for ophthalmic evaluation. Initial evaluation in the referring institution revealed a mild corneal apical scar, retinal detachment in the right eye, and vitreous hemorrhage (VH) in both eyes, for which he was referred to our center for further assessment and management.

On examination, there was light aversion in both eyes, more pronounced in the left eye. Anterior segment examination of both eyes was remarkable for a central corneal opacity and anterior polar cataract in the right eye. The corneal diameter was 10 mm horizontally and vertically in both eyes. Dilated fundus examination of the right eye showed moderate VH along with tractional retinal detachment (TRD) involving the macula and a fibrovascular membrane extending peripherally [Fig. 1]. In the left eye, there was a moderate preretinal hemorrhage partially covering the posterior pole and mid-peripheral retina [Fig. 2]. The working diagnosis was Familial Exudative Vitreoretinopathy (FEVR), and he was booked for examination under anesthesia (EUA) the following day.

Intraocular pressure under anesthesia was 6 and 7 mmHg in the right and left eye, respectively. Fundus fluorescein angiography (FFA) of the right eye showed severe retinal non-perfusion and blockage effect from blood [Fig. 3], while in comparison, the left eye had better retinal perfusion [Fig. 4]. Macular spectral-domain optical coherence tomography (OCT) (Bioptigen, Leica Microsystems, Wetzlar, Germany) of the left eye revealed poor lamination and absent outer retinal layers [Fig. 5]. Given that the OCT findings were not typical for FEVR, protein C activity was measured and the result was 2.189 % (normal value 70–132 %). Whole Exome Sequencing (WES) was ordered to identify any pathogenic variants causing this presentation. Laser photocoagulation was applied to the ischemic retina in both eyes and planned for pars plana vitrectomy (PPV) and membrane peeling (MP) to the right eye once the disease has regressed.

EUA three weeks after laser ablation showed partial resolution of the blood in both eyes along with a tractional nasal radial fold with a pumpkin-like lesion posteriorly in the right eye [Figs. 6 and 7]. PPV, MP, and silicone oil injection were performed to the right eye (supplemental video). Silicone oil was used because there was a suspicious area of retinal break after membrane peeling posteriorly. The postoperative period was uneventful, and silicone oil was removed after 4 months. At the time of removal, examination showed complete resolution of the vitreous hemorrhage and flat retina bilaterally, with a residual dry fold (no subretinal fluid) and no retinal break after retina settled in the right eye, while FFA revealed improved perfusion in the previously ischemic areas of the retina [Figs. 8 and 9]. WES revealed a homozygous likely pathogenic missense variant of the *PROC* gene c.1297G > A:P.(Gly433Ser), which causes PCD and therefore explains the ocular findings. There was no family history of PCD and the patient was referred to pediatric hematology for further management.

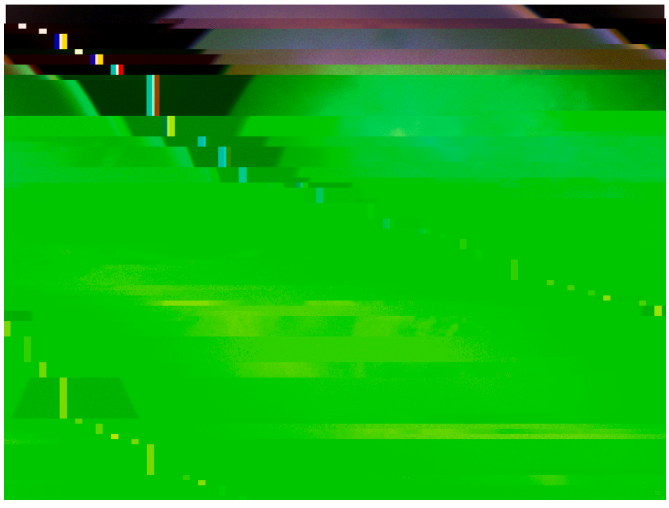

Fig. 1. Color fundus photograph of the right eye at presentation showing tractional retinal detachment and vitreous hemorrhage. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

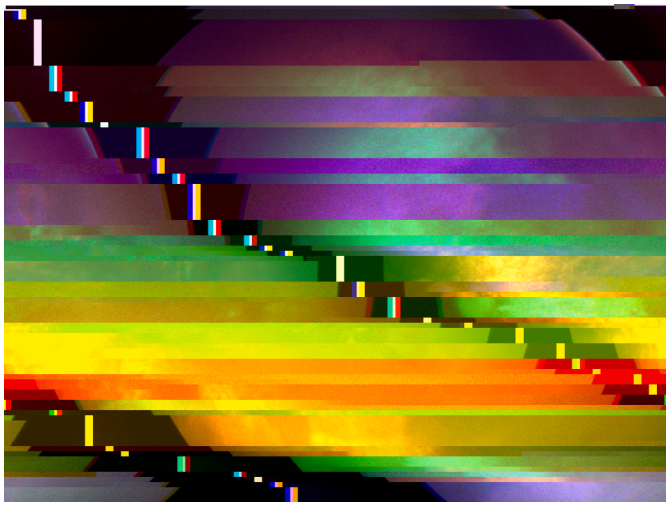

Fig. 2. Color fundus photograph of the left eye showing attenuated retinal vessels and preretinal hemorrhages. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

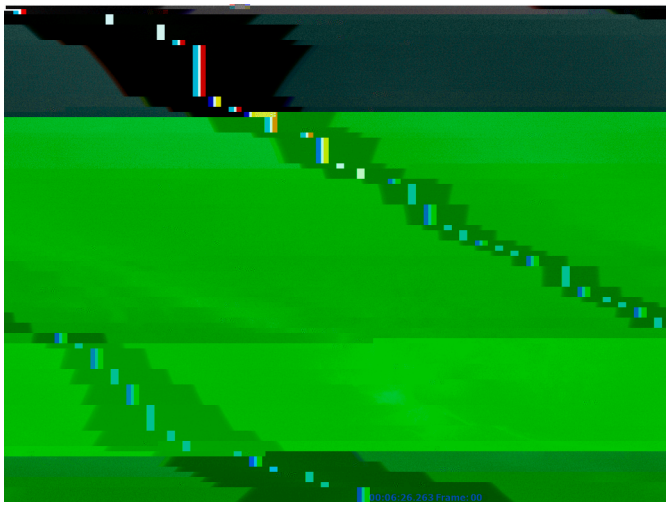

Fig. 3. Fundus fluorescein angiography of the right eye showing severe retinal non-perfusion as well as blockage effect from the blood.

3. Discussion

Protein C is a vitamin K-dependent zymogen that plays a significant role in anticoagulation. Activated protein C inhibits coagulation by the degradation of factor VIIa and factor Va, which are cofactors that activate factor X and prothrombin. Protein C is encoded by the *PROC* gene present on the long arm of chromosome 2, and its deficiency could be acquired or inherited, with around 200 pathogenic variants described in the literature.[6] The inherited form is further divided into 2 types. Type 1 results in reduced levels and quantitative deficiency in protein C, while type 2 results in qualitative deficiency, thus reduced activity of protein C.[7] In the inherited form of PCD, one of the serious presentations is neonatal purpura fulminans, a dermatological emergency that is characterized by purpuric and subsequent ischemic skin lesions prone to secondary infections, and usually presents within the first few hours

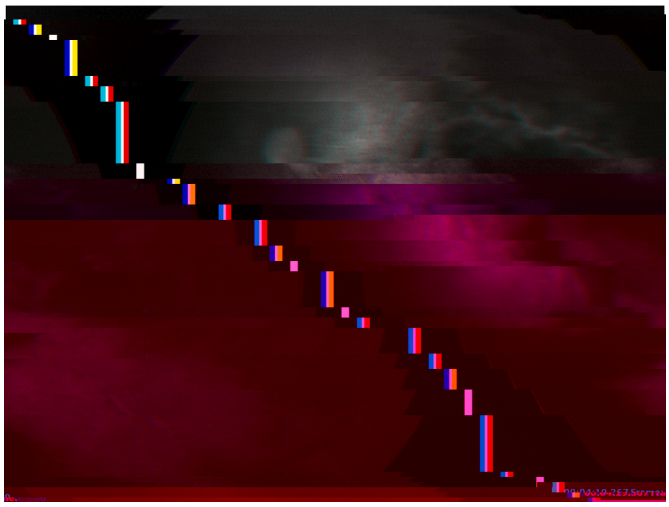

Fig. 4. Fundus fluorescein angiography of the left eye showing retinal perfusion limited to the posterior pole.

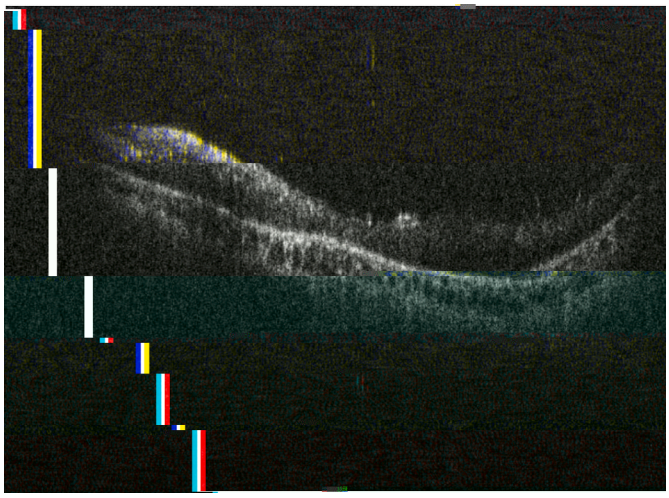

Fig. 5. Macular optical coherence tomography of the left eye showing poor lamination and absent outer retinal layers.

after birth.[8] Several studies have reported PCD presenting with ocular signs and symptoms, such as retinal vein occlusion, retinal detachment, and leukocoria.[4,5]

Our case posed a diagnostic challenge since the systemic features of PCD may present after the ocular signs. The main clue for the diagnosis was the ocular findings of vitreous hemorrhage and the poor retinal lamination on OCT which is not typically present in FEVR or retinopathy of prematurity. The absence of early-onset systemic features is not unusual. Baothman AA et al. described 5 patients with homozygous PCD who presented with severe ocular manifestations at birth. Systemic signs such as purpura fulminans (all patients) and intracranial hemorrhage (4 out of 5) only presented at around 11–16 months of age.[9] Although PCD is a pro-thrombotic disease, the resultant ischemia that occurred early in fetal development likely led to neovascularization and bilateral vitreous hemorrhage in our patient.

Ghassemi et al. reported a case of a 5-month-old boy with PCD who presented with unilateral leukocoria. Ophthalmic examination of the left eye revealed anterior segment dysgenesis along with closed funnel retinal detachment on ultrasonography. The right eye had a normal anterior segment examination, but fundus examination revealed severe retinal ischemia and neovascularization confirmed by FFA. Laser ablation of the avascular retina led to disease regression.[4] Our patient

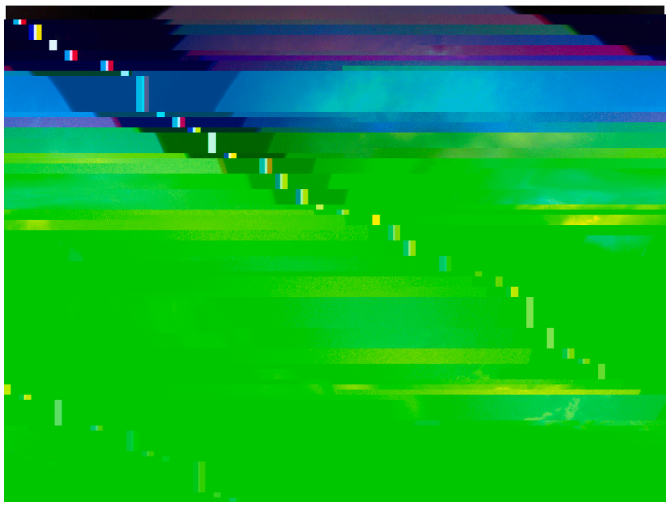

Fig. 6. Color fundus photograph of the right eye three weeks after the initial presentation and laser therapy showing partial resolution of vitreous hemorrhage, posterior tractional retinal detachment, and a nasal retinal fold. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

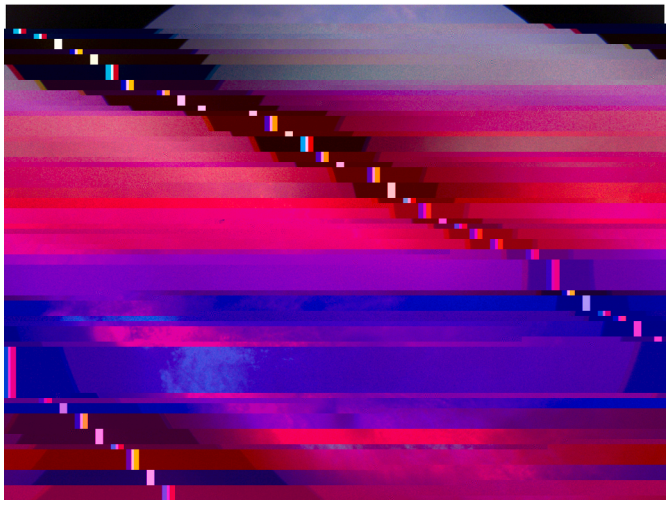

Fig. 7. Color fundus photograph of the left eye three weeks after the initial presentation showing regression of the disease with partial resolution of the blood. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

received laser ablation prior to surgery which achieved disease quiescence.

Alotaibi et al. reported two siblings with homozygous protein C deficiency (*PROC* gene mutation NM_000312.3: c.1297G > A: p. Gly433Ser) who presented with severe advanced ocular manifestations. Both presented with bilateral closed funnel retinal detachment along with iris neovascularization.[10] It appears from the literature that congenital PCD manifests an early-onset and rapidly progressive form of ischemic vitreoretinopathy advancing to TRD, rarely amenable to surgical repair. The severity may be in part related to the level of protein C activity.

A recent report from Japan described lensectomy and vitrectomy for two eyes of two infants with compound heterozygous PC deficiency. The intervention was successful in maintaining partial retinal attachment in one eye.[11] In our case, the disease was less severe, which allowed salvaging one eye with laser ablation and lens-sparing vitrectomy in the fellow eye.

Severe phenotypic presentation of pediatric ischemic vitreoretinopathy, such as FEVR and Norrie s disease may lead to retinal detachment in utero. Prenatal genetic diagnosis utilizing villous blood sampling in addition to ultrasonography has been employed in these conditions. This permits early delivery of laser intervention prior

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ajoc.2024.102206.

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