HLA-B39 and Asymmetric Arthritis

Key words: juvenile rheumatoid arthritis, adult onset Still's disease, psoriatic arthritis

The diagnosis and treatment of rheumatic diseases are often complicated for physicians, because signs and symptoms of rheumatic diseases tend to be non-specific, including those of arthritis. However, even apparently non-specific symptoms such as those of arthritis can sometimes offer important clues to the diagnosis of rheumatic diseases.

Symmetric polyarthritis is characteristic of rheumatoid arthritis (RA). When polyarthritis is asymmetric, diseases other than RA such as juvenile rheumatoid arthritis (JRA) or seronegative spondyloarthritis (SNSA) should be considered.

JRA is the term for a group of diseases having in common idiopathic chronic synovitis in children, and such arthritis beginning after age 16 is called adult onset Still’s disease (AOSD). Whether JRA includes several distinct entities and whether it is a disease different from adult RA cannot be known until etiology and pathogenesis become clear. The American College of Rheumatology definition of JRA is the persistent arthritis of one or more joints for at least 6 weeks if other conditions causing or simulating arthritis are excluded. Subjective symptoms without objective joint findings are insufficient for diagnosis. Manifestations during the first 6 months of disease determine the 3 onset subtypes, systemic onset type, pauciarticular onset type, and polyarticular onset type.

JRA of the systemic onset type, called Still’s disease, is characterized by high spiking fever, lymphadenopathy, hepatosplenomegaly, polyserositis and typical skin salmon pink macules of variable size, appearing mostly on the trunk and proximal extremities, and less commonly on the face and distal extremities. The rash is evanescent, appears commonly with fever and rarely pruritic. Arthritis may not be apparent in the first weeks or months of disease. It can be a minor aspect of the illness occurring only during febrile flares, or it can progress to severe polyarthritis in about 20% of patients. Myalgias and myositis may be seen. Granulocytosis, thrombocytosis and increased C-reactive protein are characteristically observed.

JRA of the pauciarticular onset type is characterized by high incidence of chronic uveitis. Young age at onset (average 3 years), positive test for anti-nuclear antibody (ANA), and female sex are strong risk factors for uveitis. The knee is more commonly involved than the ankle, hip, elbow, wrist, and small joints of hands or foot. Arthritis is often asymmetrical and mild. Adolescent boys with involvement primarily of hips and knees often demonstrate sacroiliitis clinically or on X-ray. More than 50% are positive for HLA-B27, and a high proportion develop ankylosing spondylitis.

JRA of the polyarticular onset type is defined as involvement of 5 or more joints at onset. Rheumatoid factor-positive patients in this subset tend to be adolescents, often girls, and frequently have severe erosive arthritis similar to adult RA. Systemic symptoms are less severe. Rheumatoid factor-negative patients with polyarticular arthritis may present at any age in childhood, may be male or female, and less destructive arthritis.

AOSD, first described by Bywaters in 1971, is characterized by high spiking fever, arthritis, typical rash and lymphadenopathy (1). Laboratory abnormalities such as leukocytosis, increased C-reactive protein, anemia and abnormal liver tests are commonly seen. Joints such as wrists, knees, elbows, interphalangeal joints and ankles are frequently involved (2).

In this issue of Internal Medicine, Maeda et al (3) reported a family in which AOSD was seen in a young man and psoriatic arthritis was found in his father, and both were positive for HLA-B39.

See also p 77.

The HLA-B39 has been shown to be overrepresented in patients with psoriatic arthritis, HLA-B27-negative ankylosing spondylitis and JRA of pauciarticular onset type (4, 5). The association with AOSD has not been reported. However, patient 1 of ref. 3 has some common clinical features of JRA of the pauciarticular onset type including arthritis in large joints such as knees and ankles and uveitis. The typical skin rash usually present in AOSD was not found in this patient. Therefore, in addition to the diagnosis of AOSD, the diagnosis of JRA of the pauciarticular onset type plus JRA of the systemic onset type can be made for patient 1. This is consistent with the finding that adolescent boys with pauciarticular JRA are very often positive for HLA-B27 and the involvement primarily of hips and knees often demonstrate sacroiliitis clinically or on X-ray. The distinction between JRA of the systemic onset type, so-called Still’s disease, and AOSD is unclear at present clinically except for onset age.

The association of HLA-Bw16 (B38, B39) with HLA-B27 negative patients with ankylosing spondylitis was originally reported in Caucasians (6). The association of HLA-B39 with early-onset pauciarticular JRA (5, 7) and with spondylitis in patients with psoriatic arthritis (8) was also reported. The peptides possessing Arg at position 2 and hydrophobic/aromatic amino acids other than Tyr (most likely Phe or Leu) at the C-terminus presented on the cell surface in the context of HLA-
B27 and HLA-B39 have been proposed to be potentially arthritogenic (9). The son and father reported herein by Maeda et al (3) seemed to have a common genetic background, in which HLA-B39 presented potentially arthritogenic peptides to the T cells to evoke asymmetric, axial polyarthritis typically seen SNSA. A kind of a story of Klebsiella infection revisited.

Shunichi Shiozawa, MD, PhD
Kobe University School of Medicine Faculty of Health Science,
7-10-2 Tomogaoka, Suma-ku, Kobe 654-0142

References