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Competing interests: None declared.

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Accepted 23 April 2006

REFERENCES

- 1 **Drenth JP**, Cuisset L, Grateau G, Vasseur C, van de Velde-Visser SD, de Jong JG, *et al*. Mutations in the gene encoding mevalonate kinase cause

hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. *Nat Genet* 1999;**22**:178–81.

- 2 **Drenth JP**, Haagsma CJ, van der Meer JW. Hyperimmunoglobulinemia D and periodic fever syndrome. The clinical spectrum in a series of 50 patients. International Hyper-IgD Study Group. *Medicine (Baltimore)* 1994;**73**:133–44.
- 3 **Simon A**, Mariman EC, van der Meer JW, Drenth JP. A founder effect in the hyperimmunoglobulinemia D and periodic fever syndrome. *Am J Med* 2003;**114**:148–52.
- 4 **Topaloglu R**, Saatci U. Hyperimmunoglobulinemia D and periodic fever mimicking familial Mediterranean fever in the Mediterranean. *Postgrad Med J* 1991;**67**:490–1.
- 5 **Miyagawa S**, Kitamura W, Morita K, Saishin M, Shirai T. Association of hyperimmunoglobulinemia D syndrome with erythema elevatum diutinum. *Br J Dermatol* 1993;**128**:572–4.
- 6 **Hammoudeh M**. Hyperimmunoglobulinemia D syndrome in an Arab child. *Clin Rheumatol* 2005;**24**:92–4.
- 7 **Klasen IS**, Goertz JH, van de Wiel GA, Weemaes CM, van der Meer JW, Drenth JP. Hyper-immunoglobulin A in the hyperimmunoglobulinemia D syndrome. *Clin Diagn Lab Immunol* 2001;**8**:58–61.

HLA-DRB genotyping of an Italian mummy from the 16th century with signs of rheumatoid arthritis

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Ann Rheum Dis 2006;**65**:1676–1677. doi: 10.1136/ard.2006.051490

Some paleopathological studies suggest that rheumatoid arthritis originated in the New World (among ancient Native Americans in Tennessee and neighbouring areas, 5000–500 BC); only after the discovery of America was the origin of the disease attributed to the Old World.¹ In 1996, under the floors of the San Francisco church (Arezzo, Italy), a female mummy was discovered. This 50–55-year-old woman, re-named the “Braids Lady”, died at the end of the 16th century. Several diagnostic examinations disclosed distinctive rheumatoid arthritis skeletal deformities due to rheumatoid arthritis in her body: large erosions of the metacarpophalangeal joints of the left hand; lateral deviation of all the fingers, with a typical “Z” deformation of the first one; and partial overlapping and fibular deviation of the toes, but no involvement of sacroiliac articulation, a prominent symptom of ankylosing spondylitis.²

It is well known that several autoimmune disorders are related to highly polymorphic and codominantly expressed antigens encoded by the human leucocyte antigen (HLA) complex. The association between rheumatoid arthritis and some of the alleles of the HLA-DRB1 locus, such as DRB1*0101, DRB1*0401, DRB1*0404, DRB1*0405, DRB1*1402, and to a lesser degree DRB1*1001, has been well established. A high percentage (>90%) of people affected by this disorder possess some alleles of the DRB1*01 or DRB1*04 gene families.³ Therefore, the purpose of this study was to define the HLA-DRB genotype of the “Braids Lady” and establish the presence or not of rheumatoid arthritis susceptibility genes. Molecular analysis was performed on DNA extracts of the mummy, and two different HLA typing techniques, polymerase chain reaction-sequence-specific oligonucleotides (PCR-SSO) and PCR-sequence-specific primers (PCR-SSP), were used to identify HLA-DRB alleles. The PCR-SSO analysis showed the presence of the DRB1*0101 and DRB1*1101 alleles (corresponding to DR1 and DR11 serotypes, respectively), with positivity for the DRB3 gene (phenotypically DR52). The assignment of the allele DRB1*0101 was confirmed by the results of the PCR-SSP test.

A pathogenetic hypothesis of rheumatoid arthritis that might well explain its worldwide diffusion is “molecular mimicry”, resulting from a cross-reactive antibody response

between certain microbial antigens (among which are *Proteus mirabilis* haemolysins and Epstein–Barr virus glycoprotein 110) and shared epitopes of some specific HLA-DR1, DR4 and DR14 susceptibility genes.^{4–6} Additionally, HLA-DRB1 alleles and the frequency of their shared epitopes may vary between different ethnic groups. For example, DRB1*0101, DRB1*0401, and *0404–05 share the epitope Q(K/R)RAA, which is associated with rheumatoid arthritis in Mediterranean patients, including Italians;⁷ DRB1*1402, 0802 and 0407, on the other hand, are absent or poorly represented in the Italian population, have a significantly higher gene frequency among Native Americans than other DRB1 alleles (Navajo and Pimans of the Gila River Indian community of Arizona, the Lakota Sioux, the Seri tribe of Northwest Mexico).^{8,9} Interestingly, among patients with rheumatoid arthritis from several Native American groups, neither HLA-DR1 nor DR4 was found to be associated with specific features of rheumatoid arthritis or the severity of the disease.¹⁰ Hence, it is more than probable that various aetiological agents could have acted on different susceptibility HLA alleles bearing shared epitopes and occurring with different frequencies within populations. Although the possession of rheumatoid arthritis risk-factor genes cannot be considered a diagnostic marker, the positive result for DRB1*0101 and the presence of rheumatoid arthritis features in the Italian mummy support the idea that this disease was present in the Old World since at least the mid-16th century.

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Abbreviations: HLA, human leucocyte antigen

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Accepted 21 May 2006

REFERENCES

- 1 Rothschild BM, Woods RJ, Rothschild C, Sebes JL. Geographic distribution of rheumatoid arthritis in ancient North America: implication for pathogenesis. *Semin Arthritis Rheum* 1992;22:181–7.
- 2 Ciranni R, Garbini F, Neri E, Melai L, Giusti L, Fornaciari G. The "Braids Lady" of Arezzo: a case of rheumatoid arthritis in a 16th century mummy. *Clin Exp Rheumatol* 2002;20:745–52.
- 3 Gonzalez-Gay MA, Garcia-Porrúa C, Haajer AH. Influence of human leukocyte antigen-DRB1 on the susceptibility and severity of rheumatoid arthritis. *Semin Arthritis Rheum* 2002;31:355–60.
- 4 Nepom GT, Hansen JA, Nepom BS. The molecular basis for HLA class II associations with rheumatoid arthritis. *J Clin Immunol* 1987;7:1–7.
- 5 Roudier J, Petersen J, Rhodes GH, Luka J, Carson DA. Susceptibility to rheumatoid arthritis maps to a T-cell epitope shared by the HLA-Dw4 DRB-1 chain and the Epstein-Barr virus glycoprotein gp110. *Proc Natl Acad Sci USA* 1989;86:5104–8.
- 6 Ebringer A, Cunningham P, Ahmadi K, Wrigglesworth J, Hosseini R, Wilson C. Sequence similarity between HLA-DR1 and DRA subtypes associated with rheumatoid arthritis and Proteus/Serratia membrane haemolysins. *Ann Rheum Dis* 1992;51:1245–6.
- 7 Bongi SM, Porfirio B, Rombola G, Palasciano A, Beneforti E, Bianucci G. Shared-epitope HLA-DRB1 alleles and sex ratio in Italian patients with rheumatoid arthritis. *Joint Bone Spine* 2004;71:24–8.
- 8 Williams RC, Jacobsson LT, Knowler WC, del Puente A, Kostyu D, McAuley JE, et al. Meta-analysis reveals association between most common class II haplotype in full-heritage Native Americans and rheumatoid arthritis. *Hum Immunol* 1995;42:90–4.
- 9 Leffell MS, Fallin MD, Hildebrand WH, Cavett JW, Iglehart BA, Zachary AA. HLA alleles and haplotypes among the Lakota Sioux: report of the ASHI minority workshops, part III. *Hum Immunol* 2004;65:78–89.
- 10 Templin DW, Boyer GS, Lanier AP, Nelson JL, Barrington RA, Hansen JA, et al. Rheumatoid arthritis in Tlingit Indians: clinical characterization and HLA associations. *J Rheumatol* 1994;21:1238–44.

Successful treatment of cerebral vasculitis in an HIV-positive patient with anti-CD25 treatment

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Ann Rheum Dis 2006;65:1677–1678. doi: 10.1136/ard.2005.044867

A 33-year-old HIV-seropositive man presented with recurrent oral candidiasis, weight loss, and lymphadenopathy.¹ CD4 count was 73 cells/ml, and viral load was 296 000 copies/ml. Zidovudine, lamivudine and efavirenz were started, after which the patient showed an increase in CD4 count to 444 cells/ml. In the following weeks he developed progressive paresis of his left arm, left-sided facial weakness, bulbar dysarthria and dysphagia, which remitted when highly active antiretroviral therapy (HAART) was discontinued. However, his condition worsened again on resumption of HAART. Laboratory results showed a CD4 count of 441 cells/ml, a viral load of 105 copies/ml, a C reactive protein concentration of 18 mg/l and a sedimentation rate of 107 mm in the first hour. Serological tests for hepatitis B, hepatitis C and syphilis were negative, as were those for ANA, ANCA, rheumatoid factor and cryoglobulins. Complement (CH50) was normal. Magnetic resonance imaging of the brain showed bilateral hyperintense lesions on T2 images in the frontoparietal cortex. Brain biopsy showed lymphocytic vasculitis,² mainly of small vessels, with predominantly CD3 cells, some CD68 macrophages and some CD20 plasma cells. Giant cells were absent, and specific staining for fungi, acid-fast bacilli, cytomegalovirus, human simian virus, Fe and p24 antigen was negative. Polymerase chain reaction was positive for *Mycobacterium chelonae*, but cultures remained negative. Abavavir, lamivudine and nelfinavir were continued. The patient was treated with 1000 mg/day solumedrol for 3 days, followed by 40 mg prednisone, with an initially good response. When prednisone was tapered to 25 mg, his symptoms recurred. To exclude mycobacterial immune restoration vasculitis, the patient received clarithromycin 1000 mg/day for 10 weeks, without any neurological improvement. Subsequently, he was treated with prednisone with mycophenolate mofetil 1000 mg twice daily for 6 months, prednisone with azathioprine 2 mg/kg for 6 months, and prednisone with azathioprine and ciclosporin A 2 mg/kg. Under each regimen, his symptoms recurred when prednisone was tapered to 25 mg. Phenotypic analysis of PBMCs under immunosuppression showed 443 CD4 cells/μl (normal 224–1471 cells/μl) with 50%

CD25 positivity (normal 2.4–35.2%), and 1157 CD8+ cells/μl (normal 158–648 cells/μl) with 20% CD25 positivity (normal 0–10.5%). We postulated that activated, CD25-expressing T cells played an important part in the pathogenesis of his immunorestitution cerebral vasculitis. Therefore, we started treatment with daclizumab after the patient gave informed consent. Treatment consisted of 1 mg/kg on days 1 and 14, whereas prednisone, ciclosporin A and azathioprine were tapered. Single-dose infusions (1 mg/kg) were given 8 and 12 months after initial treatment. Subsequently, prednisone could be stopped. CD4 cell counts stabilised to between 400 and 600 cells/ml, whereas CD25 T cells dropped dramatically after each infusion (fig 1). Viral load and autoantibodies were undetectable. The disease course was complicated by cutaneous varicella zoster infection (2 years after neurological symptoms), condylomata acuminata (after 3 years) and verrucae vulgaris.

Daclizumab is a human immunoglobulin G1-κ recombinant antibody that binds CD25, the IL2 α-chain expressed on activated T cells. It interferes with T cell proliferation and survival, and has been successful in steroid-free anti-rejection regimens in renal allografts and in several immunological disorders, including autoimmune uveitis,³ graft-versus-host disease,⁴ pemphigus vulgaris,⁵ a hemophagocytic lymphohistiocytosis,⁶ ulcerative colitis⁷ and multiple sclerosis.⁸

Daclizumab interferes either by promoting death by antagonising the anti-apoptotic effect of IL2 or by competitive binding for the receptor, leading to cytokine-starvation-induced death. In HIV, CD25 is up regulated during reconstitution of the CD4 compartment on HAART. Recall responses to persistent (auto)antigens are reconstituted and associated with increased production of IL2.⁹ This might explain the development of immune restoration cerebral vasculitis on starting HAART, as well as the development of other forms of autoimmunity after immune reconstitution in patients infected with HIV. CD25 is also expressed on regulatory T cells; thus, daclizumab treatment might be complicated by autoimmune phenomena, as autoimmunity has been described in animal models where regulatory T cells