Blau syndrome—the skin as a warning sign

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Abstract

Blau syndrome is an autosomal dominant chronic inflammatory disease, which may begin with skin manifestations in the first months of life, alerting physicians to the diagnosis. This case reports a patient diagnosed jointly by pediatric dermatology and rheumatology consultants at two years of age.

Keywords: arthritis, autoinflammatory, Blau, early, granulomatous, monogenic, mutation, NOD2, rheumatoid, syndrome

Introduction

Blau syndrome (BS) is a rare monogenic auto-inflammatory disease characterized by the triad of granulomatous dermatitis, early-onset polyarthritis, and uveitis. Despite the exceptions, skin lesions are an early sign. They appear before the age of four and are often the first signs. Blau syndrome results from mutations in the *NOD2* gene and its exact prevalence is unknown [1]. A Danish registry recorded an estimated annual incidence of 1/1,670,000/year for children under five years of age [2].

Since BS is a progressive disease, it can lead to joint deformities and blindness; early treatment reduces the incidence and severity of the sequelae [3].

Herein, we present a boy with erythematous skin lesions characteristic of Blau syndrome granulomatous dermatitis since the age of two months. He was misdiagnosed initially as having atopic dermatitis. His cutaneous eruption showed progressive worsening and the diagnosis was only established when he started having difficulty walking at two years of age. We report the effectiveness of the treatment and the evolution to the age of eight.

Case Synopsis

A 7-year-old boy initially presented to his physicians at two months of age because of skin eruptions characterized by erythematous papules on the lower limbs and abdomen. With time these spread to the trunk and upper limbs, without any known aggravating factors. The lesions were not itchy. He was diagnosed with ichthyosis and atopic dermatitis and experienced periods of partial remission with the use of systemic corticosteroids and skin hydration. His history included fever of unknown origin during the first year of life, about four episodes a year, lasting five to seven days.

Over the next two years, the condition evolved with the appearance of asymptomatic 1-2cm nodules on the extremities; the child had difficulty and pain with walking. His first evaluation in the pediatric dermatology service was at the age of two, when his skin presented a disseminated rash consisting of flattened and soft erythematous papules (**Figure 1A**) and soft, mobile, and painless nodules (**Figure 1B**) on the back of the hands, feet, and ankles. His parents and brother were healthy. Rheumatoid

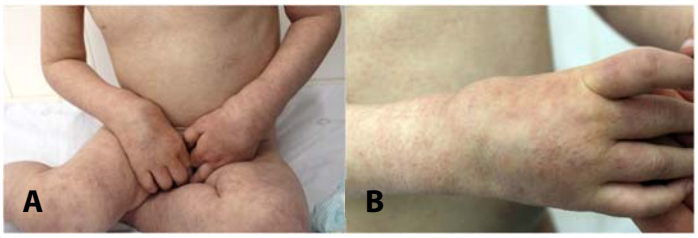

Figure 1. ***A)*** *Difuse erythematous maculopapular fine scaly rash.* ***B)*** *Nodules on the back of the hand.*

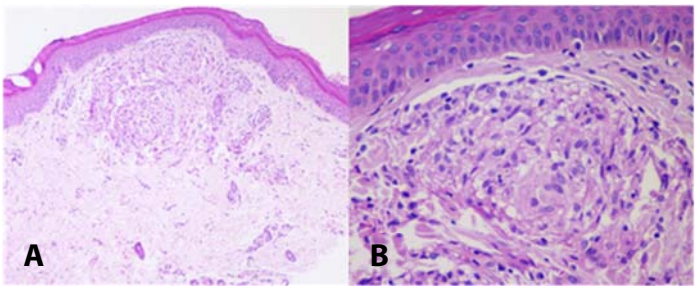

Figure 2. *H&E histopathologic findings* ***A)*** *Noncaseating granulomas in the dermis with sparse lymphocyte infiltration at the periphery, 10×.* ***B)*** *Noncaseating granulomatous inflammation with multinucleated giant cells, 40×.*

factor, antinuclear antibodies, and blood cell count were normal; ophthalmologic evaluation was normal and extremity radiographs showed soft tissue swelling. In interconsultation with a pediatric rheumatologist on the same day, the possibility of Blau syndrome was raised.

The skin histological evaluation showed the presence of epithelioid cells and multinucleated giant cells organized in noncaseating granulomas (**Figure 2**). Genetic testing identified a mutation in the *NOD2* gene, confirming the clinical and histological suspicion of Blau syndrome.

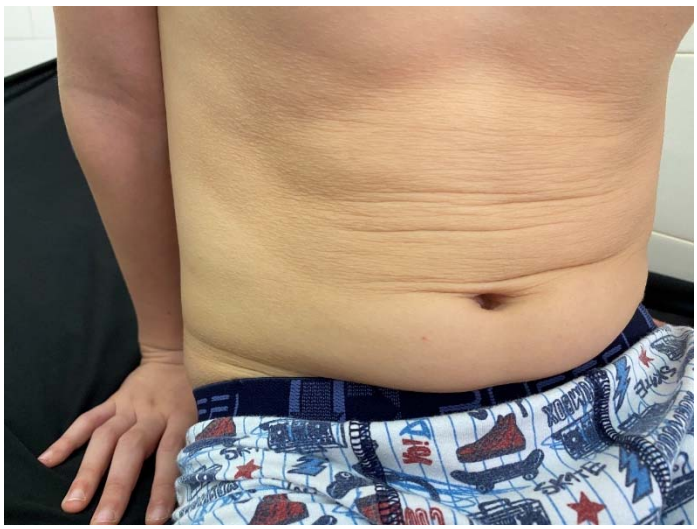

Figure 3. *Small pitted scars remain.*

Initial treatment included naproxen 15mg/kg/day and methotrexate 0.5ml/week (13mg/m^2) associated with folic acid 5mg/week. The skin improved, but joint response occurred only after four months. Then, etanercept 0.8mg/kg/week was used for six months. Arthritis persisted and the medication was replaced with adalimumab 20mg every 14 days. The joint changes improved significantly.

At seven years of age, the patient continues to use adalimumab with control of skin and joint lesions. His skin has small pitted scars (**Figure 3**).

Case Discussion

Blau syndrome is an autosomal dominant chronic inflammatory disease with onset before the age of four. It is characterized by the clinical triad of granulomatous dermatitis, arthritis, and uveitis [3-5]. Skin rashes are the first symptoms and appear in the first year of life. At about four years of age, polyarthritis and uveitis begin [6].

The syndrome arises through gain-of-function in the *NOD2* gene (also called *CARD15*), an intracellular sensor for the bacterial cell wall component muramyl dipeptide (MDP). NOD2 bound to MDP oligomerizes to form a signaling complex that triggers classical nuclear factor kappa B (NFκB) activation. NFκB corresponds to a family of proteins that acts by regulating the expression of a wide variety of genes, being a central pathway of the immune system, with participation in innate and adaptive immune responses. With the mutation, the cells do not exhibit either spontaneous NFκB activation or enhanced sensitivity to MDP, but instead trigger NFκB with exposure to otherwise insufficient stimuli including interferon gamma. This results in enhanced production of multiple proinflammatory cytokines [5,7,8]. In most cases, it is a sporadic mutation, but it can be familial [5].

Skin manifestations are often the first symptoms, beginning in the first months of life and alerting physicians to the diagnosis. Asymptomatic, papular,

erythematous and desquamative eruptions appear on the trunk and extremities, evolving with brownish color and periods of remission and recurrence [4]. Skin lesions can be misdiagnosed as atopic dermatitis or, when the scaling is intense, ichthyosis vulgaris [6] as in our patient. The disease can also manifest as a mildly desquamative rash or simply a case of "strange" rash during childhood [4], which may disappear spontaneously and often goes unnoticed without a proper diagnosis. Skin biopsy allows diagnosis before the onset of joint manifestations.

Skin eruptions are followed months later by joint symptoms. The arthritis is symmetrical, polyarticular, with a tendency to joint deformity [6]. Despite this fact and the chronicity of exuberant arthritis, joint destruction is uncommon [5]. Wrists, knees, ankles, and proximal interphalangeal joints are the most affected joints. The absence of arthralgia in the presence of joint edema is important for differentiation from juvenile idiopathic arthritis [3].

Ocular manifestations are the last of the triad. Uveitis occurs in up to 80% of patients, affects both eyes [4], and commonly consists of an insidious granulomatous iridocyclitis with posterior uveitis [5]. One-third of patients have moderate-to-severe vision loss, which can lead to glaucoma and blindness [1]. The patient in this case report had no ocular changes during the six-year follow-up, although they are frequent in childhood, perhaps because treatment was started at two years of age.

Less frequent manifestations include fever, cranial neuropathies, arteritis, and granulomatous involvement of visceral organs. Although fever is not included in the triad of symptoms, it is an important clinical feature. Matsuda et al. analyzed the clinical manifestations of fifty patients with Blau syndrome in Japan and showed that in 26 cases out of 50, fever occurred in the first years of life [9]. De Rose et al. suggested considering Blau syndrome as a cause of fever of unknown origin in children up to four years of age is essential [10]. The patient in this case report also manifested this additional symptom, and along with the rash, should suggest the need for a skin biopsy.

Histopathology showed a noncaseating granulomatous inflammatory infiltrate located in the dermis and other affected tissues [4]. Skin manifestations that show a granulomatous infiltrate histologically, associated with arthritis allows the diagnosis of Blau syndrome. Genetic testing is confirmatory [5,11].

Blau syndrome was once considered a type of sarcoidosis (early onset), as both share the common histological feature of noncaseating granulomas and can affect similar organ systems. It is now considered a distinct entity as it is known that BS is inherited in an autosomal dominant fashion, whereas early-onset sarcoidosis is related to a mutation that occurs sporadically in the same gene [12,13]. It is important to distinguish these two entities: sarcoidosis begins most commonly in the second-to-fourth decade of life and Blau syndrome in the first 5 years of life. Arthritis in sarcoidosis presents with a symmetrical oligoarticular pattern, in contrast to the polyarthritis observed in BS. The skin eruption of sarcoidosis may be of a similar color, but with larger lesions than those seen in Blau syndrome, although in both can resolve spontaneously. Both have uveitis as manifestation, but the visual outcome of uveitis in sarcoidosis tends to be favorable. The lung is commonly involved in sarcoidosis and rarely in Blau syndrome [12]. Studies focusing on the genetic background of Crohn disease have highlighted its susceptibility in patients with mutations in the same *NOD2* gene. However, the isolated mutation is not a determinant of the disease, since Crohn disease presents with heterogeneous clinical aspects and an important presence of an autoinflammatory and autoimmune response, despite not having a well-understood pathogenesis [13,14].

Blau syndrome has no specific treatment based on its etiology. The treatment involves several therapies and includes systemic corticosteroids, methotrexate, cyclosporin A, or mycophenolate mofetil, but the disease has no cure and the relationship between the gene mutation variant and the response to treatment is unknown [3]. Tumor necrosis factor inhibitors and interleukin-1 blockers are effective in promoting remission of uveitis [5]. Recent studies show good results with tofacitinib, a Janus kinase

inhibitor and it may be a promising agent for patients with Blau syndrome with unsatisfactory responses to previous treatments [15].

Conclusion

Our pediatric patient had a late diagnosis in his second year of life, even with classic skin signs of Blau syndrome. Early diagnosis is essential, and pediatricians and dermatologists need to recognize this disease, allowing treatment and minimizing sequelae.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Harada J, Nakajima T, Kanazawa N. A case of Blau syndrome with NOD2 E383K mutation. *Pediatr Dermatol*. 2016;33:e385–7. [PMID: 27339507].
2. Rose C, Wouters C. Blau syndrome. Orphanet Enciclopédia, 2012. https://www.orpha.net/consor/cgi-bin/Disease_Search.php?data_id=12018&lng=en. Accessed on April 1, 2023.
3. Matsuda T, Kambe N, Takimoto-Ito R, et al. Potential benefits of TNF targeting therapy in Blau syndrome, a NOD2-associated systemic autoinflammatory granulomatosis. *Front Immunol*. 2022;13:895765. [PMID: 35711422].
4. Stoevesandt J, Morbach H, Martin TM, et al. Sporadic Blau syndrome with onset of widespread granulomatous dermatitis in the newborn period. *Pediatr Dermatol*. 2010;27:69-73. [PMID: 20199415].
5. Wouters CH, Maes A, Foley KP, Bertin J, Rose CD. Blau syndrome, the prototypic auto-inflammatory granulomatous disease. *Pediatr Rheumatol Online J*. 2014;12:33. [PMID: 25136265].
6. Rose CD. Blau Syndrome: A systemic granulomatous disease of cutaneous onset and phenotypic complexity. *Pediatr Dermatol*. 2017;34:216-218. [PMID: 27874205].
7. Takada S, Kambe N, Kawasaki Y, et al. Pluripotent stem cell models of Blau syndrome reveal an IFNγ-dependent inflammatory response in macrophages. *J Allergy Clin Immunol*. 2018;141:339-349.e11. [PMID: 28587749].
8. Miceli-Richard C, Lesage S, Rybojad M, et al. CARD15 mutations in Blau syndrome. *Nat Genet*. 2001;29:19-20. [PMID: 11528384].
9. Matsuda T, Kambe N, Ueki Y, et al. Clinical characteristics and treatment of 50 cases of Blau syndrome in Japan confirmed by genetic analysis of the NOD2 mutation. *Ann Rheum Dis*. 2020;79:1492-1499. [PMID: 32647028].
10. De Rose DU, Coppola M, Gallini F, et al. Overview of the rarest causes of fever in newborns: handy hints for the neonatologist. *J Perinatol*. 2021;41:372-382. [PMID: 32719496].
11. Jindal AK, Pilania RK, Suri D, et al. A young female with early onset arthritis, uveitis, hepatic, and renal granulomas: a clinical tryst with Blau syndrome over 20 years and case-based review. *Rheumatol Int*. 2021;41:173-181. [PMID: 31062074].
12. Kaufman KP, Becker ML. Distinguishing Blau Syndrome from Systemic Sarcoidosis. *Curr Allergy Asthma Rep*. 2021;21:10. [PMID: 33560445].
13. Negroni A, Pierdomenico M, Cucchiara S, Stronati L. NOD2 and inflammation: current insights. *J Inflamm Res*. 2018;11:49-60. [PMID: 29483781].
14. Caso F, Galozzi P, Costa L, Sfriso P, Cantarini L, Punzi L. Autoinflammatory granulomatous diseases: from Blau syndrome and early-onset sarcoidosis to NOD2-mediated disease and Crohn's disease. *RMD Open*. 2015;1:e000097. [PMID: 26509073].
15. Zhang S, Cai Z, Mo X, Zeng H. Tofacitinib effectiveness in Blau syndrome: a case series of Chinese paediatric patients. *Pediatr Rheumatol Online J*. 2021;19:160. [PMID: 34781959].