Letters to the Editor

Coexistence of familial Mediterranean fever and Sjögren's syndrome in a Japanese patient

Sirs,

The association with typical autoimmune diseases, such as lupus, has rarely been described in FMF (1), and the coexistence of FMF and Sjögren's syndrome (SS) has not been described. In this report, we present for the first time a Japanese FMF patient complicated by SS who was homozygous for the pyrin M6941 mutation. A 42-year-old Japanese woman was admitted to our hospital because of a recurrent high fever on June 12, 2006, She experienced monthly episodes of acute chest pain and fever lasting for 2-3 days and intermittent knee joint arthritis from the age of 20. She was first seen in a rheumatic clinic at the age of 35 with recurrent attacks of fever and knee joint arthritis. In a routine investigation, she tested positive for anti-nuclear antibody (x1280) and hypocomplementemia. A diagnosis of SLE was suspected, and prednisolone (20mg/day) was administered. However, recurrent fever continued.

Physical examination revealed neither skin sclerosis nor knee joint deformity. Oral mucosa was dry (Saxon test; 1.62ml/2min) and ophthalmologic examination revealed keratoconjunctivitis and positive results in the Schirmer's test (rt 4mm, lt 3mm). Routine hemogram and blood biochemistry were normal except for elevated levels of C-reactive protein and an elevated erythrocyte sedimentation rate (CRP 2.35mg/dl, ESR 48mm/hr). Renal function was normal (serum creatine 0.8mg/dl) and there was no abnormality in urine sediment. Serological examination revealed positive ANA with high titers (x1280, centromere pattern) and mild hypocomplementemia (CH50 26U/ml, normal range 28 ~ 48U/ml). Although neither anti-double-stranded DNA, anti-Ro/SS-A. anti-La/SSB nor anti-hepatitis C virus (HCV) antibodies were detected, anti-centromere antibodies and anti-β2-GPI antibodies were positive in high titers, with a concentration of 134EU/ml (normal range, 0-10EU/ml) and anti-β2-GPI antibodies measured at 27EU/ml (normal range, 0 ~ 3.5EU/ml). Sialography demonstrated apple tree-like changes, which are consistent findings of SS (Fig. 1). After informed consent was obtained, genomic DNA extracted from peripheral blood, followed by sequencing of all 10 exons of the MEFV gene (sequence of PCR primers and experimental condition will be reported elsewhere and are available upon request). We detected a homozygous mutation (ATG to ATA) in codon 694 in exon 10 of the MEFV gene that resulted in a substitution of isoleucine for methionine (M6941). A diagnosis of FMF complicated with SS was made and the patient was started on colchicine at a dose of 1.0mg/day taken orally. The patient demonstrated a stunning response to colchicine with complete cessation of recurrent high fever, chest pain and knee joint pain. Her elevated levels of ESR and CRP were normalized within a week. Interestingly, the marked elevated serum levels of serum amyloid A (SAA) and IL-18 were also reduced by this treatment (Table I).

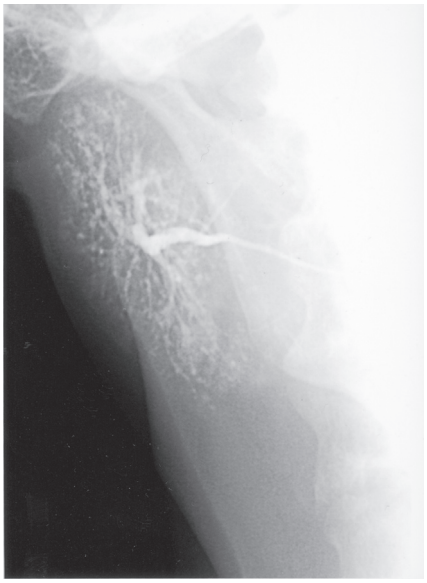

Fig 1.

Table I. The effects of colchicine on cytokines and SAA levels.

Variables	Before treatment (June 20, 2006)	After treatment (June 28, 2006)
CRP (mg/dl)	2.47	< 0.30
ESR (mm/hr)	45	11
SAA (μg/ml)	264	6.4
IL-1β (pg/ml)	< 10	< 10
IL-18 (pg/ml)	7950	1920
IL-6 (pg/ml)	2.5	1.2
TNF-α (pg/ml)	< 5	< 5

To our knowledge, this is the first case report in the literature in which SS is complicated in FMF. Anti-centromere antibody (ACA), which was detected in our case, has been accepted as a diagnostic marker of the CREST variant of scleroderma (2). SS is also accepted as a representative variant of ACA positive autoimmune disease (3). Our patient fulfilled the international diagnostic criteria for primary SS (4). We concluded that she was indeed suffering from FMF, and that subsequently the FMF was complicated with SS. FMF seems to be complicated by vasculitis syndrome, such as polyarteritis nodosa and Henoch-Schönlein purpura (5). The novel association between FMF and SS suggests the possibility that the FMF-related autoinflammation (6) could be linked to this rare association. It was suggested that IL-18 contributes to the cytokine network in the inflammatory cascade of FMF (7). Serum levels of IL-18 were predominantly elevated in our case. Therefore, it is possible that FMF-related dysregulated IL-18 production and chronic inflammation could be linked with the occurrence of SS in this case. This case prompted us to investigate the role of MEFV gene mutations in human autoimmune diseases.

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