OBSERVATION

Laser-Induced Chorioretinal Anastomosis in Neurofibromatosis Type 1

Report of a Case | A 38-year-old woman with neurofibromatosis type 1 (NF1) presented for routine ophthalmic examination. The patient had long-standing peripheral retinal capillary nonperfusion in the left eye, which had been treated years ago with panretinal photocoagulation. Both eyes showed choroidal Yasunari nodules, which are choroidal lesions not easily detected on ophthalmoscopic examination but readily visible by near-infrared photography.[1] The right eye showed no other pathologies. Visual acuity was 20/20 OU with correction. Recent magnetic resonance imaging of the neuraxis and orbits showed no gliomas. The patient was not known to have any systemic vasculopathy.

Multimedia

Compared with a visit 3 years earlier, the central retinal artery and branching arcades had thinned. A chorioretinal anastomosis had formed in the superotemporal macula at the site of a photocoagulation scar; a spiral-shaped choroidal vessel interconnected with both arterial and venous vessels from the superior arcades and a vein from the inferior arcade, which perfused the arterial supply of the central retina, including the fovea (**Figure 1**). Fluorescein angiography confirmed the new retrograde arterial supply through the anastomosis (**Figure 2**; **Video**). The formation may have been associated with a combination of a hydrostatic pressure gradient over the retinal pigment epithelium in the direction of the retina and vascular endothelial growth factor production associated with retinal capillary nonperfusion.

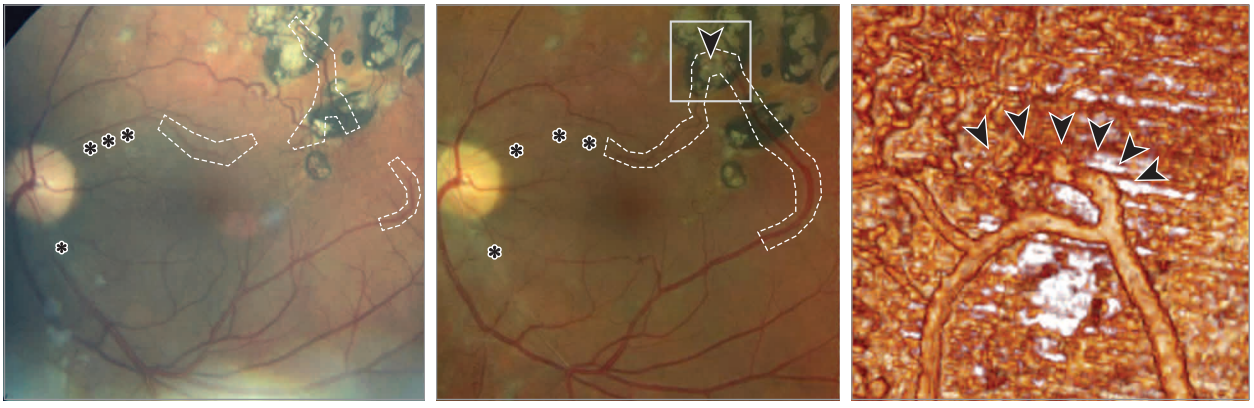
Discussion | Recent studies of larger cohorts have found the prevalence of retinal vascular abnormalities in individuals with NF1 to be 17% to 37%, according to various definitions.[2,3] Severe retinal vascular abnormalities in NF1 are considered rare,[4] but at least 13 previous case reports describe peripheral or central retinal vascular occlusion, neovascular glaucoma, or occlusion of the central retinal artery or ophthalmic artery. Like this case, mostly young patients with unilateral impaired arterial inflow and progressive retinal capillary nonperfusion are described. Preservation of choroidal perfusion in this patient suggests that vasculopathy was confined to arteries distally to the branching of the posterior ciliary arteries from the ophthalmic artery.

Figure 1. Color Fundus Photography of the Left Eye Before and After Formation of the Chorioretinal Anastomosis

A Color fundus photography at baseline

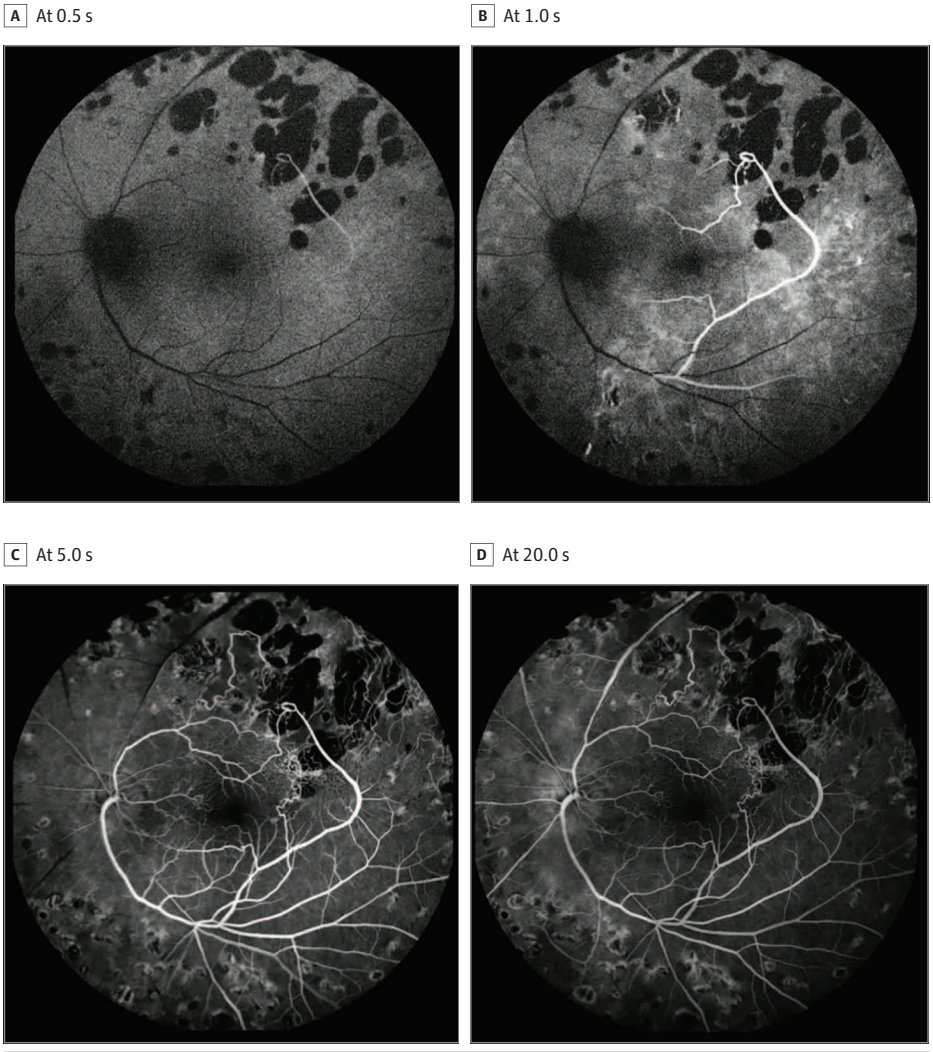
B Color fundus photography at 3-y follow-up

C Optical coherence tomography angiography reconstruction at 3-y follow-up



A and B, Marked thinning of the retinal arteries (asterisks) was observed compared with a visit 3 years earlier. A chorioretinal anastomosis had formed in a photocoagulation scar (arrowheads) interconnecting both arterial and venous vessels from the superior arcade and a venous vessel from the inferior arcade (dashed line markings). C, Corresponding to the white square in panel B, a volume-rendered optical coherence tomography angiography reconstruction revealed a spiral shape of the chorioretinal anastomosis (arrowheads).

Figure 2. Fluorescein Angiography Filling Sequence in the Left Eye



Fluorescein angiography sequence at 0.5, 1, 5, and 20 seconds showing a conspicuous, rapid initial filling of the temporal macular vasculature by retrograde circulation through the laser-induced chorioretinal anastomosis in the superotemporal macula (0.5-second and 1-second frames), which is sequentially followed by anterograde filling of the central retinal artery branches that brings perfusion to the nasal retina (5-second and 20-second frames).

High-energy photocoagulation treatment can cause iatrogenic breaks in the Bruch membrane and facilitate the formation of choroidal neovascularization, which, under certain conditions, can develop into a laser-induced chorioretinal anastomosis (LICRA). McAllister[5] has proposed the use of this phenomenon as a treatment for nonischemic central retinal vein occlusion (CRVO). The intended mode of action is to create auxiliary flow between the obstructed high-pressure retinal venous circulation and the unobstructed low-pressure choroidal venous circulation, thus normalizing retinal venous pressure. A trial including 58 selected patients with nonischemic CRVO who received intravitreal ranibizumab injections and were randomized to a LICRA procedure or sham found that the LICRA group had superior visual acuity and required fewer anti-vascular endothelial growth factor injections than controls after 2 years. However, only 2 in 3 attempts to create an anastomosis were successful, and procedure-related complications requiring secondary surgery occurred for every third patient.[5] Attempts to create LICRAs in eyes with ischemic CRVO have been mostly unsuccessful, perhaps due to severe endothelial cell damage secondary to ischemia and venous thrombosis across the retinal circulation.[6]

In this patient with NF1, an unintended, iatrogenic LICRA potentially salvaged the retina and preserved 20/20 visual acuity in an eye with severe, progressive retinal arterial occlusive disease. Here, the mechanistic mode of action of the LICRA differed from that of eyes with CRVO, in that the chorioretinal anastomosis causes inflow of oxygenated blood to the retina rather than outflow from congested retinal veins to the choroid. However, due to the year-long, extensive vascular remodeling seen in this case, more evidence is needed to suggest that therapeutic LICRAs can be created in patients with severe, progressive retinal arterial occlusive vasculopathy where choroidal perfusion is still intact.

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Bruton Tyrosine Kinase Inhibitor in 2 Patients With Vitreoretinal Lymphoma

Tirabrutinib is an orally administered, small-molecule, second-generation Bruton tyrosine kinase inhibitor, approved in Japan for treating recurrent or refractory central nervous system (CNS) lymphoma.[1] Approximately 15% to 25% of patients with CNS lymphoma present with or ultimately develop vitreoretinal lymphoma (VRL).[2] Ibrutinib, the first selective Bruton tyrosine kinase inhibitor, showed clinical activity in the intraocular compartment in CNS lymphoma.[3] However, it is unclear whether tirabrutinib is also effective for VRL. We present 2 patients with VRL whose retinal appearances appeared to improve after the administration of tirabrutinib for treating concurrent CNS lymphoma, highlighting its potential as a new therapeutic agent for this disease.

Report of Cases | *Case 1.* An 80-year-old female patient previously treated with chemotherapy and radiotherapy for primary CNS lymphoma presented with decreased vision in the right eye (**Figure 1**A). She was diagnosed with secondary VRL. After treatment with repeated doses of intravitreal methotrexate, she achieved remission. However, the VRL recurred 1 year later (Figure 1B) and was refractory to intravitreal methotrexate. Eight days after the 11th dose of intravitreal methotrexate (Figure 1C), CNS recurrence was evident. After discontinuing intravitreal methotrexate, tirabrutinib was administered for refractory CNS lymphoma. The CNS and VRL lesions appeared less evident within 2 weeks (Figure 1D), and she remained in remission for 3 months. However, 4 months after the start of tirabrutinib, it was discontinued due to recurrent CNS lymphoma.

Case 2. A 73-year-old female patient experienced blurred vision in the right eye (**Figure 2**A and B). Three weeks later, she developed dysarthria, and a brain magnetic resonance imaging scan showed a lesion near the thalamus. A chorioretinal biopsy was performed, and a diagnosis of CNS lymphoma and VRL was confirmed by cytological examination (class V). The patient was administered tirabrutinib in suspension through a nasogastric tube due to her low Karnofsky performance status.[4] The VRL lesions rapidly became less apparent (Figure 2C and D), and she was in remission for the next 3 months. The brain lesions slowly improved, and after a month, the patient was able to take tablets. However, 3 months later she experienced a hemorrhagic stroke and the tirabrutinib was discontinued. She died 1 month later.

Discussion | The experiences of these 2 patients with coexisting VRL and CNS lymphoma and short-term remission of VRL associated with tirabrutinib suggest this Bruton tyrosine kinase inhibitor may be an effective treatment for VRL. The pivotal clinical trial for tirabrutinib approval in Japan for relapsed or refractory CNS lymphoma included 3 patients with VRL who showed a partial CNS lymphoma response. The details of the ocular lesions were not described.[1] Tirabrutinib was detected intrathecally in the trial; however, it is not clear whether it was also detected in the ocular fluid. The measurement of intraocular levels of tirabrutinib after oral administration may be associated with the changes in the VRL lesions noted after initiating this therapy.

The recommended therapy for patients with coexisting VRL and CNS lymphoma includes high-dose methotrexate-based chemotherapy, radiation therapy, and local ocular chemotherapy.[5] However, a second course of radiotherapy is not indicated for recurrence, and intensive systemic and ocular chemotherapy are difficult for older patients or those with severe cognitive impairment due to the CNS malignancy. Thus, there is an urgent need to develop new treatment strategies. Tirabrutinib may be a new option for patients who are unable to tolerate current standard treatment options.

In conclusion, we report on 2 patients who achieved remission of VRL associated with tirabrutinib treatment. A possible combination of tirabrutinib and intravitreal methotrexate injections or tirabrutinib for eyes refractory to intravitreal methotrexate may lead to better management and reduced morbidity in cases of VRL.

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