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CASE STUDY

Possible activation of effector B cells during drug-induced hypersensitivity syndrome

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Abstract

Although the development of autoimmune disorders is recognized in drug-induced hypersensitivity syndrome (DIHS), the serial change of B-cell activity has not been well-addressed. Herein, the serum levels of IL-6, IL-10, B-cell activating factor of the tumor necrosis factor family (BAFF), and a proliferation-inducing ligand (APRIL) in three DIHS patients were tracked over time. While IL-6 and IL-10 tended to be elevated according to the disease activity, BAFF and APRIL increased during the improved phase. Our results imply that the continuous activation of B cells may be involved in the prolonged disease activity of DIHS and the development of autoimmune disorders.

KEYWORDS
APRIL, B cells, BAFF, cytokines, drug-induced hypersensitivity syndrome

1 | INTRODUCTION

Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and systemic symptoms is associated with the development of autoimmune responses such as Hashimoto's disease and systemic lupus erythematosus in the resolution stage.[1] Though the development of autoimmune responses is ascribed to the protracted loss of regulatory T cells[2,3] after their increase at the disease onset,[4] the serial change of B-cell activity has not been well-addressed except for the reduced number of circulating B cells[5] and hypogammaglobulinemia[6] in the acute phase. The effect of DIHS on the already existing autoimmune disorders has not been investigated, either.

The secretion of cytokines interleukin (IL)-6 and IL-10 reflects the effector and regulatory function of immune cells including B cells, respectively.[7,8] In addition, B-cell activating factor of the tumor necrosis factor family (BAFF) and a proliferation-inducing ligand (APRIL) are regarded to regulate the activation and differentiation of B cells through the B-cell-specific receptors for these molecules.[9,10]

Herein, the serum levels of IL-6, IL-10, BAFF, and APRIL of three DIHS patients were tracked over time and compared with those from five controls. Our results suggest the sustained activation of effector B cells during the disease course of DIHS.

2 | CASE STUDY

The serum samples were collected from three DIHS patients at the time of disease onset, improved phase, recurrence, and the improved phase after the first recurrence. The patients satisfied the criteria of either typical or atypical DIHS[3] as summarized in Table 1. They experienced the recurrence of skin lesion at least once. The serum samples from five patients who underwent the resection of

TABLE 1 Patient information at the time of disease onset

Age	Gender	Causative drug	Latency period (day)	Fever	Lymphadenopathy	WBC (/μl)	Eos (/μl)	Atypical lymph (/μl)	ALT (U/L)	Serum IgG (mg/dl)	Viral reaction
33	F	Diaminodiphenyl sulfone	22	+	+	16,000	160	1200	212	1148	HHV-6
52	F	Mexiletine	60	+	+	16,100	3784	0	63	731	CMV
77	F	Mexiletine	25	+	+	26,400	9240	924	33	1074	HHV-6

cutaneous benign tumors were also collected at the time of preoperation screening and were regarded as healthy controls (1 male and 4 females, 58.8 ± 18.8 years old). The serum levels of IL-6 and IL-10 were measured by use of the BD Cytometric Beads Array Human Th1/Th2/Th17 Cytokine Kit (BD Biosciences) according to the manufacturer's protocol. Gallios Flow Cytometer (Beckman Coulter) was used for the analysis. The serum levels of BAFF and APRIL were measured by use of the ELISA kits for human BAFF (R&D Systems) and APRIL (Biogems International), respectively, according to the manufacturers' protocols. Mann-Whitney tests were performed for the comparison between two groups using the GraphPad Prism software. $p < .05$ was considered as significant.

This study was performed on human samples. All the protocols in this study were performed in accordance with the Declaration of Helsinki and are approved by the Institutional Review Board of ethical committee in University of Tsukuba Hospital (approval number: H28-1). Written consent forms were obtained from all the participants.

The serum levels of IL-6 and IL-10 were significantly elevated in the DIHS patients than in controls at the time of disease onset (Figure 1A, IL-6: 39.14 ± 15.49 pg/ml in DIHS vs 12.46 ± 2.63 pg/ml in controls, $p = .0357$; IL-10: 26.13 ± 8.34 pg/ml in DIHS vs 11.33 ± 0.71 pg/ml in controls, $p = .0357$). The serum levels of BAFF were also higher in the DIHS patients than in controls while APRIL levels were comparable (Figure 1A, BAFF: 3.87 ± 0.30 ng/ml in DIHS vs 2.13 ± 0.89 ng/ml in controls, $p = .0357$; APRIL: 13.36 ± 8.52 ng/ml in DIHS vs 7.97 ± 2.39 ng/ml in controls, $p = .5714$). In DIHS patients, IL-6 tended to be high at the time of disease onset and recurrence, and also maintained the levels higher than the average of controls at the improved phases (Figure 1B). While IL-10 also elevated according to the disease activity of DIHS, it declined more obviously at the improved phases compared with IL-6 (Figure 1B). On the contrary, the serum levels of both BAFF and APRIL increased during the improved phases of DIHS (Figure 1B).

The patient 1 had a disease history of pemphigus foliaceus (PF) and developed DIHS during the treatment with diaminodiphenyl sulfone as we reported previously.[11] The existing PF became unruly during the treatment of DIHS with strong immunosuppressive medications in this case, and the titer of anti-desmoglein 1 antibody (aDSG1ab) turned out to be dramatically increased following the elevation of BAFF and APRIL (Figure 1C), possibly in line with the decrease of IL-10.

These results suggest that the continuous activation of effector B cells occurs throughout the disease course of DIHS, especially during the improved phases.

3 | DISCUSSION

IL-6, IL-10, and their receptors are expressed in various immune cells including B cells and T cells. IL-6 signaling is required for the differentiation of B cells and the production of antibodies.[12,13] IL-10 is a regulatory cytokine which diminishes the inflammatory reactions of immune cells.[14] The functional mechanism of regulatory T cells and

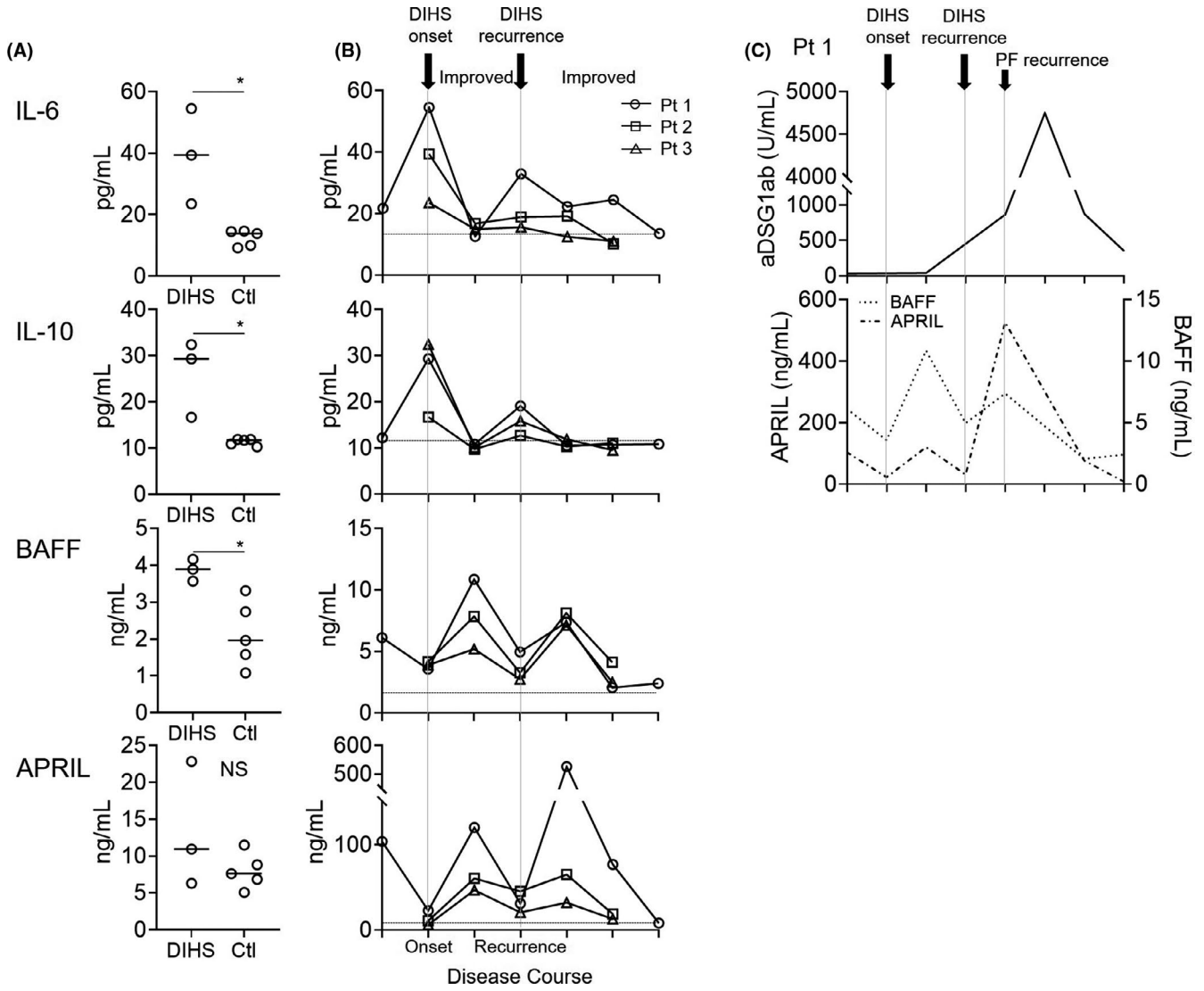

FIGURE 1 (A) The serum levels of IL-6, IL-10, BAFF, and APRIL in the three DIHS patients and five controls. *$p < .05$. (B) The serial changes of serum IL-6, IL-10, BAFF, and APRIL levels in the DIHS patients (Pt 1-3). The timepoints of DIHS onset and recurrence are indicated by the black arrows. All the three patients experienced the recurrence of skin lesions at least once. The dotted line in each graph indicates the average value in the five controls as in figure A. (C) In the Pt 1, who had PF before the onset of DIHS, the serial change of aDSG1ab was compared with the serum levels of BAFF and APRIL. The timepoints of DIHS onset, recurrence, and PF recurrence are indicated by black arrows. The onset and recurrence are defined by the skin manifestation

regulatory B cells is generally regarded to include the secretion of IL-10.[15,16] In our experiments, both proinflammatory IL-6 and anti-inflammatory IL-10 were increased in the serum of DIHS patients at the time of disease onset and recurrence, in consistent with the previous reports demonstrating the elevation of IL-6 and IL-10 according to the viral reactivation.[17] While the serum IL-6 levels of the DIHS patients tended to be higher than the average of those from controls during the improved phases in our cases, IL-10 declined to the levels below the average of controls at the time of remission. These results suggest the continuous proinflammatory tendency of DIHS throughout the disease course even during the remission.

The serum levels of BAFF and APRIL increased during the improved phases of the DIHS patients. The ligands of BAFF and APRIL are expressed mainly in B cells.[18] BAFF is regarded to regulate the survival and differentiation of B cells,[19] and APRIL induces class switch and survival of plasma cells.[20] Development of the symptoms mimicking systemic lupus erythematosus (SLE) is reported in the BAFF transgenic mice,[21] and the blockade of BAFF/APRIL prevents the autoimmune symptoms.[22,23] The patient 1 in our case experienced the increase of aDSG1ab after the elevation of serum BAFF and APRIL levels during the improved phase. It is thus implied that the increase of BAFF and APRIL during the improved phase of DIHS would lead to the further activation of effector B cells and the up-regulation of plasma cells. Though the sources of these molecules could not be defined in this study, it is also possible that the reduced IL-10 during the improved phase contributes to the elevation of BAFF and APRIL. Further analyses including the direct investigation of each immune cell would be required.

Our results imply that the activation of effector B cells may be involved in the prolonged disease activity of DIHS, the development of immune-mediated disorders in the resolved phase, and the exacerbation of the already existing immune-mediated disorders. The long-term careful follow-up would be required in the treatment of DIHS.

DECLARATION SECTION

Approval of the research protocol: This study was performed on human samples. All the protocols in this study were performed in accordance with the Declaration of Helsinki and are approved by the Institutional Review Board of ethical committee in University of Tsukuba Hospital (approval number: H28-1).

Informed Consent: Written consent forms were obtained from all the participants.

Registry and the Registration No.: N/A.

Animal Studies: N/A.

CONFLICT OF INTEREST

The senior author Manabu Fujimoto is the Editor-in-Chief of the Journal of Cutaneous Immunology and Allergy. Management of the peer review process, and all editorial decision-making, for this article was undertaken by Associate Editor.

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