• Clinical Research •

Immunohistochemical clinicopathologic correlation and OCT analysis of idiopathic and secondary epiretinal membrane specimens

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Abstract

● **AIM:** To investigate correlation of clinical, optical coherence tomography (OCT), and immunohistochemistry (IHC) in idiopathic and secondary epiretinal membrane (ERM).

● **METHODS:** Retrospective review of patients undergoing pars plana vitrectomy with membrane peeling (PPV-MP). Excised membranes were evaluated by IHC staining for glial fibrillary acidic protein (GFAP), α-smooth muscle actin (α-SMA), cytokeratin, pigment, and fibrosis grading. Pre-operative and post-operative OCTs, and clinical follow-up information at least 3mo were collected.

● **RESULTS:** This study analyzed 104 eyes of 104 patients, of whom 83 (79.8%) had idiopathic ERM (iERM) and 21 (20.2%) had secondary ERM (sERM). Mean age at the time of surgery was 67.3±10.5y. OCT demonstrated greater foveal distortion (*P*=0.012), intraretinal (IR) spaces (*P*=0.009), and ellipsoid zone (EZ) discontinuity (*P*=0.022) in sERMs. Poorer pre-operative BCVA for all cases correlated with foveal distortion (*P*=0.011), loss of parallelism (*P*=0.014), IR spaces (*P*=0.027), and EZ disruption (*P*=0.012). Poorer post-operative BCVA for all cases was associated with foveal distortion (*P*=0.027). GFAP was expressed in nearly all ERMs (99%). Pigment was expressed more in sERM (61.9%) compared with iERM (21.7%; *P*=0.005) and associated with poorer post-operative BCVA (*P*=0.035) and ERM dehiscence (*P*=0.008). Fibrosis severity correlated with poorer pre-operative BCVA (*P*=0.027). GFAP intensity correlated with longer symptom duration (*P*=0.002).

● **CONCLUSION:** The high prevalence of many cell types not distinguished for iERM versus sERM suggests a common pathway of formation with local influences rather than an etiologic cell type or substrate location.

● **KEYWORDS:** epiretinal membrane; histopathology; optical coherence tomography
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INTRODUCTION

Epiretinal membrane (ERM) proliferation is characterized by cellular migration and non-neovascular proliferation on the inner retinal surface, extracellular matrix production, and tissue contraction, which may cause a spectrum of visual effects. ERM prevalence has been estimated to be about 10% among older patients; some studies report up to 39% prevalence but only about 2.6% are severe enough to cause notable symptoms[1].

Nonvascular ERMs not associated with frank proliferative vitreoretinopathy (PVR) have been variously categorized as idiopathic ERM (iERM), since the precise mechanism of formation is not well established[2], or secondary ERM (sERM) since there etiology has been intuitively associated with a breach in the peripheral retina as in retinal tears, retinal detachment, trauma, intraocular surgery, or comorbid ocular pathologies[1]. ERMs are most commonly mild and asymptomatic, and most iERM, once formed, are nonprogressive[3]. Patients with sufficiently severe visual symptoms [metamorphopsia, decreased visual acuity (VA), macropsia] are considered for pars plana vitrectomy with membrane peeling (PPV-MP)[1,4]. PPV-MPs account for a

sizeable fraction of all vitrectomies with a large fraction successfully regaining at least some of their lost vision, a process that may continue for a couple of years after surgery[5]. ERMs have been observed to manifest a cellophane or consolidated and fibrotic morphology and can present with varying degrees of surface wrinkling, axoplasmic stasis, pigmentation, intraretinal (IR) fluid accumulation, and underlying retinal pigment epithelial (RPE) pigment alterations[6-7].

Efforts to determine the etiology, pathophysiology, and prognosis initially focused on clinical features as well as histopathology of removed ERM specimens. More recently, optical coherence tomography (OCT) has provided important *in vivo* insights for management and pathophysiology. However, imaging and histopathologic features have been challenging to correlate consistently with clinical features.

The key histopathological components of removed ERM specimens, as demonstrated by transmission electron microscopy (TEM), include RPE cells, fibroblasts/myofibroblasts, and glial cells[8]. The etiology of the moderated frequency of RPE cells even in iERMs has been difficult to explain. Removed ERM specimens have been studied more recently, by immunohistochemistry (IHC), to gain insight into pathogenesis and to establish clinicopathologic correlation[9-12].

OCT is highly sensitive in detecting and characterizing ERMs *in vivo*[12]. Previous studies have identified OCT characteristic features of ERMs and aimed to correlate their impact on vision and prognosis in iERMs[13-15].

The goal of this study was to investigate and attempt to correlate ERMs with respect to the demographic characteristics, clinical impact, IHC, and OCT markers and post-operative visual outcomes. These parameters were analyzed in all patients as well as in subgroups of idiopathic and sERM, and the results were compared between groups.

PARTICIPANTS AND METHODS

Ethical Approval The institutional review board at the University of Miami Miller School of Medicine approved the study protocol (#MOD00009934). The study was conducted in accordance with the tenets of the Declaration of Helsinki.

A retrospective review of the eye pathology lab files in which ERM specimens of patients who underwent PPV-MP, at the Bascom Palmer Eye Institute, University of Miami, during January 2010 to June 2020 when specimens for that diagnosis ceased to be submitted. These were predominantly submitted by two of the authors (Smiddy WE, Flynn HW).

Demographic information, including age and gender, was collected from the clinical chart review. Each case was classified as idiopathic or secondary, but only sERMs associated with retinal tears or retinal detachment were included in the study cohort. Cases secondary to diabetic retinopathy, full-thickness macular hole, endophthalmitis, or uveitis were excluded. In addition, only cases with pre-operative and post-operative OCTs, and at least 3mo of clinical follow-up information were included. All OCT evaluations were with the Cirrhus (spectral domain) model.

The presence of visual symptoms (decreased vision or metamorphopsia), phakic status, and pre- and post-operative best-corrected visual acuity (BCVA) were recorded. The clinical findings compared between iERM and sERM cases were pre-operative BCVA, post-operative BCVA (in the 3mo post-operative period), and BCVA improvement after surgery. The VA measurements were expressed as logarithm of the minimum angle of resolution (logMAR). The duration of the symptoms (DOS) was recorded and categorized as followed: 1: <6mo, 2: 6–11mo, 3: ≥12mo.

Surgically excised ERM specimens were analyzed using IHC to evaluate the expression of α-smooth muscle actin (α-SMA) as a marker of myofibroblasts/fibroblasts, cytokeratin as a marker of retinal RPE cells, and glial fibrillary acidic protein (GFAP) as a marker of Müller cells and gliosis. The presence of free pigment was tabulated and considered to be an RPE marker. The intensity of immunostaining was graded as none (0), mild (1+), moderate (2+), or strong (3+). In addition, the degree of fibrosis was graded histologically.

Central foveal thickness (CFT) was measured from spectral-domain OCT. OCT images were graded for an array of characteristics using the standard photographic grading method analogous to that developed for and used in the Diabetic Retinopathy Studies. That is, examples of several OCT features were selected for absent to mild, moderate, or severe levels of severity (grades 0 through 2), and the study OCTs were graded for each feature as they most resembled the respective standard OCT images. These features included the degree of foveal distortion (presence of foveal pit, flattening of fovea, prolapse of fovea)[15], degree of ERM dehiscence from the internal limiting membrane (ILM), surface wrinkling, loss of retinal layer parallelism, IR cystoid spaces, external limiting membrane (ELM), and ellipsoid zone (EZ) discontinuity. The central bouquet was evaluated for the presence or absence of a vitelliform lesion (VL). All OCT images were independently reviewed by two masked ophthalmologists. Differences were then jointly adjudicated.

Statistical Analysis The Kruskal-Wallis rank-based Chi-square formula was used to evaluate the relationship among multiple clinical, IHC, and OCT findings across all cases, as well as between the two subgroups. A Cochran-Armitage trend test was used to assess the relationship between ERM type and histologic marker expression level.

RESULTS

Baseline Demographics This study analyzed 104 eyes of 104 patients, of whom 83 (79.8%) had iERM and 21 (20.2%)

Table 1 Comparison of pre-operative and post-operative logMAR visual and anatomical parameters between idiopathic and secondary ERM mean±SD

Parameters	Idiopathic ERM (*n*=83)	Secondary ERM (*n*=21)	Test statistic	*P*
Pre-operative BCVA	0.64±0.30	0.81±0.25	*Z*=1.94[a]	0.052[b]
Post-operative BCVA	0.30±0.33	0.55±0.25	*Z*=2.46[a]	0.014[a]
BCVA improvement	0.33±0.16	0.25±0.14	*Z*=−1.01	0.311

Tests used: Wilcoxon rank-sum or Kruskal-Wallis test. *P*<0.05 considered statistically significant. [a]Statistically significant; [b]Borderline statistically significant. logMAR: Logarithm of the minimum angle of resolution; SD: Standard deviation; ERM: Epiretinal membrane; BCVA: Best-corrected visual acuity.

had sERM. Mean age at the time of surgery was 67.3±10.5y. Patients with iERM were older (68.8±9.0y) than those with sERM (61.5±13.7y; *P*=0.03). Males predominated overall (62.5%, *P*=0.584) and within both the iERM (60.2%) and sERM (71.4%) subgroups and were not different between diagnostic subgroups (*P*=0.49).

Clinical Results in iERM Versus sERM Patients with iERM had mean pre-operative BCVA Snellen equivalent of 20/87 compared to the patients with sERM with mean 20/135 (Table 1). Mean post-operative BCVA was better for iERM (20/39 Snellen equivalent) than for sERM (20/71 Snellen equivalent).

The improvement in BCVA post-operatively was not different between iERM and sERM (*P*=0.311). The mean duration of symptoms was significantly longer in patients with iERM (6–11mo to ≥12mo) compared to those with sERM (<6–11mo; *P*=0.003).

OCT Features of iERM Versus sERM The interobserver agreement exceeded 86% for all features. Mean pre-operative CFT was similar in both the iERM group and in the sERM group. Eyes with sERMs had more severe foveal distortion, more severe IR spaces, and more common EZ disruption.

Surface wrinkling, retinal cell layer parallelism, ERM dehiscence from the surface, and presence of a were not different in iERM and sERM. Mean CFT was similar preoperatively in both the iERM and sERM groups, and was reduced post-operatively for both iERMs (to 362.82±76.97 μm post-operatively; *P*<0.001) and sERMs (to 383.65±142.53 μm; *P*=0.010). No difference in the magnitude of change was observed (*P*=0.950) between the two groups (Table 2).

Correlation of OCT and Clinical Features Increased pre-operative CFT correlated with foveal distortion, loss of parallelism, EZ, and absence of VL. There was no correlation between CFT and the presence of IR spaces, retinal surface wrinkling, or dehiscence of ERM. Poorer pre-operative BCVA was associated with foveal distortion, loss of layer parallelism, EZ discontinuity, and the presence of IR spaces. However, VL, retinal surface wrinkling, and ERM dehiscence were not correlated with pre-operative BCVA.

Poorer post-operative logMAR BCVA was associated with increased foveal distortion; mean post-operative logMAR BCVA was 0.22 (20/33 Snellen) with no distortion, 0.31 (20/41) with mild distortion, and 0.47 (20/59) with marked distortion (*P*=0.039). Poorer post-operative logMAR BCVA was statistically associated with EZ discontinuity and was borderline significant for IR spaces. Loss of layer parallelism, retinal surface wrinkling, ERM dehiscence, and presence of VL were not associated with post-operative logMAR BCVA. There was no statistically significant association between BCVA improvement and OCT parameters (Table 3).

Correlation of IHC Markers with Clinical and OCT Features GFAP was expressed in 99% of both iERM and sERMs with a frequency of moderate or severe expression. GFAP staining intensity had a positive correlation with longer symptom duration; this relationship was not statistically significant for other markers.

Pigment was more commonly present in sERMs than in iERMs for both moderate and severe density. Moderate to severe fibrosis (grades 2 and 3) was borderline more frequent with sERMs compared to iERMs (one sided *P*=0.034, two sided *P*=0.060). SMA and cytokeratin was not statistically significantly distributed between iERMs and sERMs (Table 4).

The only histological marker that was correlated with BCVA was increased fibrosis and poorer preoperative logMAR and pigment for poorer postoperative logMAR (Table 5). Cytokeratin, SMA, and GFAP expression did not differ between iERMs versus sERMs. More severe fibrosis was correlated with poorer pre-operative logMAR BCVA. Increased pigment expression was associated with poorer post-operative logMAR BCVA. No IHC markers was correlated with degree of post-operative BCVA improvement.

ERM dehiscence was associated with presence of pigment marker (general association *P*=0.008; row-means *P*=0.035) and GFAP level staining density (nonzero correlation *P*=0.022; row-means *P*=0.033). Other OCT features—retinal surface wrinkling, layer parallelism loss, IR spaces, and VL-were not correlated with IHC markers (Table 6).

DISCUSSION

This study evaluated potential correlations between the clinical, OCT, and IHC characteristics of iERM and sERMs

Table 2 Comparison of OCT structural features between idiopathic and secondary ERM

OCT feature	Idiopathic ERM (*n*=83)	Secondary ERM (*n*=21)	*Z* statistic[b]	*P*
Preoperative CFT (μm)	491.30±110.80	515.09±146.16	1.09	0.274
Foveal distortion (grade 0/1/2), %	9.64/61.4/28.9	0/42.9/57.1	−2.62	0.012[a]
Wrinkle (grade 0/1/2), %	21.7/63.9/14/5	19.0/52.4/28.6	−1.11	0.268
Parallelism loss (grade 0/1/2), %	6.0/53.0/40.7	00.0/42.9/57.1	−1.57	0.116
IR spaces (grade 0/1/2), %	63.9/16.9/19.3	33.3/23.8/42.9	−2.64	0.009[a]
ERM dehiscence (grade 0/1/2), %	71.1/22.9/6.0	61.9/33.3/4.8	−0.55	0.681
EZ discontinuity (grade 0/1/2), %	31.3/44.6/24.1	9.5/38.1/52.4	−2.29	0.022[a]

The grading system for different OCT features are as follow: foveal distortion presence of foveal pit=0, flattening of fovea=1, prolapse of fovea=2; ERM dehiscence from the ILM categorized as mild (<30%)=0, moderate (30%–50%)=1, and severe (>50%)=2, surface wrinkling: non=0, mild=1, moderate=2; loss of retinal layer parallelism as mild=0, moderate=1, severe=2; IR cystoid spaces as percent of the macular thickness: mild (<10%)=0, moderate (10%–50%)=1, or severe (>50%)=2, EZ discontinuity was graded as mild (no EZ disruption)=0, moderate (attenuated EZ)=1, or severe (complete EZ loss)=2. [a]*P*<0.05. [b]Cochran-Armitage trend test. OCT: Optical coherence tomography; ERM: Epiretinal membrane; CFT: Central foveal thickness; EZ: Ellipsoid zone; ILM: Internal limiting membrane; IR: Intraretinal.

Table 3 Association of OCT features with clinical and visual parameters in eyes with ERM

OCT feature	CFT	Pre-operative logMAR BCVA	Post-operative logMAR BCVA	logMAR improvement
Foveal distortion	*P*<0.001 (p)	*P*=0.011 (n)	*P*=0.027 (n)	*P*=0.960
Loss of parallelism	*P*=0.004 (p)	*P*=0.014 (n)	*P*=0.221	*P*=0.390
EZ discontinuity	*P*=0.007 (p)	*P*<0.001 (n)	*P*=0.039 (n)	*P*=0.303
IR spaces	*P*=0.370	*P*=0.027 (n)	*P*=0.059	*P*=0.194
Vitelliform lesion	*P*=0.022 (n)	*P*=0.295	*P*=0.753	*P*=0.548
Wrinkling/dehiscence	*P*=0.107/*P*=0.596	*P*=0.377/*P*=0.592	*P*=0.873/*P*=0.745	*P*=0.830/*P*=0.921

Statistical tests: Kruskal-Wallis and Wilcoxon rank-sum tests, as appropriate. p: Positive association; n: Negative association; ERM: Epiretinal membrane; OCT: Optical coherence tomography; CFT: Central foveal thickness; BCVA: Best-corrected visual acuity; EZ: Ellipsoid zone; IR: Intraretinal; logMAR: Logarithm of the minimum angle of resolution.

Table 4 Comparison of histologic marker expression between primary and secondary ERM groups

Histologic marker	Idiopathic ERM, Grade 0+1 (0–1)/2+3 (2–3), %	Secondary ERM, Grade 0+1 (0–1)/2+3 (2–3), %	*P*[b]
GFAP	18.0 (0.00–18.07)/81.9 (49.40–32.53)	14.2 (4.76–9.52)/85.7 (66.7–19.0)	0.396
Pigment	93.9 (78.31–15.66)/6.02 (4.82–1.20)	85.7 (38.1–47.2)/14.2 (14.2–0)	0.005[a]
Fibrosis	50.6 (6.02–44.58)/49.3 (48.19–1.20)	38.1 (0–38.1)/61.9 (47.6–14.2)	0.060
SMA	47.9 (10.84–36.14)/53.0 (50.60–2.41)	38.0 (0–38.1)/61.9 (57.1–4.76)	0.192
Cytokeratin	39.7 (9.64–30.1)/60.2 (56.6–3.61)	14.2 (4.76–9.52)/85.7 (80.9–4.7)	0.065

Grades 0–1: Absent or mild expression; Grades 2–3: Moderate to strong expression. [a]*P*<0.05. [b]Cochran-Armitage trend tests. ERM: Epiretinal membrane; GFAP: Glial fibrillary acidic protein; SMA: Smooth muscle actin.

Table 5 Association between histological markers and visual acuity

Marker	Preoperative logMAR	Best postoperative logMAR	logMAR improvement
Pigment	0.798	0.035[a]	0.301
Fibrosis	0.027[a]	0.217	0.950
SMA	0.303	0.438	0.735
Cytokeratin	0.462	0.627	0.559
GFAP	0.737	0.853	0.927

All *P*-values were obtained using the Kruskal-Wallis nonparametric test. [a]*P*<0.05. GFAP: Glial fibrillary acidic protein; SMA: Smooth muscle actin; logMAR: Logarithm of the minimum angle of resolution.

in a modest-sized cohort. The most notable finding in the current paper was the relatively few correlates between IHC markers and the category of ERM, and IHC markers between clinical or OCT parameters. GFAP indicating glial cells was present in almost all specimens regardless of etiology (iERM *vs* sERM), but the intensity of staining was correlated with duration of the ERM-related visual symptoms (more in longer duration). Pigment was more commonly found in sERMs, but the presence of cytokeratin (RPE staining) was not statistically significantly different between iERM and sERM specimens. Pre-operative BCVA was associated with more severe fibrosis and pigment (along with sERMs) and with poorer postoperative BCVA. The current study cohort was mostly consistent with reported demographics, as patients with iERMs were older, had better pre- and post-operative BCVA, and had longer duration of symptoms than sERMs[16].

Table 6 Association of OCT parameters with histologic markers (*P* values)

OCT parameter	Pigment	Fibrosis	SMA	Cytokeratin	GFAP
Preoperative CFT	0.164	0.078	0.131	0.501	0.157
Foveal distortion	0.468	0.090	0.966	0.980	0.479
Wrinkle	0.396	0.370	0.121	0.536	0.224
Parallelism loss	0.773	0.501	0.111	0.855	0.364
IR spaces	0.400	0.103	0.580	0.833	0.208
Dehiscence	0.008[a]	0.738	0.493	0.132	0.064[b]
Vitelliform lesion	0.152[c]	0.586[c]	0.525[c]	0.790[c]	0.715[c]

[a]Also "row means differ" *P*=0.0346. [b]Although the overall *P*=0.0639, nonzero correlation *P*=0.0225 and row means differ *P*=0.0331 were significant. [c]Cochran-Armitage trend test (two-sided). All other entries are CMH "general association" two-sided *P* values. OCT: Optical coherence tomography; CFT: Central foveal thickness, IR: Intraretinal; GFAP: Glial fibrillary acidic protein; CMH: Cochran-Mantel-Haenszel.

Many OCT features have been studied for their correlation with clinical features, including foveal distortion, IR spaces, and EZ discontinuity were more common and severe in sERMs. Studies have mostly highlighted inner retinal features such as displacement by traction effects[15-17] or deeper retinal effects such as EZ integrity, ELM continuity, and cone outer segment tip (COST) line[18-19]. The current study also found foveal distortion and EZ discontinuity to be predictors of poorer visual outcomes. Additionally, many have observed cystoid change to indicate chronicity and to be associated with poorer surgical prognosis[20].

The paucity of clinical and OCT feature associations with IHC features was contrary to the hypothesized concepts of previous histologic studies and theories. RPE cells have been found to be the most common cell type in removed iERM specimens by TEM[5]. Although a high proportion of glial or contractile-potent cells have been found in both iERMs and sERMs; a comprehensive, comparative study is lacking in the literature. Increased pigment in sERMs has been reported and is intuitive to the presumption that liberated RPE cells are the substrate for sERMs, but cytokeratin staining does not support that theory. The higher frequency of pigment might imply the incorporation of liberated free pigment from the RPE, or originally RPE cells that subsequently transformed to glial cells. The current study did not find a predominance of RPE cells in sERMs. The predominance of inner retinal cells has been widely reported in histological studies[8-9,11], sometimes specifically identified as Müeller cells[10,21], or hyalocytes[11].

Studying cell types can help elucidate pathogenic mechanisms. Pathogenic theories have been comprehensively reviewed by Tsotridou *et al*[22]. Glial cells may contribute to membrane development through migration, extracellular matrix production, and of gaining contractile potential. While it is intuitive that they are the closest cell source to ERMs, the finding of other cells (RPE, fibrocytes, myofibroblasts) suggests a more complex mechanism. Some have suggested that trans-differentiation into other cells might be mediated through an as yet incompletely defined process of proteomic/epigenetic expression mechanism[23-24] (possibly stimulated by inflammatory, growth factor, or angiogenic signaling)[25]. Yang *et al*[9] has provided some evidence that transforming growth factor (TGF)-beta1 can mediate trans differentiation. Proteomic and cytokine studies implicate interleukin (IL)-6, TGF-β, and monocyte chemoattractant protein (MCP)-1 in driving glial activation and myofibroblastic differentiation, suggesting biochemical parallels with PVR. Studies by Sheybani *et al*[26] further demonstrated that inflammatory cells predominate in uveitis-associated sERM, emphasizing that histologic heterogeneity reflects the underlying systemic or retinal condition.

Machemer and Laqua[27] may have observed this process long before recent cell biology discoveries and techniques in his seminal studies in a PVR monkey model from which he hypothesized the distribution of cell types fit a temporal stage of development with the initiating cell being the RPE, followed by inflammatory macrophages and subsequently fibrocytes (which he hypothesized metaplased from the RPE cells). He did not describe glial cells as a component in his experimental system. However, glial cells (the predominant cell type in most other studies) were observed in the current study to be more numerous with longer duration on symptoms, as has been previously observed[28]. It is possible that glial cell dominance at a later stage reflects a quiescence of the other, formative, acute phase factors. The finding that there are not overtly different cells in the iERMs versus sERMs in the current study, and the lack of a clear and consistent association with the OCT features, suggests such a, temporally dependent population of the ERM cells, if there is a common pathway, then studies of PVR pathogenesis might be more applicable to iERM than otherwise though. This may even suggest that the cellular pathways to ERM formation due to various inciting stimuli might be more common than has been hypothesized[26]. The

moderately high frequency of RPE cells in iERM specimens, discovered in the earliest histologic studies of specimens[29] remains an enigma, but might be the product of similar genomic mechanisms.

The current study suggests glial cells as the final, even cicatricial manifestation of the process, since these specimens were derived from a quiescent process after a more active, inflammatory driven formation process that began with either a different cell type or a different IHC expression profile.

Future translational studies integrating OCT biomarkers with molecular and cytokine profiling may enable earlier pharmacologic interventions to prevent irreversible glial remodeling and improve visual prognosis[30].

This study is limited by its retrospective design. Non-consecutive submission of specimens to the pathology may introduce selection bias toward more symptomatic or severe cases requiring PPV-MP, as well as a potential bias toward larger, more cohesive ERMs that are of appropriate size to be submitted and processed. Also, surgeries were done by different surgeons who each may have had different selection biases towards surgical case selection or specimen submission.

In conclusion, this study demonstrates that IHC composition somewhat surprisingly did not correlate well with the underlying etiology of ERM (iERM *vs* sERM) and correlates weakly with key OCT features that suggest more aggressive or intense ERM nature. The non-distinguishing cell marker distribution might suggest a more common pathway of formation than previously thought.

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