Histology of myopic posterior scleral staphylomas

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ABSTRACT.

Purpose: Since histomorphometric descriptions of posterior scleral staphylomas, although forming a major part of myopic maculopathy, have been scarce so far, we histomorphometrically examined scleral staphylomas in enucleated human eyes.

Methods: Using light microscopy, we histomorphometrically examined sagittal histological sections of human globes enucleated due to malignant choroidal melanomas or secondary angle-closure glaucoma.

Results: Out of 246 globes included into the study, posterior scleral staphylomas were detected in 10 eyes (mean length: 31.4 ± 3.0 mm; range: 28.0–37.0 mm). In the staphylomatous region in the study group as compared with the corresponding region of a control group adjusted for age and axial length, scleral thickness was significantly lower (109 ± 25 μm versus 219 ± 161 μm; p = 0.001). The study group in the staphylomatous region as compared to the highly myopic control group in the corresponding region did not differ significantly in retinal pigment epithelium (RPE) cell density (19.6 ± 4.9 cells/300 μm² versus 21.1 ± 5.7 cells/300 μm²; p = 0.84) and RPE height (8.2 ± 2.8 μm versus 6.1 ± 2.5 μm; p = 0.13), Bruch’s membrane (BM) thickness (3.5 ± 1.3 μm versus 4.2 ± 2.3 μm; p = 0.40) and choriocapillaris thickness (5.3 ± 2.8 μm versus 4.4 ± 2.8 μm; p = 0.49) and density (164 ± 99 μm² versus 226 ± 38 μm²; p = 0.13). All staphylomatous regions showed a localized BM defect.

Conclusions: Marked scleral thinning and spatially correlated BM defects histologically characterized myopic scleral staphylomas, while thickness and density of the choriocapillaris and RPE and BM thickness did not differ significantly between staphylomatous versus non-staphylomatous eyes in the respective regions. These findings support the notion that a locally reduced scleral resistance against a backward pushing BM led to a local scleral outpouching. The outpouching-associated increase in curvature length may stretch BM with the sequel of a localized BM rupture.

Key words: Bruch’s membrane – choriocapillaris – myopia – myopic maculopathy – scleral staphyloma

Jost B. Jonas is a member of EVER

Introduction

Posterior scleral staphylomas belong to the hallmarks of myopic maculopathy and have clinically been defined by Spaide and Ohno-Matsui as an outpouching of the sclera with its curvature radius being smaller than the curvature radius of the surrounding eye wall (Spaide 2013; Ohno-Matsui 2014; Ohno-Matsui et al. 2015). In previous hospital-based studies and population-based investigations, the presence of posterior scleral staphylomas was associated with an increased risk of progression of myopic maculopathy (Yan et al. 2018). Although the next generation of optical coherence tomographic (OCT) imaging of the myopic fundus by wide-angle swept-source OCTs and magnetic resonance imaging have markedly increased the clinical knowledge about the prevalence of posterior scleral staphylomas and their associations, histological studies describing the microscopic structure of staphylomas have been scarce so far (Grossniklaus & Green 1992; Moriyama et al. 2011; Ohno-Matsui, 2014; Wang et al. 2016; Shinohara et al. 2017, 2018; Shinohara et al. 2019). We, therefore, conducted this histomorphometric investigation to explore the histological appearance of posterior scleral staphylomas in highly myopic eyes.

Methods

The study included enucleated globes of Caucasian patients, which had been removed with the diagnosis of a malignant choroidal melanoma and or end-stage painful glaucoma as cause for enucleation. The Medical Ethics Committee II of the Medical Faculty Mannheim of the Heidelberg University approved the study. The ethics committee waived the necessity of an informed consent by the patients, since the globes had been enucleated up to 50 years before the start of the study. At the time of enucleation of the eyes, no other therapeutic modalities were...
available to treat the conditions, which were the reason for enucleation. Some of the eyes included into this study had already been examined in previous investigations on different topics (Jonas et al. 2011, 2012). Eyes with congenital glaucoma were excluded.

The globes included into this study were randomly chosen out of the archives of the ophthalmic laboratory of the department of ophthalmology at Erlangen, Germany. The laboratory had started in about 1975, and the methods it had applied for tissue fixation and preparation of the histological slides had remained mostly unchanged during the following time. Immediately after enucleation, the globes had been fixed in a solution of 4% formaldehyde and 1% glutaraldehyde. The globes had remained in that solution for 1 week at room temperature, and the sagittal, vertical and horizontal globe diameter had been determined. Out of the fixed globes, a segment with a thickness of about 8 mm and running through the optic nerve head and the pupil had been prepared. The segments had been dehydrated in alcohol, imbedded it in paraffin, sectioned it for light microscopy and stained the tissues by the Periodic-Acid-Schiff (PAS) method and/or with hematoxylin eosin. All study material used in the present investigation were paraffin-embedded and stained histological sections. For the present study, we preferred sections stained by the PAS method since basal membranes, in particular Bruch’s membrane (BM) were better visualized by the PAS method than by the HE staining. The meridional orientation of the segment depended on the location of the tumour in the group of eyes with a malignant choroidal melanoma. In all other globes, the direction of the segment was horizontal. For all eyes, we took one section with a thickness of 4–6 μm and which ran through the central part of the pupil and optic nerve head, for further evaluation. The process of tissue fixation and processing of the histological slides as well as some post enucleation-associated tissue swelling, occurring before the fixative agent had fixed the tissue, had influenced the dimensions of the ocular tissue and globes. We did not correct for these changes since they might have affected the eyes of various axial length in a similar manner so that the comparison of globes of different axial length might not have been markedly affected by the changes.

Macroscopically and microscopically, we examined all globes for the presence of posterior scleral staphylomas, defined as a slight outpouching of the sclera. This outpouching was characterized by a shorter curvature radius in the staphylomatous region as compared to the neighbouring region on both sides of the staphylomatous area. Using the in-built millimeter scale in the objective of the microscope, we measured histomorphometrically within the staphylomatous region the thickness of the sclera, choroid, choriocapillaris, BM and retinal pigment epithelium (RPE) and the density of the choriocapillaris and RPE cells. For the assessment of the thickness of BM, RPE and the choriocapillaris, we used a magnification of ×400, while we measured the thickness of the sclera and whole choroid using a magnification of ×250. We determined the RPE cell density as cell count per 300 μm, and we measured the density of the choriocapillaris as cumulative length of open choriocapillaris vessels per 300 μm. In addition, we checked the BM for continuity and regularity (Figs 1–7). We defined a defect in the BM as any full-thickness interruption of BM outside of the optic nerve head region. We defined high myopia by an axial length of ≥26.0 mm (Xu et al. 2010). For subset of the eyes of the study population, we used a digitized image analysis system (Inverted microscope Axio Observer 5; Carl Zeiss Co., Jena, Germany) and re-measured the thickness of BM, choriocapillaris and RPE.

Using a statistical software program (spss for Windows, version 25.0; IBM-SPSS, Chicago, IL, USA), we assessed the mean values, standard deviations and 95% confidence intervals of the main outcome parameters (e.g. thickness of the sclera). Applying the Student t-test or the Mann–Whitney test for unpaired samples, we determined the significance of differences in these parameters between a study group consisting of eyes with a posterior scleral staphyloma and a control group of non-staphylomatous eyes matched for axial length and age with the group of staphylomatous eyes. We compared the measured parameters between various ocular regions of the same eyes using the Student t-test for paired samples. The level of significance was 0.05 (two-sided) in all statistical tests.

Results

The investigation included 246 eyes of 246 patients with a mean age of 62.3 ± 13.8 years (median: 64.0 years; range: 24–89 years). The mean axial length was 25.0 ± 2.9 mm (median: 24.0 mm; range: 20.0–37.0 mm). The study population consisted of 58 highly myopic globes (mean axial length: 29.4 ± 2.4 mm) and 188 non-highly myopic eyes (23.6 ± 1.1 mm). There were 70 (70/246 or 28.4%) glaucoma–myopic eyes (23.6/C6 24.0 mm; range: 20.0–24.0 mm) and 70 (70/246 or 28.4%) glaucoma–myopic eyes (23.6/C6 24.0 mm; range: 20.0–24.0 mm). The mean axial length was 29.4 ± 2.4 mm (median: 28.0 mm; range: 20.0–30.0 mm). The control group of non-glaucoma–myopic eyes consisted of 188 non-highly myopic eyes (23.6 ± 1.1 mm). There were 70 (70/246 or 28.4%) glaucoma–myopic eyes (23.6/C6 24.0 mm; range: 20.0–24.0 mm) and 70 (70/246 or 28.4%) glaucoma–myopic eyes (23.6/C6 24.0 mm; range: 20.0–24.0 mm). The mean axial length was 29.4 ± 2.4 mm (median: 28.0 mm; range: 20.0–30.0 mm). The control group of non-glaucoma–myopic eyes consisted of 188 non-highly myopic eyes (23.6 ± 1.1 mm). There were 70 (70/246 or 28.4%) glaucoma–myopic eyes (23.6/C6 24.0 mm; range: 20.0–24.0 mm) and 70 (70/246 or 28.4%) glaucoma–myopic eyes (23.6/C6 24.0 mm; range: 20.0–24.0 mm). The mean axial length was 29.4 ± 2.4 mm (median: 28.0 mm; range: 20.0–30.0 mm).

We determined the thickness of BM, choriocapillaris and RPE.

Fig. 1. Histophotograph [periodic acid-Schiff (PAS) staining] of a highly myopic eye with a posterior scleral staphyloma (inferior to the red arrow), with an abrupt thinning of the sclera at the border of the staphyloma (red arrow) to about 50% of the value of the neighbouring sclera (above the red arrow); Yellow arrow: Myopic retinoschisis starting at the border of the scleral staphyloma.
Scleral staphyloma was detected in 10 eyes with a mean axial length of 31.4 ± 3.0 mm (median: 31.5 mm; range: 28.0–37.0 mm). The prevalence of the scleral staphylomas increased significantly with axial length (Fig. 8).

The mean scleral thickness was 109 ± 25 µm in the centre of the staphyloma, and it was 280 ± 102 µm at the edge of the staphyloma. The mean height of the RPE cells measured 8.2 ± 2.8 µm, the mean RPE cell density was 19.6 ± 4.9 cells per 300 µm, and the mean BM thickness was 3.5 ± 1.3 µm. The mean thickness of the choriocapillaris measured 5.3 ± 2.8 µm and of the choroid as whole 21.5 ± 14.8 µm. The choriocapillaris density was 164 ± 99 µm per 300 µm. All eyes with a scleral staphyloma showed a collateral defect in BM. Within the group of eyes with scleral staphylomas, the BM defects were located at the border of the staphyloma as well as inside of the staphylomatous region. The length of BM defects ranged between 200 µm and 3 cm, and the number of BM defects within a staphyloma region ranged between 1 and 2.

The scleral staphyloma group was compared with a control group adjusted for age and axial length with the scleral staphyloma group. The control group included 33 eyes of 33 patients with a mean age of 56.6 ± 15.8 years and a mean axial length of 30.0 ± 1.9 mm (Table 1). The staphyloma group showed a significantly (p < 0.001) thinner sclera in
the centre of the staphyloma as compared to the corresponding area in the non-staphylomatous eyes. The prevalence of BM defects was significantly (p < 0.001) higher in the staphylomatous group (Table 1). Both groups did not differ significantly in RPE cell density (p = 0.84) and height (p = 0.13), BM thickness (p = 0.40), thickness of the choriocapillaris (p = 0.49) and density of the choriocapillaris (p = 0.13) (Table 1). The thickness of the sclera at the edge of the staphyloma was thinner, however not significantly thinner (p = 0.51) in the scleral staphyloma group than in the control group.

In a next step, the staphylomatous group was compared with the non-highly myopic group which consisted of the remaining eyes of the total study population. BM thickness in the staphylomatous regions as compared to BM thickness in corresponding regions in the non-highly myopic eyes did not differ significantly between both groups [3.5 ± 1.3 µm (range: 2–5 µm) versus 4.0 ± 1.4 µm (range: 1–6 µm); p = 0.28]. In a similar manner, the choriocapillaris thickness in the staphylomatous regions as compared to the choriocapillaris thickness in corresponding regions in the non-highly myopic eyes did not differ significantly between both groups [5.3 ± 2.8 µm (range: 0–9 µm) versus 4.5 ± 2.3 µm (range: 0–8 µm); p = 0.51].

Within the staphylomatous study group, BM thickness did not vary significantly between the staphylomatous region (3.5 ± 1.3 µm) and other regions of the eye [posterior pole: 4.2 ± 2.3 µm (p = 0.29); equator: 4.0 ± 1.4 µm (p = 0.68)]. In a similar manner, the choriocapillaris thickness did not vary significantly between the staphylomatous region (5.3 ± 2.8 µm) and other regions of the eye (posterior pole: 6.0 ± 9.2 µm (p = 0.72); equator: 5.9 ± 3.3 µm (p = 0.50)).

Using the digitized image analysis system, the re-measurements of the thickness of BM, choriocapillaris and RPE revealed results which did not differ significantly (all p > 0.05) from the results of the measurements performed with the in-built calibre.

**Discussion**

In this histomorphometric study on human globes, highly myopic eyes with posterior scleral staphylomas as compared to highly myopic eyes without staphylomas and as compared to non-highly myopic eyes were characterized by a statistically significant thinning of the sclera in the centre of the staphyloma and by a spatial correlation with a BM defect in the staphylomatous region. In contrast, the thickness of BM and choriocapillaris, choriocapillaris density, and density and height of the RPE did not differ significantly between both groups in the corresponding regions.

These histomorphometric findings agree with clinical OCT-based observations on posterior scleral staphylomas. These clinical studies reported about a marked choroidal thinning, which was most marked at the edge of the staphyloma and which occurred in addition to the axial elongation-associated choroidal thinning (Shinohara et al. 2016; Ohno-Matsui & Jonas 2019). In our histological study, it was mostly the sclera which showed in some eyes an almost abrupt change in its thickness at the edge of the staphyloma, while changes in thickness of the choroid were mostly smooth (Fig. 1). It has however to be taken into account, that in our study the choroidal thickness was prone to post-enucleation...
changes, such as a thinning due to loss of blood and spreading due to mechanical forces after opening of the globes for further histologic processing.

A new finding of our study as compared to clinical OCT-based investigations was that BM thickness did not differ between the staphylomatous region and other regions of the eye, and that BM thickness in the staphylomatous region as compared to BM thickness in corresponding regions in non-staphylomatous eyes neither varied significantly between the study group and control groups. It suggested that the whole complex of BM, RPE cells and choriocapillaris, except for the presence of a localized BM defect, were not markedly affected by the presence of the scleral staphyloma.

Another new finding of the present study was that the thickness of the choriocapillaris did not differ significantly between the staphylomatous group and the highly myopic control group (p = 0.49) or between the staphylomatous group and the non-highly myopic control group (p = 0.51). In a similar manner and fitting with the observation that BM thickness in the staphylomatous region did not differ between the study group and control groups, the RPE cell density in the staphylomatous region as compared to the RPE cell density in corresponding regions in non-staphylomatous eyes neither varied significantly between the study group and control groups. It suggested that the whole complex of BM, RPE cells and choriocapillaris, except for the presence of a localized BM defect, were not markedly affected by the presence of the scleral staphyloma.

A major finding of the present investigation was the association between posterior scleral staphylomas and localized BM defects in the highly myopic eyes (Figs 2 and 3). Although some highly myopic eyes without a staphylomatous region also showed localized BM defects, the association between the BM defects and scleral staphylomas was statistically significant (p < 0.001) (Table 1). In addition, there was a spatial correlation between the BM defect with the staphylomatous region, since the BM defect was located either inside of the staphylomatous region or close to it. It may suggest a pathogenic correlation between both morphological features. Interestingly, non-highly myopic eyes with secondary BM defects, for example, due to a toxoplasmotic scar, can show localized staphylomas of the sclera (Jonas & Panda-Jonas 2016). In these eyes with a secondary BM defect, the collateral sclera is usually bowed backward widely with a secondary widening of the choroidal space (sometimes called choroidal cavitation). In contrast, the eyes of our investigation showed a marked thinning of the choroidal space. A recent experimental investigation revealed that the elastic moduli of BM of porcine eyes was comparable to or higher than those for the sclera and cornea (Wang et al. 2018). Correspondingly, burst tests showed that, on average, BM could sustain an intraocular pressure of about 80 mmHg before rupture occurred (Wang et al. 2018).

In relationship to the tissue thickness, the BM stiffness was comparable or higher than those of other ocular tissues including the sclera. This finding of a relatively strong biomechanical strength of BM was supported by histomorphometric investigations that revealed that BM thickness was not associated with axial length (Jonas et al. 2014; Bai et al. 2017; Dong...
These and other findings led to the notion that axial elongation may occur by the production of BM in the equatorial region pushing BM at the posterior pole backward (Jonas et al. 2017). If that notion of BM playing a primary role in the process of axial elongation is valid, the question arises how the findings of the present study may be explained. A possible explanation could be that eyes with a posterior staphyloma have a locally decreased resistance of their sclera against the backward push of BM so that a local outpouching of the sclera developed. BM covered the bulged sclera on its inner side with the choroid interposed between and potentially compressed by, BM and sclera. The outpouching-associated increase in the circumference of the sclera and BM might have secondarily led to an over-stretching of BM resulting in a BM defect. A similar mechanism may be present in the development of macular BM defects in highly myopic eyes, in which due to the increase in the horizontal and vertical globe diameters, BM at the posterior pole may get stretched, first leading to an enlargement of the physiologic BM defect in the region of the optic nerve head (with development of a circular parapapillary gamma zone), and if the enlargement of the optic nerve head BM-opening is not sufficient to release the within-BM

Table 1. Histomorphometric measurements in the scleral staphyloma study group and the control group.

| Parameter                                                                 | Scleral staphyloma group (n = 10) | Control group (n = 33) (adjusted for age and axial length with the scleral staphyloma group) | Remaining group (n = 203) |
|---------------------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------------|-------------------------|
|                                                                           | Mean ± Standard deviation or Number | Range                                                                 | p-value*                | Mean ± Standard deviation or Number | Range | p-value**          |
| Age (years)                                                              | 63.6 ± 18.5                       | 36–82                                                                 | 62.2 ± 13.5             | 24–89 | 0.66              |
| Glaucoma                                                                 | 7 (70%)                           | 120–456                                                                | 6.0 ± 8.3               | 11–56 | 0.001             |
| Axial length (mm)                                                         | 31.4 ± 3.0                        | 28–37                                                                  | 23.9 ± 1.3              | 20.0–27.0 | <0.001 |
| Scleral thickness in staphyloma centre or in corresponding regions (µm) | 109 ± 25                          | 72–156                                                                 | 407 ± 81               | 264–568 | 0.004             |
| Scleral thickness at staphyloma edge (µm)                                | 280 ± 102                         | 120–456                                                                | 6.0 ± 8.3               | 11–56 | 0.002             |
| Retinal pigment epithelium cell density per 300 µm in staphyloma centre or corresponding regions | 19.6 ± 4.9 | 12–27 | 21.1 ± 5.7 | 6–28 | 0.84 | 26.5 ± 8.3 | 11–56 | 0.002 |
| Retinal pigment epithelium height in staphyloma centre or in corresponding regions (µm) | 8.2 ± 2.8 | 4–12 | 6.1 ± 2.5 | 3–11 | 0.13 | 6.6 ± 1.8 | 4–9 | 0.19 |
| Bruch’s membrane thickness in staphyloma centre or in corresponding regions (µm) | 3.5 ± 1.3 | 2–5 | 4.2 ± 2.3 | 2–10 | 0.40 | 4.0 ± 1.4 | 1–6 | 0.28 |
| Bruch’s membrane defects                                                  | 10/10 (100%)                      | <0.001                                                                 | 1                      | <0.001 |
| Choriocapillaris thickness in staphyloma centre or in corresponding regions (µm) | 5.3 ± 2.8 | 0–9 | 4.4 ± 2.8 | 2–11 | 0.49 | 4.5 ± 2.3 | 1–8 | 0.51 |
| Choriocapillaris density per 300 µm in staphyloma centre or in corresponding regions (µm/µm) | 164 ± 99 | 0–264 | 226 ± 38 | 180–276 | 0.13 | 166 ± 71 | 18–270 | 0.84 |
| Choroidal thickness, total, in staphyloma centre or in corresponding regions (µm) | 21.5 ± 14.8 | 9–54 | 42.3 ± 39.6 | 15–126 | 0.20 | 35.8 ± 23.3 | 14–100 | 0.97 |

* p-value for the comparison between the scleral staphyloma group and the control group adjusted for age and axial length with the scleral staphyloma group.

** p-value for the comparison between the scleral staphyloma group and the ‘Remaining Group’.
stress, secondary cracks in BM (lacquer cracks) and holes (BM defects) may develop (Jonas et al. 2013; Zhang et al. 2019).

Interestingly, the thickness of the choriocapillaris in the staphylomatous region (outside of the area of the BM defect) was similar to the choriocapillaris thickness in corresponding areas of highly myopic eyes without staphylomas or non-highly myopic eyes (Table 1). Correspondingly, the density of the RPE cells in the staphylomatous region did not differ between the staphylomatous study group and the control groups. Taking into account, that BM thickness in the staphylomatous region was neither different between the study groups and the control groups, the findings suggest that in the region of the staphyloma BM may not primarily be changed, in particular it may not have been elongated. Otherwise, the RPE cell density and the choriocapillaris density would have been reduced due to a stretching effect.

When we discuss the findings of our study, the study’s limitations have to be taken into account. First, post enucleation changes such as tissue swelling due to the ischaemia before fixation and fixation-related shrinkage of the tissue will have in general affected the dimensions of the ocular tissues. In addition, mechanically induced changes during the histological processing of the globes may have affected the width of the choroidal space in particular, leading to a falsely thick choroid. In addition, rapid blood loss out of the choroid shortly after enucleation before fixation may have decreased the choroidal volume. It makes one infer, that the choroidal thickness measurements could be only rough estimates of the real intravital dimensions. Other tissues such as the RPE and BM as compared to the choroid may have been affected to a lower degree by post-mortem ischaemia-related and fixation-induced parameters. Second, due to its design as a retrospective histologic study, our investigation may have a marked selection bias and could not give reliable information on the prevalence of changes, such as the presence of BM defects, in the general population. In view of the scarcity of enucleated human globes, however, there may not be a major alternative to avoid this limitation. Third, the globes included into our investigation were enucleated for specific clinical reasons, so that the results obtained may not directly be generalizable to eyes without these diseases. Fourth, serial sections of the globes were not available so that it could not be confirmed that the section was located exactly in centre of the optic nerve head. It also implies that only those staphylomas could be detected which were located in the histological section. It is another reason why the findings of our study could not be used to describe representative percentages. Fifth, the number of eyes with staphylomata was relatively small limiting the power of a statistical analysis to detect clinically significant differences. Sixth, the study design did not allow us to examine whether the eyes with staphylomas had collagen defects predisposing them to a staphyloma formation. Seventh, the eyes included into our study were of patients of European descent so that it has remained unclear whether and to which degree the results of our investigations can be transferred onto patients from Asia. This limitation may be of particular interest since East Asia and Southeast Asia have witnessed a marked increase in the prevalence of axial myopia in the young generation during the last three decades, and one has assumed that myopic maculopathy including scleral staphylomas could further increase in its importance as one of the most common causes of irreversible blindness (Morgan et al. 2012; Dong et al. 2019b). Eighth, the measurement of the thickness of choriocapillaris and BM upon light microscopy is limited by the maximal magnification of the image by the light microscope (Okubo et al. 1999). Considering that the thickness of BM and choriocapillaris is in the range of 2–5 µm, the spatial resolution of the light microscope may not be fully sufficient for an accurate measuring of these small dimensions. It may lead to an increase noise in the measurements preventing the detection of significant associations between parameters or significant differences between groups.

In conclusion, the histomorphometric examination of posterior scleral staphylomas revealed that the RPE and choriocapillaris density, thickness of BM and choriocapillaris and the RPE height did not differ significantly between highly myopic eyes with scleral staphylomas, highly myopic eyes without staphylomas and non-highly myopic eyes in the corresponding regions. The sclera in the staphylomatous region was markedly thinned, in some eyes with an abrupt change in scleral thickness at the edge of the staphyloma. Scleral staphylomas were significantly associated with an increased prevalence of localized BM defects within the staphylomatous region. Combining these histological findings may lead to the notion that a locally reduced resistance of the sclera against a backward pushing BM leads to a local outpouching of the sclera. The outpouching-associated increase in curvature may stretch BM with the sequel of a localized BM rupture (defect). This notion supports the role BM may potentially play in process of axial elongation in myopic eyes.

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