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**Choroidal thickening prior to anterior recurrence in patients with
Vogt-Koyanagi-Harada disease**

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Sub-title: Choroidal thickening was detected in the anterior segment recurrence of Vogt-Koyanagi-Harada disease by enhanced depth imaging optical coherence tomography, and this thickening was observed prior to the recurrence.

ABSTRACT

Aim To assess choroidal thickness changes associated with anterior segment recurrences in patients with Vogt-Koyanagi-Harada (VKH) disease using enhanced depth imaging optical coherence tomography (EDI-OCT).

Methods EDI-OCT images were obtained periodically from 11 VKH disease patients (22 eyes) who were followed-up due to anterior segment recurrences. Subfoveal choroidal thickness (SCT) values at the following stages were evaluated: (1) during the remission phase, (2) one month before detecting the anterior recurrence, (3) during the anterior recurrence, and (4) after systemic prednisolone (PSL) treatment leading to remission. In comparison with SCT values in remission as baseline, the changing ratios of SCT were statistically analyzed at subsequent three stages.

Results The average of the SCT changing ratios compared to the remission phase significantly increased to 1.45 ± 0.11 during anterior segment recurrences ($P=0.00044$) lacking any funduscopic signs of posterior involvement. Interestingly, the average SCT ratio one month before detecting the recurrence had already increased to 1.30 ± 0.08 ($P=0.002$). After the PSL treatment, the ratio of SCT recovered to 0.95 ± 0.03 which

was equivalent with the remission level. However, in patients with their remission SCT values less than 240 μm , the SCT ratio did not increase significantly at any time points evaluated.

Conclusions The choroid in eyes with VKH disease thickened in association with the anterior segment recurrence, and this thickening was observed prior to the recurrence. EDI-OCT may be useful for detecting latent choroidal inflammation in VKH disease, whereas it may not for patients with the relatively thin choroid.

INTRODUCTION

Vogt-Koyanagi-Harada (VKH) disease is a systemic disorder affecting organs with rich melanin pigments, including the eyes, meninges, skin, and inner ears [1] and is believed to be a cell-mediated autoimmune disease of melanocytes.[2 3] At the initial onset of VKH disease, patients usually show signs of panuveitis or posterior uveitis with serous retinal detachment. Indocyanine green angiography (ICGA) and laser speckle flowgraphy reveal impaired choroidal circulation,[4 5] and enhanced depth imaging optical coherence tomography (EDI-OCT) shows the markedly thickened choroid in eyes with VKH disease.[5-7]

In contrast, the recurrence of intraocular inflammation usually occurs in the anterior segment, and recurrences with posterior uveitis are rarely presented.[8] Bascal et al. reported that some patients with an isolated anterior segment recurrence showed substantial changes on ICGA indicative of subclinical choroidal inflammation.[9] Repeated anterior recurrences with subclinical choroidal inflammation may result in loss of vision due to choroidal neovascularization or atrophy.[8 10]

To the best of our knowledge, there has been no investigation into choroidal thickness during the anterior segment recurrence in VKH disease. In this study, we assessed the sequential changes in choroidal thickness in association with the anterior segment recurrence using EDI-OCT.

MATERIALS AND METHODS

Patients

We retrospectively assessed 11 patients with VKH disease who were followed-up in the Intraocular Inflammation Clinic at Hokkaido University Hospital, Japan. The current study was approved by the ethics committee of Hokkaido University Hospital and followed the tenets of the Declaration of Helsinki. A diagnosis of VKH disease was previously made for all patients according to the diagnostic criteria proposed by the International Committee in 2001.[11] Patients who showed anterior segment recurrences from October 2011 to September 2013 and received monthly EDI-OCT monitoring were included in this study. The criteria for the anterior segment recurrence were based on those previously reported [9] with minor modifications: (1) presence of anterior chamber inflammation of at least 1+ cells after a period of quiescence of three months or more with or without treatment, (2) absence of posterior vitreous cells and fundus lesions (serous retinal detachment, choroidal folds, etc), examined by slit-lamp biomicroscopy, funduscopy and OCT.

Subfoveal choroidal thickness (SCT) measurements

SCT was manually measured from EDI-OCT (RS-3000 AdvanceTM; Nidek, Gamagori, Japan) images taken from patients with VKH disease on a routine basis in our clinic. If SCT was extremely thick and over the range of instrument capability (approximately

800 μm), then SCT was calculated as 800 μm . SCT was measured at every visit, and values of SCT at the following stages were evaluated in this study: (1) during the remission phase, (2) one month before detecting the anterior recurrence, (3) during the anterior recurrence, and (4) after systemic prednisolone (PSL) treatment leading to remission, which was defined as the time point when SCT decreased and reached a plateau with PSL treatment. Fig. 1 shows a representative case (right eye of Case 2) with no funduscopically apparent lesions in the posterior segment.

Treatments

During the remission phase, patients were controlled with the maintenance doses of PSL ranging from 0.03 to 0.2 mg/kg, and monitored basically almost every month. The patients were notified at the routine visit of having developed anterior recurrences because the recurrent inflammation was so mild and asymptomatic. When the anterior segment recurrence was found to have developed, patients received treatments with the increased doses of 0.3 to 0.5 mg/kg of PSL and betamethasone eye drops depending on the degree of anterior chamber inflammation.

Statistical analyses

Statistical analyses were performed with a paired t-test. For all tests, P values of less than 0.05 were considered significant.

RESULTS

Patient characteristics

Twenty-two eyes from 11 cases with VKH disease showing anterior segment recurrences were examined (Table 1). All patients were Japanese (4 men and 7 women). The mean age \pm standard deviation (SD) at the initial visit was 38.1 ± 13.4 years (range, 12 to 60 years). The mean follow-up duration \pm SD was 34.6 ± 19.1 months (range, 6 to 76 months). As for the past history of VKH disease, the mean number of previous recurrences was 2.6 ± 1.1 (range, 1 to 4). Six eyes of 3 patients experienced the first recurrence in this study.

Ocular findings during the anterior segment recurrence

All eyes with anterior segment recurrences showed mild anterior chamber inflammation with 1 to 3+ cells. Fine keratic precipitates (KPs) were found in three eyes and mutton-fat KPs in seven eyes. Hypopyon or fibrin formation was not seen. As described in the definition of the anterior segment recurrence, none of the eyes had posterior vitreous cells or active fundus lesions, including serous retinal detachment or choroidal detachment or fold. Sunset-glow fundus was observed in 20 eyes.

Increases in SCT before and during the anterior segment recurrence

We assessed the sequential changes in the average SCT before and after the anterior segment recurrence in 22 eyes with VKH disease (Fig. 2). In comparison with SCT values during the remission phase as baseline, the changing ratios of SCT were statistically analyzed. The average of the SCT changing ratios \pm standard error significantly ($P=0.00044$) increased to 1.45 ± 0.11 during anterior segment recurrences lacking any obvious fundoscopic signs of posterior involvement. Interestingly, the average SCT ratio one month before detecting the recurrence had already increased to 1.30 ± 0.08 with a statistical significance ($P=0.002$). All patients except Case 8 showed choroidal thickening one month before detecting the recurrence, during the recurrence, or at both stages. After the PSL treatment, the ratio of SCT recovered to 0.95 ± 0.03 , which was equivalent with the remission level.

Differential changes in SCT at recurrence determined by a border value of SCT in remission

To further analyze any possible trends in the difference of SCT between the remission (baseline) and the anterior recurrence, all the 22 eyes enrolled was plotted on the graph showing the SCT values during remission and recurrence in the horizontal and vertical axes, respectively (Fig. 3). As a result, eyes with the relatively thin choroid at baseline (i.e., less than $240 \mu\text{m}$) were revealed to undergo minimal changes in SCT, whereas almost all of those with the thicker choroid (i.e., more than $240 \mu\text{m}$) exhibited

substantial increases in SCT at recurrence.

Recurrence-associated choroidal thickening seen in the thicker, but not the thinner, choroid

Next, we statistically compared the changing ratios of SCT between the two groups divided by the border SCT value of 240 μm in remission. In eyes with the thicker choroid, the SCT changing ratio during the anterior recurrence significantly ($P=0.00019$) increased to 1.68 ± 0.13 in comparison with the remission as baseline (Fig. 4a). Moreover, the SCT ratio at one month before detecting the anterior recurrence also significantly ($P=0.004$) increased to 1.40 ± 0.12 (Fig. 4a) in a similar but enhanced manner compared to the analysis of whole eyes (Fig. 2). After the PSL treatment, the ratio returned to 0.95 ± 0.05 , which was almost the same level as in remission (Fig. 4a). By contrast, the SCT ratio did not change significantly in eyes with the thinner choroid at any time points evaluated (Fig. 4b).

DISCUSSION

EDI-OCT previously demonstrated that the choroid markedly thickened at the initial onset of VKH disease.[6 7 12 13] Furthermore, choroidal thickening was detected during the posterior recurrence.[6 14] In the present study, we revealed that the choroid also thickened during the anterior segment recurrence without any obvious findings in

the posterior segment, and that this choroidal thickening had already been observed one month before detecting the recurrence. Although choroidal thickness alterations without any funduscopy findings have been examined in a few case reports,[15 16] this study is the first case series to describe the detailed sequential changes in choroidal thickness in relation to the anterior recurrence of VKH disease.

The choroidal thickening recovered to almost the same level as the remission-phase thickness following the treatment of increased doses of PSL. This result suggests that the choroidal thickening seen at the anterior recurrence is due to inflammatory reaction. In this sense, EDI-OCT may be a useful instrument to detect such subclinical choroidal inflammation. Interestingly, the choroidal thickening had already been detected prior to the anterior recurrence without any funduscopy signs of posterior involvement. This finding suggests that subclinical choroidal inflammation may precede the appearance of anterior uveitis and subsequently spread to the anterior segment at the recurrence of VKH disease.

In a recent case series by Nakayama et al., however, EDI-OCT revealed a massive thickening of the choroid at the acute stage of VKH disease, which subsided along with corticosteroid application but rebounded in part of the patients without any accompanying sign of recurrent inflammation.[7] Choroidal thickening may not necessarily be linked with anterior recurrence. Indeed, we experienced several cases showing choroidal thickening without any apparent inflammatory findings, which

spontaneously resolved with no additional treatment (data not shown).

On the other hand, the present case series included some eyes showing little or no increase in choroidal thickness one month before or at the detection of the recurrence. Importantly, these eyes were revealed to have the relatively thin choroid during the remission phase. Indeed, the choroid turned out to be progressively thinner on EDI-OCT during the convalescent stage of VKH disease.[17-19] In this study, we divided the recurrent VKH patients into two groups based on the remission SCT of 240 μm as a border value to explain the differential changes in SCT at recurrence. Given that the average choroidal thickness of healthy adults was reported to be 253.8 ± 107.4 , 280 ± 81 , 287 ± 76 , and $305.9 \pm 78.2 \mu\text{m}$,[20-23] the cut-off value of 240 μm is a relatively low value within the normal range of choroidal thickness. Reasonably, the subclinical choroiditis during anterior recurrence, especially if repeated or prolonged, would render the choroidal tissue gradually atrophic and thinner, leading to poor response in thickness. The potential usefulness of EDI-OCT for detecting subclinical choroiditis may presumably wane in eyes with inflammation-related choroidal thinning and atrophy.

It was already reported that subclinical choroidal inflammation could also be detected by ICGA during the anterior recurrence of VKH disease without any funduscopic findings in the posterior segment.[9 24] Bouchenaki et al. recommended the ICGA-guided management, in which patients undergoing the test every 6 ± 2

weeks could receive occasional treatments required according to angiographically confirmed inflammatory signs.[9 24] As compared to EDI-OCT, however, ICGA is time-consuming, invasive, and risky in terms of inducing, though rare but serious, systemic allergic reactions to the dye. Further studies are needed to determine how to utilize these two methods most effectively for detecting inflammatory signs in the choroid. Nevertheless, our current results indicated the possibility of improving the visual prognosis of VKH disease by detecting subclinical choroidal inflammation with EDI-OCT for timely and adequate interventions.

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Table 1 Clinical characteristics and subfoveal choroidal thickness

Case	Age (years)	Sex	Follow-up Period (months)	Recurrence number	R/L	Subfoveal choroidal thickness (μm)			
						Remission	One month before the recurrence	Anterior recurrence	After the treatment
1	31	F	42	4 th	R	407	508	672	405
					L	292	333	422	291
2	23	M	13	3 rd	R	307	474	581	293
					L	326	577	581	339
3	29	M	6	3 rd	R	394	>800*	464	252
					L	345	>800*	570	309
4	60	F	26	1 st	R	319	562	>800*	289
					L	360	538	>800*	338
5	44	F	30	1 st	R	144	140	169	145
					L	145	142	152	132
6	31	M	51	4 th	R	135	206	164	144
					L	161	183	183	176
7	59	F	20	4 th	R	228	235	179	167
					L	183	307	209	151
8	47	M	76	3 rd	R	166	166	152	152
					L	214	163	201	213
9	39	F	31	1 st	R	299	303	366	239
					L	333	335	456	218
10	44	F	60	2 nd	R	251	272	655	267
					L	247	239	434	299
11	12	F	26	3 rd	R	363	408	433	401
					L	276	293	285	333

R: right eye, L: left eye

* Choroid thickened over the range of performance limitation (> 800 μm).

FIGURE LEGENDS

Figure 1: Representative case showing changes in choroidal thickness at recurrence and after treatment. Note the dramatic change in choroidal thickness from 581 μm at anterior recurrence **(a)** to 293 μm after PSL treatment **(b)** in the right

eye of Case 2, which did not even show any obvious funduscopy findings in the posterior segment during follow-up.

Figure 2: Choroidal thickening before and during the anterior segment recurrence of VKH disease. The average changing ratio of subfoveal choroidal thickness (SCT) was assessed in comparison with the baseline (i.e., remission) SCT. The SCT changing ratio significantly increased not only during the anterior recurrence but also one month prior to the recurrence. After the PSL treatment, the ratio of SCT recovered to the equivalent level to the baseline. ** $P < 0.05$. $N = 22$ eyes.

Figure 3: Differential changes in SCT at recurrence determined by a border value of SCT in remission. Note that eyes with the relatively thin (less than $240 \mu\text{m}$) choroid at baseline underwent minimal changes in SCT at recurrence. In contrast, eyes with the thicker (more than $240 \mu\text{m}$) choroid exhibited substantial increases in SCT at recurrence.

Figure 4: Recurrence-associated choroidal thickening seen in the thicker, but not the thinner, choroid. (a) Note the sequential changes in the SCT ratio of eyes with the thicker (more than $240 \mu\text{m}$) choroid in a similar but enhanced manner compared to the whole eyes (Fig. 2). (b) By contrast, the SCT ratio change in eyes with the thinner (less

than 240 μm) choroid almost flattened.

Fig. 1

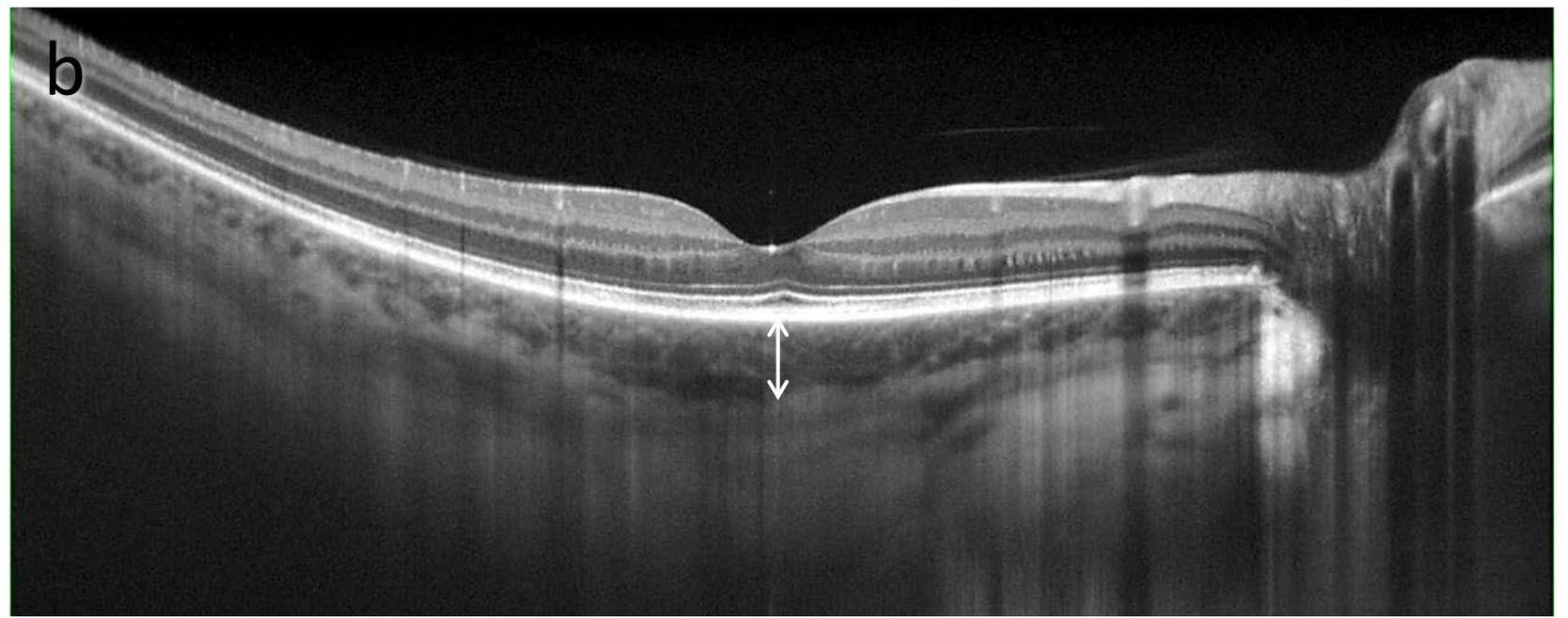
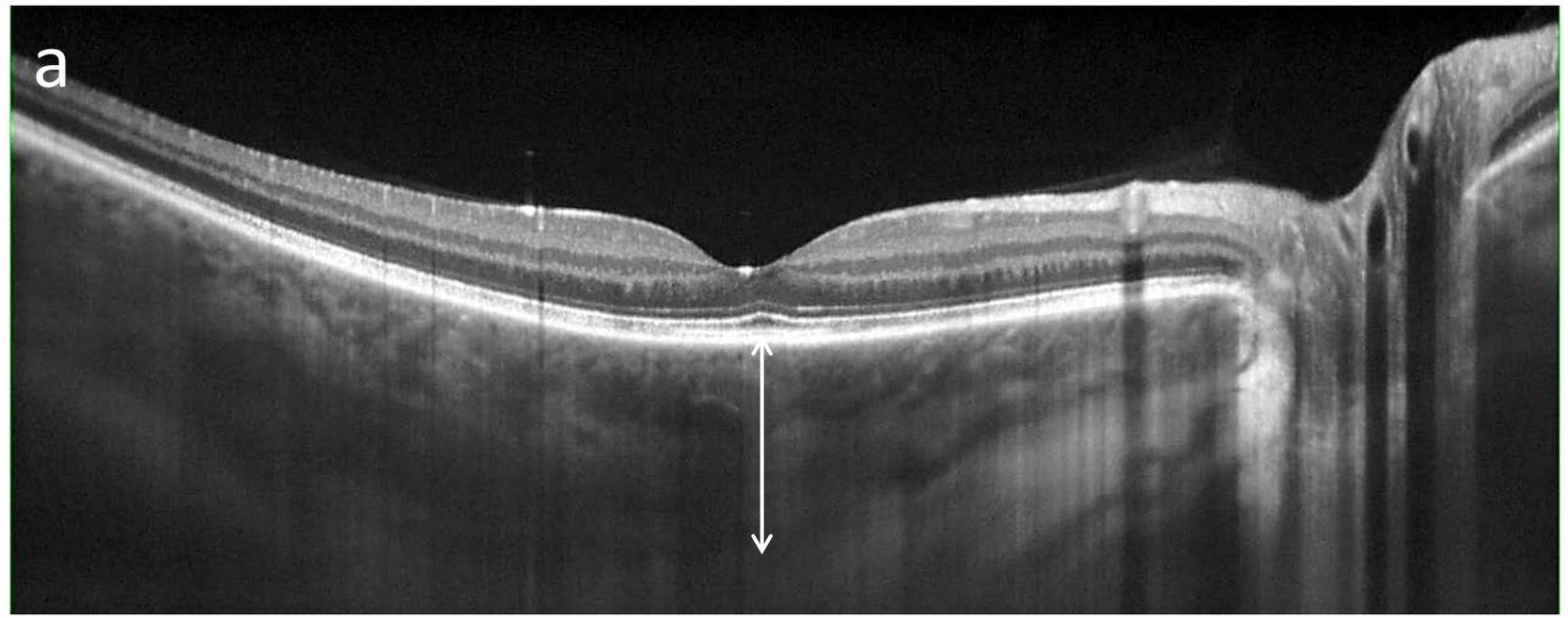


Fig. 2

SCT ratio

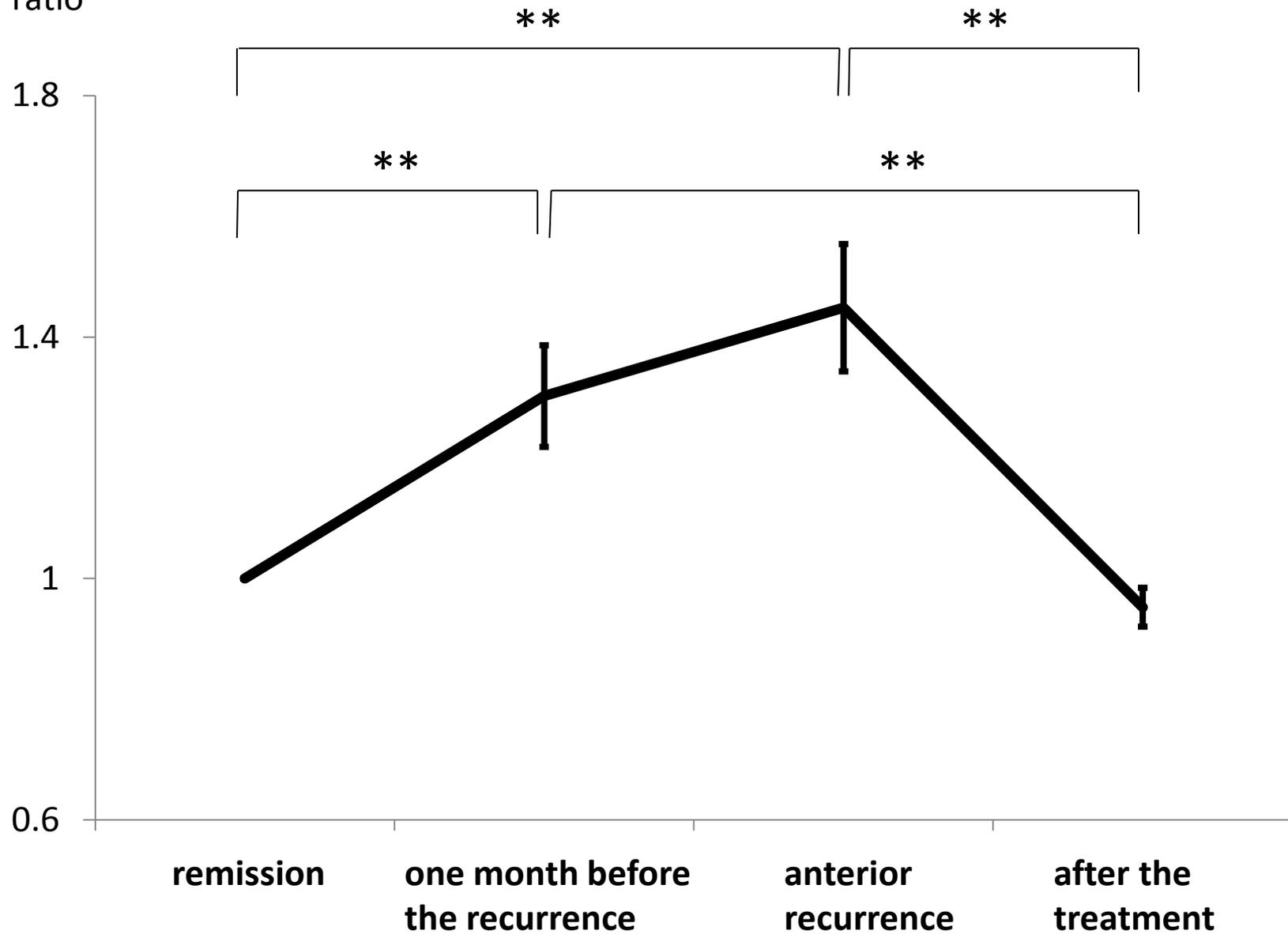


Fig. 3

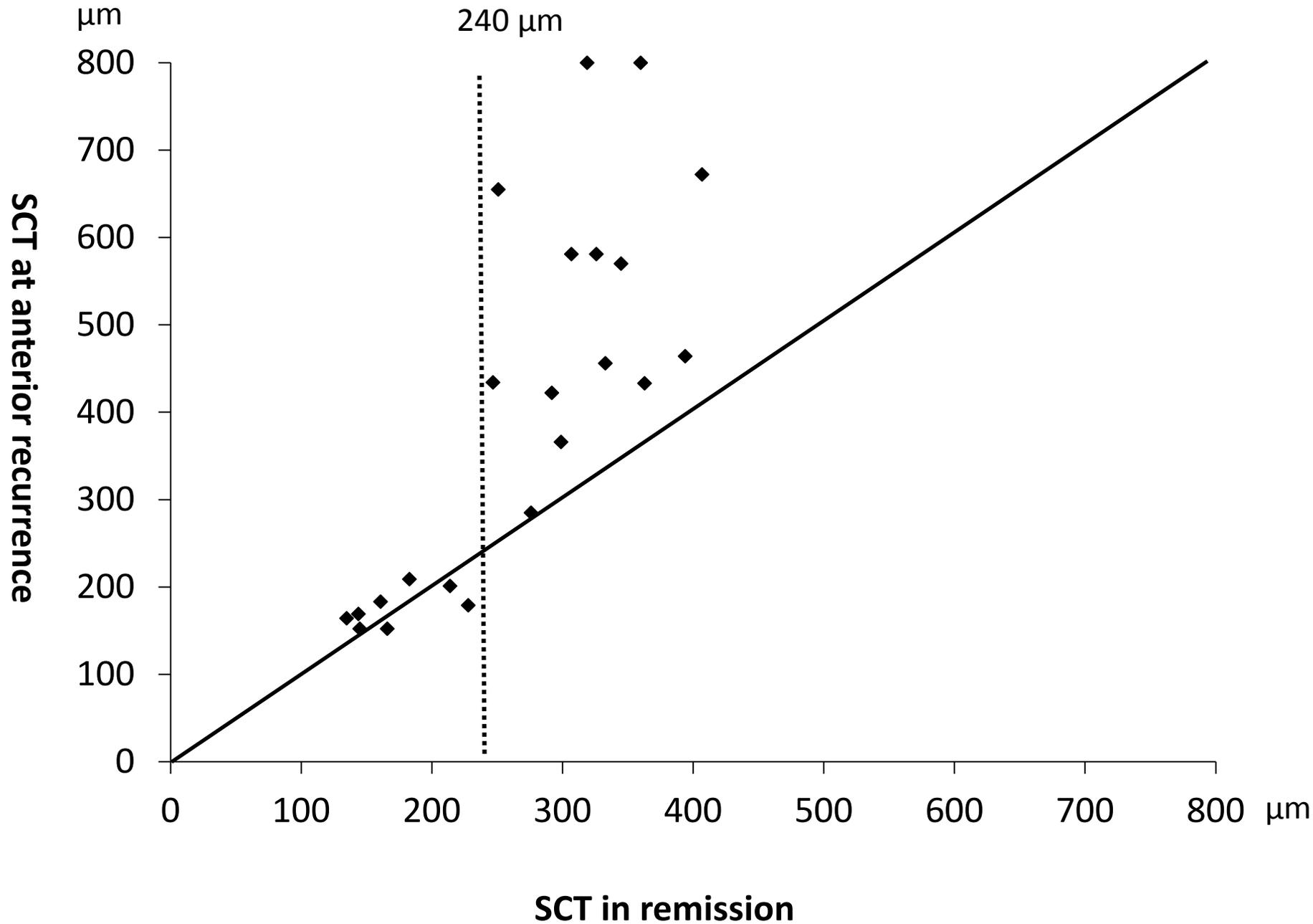
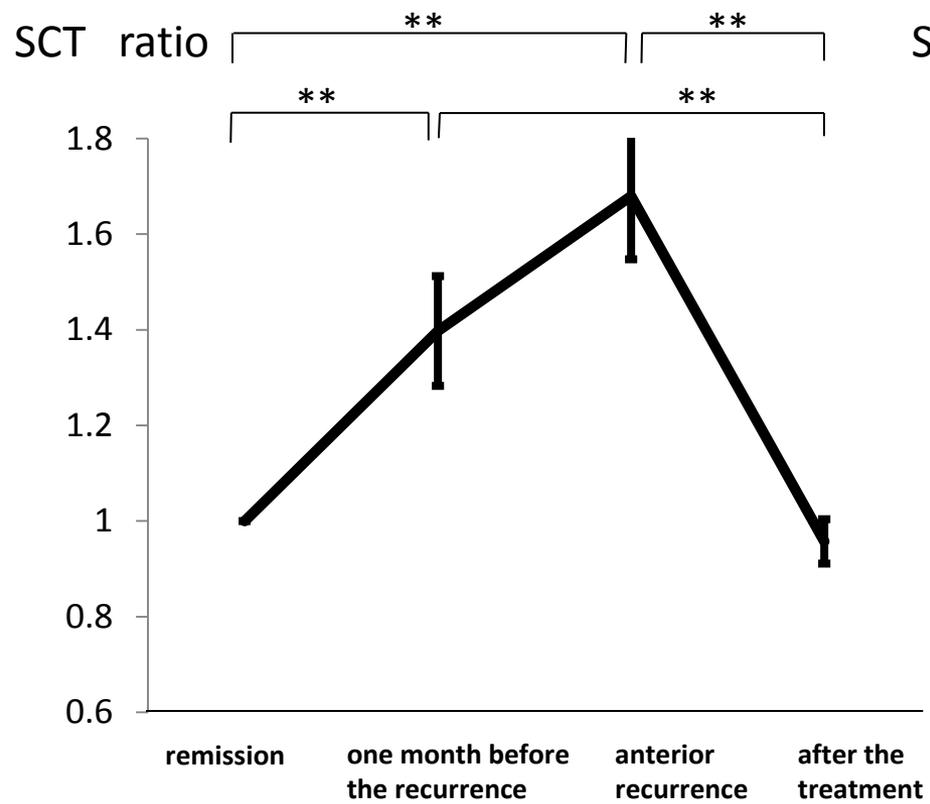


Fig. 4

a



b

