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

Sirs,

Erythema nodosum (EN) is generally a benign and self-limiting hypersensitivity reaction characterised 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 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. Interleukin-1 receptor antagonist (IL1-Ra) is an endogenous antiinflammatory agent that binds to IL-1 receptor and thus competitively inhibits the binding of IL1-alpha and IL1-beta (3). The gene for IL-1ra is mapped to chromosome 2q14-q21 (4). Tarlow *et al*. described a variable copy numbers of an 86-base pair tandem repeat (VNTR polymorphism) in intron 2 of this gene. Five alleles of this polymorphism have been described (5). Allele 1 and 2 of this polymorphism, which correspond to four and two repeats respectively, are more common in the general population and association of allele 2 with various autoimmune diseases has been observed (6-8).

IL-1Ra VNTR gene polymorphism has been associated with susceptibility to non-autoimmune diseases like cancer (9). Also, the IL-1Ra VNTR gene polymorphism was implicated in the development of inflammatory autoimmune diseases. In this regard, this polymorphism was directly implicated in the severity and outcome but not in the susceptibility of unselected patients with inflammatory cutaneous vasculitis (10).

While no association of this polymorphism was observed in vasculitis limited to skin, the carriage of ILRN*2 allele in patients with Henoch-Schönlein purpura was associated with a higher risk of severe renal manifestations and renal sequelae (10).

In the present study we have examined, for first time, the potential influence of the IL-1Ra VNTR gene polymorphism in the susceptibility to and clinical spectrum of patients with biopsy-proven EN from a well-defined population (11).

One hundred and one consecutive patients with biopsy-proven EN and 109 ethnically matched controls from the Lugo region in Galicia (northwestern Spain) were genotyped for IL1-Ra intron 2 VNTR polymorphism as previously reported (10).

Clinical data of the patients included in the present study have previously been described (11, 12). Briefly, 36 patients were diagnosed as having idiopathic EN. The remaining 65 patients were diagnosed with EN secondary to sarcoidosis (n=31) or developed EN in the context of other conditions (n=34). Informed consent and ethical approval was obtained.

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

In our population only allele 1 and 2 of the IL-1Ra VNTR polymorphism were detected. As shown in Table I, no significant differences in the allele and genotype distribution of the IL-1Ra VNTR polymorphism between patients with EN and controls were observed.

As described for other gene polymorphisms implicated in the inflammatory response (12, 13), the clinical heterogeneity of conditions presenting with EN may explain the negative association observed between the IL-1Ra VNTR polymorphism and our series of unselected patients with EN.

However, in assessing specific subgroups of patients with EN, 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 (14-16). Due to this, 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 the IL-1Ra VNTR polymorphism were found (Table I).

Taking into account the complex pathologic mechanisms involved in the development of EN, further studies are still needed to fully determine the exact contribution of gene polymorphisms of other mediators involved in the immune and inflammatory response in the pathogenesis of EN.

Table I: Frequency of IL-1Ra VNTR 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	109 (%)	101 (%)	36 (%)	65 (%)	31 (%)	34 (%)
Allele						
1	157 (72%)	141 (70%)	52 (72%)	89 (68%)	46 (74%)	43 (63%)
2	61 (28%)	61 (30%)	20 (28%)	41 (32%)	16 (26%)	25 (37%)
Genotype						
11	59 (54%)	50 (49%)	19 (53%)	31 (48%)	16 (52%)	15 (44%)
12	39 (36%)	41 (41%)	14 (39%)	27 (41%)	14 (45%)	13 (38%)
22	11 (10%)	10 (10%)	3 (8%)	7 (11%)	1 (3%)	6 (18%)

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

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Competing interests: none declared.

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