Discussion

Blau syndrome is a rare, autosomal-dominant, granulomatous inflammatory disease classically characterized by a triad of dermatitis, polyarthritis, and uveitis. The familial form was first described in 1985 by Blau[1] and Jabs and colleagues.[2] Blau syndrome has since been linked to a gain-of-function mutation in *NOD2*, which can be inherited or occur de novo.[3] The normal NOD2 protein remains folded in its inactive state; activation occurs when it interacts with muramyl dipeptide found in bacterial cell walls, leading to subsequent downstream nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) protein activation and inflammatory cytokine production.[4] In Blau syndrome, this signaling pathway is persistently active, leading to overstimulation of the innate immune system.

Although the syndrome is defined by its classic triad, variability can exist in severity and symptomatology. In the original family described by Blau, only 2 of the 11 individuals presented with the classic triad.[1] Subsequent reported cases have described additional findings including fever, lymphadenopathy, transient peripheral neuropathies, hypertension, pericarditis, as well as hepatic, splenic, renal, and pulmonary involvement.[5,6] Additionally, asymptomatic carriers of the *NOD2* gene mutation have been identified through genetic analysis of family members of Blau syndrome patients.[7]

Ocular involvement in Blau syndrome varies from mild to severe, with the most devastating outcome being severe visual impairment.[5,8] About 80% of Blau patients develop ocular disease, with the median age of onset being 4.4 years.[5,8] Arthritis and dermatitis usually precede ocular involvement. Granulomatous uveitis (posterior, anterior, or panuveitis) has been described and can result in visually significant sequelae, including cataracts, band keratopathy, glaucoma, macular edema, and retinal detachment.[5,8] Raiji and colleagues[9] previously described corneal opacities and conjunctival nodules in a patient with Blau syndrome. In their patient conjunctival biopsy showed lymphoplasmocytic inflammation and foreign-body type giant cells but no distinct granulomas. Of note, ocular involvement was preceded by arthritis and dermatitis. Our case is unique in that the appearance of conjunctival nodules occurred concurrently with dermatitis and prior to development of arthritis. Also, biopsy of the conjunctiva revealed evident noncaseating lipogranulomas, prompting the diagnosis of Blau syndrome. Of note, the corneal opacities and conjunctival nodules were not symptomatic or visually significant, and the patient did not develop signs of uveitis for nearly 3 years after the initial onset of ocular signs.

This case broadens the spectrum of presentation in Blau syndrome, the findings for which may be instrumental in early diagnosis.

Literature Search

PubMed, JSTOR, Directory of Open Access Journals, Oxford Journal, University Libraries, and Yale University Library databases were searched on August 13, 2016, without date restriction using the following phrases, with results restricted to the English language: *subconjunctival granulomas Blau syndrome*, *conjunctival granulomas Blau syndrome*, and *conjunctiva Blau syndrome*.

References

1. Blau EB. Familial granulomatous arthritis, iritis, and rash. J Pediatr 1985;107:689-93.
2. Jabs DA, Houk L, Bias WB, Arnett FC. Familial granulomatous synovitis, uveitis, and cranial neuropathies. Am J Med 1985;78:801-4.
3. Miceli-Richard C, Lesage S, Rybojad, et al. *CARD15* mutations in Blau syndrome. Nat Genet 2001;29:19-20.
4. Strober W, Watanabe T. *NOD2*, an intracellular innate immune sensor involved in host defense and Crohn's disease. Mucosal Immunol 2011; 4:484-95.
5. Wouters CH, Maes A, Foley KP, Bertin J, Rose CD. Blau syndrome, the prototypic auto-inflammatory granulomatous disease. Pediatr Rheumatol 2014;12:33.
6. Rosé CD, Aróstegui JI, Martin TM, et al. *NOD2*-associated pediatric granulomatous arthritis, an expanding phenotype: study of an international registry and a national cohort in Spain. Arthritis Rheum 2009;60: 1797-803.
7. Harada J, Nakajima T, Kanazawa N. A case of Blau syndrome with *NOD2* E383K mutation. Pediatr Dermatol 2016;33:385-7.
8. Rosé CD, Pans S, Casteels I, et al. Blau syndrome: cross-sectional data from a multicentre study of clinical, radiological and functional outcomes. Rheumatology (Oxford) 2015;54:1008-16.
9. Raiji VR, Miller MM, Jung LK. Uveitis in Blau syndrome from a de novo mutation of the *NOD2/CARD15* gene. J AAPOS 2011; 15:205-7.

Craniofacial linear scleroderma associated with retinal telangiectasia and exudative retinal detachment

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Linear scleroderma is a characteristic form of scleroderma that typically affects children. Ocular manifestations may be present,

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especially when the frontoparietal area of the head is affected. We present the case of a 5-year-old boy with craniofacial linear scleroderma ("en coup de sabre") who developed exudative retinal detachment. Angiographic and neuroimaging findings are presented, and the importance of regular fundus examination is highlighted.

Scleroderma is a clinically heterogeneous connective tissue disorder characterized by fibroblast dysfunction, small-vessel vasculopathy, and autoantibody production.[1,2] Although the majority of patients have progressive skin thickening, disease manifestations vary from small skin lesions with minimal systemic involvement (limited cutaneous scleroderma) to widespread skin abnormalities with significant internal organ involvement (diffuse cutaneous scleroderma).[1] Linear scleroderma, the most frequent form of scleroderma in childhood,[2] is a subtype of limited cutaneous scleroderma characterized by one or more linear streaks of cutaneous induration. Ocular and ocular adnexal manifestations may be present, especially when the face and/or scalp are involved.[3] Retinal vascular abnormalities are rarely present.[4-7] We report a case of linear scleroderma "en coup de sabre" with retinal telangiectasia and exudative retinal detachment.

Case Report

A 5-year-old boy presented to rheumatology at Royal Manchester Children's Hospital with a left-sided headache and a linear area of skin discoloration on the left side of the forehead (Figure 1G,H). The latter started 2 years before as a localized area of hair loss over the left frontal scalp and extended vertically to affect the left eyebrow and eyelid, causing indentation and loss of eyelashes. There were no other skin lesions and no joint pain or swelling. Neurological and systemic examination were otherwise unremarkable and the diagnosis of linear scleroderma "en coup de sabre" was made. The patient was treated with intravenous methylprednisolone, subcutaneous methotrexate, and, subsequently, oral mycophenolate mofetil. Ophthalmic assessment was requested and revealed normal unaided visual acuity of (−0.06 logMAR in each eye [20/17 Snellen equivalent]) and no ocular pathology except for superficial left optic disk drusen, which were confirmed by ultrasound.

Two years later, the patient complained of acute decrease of vision in his left eye despite being on mycophenolate mofetil. On examination, visual acuity was −0.04 logMAR in the right (20/18 Snellen equivalent) and 1.04 logMAR in the left eye (20/220). There was a superonasal area of abnormal episcleral vessels. Fundus examination revealed an extensive left exudative retinal detachment (Figure 1A,D,E). Examination under anesthesia with fundus fluorescein angiography and intravitreal anti-VEGF injection (bevacizumab 1.25 mg) were performed, and further immunosuppressive treatment was initiated (6-week course of intravenous methylprednisolone). Abnormal retinal vessels and areas of capillary dropout were noted on angiography (Figure 1B). Subsequent examinations revealed no improvement despite treatment (Figure 1C,E) and left visual acuity at his last visit was 1.30 logMAR (20/400 Snellen equivalent). As the patient was complaining of ongoing, severe left-sided headaches, magnetic resonance (MR) imaging and angiography were performed. MR angiogram from the arch of the aorta to the circle of Willis demonstrated normal caliber intracranial and extracranial vessels with no signs of stenosis or occlusion. Brain MR imaging revealed lesions consistent with intraparenchymal calcifications within the left thalamus and frontal lobe; these were best detected with the susceptibility-weighted imaging (SWI) sequence (Figure 2). Repeat imaging 6 months later revealed stable appearance with no evidence of progression.

Discussion

Individuals with craniofacial linear scleroderma are known to be at risk of developing ocular complications.[3] Anterior segment inflammation is the most frequent finding, and some authors have recommended regular screening of affected children for uveitis.[8] Our patient had an unusual presentation, with an episcleral vascular anomaly and a Coats-like response (ie, retinal telangiectasia with intraretinal/subretinal exudation, and exudative retinal detachment). Such a response has been previously described in a small number of cases with linear scleroderma (7 with progressive hemifacial atrophy[7] and 3 with "en coup de sabre"[4-6]). These findings are perhaps not surprising, because scleroderma is known to be associated with vascular abnormalities, including endothelial cells loss, increased vascular permeability, and defective angiogenesis.[1] Widefield fundus angiographic studies in individuals with scleroderma, ocular adnexal involvement and apparently normal retinal examination are expected to provide further insights.

Our patient complained of severe headaches. Notably, neurological involvement is common in craniofacial linear scleroderma, with more than two-thirds of cases having epilepsy and one-third of cases complaining of headaches.[9,10] Thus, neuroimaging should be considered, especially when neurologic symptoms are present. However, symptoms might not be a predictor of MR imaging abnormalities, and interpretation should take into account the known radiographic stigmata of scleroderma.[10] These include intraprenchymal calcifications and vascular malformations ipsilaterally to the facial features.[9] Here we show that SWI is very sensitive in detecting some of these abnormalities, and it is therefore advisable to include this sequence when imaging individuals with scleroderma.

This report highlights the importance of regular fundus examination in children with craniofacial linear scleroderma; the retinal vascular abnormalities were not detected