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Case report

Ophthalmological treatment of early-onset sarcoidosis/Blau syndrome in a Colombian child: A case report

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ABSTRACT

Purpose: To report the ophthalmological approach of a patient with Blau syndrome (BS) in Colombia.
Observations: We describe a 9-year-old Colombian boy with sporadic BS due to a *de novo* nucleotide-binding oligomerization domain containing 2 (NOD2) mutation, who presented with joint and dermatologic symptoms. He was referred to the uveitis service with a single functional eye, due to retinal detachment in the other eye. Despite treatment with corticosteroids, methotrexate, and adalimumab, the patient continued to exhibit progressive disease.
Conclusion: BS-related uveitis is characterized by severe ocular morbidity. Appropriate interdisciplinary treatment is necessary for the correct identification and management of the disease, considering the inherent difficulty in its diagnosis due to its diverse clinical manifestations. The severity of BS-related uveitis in this report highlights the need for more effective therapies.

1. Introduction

Blau syndrome (BS), also known as early-onset sarcoidosis (EOS), is an uncommon monogenic auto-inflammatory granulomatous disease, which results from an autosomal dominant mutation in the pattern recognition receptor nucleotide-binding oligomerization domain containing 2 (NOD2) and caspase activation and recruitment domain member 15 (CARD15) genes.[1] The CARD15/NOD2 gene is located on chromosome 16q12 and is principally expressed in antigen-presenting cells, dendritic cells, and intestinal Paneth cells.[2] The most frequent mutations in the CARD15/NOD2 gene are missense substitutions at position 334 (R334W or R334Q); moreover, NOD2 is a member of the NOD-like receptor family, which is important in the innate immune response.[1]

BS was first described in 1985 by Blau and Jabs.[3,4] This syndrome classically presents as a triad of granulomatous dermatitis, arthritis, and uveitis.[5] After causative mutations in NOD2 were discovered in patients with BS,[2] studies of patients with EOS were performed[1,6] these studies revealed that BS and EOS are the respective familial and sporadic forms of the same disease.[1,6,7] BS is known to occur mainly in Caucasians, but might also occur in Asians and African-Americans. It typically begins at the age of 3–4 years. Initial symptoms are cutaneous and articular; these are followed by ocular symptoms. Joint manifestations involve symmetric polyarthritis involving metacarpophalangeal joints, wrists, first metatarsophalangeal joint, interphalangeal joints, and elbows. Occasionally painless cysts may appear on the posterior aspect of the feet and wrists, causing finger deformities and eventually leading to camptodactyly and reduced motion of large joints, similar to juvenile idiopathic arthritis (JIA). There are two types of dermatological manifestations in which eruption can appear: a papulonodular brownish rash associated with multiple firm subcutaneous nodules, as well as an erythema with a maculopapular fine scaly pattern located on the trunk and extremities. Persistent and intermittent fever have also been described. Ophthalmic manifestations are characterized bybilateral uveitis that begins as granulomatous iridocyclitis and posterior uveitis, resulting in panuveitis. In addition, cataract, band keratopathy,

Abbreviations: (BS), Blau syndrome; (NOD2), Nucleotide-binding oligomerization domain containing 2; (EOS), Early-onset sarcoidosis; (CARD15), Caspase activation and recruitment domain member 15; (JIA), Juvenile idiopathic arthritis; (BCVA), Best-corrected visual acuity

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bilateral chorioretinal lesions surrounded by retinal hemorrhages, and subretinal fibrosis have been observed. Complications that lead to visual impairment and blindness in affected patients include glaucoma, cataract, and retinal detachment. Other systemic manifestations of this syndrome include lymphadenopathy, erythema nodosum, leukocytoclastic vasculitis, granulomatous glomerular and interstitial nephritis, arterial hypertension, pericarditis, pulmonary embolism, chronic renal failure, hepatic granulomas, and cranial neuropathies (e.g., facial palsy).[1]

2. Case presentation

A 4-year-old boy initially presented to the uveitis service at Rosario University in Bogotá, Colombia, following referral by a retina specialist. The patient had been diagnosed with bilateral uveitis secondary to BS. The patient had been born following twin pre-term labor; he exhibited low weight and congenital hypothyroidism. The first clinical manifestations of the disease began at 4 months of age; his mother had observed lesions (small brown papules) on the legs. At 9 months of age, a skin biopsy showed normal epidermis; however, non-necrotizing granulomas were observed in the superficial and deep dermis.

The patient was first assessed by a pediatric rheumatologist when he was 2 years of age. The examination revealed compromised joints, due to edema; it also revealed limited movement of wrists, elbows, knees, ankles, metacarpophalangeal joints, and interphalangeal joints. Magnetic resonance imaging examination of the hands revealed tenosynovitis of the extensors in both hands, as well as mild periarticular inflammatory changes in the carpus. Laboratory analysis showed an elevated C-reactive protein level and erythrocyte sedimentation rate, as well as mild anemia and thrombocytosis. At that time, the patient was also evaluated by an ophthalmologist (following referral by the rheumatologist); the examination results were normal.

At 3 years of age, the patient began treatment with prednisolone and methotrexate at a dose of 20 mg/m^2 weekly, which resulted in favorable evolution of arthritis symptoms. Five months later, the patient exhibited 360-degree synechiae in both eyes, as well as corneal epithelial opacities and cataracts. A synovial biopsy showed chronic synovitis with noncaseating granulomas (Fig. 1). Based on these findings, the patient was diagnosed with JIA. Genetic analysis at the age of four years revealed a *de novo* p. Arg334Trp variant in the NOD2 gene, which supported a diagnosis of EOS/BS. The patient was then treated with adalimumab due to uveitis reactivation, with adequate initial responses of the joints and eyes. During follow-up, the patient had several relapses, typically distinguished by previous episodes of fever, rash, and joint inflammation.

When the patient was 5 years of age, an ophthalmologist observed cataracts in both eyes; ocular ultrasound then revealed posterior vitreous detachment and peripapillary vitreoretinal adhesions in both eyes, as well as traction retinal macular detachment in the right eye. A retina specialist performed vitrectomy + cataract extraction surgery in the patient's right eye. After the surgical procedure, the patient's right eye exhibited recurrent retinal detachment. He was then referred to the uveitis service. At the uveitis service at Rosario University, ocular examination revealed best-corrected visual acuity (BCVA) of no light perception in the patient's right eye, whereas it showed BCVA of 20/40 in his left eye. Anterior segment examination of the right eye revealed mild conjunctival hyperemia, temporal band keratopathy, inflammatory cells in the anterior chamber (1+), aphakia, and vitritis (3+); examination of the left eye revealed band keratopathy and inferior pannus, endothelial keratic precipitates, 360-degree posterior synechiae, pigment on the lens, and lens opacity. Ocular fundus examination was difficult to perform due to media opacity.

During the follow-up period, the patient experienced blunt trauma to the right eye, with posterior hyphema that led to worsening of ocular symptoms (photophobia and blepharospasm). Subsequently, the patient exhibited atalamy and hypotonic eye, which resulted in pre-pthisis in his right eye (Fig. 2). This episode was associated with a systemic reactivation of disease, with elevated acute phase reactants, joint edema, and skin lesions. The most recent ophthalmological exam, when the patient was 8 years of age, confirmed the presence of a narrow anterior chamber with 2+ cells, flare, iris-endothelial touch at the periphery (compatible with *iris bombe*), and pupil seclusion leading to secondary angle closure. Iridectomy was performed without complications and the patient continued to undergo close monitoring (Fig. 3). He is currently undergoing treatment with adalimumab weekly, as well as methotrexate, oral prednisolone, folic acid, and topical prednisolone. Despite this therapy, the ocular inflammation has persisted and the patient's BCVA has declined to counting fingers in his left eye.

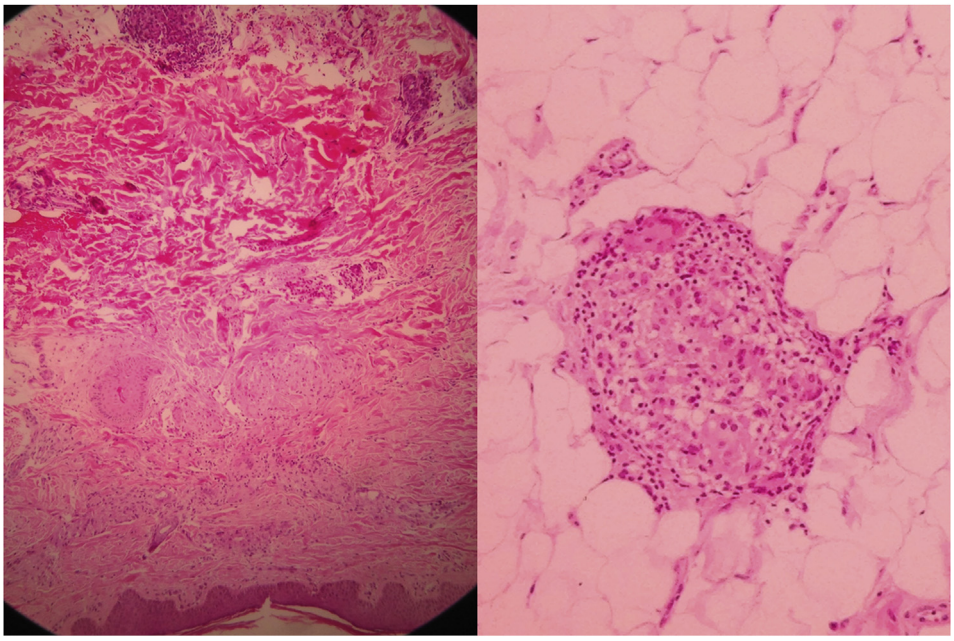

Fig. 1. Severe lymphoplasmacytic infiltrate with numerous non-necrotizing granulomas comprising epithelial histiocytes.

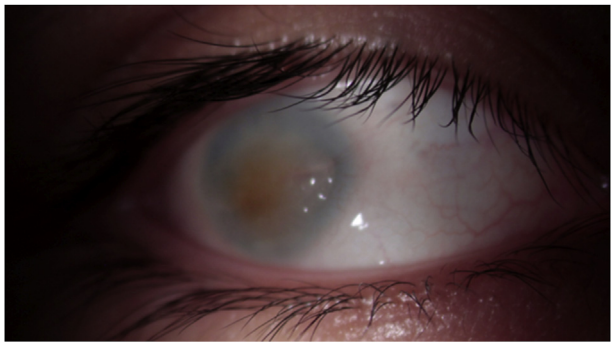

Fig. 2. Pre-pthisis bulbi of the right eye.

3. Discussion

This is the first report of BS in a patient in Colombia. There have been reports of this condition in Mexico[8]; moreover, patients with BS were identified in Brazil and Argentina in two separate cross-sectional multicentric studies.[6,9]

BS is a rare, autoinflammatory, granulomatous entity, which is clinically characterized by the triad of granulomatous dermatitis, uveitis, and recurrent non-caseating granulomatous symmetric arthritis.[3] Sfriso et al.[1] reported that there were only 193 patients with BS among 63 families worldwide, as of April 2012. As observed in our patient and according to literature, BS typically begins between 3 and 4 years of age with cutaneous and articular symptoms, followed by ocular symptoms and joint manifestations (e.g., symmetric polyarthritis). Our patient exhibited joint inflammation in the knees, ankles, and wrists. Chronic tenosynovitis and non-caseating granulomas are also identified in this disease; in our patient, these were identified by hand magnetic resonance and synovial biopsy. Exanthema, also present in our patient, appears as erythema with a maculopapular fine scaly pattern, located on the trunk and extremities. Intermittent fever has also been described[1]; this was the principal clinical manifestation of relapses in our patient.

The most frequently described ocular symptoms in BS are eye pain, photophobia, and blurred vision. In a recent 5-year follow-up study published by Sarens et al., which included 50 patients from 25 centers worldwide (i.e., USA, Europe, Canada, Latin America, and Asia), 38 exhibited ocular involvement. The most frequent clinical manifestations were anterior segment involvement (99%), intermediate involvement (65%), posterior segment involvement (56%), bilateral uveitis (97%), optic disc changes (29%; i.e., pallor discs, peripapillary nodules, disc edema, and macular edema), and chorioretinal lesions (39%). Complications of uveitis were also described: band keratopathy (21%), posterior synechiae (45%), cataract (55%), and elevated intraocular pressure (25%).[6] Our patient developed cataract, band keratopathy, and secondary glaucoma in his single functional eye due to *iris bombe,* vitritis, and retinal detachment.

The main differential diagnosis of BS from the ophthalmological perspective is JIA; thus, BS is occasionally misdiagnosed. JIA typically results in anterior uveitis (10%–20% of patients), while BS typically causes panuveitis (76% of patients). These two entities also differ in terms of visual prognosis: the effects of JIA on BCVA are less severe (typically not worse than 20/40), compared with the effects of BS on BCVA (due to the occurrence of panuveitis and related complications).[6]

There remains no optimal treatment for BS—glucocorticoids are the first-line treatment; however, additional immunosuppresive agents are necessary if the response is poor or if a high maintenance dose is needed (> 10 mg/day). Biologics constitute the second-line treatments, such as tumor necrosis factor inhibitor or interleukin-1 antagonist. Nevertheless, an international multicenter study showed that, of patients who received biologic therapy, systemic steroids, and immunosuppresive agents, 60%–70% continued to exhibit active uveitis and arthritis.[10] In our patient, the severity of disease was unaffected by therapy.

Moderate to severe visual loss has been described in 32% of patients with BS.[9] Visual prognosis is an important factor that affects the quality of life of patients with BS and their families. Our patient currently exhibits BCVA of counting fingers in his only functional eye, and the inflammation remains unresolved. Thus, we are considering the use of alternative biological therapies such as tocilizumab, canakinumab, or anakinra[11–13]; these have yielded favorable outcomes, according to published case reports.

3. Conclusion

BS-related uveitis is a late-stage manifestation of the syndrome and is characterized by severe ocular morbidity, despite continuous systemic and local immunomodulatory therapies. Early diagnosis and appropriate interdisciplinary treatment are necessary for patients with BS. Knowledge of the diverse systemic manifestations (i.e., joint, ocular, and dermatologic symptoms) might help ophthalmologists to identify this rare entity and avoid misdiagnosis and delayed management, thereby improving quality of life and visual outcomes for affected patients. The severity of BS-related uveitis in this report highlights the need for more effective therapies.

Patient consent

The patient's legal guardian provided written informed consent for publication of this case report.

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Authorship

All authors attest that they meet the current ICMJE criteria for

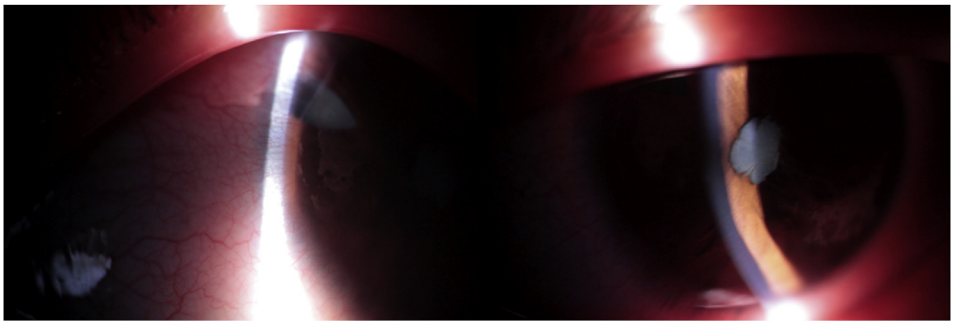

Fig. 3. Band keratopathy, 360-degree posterior synechiae, iridectomy, pigment on the lens, and lens opacity.

Authorship.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ajoc.2020.100714.

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