A 40-year-old man with diabetic ketoacidosis showed marked leukocytosis reaching 60,970/mm³ which subsided within 5 days to a level of 4,140/mm³. He had no evidence of infection. During the entire clinical course, no elevation of granulocyte colony-stimulating factor (G-CSF) was observed. No case of leukemoid reaction associated with diabetic ketoacidosis has been reported with the determination of plasma G-CSF levels.

Key words: leukocytosis, diabetes mellitus

Introduction

Diabetic ketoacidosis (DKA) is described as an underlying disease of leukemoid reaction (1), but to the best of our knowledge there is only one report on this association (2). In leukemoid reaction, granulocyte colony-stimulating factor (G-CSF) is claimed to play an important role in increasing the white blood cell (WBC) count (1). However, the actual level of G-CSF has not been reported yet in leukemoid reaction associated with DKA. Here we describe a case of DKA with leukemoid reaction and also report the plasma levels of G-CSF determined in this case.

Case Report

A 40-year-old man was admitted complaining of general fatigue. He had been physically well until age 28, when he suffered from thirst and polyuria with acute onset and was diagnosed as having diabetes mellitus. Since then he has received insulin injections regularly. On October 17, 1992, he played golf from morning until evening, drank a large amount of an alcoholic beverage and came home late at night. The next day he had nausea and vomited food residue several times, probably due to acute gastritis induced by alcohol. He could not eat any food that day and neglected his insulin injection; moreover he could not get in touch with his doctor. On the 19th, his self-monitored blood glucose was 360 mg/dl and he informed his doctor of the situation. His doctor referred him to our department.

On admission, a somnolent, slender man with tachypnea was observed. His pulse rate was 110/min, supine blood pressure 110/80 mmHg, respiration rate 40/min, and body temperature 36.0°C. His height was 170 cm, and body weight 56.2 kg. Jaundice and anemia were not seen in conjunctiva bulbi and palpebrae, respectively. Heart sounds and breath sounds were unremarkable. The abdomen was soft and flat without tenderness. No abnormal neurologic focal sign was observed, and fundoscopic examination showed simple diabetic retinopathy. An electrocardiogram revealed a sinus tachycardia. No abnormal shadow was seen on an X-ray film of the chest.

Laboratory data on admission (Table 1) included sodium 121 mEq/l, potassium 7.2 mEq/l, and chloride 88 mEq/l, BUN 56.6 mg/dl, creatinine 1.7 mg/dl and glucose 381 mg/dl. Arterial blood gas analysis revealed a pH of 6.914 and base excess of -30.2 mmol/l. Urinalysis revealed marked ketonuria, glucosuria and mild proteinuria, but no cells or bacteria were seen on microscopic examination. The initial WBC count was 60,970/mm³ with marked neutrophilia.

Therapy was instituted with intravenous fluids, insulin, electrolyte supplementation, and antibiotics (piperacillin 2 g/day for 2 days). A remarkable response to treatment was observed; the blood glucose and arterial pH were normalized to 120 mg/dl and 7.39, respectively (Fig. 1). On the 5th day, WBC count was normalized to 4,140/mm³. During the entire clinical course, C-reactive protein, a sensitive marker of inflammation, did not increase markedly. Also, plasma G-CSF remained at a

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Table 1. Results of Laboratory Examination

<table>
<thead>
<tr>
<th>Examination Type</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis</td>
<td>pH 5.0, Prot (+), Ketone (3+)</td>
</tr>
<tr>
<td>Hemogram</td>
<td>WBC 60,970/mm³ (Band 5%, Seg 74%, Mono 5%, Lym 13%), Hb 14.5 g/dl, Ht 47.4%, Pt 3.2×10⁵/mm³</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td>TP 6.3 g/dl, Alb 4.2 g/dl, T-Bil 0.7 mg/dl, GOT 34 IU/l, GPT 9 IU/l, ALP 162 IU/l, Ch-E 1.12 ApH, γ-GTP 15 IU/l, Amylase 165 IU/l, T-Chol 223 mg/dl, Trigly 97.5 mmol/l, HCO₃⁻ 2.3 mmol/l, BE -30.2 mmol/l</td>
</tr>
<tr>
<td>Arterial blood gas</td>
<td>pH 6.914, PCO₂ 1 1.5 mmHg, PO₂ 1 17.5 mmHg, HCO₃⁻ 2.3 mmol/l, BE -30.2 mmol/l</td>
</tr>
<tr>
<td>Myelogram</td>
<td>NCC 56,000/mm³, MgK 78/mm³, abnormal cell (-)</td>
</tr>
</tbody>
</table>

Differential count of WBC was performed microscopically by a technician.

Fig. 1. Clinical course of the first 20 hours. BG: blood glucose, 5% G: 5% glucose solution, As-K: 1-aspartate potassium infused at a rate of 5 mEq/hr as potassium.

Table 2. Changes in Cardinal Markers of Clinical Course

<table>
<thead>
<tr>
<th>Day</th>
<th>WBC (10⁹/mm³)</th>
<th>Neut (%)</th>
<th>Lymph (%)</th>
<th>Mono (%)</th>
<th>Eos (%)</th>
<th>Bas (%)</th>
<th>LUC (%)</th>
<th>Blood glucose (mg/dl)</th>
<th>Insulin dosage (U/day)</th>
<th>CRP (mg/dl)</th>
<th>G-CSF (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day</td>
<td>60,970</td>
<td>85.3</td>
<td>7.9</td>
<td>5.3</td>
<td>0.1</td>
<td>1.0</td>
<td>0.5</td>
<td>831→143</td>
<td>80</td>
<td>0.3</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>2nd day</td>
<td>23,770</td>
<td>92.0</td>
<td>3.0</td>
<td>4.3</td>
<td>0.0</td>
<td>0.2</td>
<td>0.5</td>
<td>127→216</td>
<td>48</td>
<td>1.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>3rd day</td>
<td>9,180</td>
<td>71.9</td>
<td>20.3</td>
<td>6.4</td>
<td>0.2</td>
<td>0.3</td>
<td>0.9</td>
<td>108→271</td>
<td>46</td>
<td>0.0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>4th day</td>
<td>4,140</td>
<td>55.3</td>
<td>35.1</td>
<td>5.6</td>
<td>1.1</td>
<td>1.0</td>
<td>1.8</td>
<td>151→268</td>
<td>48 (U/day)</td>
<td>0.0</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

Differential count of WBC was performed mechanically by means of Technicon H₂ system (Nippon Technicon, Ltd., Tokyo, Japan). G-CSF was determined in the laboratory of Kirin Brewery Co., Ltd. (Tokyo, Japan), and the detection limit of the substance was 39 pg/ml (6). LUC, large unstained cell with negative peroxidase response.

low level (Table 2). On the 10th hospital day, bone marrow puncture was performed, and the myelogram showed no evidence of leukemia. On the 20th hospital day, the patient was discharged with good glycemic control.

Discussion

In the present case, blast cells were not seen in the peripheral blood specimen nor in bone marrow. These findings rule out leukemia completely. Generally, leukocytosis over 25,000 to 30,000/mm³ without leukemia is called leukemoid reaction (1). Basically, dehydration in DKA promotes leukocytosis, but the WBC count in the present case cannot be explained by dehydration alone.

Various diseases and conditions can induce leukemoid reaction. Among them, infection is one of the most frequent causes. Infection is also an important precipitating factor for DKA. It is possible that infection might have induced both DKA and leukemoid reaction in the present case. However, markers of inflammation remained at a low level, and no evidence of infection was seen during the course. Therefore, we conclude that infection was not the cause of DKA.

G-CSF is one of the main granulopoietic factors (3, 4). Its production is believed to be augmented in conditions with inflammation or stress, and this substance increases the size of the peripheral blood and extravascular pools and may lead to leukemoid reaction (1). DKA is clearly a very stressful situation. In the present case, however, we could not detect any elevation of plasma G-CSF.

Therefore, a probable mechanism of induction of leukemoid reaction may be demargination from a vascular wall – a shift of neutrophils from the marginated to the circulating pool (1, 4). This response is rapid and can be induced by epinephrine, which is usually elevated in DKA. Secondly, neutrophils may have been released from the storage pool in marrow into the circulating pool in response to endogenous glucocorticoids (1, 4).

It is also possible that G-CSF may have increased only in the very early phase of the disorder. Its half-life is reported to be very short (1), and that may be why we could not detect an elevation of G-CSF levels. Also, commitment of granulocyte-macrophage colony-stimulating factor (GM-CSF) and other cytokines cannot be ruled out (5), which were not measured in the present case.

In conclusion, our report presents a case of leukemoid reaction associated with DKA. This is the second such report in the English-language literature, and may be the first to describe the actual plasma levels of G-CSF in this condition.

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References

Leukemoid Reaction with DKA