

# Multiple Successive Branch Retinal Artery Occlusions in a Patient With Antiphospholipid Syndrome Despite Anticoagulation

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## Abstract

**Purpose:** To describe a patient with antiphospholipid syndrome presenting with branch retinal artery occlusions (BRAO) despite anticoagulation. **Methods:** A single case was evaluated. **Results:** A 53-year-old woman with antiphospholipid syndrome on anticoagulation presented for a routine ophthalmic examination. She had no visual complaints, and the visual acuity was 20/25<sup>-1</sup> OD and 20/30<sup>-1</sup> OS. A BRAO was found in the right eye. Despite treatment with aspirin, warfarin, prednisone, plasmapheresis, and rituximab, multiple new occlusions were found when the patient returned the next month. She ultimately had a stroke, which led to her death. **Conclusions:** This case underscores the importance of interdisciplinary care for patients with antiphospholipid syndrome presenting with BRAOs despite anticoagulation.

## Keywords

antiphospholipid syndrome, branch retinal artery occlusion, fluorescein angiography, OCT

## Introduction

Antiphospholipid syndrome is an acquired autoimmune disease that causes hypercoagulability due to the presence of antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin, and anti-beta 2 glycoprotein I.<sup>1</sup> The presentation is typically thrombotic (arterial, venous, or microvascular) or pregnancy-related morbidity. Microvascular thrombosis, such as diffuse alveolar hemorrhage, nephropathy, cardiac microthrombosis, or adrenal hemorrhage, is a less common presentation. Catastrophic antiphospholipid syndrome, characterized by rapid-onset, large-vessel, and microvascular involvement of multiple organ systems, is a rare development.

Data suggest that there is an increased rate of antiphospholipid syndrome in women; however, when patients with systemic lupus erythematosus are excluded, the ratio of women to men decreases.<sup>2</sup> There is no predilection regarding sex in the pediatric population, and in the older adult population, a higher percentage of men may present with the syndrome.<sup>2</sup> There is no consensus regarding the typical age of onset.

High antiphospholipid antibody titers can be seen in the general population and may be transiently elevated in the setting of infection, malignancy, or certain medications; repeat confirmatory testing should be performed after 12 weeks.<sup>3</sup> Antiphospholipid antibody titers are elevated in 12% to 30% of those with systemic lupus erythematosus.<sup>4</sup> Common thrombotic clinical presentations include pulmonary embolism, deep vein thrombosis, stroke, or myocardial infarction. Although retinal artery occlusion (RAO) is a very rare initial presentation

of antiphospholipid syndrome, it has been documented.<sup>5</sup> Patients who have had a thrombotic event are typically treated with anticoagulants; however, recurrent thrombosis is common despite this therapy.<sup>4</sup> In 1 study, the cumulative incidence of thromboembolic events after 10 years in patients with antiphospholipid syndrome was 44.2%; however, the rate was significantly higher in patients not taking oral anticoagulants.<sup>6</sup> There is a known association between antiphospholipid syndrome and mortality, with severe thrombotic events, including myocardial infarction, stroke, and pulmonary embolism, the most common causes of death.<sup>7,8</sup>

Catastrophic antiphospholipid syndrome has a mortality rate of approximately 50%<sup>7</sup> but only develops in approximately 1% of patients with the condition.<sup>8</sup> In a prospective study of 1000 patients with antiphospholipid syndrome, 9.3% of patients died over a 10-year period. No difference in the percentage of deaths was found between patients with associated systemic lupus erythematosus and those without.<sup>7</sup> An association was also found between RAO and mortality. A Korean cohort study from 2002 to 2018 found mortality rates to be significantly higher in patients with central RAOs (CRAOs) and branch RAOs (BRAOs) than in

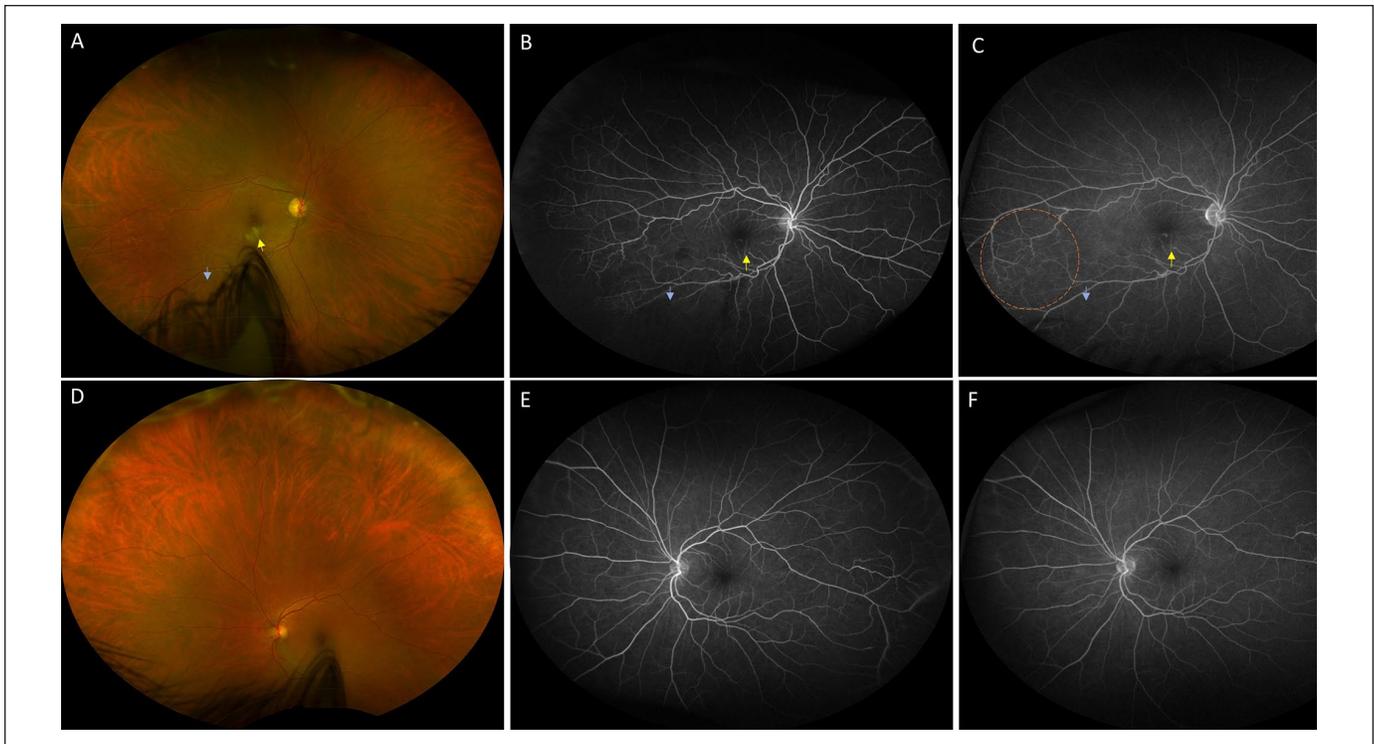
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**Figure 1.** (A) Fundus photograph of the right eye. (B) Fluorescence angiography (FA) in the early arteriovenous phase and (C) in the venous phase shows inferior macular arteriolar occlusion (yellow arrows) as well as arteriolar attenuation (blue arrows). (B) Delayed transit is also noted inferotemporally, and (C) there is late staining from telangiectasias inferotemporally (dashed orange line). (D) Fundus photograph of the left eye. (E) FA in the early arteriovenous phase and (F) in the venous phase shows no acute changes.

the general population (standardized mortality ratio, 7.33).<sup>9</sup> Although no correlation between antiphospholipid syndrome with that study's population was made, 36.4% of patients were on antiplatelet drugs and 6.7% were on anticoagulation.

We describe a case of successive BRAOs in a patient with antiphospholipid syndrome on long-term anticoagulation treatment who succumbed to her illness within 2 months of her ophthalmologic presentation.

## Case Report

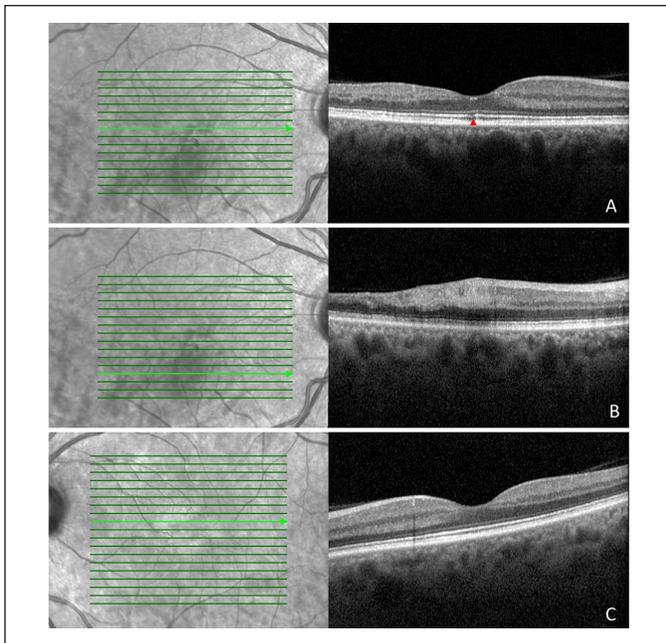
A 53-year-old woman with known antiphospholipid syndrome with positive lupus anticoagulant, anticardiolipin, and anti- $\beta 2$  glycoprotein antibodies (triple-positive antiphospholipid antibodies) presented with no visual complaints for an annual ophthalmic examination. Her history included a stroke at age 25 years, 2 miscarriages 8 years and 10 years previously, cardiac surgery with mitral and tricuspid valve repair 2 years earlier, and diffuse alveolar hemorrhage diagnosed 1 year previously.

The patient's best-corrected visual acuity (BCVA) was 20/25<sup>-1</sup> OD and 20/30<sup>-1</sup> OS. A dilated fundus examination showed generalized arteriolar narrowing in both eyes and an inferior macular arteriolar occlusion with retinal whitening in the right eye (Figure 1). Fluorescein angiography (FA) of the right eye also showed the arteriolar occlusion in the inferior macula and delayed transit in the inferotemporal arcade, with temporal staining from telangiectasias and no leakage (Figure 1). FA of the left eye

showed normal arteriovenous transit with no leakage (Figure 1). Spectral-domain optical coherence tomography (SD-OCT) of the right eye showed inner retinal hyperreflectivity in the inferior macula, subfoveal ellipsoid zone (EZ) disruption, and inferotemporal retinal thinning. No acute findings were seen in the left eye on SD-OCT (Figure 2). A diagnosis of BRAO in the right eye was made.

For several years, the patient had been on metoprolol, aspirin 81 mg, and warfarin. She was also on oral prednisone 50 mg/day and enteric-coated mycophenolate sodium for the past 1.5 years per her rheumatologist. She received 5 sessions of plasmapheresis and her first dose of rituximab 4 months earlier, with a plan for a second infusion 1 month later and subsequent infusions every 6 months. One week before the patient presented, hydroxychloroquine was started at a dose of 5.9 mg/kg/day, which is higher than American Academy of Ophthalmology guidelines for weight-based dosing of 5 mg/kg/day or less to reduce the risk for hydroxychloroquine retinal toxicity.<sup>10</sup> The patient and her rheumatologist were advised of the EZ disruption at presentation; given the concern for toxicity at this dose if continued long term, the patient was encouraged to discontinue hydroxychloroquine in favor of other treatment options that did not have such a risk to the retina.

The patient presented the next month for follow-up, at which time the BCVA remained 20/25<sup>-1</sup> OD and 20/40<sup>-1</sup> OS. A dilated fundus examination of the right eye showed sclerotic vessels along the inferior vascular arcade and multiple occluded arterioles with skip lesions in the superior arcade (Figure 3). There



**Figure 2.** Optical coherence tomography (OCT) of the macula at presentation. (A) Subfoveal ellipsoid zone disruption is seen in the right eye (red arrowhead). (B) Inferotemporal disruption, hyperreflectivity, and thinning of the inner retinal layers is seen in the right eye. (C) OCT of the left eye shows a flat macula with intact internal and external retinal layers.

were no changes seen in the left eye. FA of the right eye showed delayed transit in the inferotemporal arcade with a new temporal region of capillary nonperfusion; there was no change in the left eye (Figure 3). Once again, SD-OCT of the right eye showed inner retinal hyperreflectivity in the inferior macula, subfoveal EZ disruption, and inferotemporal inner retinal thinning. The fovea of the left eye was flat with intact retinal layers (Figure 4). Given multiple new arterial occlusions, the patient was referred to cardiology for an echocardiogram and a carotid Doppler, as well as referred to neurology for a stroke workup.

Approximately 1 week after this follow-up visit, the patient was hospitalized. She was treated in the intensive care unit for pulmonary issues, including bacterial and fungal lung infections as well as kidney failure, requiring dialysis. While hospitalized, she received 5 more sessions of plasmapheresis followed by intravenous immunoglobulin (Ig). Early in this hospitalization, magnetic resonance imaging (MRI) of the brain showed findings concerning for a new stroke. A repeat brain MRI later in the hospitalization showed a massive new stroke with midline shift, which ultimately led to the patient's death.

## Conclusions

We describe a patient with antiphospholipid syndrome who developed multiple successive BRAOs in 1 eye despite aggressive therapy that included anticoagulation, rituximab, and plasmapheresis. Our case adds to the growing body of literature suggesting that anticoagulation is ineffective in preventing microvascular thrombosis in patients with antiphospholipid syndrome. Although

large-vessel disease is more common, roughly 10% of patients with the condition develop microvascular disease<sup>11</sup> and only 1% to 2% have CRAO or BRAO.<sup>8</sup> Management remains challenging because of the heterogeneous clinical manifestations and organ involvement.<sup>12</sup> Moreover, systematic studies of treatments for microvascular antiphospholipid syndrome are lacking, in particular in regard to retinal thromboses.

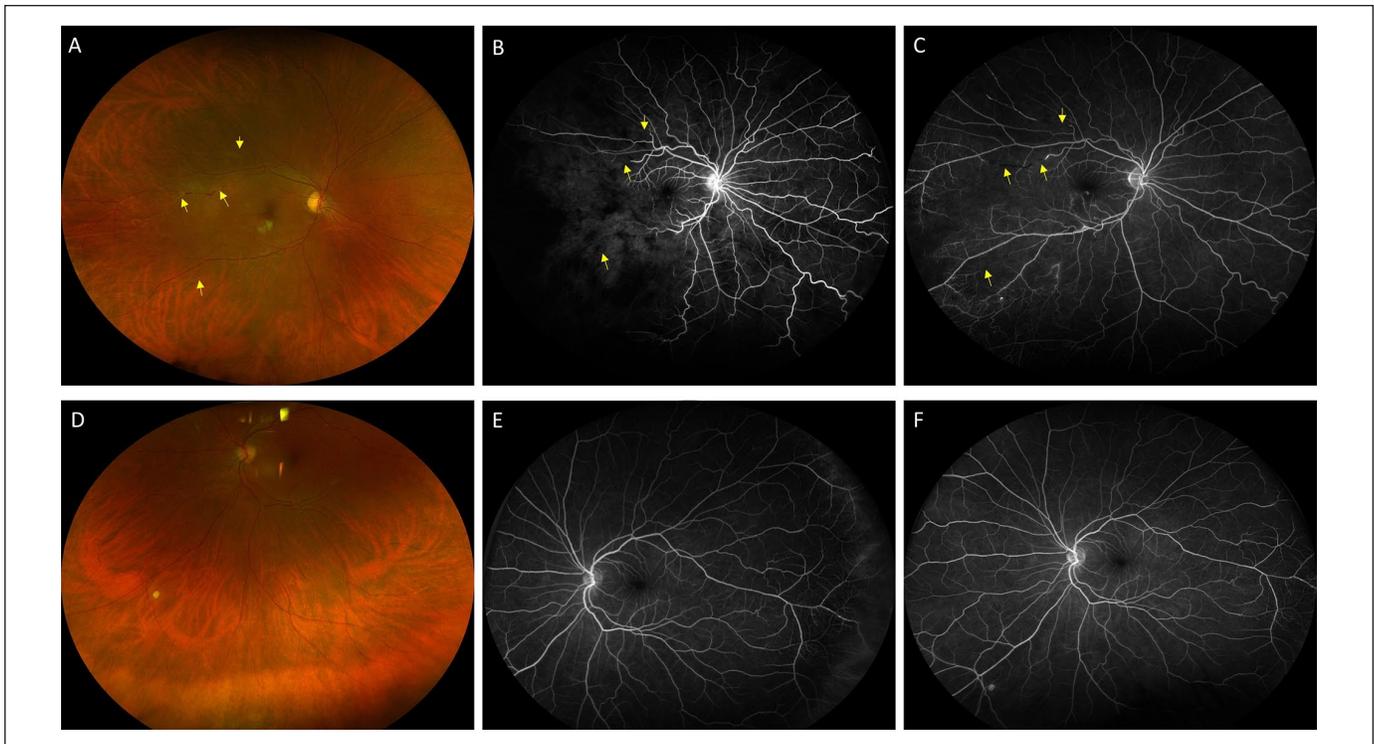
A study of 312 patients with primary antiphospholipid syndrome and a mean follow-up of 10 years reported that 100 of 143 patients (70%) suffered from recurrent thrombosis despite preventive therapy.<sup>13</sup> Of this group, 81% were treated with anticoagulants with or without antiplatelet agents. However, thrombotic events in this study included stroke, limb ischemia, deep vein thrombosis, and pulmonary embolism, but not microvascular events such as BRAO.

One recent case series described 3 middle-aged patients (2 women and 1 man) with systemic lupus erythematosus and severe vaso-occlusive retinopathy, none of whom had recurrent BRAO after starting anticoagulation.<sup>14</sup> Patient 1 had branch retinal arteriolar insufficiencies in the right eye and multiple BRAOs in the left eye. Patient 2 had an inferotemporal BRAO combined with a nonischemic central retinal vein occlusion (CRVO) that evolved into an ischemic CRVO in the same eye. Patient 3 had an inferotemporal BRAO with a nonischemic CRVO in the same eye.

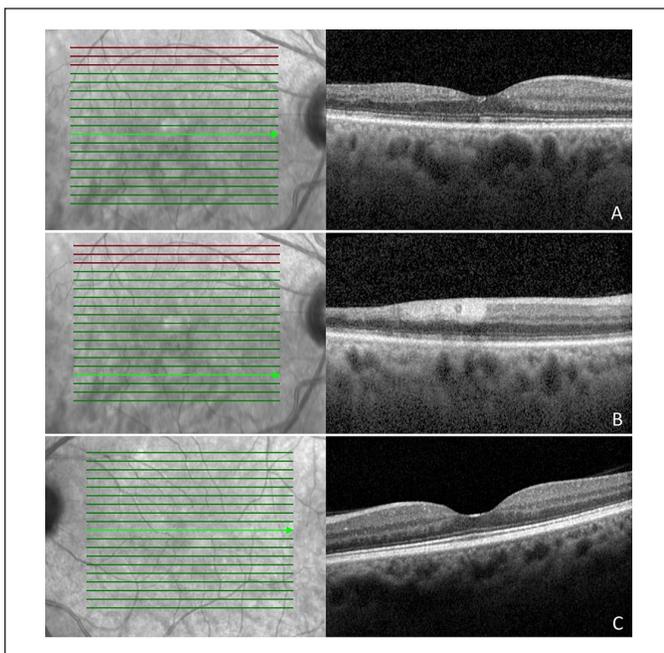
The patients were treated with 3 doses of intravenous methylprednisolone 1 g/day followed by an oral prednisone taper and maintenance doses of hydroxychloroquine and azathioprine. Patient 1's regimen also included intravenous rituximab. Patient 2's regimen also included enoxaparin, warfarin with an international normalized ratio goal of 2 to 2.5, and 3 monthly doses of intravitreal (IVT) ranibizumab. Patient 3 had enoxaparin, 3 doses of IVT ranibizumab, and folic acid for homocysteinemia added to the regimen. Of note, Patient 1 and Patient 3 did not have antiphospholipid syndrome; patient 2 did have antiphospholipid antibodies, and patient 3 had homocysteinemia, both of which contribute to an increased hypercoagulable state. Follow-up was only reported through 6 months, however, so it is possible that there was a subsequent consecutive vaso-occlusive episode after that time period. A longer follow-up in patients with antiphospholipid syndrome is associated with a higher recurrence of arterial, venous, or combined thrombotic events.<sup>14</sup>

In patients with recurrent thrombosis despite an international normalized ratio in the therapeutic range, some common alternatives include the use of higher-intensity warfarin (international normalized ratio 3–4), switching to low-molecular-weight heparin, or adding low-dose aspirin, hydroxychloroquine, a statin drug, or a combination.<sup>15</sup> Particularly in patients with triple-positive antiphospholipid antibodies or arterial thrombosis, direct oral anticoagulants are not recommended given the worse outcomes reported in these groups.<sup>16</sup>

Intravenous Ig can also be considered for prevention of recurrent thrombosis in cases refractory to standard therapy. One study compared the outcomes of 14 patients with antiphospholipid syndrome. Seven patients received infusions at a monthly dose of 400 mg/kg/day for 2 consecutive years, and 7 control



**Figure 3.** Images 1.5 months after presentation. (A) Fundus photograph of the right eye. (B) Fluorescence angiography (FA) in the early arteriovenous phase and (C) in the venous phase shows several new arteriolar occlusions (yellow arrows). (C) A new region of capillary nonperfusion is seen inferiorly and inferotemporally. (D) Fundus photograph of the left eye. (E) FA in the early arteriovenous phase and (F) in the venous phase shows a small inferonasal change in the retinal pigment epithelium; otherwise, no acute findings.



**Figure 4.** Spectral-domain optical coherence tomography of the macula 1.5 months after presentation. (A and B) Temporal and inferior macular thinning, disruption, and hyperreflectivity of the inner retinal layers is seen in the right eye. (C) A flat macula with intact retinal layers is seen in the left eye.

patients received no infusions after their conventional therapy.<sup>17</sup> During the 2-year follow-up period, no additional thrombotic events occurred in the group treated with intravenous Ig, while 2 patients in the control group had subsequent strokes and 1 patient developed subsequent deep vein thrombosis.<sup>17</sup> Despite this apparent efficacy in preventing thromboembolic events, intravenous Ig has also been associated with an increased risk for thromboembolic events<sup>18,19</sup>; therefore, the risks and benefits of this therapy must be weighed on a case-by-case basis. However, as previously mentioned, much of these data are based on large-vessel disease and little information exists regarding the best approach for microvascular thrombosis.

Given the inefficacy of anticoagulation for recurrent thrombosis in antiphospholipid syndrome, there are several newer treatments under investigation. Rituximab is thought to work in these patients in 2 ways. First, it depletes B cells and antibody production. Second, the immune complexes formed by the binding of rituximab to CD20 act as a decoy, attracting monocytes and macrophages and reducing pathologic inflammation elsewhere. Notably, studies have shown decreased antiphospholipid antibody titers after the use of rituximab; however, monotherapy with rituximab has not been shown to result in a negative antiphospholipid antibody profile in patients with the syndrome. Belimumab, eculizumab, sirolimus, defibrotide, and peptide therapy are also under investigation; however, there are not enough data to formulate recommendations regarding their use for retinal thromboses.<sup>20</sup>

In summary, we present a case of multiple successive BRAOs in a patient with triple-positive antiphospholipid antibody antiphospholipid syndrome despite anticoagulation, emphasizing that systemic anticoagulation is ineffective in preventing microvascular thrombosis. The prevention of recurrent thrombosis in this syndrome is challenging, with many proposed treatments under investigation and minimal data regarding their effect on microvascular thrombosis, such as those involving retinal arterioles. Antiphospholipid syndrome is a rare cause of RAOs, and a high index of suspicion for the condition should exist when encountering multiple RVOs or RVOs in the setting of thrombotic manifestations in other organ systems. Considering the multiorgan involvement in antiphospholipid syndrome, a multidisciplinary approach is warranted to care for these patients.

### Ethical Approval

This case report was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient Health information was performed in a US Health Insurance Portability and Accountability Act-compliant manner.

### Statement of Informed Consent

The patient provided informed consent, including permission for publication of all photographs and images included herein.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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