Cluster of differentiation (CD) markers in erythrodermic patients: A case series study

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Background: Erythroderma is an inflammatory disorder. It has various differential diagnoses, among which one of the most important is mycosis fungoides. Erythroderma itself can be a challenging disorder. Diagnosis of a mycosis fungoides patient presenting with erythroderma specially requires a careful assessment of the peripheral blood. Studies such as CD markers can lead to a more accurate diagnosis of mycosis fungoides.

Methods: In this study, we evaluated ten erythrodermic patients in order to identify the source of their erythema. The underlying causes were both benign such as eczema, psoriasis, pityriasis rubra pilaris, acute generalized exanthematous pustulosis and malignant like hypereosinophilic syndrome and mycosis fungoided.

Results: The CD4/CD8 ratio was greater than 10 in 2 out of 10 erythrodermic patients. These patients had decreased levels of CD7 and CD26 expression. While one of the two patients fulfilled the criteria of hypereosinophilic syndrome, the other one did not have a documented clincopathologic diagnosis and had a pathology report of lichenoid tissue reaction with eosinophilia in favor of drug reaction. Both patients had decreased levels of CD7 and CD26 expression.

Conclusion: Since pathology is usually non-specific and cannot differentiate between the causes of erythroderma in erythrodermic patient with CTCL, peripheral blood findings including flow cytometry and the analysis of CD4/CD8, CD7, CD26 and CD27 expression are useful techniques which can be used for a prompt diagnosis.

Keywords: cluster of differentiation erythroderma, flow cytometry, hypereosinophilic syndrome

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INTRODUCTION

Erythroderma is an inflammatory disorder in which erythema and scaling occur in a generalized distribution involving more than 90% of the body surface [1]. Erythroderma is a morphological reaction pattern of the skin with various differential diagnosis such as mycosis fungoides (MF), Sézary syndrome (SS), pityriasis rubra pilaris, psoriasis, and atopic dermatitis [2]. cutaneous T-cell lymphoma (CTCL) accounts for approximately 5% of the cases of generalized erythroderma [3,4] therefore, it is a very important cause of erythroderma. A histologic diagnosis of erythrodermic CTCL can be made with certainty only in a percentage of the cases that have epidermotropism of atypical cells, Pautrier microabscess formation, or larger abnormal lymphocytes in the dermal infiltrate, but unfortunately they do not appear in all biopsy specimens. Therefore, peripheral blood studies are helpful in establishing a diagnosis [5,6]. Flow cytometry can be used to detect neoplastic cells in the peripheral blood.

In this study, we evaluated colony differentiation (CD) markers in the peripheral blood of erythrodermic patients and their relationship with pathologic findings.

PARTICIPANTS AND METHODS

Ten erythrodermic patients admitted to Shohada-e Tajrish Hospital, Shahid Behashti University of Medical Sciences, Tehran, Iran were included in the study. The patients were clinically evaluated with a detailed history and complete physical examination. The history included the onset and progression of erythroderma, history of skin diseases, previous episodes of erythroderma if any, aggravating factors, any associated disorder, and drug intake. Then, the patients underwent a punch biopsy to confirm the diagnosis.

For detection of CD4, CD7, CD8, CD26 and CD27 markers on the peripheral blood immune cells in erythrodermic patients, peripheral blood samples were stained with the mentioned monoclonal antibodies and their isotype-matched negative control, according to the manufacturer's guidelines (BD, USA). In biotechnology, flow cytometry is a laser based biophysical technology employed in cell counting, cell sorting biomarker detection, and protein engineering by suspending cells in a stream of fluid and passing them by an electronic detection apparatus. Flow cytometry is routinely used in the diagnosis, especially for blood disorders, but it has many other applications in basic research, clinical practice, and clinical trial studies.

Statistical analysis

Statistical analysis was performed using the statistical software PASW 18.0 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean ± standard deviation (SD) and median (range). Categorical data are expressed as number.

RESULTS

This study included 10 erythrodermic patients (two females and eight males). The mean ± SD of age of the patients was 56.7 ± 18.6 years (range: 28-80 years). Table 1 shows the baseline demographic characteristics, clinical and pathological diagnosis, and peripheral blood findings of the study participants.

The CD4/CD8 ratio was more than 10 in two out of 10 erythrodermic patients (Table 1). These patients had decreased levels of CD7 and CD26 expression (Table 1). Peripheral blood findings of the patients are summarized in Table 2.

Table 1. Baseline demographic characteristics, clinical and pathological diagnoses, and peripheral blood findings of the erythrodermic patients

Patients	Age	Sex*	Clinical diagnoses	Pathological diagnoses	$CD4^+$	$CD8^+$	CD4/CD8 ratio	$CD7^+$	$CD26^+$	$CD27^+$
1	54	M	Psoriasis/Eczema	Psoriasis	49.34	28.86	1.71	65.01	52.09	66.82
2	62	M	Eczema/Drug reaction	Drug reaction	71.45	26.83	2.66	20.25	33.76	48.94
3	37	F	Drug reaction/PRP	HES	96.88	3.38	28.66	1.59	1.33	24.54
4	67	M	Psoriasis	Psoriasis	37.48	34.50	1.09	52.83	38.55	50.19
5	69	M	Psoriasis/Drug reaction/MF	LTR/Drug reaction	91.73	1.10	83.39	5.40	5.93	90.16
6	28	M	Psoriasis	Psoriasis	72.25	27.54	2.62	56.48	61.83	61.35
7	79	F	Psoriasis	Psoriasis	72.01	26.61	2.71	57.80	62.61	61.81
8	58	M	Eczema/Psoriasis/PRP	Chronic dermatitis	44.26	32.09	1.38	44.52	46.81	52.04
9	80	M	PRP/ Eczema/ Drug reaction	PRP	45.38	28.93	1.57	37.66	52.03	57.70
10	33	M	Psoriasis/Drug reaction/MF	AGEP	38.35	42.72	0.90	72.88	45.04	64.57

Table 2. Summary of peripheral blood findings of the erythrodermic patients

Markers	Mean (SD)	Median (range)
CD4,%	61.91 (21.88)	60.40 (37.48-96.88)
CD8,%	25.26 (13.06)	28.20 (1.10-42.72)
CD4/CD8 ratio	-	2.16 (0.90-83.39)
CD7,%	41.44 (24.78)	48.68 (1.59-72.88)
CD26,%	40.00 (2.21)	45.92 (1.33-62.61)
CD27,%	57.81 (16.60)	59.52 (24.54-90.16)

Note: CD4:CD8 ratio was not normally distributed and median (range) was only reported for

DISCUSSION

Erythroderma is a morphological reaction pattern of the skin that has various underlying causes, including pre-existing skin conditions such as psoriasis, atopic dermatitis, contact dermatitis, and systemic skin conditions including malignancy and drug reaction. In our research, there was a male predominance in erythrodermic patients, with a male to female ratio of 4/1 as reported by previous studies [7,8].

Flow cytometry is unknown as the most useful method of peripheral blood assessment in erythrodermic patients, which should at least make the clinicians consider a diagnosis of MF. The importance of peripheral blood flow cytometry is highlighted by the International Society of Cutaneous Lymphoma (ISCL) recommendations for diagnosis that include one or more of the following criteria: absolute Sezary cell count of at least 1000/μL, phonotypical abnormalities demonstrated by flow cytometry including a CD4/CD8 ratio more than 10, aberrant expression of pan-T-cell markers including CD2, CD3, CD4, deficient CD26 ($CD4/CD26^- \geq 30\%$) and CD7 expression ($CD4/CD7^- \geq 40\%$), and evidence of a T-cell clone in the blood by Southern blot or PCR [9,10].

Flow cytometry of the peripheral blood, especially with the use of multiple markers, is informative in the evaluation of MF in patients who present with erythroderma and a non-diagnostic biopsy report [11]. Unexpectedly, we found very interesting results in this study. In our study, 2 cases (#3 and #5) were clinically suspicious to have MF while the biopsy report was not diagnostic of MF in one of them (case 5) and histology only showed a lichenoid pattern tissue reaction with a mild eosinophilia mimicking a drug reaction. However, flow cytometry revealed a diagnosis of MF because of a CD4/CD8 ratio more than 10 and loss of CD7 and CD26 expression. Case number 3 had an established diagnosis of hypereosinophilic syndrome according to clinicopathologic findings. Peripheral blood flow cytometry can detect aberrant T-cell populations even when there is no lymphocytosis or an elevated total WBC count.

Neoplastic cells in MF express mature memory T-cell markers, including $CD3^+CD4^+CD8^-CD45RA^-CD45RO^+$. Neoplastic T cells are both clonal and atypical, expressing phenotypic abnormalities including loss of CD7 and CD26, and altered CD27 expression.

Considering the fact that T-cell populations in MF are typically CD4, the ratio of CD4/CD8 is often increased in patients with Sezary syndrome (SS). An elevated CD4/CD8 ratio is neither sensitive nor specific for MF [9,12], but studies have found that the ratio is still significantly higher in patients with SS than in patients with inflammatory erythroderma [13-15]. Therefore, ISCL uses a CD4/CD8 ratio greater than 10 as a diagnostic criterion for SS.

CD7 may have a role in T-cell activation and/or adhesion, which is normally expressed in 80% to 90% of $CD4^+$ T cells although all CD8 T cells are essentially $CD7^+$ [12,16]. Studies have found that $CD4^+CD7^-$ cells are the dominant T-cell subset in the majority of patients with MF 17. Earlier studies indicated that in some cases, the malignant T-cell population may have lost CD7 whereas CD7 may be retained on the cell surface in others [11,17,18]. Reinhold *et al.* [19], showed that 10% of the normal T cells could also be associated with a loss of CD7 expression. In our cases, two patients (#3 and #5) had decreased levels of CD7 in the peripheral blood, and 8 of the 10 cases had benign conditions such as eczema, drug reaction, psoriasis, PRP, and AGEP. Harmon *et al.* [13] and Bernengo *et al.* [20] found that 46% and 55% of patients with SS showed 40% or more $CD4^+CD7^-$ cells in the blood, respectively. None of the patients with benign inflammatory erythroderma reached the 40% threshold of $CD4^+CD7^-$ T cells, making this ratio a useful cutoff as a specific, but not sensitive, diagnostic tool.

CD26 expression is another focus of research in MF. With decreased expression of CD26 in malignant cells, increased homing of T cells to the skin is expected [21]. Increased circulating $CD26^-$ subpopulations are common hallmarks of the peripheral blood involvement in SS and MF [11]. Jones *et al.* [14], found that the CD4/CD26 expression could be used to separate abnormal T-cell populations in 96% of the patients with MF and SS. Popdavid *et al.* [22] showed that 14.2% of the patients with benign erythroderma had well-formed clusters of $CD4^+/CD26^-$ populations; similarly, two of our patients had decreased levels of CD26 in the peripheral blood (# 3 and #5). In line with previous studies, our study also confirmed that more than 30% lymphocytes was a diagnostic criterion.

In a study of patients with SS and MF who had leukemic involvement, it was found that a cut-off value of 30% $CD4^+CD26^-$ cells had a sensitivity of 97% and a specificity of 100% [23].

CD27 has been proposed as a useful marker in diagnosing MF in erythrodermic patients. Earlier studies found that that the $CD4^+CD27^-$ population in erythrodermic patients with benign inflammatory erythroderma was significantly higher than in patients with SS [24,25]. SS and in those with benign inflammatory diseases found In our cases, there was no report of decreased or increased levels of CD27 positive cells in the peripheral blood.

Interestingly, our case #3 was diagnosed with hypereosinophilic syndrome (HES). However, the ratio of CD4/CD8 was greater than 10 like MF. This case had decreased levels of CD7 and CD26. A diagnosis of lymphocytic HES was confirmed in this case. In this patient, further studies such as evaluations for abnormal peripheral T-cell receptor gene rearrangement and measurement of T-cell IL-5 production should be done. Also, the patient # 5 had no definite diagnosis according to pathologic findings but flow cytometry revealed a diagnosis of MF.

According to our findings, peripheral eosinophilia should be considered as an indicator for further investigation for the diagnosis of CTCL. Eosinophilia is not specific for CTCL. Peripheral eosinophilia is observed in approximately 20% of the patients with CTCL. Two patients in our study (#3 and #5) had eosinophil in their pathology, and their flow cytometry results were suspicious of MF because they had aberration changes in the CD markers (the CD4/CD8 ratio was similar to MF and they also had decreased levels of CD7 and CD26). Therefore, if measurement of the eosinophil count was a routine part of pathology, we should have considered MF as a differential diagnosis.

According to the results of previous studies on CD markers, none of these markers alone is completely specific nor sensitive. Therefore, in a patient with idiopathic erythroderma, peripheral blood findings as well as the CD4/CD8 ratio and CD7, CD26, and CD27 expression may be useful in unveiling the correct diagnosis. Our results in this case series, like earlier studies, encourage clinicians to evaluate the peripheral blood in patients with idiopathic erythroderma.

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