Investigation of Atopy in Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

Vonderheid EC¹*, Hamilton RG² and Kadin ME³

¹Sydney Kimmel Cancer Center, Johns Hopkins Medical Institutions, USA
²Asthma and Allergy Center, Johns Hopkins University School of Medicine, USA
³Department of Pathology and Laboratory Medicine, Rhode Island Hospital and Department of Dermatology, Boston University and Roger Williams Medical Center, USA

*Corresponding author: Eric Vonderheid, 37580 S. Desert Sun Drive, Tucson, AZ 85739, USA, Tel: +520-825-2699; E-mail: evonder1@jhmi.edu

Abstract

Background: A link between atopy and primary cutaneous CD30+ lymphoproliferative disorders (CD30CLPD), which encompasses lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (pcALCL), has been suggested in the literature.

Objective: Investigate whether patients with CD30CLPD have an atopic diathesis.

Methods: We reviewed our experience with 157 patients with LyP and 23 patients with pcALCL for: (1) the patients’ personal history of seasonal allergic rhinitis, allergic asthma or atopic dermatitis/eczema, (2) a history of these conditions in a first degree family member, and (3) a serum total IgE level that exceeds 100 IU/mL which in adults has been used to signify “probable atopy”. Also recorded were a history of patients’ allergic reactions to medications and absolute peripheral blood eosinophil counts.

Results: A personal history of at least one atopic disorder was noted for 38% and 17% of patients with LyP and pcALCL, respectively. Allergic rhinitis was the most frequent allergy in both LyP and pcALCL subsets (27% overall) with asthma and eczema reported in 10% or fewer cases. The prevalence of allergic rhinitis in these subsets was significantly lower than the 38.2% prevalence observed for healthy controls derived from the Interlymph project. However, recall bias and unstructured collection of data may contribute to these different results. The frequency of allergic drug reactions, most often to penicillin type drugs, were similar for both LyP and pcALCL subsets (28% overall). The frequency of penicillin reactions for patients with pcALCL was significantly higher than the 11.46% rate reported by Albin (P= 0.01). At least one atopic condition was recorded for a parent, sibling or child in about 20% of patients with either LyP or pcALCL. Multiple atopic conditions in first degree family members occurred in about a third of these cases, in particular for family members of patients with LyP-C. Mean total serum IgE values were significantly increased in patients with LyP and pcALCL compared to published reference values for non-atopic adults in the US and Europe. Between 30 to 36% of
patients with LyP type A, LyP type C and pcALCL, but not LyP type B, had total IgE values that exceeded 100 IU/ml. Although not statistically significant, mean IgE levels tended to increase from LyP-B to LyP-A to LyP-C and pcALCL, suggesting a possible role of atypical CD30+ cells in directly stimulating IgE production. Eosinophilia was present in 4% of cases. **Conclusion**: This study provides evidence that serum total IgE is often increased in patients with CD30CLPD. The IgE>100 IU/ml threshold for probable atopy was exceeded in about a third of patients with LyP-A, LyP-C and pcALCL, but not LyP-B. However, a link with atopy was not supported by review of the patients’ personal and family history that was obtained at the time of the initial examination rather than using a formal questionnaire. Additional studies with measurement of allergen specific IgE antibodies with attention to bacterial superantigens might be more informative.

**Keywords**: Atopy; Lymphomatoid papulosis; Anaplastic large cell lymphoma; IgE

**Abbreviations**: CTC: Cutaneous T Cell Lymphoma; ECTCL: Erythrodermic CTCL; MF: Mycosis Fungoides; IgE-t: Serum Total IgE; CD30CLPD: Primary Cutaneous CD30+ T-cell lymphoproliferative Disorders; LyP: Lymphomatoid Papulosis; pcALCL: Primary Cutaneous CD30+ anaplastic large cell lymphoma; GM: Geometric Mean.

**Introduction**

Atopy has been defined as a personal or familial tendency to produce IgE antibodies in response to allergen exposure, usually to aerosolized, injected or ingested proteins, and to develop typical symptoms such as asthma, rhino conjunctivitis, or eczema/dermatitis [1]. For most epidemiological studies, atopy requires a demonstration of an increased allergen-specific serum IgE response (> 0.35 kUA/L) or positive prick skin test to any common food or inhalant allergen. An increased level of total serum IgE (IgE-t) has also been associated with atopic conditions (especially asthma) with an IgE-t value > 100 IU/mL used to define “probable atopy” [2,3]. However, some atopic individuals have IgE-t values less than 100 IU/mL and IgE-t may be increased in individuals with various non-atopic conditions (Supplementary Table 1).

In this study, we report our experience with atopy in patients with primary cutaneous CD30+ T-cell lymphoproliferative disorders (CD30CLPD) which encompass lymphomatoid papulosis (LyP) at one end of the clinical spectrum and primary cutaneous anaplastic large cell lymphoma (pcALCL) at the other end [4,5]. The possibility of a biologic relationship between CD30CLPD and atopy has been suggested by several studies. Nijsten [6] noted an atopic condition in 18 of 35 (51%) cases of childhood LyP (allergic rhinitis in 12 patients, allergic asthma in 3 patients, atopic dermatitis in 2 patients and allergic rhinitis plus asthma in 1 patient). Fletcher [7] reported 3 cases of pcALCL and one case of LyP associated with active atopic dermatitis, and Ishida [8] added one additional case of pcALCL with atopic dermatitis. In the study by the International Lymphoma Epidemiology Consortium (InterLymph), Wang [9] found a significantly higher personal history of hay fever in patients with pcALCL (46%) than controls (21%).

**Materials and Methods**

Data were obtained from a Cutaneous Lymphoma Registry approved by the Institutional Review Board at Johns Hopkins University. CD30CLPD cases were classified into 5 subtypes of LyP (types A to E) and pcALCL based on recommended clinical-pathological correlations [4,10]. Because histopathological findings vary among lesions and over time, all available skin biopsy specimens were reviewed for each patient. In two prior series of LyP [11,12], cases that had more than one LyP subtype were placed in a “mixed LyP” category. Because multiple specimens were reviewed, 35 patients in this series with LyP fell into this category, i.e., LyP-A + LyP-B (13 patients), LyP-A + LyP-C (21 patients), and LyP-C + LyP-B (1 patient). In addition, 5 patients with pcALCL had evidence of LyP-A on at least one other specimen including 2 patients with both LyP-A and LyP-C. It is worth noting that LyP-C was the most frequent LyP subtype within the “mixed LyP” category in our series (22/35 patients) and that reported by El Shabrawi (6/7 patients) [11]. Additionally, patients with “mixed LyP” may have an increased risk of developing another
lymphoma [12]. For this reason, patients that might otherwise be classified as “mixed LyP” in our study were diagnosed using the most “advanced lesion” encountered for each patient. Accordingly, LyP-A + LyP-B cases were included in the LyP-A category, LyP-A + LyP-C cases were included in the LyP-C category, etc. The review also identified one case each of the recently described LyP-D and LyP-E subtypes and these were classified separately.

The patient population consisted of 157 patients with LyP (63 non-Hispanic White males, 77 non-Hispanic White females, 4 Black males, 10 Black females, and 3 Asian males; median age, 52 years, range 2 to 92 years) and 23 patients with pcALCL (14 non-Hispanic White males, 5 non-Hispanic White females, 2 Black males, 1 Black female, and 1 Hispanic male; median age, 56 years, range 19 to 75 years). The LyP cohort was comprised mostly of LyP type A (109 patients) followed by LyP-C (37 patients), LyP-B (9 patients) and single instances of LyP-D and LyP-E. The relative proportions of LyP-A, B and C (69.4%, 5.7% and 23.6%) are similar to other series [11,12].

An atopic diathesis was investigated in 3 ways using information obtained at the time of the initial evaluation: (1) The patients’ personal history of seasonal allergic rhinitis (hay fever), asthma or atopic dermatitis/eczema. (2) A history of these conditions in a first degree family member (parents, siblings, or children). (3) A serum IgE-t level that exceeds 100 IU/mL (serologic evidence of atopy) [2,3].

Also recorded were a history of the patients’ allergic reactions to medications and their absolute peripheral blood eosinophil counts. Skin tests for allergy were not performed.

In the absence of suitable control populations at our center, we compared our findings with normal adult controls reported in various publications. For the lifetime prevalence of atopic disorders, controls were selected from the InterLymph Project [13]. Because lifetime prevalence of atopic diseases differs significantly between European and North American centers, the odds ratios were calculated for controls evaluated at 5 centers in the United States (Figure 1) [14]. Specifically the calculated rates for allergic rhinitis/hay fever, asthma and eczema were 38.2% (1139/2982), 10.32% (443/4291), and 7.21% (156/2163), respectively. For the prevalence of allergic reactions to penicillin or derivatives, we used the 11.46% (1348/11,761) frequency from Albin’s survey [15]. IgE-t levels were compared against several published series of non-atopic controls [2,16-23].

Between 1980 and 2002, IgE-t was quantified in various commercial reference laboratories. IgE-t values were expressed as international units/ml (IU/mL) which is the same as kilounits/liter (kU/L). For samples after 2002, IgE-t was measured in the Johns Hopkins Dermatology Allergy and Clinical Immunology Reference Laboratory using an FDA approved immunological method (Immuno CAP, Thermofisher Scientific, Uppsala, Sweden). The assay was calibrated using the World Health Organization Human IgE reference preparation [24]. Values expressed as nanograms/ml were converted to IU/mL by dividing by 2.4 [25].

The reference value for healthy non-allergic adults provided by these laboratories was a geometric mean of 14 IU/mL (mean log_{10} IgE-t, 1.146 IU/mL) with 122 IU/mL given as the geometric mean plus 2 standard deviations (SD). Thus, assuming the population studied was representative, values of IgE-t up to 122 IU/mL should encompass 97.5% of the healthy non-allergic (non-atopic) adult population. These reports also indicate that type 1 hypersensitivity (atopic genesis) is “highly probable” if serum IgE-t values exceed 100 IU/mL whereas values less than 20 IU/mL indicate that an atopic predisposition was unlikely. These guidelines were derived from a 1981 Swedish study of 175 non-atopic adult patients for which the IgE geometric mean was 13.2 IU/mL (mean log_{10} IgE-t, 1.121 IU/mL) and geometric mean plus 2SD of 114 IU/mL [2]. Of note, in a more recent study, the geometric mean for IgE-t at a center in Portland, Oregon was similar to that of Sweden [26]. Therefore, for this study, we used total serum IgE-t > 100 IU/mL threshold to indicate an atopic predisposition in adults and > 122 IU/mL as an abnormally high value.

Statistics

Results of laboratory studies were given as mean values ± 1 standard deviation (SD) and/or median value with a range. Because IgE-t values and absolute eosinophil counts from population samples are skewed right, the distribution of these variables were normalized by log transformation and the geometric mean, i.e., the anti-log of the mean log_{10} IgE-t value [27]. This allows for comparisons of mean values using parametric statistical tests (analysis of variance and t-tests). Welch’s unequal variances t-test was used to compare CD30CLPD results with large control populations. Results were confirmed using non-parametric tests (Mann-Whitney and Kruskal-Wallis tests) on non-transformed data in some instances. For cases without eosinophils reported on manual white cell differential counts, the absolute eosinophil count was
set at 3.5 cells/µL to allow calculation of log values. Fisher’s and Pearson’s chi-square exact tests were used to test categorical data in 2 by 2 and R by C tables, respectively. Pearson’s correlation coefficient was used to determine the correlation between log IgE-t and log absolute eosinophil counts. The statistical software used in the study were SYSTAT10 and SPSS 13.0 for Windows, SPSS, Inc. (Chicago, IL) and StatXact-3, Cytel, Inc. (Cambridge, MA).

**Results**

Personal and family history of allergy and diagnostic group

| Diagnosis         | Atopic History* | Allergic Rhinitis | Asthma | Eczema | Penicillin Allergy | 1° Relatives with Atopy† |
|-------------------|-----------------|-------------------|--------|--------|-------------------|--------------------------|
| All CD30CLPD‡     | 64/180 (35.6)   | 49/180 (27.2)     | 13/180 (7.2) | 17/180 (9.4) | 31/180 (17.2) | 37/174 (21.3)            |
| LyP               | 60/157 (38.2)   | 46/157 (29.3)     | 13/157 (8.3) | 16/157 (10.2) | 24/157 (15.3) | 34/154 (22.1)            |
| Type B            | 5/9 (56)        | 5/9 (56)          | 1/9 (11)  | 1/9 (11)  | 2/9 (22)         | 4/9 (44)                 |
| Type A            | 38/109 (34.9)   | 30/109 (27.5)     | 10/109 (9.2) | 7/109 (6.4) | 17/109 (15.6) | 17/107 (15.9)            |
| Type C            | 17/37 (46)      | 11/37 (30)        | 2/37 (5)  | 8/37 (22) | 5/37 (14)       | 12/36 (33)               |
| pcALCL            | 4/23 (17)       | 3/23 (13)         | 0/23 (0)  | 1/23 (4)  | 7/23 (30)       | 4/23 (17)                |

Table 1 summarizes the information about personal and family history of allergy obtained at the time of the initial evaluation for patients with CD30CLPD. At least one atopic disorder (allergic rhinitis/hay fever, asthma or eczema) was noted for 38% and 17% of patients with LyP and pcALCL, respectively. Indeed one of our patients with LyP-C had long standing active atopic dermatitis when evaluated. The difference in the frequency between LyP and pcALCL was not statistically significant (P= 0.063). There also was no difference among the 3 major subtypes of LyP (P= 0.296). Allergic rhinitis was the most frequent allergy in both LyP and pcALCL subsets (27% overall) with asthma and eczema reported in 10% or fewer cases. More than one atopic condition occurred in 13 (8.3%) of LyP patients and none of the pcALCL patients (P= 0.379).

**Abbreviations:** CD30CLPD: primary cutaneous CD30+ lymphoproliferative disorders; LyP: lymphomatoid papulosis; pcALCL: Primary cutaneous anaplastic large cell lymphoma

*Atopy limited to allergic rhinitis/hay fever, asthma or atopic dermatitis/eczema.

†Parents, siblings or children.

‡Includes one case each of LyP-D and LyP-E.

When compared to data derived from the Inter-lymph project, the lifetime prevalence of allergic rhinitis in both the LyP and pcALCL subsets was statistically lower than the 38.2% prevalence observed in controls (LyP vs. control, P= 0.028; pcALCL vs. control, P= 0.016). The frequency of allergic drug reactions were similar for both LyP and pcALCL subsets (28% overall) with reactions to penicillin type drugs reported most often in both cohorts. When compared to the 11.46% frequency of penicillin reactions reported by Albin, [15] only the pcALCL cohort had a significantly higher allergy rate (P= 0.012).

With regard to atopy in first degree family members (parents, siblings, children), similar frequencies (about 20%) were reported for both LyP and pcALCL cohorts (P= 0.788). More than one atopic condition in family members was reported in about a third (12/37) of these cases. Overall patients with CD30CLPD who had a personal history of an atopic disorder were twice as likely to have a family member with atopy as patients without atopy.
(21/63 or 33% vs. 17/114 or 14.9%, P= 0.007). This was true for LyP-C patients (P= 0.014) but not for LyP-A, LyP-B nor pcALCL. However, the strong family history of atopy recorded for patients with LyP-C (12/36 or 33%) was not statistically higher than the 27% frequency for 147 adult controls reported by Hajdarbegovic (P = 0.537) [28].

**Serum total IgE**

| Diagnosis       | No. | Mean ± SD [GM] | < 20 | 20-100 | > 100 | > 122 |
|-----------------|-----|----------------|------|--------|-------|-------|
| All CD30CLPD    | 130 | 1.64 ± 0.77 [43.7] | 41 (32%) | 50 | 39 (30%) | 36 (28%) |
| LyP#*           | 116 | 1.62 ± 0.78 [41.7] | 37 (32%) | 45 | 34 (29%) | 31 (27%) |
| Type-B          | 5   | 1.32 ± 0.38 [20.9] | 2 (40%) | 3 | 0 (0%) | 0 (0%) |
| Type-A          | 84  | 1.62 ± 0.82 [41.7] | 27 (32%) | 32 | 25 (30%) | 24 (29%) |
| Type-C*         | 26  | 1.71 ± 0.73 [51.3] | 7 (27%) | 10 | 9 (35%) | 7 (27%) |
| pcALCL          | 14  | 1.76 ± 0.66 [57.5] | 4 (29%) | 5 | 5 (36%) | 5 (36%) |

Table 2: Serum total IgE in primary cutaneous CD30+ lymphoproliferative disorders and other selected conditions.

**Abbreviations:** CD30CLPD: Primary cutaneous CD30+ lymphoproliferative disorders; LyP: Lymphomatoid papulosis; pcALCL: Primary cutaneous anaplastic large cell lymphoma.

#Includes one case of LyP-E with IgE 9 IU/mL.

*Excludes one case of LyP-C with active atopic dermatitis.

¶Includes one case of hypopigmented MF and LyP-E with IgE-t of 27 IU/mL.

†GM, geometric mean = anti-log of mean log IgE-t value.

Comparison of mean log_{10} IgE-t values showed no statistically significant differences between LyP patients and pcALCL patients (P= 0.48). Although mean IgE-t levels tended to increase from LyP-B to LyP-A to LyP-C (Table 2, Figure 1), there was no significant difference among the 3 main LyP subtypes (P= 0.61). Therefore the values for all LyP and pcALCL patients were combined for subsequent comparisons.

IgE-t levels were measured on 117 with LyP and 14 patients with pcALCL (Table 2). One patient with LyP-C co-existing with active atopic dermatitis had an exceedingly high IgE-t value (11,146 IU/mL) and was excluded from the analysis. Above normal IgE-t values, defined as > 122 IU/mL (geometric mean + 2 standard deviations) on laboratory reports, occurred in 31/116 (27%) of LyP and 5/14 (36%) pcALCL patients (27.7% overall).

Several publications have provided IgE-t values for non-atopic adults to establish normal reference ranges (Table 3) [2,16-22]. Because these studies likely concerned mostly White adult patients, we excluded non-White patients and patients under the age of 17 from our series for comparison with these published reference values.

IgE-t in our White adult patients with CD30CLPD (geometric mean 42.7 IU/mL) was not only significantly higher than non-atopic adults from Zetterström’s original study from Sweden (geometric mean 13.2), but also more recent studies from other European centers that tend to have higher IgE-t values than for Sweden [26]. Mean IgE-t values for CD30CLPD were also higher than non-atopic patients studied in Canada (geometric mean 12.1) [16].

More recently, IgE-t has been measured in two large population surveys in which non-atopic individuals were identified in the absence of allergen-specific IgE antibodies. For 4407 non-atopic adult subjects studied in the European Community Respiratory Health Survey [21],...
the IgE-t geometric mean was 23.8 IU/mL and for 3972 patients aged 6 years and older studied in the United States Health and Nutrition Examination 2005-2006 Survey, [23] the IgE-t geometric mean was 21.7 IU/mL. These results are statistically lower (P< 0.001) than the mean IgE values for our patients with CD30CLPD (Table 3).

In addition, given that IgE-t levels are higher in men than women, [19-21,23] we also compared our results with several centers that provided data on men and women (Table 3). For our 51 adult White men with CD30CLPD, the geometric mean was 66 IU/mL and this was significantly higher (all with P< 0.001) than geometric mean values reported for non-atopic men in the southwestern United States (geometric mean 20.3 IU/mL), Canada (geometric mean 12.6 IU/mL), Greece (geometric mean 38.0 IU/mL), northern Italy (geometric mean 28.8 IU/mL), and Iran (geometric mean 19.1 IU/mL). Likewise the mean IgE-t values for the 53 adult White women with CD30CLPD in this series (geometric mean 28.2 IU/mL) was significantly higher than female controls from these same regions with the exception of Greece (geometric mean 29.3 IU/mL, P= 0.899) and Iran (geometric mean 23.9 IU/mL, P= 0.407).

| Reference                | Location     | No. | Gender | Mean log_{10} IgE ± SD [GM]* | P-value§ |
|--------------------------|--------------|-----|--------|-------------------------------|----------|
| Current study†           | Eastern USA  | 51  | M      | 1.82 ± 0.79 [66.1]            |          |
| Holford-Strevens         | Canada       | 130 | M      | 1.100 ± 0.477 [12.6]          | < 0.001  |
| Klink                    | Southwest USA| 643 | M      | 1.307 ± 0.688 [20.3]‡         | < 0.001  |
| Grigoreas                | Greece       | 536 | M      | 1.580 ± 0.450 [38.0]          | 0.037    |
| Simoni                   | Northern Italy| 226| M      | 1.46 ± 0.52 [28.8]            | 0.003    |
| Shoormasti               | Iran         | 219 | M      | 1.27 ± 0.62 [19.1]            | < 0.001  |
| Current study            | Eastern USA  | 53  | F      | 1.45 ± 0.74 [28.2]            |          |
| Holford-Strevens         | Canada       | 242 | F      | 1.072 ± 0.491 [11.8]          | < 0.001  |
| Klink                    | Southwest USA| 786| F      | 1.090 ± 0.658 [12.3]‡         | < 0.001  |
| Grigoreas                | Greece       | 276 | F      | 1.467 ± 0.479 [29.3]          | 0.923    |
| Simoni                   | Northern Italy| 331| F      | 1.27 ± 0.58 [18.6]            | 0.072    |
| Shoormasti               | Iran         | 147 | F      | 1.37 ± 0.66 [23.9]            | 0.428    |
| Current study            |              | 104 | M+F    | 1.63 ± 0.79 [42.7]            |          |
| Commercial labs          | Eastern USA  | NS  | M+F    | 1.146 [14.0]                 |          |
| Zetterström              | Sweden       | 175 | M+F    | 1.121 ± 0.468 [13.2]          | < 0.001  |
| Holford-Strevens         | Canada       | 372 | M+F    | 1.083 ± 0.477 [12.1]          | < 0.001  |
| Peltonen                 | Finland      | 134 | M+F    | 1.161 ± 0.416 [14.5]          | < 0.001  |
| Simoni                   | Northern Italy| 588| M+F    | 1.462 ± 0.519 [29.0]          | 0.025    |
| Shoormasti               | Iran         | 366 | M+F    | 1.32 ± 0.643 [20.8]           | < 0.001  |
| Carosso¶                 | Europe       | 4407| M+F    | 1.377 ± 0.544 [23.8]          | < 0.001  |
| Gergen¶                  | USA          | 3972| M+F#   | 1.337 ± 0.538 [21.7]**        | < 0.001  |

Table 3: Serum total IgE laboratory reference ranges for non-atopic adults from various centers.
Total IgE and smoking history

It has been suggested that IgE-t levels increase as a result of smoking and this might contribute for the higher IgE-t levels in men than women [3,21,29-31]. Accordingly, information about the smoking habits of White adult men and women with CD30CLPD and corresponding IgE-t levels is shown in (Table 4). Although IgE-t levels were slightly higher in prior and active male smokers compared to non-smokers, the differences were not significant (P= 0.40). Moreover, for both genders, heavy smokers tended to have lower IgE-t levels than light smokers. The distribution of number of patients according to their smoking habit (never, prior and active) for LyP and pcALCL cohorts was also compared and was not significant (P= 0.675, data not shown). We conclude smoking habit has a negligible effect on IgE-t in our patient population.

| Cohort§ | Smoking History | No. | Mean ± SD [GM] | P-value | IgE> 100 | P-value |
|---------|----------------|-----|----------------|---------|----------|---------|
| White Male (n= 46) | Never | 16 | 1.64 ± 0.68 [43.7] | 0.400* | 4 (25%) | 0.330† |
| | Prior | 14 | 1.80 ± 0.97 [63.1] | 5 (36%) |
| | Current | 16 | 2.04 ± 0.77 [109.6] | 8 (50%) |
| | Light | 4 | 2.35 ± 0.61 [223.9] | 3 (75%) | 0.569# |
| | Heavy | 12 | 1.93 ± 0.81 [85.1] | 5 (42%) |
| White Female (n= 47) | Never | 25 | 1.37 ± 0.62 [23.4] | 0.990* | 4 (16%) | 0.376† |
| | Prior | 5 | 1.33 ± 0.80 [21.4] | 1 (20%) |
| | Current | 17 | 1.39 ± 0.93 [24.5] | 6 (35%) |
| | Light | 5 | 2.05 ± 0.43 [112.2] | 3 (60%) | 0.077# |
| | Heavy | 10 | 0.82 ± 0.72 [6.6] | 1 (10%) |

Table 4: Correlation of smoking history and serum total IgE in adult White patients with primary cutaneous CD30+ lymphoproliferative disorders.**

** Smoking history was available on 136 patients with lymphomatoid papulosis and 17 patients with primary cutaneous anaplastic large cell lymphoma.
§ No significant difference in the frequencies among non-smokers, ex-smokers, and active smokers (P= 0.75). Therefore groups combined into CD30CLPD cohort.
* Analysis of variance: never vs. prior vs. current smoking
† t-test: light vs heavy smoking
‡ Chi-square exact test
# Fisher’s exact test

Total IgE> 100 IU/mL and atopic predisposition

Another criterion used to identify atopic predisposition is a IgE-t value that exceeds 100 IU/mL [2,3]. For patients with CD30CLPD, an IgE-t value > 100 IU/mL was more likely to be associated with personal
history of allergic rhinitis/hay fever, asthma or eczema than IgE values ≤ 100 IU/mL (P= 0.046, Table 5). This occurred primarily because of patients with LyP-A (P= 0.024). However there was no association between IgE-t >

| Diagnosis     | IgE-t > 100 IU/mL | Patients with atopy/total | P-value | 1° Relatives with atopy/total‡ | P-value |
|---------------|------------------|---------------------------|---------|-------------------------------|---------|
| All CD30CLPD† | No               | 26/91 (29%)               | 0.046   | 23/89 (26%)                   | 0.826   |
|               | Yes              | 19/40 (48%)               |         | 9/40 (23%)                    |         |
| LyP†          | No               | 26/82 (32%)               | 0.097   | 20/80 (25%)                   | 1.0     |
|               | Yes              | 17/35 (49%)               |         | 9/35 (26%)                    |         |
| Type A        | No               | 15/59 (25%)               | 0.024   | 10/57 (18%)                   | 0.766   |
|               | Yes              | 13/25 (52%)               |         | 5/25 (20%)                    |         |
| Type C        | No               | 9/17 (53%)                | 0.695   | 7/17 (41%)                    | 1.0     |
|               | Yes              | 4/10 (40%)                |         | 4/10 (40%)                    |         |
| pcALCL        | No               | 0/9 (0%)                  | 0.11    | 3/9 (33%)                     | 0.258   |
|               | Yes              | 2/5 (40%)                 |         | 0/5 (0%)                      |         |

Table 5: Relationship between serum total IgE as a serologic marker for atopy and personal and family history of an atopic disorder.

**Abbreviations:** CD30CLPD: Primary cutaneous CD30+ lymphoproliferative disorders; LyP, lymphomatoid papulosis; pcALCL: Primary cutaneous anaplastic large cell lymphoma.

* History of an atopic disorder (allergic rhinitis/hay fever, asthma or atopic dermatitis/eczema).
† includes patient with LyP-C and active atopic dermatitis.
‡ Parents, siblings or children.

**Eosinophil counts**

Eosinophils are often increased in the peripheral blood of patients with an ongoing allergy. The reference range for absolute eosinophil count ranges between 5 and 500 cells/µL [32]. Of patients with CD30CLPD, 7 of 174 (4%) had absolute eosinophil counts that exceeded 500 cells/µL (Table 6). There was no difference in mean absolute eosinophil counts between LyP and pcALCL (P= 0.40) nor among LyP-A, LyP-B and LyP-C subtypes (P= 0.86).

| Diagnosis     | No.  | Median (range) | Log Absolute Count ± SD [GM]# | ≤ 500 | > 500 |
|---------------|------|----------------|-------------------------------|-------|-------|
| All CD30CLPD  | 174  | 135.5 (0-4788) | 1.92 ± 0.76 [83.2]            | 167   | 7 (4.0%) |
| LyP†          | 152  | 138 (0-4788)   | 1.94 ± 0.73 [87.1]            | 146   | 6 (4.0%) |
| Type A        | 108  | 141 (0-4788)   | 1.94 ± 0.76 [87.1]            | 103   | 5 (4.6%) |
| Type B        | 8    | 108 (50-312)   | 2.11 ± 0.31 [128.8]           | 8     | 0 (0%)  |
| Type C†       | 34   | 138 (0-792)    | 1.91 ± 0.76 [81.3]            | 33    | 1 (3%)  |
| pcALCL        | 22   | 96 (0-1114)    | 1.76 ± 0.90 [57.5]            | 21    | 1 (5%)  |

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Although the 62 CD30CLPD patients with personal history of atopy had a slightly higher absolute eosinophil count (median 144/µL, range 0-1114]) than 112 patients without atopy (median 125/µL, range 0-4788), the difference was not statistically significantly (P= 0.11). Furthermore, there was no correlation between eosinophil and IgE-t levels (Pearson’s correlation, r= 0.04).

Discussion

In contrast to prior publications [6-9], our patients’ personal and family history did not support the hypothesis that atopy is associated with CD30CLPD. Indeed, the rate of allergic rhinitis in our patients with pcALCL (13%) in this retrospective study was much lower than the 46% reported for pcALCL in the InterLymph study [9]. However, the observed frequencies in our study may be erroneously low for several reasons: (1) a patients’ history of allergic rhinitis or asthma might not have been recorded as part of a routine dermatologic evaluation whereas such information would be captured on a formalized questionnaire, (2) dermatologists identify atopic dermatitis as a specific entity whereas cited epidemiologic studies might include other eczematous dermatoses under a broader category of atopic eczema, and (3) a significant proportion of adults (> 40%) with an atopic condition in childhood do not recall that they had the problem (recall bias) [33]. For these reasons, we place more reliance on measurements of IgE-t and eosinophil counts as indicators of atopy even though these tests are not specific. A study that measures allergen-specific serum IgE levels in CD30CLPD would be more informative [34].

For patients with CD30CLPD, mean IgE-t levels are significantly higher than for non-atopic adult controls and 30% of patients have values that exceed 100 IU/mL, a criterion used in our study to define probable atopy [2,3]. Several hypotheses might be considered to explain the increased IgE-t in CD30CLPD patients. The first is that atopic individuals might be at increased risk to develop CD30CLPD. To investigate this further, it would be necessary to compare CD30CLPD rates in atopic and non-atopic populations.

An alternative hypothesis is that development of CD30CLPD in atopic individuals results in increased IgE-t production in response to antigens encountered specifically in the skin. By definition, atopic individuals are genetically programmed to have heightened IgE responses to antigenic stimulation. This leads to the question of whether the increase in IgE-t in the setting of CD30CLPD is a non-specific response to inflammation in the skin or whether a specific response to one or more activating antigens encountered in skin lesions is playing a role. A third possibility is that the atypical CD30+ cells of LyP and pcALCL are elaborating cytokines that enhance production of IgE-t. These possibilities are not mutually exclusive.

It has been suggested that increased IgE-t in atopic individuals is comprised of a least two independent components: a cognate IgE fraction associated with atopic sensitization (i.e., allergen-specific IgE antibodies) and a non-cognate IgE fraction unrelated to atopic disease [35]. In support of a non-cognate response in CD30CLPD is the observation that IgE-t may be increased in some patients with a variety of inflammatory skin disorders other than atopic dermatitis (listed in Supplementary Table 1). However, it is possible that heightened IgE-t responses in these situations are occurring in individuals genetically predisposed to atopy. This includes entities such as burns and hidradenitis suppurativa that do not have an apparent allergic, eczematous or autoimmune component as part of the inflammatory response [36-38]. Pascual hypothesized that elevated IL-10 in hidradenitis suppurativa promotes B cell differentiation to plasma cells that produce the IgE [38,39].

Consideration must also be given to the possibility of a cognate IgE response to a specific antigen in CD30CLPD. Although the pathogenesis of LyP and pcALCL is unknown, we and other investigators have speculated that a virus or other persistent antigen source acts to stimulate susceptible memory T cells that ultimately develop genetic alterations that favor disease development and progression [40,41]. In this regard, it
might be informative to study CD30CLPD for IgE antibodies against staphylococcal and streptococcal superantigens, given the role of staphylococcal superantigens in the pathogenesis of atopic dermatitis [42], and the similar eruptive nature of LyP and acute guttate psoriasis which has been shown to be mediated by streptococcal superantigens [43,44].

A third possibility that was suggested by the possible increase in IgE-t with more advanced CD30CLPD (Table 2 and Figure 1) is that the atypical CD30+ cells are elaborating cytokines that promote IgE-t production. For example, Yagi showed that IL-4 and IL-10 mRNA is increased in lesions of LyP and pcALCL [45]. Moreover, preliminary data from the Kadin laboratory indicates that these cells have readily detectable IL-13 in their cytoplasm by immunohistochemistry and that Mac-2A/2B cell lines derived from a patient with CD30CLPD secrete IL-13. IL-13 is known to promote Ig class switch of B cells to IgE synthesis [46]. The local production of IL-13 would explain the local accumulation of eosinophils in many lesions of CD30CLPD, but usually not LyP-B which often lack CD30+ cells [47]. It remains to be determined if the amount of cytokines secreted by the total biomass of CD30+ atypical cells in the skin is sufficient to cause an increase in IgE-t as suggested in Figure 1. In addition, whether the cytokine profile of the atypical CD30+ cells in atopic and non-atopic individuals differs requires further study.

**Conclusion**

In conclusion, we provide evidence that serum IgE-t is often increased in patients with CD30CLPD, specifically 27% and 36% of patients with LyP and pcALCL, respectively. The IgE-t > 100 IU/ml threshold for probable atopy was exceeded in 30-36% of LyP-A, LyP-C and pcALCL, but not LyP-B. Eosinophilia was present in 4% of cases. However, a link with atopy was not supported by review of the patients’ personal and family history that was obtained at the time of the initial examination rather than using a formal questionnaire. Additional studies with measurement of allergen-specific IgE antibodies with attention to bacterial super antigens might be informative.

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