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Altered T cell Immunity in Patients with Posner-Schlossmann Syndrome

최진아, 노승준, 백수영, 박찬기

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Purpose: Herpes viruses have become increasingly recognized in Posner-Schlossmann syndrome (PSS). It is hypothesized that PSS is associated with immunological changes to antigenic stimulation. We investigated the changes in T cell immunity in patients with PSS.

Methods: In this prospective cross-sectional study, peripheral blood samples were obtained at the hypertensive phase with aqueous inflammation in study patients (n = 15), and during cataract surgery in controls (n = 11) from March 2014 to February 2015. All patients underwent a serological screening for IgGs against herpes simplex virus and cytomegalovirus. The counts of each T-cell subpopulation were determined via flow cytometry. The concentrations of inflammatory cytokines were measured using Luminex multiplex bead immunoassay.

Results: The baseline intraocular pressure of the PSS group was significantly higher than that of the control group ($p < 0.001$) and the corneal endothelial cell count in the PSS group was significantly lower than that of the control group ($p < 0.001$). The PSS group had a significantly lower absolute lymphocyte count ($1,931 \pm 325$ cells/mm³) than the control group ($2,328 \pm 507$ cells/mm³; $p = 0.041$) and reduced numbers of CD8+ T cells ($p = 0.029$). In the same group, the CD8+CD28- and CD8+CD57+ T cell numbers, indicating the T cell immunosenescence were marginally lower than in the control group ($p = 0.085$ and 0.085 , respectively). Serum TGF- β 1 levels were significantly lower in the PSS than the control group ($p = 0.012$).

Conclusions: PSS patients do not appear to exhibit typical immune aging. Rather, PSS seems to be associated with systemic immune activation and relative lymphopenia.

Key words: Cytokines, Cytomegalovirus, Flow cytometry, Immunosenescence, Herpesviridae

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서론

Posner-Schlossmann syndrome (PSS) is characterized by recurrent attacks of mild anterior uveitis associated with marked elevations of intraocular pressure (IOP).^{1,2} Allergic conditions, gastrointestinal diseases, a genetic predisposition, and viruses have been proposed to play roles in PSS pathogenesis.²⁻⁶ However, the etiology of PSS remains poorly understood.

The immunogenetic factors associated with histocompatibility complex have been suggested to play a role in the

pathogenesis of the disease. In a Japanese case series, HLA-Bw54 was expressed by 41% of PSS patients.⁴ Considering that HLA-B presents peptides to CD8+ T cells,⁷ PSS may be associated with immunological changes to certain forms of antigenic stimulation.

As a cause of PSS, the herpes viruses have emerged. Recently, human cytomegalovirus (CMV) has become increasingly recognized in PSS.^{2,5,6,8-10} CMV-positive PSS may be associated with vision-threatening complications, because this condition is accompanied by severe loss of corneal endothelial cells and an increased requirement for glaucoma-filtering surgery, compared to CMV-negative PSS.⁹

In healthy subjects, CMV reactivation is normally prohibited by the immune system. And CMV usually causes diseases such as retinitis in immunocompromised patients. However, in case of PSS, CMV reactivates in anterior chamber of patients who are clinically immunocompetent.

In the immunocompetent adults, CMV does not manifest as an active infection. However, it can establish lifelong latency, and reactivation thereof triggers T cell activation. Therefore, chronic CMV infection exhausts the immune system in immunocompetent.^{11,12} T cell functional dysregulation (a CD4:CD8 ratio < 1; poor proliferative responses to mitogens; increases in CD8+CD28- and CD8+CD57+ T cell numbers; and reduced levels of IL-2 and interferon-gamma) and CMV seropositivity are biomarkers of the immune aging (immunosenescence).^{12,13} The immunosenescence is associated with mortality and morbidity caused by cardiovascular disease, various autoimmune conditions, inflammatory disease, and even cancer.¹¹⁻¹⁴

Therefore, our principal question was whether patients with PSS exhibited altered T cell immunity at the time of exacerbation of inflammation. Thus, the present prospective cross-sectional study investigated the immune status of patients with PSS.

Materials and Methods

Study Subjects

This prospective study was performed in the Department

of Ophthalmology of St. Vincent's Hospital, the Catholic University of Korea, from March 2014 to February 2015. The institutional review board of the Catholic Medical Center approved the study, which was conducted according to the tenets of the Declaration of Helsinki. All patients gave the written informed consent after they received a detailed explanation of the study purpose and design prior to inclusion in the study.

A diagnosis of PSS was based on the following findings: (1) recurrent episodes of mild iritis; (2) the presence of endothelial keratic precipitates and/or corneal edema; (3) an elevated IOP during an attack; (4) the absence of posterior synechiae or posterior inflammation; (5) an attack duration ranging from a few days to a few weeks; and, (6) a normal IOP and the absence of iritis between attacks.^{2,9} Age-matched patients scheduled for cataract surgery served as controls. Eyes with any ocular disease other than cataracts, and/or that had undergone previous vitrectomy and/or laser treatment, were excluded from the control group.

All individuals were ambulatory and generally healthy, as determined by clinical assessment. No patient had an acute systemic or serious concurrent illness; a history of immunodeficiency; any known or suspected impairment of immunological function; any clinically evident liver disease; diabetes mellitus that required insulin injections; moderate-to-severe renal disease; blood pressure >150/95 mmHg at screening; chronic hepatitis B or C infection; or any recent or current use of immunosuppressive medication. In addition, no patient gave or received blood or blood products during the prior 6 weeks and 6 months, respectively.

All individuals underwent complete ophthalmic examinations including evaluation of best-corrected visual acuity (BCVA), IOP measurement via Goldmann applanation tonometry, and slit-lamp biomicroscopy of the anterior and posterior segments of the eye, both at baseline and at each follow-up visit. Non-contact specular microscopy (NSP-9900®, Konan Medical, Inc., Hyogo, Japan) was performed at baseline examination.

Sterile aqueous taps were performed at the time of exacerbation of aqueous humor inflammation in PSS patients, and during cataract surgery in controls. All aqueous humor

samples were subjected to polymerase chain reaction (PCR) to detect herpes simplex virus (HSV) and CMV DNAs, which were extracted using a QIAamp DNA Minikit (Qia-gen, Valencia, CA, USA). Quantitative CMV-DNA PCR was performed with the aid of an AccuPower CMV Quantitative PCR Kit (Bioneer, Daejeon, Republic of Korea); an HSV 1/2 PCR Kit (Bio-Core, Seoul, Republic of Korea) was used to detect HSV. All patients underwent laboratory work-ups, including complete blood, white cell, and differential counts; measurement of C-reactive protein level; and serological screening for IgGs directed against HSV and CMV.

Measurement of T lymphocyte Subpopulations

Peripheral blood samples (10 mL) were obtained on the days of aqueous humor sampling. Monoclonal antibodies, including appropriate isotype controls, were purchased from Beckman Coulter (Bordeaux, France). All data were acquired using a Navios flow cytometer (Beckman Coulter) running Kaluza software version 3.0. The four-color staining protocol featured CD4PE-CY5.5/CD8PE-CY7/CD28PE/CD57FITC. In tube 1, control IgG1PE-CY5.5/IgG1PE-CY7/IgG1PE/ IgM-FITC was used to create an analysis gate; lymphocytes were included in the forward- rather than the side-scattered light, and the fluorescence quadrant markers

of fluorescent light channels 1 and 2 were set to detect any non-antigen-specific antibody binding. CD4PE-CY5.5/CD8PE-CY7/CD28PE/CD57FITC was added to the second tube. All samples were incubated for 15 min at room temperature and lysed with Versalyse (Beckman Coulter) for 10 min at room temperature. Quality control employed Flow Check Fluorospheres, which were used to set the photomultiplier tube voltages and fluorescence compensation, and to check instrument sensitivity prior to use.

Serum Cytokine Levels

The concentrations of IFN- γ , IL-2, TGF β 1, TGF β 2, and TGF β 3 were measured in all samples using Luminex multiplex bead immunoassay (Human Cytokine LINCOplex kit; LINCO Research, St. Charles, MO, USA) performed according to the manufacturer's instructions, and employing Luminex laser-based fluorescent analytical test instrumentation.

The level of Programmed Death Ligand-1 (PD-L1/CD274) was measured using a sandwich ELISA technique employing a kit (catalog no. MBS703117) supplied by MyBio Source (San Diego, CA, USA). Purified human recombinant PD-L1/CD274 was used to calibrate the kit and to prepare standard curves. We included controls to ensure that among-plate variation was <20%, and each

Table 1. Demographic and clinical characteristics of patients with Posner-Schlossman syndrome and controls

Characteristic*	PSS patients (N = 15)	Controls (N = 11)	p-value
Demographic characteristics			
Age (years)	61.2 (11.6)	63.4 (7.2)	0.590 [†]
Female (%)	46.1	36.4	0.697 [‡]
Ocular characteristics			
BCVA	0.63 (0.23)	0.59 (0.32)	0.982 [†]
Corneal endothelial cell count (per mm ²)	2,098.1 (650.2)	2,796.9 (333.2)	0.001 [†]
Lens status (phakic,%)	83.3	100.0	0.055 [‡]
Spherical equivalent (D)	-0.6 (1.6)	-0.3 (1.9)	0.664 [†]
Baseline IOP (mmHg)	30.7 (19.5)	17.7 (3.2)	0.014 [†]
Maximum IOP (mmHg)	35.8 (14.1)	n/a	
Number of anti-glaucomatics taken	2.2 (0.8)	0.0 (0.0)	<0.001 [†]

PSS = Posner-Schlossmann syndrome; BCVA = best-corrected visual acuity; IOP = intraocular pressure; n/a = not applicable.

*Unless otherwise indicated, data are expressed as mean (SD); [†]Indicates comparison between study groups by Mann-Whitney U-test;

[‡]Indicates comparison between study groups by χ^2 test.

sample was assayed in duplicate. The assay range was 15.6–1,000.0 pg/mL.

Statistical Analysis

The non-parametric Mann-Whitney *U*-test and the χ^2 test were used to compare between-group means and percentages among independent samples. A *p*-value < 0.05 was considered to reflect statistical significance. All analyses were performed with the aid of SPSS software (version 14.0 for Windows; IBM Corp., Armonk, NY, USA).

Results

We enrolled 26 patients, 15 with PSS and 11 controls. Baseline demographic and clinical characteristics are shown in Table 1. There were no differences in either age or sex between the two groups. The baseline IOPs in the PSS and control groups were 30.7 ± 19.5 and 17.7 ± 3.2 mmHg, respectively ($p < 0.001$), and the maximum IOP during follow-up in the PSS group was 35.8 ± 14.1 mmHg. The number of PSS patients requiring anti-glaucoma eyedrops

Table 2. Laboratory data on Posner-Schlossman syndrome patients and controls

Characteristic*	PSS patients (N = 15)	Controls (N = 11)	<i>p</i> -value
Complete blood count			
WBC count (cells/ μ L)	6,100 (170)	7,400 (230)	0.148 [†]
Neutrophil (%)	56.9 (11.2)	57.7 (8.6)	0.857 [†]
Lymphocyte (%)	31.2 (8.1)	33.2 (8.1)	0.552 [†]
Monocyte (%)	8.0 (2.9)	7.0 (1.4)	0.274 [†]
Eosinophil (%)	3.4 (3.2)	1.9 (1.4)	0.181 [†]
Basophil (%)	0.6 (0.3)	0.5 (0.2)	0.302 [†]
RBC count ($10^6/\mu$ L)	4.2 (0.4)	4.5 (0.3)	0.086 [†]
Hemoglobin (g/dL)	13.1 (1.4)	14.0 (1.5)	0.178 [†]
Platelet count ($10^3/\mu$ L)	228.6 (63.0)	228.7 (41.7)	0.996 [†]
C-reactive protein (mg/L)	0.26 (0.42)	0.07 (0.04)	0.176 [†]
Immunology			
HSV IgG titer (AU/mL)	6.6 (2.3)	8.0 (0.0)	0.119 [†]
CMV IgG titer (AU/mL)	208.2 (55.8)	168.4 (73.8)	0.303 [†]

PSS = Posner-Schlossmann syndrome; WBC = white blood cell; RBC = Red Blood cell; HSV = herpes simplex virus; CMV = cytomegalovirus.

*Unless otherwise indicated, data are expressed as mean (SD); [†]Indicates comparison between study groups by Mann-Whitney *U*-test.

Figure 1. Absolute blood cell counts of Posner-Schlossman syndrome (PSS) patients and controls. Patients with PSS had a significantly lower absolute lymphocyte count ($1,931 \pm 325$ cells/mm³) than the control group ($2,328 \pm 507$ cell/mm³; $p = 0.041$). Seg = segmented neutrophil; Lympho = lymphocyte.

Figure 2. lymphocyte subpopulations (numbers of cells/mm³) in Posner-Schlossman syndrome (PSS) patients and controls. The PSS and control groups differed significantly in T-cell subpopulation numbers; these were generally lower in the PSS group, particularly the numbers of CD4+ (A) and CD8+ T cells (B), ($p = 0.058$ and 0.029 , respectively). In the PSS group, the CD8+CD28- (D) and CD8+CD57+ T cell numbers (E), indicating immunosenescence were also lower than in the control group, but the differences were marginally significant ($p = 0.085$ and 0.085 , respectively).

(2.2 ± 0.8) was significantly higher than in the control group (0.0 ± 0.0) ($p < 0.001$). The corneal endothelial cell count of the PSS group ($2,098.1 \pm 650.2$ cells/mm²) was significantly lower than that of the control group ($2,796.9 \pm 333.2$ cells/mm²) ($p = 0.001$).

Table 2 shows laboratory data on the PSS and control groups. The complete blood cell count, the C-reactive protein level, and the anti-HSV and -CMV IgG titers did not significantly differ between the groups. However, the PSS group had a significantly lower absolute lymphocyte count ($1,931 \pm 325$ cells/mm³) than the control group ($2,328 \pm 507$ cells/mm³; $p = 0.041$) (Fig. 1). No patient had HSV or CMV DNA in the aqueous humor.

The PSS and control groups differed significantly in T-cell subpopulation numbers; these were generally lower in the PSS group, particularly the numbers of CD4+ and CD8+ T cells ($p = 0.058$ and 0.029 , respectively) (Fig. 2). In the PSS group, the CD8+CD28- and CD8+CD57+ T cell numbers were also lower than in the control group, but the differences were marginally significant ($p = 0.085$ and 0.085 , respectively). The CD4+/CD8+ ratio did not differ

between the groups ($p = 0.910$).

The TGF- β 1 were significantly lower in the PSS group than in the control group ($p = 0.012$). IL-2 and the TGF- β 2 tended to be lower in the PSS than the control group with marginal significance ($p = 0.056$ and 0.062) (Fig. 3). The IFN- γ , IL-6, and PD-L1 levels did not differ between the groups ($p = 0.194$, 0.306 , and 0.186).

Discussion

In this prospective study, we investigated the systemic immunological status of PSS patients. To the best of our knowledge, this is the first study to investigate changes in T cell immunity among PSS patients at the time of the attack.

Human CMV is the emerging cause of PSS. It is well known that upon persistent antigenic stimulation by latent viruses such as CMV, late-differentiated T cells within CD8+ T cell compartment are gradually accumulated. They are characterized by a loss of CD28 and gain of CD57 expression, and increases in the numbers of such cells indicate T cell immunosenescence.^{12,13} In this study, however,

Figure 3 . Cytokine levels of Posner-Schlossman syndrome (PSS) patients and controls. The TGF-β1 were significantly lower in the PSS group than in the control group (D), ($p = 0.012$) IL-2 and the TGF-β2 tended to be lower in the PSS than the control group with marginal significance (E). TGF = transforming growth factor; IL = interleukin; IFN = interferon; PD-L = Programmed Death- ligand 1.

PSS patients did not exhibit T cell immunosenescence, compared to age-matched controls. Rather, the numbers of CD8+CD28- and CD8+CD57+ T cells, indicating T cell immunosenescence were reduced in PSS patients compared to controls ($p = 0.085$ and 0.085 , respectively; Fig. 2)

Intriguingly, the absolute lymphocyte count was significantly lower in PSS patients than controls ($p = 0.041$, Fig. 1). Relative peripheral blood lymphopenia has several causes, such as recent infection, corticosteroid use, malnutrition, rheumatic disease, severe stress, intense physical exercise, and some forms of cancer.^{15,16} The most common cause of transient relative lymphopenia is redistribution of circulating lymphocytes from the blood to other lymphoid compartments, termed “lymphocyte homing”. IFN-α, IFN-γ, IL-2, and TNF-α play key roles in regulating peripheral blood cell traffic; these cytokines influence the homing patterns of peripheral blood leukocytes.¹⁷ In this study, the levels of IFN-γ and IL-2, which are associated with T cell activation and maturation, were relatively higher in PSS patients compared to controls ($p = 0.194$ and 0.056 , respectively; Fig. 3). However, the levels of TGF-β1 and TGF-β2, the immuno-

suppressing cytokines, were lower in the PSS compared to the control group ($p = 0.012$ and 0.062 , respectively). In this context, PSS seems to be associated with systemic immune activation, and relative lymphopenia, rather than T cell immunosenescence. In agreement with this suggestion, Li et al.¹⁸ found that PSS patients had elevated aqueous humor chemokine levels, compared to controls.

The cause of systemic T cell activation in PSS patients remains unclear. None of our patients had CMV or HSV DNA in their aqueous humor samples, although all patients were seropositive for the CMV virus. Hirose et al.⁴ suggested that immunogenetic factors associated with HLA-Bw54 may play important roles in the pathogenesis of PSS. Classically, HLA-B presents peptides to CD 8+ T cells, and HLA-B alteration has been reported in several autoimmune diseases.⁷ Notably, HLA-Bw54 was altered in patients with Vogt-Koyanagi-Harada’s disease¹⁹ and juvenile diabetes.²⁰ Böhringer et al.²¹ reported that the HLA-B27 phenotype promoted recurrence of herpetic corneal diseases following penetrating keratoplasty, and suggested that prophylactic antiviral therapy should be considered for such patients.

Uniquely, the anterior chamber exhibits strong immunosuppressive features, particularly in the context of cellular immunity, associated with immune deviation and a high level of TGF- β .²² Thus, transient reactivation of a latent virus (HSV or CMV) in a healthy anterior chamber is to be expected. Further studies are required to explore associations between immunogenetic factors and predisposition to viral infection in PSS patients.

T lymphocyte activation is regulated both positively and negatively upon presentation of an antigen to the T cell receptor. PD-L1 is the ligand of the Programmed Death-1 (PD-1) receptor, and the PD-1/PD-L1 complex sends an inhibitory signal when antigen-presenting cells promote T cell activation.²³ PD-1/PD-L1 signaling is markedly up-regulated during chronic infection with CMV or HBV, to inhibit adaptive antiviral responses to host immunity.²⁴⁻²⁶ We measured only soluble PD-L1 levels, and these did not significantly differ between the PSS and control groups ($p = 0.186$; Fig. 3F). Cell-specific expression of PD-1 in PSS patients requires further investigation.

As expected, the baseline IOP was significantly elevated in PSS patients compared to controls ($p = 0.014$; Table 1). The corneal endothelial cell count was also significantly lower in patients with PSS ($p = 0.001$); this is typical of patients with CMV-mediated anterior uveitis.^{2,6,8,9} CMV is the principal cause of corneal endothelial failure in patients with this condition. A recent study from Taiwan found that CMV-positive PSS patients (compared to CMV-negative PSS patients) exhibited extensive corneal endothelial cell loss, and a greater number of eyes required glaucoma-filtering surgery.⁹

Our study had certain limitations. First, the aqueous humors were sampled only once. Repeat PCR testing during attacks may have yielded more information. Second, we cannot demonstrate a causal relationship between relative lymphopenia and PSS because our patient numbers were small and our study cross-sectional in design.

In conclusion, we found that PSS patients do not exhibit typical immune aging. PSS rather seems to be associated with systemic immune activation triggering relative lymphopenia. This is the first description of the altered T cell

immunity in PSS patients.

Study approval

For the prospective component, ethical approval was obtained from the institutional review board of the Catholic Medical Center (ref. XC14TIMI004V). The study was conducted according to the principles set out in the Declaration of Helsinki. Written informed consent was obtained from all prospective patients prior to inclusion in the study, which was conducted according to the tenets of the Declaration of Helsinki.

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Conflict of interest statement

The authors have declared that no conflict of interest exists.

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