Interleukin-6 promoter polymorphism at position -174 in biopsy-proven patients with erythema nodosum from a defined population

Sirs,

Erythema nodosum (EN) is the most common type of panniculitis (1). It may be idiopathic or secondary to a wide variety of diseases (2). A question still unanswered is whether polymorphisms of proinflammatory cytokine genes may mediate an abnormal inflammatory response leading to the development of EN.

In the present study we aimed to assess the potential role of the *IL-6 gene (-174 G/C*) promoter polymorphism in the pathogenesis of EN. Since we have previously reported some immunogenetic differences between idiopathic and secondary EN, in particular in those cases associated to sarcoidosis (3, 4), we also studied whether potential differences in the *IL-6 gene (-174 G/C*) promoter polymorphism might be useful to discriminate patients with EN associated to sarcoidosis from other patients presenting with EN.

As previously described (5), 100 consecutive patients with biopsy-proven EN and 118 ethnically matched controls from the Lugo region in Galicia (Northwestern Spain) were genotyped for a single biallelic (G/C) nucleotide polymorphism in the promoter region at the position -174 of the IL-6 gene by a polymerase reaction chain-restriction fragment length polymorphism method. Informed consent was obtained to perform this study.

Clinical data of the patients included in the present study have previously been reported (6, 7). Thirty-six 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) such as an infectious diseases, drug-intake, and more rarely, in the setting of an inflammatory bowel disease or Sweet's syndrome (3, 4, 6, 7).

In controls, no evidence of departure from Hardy-Weinberg equilibrium was observed. No significant differences in the allele and genotype distribution of the *IL-6 gene (-174 G/C)* between patients with EN and controls were observed (Table I).

However, the genotype distribution differed significantly in patients with EN secondary to sarcoidosis from that observed in patients with idiopathic EN and EN secondary to other conditions different from sarcoidosis (p=0.036) (Chi-square) (Table I). In this regard, 6 of the 10 patients from the whole series of 100 biopsy-proven EN who carried the homozygous CC genotype were diagnosed with sarcoidosis (CC *vs*. GG+GC in the 31 patients with EN secondary to sarcoidosis compared with the remaining 69 EN patients: p=0.038; OR: 3.90 [95%CI: 1.01- 14.99]) (Fisher exact test) (Table I).

Interestingly, Maver *et al*. showed an increased frequency of IL-6/-174C allele and also an increased genotype frequency of IL-6/-174 CC and CG carriers among sarcoidosis patients compared to healthy controls (8). Also, Grutters *et al*. showed that the IL6-174C allele might have a role in the genetics underlying sarcoidosis severity or the progression towards pulmonary fibrosis in a particular subgroup of patients with sarcoidosis (9).

As observed for other gene polymorphisms (10), the clinical heterogeneity of conditions presenting with EN might explain the negative association observed between the *IL-6 gene (-174 G/C*) promoter polymorphism and EN when our series of unselected patients with biopsy-proven EN where assessed altogether. However, the present study does not support a role of the *IL-6 gene (-174 G/C*) polymorphism in the susceptibility to develop EN in patients with idiopathic (primary) EN from Northwestern Spain. In contrast, our results show that IL-6/-174 CC genotype characterizes a subgroup of patients who are at higher risk of developing EN in the setting of sarcoidosis. In any case, further controlled studies of biopsy-proven EN patients must be performed to confirm these results.

M.M. AMOLI[1,2], *MD, PhD*
J.A. MIRANDA-FILLOY[3], *MD*
M.L. FERNANDEZ-DIAZ[4], *MD*
J. MARTIN[5], *MD, PhD*
W.E.R. OLLIER[1], *PhD*
M.A. GONZALEZ-GAY[3], *MD, PhD*

From [1]the Centre for Integrated Genomic Medical Research, School of Epidemiology, and Health Sciences, the University of Manchester, Manchester, United Kingdom; [2]the Endocrinology and Metabolism Research Centre, Tehran University of Medical Sciences, Tehran, Iran; the [3]Rheumatology and [4]Dermatology Divisions, Hospital Xeral-Calde, Lugo, Spain; [5]CSIC, Granada, 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

Competing interests: none declared.

References

1. GONZALEZ-GAY MA, GARCIA-PORRUA C, PUJOL RM, SALVARANI C: Erythema nodosum: a clinical approach. *Clin Exp Rheumatol* 2001; 19: 365-8.
2. MERT A, KUMBASAR H, OZARAS R, ERTEN S, TASLI L, TABAK F, OZTURK R: Erythema nodosum: an evaluation of 100 cases. *Clin Exp Rheumatol* 2007; 25: 563-70.
3. AMOLI MM, DONN RA, THOMSON W *et al.*: Macrophage migration inhibitory factor gene polymorphism is associated with sarcoidosis in biopsy-proven erythema nodosum: *J Rheumatol* 2002; 29: 1671-3.
4. AMOLI MM, LLORCA J, GOMEZ-GIGIREY A *et al.*: E-selectin polymorphism in erythema nodosum secondary to sarcoidosis. *Clin Exp Rheumatol* 2004; 22: 230-2.
5. AMOLI MM, MARTIN J, MIRANDA-FILLOY JA, GARCIA-PORRUA C, OLLIER WE, GONZALEZ-GAY MA: Lack of association between interleukin-6 promoter polymorphism at position -174 and

Table I. Allele and genotype frequencies of the *IL-6–174 (G/C)* polymorphism at the promoter region in biopsy-proven erythema nodosum (EN) patients and controls from Northwestern Spain*.

	Controls *	EN Total *	EN Idiopathic¶ a)	EN Secondary	EN due to Sarcoidosis¶	EN secondary to other conditions¶ b)
No. individuals	118 (%)	100 (%)	36 (%)	64 (%)	31 (%)	33 (%)
Genotype						
GG	54 (45)	53 (53)	22 (61)	31 (48)	18 (58)	13 (39)
GC	51 (43)	37 (37)	13 (36)	24 (38)	7 (23)	17 (52)
CC	13 (11)	10 (10)	1 (3)	9 (14)	6 (19)	3 (9)
Allele (2N)	236 (%)	200 (%)	72 (%)	128 (%)	62 (%)	66 (%)
G	159 (67)	143 (72)	57 (79)	86 (67)	43 (69)	43 (65)
C	77 (33)	57 (28)	15 (21)	42 (33)	19 (31)	23 (35)

* No statistically significant differences between the whole group of EN patients and controls were found. ¶ EN secondary to sarcoidosis compared to EN related to other etiologies (¶ a) Idiopathic + ¶ b) secondary to other conditions different from sarcoidosis): Genotype distribution; p= 0.036.
Distribution of CC genotype versus GC+GG genotypes in patients with EN secondary to sarcoidosis compared with EN due to other etiologies (Idiopathic + secondary to other conditions different from sarcoidosis): p= 0.038; OR: 3.90 [95%CI: 1.01- 14.99]).