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# Blood eosinophilia: A poor prognostic factor for primary cutaneous T cell lymphomas? A cohort of 72 cases

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## ABSTRACT

**Introduction:** Blood eosinophilia (BE) is described as a poor prognosis marker for some T cell malignancies. **Objective:** to detect the presence and the prognostic significance of BE in patients with cutaneous T cell lymphoma (CTL). **Methods:** This was a retro prospective study of 72 patients with CTL. Patients with other factors that may increase BE were excluded. **Results:** We had 14 cases of BE, 10 cases were in the erythrodermic stage of the disease and 6 in the tumoral stage and we had 4 cases of death. The BE was associated with deterioration of the general condition (p=0.001); depilation of the body (p=0.04), erythroderma (p=0.008), scalp and nails involvement (p=0.000), high rate of lactate Dehydrogenase (LDH) (p=0.000) and beta 2 microglobulin (B2M), (p=0.000), the histological type of Mycosis fungoides (MF) with positive Immunohistochemistry for CD4 (p=0.014) and CD3(0.05). **Conclusions:** BE was significantly related to MF, to advanced stages of the disease, to pejorative clinical signs and to elevated rate of LDH and B2M which are poor prognostic factors of MF with four cases of death, which prove that BE is also a poor Prognostic factor of MF.

**Key words:** Primary cutaneous T cell lymphoma; Mycosis fungoides; Blood eosinophilia; Marker of poor prognosis; Noninvasive; Clinical and therapeutic implications

## INTRODUCTION

Primary cutaneous lymphomas (PCL) is the second frequent localization of extra nodal lymphomas, and the T cell lymphomas (PCTL) represent almost 80% of PCL. It's characterized by epidemiological, clinical, histologic, immunophenotypic and prognosis variety [1].

PCLT are dominated by the mycosis fungoides (MF), but others entities defined by the European Organization for Research and Treatment of Cancer (EORTC) classification are also reported: $CD30^+$ large T-cell lymphomas ($CD30^+$); Sezary syndrome (SS) and $CD30^-$ large T-cell lymphomas ($CD30^-$), pleomorphic small-to medium-sized CTCLs (PSMs), and it had a prognosis not yet well defined [2].

These lymphomas are becoming more and more aggressive, that's why many studies have attempted to identify some predictors of poor prognosis which will surely have therapeutic implications.

The blood eosinophilia (BE) is well Studied and reported as a marker of a poor prognosis in some T-cell malignancies: nodal T-cell lymphoma and Hodgkin's disease, but this eosinophilia is less studied in PCTL.

The aim of our study was to detect the presence of BE in patients with PCTL and its prognostic significance.

## MATERIALS AND METHODS

This was a unicentric retro prospective study (retrospective since 2008 until June 2013 and prospectively from June

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2013 to October 2014) of patients followed for cutaneous lymphomas in the Department of Dermatology of the hospital Hassan II of Fez.

All patients with PCLT were included. The diagnosis of PCTL was based on the combination of clinical, histologic, and immune phenotypic criteria of the EORTC classification.

For survival analysis, we considered only disease-specific death, defined as death related to PTCL or its specific treatment.

Patient data have been collected by our doctors in the Department of Dermatology of the hospital Hassan II of Fez.

The medical records of our patients included: socio-demographic data such as "age, gender, work, ethnicity, the notion of personal or familial atopy, iatrogenic immunosuppression, viral immunosuppression (HIV), exposure to a toxic or irradiation". Clinical data such as: functional signs (Deterioration of the general condition,pruritus, Pain) and physical signs (plaques, nodules, tumors, erythroderma, scalp, nails and mucosal involvement). Paraclinical data: serum rate of lactate dehydrogenase (LDH) and B2 microglobulin, standard histology and immunohistochemistry results.

Deterioration of the general condition or alteration of the general condition (AEG) is a syndrome combining three clinical signs: Anorexia, asthenia and weight loss greater than or equal to 5% of normal weight.

Scalp involvement: especially in folliculotropic lymphoma such as alopecia.

Nail involvement because of the lymphoma or a reaction processe of paronychial inflammation: pachyonychia, xanthonychia, lines of beau.

Raised blood eosinophil count was defined as: >500 elements/mm$^3$. In patients with BE, an etiologic investigation has been achieved and only patients with a BE proved as "idiopathic" were selected. Patients with other factors that may increase blood eosinophilia were excluded.

High serum level of lactate dehydrogenase (LDH) in Adult was defined as >390 UI/l.

High serum level of B2 microglobulin (B2M) was defined as > 2.5 UI/l.

Two kinds of analysis were Performed: descriptive and univariate analysis.

The analysis was performed using the SPSS 20 software.

## RESULTS

Our serie includes 72 cases of PCTL. The average age was 17.6 ± 55.12 years old and most of patients were aged more than 45 years (76.3%) and we had a slight female predominance (54.1%).

The study group included patients with classical and variants of MF (62 cases), Sezary syndrome (1 case), and non epidermotropic lymphoma (NEL): CD30$^+$ anaplastic large T-cell lymphomas (7 cases), CD30$^-$ large T-cell lymphomas (2 cases).

We had 14 cases (19.4%) of BE in our patients (Table 1).

The BE was most notable in patients aged more than 45 years, females with a disease duration between 5 and 10 years. Many clinical signs were noted in these patients (summarized in Table 1) with frequency of unusual pigmented plaques.

Biological abnormal signs found in these patients were: increased rate of LDH and B2M, with histological phenotype of classic, folliculotropic and transformed mycosis MF.

The means of molecular biology for the analysis of lymphocyte clonality were not available in our hospital and have not been used in any of our patient.

8 cases of our patients with eosinophilia were in the erythrodermic stage of the disease and 6 in the tumoral stage and we had 4 cases of disease-specific death.

Finely, in our study population, the BE was significantly related to some clinical and paraclinical signs such as: Deterioration of the general condition, Depilation of the body, Erythroderma, sclap and nails involvement. Increased rate of LDH and B2M, Histological type of MF with positive Immunohistochemistry for CD4 and CD3 (Table 2).

## DISCUSSION

Several studies, mostly focusing on the epidermotropic lymphomas such as the MF and Sezary syndrome groups, have attempted to identify clinical, biological,

**Table 1:** Showed the principal epidemiological, clinical and paraclinical characteristics of patients with and without BE

| PCTL (72) | PCTL (N=/%) | PCTL with BE (N/%): 14/19.4% |
|---|---|---|
| Epidemiological characteristics | | |
| Age groups | | |
| 15-45 years | 17/23.6 | 4/28.5 |
| >45 years | 55/76.3 | 10/71.4 |
| Gender | | |
| F | 39/54.1 | 9/64 |
| M | 33/47.1 | 5/35.7 |
| Disease duration | | |
| <5 years | 28/38.9 | 5/35.7 |
| 5-10 years | 29/40.2 | 7/50 |
| >10 years | 15/20.8 | 2/14.3 |
| Clinical characteristics | | |
| Pain | 2/27.7 | 1/8.1 |
| Pruritus | 53/73.6 | 14/100 |
| Deterioration of the general condition | 6/83.3 | 4/28.5 |
| Erythematous plaques | 1/1.38 | 3/21.4 |
| Erythematous scaly patches | 32/44.4 | 8/57.1 |
| Papules | 12/16.6 | 1/7.1 |
| Nodules | 14/19.4 | 4/28.5 |
| Ulceration | 15/20.8 | 4/28.5 |
| Pigmented patches | 23/31.9 | 5/35.7 |
| Tumors | 12/16.6 | 3/21.4 |
| Erythroderma | 20/27.7 | 8/57.1 |
| Depilation of the body | 9/12.5 | 4/28.5 |
| Poikiloderma | 4/5.5 | 1/7.1 |
| Ichthyosiform state | 1/1.38 | 1/7.1 |
| Localization in the hidden areas | 59/81.9 | 6/42.8 |
| Palmoplantar keratoderma (PPK) | 13/18 | 4/28.5 |
| Lymphadenopathies | 32/44.4 | 9/66.3 |
| Mucosal involvement | 4/5.5 | 3/21.4 |
| Scalp involvement | 18/25 | 10/71.4 |
| Nails involvement | 17/23.6 | 7/50 |
| Leonine facie | 4/5.5 | 1/7.1 |
| Paraclinical characteristics | | |
| High serum level of lactate dehydrogenase (LDH) | 18/25 | 11/78.5 |
| High serum level of B2 micoglobulin (B2M) | 16/22.2 | 12/85.7 |
| Sezary cells | 1/1.38 | 0/0 |
| Histological type | MF 62/86.1 | |
| | Classical MF: 52/83.8 | 10/71.4 |
| | Folliculotropic MF: 8/12.9 | 1/7.1 |
| | Transformed granulomatous MF CD30+: 1/1.6 | 1/7.1 |
| | MF transformed into high-grade CD 30- : 1/1.6 | 1/7.1 |
| Immunohistochemistry | CD4: 43/59.7 | CD4: 12/85.7 |
| | CD3: 48/66.6 | CD3: 10/71.4 |
| | CD30: 1/1.38 | CD30: 1/7.1 |

histopathologic, or immunophenotypic characteristics that can predict outcome.

**Table 2:** The clinical, paraclinical and histological signs significantly associated with BE in our patients

| BE (14 cases/72 PCTL ) | P value |
|---|---|
| Deterioration of the general condition | 0.001 |
| Depilation of the body | 0.04 |
| Erythroderma | 0.008 |
| Scalp involvement | 0.000 |
| Nails involvement | 0.001 |
| Increased rate of LDH | 0.000 |
| Increased rate of B2M | 0.000 |
| Histological type of MF | 0.014 |
| Immunohisto chemistry: CD4 | 0.015 |
| CD3 | 0.04 |

So far, the main prognostic factors identified in this group are the type and extent of the skin involvement, extra cutaneous spread of the disease, initial response to treatment, histologic transformation, high serum level of lactate dehydrogenase (LDH), and the detection of a cutaneous or peripheral blood T-cell clone by polymerase chain reaction [3,4].

Besides, there are a few observations that detect the prognostic significance of BE in patients with T cell malignancies and rarely in PCTL.

BE is associated with a number of different etiologies including parasitic diseases, atopy, allergic reactions, inflammatory bowel disease, rheumatoid arthritis, vasculitis and lymphoma [5].

This BE was reported as a marker of a poor prognosis in Some T-cell malignancies: nodal T-cell lymphoma and Hodgkin's disease.

For exemple, there was a study of 99 consecutive patients with "idiopathic" eosinophilia that demonstrated the presence of clonal T-cells in blood, bone marrow, or other tissue samples of 14 patients including 6 patients who had an overt T-cell malignancy [6].

In Hodgkin disease, several studies investigating eosinophilia [7]: found a worse relapse-free survival rate in patients with eosinophilia than in those without [8-9]. In a more recent study, tissue eosinophilia has been shown to be the strongest prognostic factor for poor relapse-free survival and overall survival in nodular sclerosing hodgkin disease.

Concerning PCTL, Some publications reported the presence of BE [10,11] in patients with cutaneous T non-Hodgkin's lymphoma, and was considered as a poor prognostic factor, but these publications were based on a case report.

In two retrospective inception cohort, this BE was also demonstrated to be related to a poor prognosis of the disease.

The first study was a cohort that included 104 patients with cutaneous T-cell lymphoma, BE was a significant indicator of poor prognosis and increased disease-specific death [12].

The second and recent study [13], demonstrated that: BE was a predictive of more advanced disease ($P < .0001$), increased number of treatment types ($P < .002$), and less responsiveness to treatment ($P < .0006$).

In our study, we found 14 cases of BE, which was significantly related to the histological type of MF, to advanced stages of the disease (tumor and erythrodermic stage), to pejorative clinical signs (deterioration of the general condition, depilation of the body and nail involvement) and to the high levels of the LDH and B2M which are known factors of poor prognosis of MF.

We also had four disease-specific deaths in our patients with BE, which leads us to conclude that blood eosinophilia is also a poor prognostic factor for PCTL - especially for MF - in our study.

Some hypothesis were reported to explain this BE in PCTL and in T cell malignancies: It has been related to the predominant secretion of T helper cell type 2 ($T_H2$) eosinophilopoietic or eosinophilotactic cytokines (interleukin (IL) 3, IL-5, and sargramostim) by neoplastic cells [14,15]. This $T_H2$ differentiation has been associated with a relative defect of the antitumoral and anti-infectious response [16], so the hypothesis that eosinophilia might be an indicator of poor prognosis was raised, another theory of Depressed cell-mediated immunity and deficiency in IL-2 and interferon γ production and finally Increased production of IL-4, IL-5, and IL-10 [17,18].

Indeed, In view of these notions, these hypothesis must be tested in further prospective, large-scale studies, and such research might help to identify subgroups of patients who might benefit from immunotherapeutic approaches such as IL 12, IL 2, and interferon gamma, which are likely to correct the abnormal cytokine production observed in PTCL [19-21].

This fact that BE is a poor prognosis factor, must leads clinicians to choose some therapeutic options and aggressive treatments from the beginning instead of losing time by applying topical therapies.

This study have some limitations such as: the limited number of patients, the duration of follow-up is unsatisfactory for the study of survival and there was no correlation between the BE and molecular biology to the study of lymphocyte clonality.

## CONCLUSION

Blood eosinophilia must be taken Into account in patients having PCTL especially MF because it's a non invasive factor for evaluating the disease prognosis and therapeutic options.

### Statement of Human and Animal Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

### Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

### Abbreviations

Blood eosinophilia: BE; Cutaneous T cell lymphoma: CTL; Mycosis fungoides: MF; Beta 2 microglobulin: B2M; Lactate Dehydrogenase: LDH; Primary cutaneous lymphomas: PCL T cell lymphomas: PCTL; Pleomorphic small-to medium-sized CTCLs: PSMs; The European Organization for Research and Treatment of Cancer classification: EORTC classification; Sezary syndrome: SS; Palmoplantar keratoderma: PPK

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