SHORT COMMUNICATION

Diagnosis and Treatment of Blau Syndrome/Early-onset Sarcoidosis, an Autoinflammatory Granulomatous Disease, in an Infant

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Blau syndrome (BS), or early-onset sarcoidosis (EOS), is a rare monogenic autoinflammatory granulomatous disease, caused by an autosomal dominant mutation in the *NOD2* (nucleotide-binding oligomerization domain containing 2) gene (1, 2). In some publications, BS and EOS, refer, respectively, to the familial and sporadic forms of the paediatric granulomatous autoinflammatory disease, while others use the terms Blau syndrome, sporadic or inherited form. Previously, 208 cases of BS have been identified (62 sporadic and 146 inherited) in 2014 (3). In a recent international registry study from 2015, a further 31 cases of Blau syndrome from 11 countries were identified (20 with sporadic and 11 inherited) (4). BS/EOS is clinically presented by granulomatous skin eruption, recurrent uveitis, and polyarthritis. Untreated, the disease may cause blindness and severe disability with exuberant arthritis with joint deformity. We present here a case of BS sporadic form or EOS with onset in infancy.

CASE REPORT

A 10-month-old girl was seen in our dermatological clinic due to a papular rash. Skin-coloured papules, with a diameter of 2–3 mm, had spontaneously evolved on her left knee at the age of 7 months (**Fig. 1a**). Over the next 4 months the rash became universal with dark-red papules (Fig. 1b). Otherwise, physical examination was normal. However, the family reported the patient had episodes of unexplained fever and failure to thrive.

A 4-mm biopsy from lesional skin showed acute and chronic non-caseating granulomatous inflammation (Fig. S1[1]). Ziehl-Neelsen staining was negative for mycobacterium species. Chest X-ray and levels of serum-angiotensin-converting enzyme (ACE) were normal. Elevated erythrocyte sedimentation rate (ESR) was 53 mm/h (normal < 15 mm/h) and C-reactive protein (CRP) level was 42 mg/l (normal < 8 mg/l). Additional blood and urine tests did not reveal signs of infectious disease.

Two months later the patient presented with a slightly red right eye and dilated left pupil (Fig. 1c). A paediatric ophthalmologist observed iris nodules at the pupillary margin (Koeppe's nodules) in the right eye and in the left eye a few conjunctival nodules were seen, so ocular sarcoidosis was suspected. In addition, the parents had observed arrest of her gross motor skills. Examination of the joints showed arthritis in the right wrist and both ankles, with pain and considerable limitation of motion. Seven months after the onset of exanthema, our patient had developed the triad of BS; generalized granulomatous exanthema, granulomatous uveitis and arthritis. The diagnosis of BS was confirmed by molecular genetic analysis. A pathogenic, *de novo* mutation *NOD2*[NM_022162.2]:c.[1001G>A];[=] (p.(R334Q)) in *NOD2* was detected. The cutaneous sarcoidosis was treated with group II and III steroid cream with minor improvement in symptoms. The eye symptoms disappeared after treatment with glucocorticoid eye drops (fluormetholone 1 mg/ml) 1–2 times daily. The therapy of arthritis included non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroid injections (IACS) supplemented with oral methotrexate (MTX), 5 mg weekly, from the age of 15 months. The addition of MTX showed a good effect on cutaneous sarcoidosis, but the arthritis was still active. A vaccination programme was initiated prior to biological treatment with tumour necrosis factor-α (TNFα) inhibitor. Interestingly after receiving the combined diphtheria/tetanus/pertussis/polio/*H. influenza*/pneumococcal vaccine, a massive flare-up of the skin symptoms was observed. After 7 weeks' treatment with MTX, 60 mg (6.7 mg/kg) infliximab was given on days 1, 15 and 28. Thereafter, the dose was increased to 100 mg (10 mg/kg) every 4 weeks. After only 2 infusions of infliximab the patient markedly improved, both in the skin (Fig. 1d) and the joints. Ophthalmological examination showed no inflammation, and blood tests were normal. The disease activity fluctuated and we observed increased disease activity following upper respiratory infections. Motor development improved considerably as joint pain decreased. After 6 months MTX dose was decreased to 2.5 mg weekly due to intolerance, and shortly after disease activity flared in both ankles and finger joints. There were no signs of disease activity in the skin or eyes. However, the patient responded well to repeated IACS and shifted to adalimumab, 10 mg, subcutaneously every other week. At the age of 2 years and 8 months the adalimumab dose was increased to 20 mg every other week after a period of increased activity in arthritis and cutaneous sarcoidosis.

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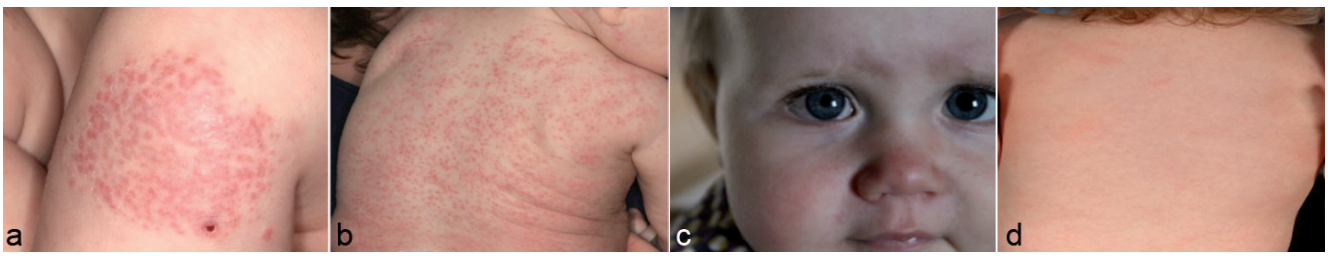

Fig. 1. Clinical characteristics. (a) Granulomatous dermatosis on the left knee. (b) Generalized granulomatous rash at 11 months of age. (c) Dilated left pupil (family photograph). (d) Clinical response after 2 infusions of infliximab. A written permission from the parents is given to publish these photos.

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DISCUSSION

The first inherited cases of BS in a 4-generation family were reported in 1985 (2). BS (OMIM 186580) and EOS (OMIM 609464) are caused by a mutation in the *NOD2* gene, located on chromosome 16q12.2-13. The *NOD2* gene is encoding a protein in the NOD-like receptor family (NLR), which is expressed in macrophages, dendritic cells and epithelial cells and function as regulators of apoptosis and activation of nuclear factor kappa β (NF-kβ) (3, 4). The activation of NF-kβ is 4 times higher in persons with BS (5). The augmented activation of NF-kβ leads to increased transcription of inflammatory genes with subsequent dysregulation of the immune system and multisystem granulomatous inflammation (5). Genetic analyses have shown that identical *NOD2* mutations cause both EOS and BS (3). The missense mutation R334Q, as found in our case, has been described in 9 out of 31 cases (29%) in a recent publication (4).

The manifestations of BS/EOS usually present during early childhood and, over time, most patients develop all 3 features. Skin lesions are generally the first feature to appear and are mainly seen as yellowish to brown-red flat-topped papules. Our patient developed a cluster of papules on her left knee, with subsequent truncal spreading, which is also the most frequent route of dissemination. Interestingly, her cutaneous symptoms flared in connection with upper airway infections and after vaccination, possibly due to dysregulation of the immune response to infectious agents and vaccines. Early diagnosis of arthritis in infants is often a challenge and, in this case, articular involvement was mistakenly interpreted as delayed motor development. Arthritis in BS/EOS manifests as a polyarticular, often exuberant, synovitis, involving mainly the wrists, ankles, knees and proximal interphalangeal (PIP) joints. Often tendon sheaths are characteristically enlarged. The PIP joints often develop contractures early during the disease course, leading to camptodactyly (6). If untreated, the arthritis can cause severe disability with joint deformity and ankylosis. The last clinical feature to develop is often uveitis. The usual ophthalmological complaints are photophobia, blurred vision and ocular pain. The long-term risk of undiagnosed uveitis is visual impairment due to pupillary synechiae, cataract, glaucoma, band keratopathy, chorioretinitis and optic nerve inflammation (6, 7). In a recent multicentre study involving 31 patients (18 children), 80.6% of the patients had ocular symptoms and 33% had moderate-to-severe loss of vision. Thirty-five percent of the patients had anterior uveitis like our patient (4). Also, liver, renal, pulmonary involvement and bone dysplastic changes have been reported (4, 8, 9).

Treatment of BS/EOS in childhood is challenging. If local treatment fails, oral prednisolone alone or in combination with MTX, azathioprine and mycophenolate mofetil, can be introduced (4). High-dose prednisolone can be used during attacks and low dose in more stable periods (10). Also, TNF-α inhibitors, such as infliximab and adalimumab, are used in BS/EOS (10, 11). Interleukin (IL)-1β receptor antagonist, such as anakinra and canakinumab, have been used with variable clinical outcome (3, 12). In cases with severe uveitis canakinumab may be useful (12). In our case infliximab in combination with MTX induced remission for 8 months. However, when the MTX dose was decreased, symptoms reoccurred. Adalimumab improved uveitis and arthritis, but not cutaneous eruption.

The authors declare no conflict of interest.

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