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Chronic Refractory Uveitis in a Patient with Childhood-Onset Cyclic Neutropenia

Li-Li Chen Mitsuko Toyoguchi Machiko Shimakawa
Sadao Hori

Department of Ophthalmology, School of Medicine, Tokyo Women's Medical University, Tokyo, Japan

Key Words

Cyclic neutropenia · Uveitis · Granulocyte colony-stimulating factor · Behçet's disease

Abstract

We report a rare case of chronic refractory uveitis in a patient with childhood-onset cyclic neutropenia (CN). A 19-year-old woman, who had a history of CN beginning at age 2, presented with bilateral chronic nongranulomatous uveitis, complicated cataract, retinal vasculitis, cystoids macular edema, and vitreous hemorrhage. She had recurrent episodes of oral ulcers, tonsillitis, genital ulcers, and folliculitis during neutropenic nadir. After the resumption of granulocyte colony-stimulating factor therapy for her CN, vitreous hemorrhage in both eyes followed. Her eyes were treated with topical corticosteroids, retinal photocoagulation, and cataract surgery. Blood and bone marrow test results confirmed the diagnosis of CN. She also fulfilled the diagnostic criteria of Behçet's disease, though clinical features of her uveitis were dissimilar to those found in that disease.

Introduction

Cyclic neutropenia (CN) is a rare disorder characterized by regular oscillation in peripheral neutrophil counts with 21-day periodicity. Affected individuals typically experience recurrent aphthous stomatitis, fever, malaise, and, occasionally, cutaneous or subcutaneous infections. According to the International Study Group of Behçet's Disease (ISGBD), recurrent oral ulceration with any two of recurrent genital ulceration, eye lesions, skin lesions, and positive pathergy test is diagnostic of Behçet's disease (BD). Although the pathophysiologies of CN and BD are different, the symptom analogy between these two diseases is striking. We report on a previously unpublished case of

childhood-onset CN which showed BD-like clinical features accompanied by chronic refractory uveitis.

Case Report

A 19-year-old woman with a history of childhood-onset CN was referred to our clinic in 1999. She had had red eyes from age 6 and had been diagnosed with uveitis at age 9. From age 9 to 17 she had received granulocyte colony-stimulating factor (G-CSF) therapy for her CN. She had been under topical corticosteroid therapy for more than 10 years. On initial examination, her best-corrected visual acuity was 20/60 OD and 20/100 OS. Both eyes had moderate nongranulomatous uveitis associated with band keratopathy and complicated cataract. Neovascularization of optic disc and arcade vessels, proliferative membrane, and cystoid macular edema were also present (fig. 1, top). Vitreous hemorrhage was seen in the left eye. Fluorescein angiography (fig. 1, middle and bottom) revealed diffuse leakage in varying degrees from retinal vessels. Indocyanine green angiography in the mid-periphery demonstrated multiple faint hypo-fluorescent spots. Blood and bone marrow test results were compatible with a diagnosis of CN. Peripheral white blood cell counts ranged from 3,300/ml with 0.5% neutrophils to 6,850/ml with 60.3% neutrophils. Neutrophil function, the oxidative burst and phagocytosis ability, and serum tumor necrosis factor level were normal in both nadir and peak of the cycling. Mutation in exon 4 of the neutrophil ELA2 gene [1] was detected in DNA extracted from peripheral blood. HLA-B51 was positive and pathergy test was negative. Recurrent oral ulcers, tonsillitis, genital ulcers, and folliculitis were noted; thus, she fulfilled the ISGBD criteria. However, these symptoms diminished when she wore an isolator, gargled thoroughly with povidone-iodine and amphotericin B, and ate only pasteurized food while in the hospital. In February 2000, she resumed G-CSF therapy. Four months later she had vitreous hemorrhage in both eyes and consequently her visual acuity became impaired (fig. 2, top). Because of this event, the hematologist stopped G-CSF therapy and switched to conservative treatment. Because the patient's left eye had four instances of vitreous hemorrhage and color Doppler imaging showed strangulation of central retinal vein, we performed retinal photocoagulation. Subsequently, neovascularization of optic disc and arcade vessels subsided in both eyes despite continued chronic uveitis. In May 2005, complicated cataract had deteriorated the visual acuity to 20/200 in both eyes. Cataract extraction with posterior chamber lens implantation resulted in stable visual acuity of 20/60 OD and 20/40 OS.

Discussion

CN is a sporadic or inherited hematological disorder of myelopoiesis. Adult-onset CN can be treated with corticosteroids or with immunosuppressant, whereas childhood-onset CN does not respond to these agents, or to a variety of other therapeutic interventions. Recently, systemic administration of G-CSF gives encouraging results for treatment of CN patients. In 1997, Rodriguez et al. [2] first reported recurrent uveitis in a patient with adult-onset CN. In this case, bilateral iridocyclitis occurred during a neutropenic crisis, and inflammation resolved as the crisis subsided. The fundus was normal, and the patient was treated with topical and systemic corticosteroids. Uveitis in a patient with childhood-onset CN has not been described previously. Our patient had bilateral chronic pan-uveitis accompanied with retinal vasculitis. Most of her symptoms were aggravated during neutropenic nadir. Her ocular inflammation, however, was not associated with neutrophil cycling. Interestingly, neovascularization of the posterior poles subsided in both eyes, even though we performed photocoagulation in the left eye only. Not only inflammation- and ischemia-induced mechanisms but also G-CSF-induced retinal vasculitis may have been present. Vasculitis is a recognized complication of G-CSF. Although the safety and efficacy of long-term administration of G-CSF for CN patients has been established, a few patients so treated experienced vasculitis [3]. From our patient's clinical course, we speculate that the discontinuation of G-CSF was involved in reducing neovascularization.

BD is a multisystem inflammatory disorder with unknown cause; however, the presence of in vivo preactivated neutrophils is implicated in the pathogenesis. Disease activity is usually associated with mild neutrophilia. Thus, it is unlikely that CN and BD occur concurrently. Chronic neutropenia, however, causes BD-like symptoms [4]. Demiroğlu and Dündar [5] reported 2 cases of chronic neutropenia diagnosed as BD according to ISGBD criteria. They postulate that the complex symptoms of BD might have been caused by infectious agents rather than neutropenia itself. Because the diagnosis of BD is firmly based on the presence of a constellation of clinical findings, our patient also fulfilled two sets of diagnostic criteria. But the clinical features of our patient's ocular inflammation were dissimilar to those found in BD. Her 'chronic' uveitis did not have the recurrent, explosive nature, and quiescent periods. Furthermore, her BD-like symptoms, excluding eye lesions, diminished subsequently to commencing the aforesaid regime of infection control measures. Given these observations, we believe that CN rarely accompanies uveitis, and this case is not a concurrence of CN and BD.

Disclosure Statement

The authors do not have any proprietary interest or potential conflicts of interest in the topics discussed.

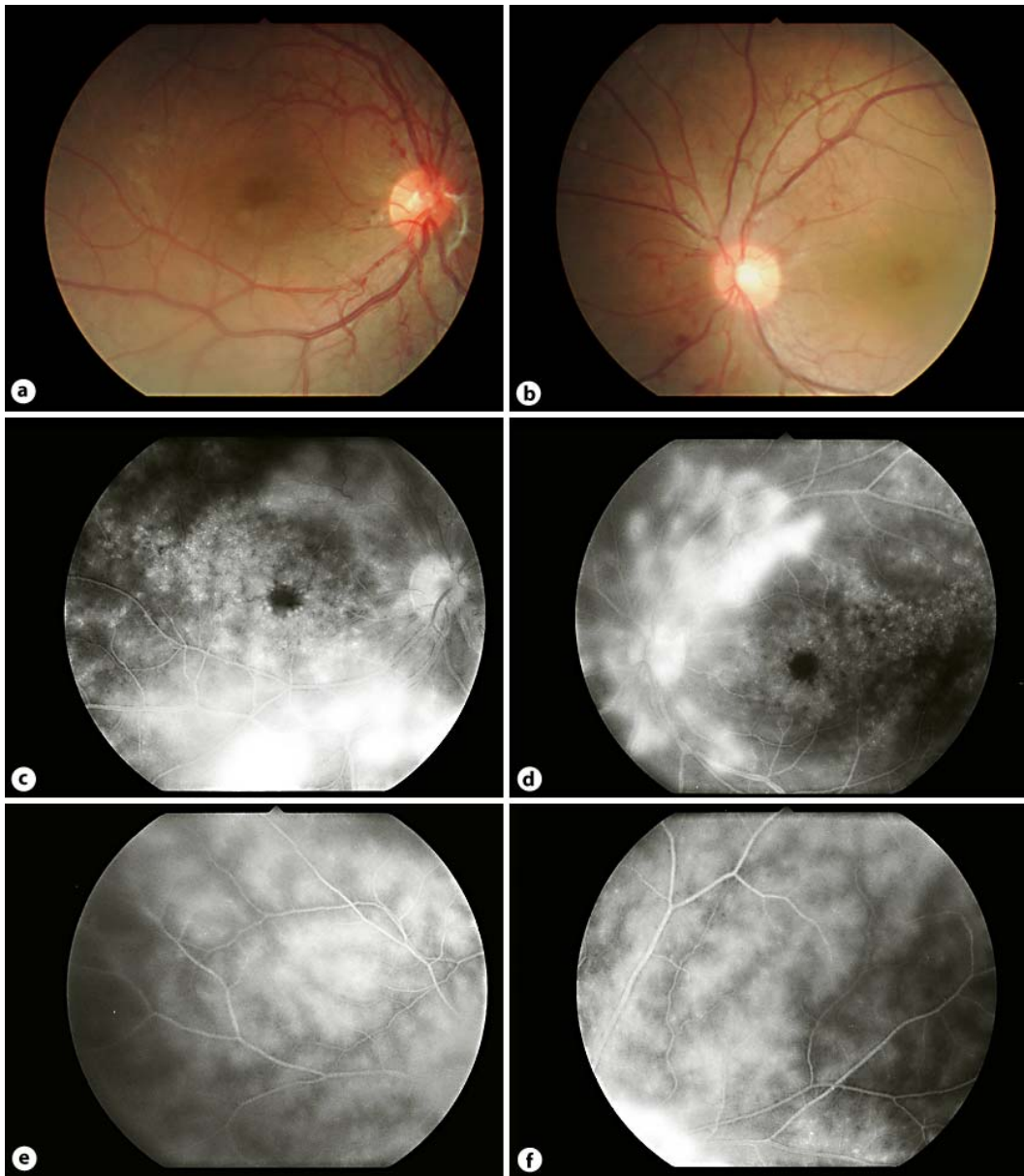


Fig. 1. Fundus photography and fluorescein angiogram on initial examination. **a, b** Fundus photographs were notable for neovascularization of arcade vessels surrounding the optic disc, proliferative membrane, and cystoid macular edemas in the right eye (**a**) and in the left eye (**b**). **c, d** Fluorescein angiogram of the right eye (**c**) and the left eye (**d**) confirmed neovascularization and cystoid macular edemas in the posterior poles. **e** Diffuse leakage in varying degrees from retinal vessels indicating vasculitis in mid-periphery of the right eye. **f** Similar findings are seen in the left eye.

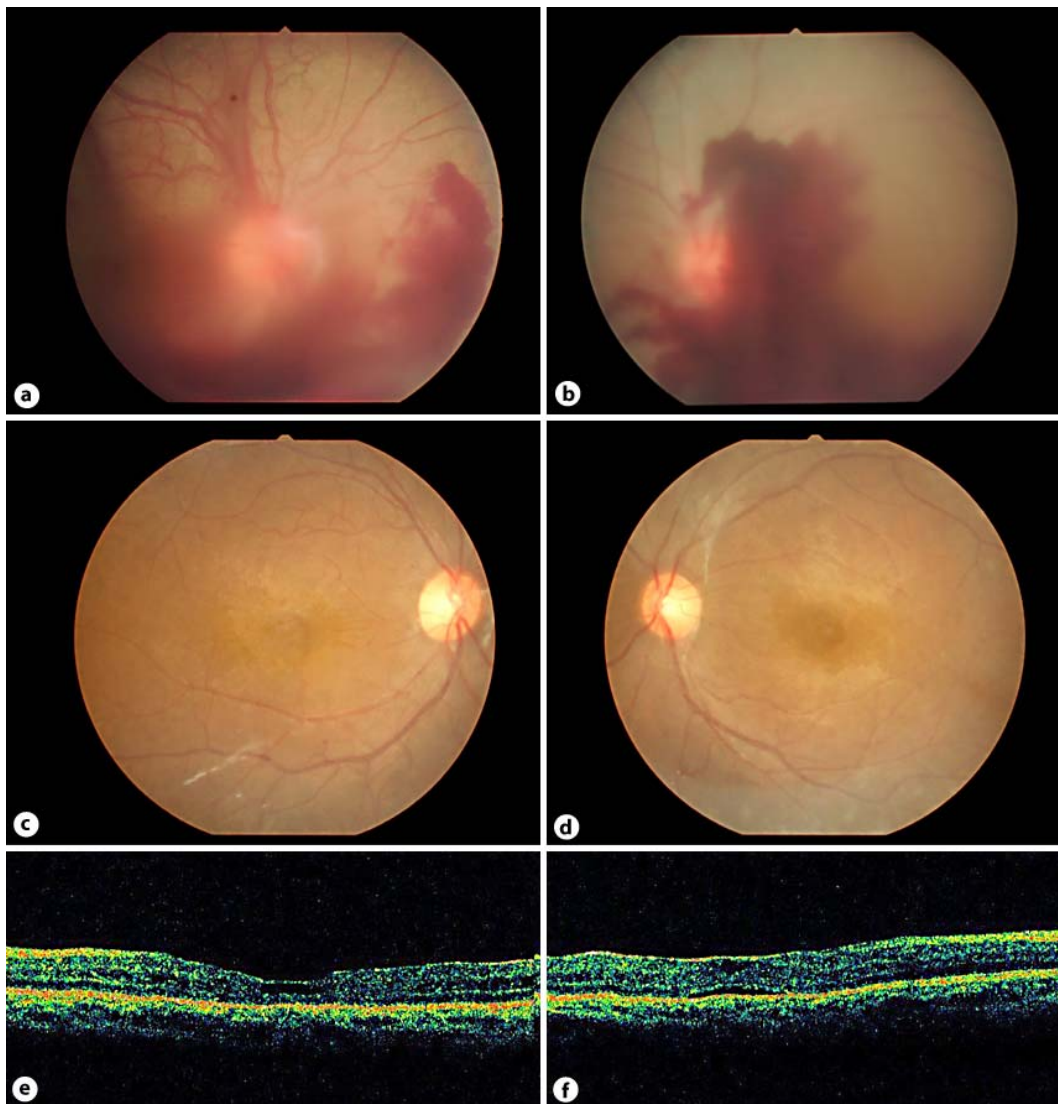


Fig. 2. **a, b** Fundus photographs at 4 months after the re-administration of G-CSF therapy of the right (**a**) and the left (**b**) eyes showed vitreous hemorrhages. **c, d** Recent fundus photographs showed marked decrease of neovascularization and cystoid macular edemas in the right (**c**) and the left (**d**) eyes. **e, f** Optic coherence tomography demonstrated a cystic change of macula in the right eye (**e**) and epiretinal membrane and serous detachment in the left eye (**f**).

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