

# ID: 56629 Distinct profiles of soluble cytokine receptors between B-cell vitreoretinal lymphoma and uveitis

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**Background:** To determine the profiles of soluble cytokine receptors and cytokines, including mostly their ligands, in the vitreous humor of patients with B-cell VRL and uveitis

**Patients & Methods:** Vitreous samples were collected from immunocompetent patients with VRL (n = 21), uveitis (n = 20), and idiopathic epiretinal membrane (n = 21) as controls. Cytometric beads assay were used to determine the vitreous concentrations of soluble receptors and cytokines.

**Results:** Vitreous levels of soluble interleukin (IL)-2 receptor  $\alpha$  (sIL-2R $\alpha$ ), sIL-6R, soluble tumor necrosis factor receptor (TNFR) 1, sTNFR2, soluble vascular endothelial growth factor receptor (sVEGFR) 1, sVEGFR2, and IL-10 were higher in patients with VRL than in those with uveitis and controls, whereas those of sIL-1R1, sIL-1R2, and sIL-4R were higher in patients with uveitis than those with VRL and controls. In analyses in patients with VRL, elevation of sVEGFR1 and sVEGFR2 levels was more prominent in patients with systemic metastatic retinal lymphoma (SMRL) than in those with primary VRL/primary central nervous system lymphoma (PVRL/PCNSL). Furthermore, sIL-2R $\alpha$  levels were increased in patients with VRL who developed subretinal lesions compared to in those who mainly had vitreous cavity opacity, positively correlated with the density of CD3<sup>+</sup> cells in the vitrectomy cell blocks.

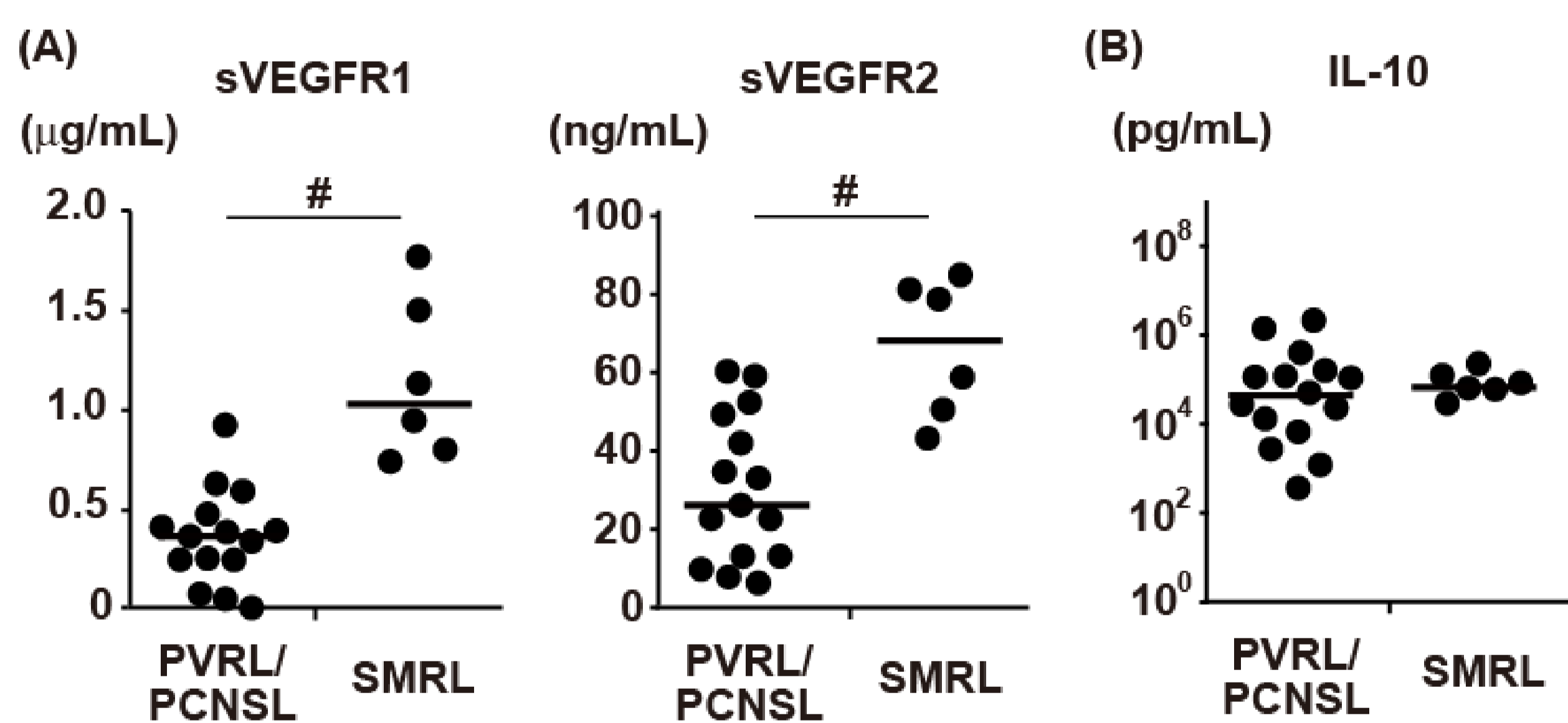
**Table 1 :** Concentrations of soluble receptors and cytokines in the vitreous humor

	Control (n = 21)	VRL (n = 21)	Uveitis (n = 20)	P Value
sIL-1R1 (ng/mL)	0 (0-0.826)	0 (0-0) <sup>##</sup>	1.23 (0.986-1.37) <sup>§§</sup>	<0.001 <sup>†</sup>
sIL-1R2 (ng/mL)	0 (0-0)	0 (0-0) <sup>##</sup>	2.66 (1.08-4.13) <sup>§§</sup>	<0.001 <sup>†</sup>
sIL-2R $\alpha$ (ng/mL)	0 (0-0)	3.40 (1.35-11.1) <sup>§§, †</sup>	0.630 (0.098-2.55) <sup>§§</sup>	<0.001 <sup>†</sup>
sIL-4R (ng/mL)	0 (0-0)	0 (0-0) <sup>##</sup>	1.35 (1.17-1.63) <sup>§§</sup>	<0.001 <sup>†</sup>
sIL-6R (ng/mL)	2.01 (1.10-3.09)	5.94 (3.61-13.3) <sup>§§</sup>	3.37 (1.85-5.13)	<0.001 <sup>†</sup>
sgp130 (ng/mL)	42.8 (27.7-53.9)	74.7 (45.7-105.0) <sup>§§</sup>	92.0 (75.8-112.3) <sup>§§</sup>	<0.001 <sup>†</sup>
sTNFR1 (ng/mL)	1.40 (0-2.80)	9.55 (5.45-16.0) <sup>§§, †</sup>	3.22 (2.06-4.58) <sup>§</sup>	<0.001 <sup>†</sup>
sTNFR2 (ng/mL)	4.32 (2.51-5.95)	92.3 (28.8-184.8) <sup>§§, ##</sup>	14.1 (7.41-32.9) <sup>§§</sup>	<0.001 <sup>†</sup>
sVEGFR1 (ng/mL)	153.5 (54.1-198.8)	404.3 (247.3-792.5) <sup>§§, ##</sup>	118.5 (101.1-141.0)	<0.001 <sup>†</sup>
sVEGFR2 (ng/mL)	17.3 (14.5-21.9)	41.4 (22.2-58.3) <sup>§§, ##</sup>	14.4 (13.3-16.6)	<0.001 <sup>†</sup>
IL-6 (ng/mL)	0 (0-0.177)	0.853 (0.344-1.65) <sup>§§</sup>	1.32 (0.695-1.68) <sup>§§</sup>	<0.001 <sup>†</sup>
IL-10 (ng/mL)	0.020 (0-0.118)	57.2 (20.5-110.1) <sup>§§, ##</sup>	0.089 (0.009-0.225)	<0.001 <sup>†</sup>
TNF- $\alpha$ (pg/mL)	0 (0-0)	0 (0-0)	0 (0-0)	0.26 <sup>†</sup>
VEGF-A (pg/mL)	0 (0-1036.6)	0 (0-1068.7)	0 (0-1098.3)	0.80 <sup>†</sup>
PIGF (pg/mL)	0 (0-114.3)	145.7 (0-269.9)	155.6 (0-602.8)	0.064 <sup>†</sup>
VEGF-C (pg/mL)	0 (0-41.1)	0 (0-1099.2)	0 (0-532.3)	0.28 <sup>†</sup>

VRL, vitreoretinal lymphoma; IL, interleukin; R, receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; PIGF, placenta growth factor. Soluble receptors and cytokines are expressed as median with interquartile range in parentheses.

<sup>†</sup>Kruskal–Wallis test. <sup>††</sup>One-way ANOVA test. <sup>§</sup> < 0.05 vs control, <sup>§§</sup> < 0.01 vs control, <sup>†††</sup> < 0.05 vs uveitis, <sup>##</sup> < 0.01 vs uveitis: Steel–Dwass test or Turkey–Kramer test

**Figure 1:** Vitreous levels of sVEGFR1 and sVEGFR2 in patients with SMRL



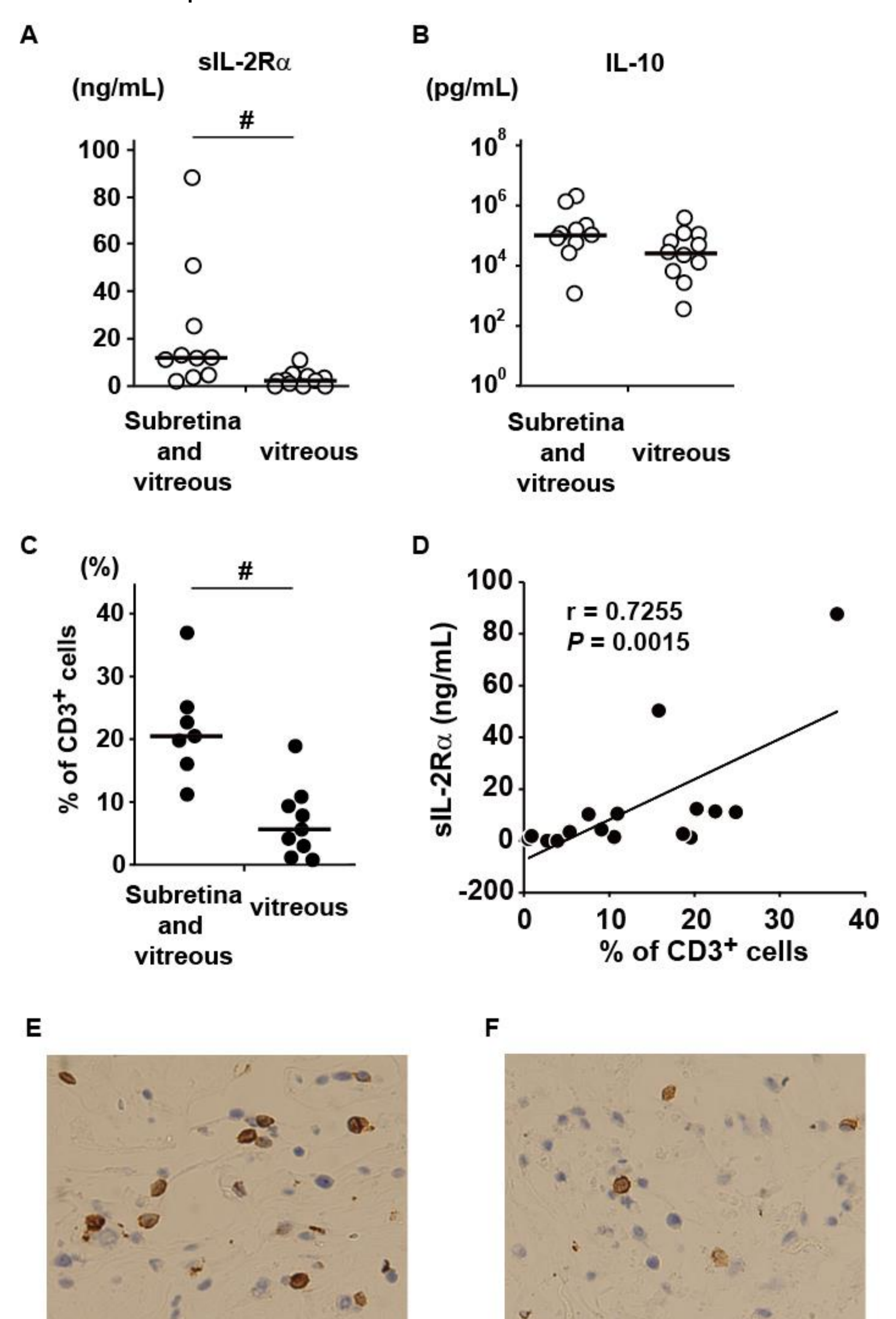
Shown are comparison of (A) sVEGFR1, sVEGFR2, and (B) IL-10 levels in the vitreous humor between patients with SMRL (n = 6) and PVRL/PCNSL (n = 15). The horizontal lines show the median concentration. The ordinate showed the concentrations of (B) IL-10 in the log scale. #P < 0.01; Mann–Whitney's U-test.

**Table 2:** Clinical data of patients with VRL

Case No.	Sex	Age at diagnosis (y)	Primary origin	Eye involved	Main ocular lesions at initial diagnosis	Brain involved	Relapse (mos. after initial diagnosis)	Outcome
1	F	51	Eye	OU	Subretina and vitreous	Yes	Brain; 16 mos.	Died 48 mos.
2	F	68	Eye	OU	Vitreous	No	No relapse	Alive
3	F	55	Eye	OU	Subretina and vitreous	No	No relapse	Alive
4	M	63	Brain	OU	Subretina and vitreous	Yes	Eye; 10 mos.	Alive
5	M	61	Brain	OU	Vitreous	Yes	Eye; 20 mos.	Alive
6	F	80	Eye	OS	Subretina and vitreous	Yes	Brain; 12 mos.	Alive
7	F	80	Brain	OS	Subretina and vitreous	Yes	Eye; 17 mos.	Died 44 mos. by pancreatic ca.
8	M	60	Eye	OU	Vitreous	Yes	Brain; 25 mos.	Lost to follow-up
9	M	45	Eye	OU	Subretina and vitreous	Yes	Brain; 48 mos.	Died 70 mos.
10	M	69	Brain	OU	Vitreous	Yes	Brain; 72 mos.	Died 120 mos.
11	F	73	Brain and eye	OU	Vitreous	Yes	Brain; 16 mos.	Died 25 mos.
12	M	59	Brain	OU	Vitreous	Yes	Eye; 33 mos.	Lost to follow-up
13	M	38	Brain	OS	Subretina and vitreous	Yes	Eye; 6 mos.	Alive
14	F	69	Brain	OU	Vitreous	Yes	Eye; 35 mos.	Alive
15	F	67	Eye	OU	Vitreous	Yes	Brain; 4 mos.	Alive
16	F	75	Abdominal LN and eye	OS	Subretina and vitreous	No	No relapse	Alive
17	F	73	Nose, Paranasal sinus	OU	Vitreous	Yes	Eye; 120 mos. Brain; 102 Mos.	Alive
18	M	78	Chest wall	OU	Vitreous	Yes	Eye; 18 mos. Brain; 24 mos.	Alive
19	M	68	Testis	OS	Subretina and vitreous	Yes	Eye; 96 mos. Brain; 84 mos.	Died 132 mos.
20	F	74	Breast	OU	Subretina and vitreous	No	Eye; 59 mos.	Died 30 mos., but not due to ML
21	F	79	Intestine	OU	Vitreous	No	Eye; 19 mos.	Alive

VRL, vitreoretinal lymphoma; F, female; M, male; OU, both eyes; OS, left eye; mos., months; ca., carcinoma; LN, lymph node; ML, malignant lymphoma.

**Figure 2:** Vitreous levels of sIL-2R $\alpha$  in patients with VRL who developed subretinal lesions



(A) sIL-2R $\alpha$  and (B) IL-10 were compared in vitreous humor in patients with VRL who developed subretial lesions and vitreous opacity (n = 10) and in those who predominantly did vitreous opacity (n = 11). The horizontal lines show the median concentration. The ordinate showed the concentrations of (B) IL-10 in the log scale. (C) Comparison of the percentages of T-cells in the vitrectomy cell blocks in patients with VRL who developed subretial lesions and vitreous opacity (n = 7) to in those who predominantly did vitreous opacity (n = 9). (D) Correlations between vitreous concentrations of sIL-2R $\alpha$  and T cell densities in vitrectomy cell blocks in patients with VRL (n = 16). (E, F) Representative images of immunohistochemistry of CD3<sup>+</sup> cells in vitrectomy cell blocks in a patient with VRL who developed subretial lesions and vitreous opacity (E, Case 3) and that who predominantly did vitreous opacity (F, Case 18). #P < 0.01; Mann–Whitney's U-test.

**Conclusions:** The profiles of soluble cytokine receptors and cytokines in patients with VRL were different from those with uveitis. In addition, sVEGFR1 and sVEGFR2 levels may be differential diagnostic markers between PVRL/PCNSL and SMRL, and sIL-2R $\alpha$  levels can anticipate infiltration of VRL cells into the subretina and/or retina.