Erythroderma is challenging to diagnose. The aim of this single-centre retrospective study was to identify factors that can be used to improve the diagnosis of erythroderma. Among 91 patients with erythroderma, 21 were diagnosed with eczema, 17 with psoriasis, 20 with drug-induced erythroderma, 13 with erythrodermic mycosis fungoides and 20 with Sézary syndrome. Nail alterations, ear involvement, and severe scaling were significantly associated with psoriasis ($p = 0.044$). Fever and hypereosinophilia were associated with drug-induced erythroderma. Expression of programmed cell death protein 1 was observed in all skin biopsies. However, with Sézary syndrome, programmed cell death protein 1 expression was significantly higher than with other aetiologies. A programmed cell death protein 1 hormone receptor score ($H$-score) $>50$ was associated with Sézary syndrome ($p < 0.001$, sensitivity 75%, specificity 92%) as well as CXCL13 expression ($p < 0.044$). CD7 loss was more frequent with erythrodermic mycosis fungoides and Sézary syndrome ($p = 0.022$). This study reports the importance of programmed cell death protein 1 expression for the differential diagnosis of Sézary syndrome and other aetiologies, including erythrodermic mycosis fungoides.

**Key words:** Sézary syndrome; erythrodermic mycosis fungoides; erythrodermic psoriasis; erythrodermic eczema; erythrodermic drug-induced erythroderma; programmed cell death protein 1.

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Erythroderma is defined as chronic, generalized erythema affecting more than 80% of the body surface area. It decreases patients’ quality of life and is potentially life-threatening (1). Erythroderma is associated with various skin disorders, which are divided into 2 categories: cutaneous T-cell lymphoma (CTCL) and inflammatory dermatoses, such as eczema, psoriasis, and drug-induced eruptions. Identifying the aetiologies of erythroderma is critical due to their different management strategies, treatments, and prognosis. However, clinical differential diagnosis of erythroderma is often challenging (2–6), even if the history of dermatosis is highly informative (7). In addition, pathological diagnosis is also complicated, as non-specific features are often seen with erythroderma (5, 6). Ram-Wolff et al. (8) showed that histological analysis provided a correct diagnosis in only 31% of 47 total skin biopsies examined. The presence of epidermotropism, intra-epidermal atypical lymphocytes, Pautrier’s micro-abscesses, and dermal cerebriform lymphocytes are criteria previously reported to differentiate erythrodermic mycosis fungoides (E-MF) from Sézary syndrome (SS) (9, 10). It was also shown that the accuracy of diagnosis could be increased by taking multiple biopsies in different areas and at different disease stages (3, 5, 11, 12). SS may also initially present as non-erythrodermic dermatitis, even though 86% of patients with SS will eventually develop erythroderma (13). Programmed cell death protein 1 (PD-1) overexpression in SS was first reported in 2010 by Samimi et al. (14), therefore associated with immunosuppressive functions of these cells as PD-1 blockade enhanced interferon γ production. Since then, PD-1 has been identified as a diagnostic marker in CTCL and inflammatory erythrodermas, and increased programmed cell death protein 1 expression on lymphocytes was associated with Sézary syndrome. Among other follicular T-helper lymphocyte markers, CXCL13 overexpression was associated with Sézary syndrome and mycosis fungoides, whereas inducible co-stimulator expression was non-discriminant. Based on these results, calculating an $H$-score for programmed cell death protein 1 expression appears to be a reproducible and effective way of diagnosing Sézary syndrome among erythroderma cases, with $H$-scores $>50$ having high specificity (92%) and sensitivity (75%).
was not assessed consistently, other inflammatory skin diseases were considered as a single category and E-MF cases were not included.

PD-1 is an inhibitory receptor in the B7/CD28 family (17, 19, 20). Both follicular T-helper lymphocytes (TFHs) and some subsets of activated T cells constitutively express PD-1. TFHs migrate to the germinal centre, where they are needed for B-cell maturation (20–23). To distinguish them from other CD4+ T cells, TFH markers include B-cell lymphoma 6 (Bcl6), CD10, PD-1, inducible T-cell co-stimulator (ICOS), and chemotactic chemokine ligand 13 (CXCL13) (20). ICOS is structurally and functionally related to CD28 (24), whereas CXCL13 is a chemokine that selectively interacts with B lymphocytes (25). The function of PD-1 in Sézary cells remains unclear, probably associated with suppressive and/or exhausted phenotype (19). Enhanced PD-1 expression has been shown in clonal Sézary cells compared with normal CD4+ T cells from SS patients or healthy individuals (19). However, PD-1 expression patterns on leukemic cells, as detected using flow cytometry, may define heterogeneous subtypes of SS and their distinctive immune environments (26). In addition, rare PD-1 gene deletions may drive aggressive disease behaviour, preventing the development of the T-cell exhaustion phenotype observed in wild-type cases (27), and PD-1 blockade in vitro may enhance tumour T-cell proliferation (19).

The aim of this study was to search for discriminant diagnostic markers in a retrospective series of 91 patients with erythroderma of differing aetiologies by analysing clinical, biological, histopathological, and immunohistochemical data, focusing on PD-1, CXCL13, and ICOS.

MATERIALS AND METHODS

Patients and samples

Data from the electronic health records of all patients with erythroderma admitted to the Dermatology Department of the University Hospital of Bordeaux between 2010 and 2020 were reviewed. Patients with the following 5 diagnoses were selected: psoriasis, eczema, drug-induced erythroderma (DE), SS, and E-MF. All selected patients had a well-defined diagnosis, available clinical photographs, available formalin-fixed paraffin-embedded (FFPE) skin biopsy sections, and a follow-up period of at least 1 year after diagnosis. SS and E-MF were diagnosed based on the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC) classification of cutaneous lymphoma (11). The data were anonymized after collection and password-protected during the study. Consent was obtained from the study participants, and the local ethics advisory board approved the study (Research Ethics comitee of the University Hospital of Bordeaux, CE-GP-2020-45).

Clinical and biological data

The patient data included their age, sex, medical history, ongoing therapies, newly introduced medications, median time from onset of erythroderma to final diagnosis, B symptoms, fever status, blood eosinophilia status, lactate dehydrogenase (LDH) level, and total IgE level. Clinical data were retrieved together with clinical photographs. Blood involvement was determined according to blood immunophenotyping data for absolute counts of CD3, CD4, CD7, and/or CD3, CD4, CD26+ T cells. The patients were categorized as follows: B0, <250/μl; B1, 250–1,000/μl; and B2, ≥1,000/μl plus T-cell clones in the blood (28). When available, data on CD158 expression were taken into account. Routine T-cell clonality data on skin and blood samples were also collected.

Histology and immunohistochemistry

All cases were assessed in a blinded procedure by 2 dermatopathologists (SM and BV). For each case, pathological diagnosis was based solely on the histological criteria without any clinical information. Histological parameters including the presence of psoriasiform hyperplasia, parakeratosis, neutrophil microabscesses, spongiosis, eosinophilic infiltration, lichenoid lesions, necrotic keratinocytes, epidermotropism, and atypical lymphocytes (lymphocytes with enlarged, irregular, and chromatic nuclei) were recorded. Automated immunostaining was performed on all FFPE skin biopsies with antibodies against PD-1 (NAT-105 clone; Bio SB, Santa Barbara, USA), ICOS (polyclonal antibody; Abcam, Amsterdam, Netherlands), CXCL13 (53610Clone; RD Systems, Minneapolis, USA), Ki-67 (MM1 clone; Leica, Nanterre, France), and CD7 (LP15 clone; Leica). The results of standard routine immunostaining (CD3, CD4, CD8) were reviewed retrospectively. The percentages of lymphocytes expressing PD-1 and ICOS were calculated from the whole lymphocytic infiltrate (epidermal and dermal) and classified into 4 categories: 0%, 1–50%, 51–75%, and ≥75%. The intensity of PD-1 and ICOS expression was scored as 0, 1+, 2++, or 3++. The hormone receptor score (H-score) was used for semi-quantitative evaluation of PD-1 and ICOS expression, and it is calculated based on the percentages of positive cells stained at different intensities, as follows: H-score=0×(%cells with score 0)+1×(% cells with score 1++)+2×(%cells with score 2++)+3×(%cells with score 3++) (29–31). The final score ranges from 0 to 300 (25, 26). CXCL13 was considered positive when more than 5% of the lymphocytic infiltrate was stained (32). Loss of CD7 expression was scored as the percentage of CD3+ cells (10, 33). Ki-67 expression served as an indicator of the proliferation of dermal infiltrating lymphocytes.

Statistical analysis

Statistical calculations were performed using R software (ver. 4.0.0; R Development Core Team, Vienna, Austria). Quantitative variables are provided as medians and interquartile ranges, and qualitative variables as numbers and percentages. Quantitative and qualitative variables were compared using the non-parametric Kruskal–Wallis test and Fisher’s test, respectively. The alpha level was set at 0.05, and the Bonferroni correction was used to adjust for multiple comparisons. Reproducibility between pathologists was assessed with intraclass correlation coefficients (ICCs) for H-scores and the intensity of PD-1 expression; the kappa coefficient was used for qualitative H-scores. A sensitivity analysis with elastic-net penalized multinomial regression was performed.

RESULTS

Demographic data

A total of 91 patients fulfilled the inclusion criteria: 17 with psoriasis, 21 with eczema, 20 with DE, 20 with SS, and 13 with E-MF. Median age at diagnosis was
Clinical findings

Clinical features are detailed in Table II. Nail damage was more frequent in patients with psoriasis (11/17, 64.7%, \( p = 0.0430 \)). Severe scaling and ear involvement occurred more frequently in the psoriasis subgroup (\( p = 0.0430 \)) (Fig. 1). Ten out of 91 patients had fever, most were in the DE subgroup (9/18, 45%).

Laboratory and T-cell clonality findings

The blood eosinophil count was higher in the DE subgroup (\( p = 0.0004 \)). An elevated LDH level was observed in 52 of 73 patients, with no significant differences between subgroups. All patients with SS had B2 stage disease; 14 patients with other diseases had an abnormal immunophenotype corresponding to “B1” stage: 5 with eczema, 4 with psoriasis, and 5 with E-MF (Table II). T-cell clonality PCR analyses revealed skin T-cell clones in all 33 patients with CTCL, and 8 of 29 patients (29%) with eczema or psoriasis. Blood T-cell clones were found in 28 of 31 patients (90%) with CTCL, as well as in 8 of 26 patients (31%) with eczema or psoriasis. However, identical skin T-cell clones in different biopsies and/or identical blood and skin T-cell clones were only seen in patients with E-MF or SS (Table III).

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### Table I. Demographic data

| Diagnosis       | Male:female sex ratio (numerical ratio) | Age, years (Median, IQR) | Pre-existing dermatoses related to the episode (n (%)) | Time from the onset of erythroderma to diagnosis, months (Median) | Follow-up time, years (Median) |
|-----------------|-----------------------------------------|--------------------------|------------------------------------------------------|---------------------------------------------------------------|--------------------------------|
| Eczema (n = 21) | 13:8 (1.6)                              | 66.0 (60.0, 75.0)        | 14 (66.7)                                            | 5.5                                                           | 2                              |
| Psoriasis (n = 17) | 16:1 (16)                              | 67.0 (63.0, 70.0)        | 13 (76.5)                                            | 1.0000                                                        | 0.0430                         |
| DE (n = 20)      | 7:13 (0.5)                              | 59.5 (48.5, 71.8)        | 2 (10.0)                                             | 6.0 (0.9, 11.0)                                               | 10.0000                        |
| SS (n = 20)      | 6:14 (0.4)                              | 70.2 (64.0, 79.3)        | 3 (15.0)                                             | 13.5                                                          | 0.0004                         |
| E-MF (n = 13)    | 6:7 (0.9)                               | 75.0 (69.0, 80.0)        | 5 (38.5)                                             | 11                                                            | 6                              |
| Total (n = 91)   | 48:43 (1.1)                             | 67.0 (60.5, 76.0)        | 37 (40.7)                                            | 4.1                                                           | 3                              |

IQR: interquartile range; SS: Sézary syndrome; E-MF: erythrodermic mycosis fungoides; DE: drug-induced erythroderma.

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### Table II. Clinical and laboratory data for the cohort and subgroups

| Clinical lesions, n (%) | Eczema, n = 21 | Psoriasis, n = 17 | DE, n = 20 | SS, n = 20 | E-MF, n = 13 | Total, n = 91 | \( p \)-value* |
|-------------------------|----------------|-------------------|------------|------------|-------------|--------------|---------------|
| Ear involvement         | 1 (4.8)        | 11 (64.7)         | 4 (20.0)   | 5 (25.0)   | 6 (46.2)    | 27 (29.7)    | 0.0430        |
| Alopecia                | 2 (9.5)        | 0 (0.0)           | 2 (10.0)   | 10 (50.0)  | 4 (30.8)    | 18 (19.8)    | 0.0430        |
| Scalp involvement       | 11 (52.4)      | 14 (82.4)         | 8 (40.0)   | 17 (85.0)  | 11 (84.6)   | 61 (67.0)    | 0.4728        |
| Nail damage             | 1 (4.8)        | 11 (64.7)         | 0 (0.0)    | 5 (25.0)   | 2 (15.4)    | 13 (14.5)    | 0.4300        |
| Paronychia              | 3 (14.3)       | 9 (52.9)          | 4 (20.0)   | 1 (5.0)    | 2 (15.4)    | 14 (15.4)    | 0.0004        |
| Major scaling           | 4 (19.0)       | 16 (94.1)         | 6 (30.0)   | 5 (25.0)   | 2 (15.4)    | 33 (36.3)    | 0.0043        |
| Palmpoplantar keratoderma | 4 (19.0)      | 13 (76.5)         | 5 (25.0)   | 14 (70.0)  | 5 (38.5)    | 41 (45.1)    | 0.0043        |
| Cheilitis               | 1 (4.8)        | 1 (5.9)           | 1 (5.0)    | 2 (15.4)   | 14 (15.4)   | 0.1289       |
| Ectropion               | 11 (52.4)      | 2 (11.8)          | 3 (15.0)   | 9 (45.0)   | 4 (30.8)    | 29 (31.9)    | 1.0000        |
| Facial oedema           | 9 (42.9)       | 7 (41.2)          | 12 (60.0)  | 7 (35.0)   | 4 (30.8)    | 39 (42.9)    | 1.0000        |
| Areas of normal skin    | 4 (19.0)       | 7 (41.2)          | 10 (50.0)  | 9 (45.0)   | 3 (23.1)    | 33 (36.3)    | 1.0000        |
| General symptoms, n (%) | 6 (28.6)       | 8 (47.1)          | 15 (75.0)  | 9 (45.0)   | 7 (53.8)    | 45 (49.5)    | 1.0000        |
| Asthenia                | 1 (4.8)        | 1 (5.9)           | 1 (5.0)    | 2 (15.4)   | 20 (22.0)   | 0.2000       |
| Weight loss, >2 kg      | 7 (33.3)       | 6 (35.3)          | 4 (20.0)   | 1 (5.0)    | 1 (5.0)     | 3 (3.3)      | 1.0000        |
| Sweating                | 1 (4.8)        | 1 (5.9)           | 0.0 (0.0)  | 1 (5.0)    | 1 (5.0)     | 0.0 (0.0)    | 1.0000        |
| Fever >38.5°C           | 0 (0.0)        | 1 (5.9)           | 9 (45.0)   | 0 (0.0)    | 0 (0.0)     | 10 (11.0)    | 0.0430        |
| Pruritus                | 21 (100.0)     | 14 (82.4)         | 13 (65.0)  | 18 (90.0)  | 13 (100.0)  | 79 (86.8)    | 0.3868        |
| Lymph node enlargement  | 9 (42.9)       | 6 (35.3)          | 9 (45.0)   | 11 (55.0)  | 6 (46.2)    | 41 (45.1)    | 1.0000        |

Laboratory parameters:

CRP, mg/l, median (IQR) | 4.0 (0.5, 17.0) | 15.0 (6.0, 49.6) | 31.5 (11.5, 69.7) | 6.0 (0.9, 8.6) | 6.4 (3.0, 16.0) | 10.0 (2.7, 34.0) | 0.0996

LDH, median (range) | 282.0 (234.0–317.0) | 244.0 (204.0–294.0) | 342.0 (237.2–397.2) | 295.0 (247.2–357.5) | 250.0 (221.0–287.0) | 270.0 (222.0–324.0) | 1.0000

Missing value | 6.0 (0.9, 8.6) | 1.0000

IgE, >1,000 kU/l | 14 | 1 | 4 | 1 | 1 | 21 | 1.0000

Missing value | 11 | 14 | 19 | 9 | 56 | 0.0004

*Missing IgE not adjusted for multiple comparisons via the Bonferroni correction. **Clinically palpable. ***At time of biopsy. SS: Sézary syndrome; E-MF: erythrodermic mycosis fungoides; DE: drug-induced erythroderma; IQR: interquartile range; CRP: C-reactive protein; IQR: interquartile range; LDH: lactate dehydrogenase. Bold values indicate a significant association between diagnosis and the clinical or laboratory parameter.
Histopathological findings

Histopathological findings of the 91 patients are summarized in Table IV and Fig. 2. Psoriasis hyperplasia, parakeratosis, and neutrophil micro-abscesses in the stratum corneum were most frequent in the psoriasis subgroup, but were also seen in the eczema and SS subgroups. Spongiosis was observed in all subgroups. Eosinophilic infiltration was frequent in patients with eczema (57.1%), DE (50%), psoriasis (47.1%), and MF-E (38.5%), but very rare in those with SS (5%). Epidermotropism was seen in 70% of the cases with DE, 92% of E-MF and 80% of the SS cases. Atypical lymphocytes were seen in 46.2% of patients with E-MF, 55% of those with SS, and 25% of those with DE. The diagnosis suggested by histopathological analysis alone was consistent with the final diagnosis in 49 of 91 patients (53.8%).

Immunohistochemical findings

The percentage of PD-1⁺ lymphocytes was significantly higher in the SS subgroup (median 75%, \( p < 0.0001 \)), with perivascular location. In 14 of 20 SS patients (70%), >50% of the T cells expressed PD-1, including 10 of 20 patients with >75% PD-1⁺ T cells. Of 20 SS patients, 1 was PD-1⁻. A PD-1 expression cut off 50% was associated with SS with 70% sensitivity and 93% specificity. The median H-score for the SS subgroup (115.0) was significantly higher than in any of the other subgroups (\( p < 0.0001 \)) (Fig. 3, Table IV). An H-score ≥100 was associated with SS (\( p < 0.001 \)) with very high specificity, but poor sensitivity (99% and 60%, respectively). An H-score ≥ 50 was also strongly associated with SS (\( p < 0.001 \)), with higher sensitivity (75%) and

![Fig. 1. Clinical features of psoriasis presenting as erythroderma. (A) Severe scaling, (B) plantar keratoderma, (C) nail damage, and (D) ear involvement.](image)

| CD4/CD8 ratio in blood, median (IQR) | Eczema, n = 21 | Psoriasis, n = 17 | DE, n = 20 | SS, n = 20 | E-MF, n = 13 | Total, n = 91 |
|-------------------------------------|----------------|-----------------|------------|------------|-------------|--------------|
| CD4/CD8 ratio >10                   | 2              | 0              | 15         | 0          | 17          |              |
| Missing value                       | 7              | 8              | 18         | 0          | 33          |              |
| Blood involvement                   |                |                |            |            |             |              |
| B0                                  | 9              | 6              | 3          | 0          | 8           | 26           |
| B1                                  | 5              | 4              | 0          | 0          | 5           | 14           |
| B2                                  | 0              | 0              | 0          | 20         | 0           | 20           |
| Missing value                       | 7              | 7              | 17         | 0          | 0           | 31           |
| Detailed B1 stage                   |                |                |            |            |             |              |
| n = 5                               |                |                |            |            |             |              |
| CD3⁺CD4⁺CD158⁺                      | 0              | 0              | 0          | 0          | 2           | 2            |
| CD3⁺CD4⁺CD7⁺                        | 1              | 2              | 0          | 4          | 7           |              |
| CD3⁺CD4⁺CD26⁺                       | 0              | 2              | 3          | 9          |             |              |
| Clonal TCR in blood                 |                |                |            |            |             |              |
| Presence                            | 6              | 2              | 0          | 19         | 9           | 36           |
| Absence                             | 10             | 8              | 5          | 0          | 3           | 26           |
| Missing value                       | 5              | 7              | 15         | 1          | 1           | 29           |
| Clonal TCR in skin                  |                |                |            |            |             |              |
| Presence                            | 6              | 2              | 0          | 20         | 13          | 41           |
| Absence                             | 11             | 9              | 2          | 0          | 0           | 22           |
| Missing value                       | 4              | 6              | 18         | 0          | 0           | 28           |
| Identical clonal TCR in skin in 2 different skin locations | | | | | | |
| Presence                            | 0              | 1              | 0          | 19         | 10          | 30           |
| Absence                             | 13             | 10             | 2          | 1          | 1           | 27           |
| Missing value                       | 8              | 6              | 18         | 0          | 2           | 34           |
| Identical clonal TCR rearrangement in skin and blood | | | | | | |
| Presence                            | 0              | 1              | 0          | 17         | 7           | 25           |
| Absence                             | 16             | 9              | 2          | 2          | 5           | 34           |
| Missing value                       | 5              | 7              | 18         | 1          | 1           | 32           |

IQR: interquartile range; SS: Sézary syndrome; E-MF: erythrodermic mycosis fungoides; DE: drug-induced erythroderma; TCR: T-cell receptor.
high specificity (93%). H-scores were not significantly different in patients with E-MF compared with those with inflammatory dermatitis (median 30, \( p = 0.4409 \)). These data were subjected to receiver operating characteristic curve analysis (Fig. 3). The reproducibility of the interpretation of PD-1 expression was evaluated. H-scores exhibited good reproducibility with an ICC of 0.81 (95% confidence interval; 95% CI 0.62–0.91) and kappa coefficient of 0.66 (95% CI 0.33–1.00). For estimations of the intensity of PD-1 expression, ICCs of 0.72 (95% CI 0.45–0.87), 0.58 (95% CI 0.24–0.80), and 0.17 (95% CI −0.25–0.53) were obtained for the +, ++, and +++ intensities, respectively.

Both the percentage of lymphocytes expressing ICOS and the ICOS H-score were slightly, but not significantly, higher in the SS subgroup. CXCL13 positivity was significantly associated with SS (70%, \( p = 0.0430 \)). CXCL13 expression was also detected in 38.5% of the E-MF patients. Among patients with inflammatory dermatitis, CXCL13 expression was rare or absent in those with eczema (19%) or psoriasis (0%), but was more common in those with DE (35%).

The median percentage CD7 loss was significantly higher in E-MF and SS patients (70% for both groups, \( p = 0.0220 \)) than in those with inflammatory dermatitis. A ≥ 50% loss of CD7 expression was observed in 16 of 20 (80%) SS patients, 11 of 13 (84.6%) E-MF patients, and 27 of 58 (46.6%) inflammatory dermatitis patients. The Ki-67 proliferative index was significantly higher for SS and DE patients (median 15.0 for both). Differences in the Ki-67 proliferative index among subgroups were relatively small (range 2–21.2). Similar results were obtained from sensitivity analysis using elastic-net penalized multinomial regression.

**DISCUSSION**

This study retrospectively investigated the clinical, biological, histological, and phenotypical features in a large cohort (\( n = 91 \)) of erythroderma patients with well-defined diagnoses. The main discriminant marker was PD-1 expression, which may be an important tool for the differential diagnosis of erythroderma. PD-1 expression in > 50% of T cells and a PD-1 H-score ≥ 50 were strongly associated with an SS diagnosis. PD-1 was also expressed in E-MF and inflammatory erythroderma patients, but at lower levels.

Previous reports have shown that PD-1 expression is a feature of SS, but it had not been precisely quantified or compared with erythroderma cases derived from other...
causes, including E-MF (10, 18). To avoid heterogeneity and increase the accuracy of PD-1 expression quantification, we decided to use the H-score as a semi-quantitative method of comparing PD-1 expression among erythroderma subgroups. In this study, a high PD-1 H-score was significantly associated with a diagnosis of SS (median 115) (Fig. 3). A PD-1 H-score ≥ 50 was more sensitive, more specific, and had greater intra-rater reliability compared with standard evaluation using percentage cell expression. Nevertheless, the evaluation of PD-1 expression using the percentage of PD-1+ lymphocytes still provides valuable data. PD-1 expression was absent in only 1 case of SS in our series, which might have been due to PD-1 deletion as previously reported in aggressive cases (27). Data series on the expression of PD-1 in E-MF cases are lacking, as most reports include only

![Fig. 2. Histopathological features in a patient with Sézary syndrome.](image)

(A) Haematoxylin-eosin staining of the lesion shows dense upper dermal infiltration with atypical lymphocytes and mild epidermotropism; (B) Programmed cell death protein 1 (PD-1) staining shows strong PD-1 positivity (PD-1 H-score 260); (C) CD3+ staining; (D) CD7+ staining shows a marked loss of signal positivity. (E) The inducible co-stimulator (ICOS) signal is less intense than for PD-1 (ICOS H-score 60); (F) CXCL13 staining reveals positive cells in the upper dermis.

![Fig. 3. Importance of programmed cell death protein 1 (PD-1) expression for erythroderma diagnosis.](image)

(A, B) PD-1 expression in the erythroderma subgroups; (A) percentage of PD-1+ T cells; (B) PD-1 expression according to the H-score. The median for each subgroup is indicated by a red bar. (C) Receiver-operating characteristic (ROC) curve reflecting the predictive value of the PD-1 H-score for diagnosing erythroderma. SS: Sézary syndrome; E-MF: erythrodermic mycosis fungoides; DE: drug-induced erythroderma.
patch/plaque patients (17, 20, 34, 35). In our study, PD-1 expression in E-MF patients was lower than in those with SS, with a median H-score of 30. PD-1 expression has also been observed in cases of inflammatory dermatosis, but precise data are not provided in the literature. In a previous study, 46% of the patients with mixed erythrodemic inflammatory dermatoses expressed PD-1 (10). Here, we determined that PD-1 expression was frequently seen with inflammatory dermatosis, but in patients with other pathologies, less than 50% of the lymphocytes expressed PD-1. In addition, H-scores were <50 in most of the non-inflammatory dermatosis cases (median for eczema: 5, median for psoriasis: 2, median for DE: 10), except for 2 patients diagnosed with psoriasis.

We considered several other TFH markers in the current study. There was no significant difference in either the median expression level of ICOS or in the ICOS H-score among the patient subgroups. Conversely, CXCL13 expression was associated with SS (70%) compared with the other subgroups, including E-MF patients (38.5%), with these results similar to those reported by Picchio et al. (25) We observed that, in most of the SS patients, atypical T cells expressed both PD-1 and CXCL13, contrary to the patients with E-MF, supporting the conclusion that SS and E-MF are distinct pathologies arising from separate T-cell functional subsets (36).

There were several correlations between clinical features and erythrodemic atrophy. Male patients, severe scaling, and ear involvement are more common in psoriasis cases (4, 37). Palmoplantar keratoderma was significantly associated with psoriasis and SS, as described previously (4, 5, 37, 38), but it was non-discriminant.

We also noted blood immunophenotype abnormalities in 5 eczema and 4 psoriasis cases. These patients’ blood immunophenotypes included CD3+CD4+CD7− or CD3+CD4+CD26− circulating T-cell populations, which correspond to stage B1 disease. These phenotypic aberrations have been previously described in patients with benign inflammatory dermatosis or infections (39, 40), and may lead to an incorrect diagnosis in the presence of erythrodermia. Conversely, molecular data, such as those indicating the presence of identical T-cell clones in different skin biopsies and/or identical skin and blood T-cell clones, may provide important information for diagnosing CTCL (41). However, T-cell clones isolated from unique skin biopsies or blood were not taken into account.

In the current study, agreement between the pathological and final diagnoses occurred in only 53.8% of cases. However, although atypical lymphocytes and epidermotropism were frequent features of both SS (55%) and E-MF (46.2%), these were also seen in patients in other subgroups, in particular in DE patients; thus these observations must be interpreted carefully (42). Moreover, an absence or paucity of epidermotropism in erythrodemic CTCL was noted in some of our cases, as reported previously (10, 42).

In conclusion, these results support the use of a PD-1 H-score as a semi-quantitative and reproducible tool for evaluating PD-1 expression. A high H-score was associated with SS diagnosis, among other causes of erythrodema, including E-MF. Future studies should focus on PD-1-depleting antibodies for the treatment of SS (43).

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