Asymptomatic Sight-Threatening Retinopathy in Multisystem Incontinentia Pigmenti Due to Neglected Ophthalmic Screening

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A 9-year-old girl had a history of fulminant systemic autoinflammation from birth, manifesting as acute respiratory failure, hand tremors, and generalized cutaneous erythema. Brain magnetic resonance imaging revealed cerebral injury, and laboratory tests showed markedly elevated inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate. At 20 months of age, she was hospitalized for life-threatening Aspergillus pneumonia complicated by liver dysfunction. During this period, a diagnosis of incontinentia pigmenti (IP) was established.

At the age of 9 years, she was referred to our ophthalmology department due to intermittent dizziness for 6 months, accompanied by headache and vomiting for 2 weeks. On ophthalmic examination, her best-corrected visual acuity was 0.2 logarithm of the minimum angle of resolution (logMAR) (logarithm of the minimum angle of resolution) in the right eye and 0.3 logMAR in the left eye. Fundus photography (Figure 1a, b) revealed tortuous peripheral retinal neovascularization (yellow arrow) and abnormal retinal vascular anastomosis (red box). Fundus fluorescein angiography (Figure 1c, d) demonstrated bilateral retinal non-perfusion areas with prominent fluorescein leakage and neovascular hyperfluorescence. According to the staging system for IP-associated retinopathy proposed by Peng et al.,[1] these findings were consistent with stage 3 IP-associated retinopathy. During this visit, we also documented characteristic extraocular manifestations of IP, including cutaneous pigmentation, dental dysplasia, and cicatricial vertex alopecia with morphological abnormalities (Figure 2a-c). These findings provided additional clinical evidence supporting the diagnosis of IP-associated retinopathy.

The patient subsequently underwent prompt retinal laser photocoagulation targeting bilateral peripheral retinal non-perfusion areas. At the 1-week follow-up, best-corrected visual acuity remained stable. Fundus examination using a Volk 90D lens showed marked regression of neovascularization in the laser-treated areas and significant absorption of retinal hemorrhage compared with the pre-treatment status. No recurrent neovascularization, fresh retinal hemorrhage, or tractional retinal changes were observed in either eye. However, due to unforeseen personal circumstances of the patient's family, the patient has not returned for medium- and long-term follow-up, and no further imaging has been performed to date.

IP is a rare X-linked dominant neuroectodermal dysplasia caused by pathogenic *IKBKG* gene variants and is characterized by multisystem involvement of the skin, central nervous system (CNS), and eyes. The diagnosis of IP is primarily based on characteristic cutaneous manifestations that evolve through four stages: erythema and blistering, verrucous keratotic papules and plaques, and hyperpigmentation along Blaschko lines. Ischemic retinopathy and retinal neovascularization represent important minor diagnostic criteria, along with alopecia, dental abnormalities, nail dystrophy, and CNS anomalies.[2] This patient met the diagnostic criteria for IP in the absence of a family history, fulfilling two major and multiple minor criteria. Genetic testing performed early in the disease course confirmed a heterozygous frameshift mutation (c.1307_1308insGCCCCCT) in the *IKBKG* gene, establishing a molecular diagnosis of IP. This *de novo* variant is highly pathogenic. Reduced expression of the NEMO protein was also confirmed, whereas genetic and protein analyses in her father, mother, and elder brother were unremarkable. This pathogenic *IKBKG*/NEMO variant directly impairs NEMO protein stability and function, leading to dysregulated NF-κB signaling across multiple developing tissues, including retinal vascular endothelium, epidermal structures, and neural crest derivatives.[3] This molecular dysfunction explains the patient's clinical phenotype, including impaired retinal vascular maturation, pathological neovascularization, defective tissue repair, and increased inflammatory susceptibility, which collectively contributed to severe early-onset retinopathy and multisystem ectodermal dysplasia.[4]

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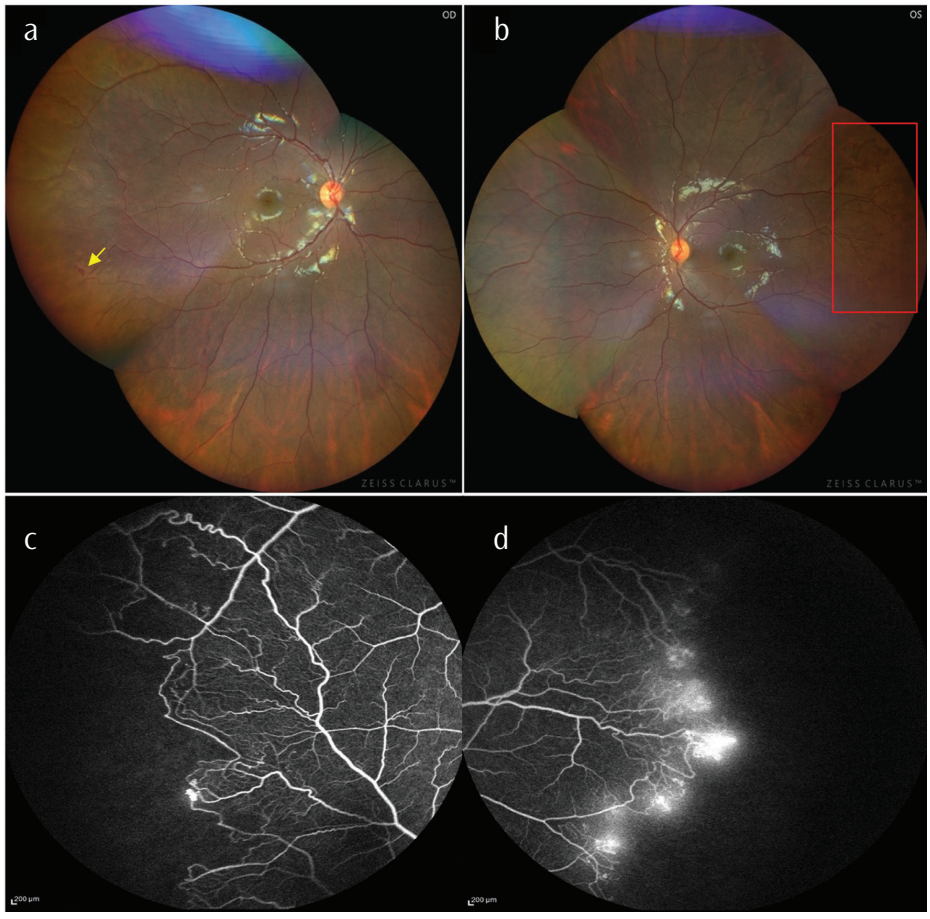

FIG. 1. (a) Color fundus photograph of the right eye (OD) showing peripheral retinal neovascularization (yellow arrow). (b) Color fundus photograph of the left eye (OS) demonstrating abnormal peripheral retinal vascular anastomosis (red box). (c) Fundus fluorescein angiography (FFA) of the OD revealing extensive peripheral retinal non-perfusion with associated neovascular hyperfluorescence. (d) FFA of the OS showing extensive peripheral retinal non-perfusion accompanied by marked fluorescein leakage from retinal neovascularization.

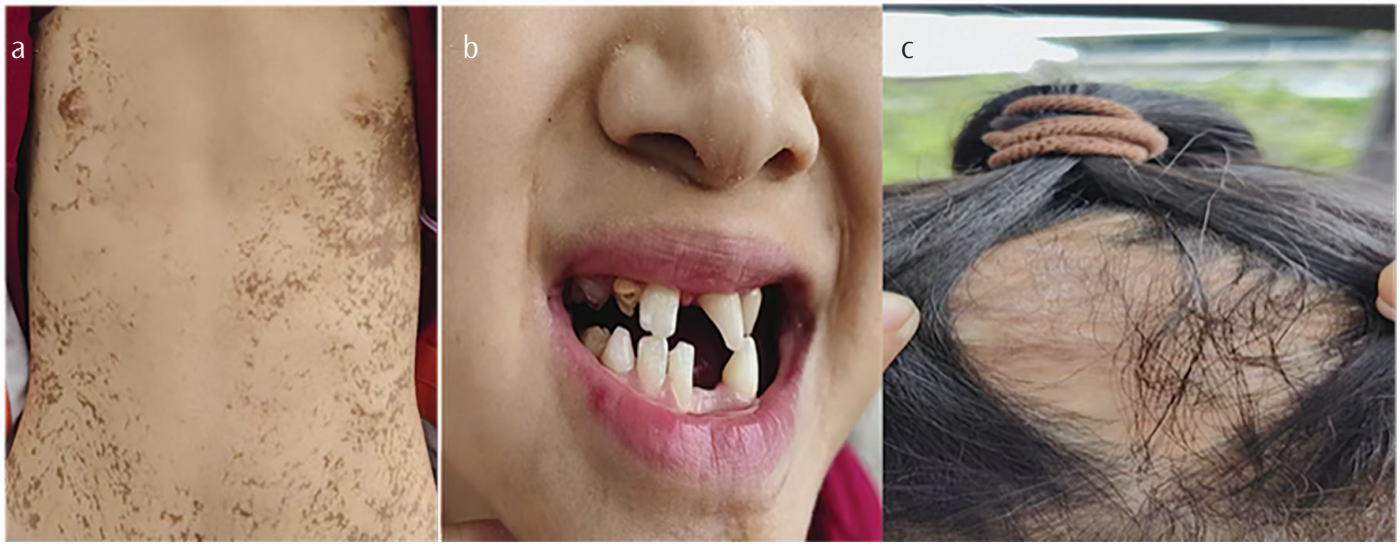

FIG. 2. (a) Linear hyperpigmentation distributed along the lines of Blaschko on the trunk; (b) Dental dysplasia with conical teeth and morphological abnormalities; (c) alopecia the vertex.

Ocular complications occur in 22.6-77% of patients with IP,[4] most commonly presenting as asymptomatic but progressive retinal vascular abnormalities that may result in irreversible vision loss. Notably, this patient had not undergone ophthalmic evaluation for nine years despite a confirmed diagnosis of IP. This delay might be attributed to several factors. Early clinical care primarily focused on managing life-threatening systemic and neurological complications, leaving limited opportunity for ocular screening. In addition, despite early genetic confirmation, the asymptomatic nature of retinal involvement and limited awareness among non-ophthalmic providers regarding the risk of progressive, sight-threatening retinopathy contributed to delayed referral. Finally, the absence of a standardized multidisciplinary surveillance protocol for patients with multisystem IP further contributed to this gap in care. Delayed recognition of sight-threatening retinal disease highlights the importance of routine ophthalmic screening in all patients with IP, even in the absence of visual symptoms. Early and regular fundus examinations enable the timely detection of retinal ischemia and neovascularization, allowing intervention before irreversible vision loss occurs. In children with genetically confirmed multisystem disease, structured multidisciplinary follow-up is essential to prevent missed ocular complications.

Informed Consent: Written informed consent was obtained from the patient's legal guardian for the publication of this clinical case and associated imaging findings.

Authorship Contributions: Concept- Y.Y., C.T.; Supervision- Y.Z.; Materials- Y.Z.; Data Collection or Processing- C.T.; Writing- Y.Y.

Conflict of Interest: The authors declare that they have no conflict of interest.

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