Interleukin-1 beta gene polymorphism in patients with biopsy-proven erythema nodosum

Sirs,

Erythema nodosum (EN), the most common cause of inflammatory nodules, is generally a benign and self-limiting hypersensitivity reaction characterised by multiple and bilateral non-ulcerating tender lesions (1). Biopsy 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 broad variety of conditions (1, 2).

Susceptibility to EN and associated clinical heterogeneity in patients with this condition may be conferred by a number of genetic loci. The interleukin-1 (IL-1) family of proteins has a major role in the inflammatory response. IL-1 promotes leukocyte extravasation by inducing the expression of adhesion molecules such as ELAM-1 (E-selectin) and ICAM and induces the production of IL-8 by endothelial cells (3). Upregulated expression of proinflammatory cytokines such as TNF, IL-6 and IL-1 has been reported in vasculitis syndromes.

Several single nucleotide polymorphisms have been found in the IL-1beta gene. A biallelic polymorphisms in the IL-1beta gene at position -511 has been described (4). This (-511C/T) polymorphism in the IL-1beta gene is thought to influence IL-1 beta production and it has been assessed in both autoimmune and non-inflammatory conditions (5). In this regard, an association of this polymorphism with severe renal manifestations and renal sequelae in patients with Henoch-Schönlein purpura was reported (6). Also, the IL-1 beta promoter (-511C/T) polymorphism was found to be an independent risk factor for association with Alzheimer's disease (7). This pro-inflammatory polymorphism in the IL-1 beta promoter gene is also associated with increased host susceptibility to Helicobacter pylori infection in Chinese people (8), and increased risk of reflux esophagitis in Taiwanese individuals (9). Also an epistatic interrelationship between IL-1beta (-511C/T) and interleukin-1 receptor antagonist gene polymorphisms was found to confer protection against gastric cancer in a low-risk Italian population (10). However, this IL-1beta promoter polymorphism was not associated with the development of amyloidosis in familial Mediterranean fever patients (11).

In the present study we have examined for the first time the potential influence of IL-1 beta gene (-511C/T) polymorphism in a series of patients with biopsy-proven EN from a well-defined population (12).

Ninety-nine consecutive patients with biopsy-proven EN and 148 ethnically matched controls from the Lugo region in Galicia (Northwestern Spain) were genotyped for IL-1beta gene (-511C/T) polymorphism by a polymerase chain reaction-restriction fragment as previously reported (6).

Clinical data of the patients included in the present study have previously been described (12, 13). Thirty-five 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 setting of other conditions (n=33). Informed consent and ethical approval was obtained.

In controls no evidence of departure from Hardy-Weinberg equilibrium was observed.

Although biopsy-proven EN showed an increased frequency of CC homozygous compared to controls (58% *vs*. 45%; odds ratio [OR]: 1.64 [95 CI: 0.98–2.74] – Woolf; p=0.06) the genotype distribution did not show statistically significant differences (p=0.17) (Table I). It was also the case when allele frequencies were compared (Table I). In this regard, allele C frequency was increased in EN patients (74%) compared to controls (66%), but the difference was out of the range of significance (OR: 1.43 [95% CI: 0.96–2.13]; p=0.08). As discussed for other gene polymorphisms implicated in the inflammatory response (13), the clinical heterogeneity of conditions presenting with EN may explain the negative association observed between the IL-1beta gene (-511C/T) polymorphism and our series of unselected patients with EN. These results are consitent with a recent study of our group that showed no association between an 86-base pair tandem repeat polymorphism in intron 2 of IL-1 receptor antagonist gene and biopsy-proven EN (14).

We previously reported differences in the polymorphism of some genes implicated in the immune response when patients with EN associated to sarcoidosis were compared with those diagnosed with idiopathic EN or with EN secondary to other conditions (15-17). Therefore, we specifically 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 the IL-1beta gene (-511 C/T) polymorphism were found (Table I).

Table I. Frequency of IL-beta gene (-511C/T) polymorphism in biopsy-proven erythema nodosum (EN) patients and controls from northwestern Spain*.

	Controls*	EN Total*	EN Idiopathic	EN Secondary	EN due to Sarcoidosis	EN secondary to other conditions
No. individuals	148 (%)	99 (%)	35 (%)	64 (%)	31 (%)	33 (%)
Allede						
C	196 (66%)	146 (74%)	51 (73 %)	95 (74%)	46 (74%)	49 (74%)
T	100 (34%)	52 (26%)	19 (27 %)	33 (26%)	16 (26%)	17 (26%)
Genotype						
CC	67 (45%)	57 (58%)	21 (69%)	36 (56%)	17 (55%)	19 (58%)
CT	62 (42%)	32 (32%)	9 (26%)	23 (36%)	12 (39%)	11 (33%)
TT	19 (13%)	10 (10%)	5 (14%)	5 (8%)	2 (6%)	3 (9%)

*No statistically significant differences between the whole group of EN patients and controls was found.

Since complex pathologic mechanisms are involved in the development of EN, more studies are required to establish the implication of different gene polymorphisms of other immune and inflammatory mediators in the pathogenesis of EN.

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