Casitas B-lineage lymphoma mutation retinopathy mimicking uveitis

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CBL mutation retinopathy mimicking uveitis

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Two unrelated young patients, with complex medical histories, were initially treated for chronic bilateral uveitis. In following their ophthalmological responses to immunosuppressants, with no improvement in the ophthalmological alterations being observed in response to successive treatments, a diagnosis of retinal dystrophy was made. Known cone-rod dystrophy variants were excluded. Whole exome sequencing revealed mutations in the Casitas B-lineage Lymphoma (*CBL*) gene.

The ocular phenotype associated with each mutation was accurately described, including the clinical aspects, colour fundus photographs, autofluorescence photographs, optic nerve head and macular optical coherence tomography (OCT), visual fields (VF), fluorescein angiography (FA), electroretinography (ERG) and the clinical course. The ocular phenotype described in detail in this article, associated with the various systemic disorders presented by our patients, could pave the way for a new description of syndromic retinal dystrophy associated with a mutation in the *CBL* gene.

Retinal dystrophies are a clinically heterogeneous group of inherited degenerative disorders characterised by damage to the retinal photoreceptors.[1] All modes of genetic transmission may be involved. The aim of this study was to describe two unrelated cases with atypical retinal dystrophy with a mutation identified in the *Casitas B-lineage Lymphoma* (*CBL*) gene.[2]

The patients underwent a comprehensive eye examination with multimodal retinal imaging, including FA and OCT, VF, ERG, repeated systemic work-up, and genetic analyses. One patient and the second minor patient's parents signed informed consents, and the study was approved by our local Ethics Committee. The study was conducted in compliance with good clinical practice and the tenets of the Declaration of Helsinki.

Two young patients showed ophthalmological and systemic similarities: presence of a chronic macular oedema (MO), vascular and papillary leakage on FA unchanged on successive immunosuppressive treatments, progressive VF worsening, progressive visual field worsening and a severe bilateral and symmetrical alteration of the retinal function seen on ERG. They also had a history of hepatosplenomegaly since childhood and severe primary infection with Epstein-Barr Virus (EBV). Aqueous humour sampling was negative for Herpes virus, including EBV, by polymerase chain reaction. Successive immunosuppressive therapies did not change retinal fluorescein leakage and failed to prevent retinal damage and VF constriction.

Case 1 was a 24-year-old female patient, complaining since the age of 17 years of sporadic decreases in vision in both eyes, with episodes of retrobulbar optic neuritis. The visual acuity (VA) was 20/32 in both eyes with night blindness. There were no signs of inflammation in the anterior segment. Anterior vitreous showed 1+ cells in both eyes. Fundus, OCT and FA are shown in figure 1. VF testing found bilateral constriction.

At the systemic level, a history of hepatosplenomegaly since childhood, a history of fibrosing interstitial lung disease due to primary infection with EBV at the age of 19, a nephrotic syndrome, a lupus profile and a right parietal pilocytic astrocytoma were found. The diagnoses of lysosomal disease and congenital immune deficiency were ruled out. Mother and maternal grandmother had normal ophthalmological examinations.

Whole exome sequencing identified a mutation with a loss of heterozygosity in the *CBL* gene: Exon 8 c.1149 A>G; p. I383M, known to be related to the RASopathy family of disorders.

Case 2 was a 13-year-old male patient who presented with a progressive decrease in vision in both eyes since the age of 6 years. The VA was 20/32 in the right eye and 20/63 in the left eye. There were no signs of cell inflammation in the anterior segment, and 1+ cells in the anterior vitreous. OCT showed bilateral MO. VF showed

slight peripheral constriction in both eyes (figure 2). ERG performed 3 years later showed scotopic alterations. Six years later, rod-cone dystrophy was diagnosed on clinical examination, autofluorescence retinography, OCT, FA, tubular VF and altered ERG.

At the systemic level, there was a history of severe EBV infection at the age of 3 years, with a hepatosplenic and peripheral lymph node tumour syndrome, and encephalitis that had responded to corticosteroid treatment.

Panel next generation sequencing identified a mutation with a loss of heterozygosity in the *CBL* gene: Exon 8 c.1141T>G; p.C381G.

Clinical features of retinal dystrophy had been described in chronic posterior uveitis. However, VF constriction and ERG abnormalities were present at admission or in the few years following the admission of the current cases. Moreover, FA leakage did not respond to successive immunosuppressive treatments. Several elements, including chronic MO, fluorescein leakage, and cells in the anterior vitreous may have lead to the initial diagnosis of autoimmune uveitis, although these three elements are compatible with the diagnosis of typical retinitis pigmentosa (RP).[1,3] Inflammatory mechanisms have been shown in typical RP, such as proinflammatory cytokines and chemokines detected in intraocular fluids that could participate in photoreceptor apoptosis via the activation of the microglia, and antiretinal antibodies detected in the serum of patients with typical RP and MO.[1,3] These findings suggest a sustained chronic inflammatory reaction that may mediate multiple events such as the recruitment of leukocytes.[4] However, a high level of immunosuppression achieved by various immunosuppressive regimens over multiple years failed to prevent photoreceptor damage and loss of visual field. Thus, MO and fluorescein leakage could be linked to several mechanisms, including the effects of cytokines on the expression of occludin and claudin in the tight junctions, and the dysregulation of dynamic neuro-glio-vascular cross-talk. [3,5]

The *CBL* gene encodes an E3 ubiquitin ligase that negatively regulates the Ras/MAPK pathway. The newly described *CBL* syndrome is characterized by constitutional and late-onset vascular disorders overlapping with Noonan syndrome and type 1 neurofibromatosis, and may be associated with juvenile myelomonocytic leukaemia.[2]

The combination of whole-exome sequencing and clinical analysis allows for more accurate diagnosis of rare syndromic retinal dystrophies.

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FIGURE LEGENDS

Figure 1: 24-year-old woman complaining of visual loss. Fundus appeared similar in both eyes . Right fundoscopy showed pigmentary changes while autofluorescence retinography did not show any hyperautofluorescent ring. Late phase fluorescein angiography showed vascular leakage at the posterior pole, while optic coherence tomography showed macular oedema with cysts in the inner nuclear layer.

Figure 2: 13-year-old boy complaining of progressive visual loss. Fundus appeared similar in both eyes. Right infrared fundus imaging showed thin vessels. Late phase fluorescein angiography showed posterior pole leakage, and optical coherence tomography showed cysts located mainly in the inner nuclear layer. Goldmann visual field testing showed slight constriction.