Regulated upon activation normal T-cell expressed and secreted (RANTES) and epithelial cell-derived neutrophil-activating peptide (ENA-78) gene polymorphisms in patients with biopsy-proven erythema nodosum

Sirs,

Erythema nodosum (EN) is generally a benign and self-limiting hypersensitivity reaction characterized by multiple and bilateral non-ulcerating lesions (1). It is the most common cause of inflammatory nodules occurring usually in the legs. A biopsy of the nodules shows acute or granulomatous septal panniculitis with primary leukocyte inflammation around the veins of the septal system (1). EN may be idiopathic or secondary to a wide variety of diseases (1,2). Chemokines are implicated in many pathological conditions including inflammation and autoimmunity (3). They consist of 70-130 amino acids characterized by the presence of conserved cysteines linked by disulfide bonds (3). They are chemotactic cytokines that activate and direct the migration of leukocytes. Chemokines act on responsive leukocyte subsets through G-protein-coupled transmembrane receptors (3). Thus, chemokines and chemokine receptors are involved in the leukocyte trafficking across different compartments from the tissue of origin and the blood to sites of homing, host defense, or disposal.

Since chemokines play an important role in the inflammatory development and progression of autoimmune diseases, investigation of the regulatory factors implicated in the expression of chemokines may be important for our understanding of the pathogenesis of EN. In this regard, in previous studies we determined the potential influence of the polymorphisms of the regulated upon activation normal T-cell expressed and secreted *(RANTES)* gene (a CC chemokine) and the epithelial cell-derived neutrophil-activating peptide *(ENA-78)* gene (a CXC chemokine) in the susceptibility to different autoimmune diseases in individuals from Northwestern Spain. In assessing the implication ofabiallelic (G/A) polymorphism occurring within the promoter region of the RANTES gene (position-403), we found a significant increase in the frequency of the allele A in patients with polymyalgia rheumatica compared with normal controls (4). Moreover, a marginal increase of this allele frequency was also observed in patients with rheumatoid arthritis (4). In contrast, no association of this biallelic polymorphism was found in patients with biopsy-proven giant cell arteritis (4) or Henoch-Schonlein purpura (5). We also studied whether a biallelic (-156 G/C) polymorphism in the promoter region of the *ENA-78*gene might be implicated in the susceptibility to different autoimmune disease in the population from Northwestern Spain. However, this polymorphism was not associated with susceptibility to Henoch-Schonlein purpura (5) or biopsy-proven giant cell arteritis (6).

In the present study we have examined, for first time, the potential influence of the polymorphism of the *RANTES* gene and the *ENA-78* gene in the susceptibility and clinical spectrum of patients with biopsy-proven EN from our well-defined population (7).

Ninety-nine consecutive patients with biopsy-proven EN and 107 ethnically matched controls from the Lugo region in Galicia (Northwestern Spain) were genotyped for a biallelic (-403 G/A) polymorphism in the promoter region of the *RANTES* gene and for detection of the promoter (-156 G/C) polymorphism in the *ENA-78* gene as previously reported (4-6).

Clinical data of the patients included in the present study have previously been described (7, 8).

Briefly, 35 patients were diagnosed as having idiopathic EN. The remaining 64 patients were diagnosed with EN secondary to sarcoidosis (n=31) or developed EN in the context of other conditions (n=33) (7, 8). Informed consent and ethical approval was obtained.

In controls no evidence of departure from Hardy-Weinberg equilibrium was observed. As shown in Table I, no significant differences in the allele and genotype distribution of the *RANTES* gene *(-403 G/A)* and the *ENA-78* gene (-156 C/G) promoter polymorphisms between patients with EN and controls were observed.

As described for other gene polymorphisms implicated in the inflammatory response (8), the clinical heterogeneity of conditions presenting with EN may explain the negative association observed between these two chemokine gene polymorphisms and our series ofunselected patients with EN.

Since we have previously observed differences in the polymorphism of some genes implicated in the immune response between patients with EN associated to sarcoidosis and those with idiopathic EN or EN secondary to other conditions (9-11), in the present study we also compared patients with EN secondary to sarcoidosis with the remaining biopsy-proven EN patients. However, no significant differences in the allele or genotype frequencies for these two chemokine

Table I. Allele and genotype frequencies of the *RANTES (-403) (G/A)* and *ENA-78 (G/C)* gene polymorphisms in patients with biopsy-proven erythema nodosum (EN) and controls from Northwestern Spain*.

	Controls	EN Total	EN Idiopathic	EN Secondary	EN due to Sarcoidosis	EN secondary to other conditions
Gene polymorphism						
RANTES (-403)						
Genotype	66 (%)	99 (%)	35 (%)	64 (%)	31 (%)	33 (%)
GG	51 (77)	73 (74)	26 (74)	47 (73)	23 (74)	24 (73)
GA	15 (23)	26 (26)	9 (26)	17 (27)	8 (26)	9 (27)
AA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Allele (2N)	132 (%)	198 (%)	70 (%)	128 (%)	62 (%)	66 (%)
G	117 (89)	172 (87)	61 (87)	111 (87)	54 (87)	57 (86)
A	15 (11)	26 (13)	9 (13)	17 (13)	8 (13)	9 (14)
ENA 78 (-156)						
Genotype	107 (%)	97 (%)	35 (%)	62 (%)	29 (%)	33 (%)
GG	79 (74)	77 (79)	28 (80)	48 (78)	22 (76)	26 (78)
GC	25 (23)	20 (21)	7 (20)	14 (22)	7 (24)	7 (22)
CC	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Allele (2N)	214 (%)	194 (%)	70 (%)	124 (%)	58 (%)	66 (%)
G	183 (86)	174 (90)	63 (90)	110 (89)	51 (88)	59 (89)
C	31 (14)	20 (10)	7 (10)	14 (11)	7 (12)	7 (11)

*No statistically significant differences were found.

gene polymorphisms were found (Table I). Since the pathologic processes involved in autoimmune diseases such as EN are complex, further studies are required to assess the relative contribution of gene polymorphisms of other mediators involved in the immune and inflammatory response in the pathogenesis of EN.

M.M. AMOLI, *MD, PhD*[1,2]
J.A. MIRANDA-FILLOY, *MD*[3]
T.R. VAZQUEZ-RODRIGUEZ, *MD*[3]
W.E.R. OLLIER, *PhD*[1]
M.A. GONZALEZ-GAY, *MD, PhD*[3]

[1]The Centre for Integrated Genomic Medical Research, School of Epidemiology, and Health Sciences, the University of Manchester, Manchester, United Kingdom; [2]Endocrinology and Metabolism Research Centre, Tehran University of Medical Sciences, Tehran, Iran; and [3]Rheumatology Division, Hospital Xeral-Calde, Lugo, Spain.

Address correspondence to:
Miguel A. Gonzalez-Gay, MD, PhD, Rheumatology Division. Hospital Xeral-Calde. c) Dr. Ochoa s/n, 27004 Lugo, Spain.
E-mail: miguelaggay@hotmail.com

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