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Case Report

Long-Term Structural Stabilization and Functional Improvement in Full-Thickness Macular Hole Following Stem Cell Therapy: A 10-Year Case Report

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Abstract

Full-thickness macular hole (FTMH) is a common macular disorder associated with progressive visual deterioration and structural worsening over time. Increasing evidence suggests that, beyond mechanical factors, inflammatory processes and immune system activation play a significant role in the pathogenesis and progression of the disease, contributing to retinal microenvironment dysregulation.

We present the case of a 33-year-old male patient with traumatic FTMH who underwent combined intravitreal and intravenous autologous stem cell therapy. Baseline optical coherence tomography (OCT) revealed a FTMH associated with intraretinal cysts, neuroepithelial detachment, and epiretinal membrane formation. Over a 10-year period, the patient reported sustained functional improvement, including increased autonomy and enhanced performance in daily and work-related activities.

Follow-up OCT demonstrated persistence of the macular hole without complete anatomical closure; however, significant structural changes were observed, including absence of neuroepithelial detachment, reduction of retinal edema, and a more homogeneous retinal architecture. Retinal thickness analysis showed a decrease from 344.3 µm at baseline to 307.8 µm at follow-up.

These findings suggest that therapeutic strategies targeting inflammation, glial dysfunction, glutamate excitotoxicity, and cellular bioenergetics may contribute to long-term retinal stabilization. This case supports the concept that structural stabilization and functional improvement may represent clinically meaningful outcomes, even in the absence of complete anatomical closure.

Keywords: *Full thickness macular hole, immunomodulation, Müller cells, stem cell therapy, optical coherence tomography.*

Abbreviations

FTMH: Full Thickness Macular Hole.

OCT: Optical Coherence Tomography

Introduction

Full-thickness macular hole (FTMH) is a common macular disorder associated with loss of central vision and an impaired quality of life. It is typically idiopathic, although it may also be associated with trauma [1]. The natural clinical course of this condition is primarily characterized by a decline in visual acuity over time and an enlargement of the macular hole. It is also associated with other pathological findings in the retina, such as drusen, retinal pigment epithelium abnormalities, and epiretinal membranes [2]. The latter is a translucent fibrous membrane forming on the internal limiting membrane. The epiretinal membrane can pull on the retina, causing damage to the inner retinal layers, and displacing Müller cells and photoreceptors, resulting in visual disturbances such as metamorphopsia and decreased visual acuity [3]. Vision impairment has a profound impact on patients, increasing the risk of falls and accidents and reducing their quality of life [4].

FTMH is defined as a foveal defect involving all retinal layers, from the internal limiting membrane to the photoreceptor layer. The most widely accepted pathogenesis of the disease is pathological anteroposterior traction of the vitreous cortex on the fovea and perifoveal area. However, this is not the only mechanism involved in the formation and progression of FTMH [5]. Another important mechanism is the formation of cysts within the outer plexiform layer; as these cysts develop, the macular hole enlarges and its edges become elevated, thus promoting the progression of the disease [6]. There is increasing evidence highlighting the central role of Müller cell dysfunction in the pathophysiology of FTMH. Müller cells are closely connected with retinal neurons, participating in glutamate recycling, substance exchange in ganglion cells and extracellular ion homeostasis, and are involved in mediate neuronal cell protection [7].

In recent years, there has been a growing interest in the role of the immune system in both the pathogenesis and repair of macular holes. An increase in pro-inflammatory cytokines, such as IL-17, IL-15, IFN-γ, and TNF-β, among others, has been detected in the aqueous humor of patients with idiopathic macular holes [8]. On the other hand, an increased peripheral blood lymphocyte count has been observed in these patients. In the pathogenesis of macular holes, Müller cells are affected, promoting an increase in the number of T helper cells, which destroy the blood-retinal barrier and come into contact with transitional pigment cells and glial cells, secreting cytokines that promote a pro-inflammatory response [9]. Although immune activation is not considered the primary initiating factor, it likely plays a significant role in the perpetuation and progression of the disease and may represent a potential therapeutic target.

Below, we will introduce the case of a patient who initially presented with FTMH and underwent stem cell therapy administered by the intravitreal and intravenous route. Ten years after therapy, we are presenting the main clinical and structural findings. These findings may provide insight into novel therapeutic approaches for this challenging condition, particularly given the immunomodulatory and neuromodulatory properties of stem cell-based therapies.

Case Presentation

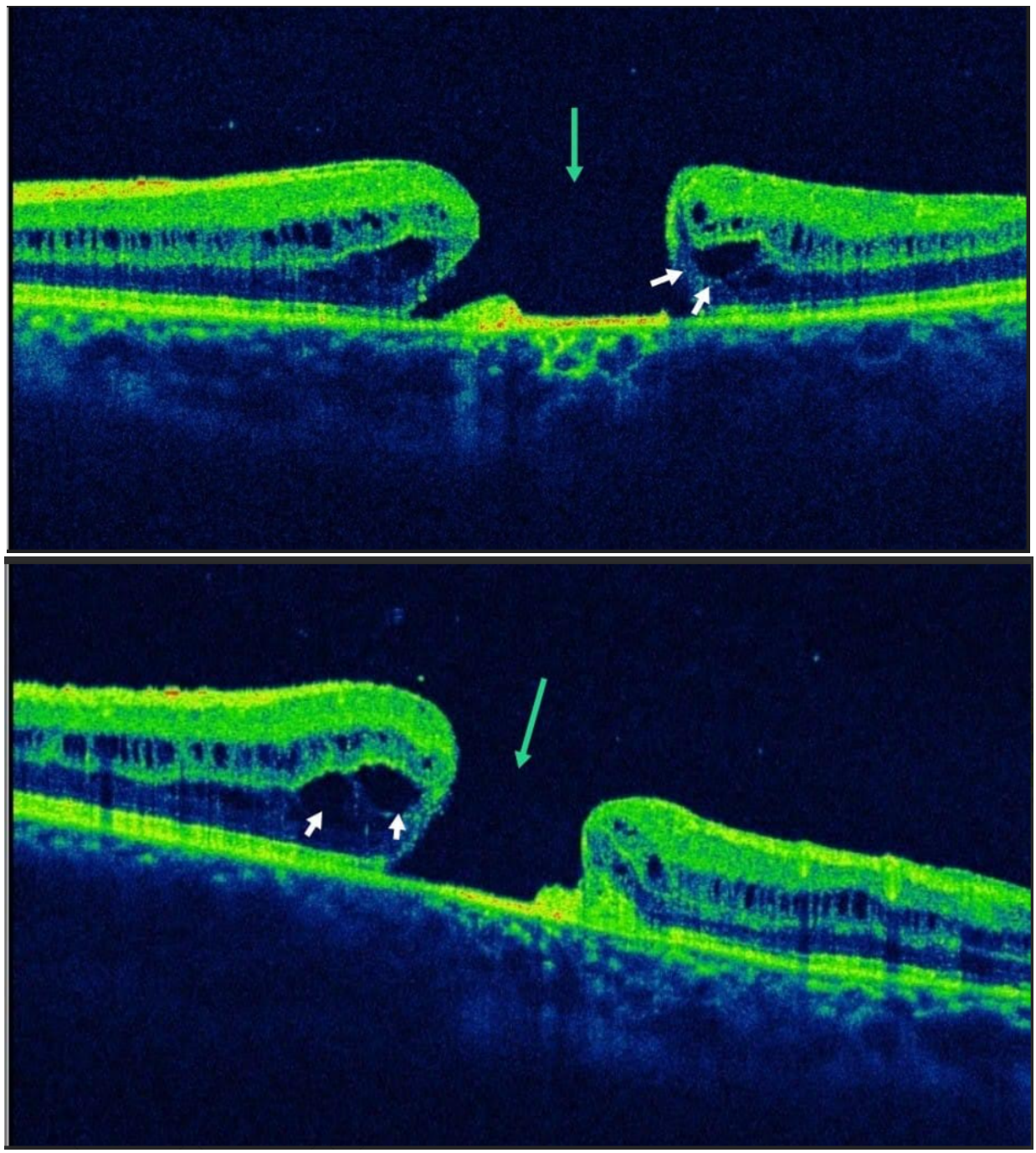
In 2016, a 33-year-old male patient with history of ocular trauma to the left eye came in for consultation. Clinically, we faced a patient with decreased visual acuity, which severely limited his daily activities as well as his normal working capacity. During the initial visit, the patient reported difficulties with activities of daily living such as reading, walking without bumping into objects, or drawing. The physical examination revealed significantly impaired visual acuity as well as visual field by confrontation. Extrinsic and intrinsic ocular motility showed no significant abnormalities. The accompanying optical coherence tomography (OCT) revealed a significant structural damage in the retinal neuroepithelium, with visualization of an FTMH in the left eye. Associated findings included disorganization of the inner retinal layers, intraretinal cysts, neuroepithelial detachment, an epiretinal membrane, and everted edges of the macular hole (Figures 1 and 2). On the other hand, retinal thickness (ILM-RPE) was of 344.3 µm on average (Figure 3).

It was proposed to initiate treatment with autologous stem cells administered both intravitreally and intravenously. The informed consent was obtained from the patient. Since these were autologous stem cells, no immunosuppression was required. Cells were obtained from samples of the superficial fascia and adipose tissue, which were then isolated ex vivo to form a concentrate. This concentrate was then administered both intravitreally and intravenously. No treatment-related adverse events were observed.

Between 2016 and 2019, the patient underwent regular clinical follow-up, including interviews with both the patient and family members. Throughout this period, the patient began to report improvements in his daily activities and autonomy, requiring less help and assistance. He reported an improvement in his reading ability, which greatly facilitated his normal working development. Both the patient and his family expressed satisfaction with the functional progress observed.

The patient was lost to follow-up after 2019 until he returned for a follow-up visit in 2026, with a new OCT performed that same year. During this visit, and based on the medical interview, the patient reported an improvement in his autonomy and ability to perform daily life activities, which had been maintained since his last visit. Likewise, the patient reported greater ease in performing his work activities, where writing, reading, and drawing skills are essential, and which were facilitated by his improved visual acuity. He also reported having undergone no medical or surgical treatment since his last visit with our team. At the patient's request,

due to time constraints, a complete physical examination was not performed. This new OCT image provided by the patient showed findings of interest, which we will present: the FTMH persisted, however, its edges were less elevated, no epiretinal membrane or hyaloid membrane was observed, peripapillary nerve fiber thickness was normal, no neuroepithelial detachment was observed and the retina was more homogeneous (Figure 4). Finally, the ILM-RPE retinal thickness averaged 307.8 µm (Figure 5).



Figures 1 and 2: Baseline OCT images (2016). FTMH (green arrow) with everted edges is observed. Presence of intraretinal cysts that impair the normal tissue structure (white arrows).

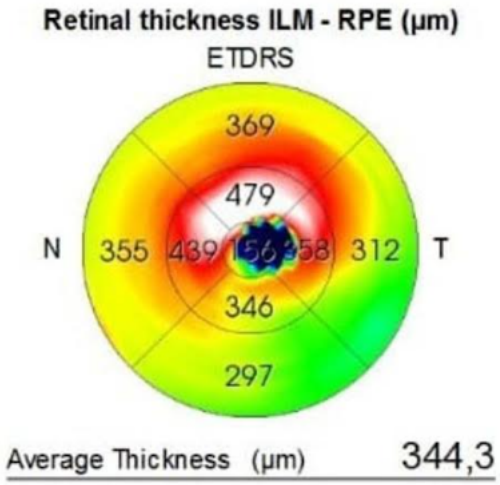


Figure 3: Baseline retinal thickness map (ILM–RPE) obtained by OCT (2016). Increased parafoveal retinal thickness, with an average thickness of 344.3 µm.

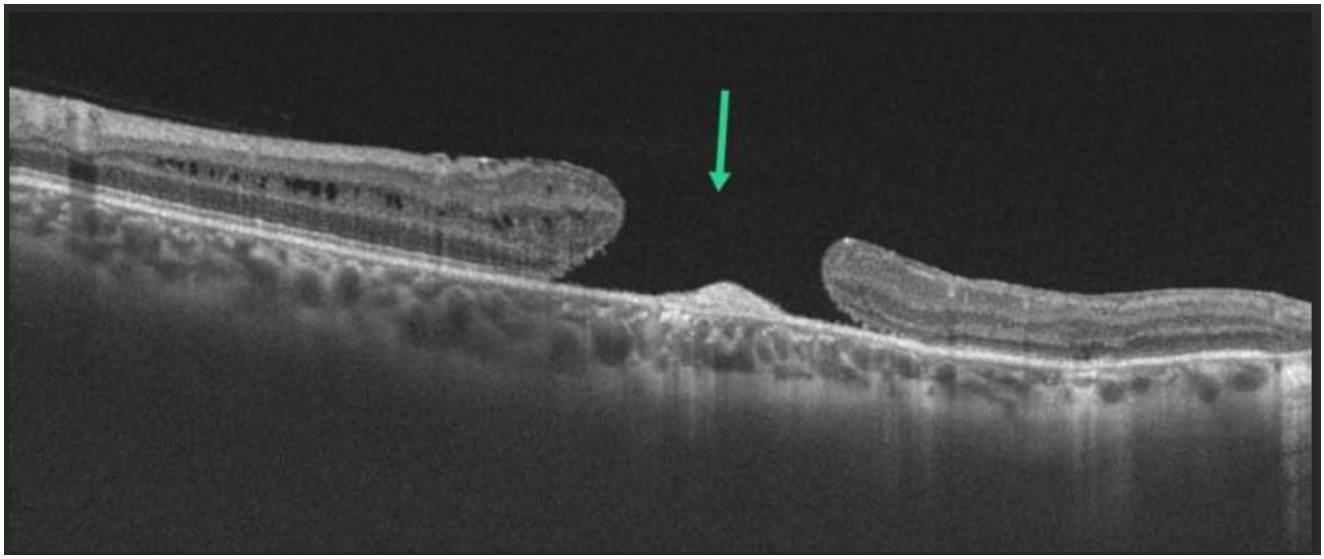


Figure 4: OCT 2026. Despite the persistence of FTMH (green arrow), the absence of an epiretinal membrane, reduced edema, and smoother edges of the macular hole are observed. The retinal architecture appears more homogeneous, suggesting a transition from a tractional and degenerative state towards a structurally stable retinal configuration.

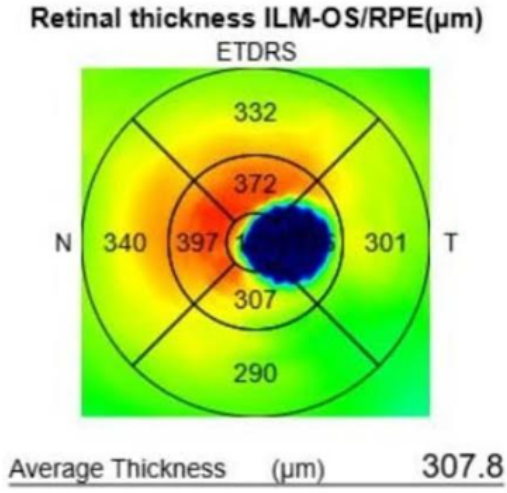


Figure 5: Retinal thickness map (ILM-RPE) 2026, mean retinal thickness of 307.8 µm.

Discussion

This case is notable due to the consistent clinical and structural findings observed over a period of 10 years. Although complete anatomical closure of the FTMH was not achieved, several mechanisms may help explain the functional improvement and structural stabilization observed in this patient. These mechanisms are consistent with the immunomodulatory and neuromodulatory properties attributed to stem cells, and include modulation of the inflammatory microenvironment, restoration of glial function, reduction of excitotoxicity, and enhancement of cellular bioenergetics in the retina.

Stem cells are undifferentiated cells with the capacity of self-renewal and differentiation into various types of tissue. They interact closely with the immune system and can act on the inflammatory microenvironment present in a large number of pathologies. Through cellular mechanisms (action on Treg lymphocytes, macrophages) and humoral mechanisms (secretomes, exosomes), stem cells exert an immunomodulatory action capable of regulating inflammation [10]. A key feature that distinguishes stem cells from most cells is their ability to migrate to differentiated tissues. Previous studies have shown the ability of stem cells to migrate to damaged tissues [11]. These characteristics of stem cells could positively influence the inflammatory environment present in the aforementioned FTMH which, while they do not initiate the pathology, they are essential for the progression and regeneration of the retinal defect.

Another key component of the pathophysiology of FTMH involves the retinal glial system, particularly Müller cells, which are essential for maintaining glutamate homeostasis and overall retinal integrity. This disruption in neurotransmitter homeostasis leads to glutamate excitotoxicity, which perpetuates damage to the retinal neural tissue. Abnormal activation of the NMDA receptor directly affects Müller cells and also increases

retinal vascular permeability to immune cell infiltration. Impaired glutamate clearance further exacerbates damage to the inner retinal layers [12]. On the other hand, sustained NMDA receptor activation has been associated with mitochondrial alterations, such as ROS production, changes in the electron transport chain, and altered calcium homeostasis [13]. The ability of stem cells to interact with injured tissues has been extensively investigated. One well-documented mechanism involves the transfer of mitochondria from stem cells to damaged cells. In injured cells, this mechanism of mitochondrial transfer restores respiration, increases ATP levels, and significantly decreases ROS levels [14]. This unique property of stem cells could promote the restoration of normal Müller cell function, which is impaired in FTMH and leads to excitotoxicity due to alterations in glutamate homeostasis.

An important point to highlight is the safety profile of adult stem cell application. A systematic review and meta-analysis of clinical trials reported no severe adverse events associated with mesenchymal stem cell therapy, supporting its overall safety in clinical settings [15]. Consistent with these findings, no treatment-related adverse events were observed in this patient over a 10-year period. Studies conducted with stem cells in retinal diseases, focusing on immunomodulation, secretion of trophic and neuroprotective factors, anti-apoptotic effects, and neuromodulation have been previously described [16-18]. However, current evidence remains heterogeneous and final conclusions regarding efficacy cannot yet be established.

These findings at the structural, immunological, cellular, mitochondrial, and neurotransmission levels could help explain the clinical improvements and structural findings observed in the patient 10 years after treatment. We are dealing with a patient who has shown objective clinical improvement, as evidenced by increased autonomy and less difficulty performing activities of daily living. This improvement has also been confirmed by the patient and his family. The observed imaging findings suggest a transition from an active tractional and degenerative state (neuroepithelial detachment, an epiretinal membrane, and everted edges of the macular hole) towards a structurally stable configuration, characterized by the resolution of mechanical forces (absence of an epiretinal membrane and neuroepithelial detachment), normalization of the retinal microenvironment, and partial neuroglial remodeling, despite the persistence of FTMH.

Conclusions

This case highlights the potential relevance of targeting the retinal microenvironment in the management of complex macular conditions such as FTMH. Although anatomical closure of the FTMH was not achieved, the long-term structural stability attained, along with the clinical improvements observed in this patient, suggests that therapeutic strategies extending beyond purely mechanical approaches may provide meaningful clinical benefits. The clinical and imaging findings observed in the patient support the concept that modulating key pathological processes, including inflammation, glutamate excitotoxicity, glial dysfunction, and mitochondrial

impairment, might contribute to the stabilization and partial recovery of the retina. In this context, stem cell-based therapies emerge as biologically plausible candidates capable of acting on the multiple interconnected pathways involved in retinal degeneration.

The findings in this case should be interpreted considering the inherent limitations of single-case reports. Further studies involving larger patient cohorts are needed to improve our understanding of the underlying mechanisms involved and to determine the role of stem cell therapies in the management of retinal diseases. This case also expands current knowledge regarding FTMH and its treatment. This case suggests that the transition from an active, traction-induced, and degenerative state to a stable state in the retinal configuration could represent a clinically relevant therapeutic endpoint, even if macular hole closure and complete structural repair are not achieved.

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