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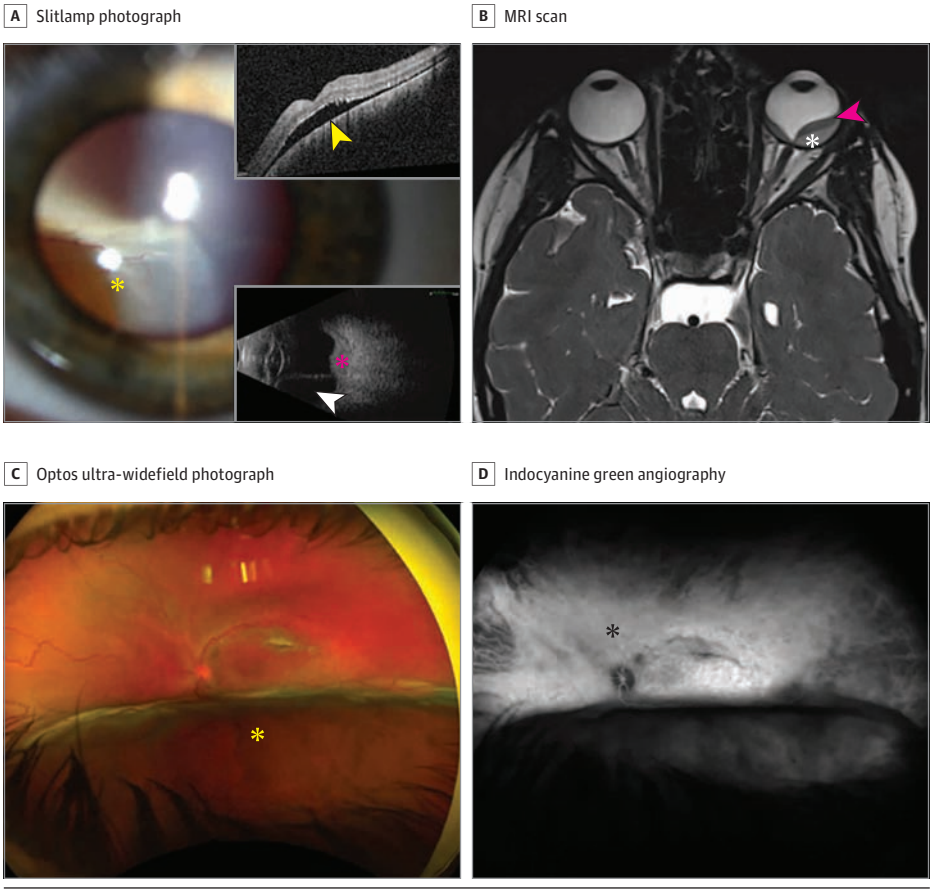
OBSERVATION

Oral Sirolimus for Diffuse Choroidal Hemangioma in Sturge-Weber Syndrome

Diffuse choroidal hemangioma (DCH), a benign vascular malformation in Sturge-Weber syndrome (SWS), may cause vision loss from exudative retinal detachment. DCH is due to a somatic mutation, p.Arg183Gln substitution in *GNAQ*.[1] Current treatment options include external beam radiation, plaque brachytherapy, and photodynamic therapy (PDT).[2] We describe an 8-year-old female with SWS who received oral sirolimus as an adjuvant therapy for pulse dye laser (PDL) of her port-wine stain and as an off-label treatment of exudative retinal detachment (ERD) secondary to DCH.

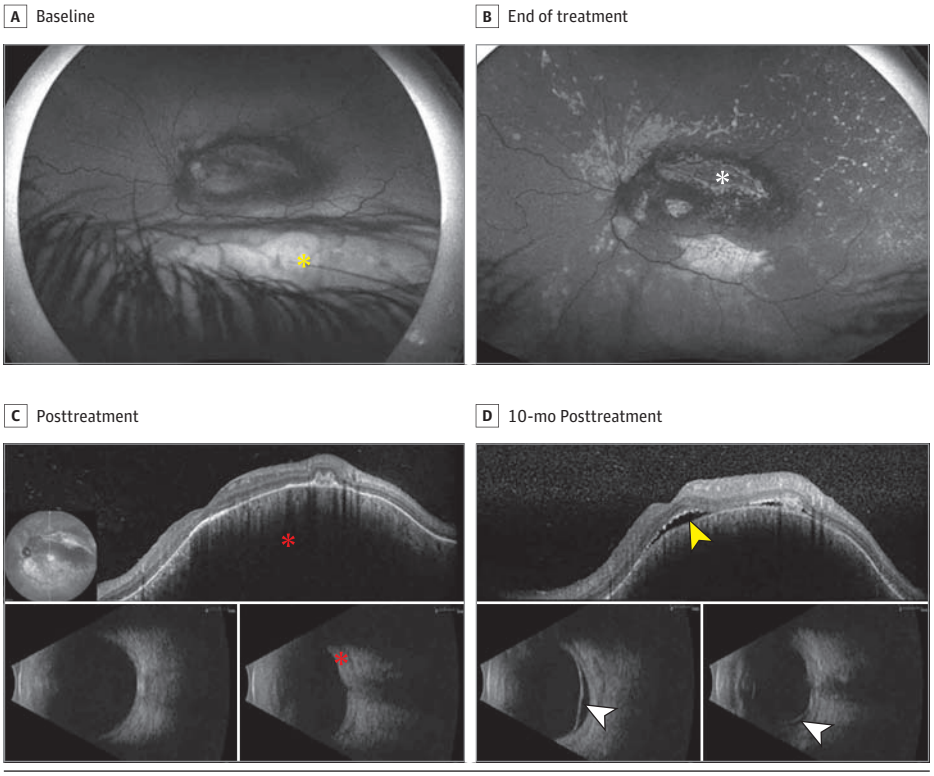
Report of Case | An 8-year-old female presented with a 5-month history of left visual loss. Left visual acuity (VA) (logMAR) was 20/600 (1.46), and intraocular pressure (IOP) was 16 mm Hg with timolol with an inferior bullous ERD (**Figure 1**A and C). Optical coherence tomography showed subretinal fluid (SRF) with acoustically dense choroidal thickening on B-scan ultrasound (Figure 1A). Indocyanine green angiography demonstrated diffuse hyperfluorescence (Figure 1D) and magnetic resonance imaging excluded leptomeningeal angiomatosis (Figure 1B). Due to a supply interruption of verteporfin in 2021, PDT was not performed initially. Oral sirolimus was commenced to treat the ERD and port-wine stain at 2 mg daily except twice a week when she took 2 mg twice a day to achieve a stable therapeutic level of 8.0 µg/L at 7 hours postdosing. Adverse effects (headaches and mouth ulcers) were monitored on systemic review and 3-monthly blood tests (complete blood cell counts, kidney and liver function, and lipid profile) were performed.

Figure 1. Photography and Imaging



Slitlamp photography (A) showing bullous detachment of the inferior retina (yellow asterisk) posterior to the lens, with corresponding optical coherence tomography demonstrating submacular fluid (yellow arrowhead), and B-scan ultrasound showing diffuse and focal thickening of the choroid (pink asterisk), which was acoustically dense associated with an inferior detachment (white arrowhead). Magnetic resonance imaging (MRI) scan (B) showed choroidal hemangioma (white asterisk) and serous detachment (pink arrowhead). Optos ultra-widefield photography (C) showed inferior bullous retinal detachment (yellow asterisk) and indocyanine green angiography (D) showed diffuse hyperfluorescence (black asterisk).

Figure 2. Baseline and Posttreatment



Ultra-widefield fundus autofluorescence at baseline (A) and at the end of the 6-month treatment (B) demonstrating inferior bullous retinal detachment (yellow asterisk) and residual subretinal fibrosis in the superior macula (white asterisk). Shortly after cessation of the first course of oral sirolimus, optical coherence tomography (OCT) and inferior and sagittal B-scan ultrasound showed resolution of subretinal fluid with persistent thickening of the choroid (red asterisk) on OCT with thickening of the posterior coat (red asterisk) on B-scan ultrasound (C). By 10 months after cessation of sirolimus, the subfoveal fluid (yellow arrowhead) as seen on OCT scan and inferior subretinal fluid (white arrowhead) had returned on B-scan ultrasound (D).

The inferior bullous ERD resolved after 4 months (**Figure 2**A and B). Despite complete resolution at 6 months, VA declined to 20/900 (1.66). Sirolimus was ceased at this point and 8 months later, VA improved to 20/160 (0.90). Ten months after cessation of sirolimus, SRF returned and VA reduced to 20/500 (1.40). Sirolimus was subsequently restarted at the same initial dose of 2 mg/d except 2 days of 4 mg/d per week (Figure 2D). SRF improved by 6 weeks with complete resolution by 3 months. VA remained stable at 20/250 (1.00) at 15 months and the patient continues to receive sirolimus. B-scan measurements showed stable tumor thickness of 4.5 mm despite resolution of SRF (Figure 2C). Timolol was ceased and IOP remained at 14 mm Hg. There was no adverse event from immunosuppression or drug intolerance during follow-up.

Discussion | Sirolimus (rapamycin) is typically used in organ transplant and more recently in slow-flow venous malformations altering the PIK3CA/mTOR pathway, which communicates with the RAS/ERK/MAPK pathway.[3,4] Notably, GNAQ interacts with the later pathway.[1] The interplay between the 2 pathways may explain the treatment effect we observed in DCH and raised IOP secondary to SWS. Sirolimus is well tolerated, with mild adverse effects including headaches, mouth ulcers, hyperlipidemia, and nausea.[5]

Reduction in SRF with sirolimus is unlikely to be coincidental. The return of SRF and the brisk response following the reintroduction of sirolimus suggests a biological effect. The delayed VA improvement after resolution of SRF suggests slow recovery of macular photoreceptors and a shift in eccentric fixation. Triana Junco et al[6] reported an infant with bilateral SWS and extensive leptomeningeal angiomatosis who had a remarkable response to PDL and remained seizure free for 2 years while receiving oral sirolimus and aspirin.[6] It is unlikely the use of PDL contributed to the resolution of ERD given the eye was closed or protected during laser. Future use of PDT or radiotherapy may still be required. Our clinical observation warrants further investigation into the use of sirolimus as a stand-alone or adjuvant therapy for DCH in SWS.

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COMMENT & RESPONSE

Methodological Concerns and Potential Confounding Factors

To the Editor We read with great interest a recent study by Tsang et al titled "Risk of Falls and Fractures in Individuals With Cataract, Age-Related Macular Degeneration, or Glaucoma."[1] The study contributes valuable insights into the association between major eye diseases and the risk of falls and fractures. However, we have several methodological concerns and suggestions.

First, the study's reliance on data from electronic health records, while comprehensive, may introduce selection bias. Patients who frequently visit health care facilities are more likely to have their falls and fractures recorded, potentially overestimating the risk associated with these eye conditions. Second, the study acknowledges the use of multivariable Cox proportional hazards regression models. However, the reader would benefit if the authors could provide greater detail regarding confounding factors, such as medications, comorbidities, and lifestyle choices that might affect falls, that were used for adjustment in the analysis models. The complexity of the association between eye diseases and falls or fractures is influenced by numerous factors, including medications, comorbidities, and lifestyle choices.[2,3] Without a thorough understanding of these adjustments, the interpretation of the hazard ratios might be misleading.

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Conflict of Interest Disclosures: None reported.

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In Reply We thank Yang and colleagues for their comments in response to our recent publication.[1] We elected to use routinely collected electronic health records to allow a large sample size and the inclusion of a wide range of covariates. These records have been shown to be nationally representative in terms of age, sex, ethnicity, and socioeconomic deprivation. The records were collated from approximately 25% of the UK population, with high validity for diagnostic coding, including fractures, to reduce the impact of selection bias.[2-4] Indeed, the limitations of this approach have already been stated in our article, including the inability to assess visual function or hospital treatments and a likelihood to report more serious falls requiring medical attention. Yet, other approaches, such as self-reporting of falls in surveys, are subject to recall bias.[5] A deeper assessment into the strengths and limitations of our population-based approach has also been explored in a helpful commentary by Pundlik and Luo.[6]

The potential influence of confounders has been already highlighted in our Outcomes and Covariates section within the Methods.[1] We controlled for a large number of potential (measured) confounders, but as in all observational studies, there is a risk of unmeasured confounding, which we acknowledge. Although no method can address for unmeasured confounding unless the mechanism is known, we have used advanced methods to try to minimize the risk of measured confounding. Thus, we conducted sensitivity analyses "using propensity scores to account for covariate imbalance between the cohorts within further Cox proportional hazard models."[1] These "inverse-weighted probability models included more than 50 confounders,"[1] with adjustments listed in eTable 4 in Supplement 1. Both approaches showed similar results, giving weight to our findings.

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