Widespread Granulomatous Dermatitis of Infancy
An Early Sign of Blau Syndrome

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Background: Pediatric sarcoidosis has traditionally been divided into 2 distinct groups: (1) school-aged children and adolescents with frequent involvement of the lungs and mediastinal lymph nodes (similar to adult sarcoidosis) and (2) infants and preschoolers with the triad of arthritis, uveitis, and a cutaneous eruption of discrete small papules, referred to as early-onset sarcoidosis. Blau syndrome, a rare autosomal dominant genodermatosis caused by mutations in the NOD2 (nucleotide-binding oligomerization domain 2) gene, has been considered as the familial form of early-onset sarcoidosis.

Observations: A 9-month-old boy developed an asymptomatic eruption of 1- to 2-mm, red-brown to pinkish tan, flat-topped papules on the face, trunk, and extremities. There was no evidence of ocular involvement or arthritis. The skin lesions were characterized histologically by noncaseating granulomas in a periadnexal distribution within the dermis. A family history of uveitis supported a diagnosis of Blau syndrome, and analysis of the NOD2 gene revealed a heterozygous gain-of-function missense mutation (Arg334Trp) that has previously been detected in Blau syndrome kindreds.

Conclusion: We draw attention to granulomatous dermatitis as an early manifestation of Blau syndrome and highlight emerging molecular evidence that this heritable autoinflammatory disorder and early-onset sarcoidosis represent a single disease entity.

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**SARCOIDOSIS**, a multisystem granulomatous disease of unknown origin, has traditionally been divided into 2 distinct pediatric forms. School-aged children and adolescents with sarcoidosis have manifestations similar to those of adults, with frequent involvement of the lungs and mediastinal lymph nodes. Skin lesions are observed in approximately one third of such cases. In contrast, early-onset sarcoidosis (EOS) (also known as preschool or lichenoid sarcoidosis) typically presents with the triad of arthritis, uveitis, and a cutaneous eruption of small papules but spares the lungs and lymph nodes. Only 5% of pediatric cases of sarcoidosis occur in patients younger than 5 years, with an incidence rate of less than 1 per 1.5 million person-years. Unlike most types of sarcoidosis, the early-onset variant favors white rather than black individuals.

Blau syndrome (BS), a rare autosomal dominant genodermatosis caused by mutations in the NOD2 (nucleotide-binding oligomerization domain 2) gene, is a heritable autoinflammatory disorder and early-onset sarcoidosis represent a single disease entity. Skin lesions represent the first manifestation of BS in more than half of patients (51 of 93 reported cases for which the information was provided), with a median age at onset of 1 year in this subgroup. Eventually, skin, joint, and eye findings are observed in 73%, 91%, and 67% of family, member 15 or CARD15) gene, has considerable overlap with EOS and is thought to represent the familial form of the disease. In addition to synovitis, uveitis, and a generalized papular skin eruption, all characterized histologically by noncaseating granulomas, individuals with BS often develop camptodactyly (flexion contractures of the proximal interphalangeal joints) and other sequelae of chronic progressive arthritis. Of note, the latter can also occur in the setting of long-standing joint disease due to sporadic EOS. The age at onset, organ systems involved, and severity of BS vary substantially, even within affected families. The disease becomes evident at a median age of 2 years (range, 4 months to 27 years). Skin lesions represent the first manifestation of BS in more than half of patients (51 of 93 reported cases for which the information was provided), with a median age at onset of 1 year in this subgroup.

**References**: 7, 12, 13, 16-27, 29, 30, 32-37.
patients with BS, respectively (a total of 174 reported cases).7,10-38

We describe an infant boy who developed a generalized eruption of discrete, flat-topped papules characterized histologically by noncaseating granulomas in a periadnexal distribution within the dermis. A family history of uveitis supported a diagnosis of BS, and analysis of the NOD2 gene revealed a heterozygous gain-of-function missense mutation. We draw attention to granulomatous dermatitis as an early manifestation of BS and discuss emerging molecular evidence that this heritable autoinflammatory disorder and EOS represent a single disease entity (hereafter referred to as BS/EOS).

REPORT OF A CASE

A 12-month-old boy of Brazilian descent presented with a 3-month history of asymptomatic, discrete papules in a widespread distribution. The eruption began on the face, then spread to the trunk and extremities. He had previously been diagnosed as having atopic dermatitis but had not responded to therapy with high-potency topical corticosteroids. A 2-week course of oral prednisolone resulted in some improvement, but the condition recurred immediately on discontinuation of the prednisolone regimen.

The patient had never traveled outside the United States and was otherwise healthy, with no fevers, joint pain or swelling, eye pain, photophobia, visual changes, cough, or abdominal discomfort. An ophthalmologic examination disclosed no abnormalities. His father, paternal uncle, and paternal grandfather (Figure 1) all had a history of chronic uveitis that had begun in adolescence and required long-term oral corticosteroid therapy. The uncle also developed granulomatous dermatitis as an adult; the father and grandfather had no history of granulomatous skin lesions. There was no family history of arthritis.

On physical examination, numerous 1- to 2-mm, red-brown to pinkish tan, flat-topped papules covered much of the face, trunk, and extremities (Figure 2). Individual lesions were closely grouped in oval clusters and linear arrays, with confluence on the face. The upper part of the chest, knees, elbows, palms, and soles were relatively spared. No oral mucosal or conjunctival lesions were evident. No joint tenderness or swelling, lymphadenopathy, or hepatosplenomegaly was found.

The following laboratory tests produced normal results: complete blood cell count, chemistry panel, serum calcium level, hepatic function panel, erythrocyte sedimentation rate, and urinalysis. The serum angiotensin-converting enzyme level was 159 U/L (reference range, 13-100 U/L). A tuberculin skin test result was negative, chest radiograph results were normal, and ultrasonography of the wrists, elbows, and knees revealed no synovial thickening or effusions.

Histologic evaluation of a biopsy specimen from a papule on the thigh demonstrated a perifollicular, perieccrine, superficial, and deep nonnecrotizing granuloma-
tous infiltrate composed of mononuclear and multinucleated histiocytes admixed with a few scattered neutrophils (Figure 3). Polarization failed to reveal foreign material, and acid-fast bacilli, Fite, and Grocott stains were negative for organisms.

Together with the clinical presentation and family history, the histologic findings supported a diagnosis of BS. Genetic analysis via direct sequencing of the \(NOD2\) gene revealed a heterozygous gain-of-function missense mutation (Arg334Trp) that has previously been detected in BS kindreds.

The patient’s cutaneous eruption faded without further therapy during the next several months, but it subsequently recurred and persisted for more than 6 months. Treatment with oral azithromycin (10 mg/kg 3 times weekly) for 2 months was associated with marked improvement. The skin lesions recurred within a month of discontinuation of azithromycin therapy and faded again when it was restarted, with residual follicular atrophoderma on the trunk and extremities. At age 2 years (while receiving azithromycin), the patient was noted at a routine dermatologic follow-up visit to have nontender, boggy synovial swelling of the wrists and knees. The joint involvement was asymptomatic and had not been evident to his parents. A complete rheumatologic evaluation is under way, with plans for treatment with a tumor necrosis factor inhibitor.

For the past 2 decades, controversy has existed regarding nomenclature for and classification of EOS and BS.8,9,39,40 In 1986, Miller8 recognized that the 2 conditions are clinically indistinguishable (apart from the presence or absence of a family history) and proposed the unifying term juvenile systemic granulomatosis. Blau9 later supported the concept that EOS and the “autosomal dominant granulomatous disease of childhood” that he first reported in 1985 actually represent the same disorder.

The recent identification of the same heterozygous \(NOD2\) mutations in individuals with sporadic EOS and members of BS families confirmed that these diseases are identical on genetic and clinical levels.29-32 Kanazawa et al31 found that 9 of 10 Japanese patients with EOS had a pathogenic, presumably de novo, \(NOD2\) mutation, whereas Wang et al11 detected \(NOD2\) mutations in 5 of 10 families with a clinical diagnosis of BS. In contrast, several studies have failed to identify \(NOD2\) mutations in patients with classic sarcoidosis of adolescent or adult onset (N=357), including those with a family history.31-43 Molecular evidence thus supports the existence of EOS/BS as a distinct disease entity. Since the \(NOD2\) mutations that characterize BS appear to have nearly 100% penetrance (ie, all individuals with these mutations express the disease phenotype) and the disorder does not affect reproductive potential,10,44,45 the de novo mutations that underlie EOS are likely to generate new Blau pedigrees.39 For example, a young girl initially reported to have sporadic EOS characterized by a papular rash, uveitis, arthritis, and large-vessel vasculitis later gave birth to a child who developed similar skin lesions and arthritis, changing the diagnosis to BS.32,45

Of note, a completely different set of \(NOD2\) variants has been associated with Crohn disease, increasing the likelihood of this complex polygenic condition 20- to 40-fold in homozygotes or compound heterozygotes. This confers a lifetime risk of approximately 10%, reflecting the need for an environmental trigger to develop clinical Crohn disease.46 The same polymorphisms lead to an increased risk of severe, acute graft-vs-host disease after hematopoietic stem cell transplantation.

The \(NOD2\) protein is a member of the \(NOD\) family of cytosolic pattern-recognition molecules. Like their transmembrane counterparts, the toll-like receptors, \(NODs\) recognize highly conserved components of microorganisms and subsequently stimulate the innate immune response.46 \(NOD2\), which is expressed by monocytes and intestinal epithelial cells (particularly within ileal crypts, a primary site of inflammation in Crohn disease), specifically recognizes the muramyl dipeptide component of bacterial cell wall peptidoglycan.47,48 This interaction leads to \(NOD2\) oligomerization and activation of the

**Figure 3.** Perifollicular distribution of a nonnecrotizing granulomatous infiltrate (A) (hematoxylin-eosin, original magnification \(\times 100\)) composed of mononucleated and multinucleated histiocytes admixed with a few scattered neutrophils (B) (hematoxylin-eosin, original magnification \(\times 400\)).
NOD2 mutations reported in patients with EOS/BS (with Arg334Gln/Trp accounting for 28 of 37 cases or families) affect the nucleotide-binding domain of the protein and lead to increased activation of NF-κB that is independent of muramyl dipeptide stimulation (i.e., constitutive gain of function). In contrast, NOD2 polymorphisms that are associated with susceptibility to Crohn disease are located in leucine-rich repeat regions of the protein product and impair responsiveness to muramyl dipeptide (i.e., loss of function). Paradoxically, despite a decrease in NOD2-induced NF-κB signaling, Crohn disease is characterized by increased levels of NF-κB target gene products such as IL-12 (interleukin 12) and tumor necrosis factor α and, as in EOS/BS, granulomatous inflammation. Possible explanations include reduced bacterial recognition and clearance (e.g., via decreased production of antimicrobial peptides such as β-defensin-2) in the gastrointestinal tract leading to impaired epithelial defense and secondary inflammation, loss of NOD2-mediated inhibition of toll-like receptor 2–induced NF-κB activation, and a variable balance of proinflammatory and anti-inflammatory consequences of defective NOD2 signaling in different contexts (e.g., mucosal epithelia with commensal bacteria vs monocytes in aseptic sites).

The asymptomatic papular eruption that characterizes EOS/BS is rarely observed in older children and adults with sarcoidosis. Discrete, pinhead-sized papules typically first appear on the face and extremities and subsequently spread to the trunk. The yellowish to red-brown, slightly scaly, flat-topped papules have been likened to “tapioca grains.” They tend to be arranged in clusters or linear arrays but can become confluent, and a perifollicular distribution may be evident. Intermittent episodes of widespread skin disease with spontaneous resolution usually occur during a period of years (in contrast to the more persistent skin lesions of sarcoidosis). Poikiloderma has been observed in older patients and pitted scars due to follicular atrophy have sometimes been apparent at sites of previous inflammatory papules. Ichthyosiform skin changes characterized histologically by a hyperkeratotic epidermis with underlying dermal granulomas have also been described in EOS/BS.

Histologically, the naked noncaseating granulomas of EOS/BS involve primarily the upper dermis and often have a perifollicular distribution. This histologic pattern is identical to that of lichen scrofulosorum, a tuberculid that is usually seen in children with tuberculous lymph nodes and bones. Lichen scrofulosorum also has a clinical appearance similar to that of EOS/BS, although it favors the trunk rather than the extremities and face. Tuberculin skin testing should therefore be considered in patients with features of EOS/BS.

The symmetric polyarthritis of EOS/BS typically presents with nontender, boggy joint swelling due to synovial thickening and effusion. The wrists, knees, and ankles are most frequently affected. Massive swelling of the tendon sheaths and synovia accompanied by a relatively normal range of motion, minimal pain, and a lack of x-ray film evidence of erosive joint changes until later in the disease process favor a diagnosis of EOS/BS instead of juvenile rheumatoid arthritis.

Anterior or panuveitis is the most common ocular manifestation of EOS/BS and may present with eye pain, photophobia, and blurred vision. Granulomatous inflammation can also involve the conjunctiva, lacrimal glands, retina, and optic nerve, and ocular complications include cataracts and glaucoma. Because early ocular disease is often asymptomatic and its onset can be delayed, slitlamp examination should be performed on a regular basis. Permanent sequelae of chronic inflammation in the eyes and/or joints develop in more than 80% of patients with EOS/BS, and anticipation (increased severity in successive generations) has been described in familial cases.

The clinical manifestations of EOS/BS can extend beyond the classic triad. Additional systemic features have included cranial neuropathies, granulomatous large-vessel vasculitis that involves the carotid, renal, and cerebral arteries; lymphadenopathy; and granulomatous inflammation of the liver, kidneys, lung, heart, and epiphyseal dysgenesis (typically occurring in later stages of the disease). Some patients have also presented with recurrent fevers, which are infrequently observed in typical EOS/BS. The inclusion of disorders initially reported as “familial granulomatous synovitis, uveitis, and cranial neuropathies” and “familial granulomatous arthritis with polyarthritis” within the clinical spectrum of BS is supported by the documentation of NOD2 mutations (including Arg334Gln/Trp) in these subsets of patients. It is likely that additional modifying genes have a role in the development of EOS/BS with prominent involvement of large blood vessels and internal organs.

The cutaneous eruption of EOS/BS may respond to potent topical corticosteroids but tends to recur once use of the corticosteroids is discontinued. In patients with uveitis, progressive joint disease, visceral involvement, or skin lesions that are extensive and/or symptomatic, therapy is often initiated with systemic corticosteroids. Because the granulomatous inflammation is prone to relapse on medication withdrawal, steroid-sparing agents such as tumor necrosis factor inhibitors (e.g., infliximab), methotrexate, cyclosporine, and other immunosuppressive medications may be required. Immunomodulatory agents that target IL-1 (a proinflammatory cytokine that is up-regulated by NF-κB) may also have therapeutic potential in EOS/BS. In our patient, azithromycin (which has anti-inflammatory properties that include inhibition of tumor necrosis factor α production) was beneficial for the skin lesions but not the arthritis.

As exemplified by our patient, EOS/BS tends to first become evident in the skin. Recognizing the characteristic cutaneous eruption and confirming the presence of granulomas via skin biopsy is critical steps to establishing the diagnosis. Dermatologists then have an important opportunity to institute monitoring that will facilitate the early detection and treatment of ocular, rheumatologic, and other systemic manifestations. In addi-
tion, genetic counseling and prenatal diagnosis based on analysis of the NOD2 gene can be offered. We disagree with the recent suggestion by Becker and Rose to rename EOS/BS pediatric granulomatous arthritis because this term does not encompass the full disease spectrum and might deter physicians from considering the diagnosis in early or "incomplete" cases as those described in this report. Arthritis is absent in half of patients at the time of initial presentation, and it never develops in approximately 10% of affected individuals.

Increased awareness of EOS/BS will allow identification and genetic testing of additional affected individuals and families, helping to expand the allelic series of underlying NOD2 mutations and further define genotype-phenotype correlations.

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