Case Report

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Therapeutic Efficacy of Leukocytapheresis for Procoagulant Microparticles during Hemophagocytic Syndrome

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Key Words
Hemophagocytic syndrome \cdot Cytokine \cdot Chemokine \cdot Monocyte-derived microparticles \cdot Lymphocytapheresis

Abstract
Hemophagocytic syndrome (HPS) presents with signs of persistent remittent fever, hepatosplenomegaly, pancytopenia, hepatic dysfunction, and disseminated intravascular coagulation (DIC) because of hypercytokinemia caused by activated T lymphocytes and macrophages. In recent years leukocytapheresis using a leukocyte removal filter (known as lymphocytapheresis, LCAP) has been applied to the treatment of various autoimmune diseases. The removal of activated monocytes during LCAP treatment appears useful for hypercytokinemia. We experienced a 32-year-old Japanese man with HPS with elevated tissue factor-enriched monocyte-derived microparticles (MDMPs) and pro-inflammatory cytokines/chemokines. Improvements in the level of MDMPs and hypercytokinemia were observed after LCAP treatment. LCAP treatment performed for HPS can be considered a therapeutic strategy for patients with a risk of fetal hemorrhage.

Introduction
Hemophagocytic syndrome (HPS) presents with signs of persistent remittent fever, hepatosplenomegaly, pancytopenia, hepatic dysfunction, and disseminated intravascular coagulation (DIC) because of hypercytokinemia caused by activated T lymphocytes and macrophages [1]. The mortality of HPS in adults is high. In particular, thrombocytopenia is often life-threatening because of a bleeding tendency [2]. On the other hand, HPS can possibly cause thrombotic abnormalities such as veno-occlusive disease [3] or thrombotic thrombocytopenic purpura [4]. The pathogenesis of HPS involves the excessive activation of monocytes/macrophages and the generation of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-\(\alpha\) and interleukin (IL)-6 [5]. As well, activated monocytes/macrophages generate the tissue factor-enriched monocyte-derived microparticles (MDMPs) [6]. Thus, activated monocytes/macrophages have an important role in the pathogenesis of HPS. In recent years leukocytapheresis using a leukocyte removal filter (known as lymphocytapheresis, LCAP) has been applied to the treatment of various autoimmune diseases [7]. The removal of activated monocytes...
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During LCAP treatment appears useful for hypercytokinemia [8]. In the present report, we describe a patient with HPS with elevated MDMPs and pro-inflammatory cytokines/chemokines. Improvements in the level of MDMPs and hypercytokinemia were observed after LCAP treatment.

Case Report

A 32-year-old Japanese man was admitted to Kishiwada City Hospital exhibiting chills and fever. Five days before admission he had a fever and loss of appetite. On admission, his temperature was 38.5, pulse rate 84 beats/min, respiratory rate 20 breaths/min, and blood pressure 104/68 mm Hg. Mild hepatosplenomegaly was noted, but there was no lymphadenopathy. Both lower extremities were slightly edematous. Laboratory findings were as follows: the WBC count was 5,110/µl with 54.7% neutrophils, 23.0% lymphocytes, and 15.1% monocytes.

Fig. 1. Photomicrograph of a specimen from bone marrow aspiration demonstrating hemophagocytosis by macrophage. May-Giemsa. ×400.

Fig. 2. Clinical course. Note the high serum concentrations of CRP, AST, ALT, LDH, ferritin, sIL-2R, and the reference values of cytokines and MDMP. SP = Steroid pulse therapy; LCAP = lymphocytapheresis.
cytes and 34.0% monocytes; the RBC count was 431 × 10^6/μl, the hemoglobin level was 12.4 g/dl, the platelet count was 58 × 10^9/μl. The prothrombin time ratio and activated partial thromboplastin time were 14.1 and 43.6 s, respectively. Blood chemistry showed total bilirubin 0.9 mg/dl, aspartate aminotransferase (AST) 183 IU/l, alanine aminotransferase (ALT) 311 IU/l, lactate dehydrogenase (LDH) 547 IU/l, alkaline phosphatase 495 IU/l, creatine phosphokinase 12 mU/ml, blood urea nitrogen 16 mg/dl, creatinine 1.07 mg/dl and ferritin 1,344 ng/ml. Serologic tests revealed EB virus CAIgM 1.6 (+), EB EBNAIgG 1.7 (+), and soluble IL-2 receptor (sIL-2R) 12,600 IU/l. We performed a bone marrow aspiration. The result of the bone marrow specimen showed an increased number of macrophages with intensive thrombocytosis (fig. 1).

The patient was diagnosed with HPS. Methylprednisolone at 1,000 mg/day was thus administered intravenously for 3 days. One week after admission, the patient’s clinical symptoms improved. However, after 2 weeks a high fever appeared and laboratory data deteriorated. Therefore, we started LCAP treatment using a column (Cellsorba E, Asahi Kasei Medical) filled with a nonwoven fabric made up of polyester fibers. With LCAP, peripheral blood is passed extracorporeally through a removal column that absorbs leukocytes while the remaining blood is returned to the patient through an intravenous line. The Cellsorba contains nonwoven polyester fibers that remove granulocytes and monocytes, lymphocytes, and some platelets. Peripheral blood samples to measure cytokines/chemokines and soluble markers were collected before and after LCAP treatment. The removal rate of peripheral blood monocytes and lymphocytes during LCAP were 62.9 and 34.1%, respectively. As shown in figure 2, the serum level of CRP, a marker of inflammation, decreased after LCAP treatment. As well, the blood levels of IL-6, IL-8, and TNF-α, pro-inflammatory cytokines, were also remarkably decreased following LCAP treatment. Monocyte chemotactic protein-1 (MCP-1), epithelial cell-derived neutrophil-activating protein-78 (ENA-78), and soluble vascular cell adhesion molecule-1 (sVCAM-1) showed high levels before LCAP treatment but exhibited a decreasing tendency after LCAP treatment, while RANTES, sP-selectin, and sE-selectin levels were not increased before treatment. On the other hand, soluble CD14 (sCD14) and MDMPs had high levels before LCAP treatment and exhibited a decreasing tendency after treatment.

Discussion

We examined the concentration of cytokines, chemokines, soluble factors, and MDMPs using serum or plasma samples obtained before and after LCAP treatment. Monocyte activation markers such as sCD14 and MDMPs were remarkably improved after LCAP treatment, along with pro-inflammatory cytokines/chemokines. LCAP treatment is considered to exert its effects against inflammatory diseases by influencing the cytokine balance through adsorption and removal of activated leukocytes, and causing functional changes of inflammatory cells [8]. In particular, Kanai et al. [7] reported that the real target of pro-inflammatory monocytes was removed during LCAP treatment of ulcerative colitis. The present study produced the same results as these previous reports. Although the pathogenic mechanism of HPS has not been elucidated, several reports show that serum concentrations of certain cytokines are elevated in HPS and that cytokinemia is associated with the pathogenesis and prognosis of HPS [1, 9, 10]. Among peripheral blood monocytes from HPS patients, CD14 (+)/CD16 (bright) cells were increased and the expansion of these monocytes could serve as indicators of the inflammatory state in HPS [11]. The clinical features of patients with HPS also include coagulopathy, possibly related to the monocyte-derived tissue factor. The tissue factor exposing MDMPs promotes the assembly of the prothrombinase complex, thereby facilitating intravascular generation of thrombin and enhanced procoagulant activity [6]. Therefore, MDMPs could cause coagulopathy in HPS. In the present case, MDMPs were at high levels before LCAP treatment and exhibited a declining tendency after LCAP treatment. Although the efficacy of therapeutic plasmapheresis for treatment of fatal HPS has been reported, some patients died of hemorrhage resulting from DIC [12]. LCAP treatment performed for HPS can be considered a therapeutic strategy for patients with a risk of fatal hemorrhage.

References


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