

# EPIDERMAL GROWTH FACTOR RECEPTOR EXPRESSION IN A CASE OF FOCAL NODULAR GLIOSIS OF THE RETINA

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**Purpose:** To describe the immunohistochemical profile in a case with focal nodular gliosis (FNG) of the retina.

**Methods:** A 56-year-old female patient presented with vitreoretinal tractional syndrome with FNG of the retina. After resection of the retinal tumor tissue during the 25-G pars plana vitrectomy, immunohistochemistry using anti-epidermal growth factor receptor (EGFR), p-53, Ki67, glial fibrillary acid protein (GFAP), CD34, and vascular endothelial growth factor antibodies was performed in the excised tissue of the FNG of the retina.

**Results:** Histopathological analysis of the tumor led to a diagnosis of FNG of the retina. Spindle cells of the tumor exhibited strong positive staining for glial fibrillary acid protein, and there was local staining for CD34 in the endothelial cells in the blood vessels. The epidermal growth factor receptor and vascular endothelial growth factor immunoreactivity were strongly observed in the endothelial cells.

**Conclusion:** This study demonstrated epidermal growth factor receptor expression in eyes with FNG of the retina. Oncogenic epidermal growth factor receptor might trigger and amplify the expression and function of endothelial vascular endothelial growth factor.

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**S**hields et al described solitary retinal vascular masses as presumed acquired retinal hemangiomas that resembled capillary hemangioma or retinal pseu-

dotumors reported in 1983.<sup>1</sup> In a subsequent study, these retinal masses were named vasoproliferative retinal tumors (VPRTs). These VPRTs are benign retinal tumors that most commonly occur on the inferotemporal or inferior quadrant and are characterized by yellowish-dull lesions accompanied by retinal exudation, vitreomacular tractional syndrome, and serous or tractional retinal detachment.<sup>2</sup> Vasoproliferative retinal tumors have two subtypes, with one classified as the idiopathic type (approximately 70%) and the other as a secondary type with vitreoretinal disease, which includes Coats disease, uveitis, and rhegmatogenous retinal detachment.<sup>3</sup> In recent years, this tumor has been classified as focal nodular gliosis (FNG) of the retina according to the WHO fourth edition classification.<sup>4–6</sup> However, there are few studies that have examined the histological findings of FNG, the results of various clinical treatment options, or the characteristics of the intraocular tumors, which are presumed to be benign tumors. Irvine et al

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described the histological features of patients who underwent local resection surgery as the management for choroidal malignant melanoma. Their results revealed the tumors to be primary benign glial proliferation with vasoproliferation.<sup>7</sup> Immunohistochemistry revealed there was strong positive immunostaining for the anti-glial fibrillary acid protein (GFAP) in the glial lesion in the FNGs.<sup>7</sup>

In this current article, we describe new clinical and interesting biological features of these rare lesions.

### Case Report

A 56-year-old female patient with visual crowding in her right eye (uncertain onset) was referred to our department for a detailed examination. Upon her initial evaluation, best-corrected visual acuity was 50/60 in her right eye and intraocular pressure was within a normal range. Anterior slit-lamp examination revealed there were no remarkable findings. Fundus examination and optical coherence tomography revealed vitreous opacification with thickness of the posterior vitreous membrane and the presence of retinal exudate and a white-yellowish retinal tumor in the inferotemporal quadrant in her right eye (Figure 1, A and C). Fluorescein angiography and indocyanine green angiography revealed rapid filling of the tumor along with dye leakage into the subretinal space (Figure 1B). In the fellow eye, the anterior segment and retinal examination including peripheral retinal examination were all normal. Magnetic resonance imaging revealed there was no brain lesion. Gene analysis was performed for the Von Hippel-Lindau gene, with the results found to be negative in the peripheral blood. The patient, who had no familial history, was clinically diagnosed with FNG of the retina and vitreomacular tractional syndrome. The patient underwent small gauge (25 G) pars plana vitrectomy combined with cataract surgery, internal limited membrane peeling, endolaser photocoagulation, and endoresection of the tumor (Figure 1D). The tumor was removed via the corneal scleral tunnel incision that was created for the cataract surgery. There was no recurrence of the tumor lesion at 6 months

after the surgery, and best-corrected visual acuity slightly improved to 60/60.

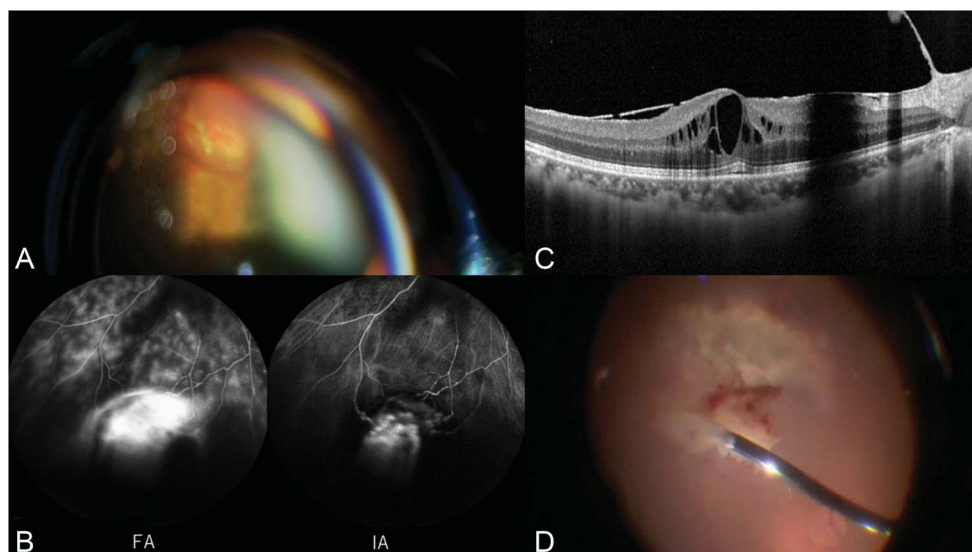
Histological examinations of the excised tissue were performed using hematoxylin and eosin (H&E) staining and immunohistochemistry with anti-GFAP antibody, anti-CD34 antibody anti-epidermal growth factor receptor (EGFR) antibody, anti-vascular endothelial growth factor (VEGF) antibody, anti-p-53 antibody, and anti-Ki67 antibody. H&E staining demonstrated that the tumor consisted of a collection of spindle cells around dilated blood vessels (Figure 2A). Spindle cells exhibited strong positive staining for GFAP, and there was local staining for CD34 in the endothelial cells in the blood vessels (Figure 2, B and C). The histological findings are consistent with VPRTs. Furthermore, the absence anti-p-53 antibody and anti-Ki67 antibody immunostaining suggested the FNGs were not malignant and that the tumor was a slowly progressive tumor (data not shown). Finally, the VEGF immunoreactivity was observed in the dilated vessels containing endothelial cells (Figure 3, A and B).

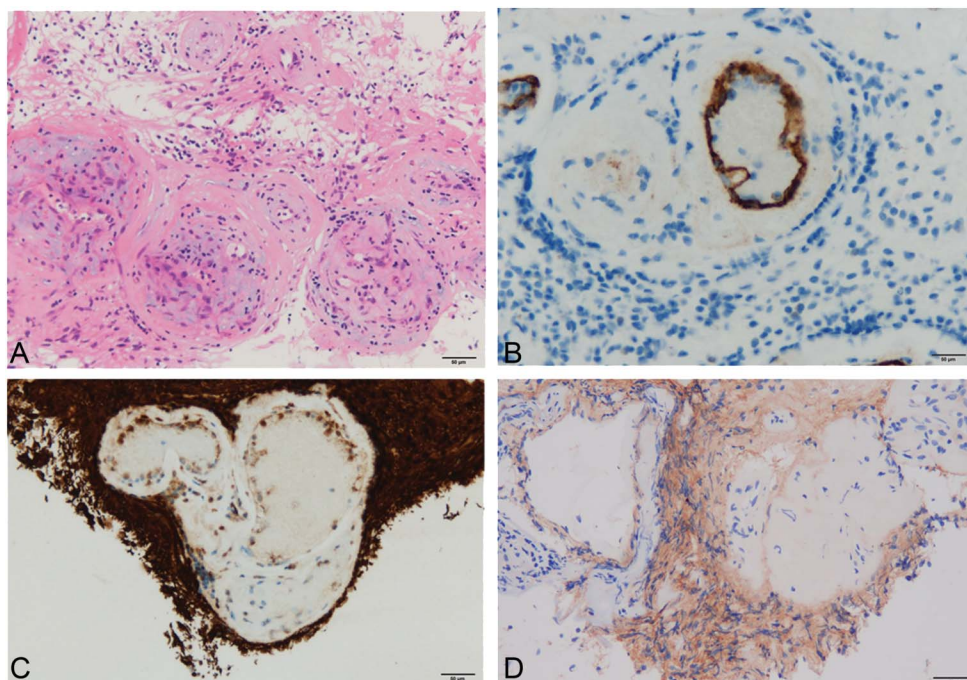
### Discussion

In the 40 years since the isolation of the cDNA encoding the EGFR and the deduction of its amino-acid sequence, intensive research efforts have led to important insights into the molecular mechanisms of receptor tyrosine kinase functions.<sup>8,9</sup> Receptor tyrosine kinases are potent oncoproteins, with abnormal activation of receptor tyrosine kinases in transformed cells shown to be causally involved in the development and progression of many human tumors.<sup>7,8</sup>

Well-known receptor tyrosine kinases in the field of ophthalmology include the VEGF families.<sup>10</sup> In previous cases of VPRTs, it has been reported that VEGF derived from FNGs causes retinal neovascularization or exudative retinal changes associated with FNGs. Furthermore, as VEGF production has been shown to increase in eyes with FNGs, anti-VEGF therapy might theoretically be effective for treating FNGs.<sup>10,11</sup>

**Fig. 1.** Photographs of the right eye with FNGs the pre-operative visits (A–C) and during PPV surgery (D). **A.** Slit-lamp examination of the fundus showing a white-yellowish retinal tumor in the inferotemporal quadrant. **B.** Fluorescein angiography (FA) and indocyanine green angiography (IA) revealed there was rapid filling of the tumor and dye leakage into the subretinal space. **C.** Optical coherence tomography (OCT) of the macula revealing vitreous-macula traction with cystoid macula edema. **D.** The tumor was resected using intraocular scissors during the 25-G PPV. PPV, pars plana vitrectomy.



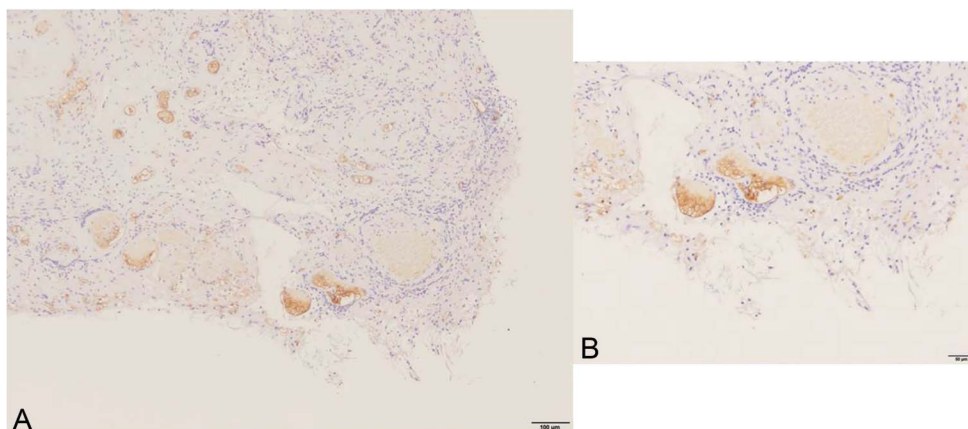


**Fig. 2.** Histology (A) and immunohistochemistry (B and C) resected retinal tumor. **A.** Light micrograph demonstrated that the tumor consists of a mass of spindle cells around dilated blood vessels (hematoxylin & eosin, bar = 50  $\mu\text{m}$ ). **B.** Immunohistochemistry for GFAP. Glial fibrillary acid protein was strongly expressed in the components of the spindle cells (bar = 50  $\mu\text{m}$ ). **C.** Immunohistochemistry for CD34. There was local expression of CD34 in the hyalinized and dilated vessels (bar = 50  $\mu\text{m}$ ). **D.** Immunohistochemistry for EGFR. EGFR expression was strongly expressed in spindle cells.

On the other hand, there have been no reports showing that EGFR plays a role in intraocular tumors, especially in FNGs. In this study, histological examination and immunoreactivities with GFAP and CD34 were compatible with those seen for the FNGs. Moreover, EGFR immunostaining corresponded to the spindle cells in the tumor.

In brain tumors, EGFR is known to be a primary contributor to glioblastoma initiation and progression and has key downstream signaling networks that are associated with the cell proliferation and diffused invasion.<sup>12,13</sup> Previous studies have also reported that FNGs were associated with gliosis.<sup>7</sup> Based on these prior reports, we developed a clinical interest in further examining the EGFR expression of FNGs.

Our current results provide evidence that there is an increased immunoreactivity for EGFR in the retinal tumor of a patient with FNGs. Al-Nedawi et al<sup>14</sup> described that oncogenic EGFR might trigger and amplify the expression and function of endothelial VEGF, contributing to the distinct nature of tumor blood vessels and their response to therapies. In other words, tumor-induced EGFR could interact with local cells exhibiting within tumor tissues, which acts as an angiogenic regulator.<sup>14</sup> Because EGFR is upstream of VEGF signaling, the EGFR-VEGF axis may be considered to be a therapeutic target. Treatment for FNGs includes laser photocoagulation, cryopexy, photodynamic therapy, and anti-VEGF therapy in past reports.<sup>4,11,12</sup> Thus, this suggests that anti-EGFR



**Fig. 3.** Immunohistochemistry for VEGF (A and B). **A.** There was local expression of VEGF in the endothelial cells and dilated vessels (bar = 50  $\mu\text{m}$ ). **B.** High power fields (bar = 100  $\mu\text{m}$ ).

therapy could possibly be used for the new treatment of FNGs for the patient of treatment resistant. There were some limitations for this current case report. First, the results presented here were for a case report that only included one patient. In addition, there was only a short follow-up period for this patient. Therefore, further studies that investigate the role of EGFR in the pathogenesis of FNGs will need to be undertaken.

**Key words:** focal nodular gliosis, epidermal growth factor receptor, minimally invasive vitrectomy surgery, immunohistochemistry.

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