

## HLA-B\*2709 and lack of susceptibility to sacroiliitis: further support from the clinic

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## ABSTRACT

*Interferons (IFN) are well known triggers of immunomediated diseases in genetically predisposed subjects. We describe the unique case of a HLA-B\*2709 positive subject who underwent IFN- $\alpha$  treatment for essential thrombocythemia and developed arthritis of the proximal interphalangeal joints of the hands but not sacroiliitis. The possible mechanisms of IFN-induced arthritis are discussed.*

## Introduction

In the recent past, increasing evidence has underlined differences between the various subtypes of the HLA-B27 alleles in conferring susceptibility to develop ankylosing spondylitis (AS). In particular two of the B27 subtypes so far defined (B\*2706 and B\*2709) have been claimed not to predispose to AS (1-2). Recently, two isolated cases of B\*2709 positive sacroiliitis have been reported, one by our group (3) and one by Olivieri *et al.* (4). It is noteworthy that the first case was also HLA-B\*1403, which is associated with AS in western Africans, while the second was a sacroiliitis in a patient with ulcerative colitis (characterised by a weaker B27 association). Nevertheless, the occurrence of these two cases have triggered new discussions among researchers on the significance of the lack of statistical association of the B\*2709 subtype and ankylosing spondylitis (5).

Interferon (IFN) therapy has been extensively shown to be able to induce, in genetically predisposed individuals, immune mediated diseases, such as thyroiditis, systemic lupus erythematosus, diabetes mellitus, psoriasis, peripheral arthritis and, noteworthy, sacroiliitis in B27 positive subjects (6-9). Furthermore, IFNs have been shown to be the strongest stimulus to enhance the promoter activity of HLA-B27 (10) and to induce a marked increase of the expression of  $\beta_2$ -microglobulin dissociated B27 molecules (which may play a role in AS pathogenesis) by *in vitro* experiments (Cauli *et al.* preliminary unpublished data).

Herein we describe the unique case of an HLA-B\*2709 positive subject who underwent IFN- $\alpha$  treatment for essential thrombocythemia and developed peripheral arthritis but not sacroiliitis.

## Case report

A 26-year-old woman was admitted to hospital (Haematology Unit) for laterocervical lymphadenopathy associated with fever, asthenia, thrombocytosis (518.000 platelets/ml) and hepatosplenomegaly. Platelets shortly increased to a peak value of 1.140.000/ml. Bone marrow aspirate for suspect chronic myeloid leukemia was negative and all the performed tests suggested the diagnosis of essential thrombocythemia. The patient was initially treated with acetylsalicylic acid and later, after plateletapheresis, was given 3 million units recombinant IFN- $\alpha$  daily. A positive response to therapy was obtained, with a fall in platelet levels to 390.000/mm<sup>3</sup>.

About 3 months later, in the course of IFN treatment, the patient developed peripheral arthritis affecting the proximal interphalangeal joints (PIP) of the right hand with swelling, pain and marked functional impairment associated with 3 hours morning stiffness. PIP of the left hand were also swollen and painful but less markedly. She then complained involvement of the right knee but never reported inflammatory back pain. The patient was referred to the Rheumatology Unit, IFN- $\alpha$  therapy was stopped but symptoms rapidly worsened and recurrence of high platelet counts was observed. Hand x-ray showed only swelling of soft tissues around PIP joints. Serological parameters and assays for the detection of infections remained negative. Rheumatoid factor testing was repeatedly negative. HLA typing was A3, 32; B27, 44; Cw1, 7; DRB1\* 12, 16; DQB1 03, 05. B27 subtype analysis demonstrated the B\*2709 subtype. Treatment was started with prednisolone 50mg/day (according to the haematology team) resulting in a rapid improvement of the platelet count and joint symptoms. The dosage of prednisolone was tapered and discontinued after 7 months. The patient is currently in clinical remission of the arthritis after four years from its presentation and she is continuing maintenance therapy with anagrelide for the haematological condition. Radiological follow-up, including sacroiliac joint CT scan performed after three years of the onset, confirmed the lack of axial involvement.

Competing interests: none declared.

## Discussion

Recombinant IFN- $\alpha$  use in clinical practice is relatively common. It has been suggested that in presence of HLA antigens predisposing to immunomediated diseases, IFN therapy represent an increased risk (6). This concept is also supported by the observation that in individuals carrying the "shared epitope" HLA phenotype (HLA DRB1\*0401, \*0404 and \*01 genes), who are predisposed to develop rheumatoid arthritis, the occurrence of symmetric polyarthritis (chronic or transient) has been observed following IFN treatment (7-8). Similarly, sacroiliitis has been reported after IFN therapy in B27 positive subjects (9). It is therefore conceivable that IFN- $\alpha$  may function as trigger for the development of immunomediated pathological processes, according to the subject predisposition.

The clinical case described in this report is peculiar and intriguing. The presence of the B27 antigen apparently predisposed this patient to an axial form of arthritis, but indeed the patient never complained of inflammatory back pain. Complete analysis of HLA class I and II antigens revealed the presence of the haplotype (A3, 32; B27, 44; Cw1, 7; DRB1\*12, 16; DQB1 03, 05) which in Sardinia harbours the B\*2709 subtype previously shown to be axial-sparing (11), and contains an HLA-E gene protective for the disease (12); indeed molecular subtyping of HLA-B27 in the patient showed the presence of B\*2709 subtype which in Sardinia is present in 20% of B27 positive healthy subjects compared to 3% in continental Italy. The reason for the different disease association is not understood but may be due to the absence of additional susceptibility genes co-inherited with B\*2705, and/or to different antigen binding properties of B\*2705 and B\*2709.

The mechanisms responsible for IFN induced arthritis are not well defined and still under debate. In this regard, it is noteworthy the work of Kerlan-Candon et al. who showed a specific overexpression of RA associated HLA-DR4 and DR1 molecules in RA patients compared with healthy individuals; this high expression of DR molecules at the surface of antigen presenting cells allows a

noteworthy presentation of low affinity peptides that under normal conditions are not efficient in generating a T cell response at physiologic surface density of the DR molecules (13). Furthermore Taurog and colleagues have shown that, in B\*2705 transgenic rats, the degree of susceptibility of the various animal lines to develop a spondyloarthropathy-like spectrum of lesions correlates with the level of B27 transgene expression at the mRNA and protein level (14). More recently our group has demonstrated a higher expression of HLA-B27 molecules on the surface of peripheral blood mononuclear cells of patients affected by AS compared with HLA-B27 positive normal controls, not due to cell activation (15). In light of these observations we can speculate that, in the course of therapeutic administration of IFN- $\alpha$  in predisposed subjects, an increased expression of HLA molecules (IFN- $\alpha$  induced) (10) may contribute to the development of arthritis. Of course we do acknowledge that the pathogenesis of arthritis is multifactorial and that other explanations are also possible. In this respect another mechanism, which is not alternative, suggests that IFNs activate macrophage-lineage cells, and that this contributes to the development of synovitis, perhaps via overproduction of pro-inflammatory mediators. Our B\*2709 positive patient did not develop spondylitis but a peripheral self-limiting form of arthritis. Furthermore a three year follow-up has shown neither recurrent nor chronic arthritis, nor radiological (CT) signs of sacroiliitis, as generally observed in HLA-B27 negative self-limiting reactive arthritis patients (16).

In conclusion, this report, although anecdotal, may support the concept that B\*2709 (and its HLA haplotype), in relation to genetic predisposition to spondylitis, may be neutral as the great majority of HLA-B alleles.

## References

1. KHAN MA, BALL EJ: Genetic aspects of ankylosing spondylitis. *Best Pract Res Clin Rheumatol* 2002; 16: 675-90.
2. MATHIEU A, SORRENTINO R: HLA-B\*2709 and Spondyloarthropathies. *Arthritis Rheum* 2003; 48: 866-7.
3. CAULI A, VACCA A, MAMELI A et al.: A Sardinian patient with ankylosing spondylitis and HLA-B2709 co-occurring with HLA-B\*1403. *Arthritis Rheum* 2007; 56: 2807-9.
4. OLIVIERI I, D'ANGELO S, SCARANO E, SANTOSPIRITO V, PADULA A: The HLA-B\*2709 subtype in a woman with early ankylosing spondylitis. *Arthritis Rheum* 2007; 56: 2805-7.
5. TAUROG JD: The mystery of HLA-B27: if it isn't one thing, it's another. *Arthritis Rheum* 2007; 56: 2478-81.
6. WATANABE U, HASHIMOTO E, HISAMITSU T, OBATA H, HAYASHI N: The risk factor for development of thyroid disease during interferon- $\alpha$  therapy for chronic hepatitis C. *Am J Gastroenterol* 1994; 89: 399-403.
7. LEVESQUE MC, WARD FE, JEFFERY DR, WEINBERG JB: Interferon-beta 1A-induced polyarthritis in a patient with the HLA-DRB1 0404 allele. *Arthritis Rheum* 1999; 42: 569-73.
8. RUSSO R, TENENBAUM S, MORENO MJ, BATTAGLIOTTI C: Interferon-beta 1a-induced juvenile chronic arteritis in a genetically predisposed young patient with multiple sclerosis: comment on the case report by Levesque et al. *Arthritis Rheum* 2000; 43:1190.
9. LOMBARDINI F, TAGLIONE E, RIENTE L, PASERO G: Psoriatic arthritis with spinal involvement in a patient receiving alpha-interferon for chronic hepatitis C. *Scand J Rheumatol* 1997; 26: 58-63.
10. ZHAO L, GRANFORS K, YU DTY: Analyses with a promoter reporter construct and its mutant showed that the response of the HLA-B27 gene to cytokines are both cytokine-specific and time dependent. *Arthritis Rheum* 2007; 56 (Suppl.): 569.
11. FIORILLO MT, CAULI A, CARCASSI C et al.: Two distinctive HLA haplotypes harbor the B27 alleles negatively or positively associated with Ankylosing Spondylitis in Sardinia: implications for disease pathogenesis. *Arthritis Rheum* 2003; 48: 1385-9.
12. CASCINO I, PALADINI F, BELFIORE F et al.: Identification of previously unrecognized predisposing factors for ankylosing spondylitis from analysis of HLA-B27 extended haplotypes in Sardinia. *Arthritis Rheum* 2007; 56: 2640-51.
13. KERLAN-CANDON S, LOUIS-PLENCE P, WIEDEMANN A et al.: Specific overexpression of rheumatoid arthritis-associated HLA-DR alleles and presentation of low affinity peptides. *Arthritis Rheum* 2001; 44: 1281-92.
14. TAUROG JD, MAIKA SD, SIMMONS WA, BREBAN M, HAMMER RE: Susceptibility to inflammatory disease in HLA-B27 transgenic rat lines correlates with the level of B27 expression. *J Immunol* 1993; 150: 4168-78.
15. CAULI A, DESSOLE G, FIORILLO MT et al.: Increased level of HLA-B27 expression in ankylosing spondylitis patients compared with healthy HLA-B27 subjects: a possible further susceptibility factor for the development of disease. *Rheumatology* 2002; 41: 1375-9.
16. LERISLAO M, SKYLV G, KOUSA M et al.: Follow-up study on patients with Reiter's disease and reactive arthritis, with special reference to HLA-B27. *Arthritis Rheum* 1982; 25: 249-59.