Adrenal Hemorrhage Associated with
Klebsiella Oxytoca Bacteremia

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Septic adrenal hemorrhage is classically caused by meningococcemia. An autopsied case is presented of a 45-year-old man with adrenal hemorrhage due to Klebsiella oxytoca bacteremia following placement of a central venous catheter. He died 5 hours after developing disseminated intravascular coagulation (DIC). The bacterial entry site may have been the catheter. The cause of death was considered to be pulmonary edema due to bacteremia rather than adrenal insufficiency due to hemorrhage. Septic adrenal hemorrhage should be recognized as a subtype of sepsis rather than adrenal insufficiency, and may be caused in conditions of severe sepsis with DIC, independent of the microorganic variety.

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Key words: sepsis, disseminated intravascular coagulation, Waterhouse-Friderichsen syndrome, central venous catheter

Introduction

Adrenal hemorrhage is an uncommon condition, and the number of autopsied cases of adrenal hemorrhage associated with death has been reported to be 85 (0.02%) of 39 1,441 within a 10-year period in Japan (1). Adrenal hemorrhage is associated with infection, postoperative state, thromboembolic disease, anticoagulant therapy, cardiac disease, tumor metastasis, burn, or trauma, and infection is the most common complication (1, 2). Fulminant meningococcemia with adrenal hemorrhage is known as Waterhouse-Friderichsen syndrome (3), while other bacteria, such as Haemophilus influenzae, have been reported to cause adrenal hemorrhage (4, 5).

Klebsiella oxytoca is one of four members of the genus Klebsiella and is a gram-negative rod bacterium. It may cause infection, such as pneumonia (6), meningitis (7), or endocarditis (8), but this is rare. Infections are found in patients who have undergone surgical or invasive procedures (7–9). Klebsiella oxytoca is recognized as an important nosocomial pathogen (6, 7).

We report an adult patient with bilateral adrenal hemorrhages associated with bacteremia due to Klebsiella oxytoca 3 months after placement of a permanent indwelling central venous catheter. This is the first documented case of adrenal hemorrhage due to Klebsiella oxytoca bacteremia.

Case Report

A 45-year-old Japanese man was diagnosed with hypokalemic periodic paralysis, non-insulin-dependent diabetes mellitus and essential hypertension, at 25 years, 21 years and 1 year before, respectively. He was treated with oral drugs. A permanent indwelling central venous catheter was placed in his body to administer potassium 3 months earlier, because oral administration of potassium to treat idiopathic hypokalemia often caused gastric ulcers. The administered dose of potassium was about 10 mEq/day. He entered the Hyogo College of Medicine Hospital due to epigastralgia, lower abdominal pain, headache, and neck to shoulder pain in June 1995.

On admission, his height, body weight (wt), blood pressure, pulse rate and body temperature were 175 cm, 93 kg, 135/100 mmHg, regular 72 beats/min and 36.8°C, respectively. On physical examination, mild tenderness without defense was found on his epigastrium and lower abdomen. In an endoscopic examination, gastric ulcer scars were observed. In barium-enema examination, diverticula were found in the ascending...
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colon. Electrocardiographic findings were within normal limits.

Laboratory data are shown in Table 1. The elevation of hemoglobin A1c was mild. C-reactive protein (CRP) was positive during the admission period, and the maximum value was 3.7 mg/dl 4 days after admission. The white blood cell (WBC) count on the same day was not elevated (8,700/μl), and the differential white blood count was almost normal (neutrophil, 58.5%; eosinophil, 2.1%; basophil, 0.8%; lymphocyte, 29.5%; and monocyte, 9.1%). Serum thyroid hormone values that were examined to determine the cause of periodic paralysis were almost normal (free triiodothyronine, 4.1 pg/ml; free thyroxine, 2.5 ng/dl). The pain and tenderness in the epigastrium disappeared 3 days after admission, although the other symptoms did not improve. Increases in his blood pressure were often found during the admission period (maximum 168/120 mmHg). He had no fever prior to the last day.

Fourteen days after admission, he suddenly developed a high fever of 39.9°C. A nonsteroidal anti-inflammatory drug was administered. WBC and platelet count were low, while red blood cell count, hemoglobin and hematocrit were elevated (Table 1). The differential white blood count was not measured. Although his fever fell to 37.3°C 3.5 hours after onset, he rapidly developed tachycardia (heart rate, 110–150 beats/min), dyspnea (respiratory rate, 20–28 breaths/min) and cyanosis. Partial pressure and saturation of arterial oxygen were low (Table 1). He was forced to inhale oxygen, lactated Ringer’s solution was infused, and hydrocortisone (500 mg) was intravenously injected. His systolic blood pressure then fell to less than 90 mmHg, and he developed shock. He fell into cardiopulmonary arrest 4.5 hours after onset. Cardiopulmonary resuscitation was performed and hydrocortisone (1,000 mg) and epinephrine (total 11 mg) were injected, however, he died 5 hours after onset. Potassium was not administered except the potassium in the Ringer’s solution. Serologic tests showed resistance to ampicillin and fosfomycin. The second and third cephalosporins, new quinolones, carbapenems and monobactams were sensitive. Skin congestion of the upper body was observed, but no

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**Table 1. Laboratory Data**

<table>
<thead>
<tr>
<th>Day after admission</th>
<th>1st</th>
<th>10th</th>
<th>14th (onset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral blood</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White blood cell (μl)</td>
<td>9,400</td>
<td>7,800</td>
<td>2,100</td>
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<tr>
<td>Red blood cell (×10^4/μl)</td>
<td>596</td>
<td>571</td>
<td>631</td>
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<tr>
<td>Hemoglobin (g/dl)</td>
<td>17.9</td>
<td>17.1</td>
<td>18.8</td>
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<tr>
<td>Hematocrit (%)</td>
<td>53.1</td>
<td>51.5</td>
<td>57.0</td>
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<tr>
<td>Platelet (×10^4/μl)</td>
<td>29.9</td>
<td>24.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>7.1</td>
<td>7.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Alanine aminotransferase (KU)</td>
<td>35</td>
<td>33</td>
<td>38</td>
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<tr>
<td>Aspartate aminotransferase (KU)</td>
<td>25</td>
<td>30</td>
<td>40</td>
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<tr>
<td>Lactate dehydrogenase (WU)</td>
<td>299</td>
<td>434</td>
<td>412</td>
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<tr>
<td>γ-glutamyltranspeptidase (IU/l)</td>
<td>94</td>
<td>71</td>
<td>NP</td>
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<tr>
<td>Alkaline phosphatase (BLU)</td>
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<td>Creatine phosphokinase (U/l)</td>
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<td>NP</td>
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<td>Creatinine (mg/dl)</td>
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<td>0.89</td>
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<td>Blood urea nitrogen (mg/dl)</td>
<td>7.2</td>
<td>5.2</td>
<td>10.6</td>
</tr>
<tr>
<td>Na (mEq/l)</td>
<td>140</td>
<td>145</td>
<td>138</td>
</tr>
<tr>
<td>K (mEq/l)</td>
<td>4.0</td>
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</tr>
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<td>Cl (mEq/l)</td>
<td>100</td>
<td>105</td>
<td>104</td>
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<tr>
<td>Fasting blood sugar (mg/dl)</td>
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<td>126</td>
<td>197</td>
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<tr>
<td>Hemoglobin A1c (%)</td>
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<td>NP</td>
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<td>Serological test</td>
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<td>C-reactive protein (mg/dl)</td>
<td>2.1</td>
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<td>Arterial blood gas (room air)</td>
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<td>pH</td>
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<td>NP</td>
<td>7.377</td>
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<tr>
<td>pCO2 (mmHg)</td>
<td>NP</td>
<td>NP</td>
<td>25.0</td>
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<td>pO2 (mmHg)</td>
<td>NP</td>
<td>NP</td>
<td>52.9</td>
</tr>
<tr>
<td>Base excess (mmol/l)</td>
<td>NP</td>
<td>NP</td>
<td>-9.7</td>
</tr>
<tr>
<td>HCO3 (mmol/l)</td>
<td>NP</td>
<td>NP</td>
<td>14.7</td>
</tr>
<tr>
<td>O2 saturation (%)</td>
<td>NP</td>
<td>NP</td>
<td>87.4</td>
</tr>
</tbody>
</table>

KU: Karmen unit, WU: Wróblewski unit, BLU: Bessey-Lowry unit, NP: not performed.
purpura. The weight of both adrenal glands was more than twice the average (left, 16.2 g; right, 15.8 g). When incising the adrenal glands, the insides were found to be massively occupied by incomplete blood clots (each about 10 g), which were mud-like in appearance, and hemorrhage were confirmed (Fig. 1). The hemorrhages were histologically identified in more than two-thirds of the area of the cortex of both adrenal glands (Fig. 2). The cortical cells in the hemorrhagic region exhibited focally degenerative changes such as vacuolar degeneration, but no apparent necrotic changes such as pyknosis. There were no microthrombi or organisms, and only a few inflammatory cell infiltrations were observed around the central vein.

In both kidneys, many microthrombi were detected in most glomeruli (Fig. 3). In the bilateral lungs, severe edema with mild congestion was histologically observed with a small amount of hemorrhaging (wt: left, 760 g; right, 970 g), and a small number of alveoli contained air. There was no marked histological finding of pneumonia in either lung. There was also no pulmonary hyaline membrane. The spleen was enlarged (wt, 240 g) and soft. Histologically, several small colonies of gram-negative bacilli were recognized (namely, infectious spleen).

A thrombus with organization (length, 5 cm) was found in the catheterized area of the left internal jugular vein (Fig. 4). Bacteria were histologically not recognized in the thrombus. In the outer area of the myocardium of both ventricles, the interstitial tissue was focally broadened and edematous with a small number of leukocytic infiltrations, although there was no coagulation necrosis of the myocardium. The thyroid showed

Figure 1. This photograph shows bilateral adrenal glands after incision. Incomplete blood clots flowed out, and the adrenal glands appeared cystic.

Figure 2. The hemorrhages are observed mainly in the zona glomerulosa and the inner half of the zona fasciculata of the cortex. There is little hemorrhaging in the medulla. The upper space is considered as the area after the blood flowed out (see Fig. 1) (HE stain, ×13).

Figure 3. Many fibrin thrombi are observed in the capillary lumen of the renal glomeruli (Phosphotungstic acid hematoxylin stain, ×130).

Figure 4. A mural thrombus with organization is observed on the vein (HE stain, ×17).
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diffuse goiter (wt, 59 g), but no thyroiditis or Graves’ disease. No marked inflammation in the peridiverticula of the ascending colon was histologically observed.

Discussion

The clinicopathological findings of our patient are similar to those of Waterhouse-Friderichsen syndrome. Friderichsen characterized this syndrome as severe acute infection with the following features: sudden onset, hyperpyrexia, intermittent cyanosis with dyspnea, purpura, shock, and adrenal hemorrhage (3). This syndrome is usually recognized by the above features, and the present findings corresponded to the above features except for purpura. Since purpura has recently been regarded as a non-essential feature of this syndrome (4, 5), the present case may be considered Waterhouse-Friderichsen syndrome. However, the term Waterhouse-Friderichsen syndrome is generally used for cases caused by meningococcemia. Therefore, the criteria for this syndrome must be clarified.

Patients with septic adrenal hemorrhage usually exhibit disseminated intravascular coagulation (DIC), and all 40 cases reported within the last 26 years have had DIC. Our patient was also considered to have had DIC, because the platelet count was markedly low and there were many fibrin thrombi in most glomeruli of both kidneys. DIC seems to be due to Klebsiella oxytoca bacteremia. The detection of this bacterium suggests that any bacterium which causes DIC, can cause adrenal hemorrhage.

The mechanism of septic adrenal hemorrhage has been proposed to be due to Shwartzman reaction (10). Briefly, experimentally in rabbits, an adrenal hemorrhage can be produced by an intravenous injection of endotoxin after pretreatment with adrenocorticotropic hormone (ACTH), but it does not occur without the pretreatment. Although the mechanism also may have been due to DIC, adrenal hemorrhage has been reported to be seen in only two (9%) of 22 patients with DIC (11). Thus, septic adrenal hemorrhage is considered to be mainly due to Shwartzman reaction rather than DIC alone. ACTH secretion is known to increase with stress such as inflammation or infection. Since our patient demonstrated repeated inflammatory reactions (the rise of CRP), the patient may have suffered from an infection prior to onset.

The entry site of the Klebsiella oxytoca detected was not determined, but it may have been present in the permanent indwelling central venous catheter. Central venous catheters are known to be the leading cause of primary nosocomial bloodstream infections (12). Thrombosis in catheterized veins has been reported to be associated with catheter sepsis (13). About half the number of Klebsiella oxytoca which is isolated in hospitalized patients is considered to be nosocomial in origin (6). Ransjö et al reported seven patients with Klebsiella oxytoca bacteremia associated with the use of invasive blood pressure monitoring equipment (9). The presence of the thrombus, the detection of Klebsiella oxytoca, and the rise of CRP before onset suggest that the catheter was infected in the present case. To detect thrombi, ultrasonography is an adequate method (14). Therefore, ultrasonographic examination should be routinely performed in patients with central venous catheters.

The immediate cause of death in our case was considered to be pulmonary edema, because the edema was severe, and arterial blood gas showed low oxygen pressure and saturation. This edema was presumed to be caused by the bacteremia. Böhm also reported that all 10 patients with Waterhouse-Friderichsen syndrome exhibited pulmonary edema (15). Whether or not our patient had adrenal insufficiency due to adrenal hemorrhages is unclear. However, adrenal insufficiency probably did not influence the cause of death, because there was no response to treatment with steroids. Fox also reported that there was no response to treatment with steroids in 13 cases of Waterhouse-Friderichsen syndrome and there was no correlation between the extent of adrenal hemorrhaging and the clinical state (16). Although septic adrenal hemorrhage is recognized as adrenal insufficiency (3), it should be recognized as one subtype of sepsis.

The physical and laboratory findings of the present patient corresponded to all of the following definitions which were proposed recently: systemic inflammatory response syndrome (SIRS), sepsis (SIRS with infection), and severe sepsis (sepsis associated with organ dysfunction, hypoperfusion or hypotension) (17). The state of septic adrenal hemorrhage with clinical features of Waterhouse-Friderichsen syndrome may be summarized as a subtype of severe sepsis, that is, severe sepsis with adrenal hemorrhage and DIC. Adrenal hemorrhage may be caused in the condition of severe sepsis with DIC. To successfully treat the condition, patients who fit both definitions of SIRS and DIC should be immediately treated as cases of severe sepsis, regardless of the presence or absence of adrenal hemorrhage.

In summary, we examined a case of adrenal hemorrhage due to Klebsiella oxytoca bacteremia associated with a central venous catheter. Any bacterium which causes DIC may cause adrenal hemorrhage. Septic adrenal hemorrhage should be recognized as a subtype of sepsis rather than adrenal insufficiency, and may be caused in the condition of severe sepsis with DIC. The definition of SIRS and DIC may be useful for diagnosis and treatment. Ultrasonographic examination to detect thrombi should be routinely performed in patients with central venous catheters.

References

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