We report a fatal case of alcoholic hepatitis with hyperleukocytosis mainly consisting of mature granulocytes in a 43-year-old woman. White blood cell count was increased in parallel with clinical deterioration to 54,800/mm³ with no immature neutrophils on a differential count. The bone marrow aspirate revealed normal maturation and no evidence of hematological malignancy. It has been postulated that severe leukocytosis accompanied by alcoholic hepatitis may be provoked by release of high levels of colony stimulating factor from damaged hepatic cells. However, the present patient showed a normal level of serum granulocyte colony stimulating factor, and could not prove the above assumption.

Key words: Colony stimulating factor, Granulocyte colony stimulating factor, Leukemoid reaction

Severe leukocytosis with a white blood cell (WBC) count of greater than $5 \times 10^9$/mm³ is rarely seen in alcoholic hepatitis (1–6). The pathogenesis of this complication is obscure. Wallach and Jacobs have supposed that a release of high levels of colony stimulating factor (CSF) may cause severe leukocytosis in alcoholic hepatitis (1). However, we could find no reports concerning the actual CSF level in alcoholic hepatitis accompanied by leukocytosis. This paper presents a fatal case of alcoholic hepatitis with hyperleukocytosis mainly consisting of mature granulocytes, in a female, in which serum granulocyte CSF (G-CSF) levels were analyzed.

CASE REPORT

A 43-year-old woman was admitted to the hospital on January 5, 1987, with jaundice, abdominal distention, and disturbance of consciousness. The patient had been an alcoholic for about 20 yr, with an average daily consumption of greater than 140 g of ethanol. One year and six months prior to this admission, she came to the hospital because of bilateral finger numbness. At that time, a diagnosis of alcoholic polyneuritis was made and alcoholic liver disorder was confirmed. The patient had a glutamic-oxaloacetic transaminase (GOT) level of 286 IU/l, glutamic-pyruvic transaminase (GPT) 323 IU/l, $\gamma$-glutamyl transpeptidase ($\gamma$-GTP) 462 IU/l, and white blood cell (WBC) count 8,600/mm³. Six months before being admitted she came to the hospital because of abdominal distention. Alcoholic liver disorder was pointed out again: GOT 615 IU/l, GPT 240 IU/l, $\gamma$-GTP 2,410 IU/l, and WBC count 8,100/mm³. The patient had been drinking heavily the 2 wk prior to admission.

On admission, she was suffering from severe jaundice. Her temperature was 38.0°C and pulse 104/min. Blood pressure was 168/60 mmHg. The patient was found to have disorientation showing hepatic encephalopathy. There were no abnormal findings in the heart or lungs. The abdomen was distended and a positive fluid wave was present. The liver was palpable 6 finger-breadths below the right costal margin. The spleen could not be palpated.
Laboratory findings on admission were as follows: hemoglobin 10.9 g/dl; hematocrit 29.8%; red blood cell count $245 \times 10^4$/$\text{mm}^3$; WBC count 11,800/$\text{mm}^3$ with a differential count of 5% band neutrophils, 80% segmented neutrophils, 9% lymphocytes, and 6% monocytes; platelet count 118,000/$\text{mm}^3$; total bilirubin 19.5 mg/dl; direct bilirubin 15.5 mg/dl; GOT 225 IU/l; GPT 68 IU/l; lactate dehydrogenase 338 IU/l; $\gamma$-GTP 775 IU/l; alkaline phosphatase 431 IU/l; cholinesterase 0.48 $\Delta\text{pH}$; blood urea nitrogen 5 mg/dl; creatinine 0.6 mg/dl; thrombo test 24.0%; heparplastin test 46.0%; prothrombin percentage activity 23.1%; hepatitis B surface antigen negative; hepatitis B surface antibody positive at a titer of 1:1280.

By the 17th hospital day the consciousness disturbance was slightly alleviated. However, jaundice and leukocytosis increased gradually (Fig. 1).

![Graph showing laboratory findings over time.](image)
Finally, total bilirubin reached 56.5 mg/dl and WBC count reached 54,800/mm$^3$ with a differential count of 8% band neutrophils, 85% segmented neutrophils, 5% lymphocytes, and 2% monocytes (Fig. 1). Immature neutrophils were absent from the blood at all measurement points. In the bone marrow aspirate on the 25th day, the nucleated cell count was $157 \times 10^3$/mm$^3$ with a differential cell count of 1.5% myeloblasts, 3.5% promyelocytes, 0.5% eosinophilic myelocytes, 12.5% neutrophilic myelocytes, 7.5% metamyelocytes, 8.5% band cells, 1.0% segmented eosinophils, 40.5% segmented neutrophils, 13.0% lymphocytes, 1.0% monocytes, 0.5% plasma cells, 1.0% polychromatophilic erythroblasts, and 7.0% orthochromatic erythroblasts. The myeloid/erythroid ratio was 9.4:1. Neutrophil alkaline phosphatase (NAP) score was 378 points (N 240–320 points). Cultures of blood, sputum, and urine were sterile. There was no sign of hemorrhage. Abdominal ultrasonography on the 24th day revealed no abnormal findings except for hepatosplenomegaly and ascites. On the 26th day the consciousness disturbance began to worsen, and on the 30th day, the patient lapsed into hepatic coma, and her urine output decreased. She died of hepatic and renal failure on the 32nd hospital day. During the hospital course, no drugs which may induce leukocytosis, e.g. steroid hormones or adrenergic agents, were administered.

Microscopic examination of a liver necropsy specimen revealed widespread hepatocellular necrosis, pericellular fibrosis, and bile plugs. The formation of Mallory bodies and the infiltration of polymorphonuclear leukocytes were observed.

G-CSF levels of the serum samples obtained on admission and on the 29th day were analyzed with an enzyme immunoassay (7). The level of both samples was less than 60 pg/ml (N < 60 pg/ml).

**DISCUSSION**

A striking feature of this case is the presence of marked leukocytosis with a WBC count of greater than $5 \times 10^4$/mm$^3$. Such a case is thought to be rare (6), although mild leukocytosis is one of the clinical characteristics of alcoholic hepatitis (8).

Throughout the course of this patient, all differential counts indicated segmented neutrophils of over 80% and no immature neutrophils. A similar pattern has been demonstrated in cases which showed what were called “leukemoid reactions” accompanied by alcoholic hepatitis (1–5). However, when the WBC count is extremely high but immature forms are absent from the blood, the term “hyperleukocytosis” is preferable to “leukemoid reaction” (9).

As in those reactions, the diagnosis of leukemia must be considered (1). In the case cited above, hematological malignancy was excluded by the normocellular bone marrow aspirate and the elevated NAP score. There was no evidence of infection, solid tumor, or other diseases as causes of hyperleukocytosis. A drug-induced phenomenon could not explain this complication either. The cause of hyperleukocytosis with alcoholic hepatitis has not been demonstrated clearly. However, we suppose that this complication can be provoked by a factor peculiar to alcoholic hepatitis, because viral hepatitis does not show leukocytosis or hyperleukocytosis in spite of the degree of histological damage comparable to that in alcoholic hepatitis (1).

The characteristic histopathological features of alcoholic hepatitis include hyaline degeneration of hepatic parenchymal cells (Mallory bodies) and polymorphonuclear leukocyte infiltration of the liver (8). This infiltration, which is induced by chemotactic function of Mallory bodies, is in striking contrast to the inflammatory infiltration seen in viral hepatitis in which mononuclear cells are predominant (8). Though there has been no report to refer to the pathogenesis of hyperleukocytosis in conjunction with the polymorphonuclear leukocyte infiltration, it is probable that the damaged liver in alcoholic hepatitis produces a factor to stimulate granulopoiesis concurrently with a factor to induce polymorphonuclear leukocyte infiltration. Hyperleukocytosis may appear when the damaged liver produced factor is excessively produced or when the granulopoietic response is extremely sensitive to it. Wallach and Jacobs suggested CSF to be the granulopoietic factor concerned with hyperleukocytosis in alcoholic hepatitis (1). With regard to hyperleukocytosis with nonhematologic malignant diseases, it has been proved that this complication is due to CSF produced by tumor cells (10). However, we could find no reports concerning the estimation of CSF production in alcoholic hepatitis.
The CSF family, a heterogeneous group of glycoproteins, is classified with different hemopoietic effects (11). Among the family, G-CSF and granulocyte macrophage CSF (GM-CSF) preferentially stimulate the formation of neutrophils (11). What differs between them is the fact that GM-CSF induces the increase of eosinophils or monocytes along with neutrophils (11). Hyperleukocytosis in the above cited case consisted of the increase of mature neutrophils without increases of other types of leukocytes. The same was demonstrated in cases which showed extremely severe leukocytosis accompanied by alcoholic hepatitis (1–6). Thus, if the CSF family is involved in the mechanism of hyperleukocytosis accompanied by alcoholic hepatitis, G-CSF could be thought to be the most probable factor. However, serum G-CSF levels in the present case were not higher than normal. That can be possibly interpreted as follows. Firstly, serum G-CSF levels in this case, which were estimated only by an enzyme immunoassay, might not reflect the increased G-CSF production induced by the damaged liver. Although we could not find an opportunity, it would be necessary to analyze that activity by a bioassay method which estimates colony counts using bone marrow cells (12), along with an enzyme immunoassay. The bioassay method reveals the exact nature of the biological activity despite having defects on specificity and sensitivity (13). Secondly, this hyperleukocytosis might be induced by another granulopoietic factor, e.g. GM-CSF. Unfortunately, factors other than G-CSF could not be estimated in this case.

In summary, we reported a case of alcoholic hepatitis with hyperleukocytosis. We supposed that a granulopoietic factor, possibly G-CSF, might have been involved in the pathogenesis of this complication. However, we could not prove that assumption. Further studies are needed in order to elucidate the mechanism of hyperleukocytosis caused by alcoholic hepatitis.

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