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Bilateral preretinal hemorrhage associated with Kikuchi-Fujimoto disease



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ARTICLE INFO	A B S T R A C T
Keywords: Retinal Subhyaloid Vitreous Bilateral hemorrhage Kikuchi-fujimoto disease HIV Disease	Purpose: To present a case of a patient with human immunodeficiency virus (HIV) disease and Kikuchi-Fujimoto disease (KFD) who presented with a unique pattern of retinopathy. Observations: A 7-year-old Taiwanese girl with HIV disease who was recently diagnosed with KFD had a sudden onset of blurry vision in both eyes one month after her KFD systemic symptoms had relatively resolved. Ophthalmic examination showed decreased visual acuity in both eyes (OU). On fundus examination, she had bilateral preretinal, subhyaloid, and vitreous hemorrhage that was more severe than anemic retinopathy. Conclusion: Ocular manifestations in Kikuchi-Fujimoto disease are rare; however, if they occur, presentations may vary. The exact etiology of the disease has remained elusive and controversial. This case is the first report of a patient with HIV disease and KFD presenting with ocular involvement. Furthermore, bilateral preretinal, subhyaloid, and vitreous hemorrhage, which was beyond anemic retinopathy, is an unprecedented manifestation of KFD that has not been previously reported. This case highlights the necessity for clinicians to consider all possible differential diagnoses when evaluating patients with similar findings to identify the best therapeutic approach and avoid unnecessary treatment.

1. Introduction

Histiocytic necrotizing lymphadenitis, commonly known as Kikuchi-Fujimoto disease (KFD), is an idiopathic disease that typically presents with lymphadenopathy, fever, myalgia, and skin eruptions.^{1,2} Extranodal involvement is atypical, except for the skin.³ Due to its usually benign course and self-limited nature, KFD tends to subside in a few months, and patients with KFD are often observed.^{4,5}

Although ocular involvement is rare, several case reports have described anterior uveitis,⁶ pan-uveitis,^{1,7} papillary conjunctivitis,⁸ and retinopathy⁹ in KFD patients. However, to our knowledge, there are no published reports of ocular hemorrhage in KFD to date.

We report a case of KFD in a young girl with human immunodeficiency virus (HIV) disease who presented with preretinal, subhyaloid, and vitreous hemorrhage in both eyes (OU).

1.1. Case presentation

A 7-year-old Taiwanese girl presented to our clinic for evaluation of

bilateral blurry vision. The blurred vision was worse in the morning with improvement during the day.

Her past medical history was significant for perinatally-acquired HIV disease and KFD. The KFD diagnosis was established five months prior to the presentation by lymph node biopsy (from the posterior triangle region of the neck) after she developed signs and symptoms of prolonged fever, cervical lymphadenopathy, headache, cardiopathy, weakness, myalgia, and weight loss. Pathology revealed necrotizing lymphadenitis with abundant apoptotic/karyorrhectic debris without acute inflammation, and no definitive granulomatous inflammation was seen (Fig. 1A-C). She was treated with two courses (3 weeks each) of systemic prednisone (1 mg/kg/day), which resolved the majority of her symptoms (except headache and cardiopathy). She was taking lamivudine, zidovudine, and nevirapine for HIV disease. Her latest absolute CD4 count was 1472 cells/ml and her HIV-1 RNA viral load had been undetectable for at least five years. Past ocular history was not significant, and she did not have any experience of trauma or strenuous exertion recently.

On ocular examination, the visual acuity was 20/40 OU without

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correction. The Ishihara color test was normal. Pupils were round and reactive. Anterior segment examinations were normal. Dilated fundus examination showed 1+ vitreous hemorrhage in the right eye (OD), preretinal, subhyaloid, and vitreous hemorrhage OU, and mildly increased vessel tortuosity OU (Fig. 2). There was no evidence of retinal ischemia, vascular sheathing, or neovascularization on clinical examination.

The patient underwent extensive laboratory evaluations through the process of diagnosis and management of her systemic disease. Complete blood count (CBC) with differential, peripheral blood smear and blood culture, coagulation tests (PT, PTT, and INR), direct Coombs test, urinalysis, urine culture, liver function tests, chest X-ray, and abdominal Xray series were taken. Except for low hemoglobin (Hgb) (2.6) and hematocrit (Hct) (7), all other results were normal. The erythrocyte sedimentation rate (ESR) was 54mm/hr (reference range, 3-13 mm/hr), Creactive protein (CRP) 7.8 mg/L (reference range, 1-3 mg/L), and lactate dehydrogenase (LDH) 298 IU/L (reference range, 105-333 IU/L). C3 and C4 were elevated to 153 mg/dl and 61 mg/dl (reference range, C3: 75-135 mg/dl, C4: 16-48 mg/dl). Serum protein electrophoresis showed increased polyclonal gamma globulins. Immunological tests (polymerase chain reaction, PCR) for Epstein-Bar virus (EBV) and Parvovirus B19 were negative. Anti-nuclear antibody (ANA) and anticardiolipin IgM were positive, 1:40 and 13, respectively. Cytoplasmic and perinuclear anti-neutrophil cytoplasmic antibodies (C-ANCA and P-ANCA), anti-double-stranded DNA, and HLA-B57 were negative. About three weeks before the ophthalmic manifestations, she had a blood transfusion due to anemia, which was attributed to KFD. Two days after transfusion, her hematologic indexes normalized (Hgb: 12.6, Hct: 36) which was 20 days before her ophthalmological symptoms commenced. Bacterial gram stain revealed few epithelial cells and no organisms. Aerobic and anaerobic bacterial cultures, fungal, acid-fast bacilli, and tissue cultures of the lymph node biopsy sample did not yield any organisms as well. Computed tomography (CT) of head and neck revealed normal orbits with multiple regions of adenopathy on the right side of the neck with the largest size of $3 \times 3 \times 1$ cm at the posterior triangle region.

Based on the temporal relationship, clinical, and laboratory findings, the preretinal/vitreous hemorrhage was thought to be associated with underlying KFD. We decided to observe the patient without any particular medical or surgical interventions. During the first year of follow-ups, her visual acuity improved to 20/30 OU. The preretinal, subhyaloid, and vitreous hemorrhage also improved (Fig. 3). At the five-year follow-up examination, the pre-retinal, subhyaloid, and vitreous hemorrhage has completely resolved.

2. Discussion

KFD, described as a benign self-limiting disease of necrotizing lymphadenitis, is a rare condition with a very low possibility of recurrence. Excisional biopsy is the gold standard method to confirm the diagnosis by ruling out other similarly presenting pathologies, such as reactive hyperplasia of lymph nodes (RHNL) and lymphoma; however, in patients with typical presentation of KFD, fine needle aspiration (FNA) would be sufficient for confirmation.^{10,11} It is estimated that in western countries, KFD is responsible for 6% of all newly found abnormal lymph node pathologies.¹² Although it has been reported worldwide, KFD mostly involves women of Asian ethnicity.^{13,14} The classical presentation of KFD includes fever and enlargement of cervical lymph nodes, though other lymph nodes may also be involved. Other manifestations include gastrointestinal pain (varies from simple epigastric pain to appendicitis-like pain),^{15–17} maculopapular rash, night sweats, anemia, and leukopenia, as well as relative lymphocytosis with atypical lymphocytes.^{13,14,18,19}

Known ocular manifestations of KFD include vaso-occlusive retinopathy, bilateral retinal vasculitis, papillary edema, oculomotor palsy, parinaud oculoglandular syndrome, frosted branch angiitis, bilateral anterior uveitis, bilateral panuveitis, eyelid edema, blepharospasm, lacrimal gland enlargement, and papillary conjunctivitis.^{1,2,6–9,20–26} Preretinal or vitreous hemorrhage has not been reported even though many KFD patients have anemia.^{18,19,27–29}

Unlike any previously reported cases, the initial presentation of sudden blurry vision in our patient was secondary to bilateral preretinal, subhyaloid, and vitreous hemorrhage. Based on the temporal relationship and equivocal laboratory findings, we believe that these findings were associated with the underlying KFD. Another unique aspect of our case is the rare ocular findings of KFD in a patient with HIV disease. Fewer than 15 cases of KFD with HIV disease have been reported in the literature; none had ocular manifestations. The youngest case, diagnosed at the age 14, was on zidovudine, lamivudine, and efavirenz.^{30–32} Our index patient was 7 years old.

Although bilateral preretinal hemorrhage has not been reported in KFD, it has been reported in autoimmune hemolytic anemia,³³ Dengue fever,³⁴ kala-azar,³⁵ Terson syndrome,^{36,37} laser in situ keratomileusis (LASIK),³⁸ aplastic anemia³⁹ (due to various etiologies, including seronegative hepatitis,⁴⁰ chemotherapy and immunosuppressive drugs),^{37,41,42} valsalva retinopathy (usually unilaterally and associated with trauma or exertion, which our patient did not have),⁴³ shaken baby syndrome, and other forms of child abuse.⁴⁴ Our patient's laboratory tests, medical history, and clinical presentations ruled out these potential diagnoses as well as infectious retinitis.

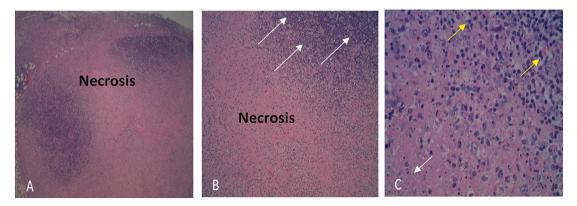


Fig. 1. A, Low-power view shows the neck's lymph node (posterior triangle region) with central necrosis (Hematoxylin-eosin; original magnification, 40X). **B**, Bright eosinophilic necrotic area with residual lymph node parenchyma in the upper right corner of medium-power view (white arrows) (Hematoxylin-eosin; original magnification, 100X). **C**, High-power magnification highlights necrosis with apoptotic debris (white arrow) and histiocytes, which are typically seen in Kikuchi lymphadenopathy (yellow arrows). Note the absence of neutrophils (Hematoxylin-eosin; original magnification, 400X). (Photo courtesy of Dr. Craig Hart, Rock Hill, South Carolina, USA). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

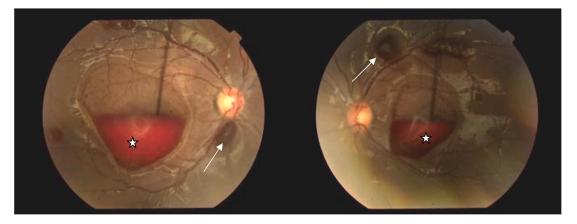


Fig. 2. Color fundus photographs showing preretinal (arrows), subhyaloid (\pm), and vitreous hemorrhage in both eyes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

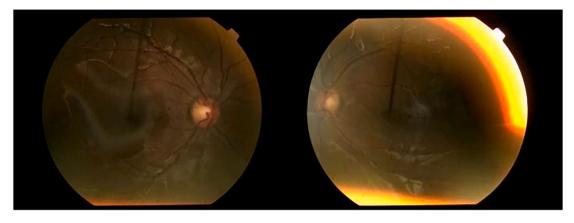


Fig. 3. Color fundus photographs. One year after the initial presentation, the preretinal, subhyaloid, and vitreous hemorrhage had improved in both eyes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

By assessing the laboratory results and patient's signs and symptoms, possible concomitant diseases that can induce retinal vessel infiltrations such as diabetes mellitus and retinal vascular disorders (e.g., granulomatosis with polyangiitis previously known as Wegener's granulomatosis, Churg-Strauss syndrome, Adamantiades - Behcet's disease, polyarteritis nodosa, and cryoglobulinemic syndrome)⁴⁵⁻⁵⁰ were ruled out as well. One of our tentative differential diagnoses on the first visit was bilateral hemorrhage due to the history of anemia, but after reviewing the patient's medical history, it was determined that the anemia had resolved 20 days prior to her ocular symptoms. To be certain that we had considered all possibilities, the hematological profile of the patient was assessed carefully, which led to two main differential diagnoses for her anemia: KFD and zidovudine. Because some of her KFD symptoms were still present and she had been taking zidovudine for more than a year, her anemia was attributed to KFD rather than zidovudine.

Although there were three weeks between the resolution of anemia and the appearance of visual symptoms, we cannot rule out the possibility of residual or lingering effects of prior anemia completely, albeit less likely. Notwithstanding, even if we consider her ocular signs to occur secondary to the anemia, based on other laboratory data and natural presentation and manifestations of KFD, of which anemia is one, we can conclude with a reasonable degree of certainty that the ophthalmological signs and symptoms were related to KFD. The severity of her bilateral ocular hemorrhage was beyond the extent that could be justified by anemic retinopathy. In addition, Amado et al. and Thomson-Glover et al. reported patients with KFD and HIV disease who had zidovudine in their therapeutic protocol; the authors did not report any ocular signs or symptoms in them.^{30,32}

Nearly all of the previous reports indicated the use of medical treatments to control and manage ocular manifestations of KFD. Rue et al. reported vaso-occlusive retinopathy in a woman with KFD and underlying lupus whom was initially treated with high-dose methylprednisolone along with pan-retinal photocoagulation.⁹ Taguri and colleagues reported bilateral pan-uveitis in a girl with KFD, whom was treated with topical corticosteroids and despite having recurrences, maintained a stable visual acuity.¹ In both cases, the authors reported KFD in females, which is consistent with our case. However, our patient's ocular presentation improved and remains asymptomatic with the stabilization of the KFD, without any direct medical or surgical intervention for the ophthalmic disease.

Several studies discussed the relationship between systematic lupus erythematosus (SLE) and KFD. SLE and KFD can overlap and subsequently be diagnosed concurrently.^{9,51,52} Therefore, monitoring for clinical signs and symptoms of each of these diseases at subsequent follow-up visits is necessary. Although the patient had low-positive ANA and anticardiolipin IgM, the lack of other diagnostic criteria of SLE helped to exclude SLE and confirm KFD diagnosis, including lack of other symptoms and signs of SLE, negativity for anti-double-stranded DNA, as well as histological biopsy consistent with KFD.⁵³

The exact underlying mechanisms of KFD are still unknown. Autoimmune and viral causes are thought to be involved; however, implications of certain viruses such as EBV, parainfluenza virus, and human herpesvirus 6 have largely been inconclusive.^{5,11,13} Moreover, possible relationships have been suggested to exist between HIV and autoimmune disorders.⁵⁴ Thus, based on the aforementioned evidence, HIV could be considered as a potential etiology that caused KFD development in this patient. However, it is still difficult to identify a specific pathogenic mechanism for KFD's ocular complications. Autoimmune reaction and injury to retinal vessels, including increased vascular permeability in response to immune-mediated cytokine release, may predispose the eye to bilateral hemorrhage. Fragility of superficial capillaries due to retinal vasculitis (although fluorescein angiography (FA) was not performed in this patient) should also be taken into consideration as probable mechanisms.^{4,55}

Due to the patient's age (7 years old), we decided to prioritize the indications and feasibility of different imaging modalities and to perform only the essential ones. Therefore, we did not utilize FA and spectral domain-optical coherence tomography (SD-OCT) for our patient, which can be considered as the study limitations. However, there was no evidence of neovascularization or vascular sheathing during the clinical examination. Using FA and SD-OCT in similar cases may be helpful to clarify the mechanism of vitreous hemorrhage (e.g., retinal vasculitis and neovascularization) and precise location of sub-hyaloid hemorrhage (i.e., between posterior hyaloid and the internal limiting membrane (ILM) or in sub-ILM), respectively.

The medical care for the index patient consisted of a multidisciplinary team, including an ophthalmologist, a pediatrician, and an immunologist.

3. Conclusion

We have described preretinal, subhyaloid, and vitreous hemorrhage as previously not reported ocular manifestations in a patient with HIV disease and KFD. Our findings underscore the importance of considering all possible differential diagnoses, including KFD, when encountering such ocular findings. Furthermore, one needs to consider the association of KFD with other autoimmune disorders, infectious diseases, and immunodeficiency syndromes, whenever relevant. At times, knowledge of the disease can lead to observation with subsequent resolution as in the index patient. Accurate and timely diagnosis can pave the way to prevent unnecessary interventions and treatments.

Patient consent

At the time of writing this article, the patient was under 18 years old (12 years old), so her mother signed the written consent form of publishing case details.

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Conflicts of interest

None of the authors has any relevant conflict of interests pertaining to the index manuscript.

Research ethics

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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