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Decreased levels of serum soluble HLA class I antigens in HLA-B27 positive spondyloarthropathies

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Human leucocyte class I antigens (HLA-I) are expressed on the surface of all nucleated cells but can also be found in soluble forms. These soluble HLA-I (sHLA-I) molecules can be produced by either membrane shedding, proteolysis of the intact heavy chain, or by alternative splicing.¹ They have been implicated in regulatory functions and have immunomodulatory properties.² Increased levels of sHLA-I were found during graft rejections, in various infectious (cytomegalovirus, hepatitis B or C, HIV infection, active tuberculosis) and autoimmune diseases.^{3–6} In systemic lupus erythematosus and rheumatoid arthritis, levels of sHLA-I antigens correlate with disease activity.^{4,6} Spondyloarthropathies (SpA) are conditions closely linked to HLA-B27, a class I antigen. Thus, in this study, we evaluated the serum concentrations of sHLA-I antigens in a large cohort of patients with SpA.

One hundred and twenty three patients who met the European Spondylarthropathy Study Group criteria for SpA⁷ were assessed (table 1). Disease activity was evaluated by the Bath Ankylosing Spondylitis Disease Activity Index and laboratory measures of inflammation (erythrocyte sedimentation rate and serum C reactive protein). The control group comprised 102 healthy subjects (63 male; mean (SD) age 39.5 (3.4)) and included 23 HLA-B27 positive subjects. Determination of sHLA-I antigens was done by a sandwich enzyme linked immunosorbent assay (ELISA; using W6/32 and an anti-β₂-microglobulin polyclonal antibody; Bouts Laboratories, Milan, Italy).

Patients with SpA had decreased sHLA-I serum levels in comparison with healthy controls (mean (SD) 0.86 (0.6) v 1.18 (0.5) µg/ml; p = 0.0003) (fig 1). HLA-B27 positive SpA showed decreased sHLA-I concentrations in comparison with HLA-B27 negative SpA (0.79 (0.26) v 1.17 (0.7) µg/ml; p = 0.007), while there was no difference between HLA-B27 positive and HLA-B27 negative controls (1.24 (0.5) v 1.17 (0.5) µg/ml; p > 0.05). Furthermore, there was no significant difference in sHLA-I concentrations between HLA-B27 negative patients with SpA and HLA-B27 negative controls

(1.17 (0.7) v 1.17 (0.5) µg/ml p > 0.05), while HLA-B27 positive SpA still had decreased sHLA-I values in comparison with HLA-B27 positive controls (0.79 (0.26) v 1.24 (0.5) µg/ml; p = 0.006). We found no correlation between serum sHLA-I concentration and any of the laboratory and clinical indexes of disease activity (regression analysis, p > 0.05).

The significance and role of the sHLA-I antigens still remain unclear. They are present in several body fluids⁸ and in synovial fluid from various arthropathies.⁹ sHLA-I antigens can bind antigenic peptides and they probably have immunoregulatory functions by the inhibition of cytotoxic T lymphocytes and natural killer cells.^{1,2} Previous studies have suggested that sHLA-I might be used as marker of disease activity or as prognostic factor in autoimmune diseases.^{4,6} On the contrary, in our series of patients with SpA we observed decreased values of sHLA-I. These results were particularly evident in HLA-B27 positive patients with SpA while HLA-B27 did not influence the level of sHLA-I in controls. Thus, both the disease and the HLA-B27 antigen

Table 1 Clinical and biological characteristics of 123 patients with spondyloarthropathies (80 ankylosing spondylitis, 8 reactive arthritis, 4 psoriatic arthritis, 10 enteropathic arthritis and 21 undifferentiated SpA)

Age (years)	41.8 (1.3)
Sex (M/F)	80/43
Disease duration (years)	8.2 (7.7)
ESR (mm/1st h)	25.0 (26.1)
CRP (mg/l)	23.1 (41.7)
HLA-B27 (+/-/ND)	99/21/3
BASDAI (0–10)	4.9 (2.0)
Extra-articular manifestations, No (%)	47/123 (38)
Peripheral disease, No (%)	42/123 (34)

Results are shown as mean (SD), unless indicated otherwise. ESR, erythrocyte sedimentation rate; CRP, C reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ND, not determined.

Figure 1 Soluble HLA class I antigens (sHLA-I) were measured by ELISA in the serum from 123 patients with spondyloarthropathies and 102 healthy controls. Results, expressed in $\mu\text{g/ml}$, were compared (Student's *t* test) between these two groups and according to the presence or absence of the HLA-B27 antigen (SpA ($n=123$); controls ($n=102$); SpA B27+ ($n=99$); controls B27+ ($n=23$); SpA B27- ($n=21$); controls B27- ($n=79$)). NS, not significant; ** $p<0.01$; *** $p<0.005$. Horizontal lines represent mean values.

itself can explain this low production of sHLA-I. However, sHLA-I molecules could not be used as markers for the evaluation or for the follow up of these diseases.

Different factors have been related to the production of sHLA-I antigens: genetic backgrounds, HLA-I haplotypes, treatments such as non-steroidal anti-inflammatory drugs. HLA-B27 can form heavy chain homodimers,¹⁰ but it is not currently known whether these HLA-B27 homodimers might influence the release or production of sHLA-I. However, such a low level of serum sHLA-I in SpA may interfere with

immune regulation or cytotoxic T lymphocyte and natural killer cell control, and this might contribute to the pathophysiology of the SpA. Further studies are required to evaluate the soluble forms of HLA-B27.

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