest radiographs are generally performed only in patients clinically suspected of having pulmonary complications, and this may why pneumonia is thought to be unusual in measles cases. Pneumonia developing in measles cases may result from extension of the viral infection, superimposed bacterial infection, a combination of these conditions, or, in atypical cases, a hypersensitivity reaction (9). Pneumonia caused by viral infection itself is considered to be the result of dissemination of viremia. However, it is difficult to prove that pneumonia is caused by the measles virus itself.

Bacterial infection is caused by impairment of general and local immune function. In the case of clinical deterioration with high-grade fever, elevated white blood cell count and purulent sputum production are suggestive of bacterial superinfection. Patient 1 was found to have Staphylococcal epiglottitis and laryngitis.

Our two cases presented severe pneumonia, and both were considered to be viral rather than bacterial pneumonia based on the radiographic findings of diffuse micronodular shadow and the microscopic findings of interstitial pneumonia in TBLB specimens. The radiographic findings common in these two cases were thickening of bronchovascular bundles, diffuse micronodular shadows randomly spread in lobules, and patchy distributed panlobular ground glass shadows which were likely to coalesce. Pathological findings of the TBLB specimens from the two cases showed thickening of the interstitium with an increase and swelling of type II pneumocytes and infiltration of inflammatory cells. In case 2, the TBLB specimen revealed multinuclear giant cells, a histologic picture considered to be characteristic of measles giant cell pneumonia. Giant cell pneumonia is also reported to appear in pneumonia caused by parainfluenza type 3 virus (10). However, infection of this virus was ruled out in case 2 because there was no titer elevation in paired antibodies to parainfluenza type 3 virus.

The preceding infection of EBV made it difficult to diagnose case 1. We imputed the eruptions of case 1 to drug allergy or recurrence of EBV infection, but we did not rule out the possibility of measles or rubella. When the pneumonia was revealed, we suspected that patient 1 had become infected with another virus or tuberculosis since pneumonia caused by EBV has been reported only very rarely (11). There is a reported case of an infant who developed encephalitis and died because of a simultaneous infection of EBV and measles virus (12).
Considering the incubation period of measles, patient 1 might have become infected with the measles virus in the acute phase of infectious mononucleosis. The origin of measles in patient 1 was not identified. There is an obscure possibility that he was infected during one of his four visits to our hospital in the acute phase of EBV infection. We presume that the EBV infection lowered the host’s immunity and made him susceptible to measles. It is reported that antibody titer to measles virus may increase when polyclonal B-cells are stimulated by EBV (13). The diagnosis of measles was definite in both cases 1 and 2 because RT-PCR detected this virus in their throat swabs and blood. Reviewing the skin manifestations of the two cases, pink eruptions of 3–7 mm in diameter emerged first on their faces and they spread to the body trunks and the extremities in 4 days. Next the eruptions coalesced, the color reddened, and about one week after their emergence, vesicles 2 mm in diameter appeared all over their bodies. The rashes and vesicles disappeared and faded to slight pigmentations during the convalescent period.

There has been an adult case of severe measles pneumonia treated successfully with vitamin A and high-dose methylprednisolone (4). Both of the present patients improved clinically and radiographically in response to the methylprednisolone therapy. It is assumed that inflammatory reactions to the hematologically disseminated virus caused minimal exudative areas which resulted in diffuse alveolar damage. Our cases suggest that high-dose steroid therapy might have suppressed this process, though the effectiveness of the treatment has not been established in measles pneumonia. Although no specific therapy is known to be effective for measles, treatment with high-dose vitamin A is reported to reduce its mortality (14). Serum retinol levels of our cases were low.

In industrialized countries where measles vaccination is in wide use, familial outbreaks of severe measles pneumonia are considered very rare. In Japan, the recent vaccination rate for measles is still only 70 to 80%. The vaccination itself is subject to the unresolved problems of primary vaccine failure, in which the vaccine fails to produce a protective immune response, and secondary vaccine failure, in which the immunity wanes with time (15). Under these circumstances, there are sporadic outbreaks of adult measles in Japan. Patient 1 reported that he had not been vaccinated for measles and patient 2 was not sure whether he had been vaccinated. Atypical measles is a well-described entity in children and young adults who are exposed to natural measles after immunization with inactivated measles vaccines (16). The maculopapular rash often begins on the wrists and ankles and progresses inward to the trunk. Pulmonary involvement is common and solitary pulmonary nodules of 2 to 5 cm in diameter may persist for years (9). The clinical manifestations of case 2 were different from manifestations of atypical measles.

The measles virus is transmitted by an airborne route and is highly contagious. With recent advances in medical treatment, a variety of immunosuppressed patients are now treated in hospitals. Some cases of measles pneumonia were not recognized in immunosuppressed patients because of the absence of the characteristic rash (17). The Centers for Disease Control and Prevention published a guideline for isolation precautions in hospitals (18) that recommended the isolation of hospitalized measles patients and the adoption of airborne precautions in addition to standard precautions to prevent secondary infection to other hospitalized patients, visitors, and medical staff.

References