with the International Contact Dermatitis Research Group guidelines. The three main allergens involved in manifestations were nickel sulphate (15 patients), potassium dichromate (11 patients) and cobalt chloride (4 patients). At the moment of blood collection all patients presented moderate-severe skin manifestations. All patients signed an informed consent to the study. Twenty-five sex- and age-matched healthy subjects were used as controls.

Serum IL-31 and IL-33 concentrations were measured by a standard sandwich ELISA kit (USCN Life Science, Houston, USA). All samples were analyzed in duplicate.

Data were expressed as median ± SEM. Differences between two unpaired groups were analyzed by Mann-Whitney test using SPSS for Windows (version 17.0). Statistical significance was set at $P < 0.05$.

Results

IL-31 levels were significantly higher in patients than in controls (8.27 ± 2.04 vs. 5.18 ± 1.46 pg/ml; P = 0.034) (**figure 1**). IL-33 serum levels were similar in patients and controls (2.67 ± 2.38 vs. 2.48 ± 1.29 pg/ml; P = 0.668) (**figure 2**). No correlation between cytokines levels and age of patients and duration of disease was found.

Discussion and conclusions

ACD is usually considered a Th1-driven disease; however, in some patients a mixed Th1/Th2 phenotype can be observed (3). Therefore, cytokines expression in ACD could be heterogeneous: in previous works elevated serum levels of IL-18 (10) and IL-22 (11) cytokines produced by different cellular subsets were found.

IL-31 is usually expressed by Th2 clones and not by Th1, Th17 or Th22. However, this expression depends on the microenvironment: indeed, it is linked to autocrine IL-4 expression, and, in presence of IL-4, Th1 clones can also express IL-31 (12).

Moreover, IL-31 seems to play an important role in pruritic skin diseases.

To our knowledge this is the first work showing a possible systemic involvement of IL-31 in ACD, one of the most common pruritic skin diseases. IL-31 levels do not seem to be related to the allergen involved, as our patients were positive to different allergens and the cytokine level did not change on the strength of the allergen involved. More likely, IL-31 levels are related to the itch.

IL-33 has been found to play a role in the pathogenesis of ACD by promoting Th2 immune responses (8,13). The expression of this cytokine is induced in human keratinocytes cell line (8) and in involved and uninvolved skin of ACD patients (9) and its blockade attenuates ACD in a murine model (8). However, the overexpression of IL-33 in ex vivo skin culture was detected in both allergic and irritant conditions (9).

We did not find significant differences in IL-33 serum levels between ACD patients and controls. This could mean that in ACD there is not a systemic involvement of this cytokine. Therefore, these data suggest that IL-33 is secreted from damaged or inflamed tissue and might function as an early warning system at the site of skin damage.

In the future, IL-31 could be a possible therapeutic target of all pruritic skin diseases resistant to conventional therapies.

References

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Figure 1 *- IL-31 serum levels in ACD patients and controls; lines represent medians.*

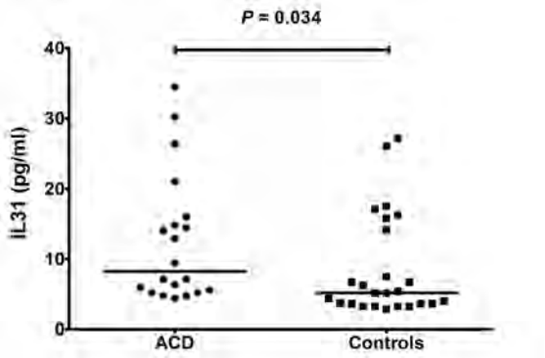

Figure 2 *- IL-33 serum levels in ACD patients and controls; lines represent medians.*