



Case report

Characterization of Blau syndrome panuveitis with wide-field fluorescein angiography

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ABSTRACT

Purpose: To describe a case of Blau panuveitis, characterized on both portable and tabletop wide-field fluorescein angiography, which resolved on systemic immunosuppression.

Observations: A 5-year-old female presented with bilateral eye pain, redness, and decreased visual acuity due to panuveitis and had a history of arthritis, tenosynovitis, and dermatitis. Similar ocular and systemic findings in the patient's mother and maternal half-brother prompted genetic testing that confirmed the diagnosis of the rare Blau syndrome. Portable Retcam and tabletop Optos wide-field fluorescein angiography congruently demonstrated retinal vascular and peripapillary leakage. The uveitis dramatically resolved after the addition of adalimumab to methotrexate. Quiescence was maintained with the substitution of infliximab for adalimumab.

Conclusions and Importance: To our knowledge, we are first to characterize Blau panuveitis retinal findings on wide-field fluorescein angiography and with the use of two different photography systems. Additionally, this report underscores the salient clinical findings of a rare disorder and suggests that robust systemic immunosuppression can effectively treat refractory ocular inflammation.

1. Introduction

Uveitis, granulomatous polyarthritis, and dermatitis compromise the triad of Blau syndrome, a rare, monogenic, autosomal dominant, inflammatory disorder.¹ The disease results from mutations in the *NOD2/CARD15* gene on chromosome 16q12.1,² which codes for the nucleotide-binding and oligomerization domain-2 receptor (NOD2-R). NOD2-R is a pattern recognition receptor expressed in a variety of cell types as part of the innate immune system and normally promotes expression of inflammatory markers when it binds its ligand.³ In Blau syndrome, the gene mutation results in constitutive activation of NOD2-R. The median age at diagnosis of uveitis is 5 years and is almost always bilateral.⁴ In patients with eye involvement, 51% have posterior uveitis, often times with optic nerve involvement.⁴ Despite topical and systemic treatment, inflammation often persists and impairs ocular anatomy and visual acuity. More than 27% of patients have a visual acuity of 20/50 or worse at baseline ophthalmic examination. Here, we report a case of Blau panuveitis responsive to systemic immunosuppression, and the use of two wide-field fluorescein angiogram modalities in detecting posterior vascular leakage.

2. Case report

A 5-year-old female with a history of dermatitis and tenosynovitis (Fig. 1A–C) was referred to ophthalmology for eye redness and worsening visual acuity. Review of family history was notable for similar skin, joint, and eye manifestations in the patient's mother and maternal half-brother. Visual acuity was 20/40 in each eye. Due to limited cooperation, the patient was examined under anesthesia (EUA) and found to have anterior uveitis with 3 + anterior chamber cell and flare, iris posterior synechiae (Fig. 2A–B), lens pigment deposition, vitreous “snow balls,” retinal vascular attenuation, and vasculitis in both eyes despite having started 7.5 mg methotrexate weekly for several months. The left eye additionally demonstrated optic nerve head hyperemia and papillitis. Retcam (Clarity Medical Systems, Pleasanton, CA) wide-field fluorescein angiography was performed during the EUA, which highlighted the fundus abnormalities and showed peripheral and mid-peripheral leakage in the left eye (Fig. 2C–D). A diagnosis of Blau syndrome was suspected and so methotrexate was uptitrated to 17.5mg with the addition of frequent topical prednisolone acetate and atropine drops. A biopsy of a keloidal plaque on the leg demonstrated a granulomatous dermatitis and subsequent genetic testing showed the *NOD2* pathogenic variant c.1000C > T (p.Arg334Trp, abbreviated R334W) missense mutation, which confirmed the diagnosis of Blau syndrome. At

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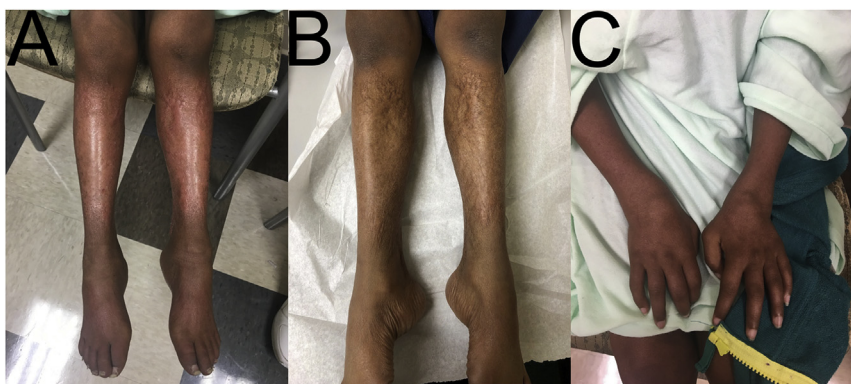


Fig. 1. Skin and joint manifestations of Blau syndrome in patient. The lower extremities show diffuse ichthyosis, fine scaling, keloidal plaques and cords most prominent near the knees and ankles; there are also atrophic plaques involving the shins and calves (A). There is improvement of bilateral lower extremity erythema six months after immunomodulatory therapy (B). The wrists and phalangeal joints have boggy subcutaneous nodules representing underlying arthritis and tenosynovitis (C).

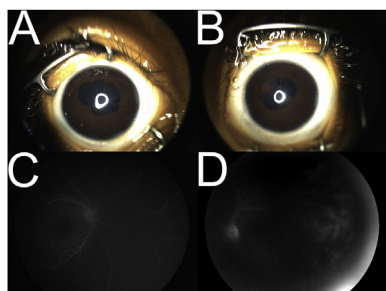


Fig. 2. Anterior segment photographs and portable wide-field Retacam fundus fluorescein angiograms obtained during examination under anesthesia. There is significant iris posterior synechiae in both eyes, resulting in irregular pupil margins (A,B). Portable, Retacam (Clarity Medical Systems, Pleasanton, CA) wide-field fluorescein angiogram of the right eye shows relative sparing of inflammation of the posterior pole and nasal periphery (C). The left eye shows hyperfluorescence of the optic disc and temporal peripheral leakage, consistent with papillitis and peripheral vasculitis respectively (D). These findings were concordant with those seen on Optos (Optos Panoramic 200; Optos PLC., Dunfermline, Scotland, United Kingdom) fluorescein imaging (Fig. 3C–D).

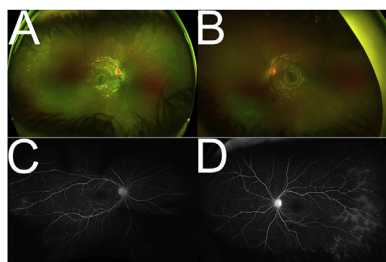


Fig. 3. Wide-field fundus photography and fluorescein angiography obtained on the Optos tabletop system. The right fundus shows vessel attenuation and peripheral “snow balls” temporally (A). Late-phase fluorescein angiogram of the right eye demonstrates peripheral leakage consistent with vasculitis (C). The left fundus photograph shows optic disc hyperemia, vessel attenuation and peripheral “snow balls” (B). Late-phase fluorescein angiogram of the left eye demonstrates optic disc hyperfluorescence and peripheral leakage, consistent with papillitis and vasculitis respectively (D).

the next follow-up visit, the patient had no improvement and new keratic precipitates. Optos (Optos Panoramic 200; Optos PLC., Dunfermline, Scotland, United Kingdom) wide-field fundus photographs and fluorescein angiograms were obtained and showed persistent posterior inflammation (Fig. 3). Therefore, 20mg/0.4mL adalimumab every two weeks was added to the patient's regimen, which resulted in complete cessation of ophthalmic inflammation by four weeks. Topical drops were then stopped. Three months later there was absence of inflammation, but infliximab 15mg/kg infusions every four weeks were

substituted for adalimumab after the patient's mother reported several episodes of facial redness immediately after adalimumab administration and the subsequent development of a facial rash. Ocular inflammation remained quiescent at serial follow-up examinations over a course of two years on a stable regimen of methotrexate 17.5mg weekly and infliximab 15mg/kg every four weeks. Visual acuity has remained 20/40 in the right eye and improved to 20/30 in the left eye.

3. Discussion

The ophthalmologist must maintain a high degree of suspicion for the diagnosis of Blau syndrome in the appropriate clinical context, despite its relative rarity. Patients with Blau syndrome may receive discrete diagnoses such as atopic dermatitis and juvenile idiopathic arthritis (JIA). As uveitis typically manifests after dermatitis and arthritis⁵ in 60–80% of patients,⁶ the ophthalmologist is in a unique position to formulate the unifying diagnosis. A positive family history is an important clue for diagnosing Blau syndrome. In this case, the half-brother of the patient has an identical phenotype, and the mother is legally blind, which increased our suspicion for the diagnosis. However, a family history is not necessary for the diagnosis as sporadic mutations of *NOD2* can occur, historically referred to as Early Onset Sarcoidosis (EOS).^{7,8} Blau syndrome and sarcoidosis are both characterized by granulomatous inflammation and the ophthalmic manifestations are similar. However, The *NOD2* gain-of-function mutation in Blau syndrome/EOS partly contributes to its earlier age of presentation.⁵ Our patient had the Arg334Trp mutation, which is one of the most common mutations in Blau syndrome.⁶

Several international, independent cohort studies^{6,9} have advanced understanding of Blau syndrome, and a multicenter, prospective case series of 50 patients with Blau uveitis has allowed for robust characterization of its ophthalmic features.⁴ These features include vitritis, progressive panuveitis, multifocal choroiditis, optic disc pallor and peripapillary excrescences. Importantly, this study showed that the development of panuveitis with multifocal choroiditis was directly correlated with disease duration and was seen in over 51% of patients at initial examination. This relatively high prevalence can be a useful distinguishing feature from JIA. JIA affects the anterior segment almost exclusively, without posterior segment involvement.¹⁰ As a result, patients with Blau syndrome are more likely to have worse baseline visual acuity and visual prognosis.⁴

A comprehensive characterization of ophthalmic image findings in Blau syndrome is still emerging. In the largest prospective case series on Blau uveitis to date,⁴ imaging examinations were not included but were emphasized as a point of interest for future studies. While a previous report¹¹ included a standard angiogram with a peripheral sweep of a single eye of a patient with Blau uveitis, we report the first case of wide-field fluorescein angiography findings in Blau uveitis. We show that peripheral and mid-peripheral leakage is a characteristic finding in active disease using both the Optos and Retacam systems. Our patient's

leakage would not have been captured by a standard 50-degree fluorescein angiogram normally centered at the posterior pole, thus highlighting an important role for wide-field imaging. While montage photography may have captured some of the leakage, Nicholson and colleagues demonstrated that wide-field angiography is more sensitive in detecting peripheral leakage and can more accurately assess the amount and severity of leakage.¹² Additionally, wide-field angiography revealed vascular leakage not seen on 9-field-montage photography in several patients and allows for simultaneous evaluation of the posterior pole and peripheral retina. Assessing the true severity of leakage has critical importance for clinician wishing to measure disease activity or treatment response. One study showed that a third of noninfectious uveitis patients had their treatment plan influenced when 200° of wide-field fluorescein angiography were analyzed compared to analysis restricted to 60° around the posterior pole.¹³ For Blau uveitis patients in particular, detection of far peripheral leakage with wide-field angiography can assist a clinician in distinguishing the diagnosis from JIA earlier. The angiographic findings in the 130-degree Retcam field were concordant with those from the 200-degree Optos system. While Optos angiography provides superior image quality to the Retcam system, it requires a cooperative patient able to sit upright. Thus, for Blau syndrome patients, who tend to be children and less cooperative with tabletop systems, Retcam wide-field angiography is suitable for detection of mid-peripheral and most peripheral leakage. Retcam angiography also adequately captured optic disc hyperfluorescence. Our findings suggest that both Optos and Retcam wide-field angiography are useful imaging modalities for clinical practice and future prospective studies.

Blau syndrome is notable for its aggressiveness and treatment resistance. Our patient demonstrated favorable clinical response after the addition of adalimumab 20mg/0.4mL to methotrexate 17.5mg. There is no standard therapeutic guidelines for Blau uveitis and there is tremendous variety in treatment patterns across providers. In general, low-level inflammation is controlled with a combination of topical steroid drops, methotrexate or NSAIDs. Persistent or more severe inflammation often requires the addition of subconjunctival steroid injections, systemic corticosteroids or systemic immune suppression with biologic agents. Facial cutaneous rash is a known adverse effect of adalimumab,^{14,15} and so the patient switched to infliximab infusions with continued treatment success.

4. Conclusions

In summary, we report a case of Blau syndrome with severe panuveitis. Family history can be pivotal to recognizing the disorder, which typically requires earlier and more intense immunosuppression than uveitis seen in JIA. In young patients, EUA may be required to detect intermediate and posterior uveitis. Wide-field fundus imaging with fluorescein angiography can detect subclinical retinal vasculitis and offers a significant advantage over standard fluorescein angiography. In most cases, prompt immunosuppression with anti-metabolites or tumor necrosis factor alpha blockade is warranted.

Patient consent

Written consent was not obtained, but the report does not contain any identifying patient information.

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Conflicts of interest

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Authorship

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

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