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Elevated serum levels of soluble CD30 in patients with atopic dermatitis (AD)

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SUMMARY

The immunopathology of AD is still unclear, but evidence for an immune response polarized towards Th2 activity has been provided. The CD30 molecule belongs to the tumour necrosis factor (TNF) receptor family and is expressed on activated T cells with a sustained expression in Th2 cells. This molecule also exists in a soluble form (sCD30). Elevated serum levels of sCD30 have been found in patients with Hodgkin's disease, chronic hepatitis B infection and HIV infection. Studies were undertaken to compare the serum levels of sCD30 in patients with AD (n=49) and healthy non-atopic controls (n=94). The presence of sCD30 was analysed with ELISA. A significantly higher concentration of sCD30 was noted in AD patients, median sCD30 level 29 U/ml (range 1–708 U/ml), compared with healthy non-atopic controls ($P < 0{\cdot}001$), where the median level was 11 U/ml with a range of 1–1042 U/ml. No correlation was found between sCD30 levels and total serum IgE, or between the AD patients' SCORAD values and concentration of sCD30. sCD30 levels were also analysed in 20 AD patients, which during ketoconazole treatment had improved their clinical scores and reduced their serum IgE and eosinophil cationic protein levels. However, no significant decrease in sCD30 levels was noted after treatment. The results show that patients with AD have elevated levels of sCD30, but without correlation to total serum IgE or disease activity.

Keywords soluble CD30 atopic dermatitis IgE psoriasis seborrhoeic dermatitis

INTRODUCTION

The 120-kD CD30 molecule was originally described as a surface antigen, expressed by Hodgkin and Reed–Sternberg cells of Hodgkin's disease and recognized by the Ki-1 antibody [1]. CD30 can be detected on various non-Hodgkin's lymphomas [2], as well as on virally transformed B and T cell lines [3]. It is also expressed on the surface of a subset of human, activated $CD45RO^+$ cells [4]. The functional role of this protein, which belongs to the tumour necrosis factor (TNF) receptor family [5], has been a controversial subject during the past 5 years. It has been shown that CD30 is limited to human activated T cells producing interferon-gamma (IFN-γ) and IL-5 [6]. It has also been proposed that CD30 is preferentially expressed by T helper (Th) cells producing type 2 cytokines (IL-4 and IL-5), and thereby could serve as a tool to help discriminate between Th1 and Th2 cells [7]. However, we have in earlier studies found that allergen-specific human $CD4^+$ T cell clones of both Th1, Th0 and Th2 type have the ability to express CD30 after activation, although with a sustained expression of CD30 only in Th2 cells [8]. Furthermore, it has been shown that short time cultures, activated with different antigens known to elicit Th1, Th0 and Th2 responses, express comparable levels of CD30, and also that CD30-expressing cells can produce IFN-γ [9]. A soluble form of CD30 (sCD30) has been described [10], which is generated when the surface molecule is site-specifically cleaved by a zinc metalloproteinase and released from the cell membrane [11]. Elevated serum levels of the sCD30 molecule have been found in patients with HIV infection [12], chronic hepatitis B infection [13] and Omenn's syndrome [14], as well as in patients with systemic lupus erythematosus (SLE) [15] and Hodgkin's disease [16]. In SLE and Hodgkin's disease, sCD30 levels have been shown to correlate with clinical features, and thus sCD30 is suggested to be a marker for evaluation of disease activity and as an independent prognostic parameter [15,16].

AD is a chronically relapsing inflammatory skin disease, which is often associated with elevated levels of serum IgE [17]. The immunopathology of AD is at present unclear, but it is known that lymphocytes infiltrating the AD lesions are predominantly of the $CD4^+$ T helper phenotype [18]. The immune response in AD

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appears to be of the Th2 type. It has been shown that in the peripheral blood of patients with AD, the proportion of IL-4-producing T cell clones is higher compared with clones producing IFN-γ [19], and also that skin-derived allergen-specific T cell clones from patients with AD are preferentially of the Th2 phenotype [20,21].

In our previous study, where we analysed CD30 expression in activated allergen-specific T cell clones, we found that Th2 cells expressed CD30 for an extended time period [8]. To approach an understanding of CD30's function *in vivo* and its possible role in atopic disease, we analysed the number of cells expressing the membrane-bound CD30 molecule in the blood of patients with AD as well as in healthy controls. However, $< 0{\cdot}2$ % of normal peripheral lymphocytes express CD30 [3,7], and we and others have found that the frequency of circulating $CD4^+$ $CD30^+$ cells in atopic patients is not significantly increased ([7], own unpublished observations). The soluble form, however, can readily be detected in patient sera, using a highly sensitive CD30 ELISA [12–16]. In this study, we analysed sCD30 in sera of patients with AD, and in non-atopic healthy controls. We also investigated the possible correlation between sCD30 concentration and total serum IgE, as well as its relation to disease activity. To compare with other inflammatory skin diseases, we analysed sera from patients with seborrhoeic dermatitis and psoriasis.

MATERIALS AND METHODS

Healthy controls

Sera from 94 non-atopic healthy blood donors served as control (Table 1). They all had serum IgE levels < 122 kU/*l* (Pharmacia CAP System IgE FEIA; Pharmacia AB, Diagnostics, Uppsala, Sweden), and were all Phadiatop-negative (Pharmacia CAP System RAST FEIA; Pharmacia AB, Diagnostics).

AD patients

Serum samples were collected from 49 patients (Table 1) with moderate to severe AD, diagnosed according to the criteria of Hanifin & Rajka [22]. Exclusion criteria were: ongoing immunotherapy, potent topical steroids, furred animals at home and UV treatment within 2 weeks before the beginning of the study. The median serum IgE level of the AD patients was 670 kU/*l* (range 23–13 900 kU/*l*, reference range 1·6–122 kU/*l*) (Table 1). Of the AD patients, 38 had elevated total serum IgE levels (> 122 kU/*l*). Forty-six of the patients were Phadiatop-positive and/or had allergen-specific IgE antibodies (Pharmacia AB, Diagnostics). The clinical condition was evaluated in 46 of the patients according to the SCORAD scoring system, where a scoring index is mathematically derived by grading the extent, severity and subjective symptoms [23]. Their mean scoring index was 41 ± 18 (mean $\pm$ s.d.), and the median 43, with a range of 0–82.

Seborrhoeic dermatitis patients

Eleven seborrhoeic dermatitis (SD) patients were included (Table 1). They had skin lesions on the trunk as well as on the scalp and facial area. Their median total serum IgE level was 37 kU/*l*, with a range of 7–121 kU/*l*. One of the 11 patients was Phadiatop-positive. The patients had not received any kind of treatment.

Psoriasis patients

Sera from 11 patients with plaque psoriasis were analysed for sCD30 (Table 1). The median total serum IgE level was 36 kU/*l* with a range of 2–1400 kU/*l* (Table 1). Four of the eleven patients were Phadiatop-positive. The psoriasis patients had not received any topical treatment or UV light for at least 2 weeks, and no systemic treatment for several months before collection of the blood samples.

Ketoconazole-treated AD patients

This group included 20 patients (Table 1) with mild to severe AD, who had attended a treatment study where they received ketoconazole, an anti-fungal agent, for 5 months [24]. The median total serum IgE level was 1244 kU/*l* with a range of 203–23 880 kU/*l* (Table 1). They all had specific IgE antibodies to the yeast *Pityrosporum orbiculare* (five patients with radioallergosorbent test (RAST) class 4, six patients with class 3 and nine patients with class 2). Patients were given ketoconazole, 200 mg daily, for 2 months, and 200 mg twice weekly for a further 3 months [24].

sCD30 assay

The concentration of sCD30 was determined by a sandwich ELISA (CD30, Ki-1 antigen, ELISA; Dako, Glostrup, Denmark), where the mouse MoAbs used for coating and those for conjugating are non-competitive and react with different epitopes on the CD30 molecule. Briefly, CD30 standards, a curve control and patient specimens were pre-diluted in buffer with protein stabilizer and added, in duplicates, together with peroxidase-conjugated anti-CD30 MoAbs to optically clear microwells pre-coated with anti-CD30. After incubation for 2 h at room temperature, and washing to remove unbound material, a chromogenic solution (a stabilized solution of tetramethylbenzidine and a stabilized H_2O_2 solution, diluted in deionized water) was added to the wells. Colour development was stopped by the addition of sulphuric acid, and absorbance measured at 450 nm (SLT-Labinstruments, Salzburg, Austria). A standard curve was then constructed from the six CD30 calibrators, and the CD30 concentration in each sample determined by interpolation on the curve. According to the manufacturer's description, for each of four specimens the imprecision was calculated from the means of up to five duplicate determinations, for five separate runs. The coefficient of variation (CV) was estimated to be < 8%. By determination of the mean absorbance + 2 s.d. of 20 measurements of the 0 U/ml standard, the detection limit of the assay was estimated to be 1 U/ml. In the present study, sera from different groups, i.e. patients and healthy controls, were analysed randomly on the same plates to avoid bias due to technical errors. Interassay variation was determined by assessing one sample in duplicates in seven assays run on different days. The CV was estimated to be < 8%. Intra-assay variation was analysed by assessing five identical duplicate samples in one assay, and here the CV was found to be < 6 %. All serum samples were kept frozen at -20°C before analysis. The study was approved by the Ethics Committee of the Karolinska Hospital.

Statistical analysis

The Mann–Whitney *U*-test was used for assessment of differences between groups of patients and healthy controls. To evaluate the relationship between observed parameters, the Spearman's rank correlation coefficient was calculated. A Friedman ANOVA by ranks test was used to determine the significance in differences between the different time points in the ketoconazole treatment study. Statistical significance was defined as a P value $< 0{\cdot}05$.

Table 1. Patients and healthy controls included in the study

	Cases (*n*)	Age (years), median (range)	Total serum IgE* (kU/*l*) median (range)	Specific IgE (Phadiatop)† (+/−)	sCD30 (U/ml) median (range)
Healthy controls	94	36 (21–69)	20 (2–115)	0/94	11 (1–1042)[a]
Males	56	40 (21–64)	16 (2–115)		12 (1–1042)
Females	38	35 (21–69)	21 (3–105)		10 (1–100)
Atopic dermatitis patients	49	30 (18–65)	670 (23–13 900)	46/3	29 (1–708)[b]
Males	17	37 (18–62)	1900 (24–9300)		42 (1–708)
Females	32	27 (20–65)	555 (23–13 900)		29 (6–476)
Seborrhoeic dermatitis patients	11	33 (13–63)	37 (7–121)	1/11	36 (4–190)[c]
Males	8	32 (23–63)	59 (13–121)		36 (4–190)
Females	3	46 (13–62)	18 (7–19)		41 (15–49)
Psoriasis patients	11	42 (23–66)	36 (2–1400)	4/7	6 (1–100)[d]
Males	9	42 (23–66)	36 (2–1400)		13 (1–100)
Females	2	48 (39–56)	69 (27–110)		2 (1–3)
Ketoconazole-treated AD patients	20	34 (20–52)	1244 (203–23 880)‡	20/0	28 (3–500)‡[e]
Males	10	34 (22–52)	2533 (213–23 880)		46 (5–300)
Females	10	32 (20–46)	757 (203–5354)		21 (3–500)

* Reference range: 1·3–263 kU/*l* for 5–20-year-old individuals and 1·6–122 kU/*l* for adults (Pharmacia CAP System IgE FEIA).
†Pharmacia CAP System RAST FEIA.
‡Values before treatment; a *versus* b, $P < 0{\cdot}001$; a *versus* c, $P = 0{\cdot}012$; a *versus* d, non-significant; and a *versus* e, $P < 0{\cdot}01$.

RESULTS

Significantly higher levels of sCD30 in AD patients compared with healthy controls

Significantly higher levels of sCD30 were noted in AD patients (median 29 U/ml, range 1–708 U/ml) compared with healthy controls (median 11 U/ml, range 1–1042 U/ml) ($P < 0{\cdot}001$) (Table 1 and Fig. 1). No statistical difference in sCD30 levels was found between males and females, neither in the AD patient group nor in the group of healthy controls. No correlation existed between the concentration of sCD30 and the age of the patients.

Relation between sCD30 concentration, total serum IgE levels and disease activity in AD patients

The correlation between levels of total serum IgE and sCD30 concentration was evaluated in the 49 cases of AD. No significant correlation was observed ($r = 0{\cdot}2$). Neither was any correlation noted between sCD30 and serum IgE levels when the 11 AD patients without elevated serum IgE levels (>122 kU/*l*) were excluded. The relationship between sCD30 values and the clinical condition of the AD patients was also investigated in 46 of the AD patients. We found no relation between levels of sCD30 and patients' clinical condition ($r = 0{\cdot}07$).

sCD30 levels in patients with SD and psoriasis

To investigate sCD30 levels in other inflammatory skin diseases, sera from 11 SD patients and 11 psoriasis patients were analysed. The median sCD30 concentration in the SD group was 36 U/ml with a range of 4–190 U/ml (Table 1, Fig. 1). This was significantly higher than in healthy controls ($P = 0{\cdot}012$). In the group of patients with psoriasis, of whom four were Phadiatop-positive, sCD30 levels were lower; median 6 U/ml with a range of 1–100 U/ml, which was not significantly different from the group of healthy controls (Table 1, Fig. 1). The four Phadiatop-positive patients did not have higher sCD30 levels than the Phadiatop-negative ones. No relation between total serum IgE and sCD30 levels was noted in any of these patient groups.

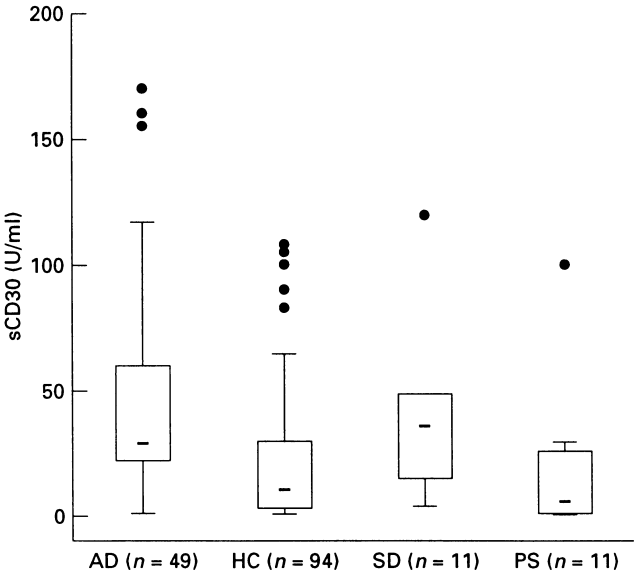

Fig. 1. Significantly higher levels of sCD30 were noted in AD patients compared with healthy, non-atopic blood donors (HC) ($P < 0{\cdot}001$). The sCD30 concentration in the seborrhoeic dermatitis (SD) patients, but not in the patients with psoriasis (PS), was significantly higher compared with HC ($P = 0{\cdot}012$). sCD30 levels were analysed in serum with an ELISA (Dako). Results are illustrated using the box plot model. Boxes cover the middle 50% of the data values, between the 25th and 75th percentiles, the central line being the median. Lines extend out to the non-outlier max. and non-outlier min. ●, Outliers. The extreme outliers are not shown.

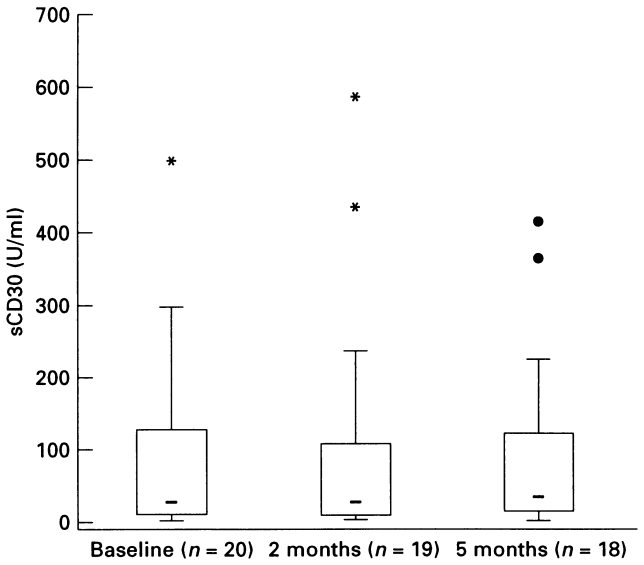

Fig. 2. Twenty patients with AD received ketoconazole treatment for 5 months. Sera were collected at different time points during treatment, and analysed for the presence of sCD30 with an ELISA (Dako). No significant difference in sCD30 levels could be noted at the different time points. For explanation of the box plot model see the legend for Fig. 1. The extreme outliers are indicated as (*).

Detection of sCD30 in ketoconazole-treated AD patients—correlation to clinical features

Twenty patients with AD were included in a study where they received ketoconazole treatment for 5 months (Table 1, Fig. 2). During this period a significant decrease could be noted in both the global disease activity score and the head and neck score [24]. Also the levels of total and *P. orbiculare*-specific serum IgE, as well as eosinophil cationic protein (ECP) were significantly decreased after 5 months [24]. To investigate the possible relationship between sCD30 levels and disease activity, and to compare these levels with the other parameters, such as total and specific serum IgE, sera collected at the different time points of the treatment study were analysed for the presence of sCD30. The concentration of sCD30 was analysed in sera from the 20 AD patients before treatment, in 19 of the AD patients after 2 months and in 18 of the patients after 5 months (Fig. 2). The median sCD30 concentration in the 20 AD patients before treatment was 28 U/ml (range 3–500 U/ml), which was significantly higher compared with the healthy controls ($P < 0{\cdot}01$) (Table 1). However, no significant difference was noted in sera collected at the different time points (Fig. 2). No correlations between concentration of sCD30 and serum IgE, *P. orbiculare*-specific IgE antibodies, disease activity or levels of ECP were found.

DISCUSSION

In the present study, we demonstrate significantly higher levels of sCD30 in sera from AD patients compared with healthy non-atopic controls (Fig. 1, Table 1). Previously, positive correlations were found between CD30 mRNA expression in peripheral blood mononuclear cells (PBMC) and serum IgE levels in atopic patients with allergic asthma/rhinitis [25]. However, in investigating the relationship between the concentration of sCD30 and serum IgE levels in the AD patients in this study, no correlation was noted. sCD30 levels were not significantly different in the group of AD patients with elevated serum IgE levels compared with the group with low total serum IgE levels. Disease activity in AD patients was evaluated by calculation of a severity index, according to the SCORAD scoring system [24]. We could not find any correlation between levels of sCD30 and patients' disease activity. This was also the case when patients' sera, from different time points in a ketoconazole treatment study [24], were analysed for the presence of sCD30 (Fig. 2), where the decreasing levels of total serum IgE, *P. orbiculare*-specific IgE antibodies and ECP, as well as head and neck score, did not relate to the concentration of sCD30.

In previous reports, levels of sCD30 detected in sera of healthy blood donors have been < 20 U/ml, which is considered to be the upper normal limit [12–16]. In these reports, the same method for detecting sCD30, the sCD30 ELISA test kit (CD30, Ki-1 antigen, ELISA; Dako) was used. Among the healthy blood donors that we analysed, however, there were a few cases of very high sCD30 levels. It has been shown previously that patients with various conditions caused by viral infections, e.g. chronic hepatitis B and infectious mononucleosis, have elevated sCD30 levels [13,26]. A possible explanation for the extreme values in our study could be that the donors with elevated sCD30 levels had a virus infection prior to blood sampling. If blood samples from these donors, collected at a later time point, had been analysed, levels of sCD30 might have been lower. Unfortunately we were not able to do that.

Serum levels of sCD30 in the psoriasis patients were not significantly different from healthy controls. This finding is interesting, since psoriasis is suggested to be a Th1-related disease [27,28]. Analysis of skin biopsy specimens from lesional and non-lesional skin from psoriasis patients by polymerase chain reaction shows a pattern of cytokines that resembles a Th1 profile [27]. Four of the psoriasis patients were Phadiatop-positive. However, sCD30 levels in these patients were not significantly different from the Phadiatop-negative psoriasis patients. In the group of patients with SD, on the other hand, the median concentration of sCD30 was significantly higher compared with healthy controls. The aetiology of this chronic skin disease is still unknown. It has been shown, however, that freshly isolated PBMC from patients with SD show an increased secretion of IL-10, as well as a reduced production of IL-2 and IFN-γ, after activation with *P. ovale*, compared with PBMC from healthy controls [29]. Since IL-10 is preferentially produced by Th2 cells, this might explain the high sCD30 levels in sera from these patients. It must be taken into consideration that the number of SD and psoriasis patients in this study was relatively low, and therefore the power of the statistical analysis is weaker.

Further investigations are required to clarify the *in vivo* function of CD30 and the role of its soluble counterpart. The CD30 ligand (CD30L) has been cloned [30] and shown to be expressed by activated T cells and macrophages [30,31]. Furthermore, recent work by Amakawa *et al*. demonstrate that CD30 knock out mice have an impaired negative selection of T cells. CD30 is thereby proposed to have a role in cell death [32].

In conclusion, this study clearly demonstrates elevated levels of sCD30 in patients with AD. However, no correlation seems to exist, either between concentration of sCD30 and total serum IgE, or with the patients' clinical features. According to these results, the sCD30 molecule is not suitable as a prognostic marker for AD, or as a reliable tool for assessing disease activity.

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