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Case Report

Documented Reperfusion of the Retina on Fluorescein Angiography after Administration of Intravenous Prostaglandin E1 for Central Retinal Artery Occlusion: A Case Report

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Abstract
Central retinal artery occlusion (CRAO) can result in devastating permanent vision loss. Presently, there is no evidence-based treatment for CRAO that is widely accepted. In the literature, multiple studies propose intravenous (IV) prostaglandin E1 (IV PGE1) as a potential treatment option for patients with CRAO. We illustrate 2 cases of CRAO successfully treated with IV PGE1. In both cases, our patients with vascular risk factors were diagnosed with CRAO of the left eye. They were started on twice daily IV 40 μg PGE1 in 100 mL normal saline, with each dose administered over 3 h. In the first case, we documented reperfusion of the retina on fluorescein angiography after administration of IV PGE1. In the second case, our patient improved from no light perception visual acuity (VA) to count fingers VA within 48 h of treatment with IV PGE1. Our study highlights the vasodilatory effect of IV PGE1. Due to its mechanism of action and safety profile, it should be considered a potential treatment option for CRAO. Further randomized controlled trials are necessary to determine the overall therapeutic effect of IV PGE1 for CRAO.

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Introduction

Central retinal artery occlusion (CRAO) is an ophthalmic emergency that presents with acute monocular vision loss. It has an incidence of 1 per 100,000 in the US population [1]. CRAO is non-arteritic etiology in 95% of cases and arteritic in 5% of cases [1]. The most common cause of non-arteritic CRAO is a proximal embolus deriving from the ipsilateral carotid artery, aortic arch, or heart [1]. Less commonly, it can be caused by thrombotic, vasculitic, or traumatic origin [2]. An embolus or thrombus in the central retinal artery leads to inner retinal ischemia. Hayreh et al. [3] showed that CRAO lasting for 240 min led to "massive, irreversible retinal damage" in elderly rhesus monkeys with atherosclerosis and hypertension (HTN). The visual prognosis of patients with CRAO is poor with 92% of patients achieving a visual acuity (VA) of count fingers (CFs) or worse [4].

Presently, there is no widely accepted evidence-based treatment for CRAO. Current therapies for CRAO have been shown to have variable efficacy and limited visual prognostic benefit [5, 6]. These therapies include systemic isosorbide dinitrate and pentoxifylline, hyperbaric oxygen, ocular massage, anterior chamber paracentesis, intra-arterial thrombolysis, and systemic or topical IOP-lowering medications [2]. Intravenous (IV) prostaglandin E1 (IV PGE1) has been hypothesized to be a potential treatment option for patients with CRAO due to its vasodilatory effect on the peripheral microcirculation [7]. PGE1 has been used in neonates to maintain temporary patency of the ductus arteriosus in ductal-dependent congenital heart disease [8], as well as to treat intermittent claudication in patients with peripheral vascular disease [7]. Intravenous PGE1 was started in our patients based on evidence from 2 prior case series showing statistically significant improvement in best corrected VA after 1 month of PGE1 treatment for acute CRAO [2, 4]. We present one case with documented reperfusion of the retina on fluorescein angiography (FA) after administration of IV PGE1 for CRAO. In the second case, our patient improved from no light perception (NLP) VA to CF VA within 48 h of treatment with IV PGE1.

Case Presentation

Case 1

A 67-year-old Caucasian male presented to the emergency department (ED) 6 h after experiencing sudden vision loss in his left eye. He denied any pain, flashes, floaters, or any history of previous vision loss. He denied headache and jaw claudication. Past medical history included type II diabetes mellitus without retinopathy, atrial fibrillation, HTN, hyperlipidemia, coronary artery disease status post coronary artery bypass graft, and congestive heart failure (CHF) status post implantable cardioverter defibrillator (ICD) placement. He reported a negative family history for eye disease, and he denied previous ophthalmic surgeries. Medications included apixaban 5 mg daily, amiodarone 200 mg daily, carvedilol 12.5 mg twice daily, furosemide 20 mg daily, lisinopril 5 mg twice daily, metformin 500 mg twice daily, and atorvastatin 40 mg daily.

Ophthalmologic examination revealed a VA of 20/70 pinhole 20/30–2 right eye (OD) and light perception left eye (OS). Confrontational visual fields were full OD. Intraocular pressures by tonopen were 17 mm Hg and 16 mm Hg in the right and left eye, respectively. A relative afferent pupillary defect was noted in the left eye. Examination of the unaffected right eye was normal except for a trace nuclear sclerotic cataract. Examination of the left eye revealed a normal anterior segment except for a trace nuclear sclerotic cataract. Dilated fundus exam OS revealed a clear vitreous, a sharp optic disc with slight pallor and cup-to-disc ratio of 0.2. The vessels were narrowed. Retinal whitening was noted in the macular area with a cherry red spot, but no embolus was identified. The peripheral retina was flat without holes or tears.

The patient was diagnosed with CRAO in the left eye. He was admitted to the neurology service for a comprehensive stroke work-up. ESR and CRP were within normal limits. The patient's ICD was not compatible to perform a magnetic resonance imaging of the brain. Computed tomography of the head without contrast showed no acute intracranial abnormality. Computed tomography angiography (CTA) of the head and neck revealed significant calcifications at the carotid bifurcation bilaterally, most prominent on the left, extending approximately 1 cm into the left internal carotid artery. Carotid and vertebral duplex examination showed mild disease of the distal common carotid, proximal internal, and proximal external carotid arteries bilaterally. Transthoracic echocardiogram (TTE) revealed no thrombus. Fundus photography was normal OD (Fig. 1a) but displayed a cherry red spot OS (Fig. 1b). FA in the left eye exhibited significantly delayed arterial filling time (Fig. 2a–f). Optical coherence tomography (OCT) examination of the macula in the left eye revealed disruption of the inner retinal architecture (Fig. 3a).

After obtaining cardiology clearance, the patient was started on twice daily 40 μg IV PGE1 in 100 mL normal saline 0.9% infusion with each dose administered over 3 h. Within 24 h of starting the IV PGE1 infusion, VA in the left eye improved to hand motion. After 48 h of treatment, VA improved to CF at 1-foot. At this time, repeat FA of the left eye demonstrated improvement in the arterial filling as well as significant improvement in the arteriovenous transit time compared to pre-treatment (Fig. 2g–l). After 4 days of hospitalization, the patient refused further treatment due to a subjective lack of improvement in his vision. The patient was discharged with close follow-up. Two weeks later, OCT of the macula in the left eye revealed extensive inner retinal edema (Fig. 3b); however, the patient left clinic prior to ophthalmic examination. Unfortunately, the patient was then lost to follow-up.

Case 2

A 58-year-old Black male presented to the ED 12 h after experiencing sudden vision loss in his left eye. He endorsed intermittent retro-orbital pain OS as well as occasional tension headaches. He denied any flashes, floaters, or any history of previous vision loss. He denied jaw claudication or scalp tenderness. Past ocular history included visually-significant cataracts in both eyes. Past medical history included HTN (not on medication) and active smoking with a 20 pack-year history. He reported a negative family history for eye disease, and he denied previous ophthalmic surgeries.

Ophthalmologic examination revealed a near VA of 20/100 pinhole no improvement OD and NLP OS. Confrontational visual fields were full OD. Intraocular pressures by tonopen were 21 mm Hg and 19 mm Hg in the right and left eye, respectively. A relative afferent pupillary defect was noted in the left eye. Examination of the unaffected right eye was normal except for a 3+ nuclear sclerotic cataract as well as attenuated vessels on fundus examination (Fig. 1c). Examination of the left eye revealed a normal anterior segment except for a 3+ nuclear sclerotic cataract. Dilated fundus examination OS revealed a clear vitreous, 1+ pallor of optic disc but sharp margins with nasal peripapillary atrophy and cup-to-disc ratio of 0.1. The vessels were attenuated. Pallor was noted in the macular area with a cherry red spot, but no embolus was identified (Fig. 1d). The peripheral retina was flat without holes or tears.

The patient was diagnosed with CRAO in the left eye. He was admitted to the neurology service for a comprehensive stroke work-up. ESR and CRP were within normal limits. Magnetic resonance imaging brain without contrast revealed mild diffuse cerebral volume loss with mild chronic microangiopathic changes with no acute infarction or intracranial hemorrhage. CTA of the head and neck revealed moderate atherosclerotic calcifications with mild luminal narrowing of the right supraclinoid ICA but otherwise WNL with no large vessel occlusion. Transthoracic echocardiogram revealed a negative bubble study with normal left

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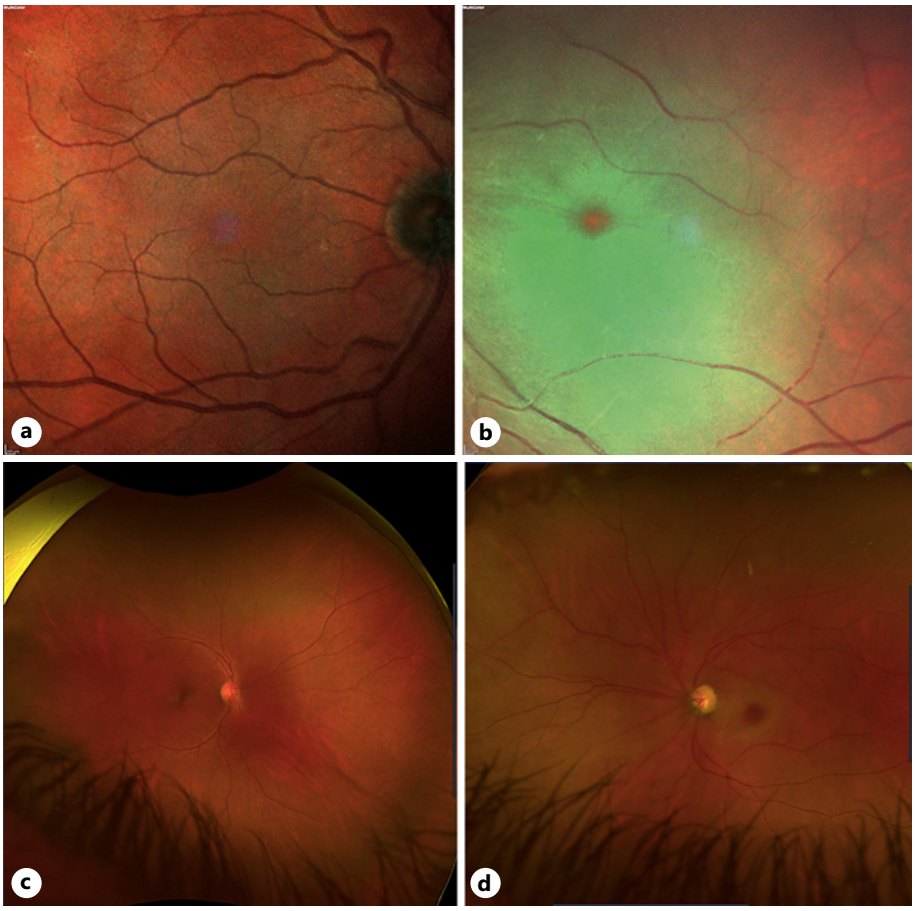

Fig. 1. a Case 1, fundus photography – WNL OD. **b** Case 1, fundus photography – cherry red spot OS. **c** Case 2, fundus photography – attenuated vessels but otherwise WNL OD. **d** Case 2, fundus photography – 1+ optic disc pallor but sharp margins, cherry red spot OS.

ventricular systolic function with estimated left ventricular ejection fraction 55–60%. Fluorescein angiography (FA) was not obtained. OCT examination of the macula in the left eye revealed foveal thinning with disruption of the inner retinal layers (Fig. 3c, d).

After obtaining cardiology clearance, the patient was started on twice daily 40 μg IV PGE1 in 100 mL normal saline 0.9% infusion with each dose administered over 3 h. Within 48 h of starting the IV PGE1 infusion, VA in the left eye improved to CF. After completing 3 days of IV PGE1 infusions, the patient refused further treatment and was discharged with outpatient retina clinic follow-up. Unfortunately, the patient was then lost to follow-up.

Discussion

Central retinal artery occlusion can result in devastating permanent vision loss. The vision loss is characterized as unilateral, sudden-onset, and painless. In both cases, we did not identify an embolus on fundus examination nor find evidence of a thrombus in the heart even with our first patient's history of atrial fibrillation. Dumitrascu et al. [1] notes that "the narrowest portion of the central retinal artery is 2 mm behind the globe at the level of the lamina cribosa explaining why not all embolic CRAOs have visible retinal arterial emboli on fundus examination." The CRAO in our first patient may have been caused by an embolus from

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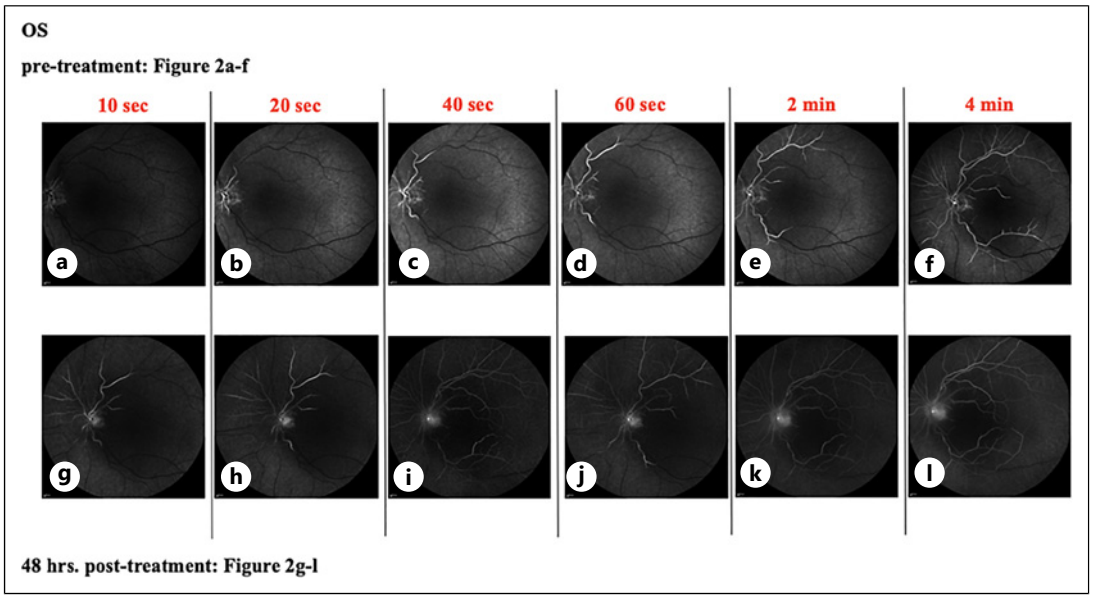

Fig. 2. **a** Pretreatment, FA at 10 sec, CRAO with significantly delayed arterial filling time OS. **b** Pretreatment, FA at 20 sec, CRAO with significantly delayed arterial filling time OS. **c** Pretreatment, FA at 40 sec, CRAO with significantly delayed arterial filling time OS. **d** Pretreatment, FA at 60 s, CRAO with significantly delayed arterial filling time OS. **e** Pretreatment, FA at 2 min, CRAO with significantly delayed arterial filling time OS. **f** Pre-treatment, FA at 4 min, CRAO with significantly delayed arterial filling time OS. 48 h posttreatment, FA at 10 s, improvement in the arterial filling, and significant improvement in the AV transit time OS. **h** 48 h posttreatment, FA at 20 s, improvement in the arterial filling, and significant improvement in the AV transit time OS. **i** 48 h posttreatment, FA at 40 s, improvement in the arterial filling, and significant improvement in the AV transit time OS. **j** 48 h posttreatment, FA at 60 s, improvement in the arterial filling, and significant improvement in the AV transit time OS. **k** 48 h posttreatment, FA at 2 min, improvement in the arterial filling, and significant improvement in the AV transit time OS. **l** 48 h posttreatment, FA at 4 min, improvement in the arterial filling, and significant improvement in the AV transit time OS.

the extensive carotid disease documented on his CTA head and neck. In the second case, our patient was at risk of CRAO due his active smoking history and primary HTN (not on medication).

Current treatment options for CRAO include IV acetazolamide, IV mannitol, topical antiglaucoma medications, pentoxifylline, inhalation of carbogen, sublingual isosorbide dinitrate, IV methylprednisolone, IV or intra-arterial recombinant tissue plasminogen activator (rt-PA), hyperbaric oxygen therapy, anterior chamber paracentesis, ocular massage, Nd:YAG laser embolectomy, or pars plana vitrectomy [9]. Dumitrascu et al. [1] recommend IV thrombolysis with alteplase for CRAO up to 4.5 h from symptom onset to help retinal reperfusion. Our patients presented to the ED 6 and 12 h after symptom onset, respectively. In addition, there is an extensive list of radiological, clinical, laboratory, and ophthalmologic contraindications to IV alteplase including but not limited to acute intracranial hemorrhage, vitreous hemorrhage, among others [1]. Takai et al. [4] report a downside to alteplase administration: it cannot dissolve cholesterol or calcified material but only platelet-fibrin thrombus which composes only 15.5% of all retinal emboli. For comparison, 74% of retinal emboli are composed of cholesterol and 10.5% are composed of calcific material [4].

Due to its mechanism of action and safety profile, IV PGE1 has been proposed as a potential treatment option for acute CRAO [2, 4], acute branch retinal arterial embolism [7], arteritic anterior ischemic optic neuropathy [10], non-arteritic anterior ischemic optic neuropathy [11], and

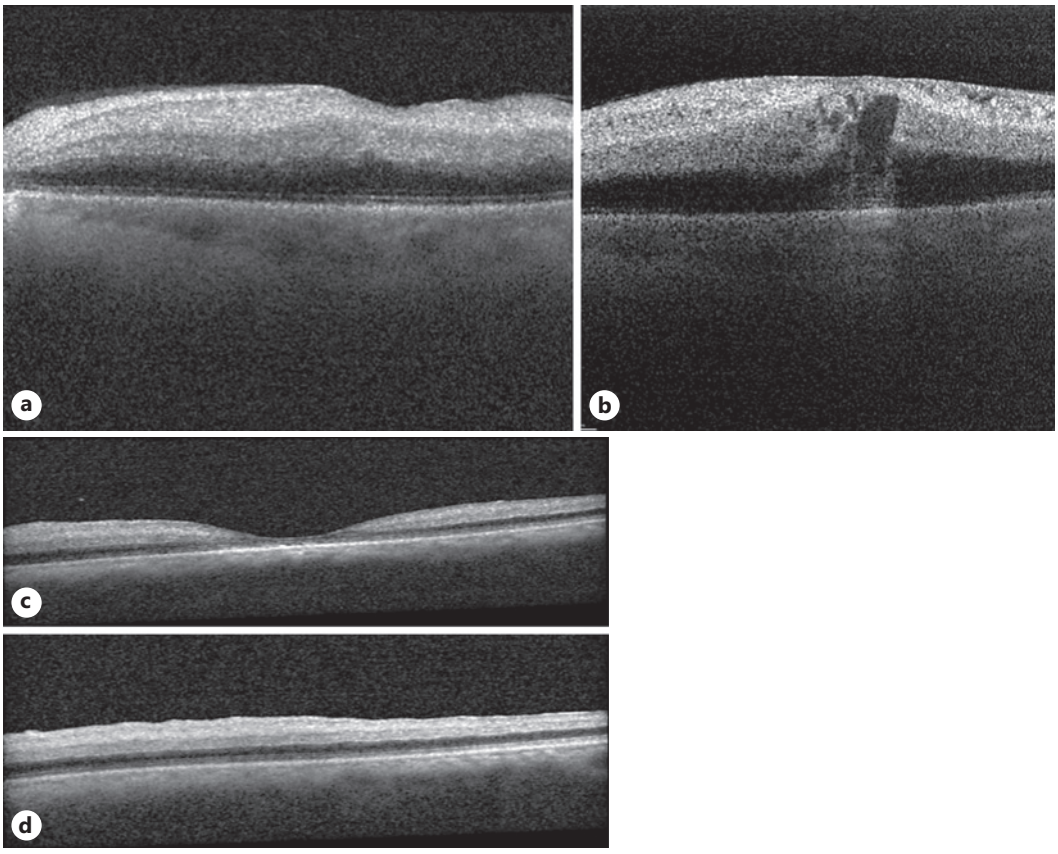

Fig. 3. a Case 1, pretreatment, OCT retina – disruption of the inner retinal architecture OS. **b** Case 1, two-week follow-up post-treatment, OCT retina – extensive inner retinal edema OS. **c** Case 2, OCT retina – foveal thinning OS. **d** Case 2, OCT retina – disruption of the inner retinal architecture OS.

non-arteritic posterior ischemic optic neuropathy [12–14]. Prostaglandin E1 has direct action on the smooth muscle of the vascular wall leading to vascular dilation [7]. In addition, it inhibits platelet aggregation via a cyclic adenosine monophosphate pathway [4]. Specifically, Kreutz et al. [15] explain that "PGE1 binds to prostacyclin receptor on platelets, raises intracellular cAMP which inhibits phospholipase C activation, and reduces Ca2+ mobilization from intracellular stores thus antagonizing the effects of P2Y1 receptor activation" (P2Y1 is a Gq-coupled receptor that is a key driver in platelet activation and aggregation). Therefore, there is potential to use systemic IV PGE1 therapy to treat acute CRAO because of the theoretical benefit of vasodilation as well as inhibition of platelet aggregation in the restoration of retinal blood flow.

Of note, one of the labeled indications for PGE1 is temporary patency of ductus arteriosus in ductal-dependent congenital heart disease [16]. It is well-studied in neonates to dilate the ductus smooth muscle to allow for oxygenated blood flow until the congenital anomaly can be surgically corrected [8]. Prostaglandin E1 is given intravenously in physiologic solution at a dose of 1 μg/kg [12]. It is rapidly metabolized by oxidation in the pulmonary circulation [7]. PGE1 has minimal side effects including a 0.5–5% incidence of angialgia and vomiting, less than 0.5% incidence of systemic hypotension, and less than 0.05% incidence of local or systemic bleeding [4]. Systemic blood pressure is monitored every 15–20 min during IV administration of PGE1 [13]. Possible contraindications for PGE1 include uncontrolled systemic HTN, CHF, and hemorrhagic status [4]. Cardiology was consulted for clearance prior to starting the IV PGE1 infusion because both patients had HTN and one with CHF. They did not experience any side effects with the infusion.

Takai et al. [4] noted that time to treatment could be a major contributor to visual prognosis when using IV PGE1. In their study, the mean time to treat was 7.1 h with a range of 1–18 h (10 eyes in 9 patients) [4]. Malbin et al. [2] recommend starting treatment within 24 h of presentation. In their study, the mean time to presentation was 8.33 h with a range of 2–12 h (6 eyes in 6 patients) [2]. Sim and Ting recommend starting any treatment for CRAO within 4 h of symptoms [9]. In our study, IV PGE1 was started within 24 h of presentation. In both cases, VA OS improved to CF from LP and NLP, respectively, within 48 h of starting the infusion.

In the first case, our patient was LP OS and demonstrated CRAO with significantly delayed filling time on FA in the left eye. After 48 h of treatment with IV PGE1, our patient improved to CF at 1-foot OS, and FA demonstrated improvement in the arterial filling as well as arteriovenous transit of the left eye compared to pretreatment. Therefore, the documented reperfusion of the retina on FA could be correlated to his treatment with IV PGE1. In the second case, our patient improved from NLP to CF VA within 48 h of treatment with IV PGE1. In both cases, it is possible that there could have been more improvement in VA with continued treatment. Our patients' improvement in VA could still be due to the spontaneous recanalization of the retinal artery.

In the literature, two previous studies have proposed IV PGE1 as a treatment option for acute CRAO [2, 4]. Our study adds two additional cases of safe and effective use of IV PGE1 for CRAO. Furthermore, it highlights the vasodilatory effect of IV PGE1, and it should be considered a potential treatment option for acute CRAO. Randomized controlled trials are necessary to determine the overall therapeutic effect of IV PGE1 for CRAO. We also need to continue to educate the public and health care providers on the importance of prompt disease recognition, as it can affect the treatment and outcome of this condition. Lastly, the "CARE Checklist" has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533404).

Statement of Ethics

Written informed consent was obtained from the patients for publication of the details of their medical cases and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflicts of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Joseph Anthony Chacko, MD: substantial contributions to the acquisition, analysis, or interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; and agreement to be

accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Heather V. Broyles, DO and Joseph George Chacko, MD: critically revising the work for important intellectual content and final approval of the version to be published. Sami H. Uwaydat, MD: substantial contributions to the conception or design of the work and the acquisition, analysis, or interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

The data supporting the conclusions of the study can be found within the manuscript. Additional questions about data availability can be addressed by the corresponding author.

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