



## Case report

## Retinopathy in lupus transitioned to Kikuchi-Fujimoto disease



Kelly S. Rue, Damien C. Rodger, Narsing A. Rao\*

University of Southern California Roski Eye Institute, Department of Ophthalmology, Keck School of Medicine of the University of Southern California, Los Angeles, CA, United States

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## ABSTRACT

**Purpose:** We present a patient with systemic lupus erythematosus with significant vaso-occlusive retinal findings mimicking antiphospholipid antibody syndrome, who developed Kikuchi-Fujimoto disease.

**Observations:** Our patient was initially diagnosed with systemic lupus erythematosus with antiphospholipid antibody syndrome given consistent serologic markers and profound retinal vascular ischemia. However, on subsequent follow up, she presented with fever and lymphadenopathy and underwent lymph node biopsy, which declared histologic findings of Kikuchi-Fujimoto disease. Repeat markers for antiphospholipid antibody syndrome were negative and she was taken off lifelong anticoagulation.

**Conclusions and importance:** Systemic lupus erythematosus and Kikuchi-Fujimoto disease may have many similar features and even biomarkers, and given the potential overlap of presentation, clinicians must carefully distinguish between these diseases to prevent unnecessary treatment.

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## 1. Introduction

Classically, Kikuchi-Fujimoto Disease (KFD) is characterized by fever and tender lymphadenopathy, typically self-limited over a period of a few months without treatment, often in young women of Asian heritage.<sup>1,2</sup> Systemic lupus erythematosus (SLE) and KFD have been reported to occur in patients at any time interval, including concurrently and sequentially to each other.<sup>3–5</sup> We present a case of a patient with SLE who presented with profound retinal ischemia mimicking antiphospholipid antibody syndrome (APLS), who developed KFD. Lymph node biopsy secured the diagnosis of KFD. Furthermore, the patient's initially elevated anti-cardiolipin antibodies when she presented with lupus flare were negative on repeat testing for APLS when she presented with clinical findings of KFD. This case did not require approval by our Institutional Review Board.

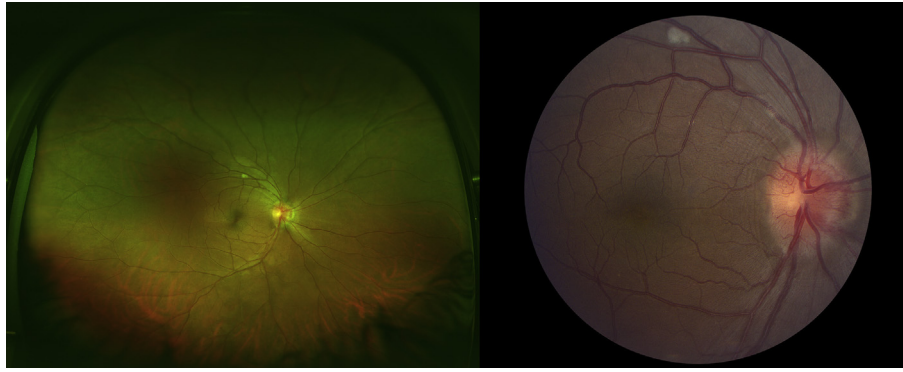
## 2. Case report

Specific personal identifying information has been removed from this report in accordance with the patient's wishes. A twenty-

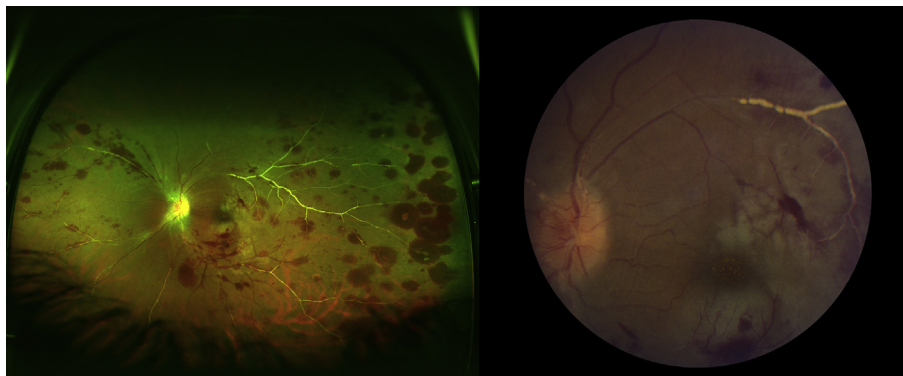
six-year old female, recently diagnosed and treated for SLE complicated by aseptic meningitis and multiple small strokes at an outside hospital 2 weeks prior, presented to our institution with complaints of painless decreased vision and right visual field deficit of the left eye (OS), occurring suddenly 12 days prior and without improvement in the intervening period. Visual acuity (VA) was 20/20 right eye (OD) and count fingers at 1 foot OS. Pupils were equal, round and reactive with a positive afferent pupillary defect OS. Brightness sense was decreased OS compared to OD and she was unable to perform color plates OS compared to 8/8 plates OD. Intraocular pressures as well as anterior segment exam were normal in both eyes (OU). Dilated fundus exam was significant for mild disc edema and a cotton wool spot along the superior arcade OD (Fig. 1). There was severe disc edema with peripapillary hemorrhage OS and an apparent cherry red spot in the macula. The vessels were sclerosed and sheathed, with many ghost vessels visible. There was diffuse retinal ischemia and retinal hemorrhages temporally in the periphery (Fig. 2). Optical coherence tomography (OCT) showed nerve fiber layer thickening corresponding to cotton wool spots. Fluorescein angiography (FA) demonstrated marked ischemia with complete nonperfusion extending from the macula (Fig. 3), in contrast to the normal perfusion in the right eye (Fig. 4). Work up revealed positive ANA (1:160, speckled), anti-smith (>8), anti-RNP (>8), SSA (3.1), anti-cardiolipin (26), with low C3 (39) and C4 (8.3) and she was diagnosed with SLE with APLS. Hypercoagulability workup including homocysteine, PT/INR, PTT were normal.

\* Corresponding author. USC Department of Ophthalmology, 1450 San Pablo Street, Los Angeles, CA, 90033, United States.

E-mail address: [Narsing.Rao@med.usc.edu](mailto:Narsing.Rao@med.usc.edu) (N.A. Rao).



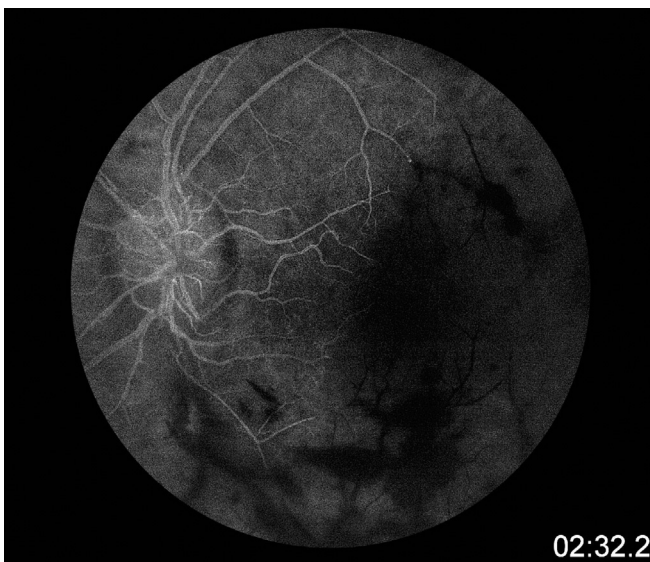
**Fig. 1.** Color fundus photo, right eye. Dilated fundus exam of the right eye was significant for mild disc edema and a cotton wool spot along the superior arcade.



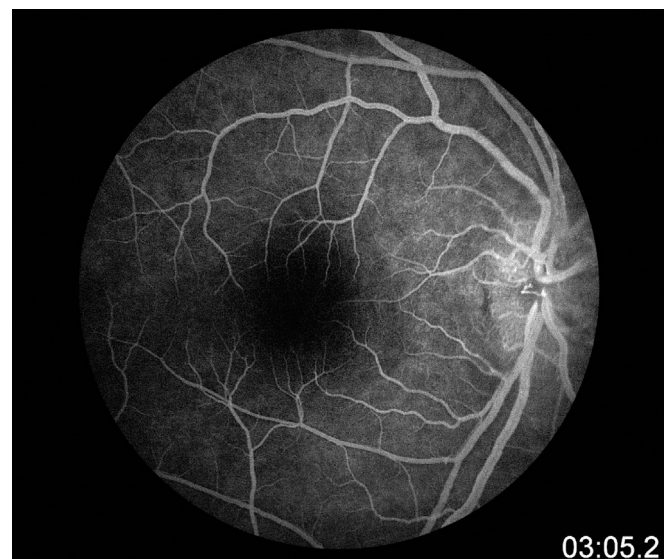
**Fig. 2.** Color fundus photo, left eye. Dilated fundus exam of the left eye was remarkable for severe disc edema with peripapillary hemorrhage, an apparent cherry red spot in the macula, sclerosed and sheathed vessels, diffuse retinal ischemia and retinal hemorrhages.

Further extensive infectious work up was negative for HIV, RPR, Quantiferon Gold, blood cultures, chest X-ray, lumbar puncture, and trans-esophageal echocardiogram. MRI was consistent with a punctate left basal ganglia lacunar infarct. MRA was normal. She was treated with high dose IV methylprednisolone starting at 1gm

for a day and quickly tapered due to presumed steroid-induced psychosis to 500 mg for 2 days, then transitioned to prednisone 20 mg every 8 hours, and she was discharged on cyclophosphamide and hydroxychloroquine because of perceived severity of her SLE, and enoxaparin was transitioned to warfarin for life long

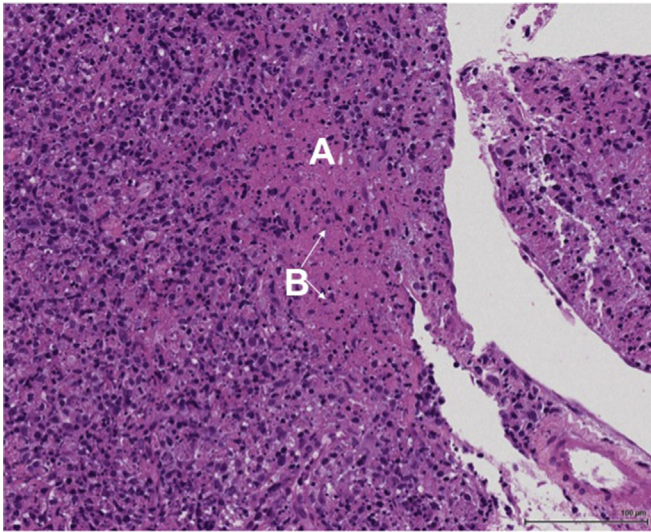


**Fig. 3.** Fluorescein angiography, left eye. Fluorescein angiography demonstrated marked ischemia with complete nonperfusion extending from the macula of the left eye.



**Fig. 4.** Fluorescein angiography, right eye. Normal perfusion.





**Fig. 5.** Pathology slide of lymph node biopsy. Lymph node biopsy revealed significant necrosis (A) and broken nuclei signifying karyorrhectic debris (B).

anticoagulation for APLS. Vision was 2ft/200 OS when she was discharged.

She returned to the hospital approximately two months later with recurrent fevers up to 102F, but extensive infectious work up was negative. She was found to have hypermetabolic cervical lymph nodes on PET-CT. Fine needle and core needle biopsy of lymph nodes were not diagnostic, and finally a cervical node core biopsy revealed histiocytic necrotizing lymphadenitis, consistent with KFD (Fig. 5). There was no morphologic or immunophenotypic evidence of lymphoproliferative disorder. Given her KFD diagnosis, APLS work up was repeated, which returned negative for anti-cardiolipin, and she was taken off what we previously presumed would be lifelong anticoagulation. Her fever and lymphadenopathy resolved. Now medically stable, she was treated with panretinal photocoagulation for retinal neovascularization and extensive retinal ischemia.

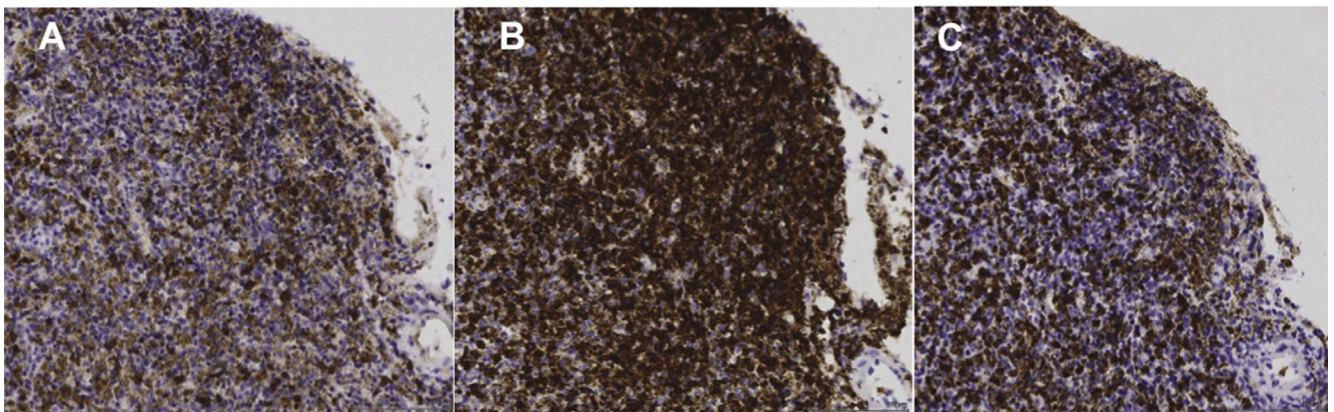
### 3. Discussion

We present retinal vascular changes in a patient initially diagnosed with SLE and APLS, which evolved to KFD.

SLE retinopathy is characterized by retinal hemorrhages, cotton wool spots, arteriolar narrowing, capillary dilation, venous dilation and tortuosity, and retinal edema and exudates from immune-complex vasculopathy.<sup>6</sup> Less commonly, occlusive retinal vasculitis may develop resulting in diffuse capillary nonperfusion and retinal ischemia.<sup>7</sup> The mechanism is incompletely understood and likely multifactorial, including immune-complex deposition, vasculitis, arteriolar constriction with systemic hypertension, and capillary microthrombosis.<sup>6–10</sup> Arteriolar occlusion can then lead to venous occlusion and neovascularization.<sup>6</sup> Such severe vaso-occlusive retinopathy is often associated with antiphospholipid antibodies.<sup>11</sup> By an unclear mechanism, these antibodies promote thrombosis, which can lead to retinal vaso-occlusive disease.<sup>12–15</sup> APLS can also present with venous tortuosity, flame-shaped hemorrhages, microaneurysms, and cotton wool spots, presumably from microvascular occlusion of immune complexes.<sup>16</sup> In contrast, ocular manifestations of KFD are rare, with reports of lacrimal gland inflammation, conjunctivitis, and panuveitis with peripheral retinal vascular sheathing occurring before, concurrently or after lymphadenopathy.<sup>17–19</sup> There has been one report of arteriolar occlusion, capillary nonperfusion, and resulting proliferative retinopathy in a patient with negative serologic workup, who had been diagnosed with KFD three days prior to onset of visual symptoms.<sup>20</sup> Thus, it is possible inflammation from both SLE and KFD contributed to the severe retinal vaso-occlusion and resulting neovascularization seen in our patient.

Classically, KFD is characterized by fever and tender lymphadenopathy, typically self-limited over a period of a few months without known treatment, often in young women of Asian heritage.<sup>1,2</sup> There has been many hypotheses regarding the etiology of KFD, including hyper-immune reaction to viruses or HLA genetic susceptibility to excessive T cell mediated response, but none proven.<sup>1,2</sup> Diagnosis is based on excisional lymph node biopsy that illustrates necrosis, karyorrhectic debris wherein nuclear chromatin fragments become distributed throughout the cytoplasm, monocytes, CD 8 + T cells, and histiocytes that express MPO and CD 68, together with a lack of neutrophils, plasma cells, eosinophils, or granulomas.<sup>1,21–24</sup> Our patient's lymph node biopsy revealed a greater proportion of CD 8 to CD 4 T cells, as well as presence of CD 68 histiocytes, with the associated CD 4, CD 8, and CD 68 markers seen on immunohistochemistry stains (Fig. 6). There was also significant cellular necrosis and karyorrhectic debris, which led to her diagnosis of KFD (Fig. 5).

Though lupus lymphadenopathy was initially on our patient's differential diagnosis, she did not have features that are specific to



**Fig. 6.** Immunohistochemistry stain of lymph node biopsy demonstrating greater proportion of CD8<sup>+</sup> to CD 4 + T cells, as well as presence of CD 68 + histiocytes. CD 4 + T cells (A). CD 8 + T cells (B). CD 68 + histiocytes (C).

SLE lymphadenitis. Histologic evaluation of SLE lymph nodes can demonstrate follicular hyperplasia, necrosis, and atypical lymphoplasmacytic and immunoblastic proliferation.<sup>25</sup> Necrotic lymphadenopathy is most similar to KFD and is characterized by many lymphocytes, plasma, mononuclear and reticulum cells, few neutrophils, and rare eosinophils.<sup>26,27</sup> There may be areas of necrosis and inflammation, classifying it as necrotizing lymphadenitis with granulocytic infiltration.<sup>28</sup> However, pathognomonic to SLE lymphadenopathy is the hematocytin body, extracellular amorphous material, though not often seen.<sup>21–24,29</sup> These H- bodies, a neutrophilic infiltrate, and large plasma cells help to distinguish SLE lymphadenopathy from KFD,<sup>21–24,29</sup> and were not seen in our patient.

SLE and KFD have been reported to occur together in patients at any time interval, including concurrently and sequentially to each other, for unknown reasons.<sup>3–5</sup> There are even cases of KFD where the patient presented with elevated biomarkers or symptoms similar to SLE, but lupus was ultimately excluded in the diagnosis.<sup>30,31</sup> Similarly, our patient initially had features of lupus and APLS, which resolved on repeat testing for APLS when she presented with KFD. The transient elevated immune marker may have heralded the impending KFD. Though retinal vasculopathy is more often seen with lupus, KFD must also be considered in the diagnosis when patients also present with lymphadenopathy.

**4. Conclusion**

Clinicians must be vigilant in the diagnosis and treatment of such patients, as SLE and KFD may have many similar features and even biomarkers. Given the potential overlap of pathology and presentation, clinicians must distinguish between these diseases to prevent unnecessary treatment for lupus when the disorder evolves into KFD, which can be treated with supportive therapy, a short course of steroids, NSAIDs, or hydroxychloroquine.<sup>1,2</sup>

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