# ERRATUM

## Erratum to: Modern Rheumatology Supplement (2010), S21, SY1-5

The complete abstract is given below.
The publisher and organizers sincerely apologize for the errors and regret the inconvenience they may have caused.

## SY1-5

### Blau syndrome and Early-onset sarcoidosis

Ikuo Okafuji[1,2]
[1]Department of Pediatrics, Kobe City Medical Center General Hospital, Kobe, Japan, [2]Department of Pediatrics, Kyoto University graduate School of Medicine

Sarcoidosis in children was first reported as early as the 1950s. The disease has characteristic phenotype expressions in children, which are apparently different from those in adults.[1)] In 1982, Hetherington et al. investigated clinical pictures of the disease in their pediatric patients and the cases reported in literature and found that the patients who had the onset at the age 5 years or younger had frequent manifestations of skin, joint, and eye disorders.[2)] After their report, sarcoidosis occurring in those children was termed "earlyonset sarcoidosis" (EOS) to distinguish it from common sarcoidosis. In 1985, two research institutes in the USA separately reported clinical syndromes of familial granulomatous disease: arthritis, iritis, and erythema reported by Blau et al.[3)] and synovitis, uveitis, and neuropathy reported Jabs et al.[4)] While these syndromes were later referred to as Blau syndrome (BS), there had been a dispute until recently whether the EOS and BS that has familial components were the identical disorder in view of the similar disease spectra such as early age of onset and phenotype expressions as lesions in the skin, joints, and eyes.[5)] We evaluated EOS patients in Japan and confirmed that BS and EOS are the same disease with a common genetic background characterized by gain-of-function mutations in the nucleotide oligomerization domain (NOD)-2, a molecule involved in natural immunity.[6,7)] Since the establishment of genetic diagnostic procedures for BS and EOS, case reports of the diseases continued and clinical features were studied throughout the world. In general, there are no obvious gender or racial differences in disease onset and clinical presentation.[8,9,10)] Although some BS or EOS patients may have been followed as having juvenile idiopathic arthritis (JIA) or rheumatoid arthritis (RA), it is evident from a careful examination of skin, joint, and eye manifestations that BS and EOS are apparently different diseases as compared to JIA and RA.[12)] BS and EOS can be identified by the following diagnostic criteria: (1) Skin lesions: Multiple non-pruritic macropapules are observed on the entire body from the trunk to extremities. (2) Joint lesions: Usually the lesions begin as early as infancy. Initially, swelling only of hand and leg joints occurs without pain and restricted motion. However, joint pain develops as the disease progresses. (3) Ocular lesions: Uveitis causes lesions in not only the anterior but also posterior region. (4)Initially, all symptoms are mild and are rarely noticed but inevitably progress with time, leading to joint dislocation and blindness in some patients. (5) Diagnosis is established when biopsy of the lesion site is conclusive of non-caseating epithelioid cell granuloma and genetic analysis identifies NOD2 genetic variants. Clinical features are also present in prior history such as "strong family history of RA" and "rheumatoid-factor-negative polyarticular JIA with little evidence of osteolysis despite a long morbidity period".

As far as can be confirmed, there are approximately 30 to 40 patients with BS/EOS in Japan, and currently gain-of-function NOD2 variations have been noted in 25 patients. The most common mutations are R334W and R334Q, similarly to the reports by foreign researchers. We have previously shown that patients carrying the R334W mutation tend to have more severe ocular lesions.[8)] Further investigations in a larger patient population are needed to confirm this tendency.

<<Issues to be addressed>>

#1:Studies of BS/EOS patients without NOD2 genetic variations: Although few in number, there are BS/EOS patients without NOD2 genetic variations. Investigations of this patient population are needed to characterize their clinical features, including the possibility that abnormalities of certain molecules other than NOD2 may be involved. #2:Mechanism of pathogenesis which causes NOD2 genetic variation: It is unclear why granulomatous lesions develop specifically in the skin, joints, and eyes. #3:Establishment of a specific therapy: Treatment for uveitis is often inadequate, necessitating a continued use of corticosteroids. Infliximab[11)] and thalidomide[12)] have been reported to be effective on uveitis, indicating that these drugs may be promising therapies for the disease. Further studies are necessary to establish a more specific therapy based on an accurate understanding of the disease.

* NOD2 is a molecule identified by Ogura and Inohara et al.[13)] to belong to the NBD-LRRs receptors (NLRs) family based on genomic database analysis on homologues of apoptosis protease activating factors (APAF1). The molecule is expressed predominantly in the cytoplasm of monocytes and macrophages, and, using muramyl dipeptides (MDP), which is a component of the bacterial cell wall, as its ligand, activated NOD2 leads to NF-kappaB and MAPK activation.[14,15)] It has also been shown to have an antiviral protective function by recognizing single-strand RNA viruses.[16)] Briefly, NOD2 is involved in innate immunity as a cytoplasmic receptor that recognizes microbes.

References

1) McGovern JP et al. Adv Pediatr 8: 97-135, 1956
2) Hetherington S. Am J Dis child 136: 13-15, 1982
3) Blau EB. J Pediatr 107:689-693,1985
4) Jabs DA et al. Am J Med 78:801-804,1985
5) Miller JJ. J Pediatr 109: 387-388, 1986
6) Kanazawa N et al. J Invest Dermatol 122:851-852,2004
7) Kanazawa N, Okafuji I et al. Blood 105:1195-1197,2005
8) Okafuji I et al. Arth Rheumat 60, 242-250, 2009
9) Rose CD et al. Arth Rheum 54:3337-3344,2006
10) Arostegui JI. et al. Arth Rheum 56:3805-3813,2007
11) Milman N et al. APMIS 114: 912-919, 2006
12) Yasui K et al. Arth Rheum 62, 250-257, 2009
13) Ogura Y, Inohara N et al. J Biol Chem 276:4812-4818,2001
14) Girardin SE et al. J Biol Chem 278:8869-8872,2003
15) Inohara N et al. J Biol Chem 278:5509-5512,2003
16) Sabbah A et al. Nat Imm 10:1073-80, 2009