Blau Syndrome

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Introduction

Blau syndrome is a dominantly inherited granulomatous autoinflammatory disease that may present with a classical triad of arthritis, dermatitis, and uveitis. Described in 1985, this familial disease is caused by a variety of mutations affecting the *NOD2* gene. It may be sporadic or autosomal dominant. Articular findings may include inflammatory involvement of both small and large joints such as the wrist, knees, ankles, and metacarpophalangeal joints. Dermatitis may present with scaly ichthyosiform or papulo-erythematous rash. The kidneys and liver may be involved but, unlike sarcoidosis, lung involvement does not usually occur. Ocular findings may be present in over 60–80% cases and is usually bilateral. The majority of patients have both anterior and posterior segment inflammation. Other manifestations include chorioretinitis and posterior synechiae. Bilateral chronic panuveitis is common, but intermediate uveitis may also occur. Multifocal scars are usually small and may be inside or outside the arcades. A nodular appearance of the peripapillary area has been observed and is thought to represent choroidal granulomas.

Due to the rarity of the disease, its natural history and outcomes are largely unknown. It may be misdiagnosed as juvenile sarcoidosis or juvenile idiopathic arthritis. Patients with ocular disease may develop significant visual loss due to complications such as cataract, glaucoma, macular edema, retinal detachment, and optic atrophy, among others. Granulomatous inflammation of other organ systems and viscera may lead to severe, life-threatening systemic illness.

Case 1: Visceral Involvement in a Case of Blau Syndrome

An 8-year-old boy was diagnosed with polyarticular juvenile idiopathic arthritis (JIA) at the age of 3 years. The patient complained of painful swelling of the joints and was being managed in pediatric rheumatology clinics. He was started and maintained on methotrexate for the past

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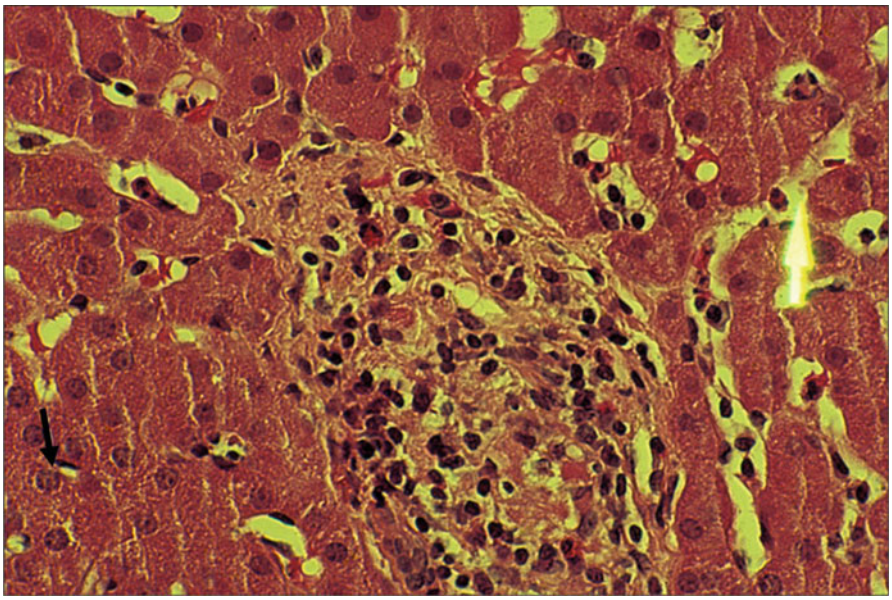

Fig. 1 Immunohistochemical features of liver biopsy in a child with Blau syndrome. The histological section shows presence of typical noncaseating granulomas in a background of otherwise normal liver parenchyma (*arrow*)

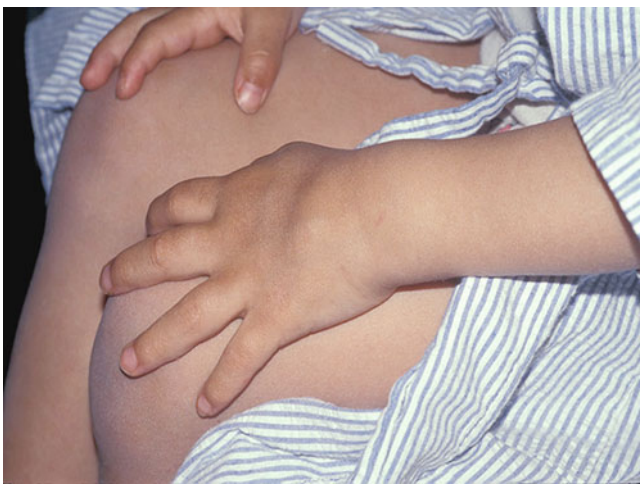

Fig. 2 Exuberant "boggy" synovitis of the wrist in a child diagnosed with Blau syndrome

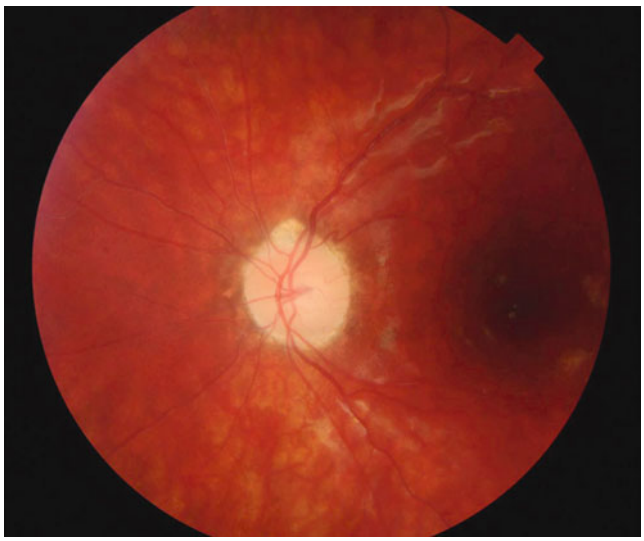

Fig. 3 Photograph of the left optic disc showing peripapillary atrophy with a nodular border

5 years. A surveillance biopsy of the liver was performed at a routine follow-up visit as a part of standard of care. On histopathology (Fig. 1), typical noncaseating granulomas were found in the presence of normal background liver parenchyma.

The diagnosis was revised to early onset sarcoidosis. Five years later, the mutation for Blau syndrome, i.e., activation of NOD2 signal transduction, was described in the literature and the patient was evaluated for such changes. He was found to have R334W mutation in the *NOD2* gene, which is the most common associated variant with the condition. The child was diagnosed with Blau syndrome and kept under close observation. He did not have any ocular manifestations of the condition during the course of the disease.

Case 2: Articular involvement in a case of Blau Syndrome

The younger brother of the patient described in Case#1 was also diagnosed initially with polyarticular JIA due to painful involvement of large and small joints. The diagnosis was revised to Blau syndrome after the results of liver biopsy were obtained for his elder brother. The younger brother was also tested for *NOD2* gene mutations and was detected to have the same R334W mutation.

The patient presented with boggy swelling of the joints. Figure 2 demonstrates synovitis of the carpus in the left hand

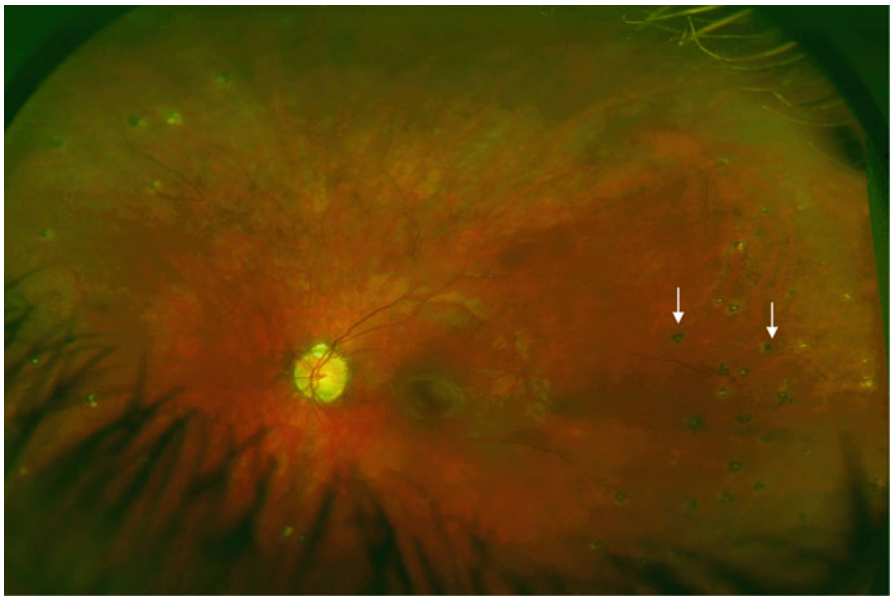

Fig. 4 Ultra-wide field retinal image of the left eye showing multifocal choroiditis with small peripheral chorioretinal scars (*white arrows*)

with relatively less degree of joint contracture than what is expected. There were no ocular features of uveitis in both the brothers.

Case 3: Ocular Manifestations in a Child with Blau Syndrome

An 18-month-old boy presented with pyrexia and was found to have a widespread erythematous rash with hepatosplenomegaly and synovitis of his fingers, wrists, and ankles. Mild anterior uveitis was detected at the age of 4 years at a routine assessment. The patient went on to develop multifocal choroiditis with bilateral panuveitis and optic disk swelling. Ten years after the initial presentation, the uveitis and systemic symptoms are reasonably well controlled on a combination of methotrexate, infliximab, and oral prednisolone. The patient has also retained good visual acuity (20/25 in both eyes) (Figs. 3 and 4).

Key Points

- Blau syndrome, or Juvenile Systemic Granulomatous Disease, is a multisystem inflammatory disease which is associated with mutations of the NOD2 gene.
- Blau syndrome typically presents with a rash and polyarthritis early in childhood which is followed by uveitis.
- Ocular manifestations include anterior, intermediate, and posterior uveitis. The uveitis is often highly sight threatening but may be managed with systemic immunomodulatory therapy, including the use of biological agents.

Suggested Reading

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