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LETTERS TO THE EDITOR

Characterization of Peripheral Natural Killer Cells and their Reduction in Drug-induced Hypersensitivity Syndrome

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Drug-induced hypersensitivity syndrome (DIHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS), is a severe adverse systemic reaction that usually occurs several weeks after exposure to certain drugs such as anticonvulsants (1). DIHS is characterized by multiorgan involvement, high fever, hypogammaglobulinemia, and sequential reactivation of various latent herpesviruses, such as human herpesvirus (HHV)-6, HHV-7, cytomegalovirus, and Epstein-Barr virus (EBV) (1). In addition to low numbers of circulating B cells and plasmacytoid dendritic cells (2), a decrease in the number of circulating natural killer (NK) cells is typically observed in DIHS (3). In human peripheral blood, 5 NK-cell subpopulations are defined on the basis of the relative expression of the markers CD16 and CD56 (4). It remains unknown, however, which NK subset predominantly decreases in the course of DIHS. In this study, we investigated the alteration of each subset of NK cells to address the pathomechanical relevance of NK-cell reduction to the development of DIHS.

MATERIALS AND METHODS

The DIHS diagnosis of 4 patients enrolled in this study (2 males and 2 females: ages of males, 33 and 62; ages of females, 49 and 67; mean age (mean ± SD), 52.8 ± 15.2 years, range 33–67) was confirmed according to the criteria proposed by a Japanese consensus group (1). All 4 patients showed fever, leucocytosis, eosinophilia, and liver dysfunction. The culprit drugs in these cases were phenobarbital (one case) and carbamazepine (three cases). In all cases, HHV-6 reactivation had been serologically confirmed. After diagnosis was made, the causative drugs were withdrawn, and treatment with prednisolone (0.5–1 mg/kg daily) was initiated. As controls, 8 age- and sex-matched healthy donors and 8 patients with generalized maculopapular drug eruption (MPE) were enrolled. After informed consent was obtained, peripheral blood mononuclear cells (PBMCs) were collected from the subjects at the first visit and at the peak of illness, as reported previously (5). PBMCs were stained with anti-CD16 and anti-CD56 antibodies. CD56 expression versus CD16 expression was evaluated.

RESULTS

The 5 NK-cell subpopulations (subsets 1–5) were detected with the expression levels of CD16 and CD56 (Fig. 1) as described previously (4). The absolute number of each population is shown in Fig. 2. Patients with DIHS had low numbers and percentages (data not shown) of circulating $CD56^{dim}CD16^{bright}$ NK cells (subset 4, the largest population of the five), especially at the peak of illness when compared to healthy subjects. In contrast, patients with MPE did not exhibit decreased levels of subset 4 (Fig. 2). Since the MPE patients were treated with 0.5–1 mg/kg prednisolone, the decrease of the NK-cell subset in DIHS could not be attributable to prednisolone. Among subset 4, the $CD56^{dim}CD16^{bright}$ $CD94^{+}$ NK cells was significantly lower in DIHS at the peak of illness (5.0 ± 3.9%) than in healthy controls (14.8 ± 5.4%). Also, the absolute number of this subpopulation of subset 4 was lower in DIHS than in healthy controls (data not shown). In general, the cytotoxic activity of $CD56^{dim}$ NK cells is higher than that of $CD56^{bright}$ cells (6). It is therefore likely that the paucity of circulating $CD56^{dim}CD16^{bright}$ NK cells results in the reduced antiviral activity in patients with DIHS.

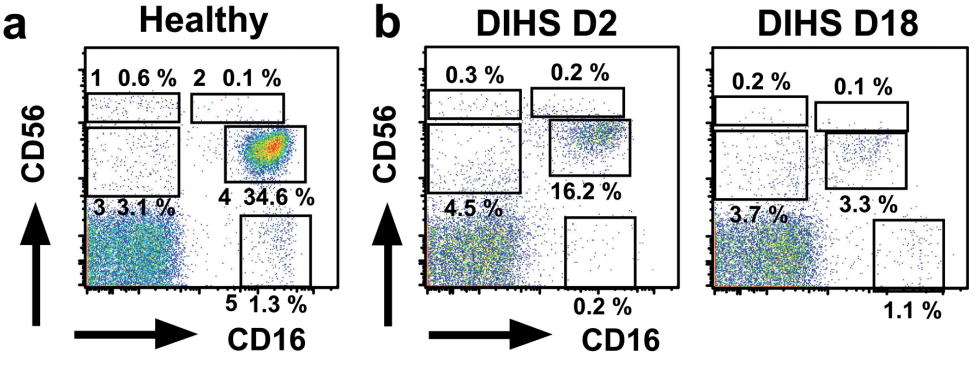

Fig. 1. The percentages of natural killer cell subsets in peripheral blood mononuclear cells (PBMCs) of patients with drug-induced hypersensitivity syndrome (DIHS), generalized maculopapular drug eruption (MPE), and in healthy controls. (a and b) Fluorescence-activated cell sorting plots of PBMCs in a healthy donor and a representative patient with DIHS 2 and 18 days after the onset, respectively.

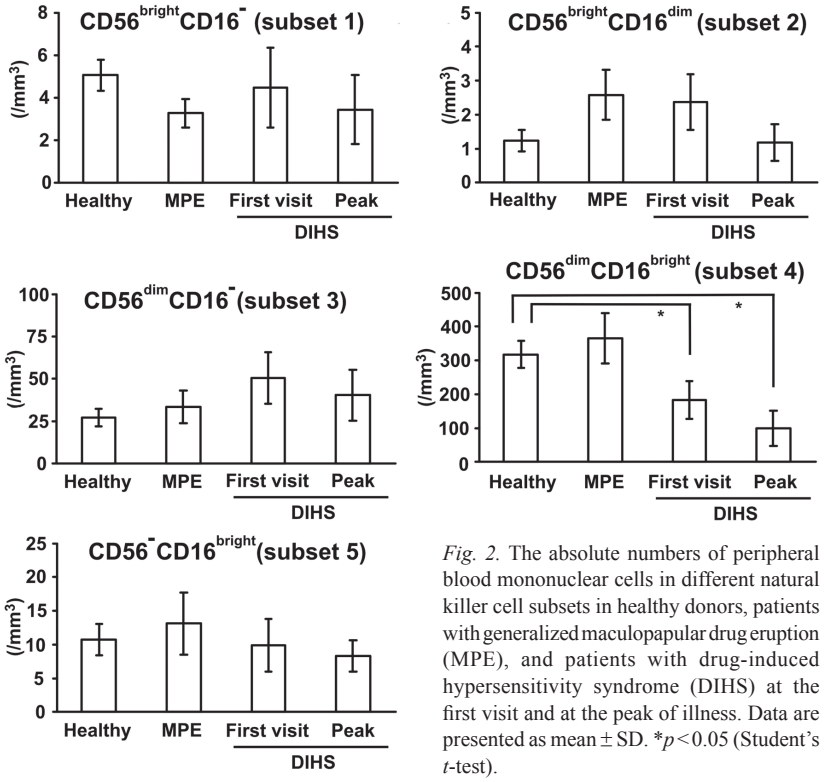

Fig. 2. The absolute numbers of peripheral blood mononuclear cells in different natural killer cell subsets in healthy donors, patients with generalized maculopapular drug eruption (MPE), and patients with drug-induced hypersensitivity syndrome (DIHS) at the first visit and at the peak of illness. Data are presented as mean ± SD. *$p < 0.05$ (Student's *t*-test).

DISCUSSION

It has been shown that the number of circulating NK cells is decreased in patients with atopic dermatitis and psoriasis (7). Accumulation of NK cells to local tissues such as skin from circulation may account for the decreased number of NK cells in these diseases. We obtained skin biopsy specimens from patients with DIHS and MPE and healthy donors, and $CD56^+$ cells in the skin were only rarely detected in all subjects and there was no obvious difference among the groups. In addition, impaired NK-cell activity and low NK-cell number have been reported in patients with autoimmune diseases (8). Significantly increased levels of IL-18 and TNF-α in sera from patients with primary Sjögren's syndrome may contribute to NK-cell reduction (8). Since the elevation of TNF-α precedes HHV-6 reactivation in DIHS (9), these cytokines may also contribute to the reduction of NK cells in patients with DIHS.

The authors declare no conflict of interest.

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