

Report

Atopy, IgE and eosinophilic cationic protein concentration, specific IgE positivity, eosinophil count in cutaneous T Cell lymphoma

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Abstract

Background Even though several case studies have reported a relationship between Cutaneous T Cell Lymphoma (CTCL) and atopic diathesis, this association is still controversial. The aim of this study was to investigate the actual presence of atopic status in CTCL patients.

Methods A total of 78 patients with both clinical and histological features typical of CTCL and 77 control cases from our outpatient dermatology clinic were included in this study. After initial evaluation and staging, all patients were investigated for history of atopic disease, serum total IgE and eosinophil cationic protein concentration (ECP), eosinophil count, serum specific IgE, and skin prick test positivity.

Results Personal atopy in CTCL group was 23,1% (n = 18) and familial atopy was 9.0% (n = 7) whereas in the control group, these values were 11.7% (n = 9) and 7.8% (n = 6), respectively. There was no statistically significant difference, however, the number of atopic patients were higher in CTCL group than the control group (p = 0.151). Serum total IgE levels were significantly increased in patients with CTCL when compared to control group (p = 0.04). Serum specific IgE panel and prick test positivity between patients and controls were significantly different, respectively (p = 0.03) (p = 0.00). Eosinophil counts and ECP levels were not significantly different, respectively (p = 0.10) (p = 0.885). In high stages of CTCL, patients were found to have elevated IgE, ECP levels and eosinophil count. These results were statistically significant (p = 0.011) (p = 0.009) (p = 0.007).

Conclusion Eventhough the number of patients with atopy in the CTCL group was higher than the control cases, there was no significant different. On the other hand high levels of serum IgE, elevated eosinophil count and specific IgE positivity may be found in CTCL patients with or without atopic disease, especially with high stages.

Introduction

The etiology of cutaneous T cell lymphoma (CTCL) remains unknown, but various theories have been postulated, such as chronic antigenic stimulation, atopy, occupational and environmental factors, as well as viral exposure.

To the best of the authors' knowledge, there are a few case control studies evaluating possible causative factors in mycosis fungoides. In one of these studies, a statistically significant difference was found between patient and control groups with regard to the family history of atopic dermatitis (AD); however, the personal history of one group did not correlate significantly with the other.¹ There are also studies reporting no increased atopy among patients with mycosis fungoides.²⁻⁴

Some patients with CTCL, especially of young age, were previously diagnosed as AD.^{5,6} In a retrospective

cohort study carried out on children with lymphomatoid papulosis, more than two thirds of the subjects were found to be atopic. This rate was significantly higher than the expected prevalence of atopy.⁷ A relationship between Sezary syndrome and atopic diathesis was suggested in various case reports.⁸⁻¹⁰ In a case report on a tumor stage mycosis fungoides, the patient had adult onset asthma and atopic-like dermatitis in conjunction with increased IgE.¹¹ Nevertheless, there are other reports pointing to increased IgE levels but no atopic history in patients with Sezary syndrome, MF or Hodgkin's disease.¹²⁻¹⁵

Characterized by allergen specific IgE production, atopy is an inheritable syndrome often with a multifactorial background and an abnormality at the level of Th1/Th2 regulation. Recently, Boss *et al.* have suggested that production of allergen specific IgE is a central abnormality in atopic syndrome and a prerequisite for the diagnosis of

atopy.¹⁶ Eosinophils may also contribute to the inflammatory response by releasing product, such as eosinophil cationic protein (ECP).¹⁷

This study is aimed at comparing patients with CTCL and the control group in terms of the actual presence of atopy history, serum IgE, ECP, allergen specific IgE and eosinophil count. The study also investigates the correlation between the stages of CTCL disease and serum IgE, ECP, and eosinophil count.

Materials and methods

Study population

A total of 78 patients (38 females – 40 males) with both clinical and histological features typical of CTCL were evaluated prospectively between 1998 and 2006. For classification and staging, patients underwent a complete physical examination, blood cell count, blood smear for Sezary cell, general chemistry panel, chest X-ray, thoracic and abdominal computed tomography scan (CT), and abdominal sonography. In patients with significant lymphadenopathy, lymph node biopsy was performed. After the initial evaluation, all the patients were staged according to the TNMB criteria of the National Cancer Institute.

The control group (77 patients; 40 females, 37 males) consisted of randomly chosen patients presenting with various dermatologic conditions.

The following evaluations and tests were applied to all the patients in the way explained below.

Atopy condition

Each patient was questioned about history of atopy, such as allergic contact urticaria, dyshidrotic eczema, allergic rhinitis, allergic asthma, allergic conjunctivitis, gastrointestinal allergy or any combination of these clinical entities. The clinical condition of atopy was evaluated in the next step.

Serum total IgE

Serum total IgE levels were determined by means of immunometric assay (Immulate Analyzer; DPC, Nutley, New Jersey, USA). The range of normal values was adjusted to age (0–52 IU/ml for 3–9 years; 0–87 IU/ml for adults).

Eosinophil cationic protein

Each sample was processed by a solid phase two-side chemiluminescent enzyme immunometric assay (Immulate ECP kit, DPC). The range of normal values in this method was found to be between 2 and 18 ng/ml.

Eosinophil count

For all patients, eosinophil counts were called as percentage of polymorphonuclear leukocyte.

Specific IgE panel

For the qualitative detection of IgE antibody-specific serum to a panel of food allergens: F1 (egg white), F2 (milk), F3 (codfish), F4 (wheat), F13 (peanut), F14 (soybean) (Immulate Allergy Food Panel FP5E, DPC, USA) and to an inhalant allergen panel: D1 (*Dermatophagoides pteronyssinus*), E1 (Cat epithelium), E5 (Dog dander), G2 (Bermuda grass), G6 (Timothy Grass), M1 (*Penicillium notatum*), M6 (*Alternaria Tenuis*), T3 (Birch), T17 (Japanese Cedar), W1 (Common Ragweed), W9 (English Plantain), W19 (*Parietaria officinalis*) (Immulate AlaTOP Allergy Screen, DPC) were measured utilizing a solid phase sequential chemiluminescent enzyme labeled immunoassay.

Skin prick test

The following purified allergens were applied to the volar forearm of each patient with a standardized prick lancet: 3-tree mix (*Alnus glutinosa*, *Betula verrucosa*, *Corylus avellana*), grasses [grass mix (*Doctylis glomerata*, *Festuca pratensis*, *Lolium preenne*, *Phelum pratensa*, *Poa pratensis*) and 4-seceale mix (*Avena*, *Hordeum*, *Triticum*)], weeds [3-herbs (*Artemisia vulgaris*, *Chenopodium album*, *Plantago lanceolata*) and *Parietaria judaica*], molds (*Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, *Penicillium notatum*, *Candida albicans*), epithelia and textiles (cat hair, dog hair, feather mix and wool), mites (*Dermatophagoides pteronyssinus*, *Dermatofagoides farinea*), foods (cow's milk, egg-white, fish, peanut, hazelnut, soybean, cacao, chicken, wheat flour, rye flour), and latex. Histamine dihydrochloride (10 mg/ml) and sodium chloride (9 mg/ml) were applied as control solutions. (Allergens were provided by Alk-Abello Laboratory).

Data analysis

Statistical analyses were performed using the SPSS (SPSS 15.0 Troy, NY; USA) computer program. Atopic diathesis was evaluated by the chi-square test. Two-tailed Mann–Whitney *U* test was used in determining statistical differences between patients and the control group with regard to such metric parameters as IgE, ECP, and eosinophil count. Prick test and specific IgE panel were evaluated by the chi-square test and Fisher's Exact Test. The difference between the stages of CTCL and the parameters of IgE, ECP, and eosinophil count was analyzed using the Kruskal–Wallis test. $P < 0.05$ was considered as significant.

Results

Patient characteristics

The CTCL group consisted of 38 female and 40 male patients with a mean age of 48 years (± 17.15 SD), and the control group consisted of 40 female and 37 male patients with a mean age of 42 years (± 16.8 SD). In the CTCL group, 67 patients were diagnosed as mycosis fungoides

(MF) according to the classification of EORTC. Diagnoses made of other conditions and the number of patients having them were as follows: Sezary syndrome (SS), (six patients); CD 30(+) anaplastic large cell lymphoma (two patients); lymphomatoid papulosis(LP), (two patients), and CD 30(-) anaplastic large cell lymphoma (one patient).

Atopic diathesis

In the CTCL group, the rate of personal atopy was 23.1% ($n = 18$) and family atopy was 9.0% ($n = 7$). In the control group, the rate of personal atopy was 11.7% ($n = 9$) and family atopy was 7.8% ($n = 6$). A total of 23.8% ($n = 16$) of the patients with MF had personal atopy and 8.6% ($n = 6$) of them had familial atopy. One of two patients with LP and one of the six patients with SS had personal atopic diathesis as well. Even though the number of subjects with atopy in the CTCL group was greater than that in the control group, no statistically significant difference was found to exist between the two groups ($P = 0.151$) (Fig. 1).

Serum total IgE

Patients with CTCL were found to have higher IgE values than the control group. The mean IgE value was 330.3 IU/ml (min 5 – max > 2000) in the former group and 140 (min 4 – max 1151) in the latter. Forty patients with CTCL and 23 controls had elevated serum total IgE. Out of the 40 CTCL patients, 34 had MF, 5 SS, and 1 LP. Out of these 40 CTCL patients, 12 had various atopic diseases, but 28 had no atopic condition. Six patients with CTCL with atopic diathesis had normal IgE levels (Fig. 2). Mann-Whitney U test was performed to determine whether any difference existed between the IgE levels (Fig. 2). The result was that there existed a significantly significant difference between these two groups ($P = 0.004$). Similarly, chi-square test was performed to determine whether any difference existed between the IgE levels of CTCL patients either with or without atopic con-

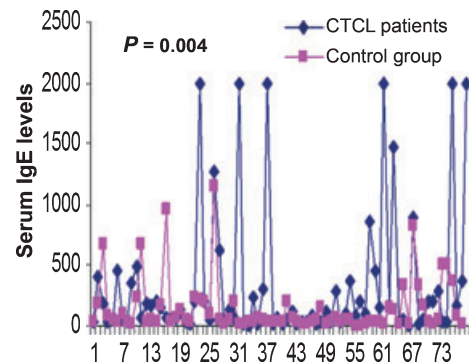


Figure 2 Serum IgE levels in CTCL and control group

dition. The difference found to exist between these two groups of patients was significant ($P = 0.020$).

Eosinophil cationic protein

A total of 24 patients with CTCL and 21 controls had elevated ECP. The mean ECP was 25.42 ng/ml (min 3 – max 171) in the former group and 19.10 ng/ml (min 3 – max 66) in the latter. The difference between the patients and controls was not significant ($P = 0.885$).

Eosinophil count

Eosinophil count in patients with CTCL was found to be higher than that in the control group. The mean eosinophil count was 4% (min 1 – max 40) in the former group and 2% (min 1 – max 5) in the latter. Nine of the 78 CTCL cases had elevated eosinophil count. The eosinophil count of the patients and the controls did not correlate significantly ($P = 0.100$).

Specific IgE panel

The rate of specific IgE panel positivity in the CTCL group was 32.1% ($n = 25$) and that in the control group was 11.8% ($n = 9$). Among the 25 patients in the former group, aeroallergens were detected in 10, food panel extract in 9 and aeroallergen together with food panel positivity in 6. There was a correlation between elevated total IgE and specific IgE panel positivity (20/25 patients of CTCL). Specific IgE panel positivity status of the patients had a statistically significant correlation with that of the controls ($P = 0.030$).

Prick test

A total of 69 CTCL patients and 69 controls underwent prick test. There were found at least one positivity in 32 out of 69 patients (46.4%), 10 out of 69 controls (14.5%), respectively (Table 1). There was a statistically significant correlation between prick test positive patients and controls ($P = 0.000$).

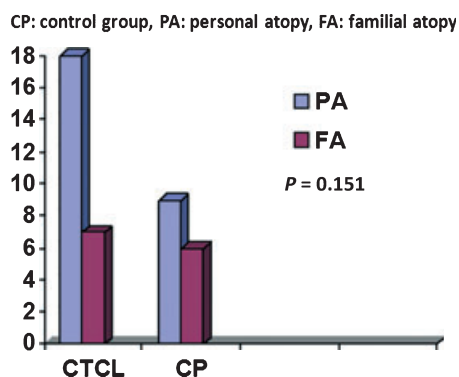


Figure 1 Prevalence of atopy among our patients

Table 1 Skin prick test and positive reactions

	CTCL patients	Control group
<i>D. pteronyssmus</i>	18	5
<i>D. farinea</i>	18	4
Trees (3-tree mix)	9	1
Grass mix	7	—
4-seceale mix	6	1
3-herbs	9	3
<i>P. judaica</i>	3	—
<i>A. alternata</i>	4	2
<i>A. fumigatus</i>	4	3
<i>C. albicans</i>	2	1
Dog hair	5	—
Cat hair	8	2
Feather mix	5	—
Wool	2	1
Egg white	5	1
Cow's milk	5	1
Fish	5	1
Peanut	5	—
Wheat	2	—
Soybean	5	—
Cacao	2	—
Rye flour	1	—
Wheat Flour	1	—
3-herbs	9	3
<i>P. judaica</i>	3	—
Latex	3	1

Table 2 Stage of CTCL and eosinophil, serum total IgE, ECP values

Stage	Mean	SD	Min	Max
Ia,Ib				
Eos	3	2	1	15
ECP	20,77	20,64	3,0	123,0
IgE	284,67	476,49	5,0	2000,0
IIa,IIb				
Eos	2	2	1	5
ECP	12,38	10,46	3,0	37,0
IgE	90,13	63,04	36,0	197,0
IIIa,IIIb				
Eos	21	15	2	40
ECP	92,50	60,18	4,0	171,0
IgE	1137,67	950,21	166,0	2000,0

Stages of CTCL, total IgE, ECP, and eosinophil counts

Patients in the late stages of CTCL were found to have elevated IgE, ECP, and eosinophil count (Table 2). Statistically significant differences were found to exist between the stage of CTCL and the following parameters: Total IgE ($P = 0.011$); ECP ($P = 0.009$) and eosinophil count ($P = 0.007$).

Discussion

Current views on the pathogenesis of CTCL suggest a persistent antigenic exposure and stimulation, associated with some immunological imbalance in the host. These factors may lead to the development of a malignant clone of T lymphocytes in a pre-existing benign lymphocyte infiltrate. The possibility of a relationship between atopic disease and CTCL has been postulated. Rogge and Han-nifin have demonstrated the presence of depressed lymphocyte transformation in severe AD. Progressive functional immunodeficiency may be a predisposing condition for the progression of CTCL.¹⁸

CTCL and atopic dermatitis have immunologic similarities. Allergen specific CD4+ T lymphocytes and increased IL-4 production were observed in AD lesional skin.¹⁹ It is known that both CTCL and atopic dermatitis are present in cases of an abnormality in Th1/Th2. The lesions of MF are characterized by infiltration with active CD4+ T cell. Pressman *et al.* have demonstrated that cell bound IgE and FcεRI dendritic cells are not restricted to atopic dermatitis, but that they also occur in MF patients. They suggested that locally-secreted lymphokines, such as IL-4, induce Fcε-receptors on dendritic cells in the cutaneous infiltrate, and that these receptors are occupied in parallel with elevated serum IgE levels.²⁰

Cytokines are believed to play an important role in the pathogenesis of CTCL. Recent studies have suggested that the cutaneous lesions of MF are characterized by an epidermal Th1-type cytokine profile (IL-2+ and INF δ), whereas both the blood and skin of patients with Sezary syndrome are characterized by a Th2 type profile (IL-4, IL-5, IL-10).²¹⁻²⁷ Wowels *et al.* have demonstrated that in all the stages of cutaneous involvement of CTCL, encompassing patch stage through tumor stage, the malignant T cells had a Th2-helper cell phenotype, and IL-4, IL-5 mRNA was variably detectable.²⁶ In contrast, Wer-meer *et al.* have reported that CD 30(-) primary cutaneous large cell lymphoma did not produce Th2 cytokines.²⁸

Therefore, Th2 pattern of cytokines (IL-4, IL5) derived lymphoma cells may give rise to elevated levels of IgE and eosinophilia and may lead to increased susceptibility to infections.^{24,29-33} Some authors suggest that eosinophilia and level of ECP might relate to prognosis of Hodgkin lymphoma and small population of patients with CTCL.³⁴⁻³⁶ These results imply why biologic response modifiers (IL-12, INFδ, INFα, retinoid) are effective therapeutic agents for CTCL.³⁶⁻³⁹

We found higher levels of total serum IgE in the CTCL group than in the controls. Late stages of CTCL were associated with significantly elevated IgE, ECP level, and eosinophilia. Another finding of this study was that 28 of

the 40 CTCL patients with elevated IgE had no atopic condition. Indeed, these patients could have latent atopic constitution. Such factors as superantigens cause exacerbation of the disease. This can also be explained by an increased IgE production induced by B cell. It is known that B cell is mediated by cytokine secretion produced by CD4⁺ T cell (Th₂). Of note, we observed that 25 patients with CTCL had specific IgE panel positivity compared to nine cases in the control group. Of these 25 cases with specific IgE panel positivity, 12 had atopic condition. Thirty-two patients with CTCL were found to be prick test positive. Twelve of these patients had atopic diathesis as well. These results may support the assertion that increased IgE production is caused by T-cell cytokine secretion.

We found that the prevalence of this condition in the CTCL and control groups was 23.1% and 11.7%, respectively. The number of CTCL cases with atopy was greater than that of the controls with the same condition. Some authors have reported that the prevalence of this condition in different regions of Turkey was between 13 and 24%.⁴⁰⁻⁴⁶ The prevalence rate of atopic disease among our patients is similar to the rates reported by these authors. Mehrany *et al.* have stated that the prevalence rates of atopy in their patients with Sezary syndrome and mycosis fungoides were 11.5 and 11.8%, respectively. The authors also stated that these rates were not significantly different from those seen in the general population.⁴ Tuyp *et al.* have reported in a case control study that the only statistically significant difference observed between their groups of patients was the family history of atopic dermatitis.¹ In our study, familial atopy of the CTCL group did not correlate significantly with that of the control group.

In conclusion, no significant differences were observed between our patients and controls with regard to atopy in those with MF or CTCL. This result is in accordance with the literature. However, the results of this study allow us to state that high levels of serum IgE and specific IgE positivity may be found in CTCL patients with or without atopic condition, especially in the late stages of the condition. This may be attributed to a latent atopic condition or mediated cytokine secretion by T-cell.

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