SERUM INTERLEUKIN-6 LEVELS IN PATIENTS WITH MELANOMA

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The interleukin-2 receptor (IL-2R) expressed by T lymphocytes consists of three chains α, β and γ (1). The IL-2R α chain (CD25) expressed alone constitutes a low-affinity receptor, whereas the association of α, β, and γ chains results in a high-affinity IL-2R. The α chain also exists in a soluble form (sIL-2R) (2). This soluble subunit is a truncated form of the protein that is expressed in the membrane and is able to bind IL-2 with the same affinity as the form anchored to the membrane. The interleukin-6 (IL-6) is a biomodulator of IL-2R expression. It induces expression of the α chain of IL-2R in T lymphocytes and synergizes with IL-2 to increase the cytotoxic activity of the T lymphocytes and of natural killer cells (3). IL-6 is produced by different types of cells, including fibroblasts, endothelial cells, keratinocytes, T and B lymphocytes and monocytes/macrophages (4). Recently it has been reported that different human melanoma cell lines also produce IL-6 and express a specific receptor for it on the membrane (5). Moreover, IL-6 can affect the growth properties of human melanomas differentially as a function of tumor progression (6).

In previous works we have reported that melanoma patients have significantly raised levels of soluble IL-2R, these values are significantly linked to metastatic progression. Due to the functional association between IL-2R and IL-6 and the correlation between their levels and certain tumor pathologies, in the present study we assessed in the same group of melanoma patients if the serum IL-6 levels are correlated with the sIL-2R levels and prognosis.

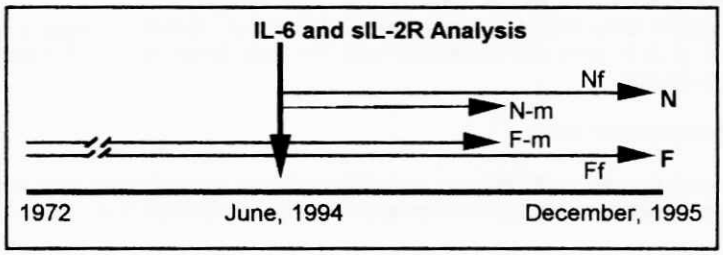

Figure 1. Diagram showing the different groups of melanoma patients analysed in the study.

Serum IL-6 levels were measured in sera from 164 patients with melanoma and 60 healthy controls, using an enzyme immunoassay kit (Immunotech International, ATOM S.A.). All patients were evaluated from June 1994 to December 1995 and were divided into two groups: the patients whose diagnosis and surgery for primary melanoma occurred during this period of time and whose serum samples were tested at least one month after surgery (Group N), and the patients who had undergone surgery for primary melanoma several years before determination of serum IL-6 (Group F) (Figure 1). For the statistical analysis, the groups of patients were both subdivided according to the metastatic progression in patients who at the time of the serum IL-6 determination were disease-free and remained disease-free during follow-up (18 months) (Nf and Ff), and patients who at the time of the serum IL-6 determination were disease-free but developed metastasis during follow-up (N-m and F-m). The Logistic and the Cox Proportional Hazards Regression Models were used with the values of group N patients in order to determine predictive factors linked to metastatic progression. Age, sex, stage (AJCC), metastatic evolution, disease-free interval, and serum sIL-2R and IL-6 levels were all taken into consideration.

Serum IL-6 levels were found to correlate with age and sex in both the control and melanoma groups (P=0.0009, P=0.03 respectively). Seventy-four of 164 (45%) melanoma patients studied had detectable serum IL-6 concentrations. IL-6 levels were also detectable in the serum of 25 of 60 (41.6%) normal controls. With regard to sex, the percentage of control women and men with detectable serum IL-6 was 37% and 50% respectively. The proportion of group N patients with detectable IL-6 levels was similar (women, 54.8% and men, 53.8%), although in group F, serum IL-6 levels were more frequently detectable in the sera of the men (60.5%) than in the sera of the women (34%).

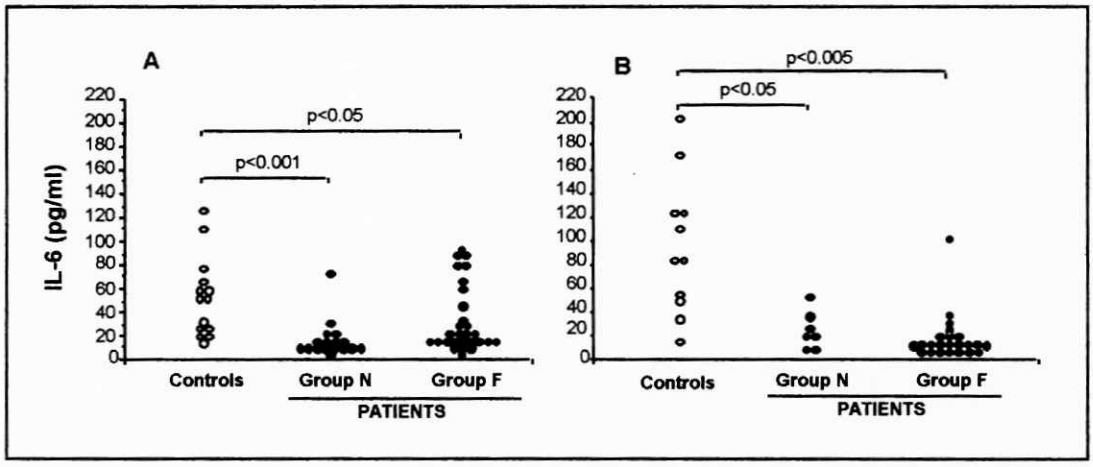

Figure 2. Serum IL-6 levels of controls and patients with detectable serum IL-6. (A) IL-6 values in the women controls and women melanoma patients; (B) IL-6 values in the men controls and men melanoma patients.

Comparison of IL-6 serum levels between controls and melanoma patients with detectable serum IL-6 was performed with the nonparametric Mann-Whitney U test. As shown in Figure 2, IL-6 values in the women (A) and men (B) melanoma patients of both group N and group F with detectable serum IL-6 was significantly lower than in controls. No significant differences were found in serum levels of IL-6 between the stages of melanoma. Finally, since sIL-2R production can be stimulated by IL-6 we analyzed the possible correlation between serum IL-6 and sIL-2R concentrations, but no significant correlation was found (r=0.044, p=not significant) (Figure 3).

In order to determine what factors might be predictive of metastatic progresion in melanoma, statistical analysis based on logistic and Cox regression models were used. Only group N met the the requirements for analysis with these methods. The statitical analysis showed that, unlike of the sIL-2R serum levels, the IL-6 levels was not linked to metastatic progression of melanoma.

In summary, in our study we have observed that serum levels of IL-6 were related to age and sex, both in the control group and the group of melanoma patients. Despite of IL-6 values in melanoma patients were significantly lower than in controls, no significant differences were found concerning the stage and metastatic progression of melanoma. Moreover, serum levels of IL-6 were not correlated with the high levels of serum sIL-2R.

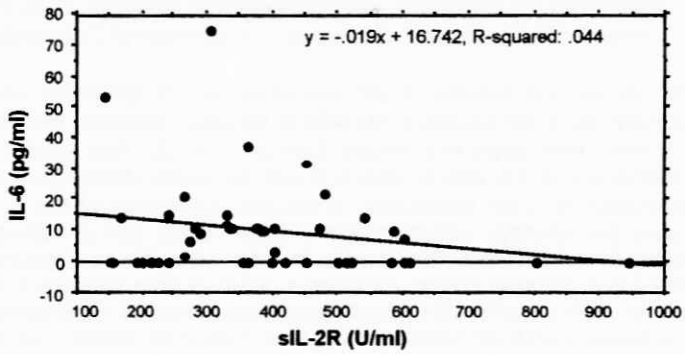

Figure 3. No correlation between the serum concentrations of sIL-2R and IL-6 in patients with melanoma.

Acknowledgements

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