Clinical Features and Perforin A91V Gene Analysis in 31 Patients with Macrophage Activation Syndrome and Systemic Juvenile Idiopathic Arthritis in China

To the Editor:

Macrophage activation syndrome (MAS) is a severe, potentially fatal complication of rheumatoid disease, especially in systemic juvenile idiopathic arthritis (sJIA). MAS has been considered reactive familial hemophagocytic lymphohistiocytosis (FHLH), and the perforin gene mutations have been identified in some patients diagnosed with the FHLH[1,2,3]. Vastert, *et al*[4] have found that the mutation rate of perforin gene A91V was significantly higher in MAS than in sJIA. Perforin deficiency may increase macrophage activation because of an increased production of interferon-γ and granulocyte-macrophage colony-stimulating factor associated with persistent lymphocyte activation[5,6,7]. These findings suggest that perforin may play a role in MAS pathogenesis.

A total of 31 patients with MAS were identified from 199 sJIA patients, with a morbidity of 15.57%, in our institute in the last 9 years. We retrospectively reviewed these cases. Gene polymorphisms of perforin A91V (US National Center for Biotechnology Information: single-nucleotide polymorphism rs35947132) were analyzed in 21 of the cases. The clinical features are shown in Table 1. Twenty-five out of 31 patients (80.64%) had possible infections for a week to 3 weeks with use of antibiotics prior to developing MAS. The sudden onset of persistent high fever was found in all patients. Progressive hepatosplenomegaly was seen in 29 patients (93.55%), and 24 patients (77.42%) had elevated aspartate transaminase. Fibrinogen was reduced in 15 patients (48.39%). All cases had > 1 series blood cell reduced and pancytopenia occurred in 13 patients (41.9%). Hemophagocytosis was confirmed in 27 cases (87.10%). Unlike data from other reports, the central nervous system dysfunction in our cases was infrequent. A PCR fragment of about 171 base pairs of the perforin A91V was amplified with the forward primer (5'-CAC CCT CTG TGA AAA TGC CCT AC-3') and reverse primer (5'-TTC CAG TCG TTG CGG ATG CTA C-3')[8]. All genotypes of these 21 MAS cases were wild-type, in contrast to the findings of Vastert, *et al*[4].

Table 1. Characteristics of 31 cases of macrophage activation syndrome.

Characteristic	No. Cases (%)
Persistent fever	31 (100)
Hepatosplenomegaly	29 (93.55)
Enlarged lymph nodes	20 (64.52)
Pancytopenia	13 (41.94)
AST > 60 U/l	24 (77.42)
Serum ferritin > 1500 ng/ml	27 (87.10)
Fibrinogen < 2.5 g/l	15 (48.39)
Triglyceride > 0.23 mmol/l	23 (74.19)
LDH > 159 U/l	27 (87.10)
Creatine kinase < 45 U/l	31 (100)
Hemophagocytosis	27 (87.10)

LDH: lactate dehydrogenase; AST: aspartate transaminase.

MAS is a complex complication of autoimmune disease. The genetic variation of main molecular participation in killing the target cell while treating with intracellular pathogens — the perforin 1 and granzyme B — may be involved in the occurrence of MAS in patients with sJIA. In our study, the A91V polymorphic fragments amplified by both primers were sequenced and no mutation was found. Ethnic and regional differences may play a role in the pathogenesis. Further studies and larger cohorts are required to make clear whether the A91V is pathogenic in MAS.

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