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ERG Is a Useful Immunohistochemical Marker to Distinguish Leukemia Cutis From Nonneoplastic Leukocytic Infiltrates in the Skin

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Abstract

Leukemia cutis (LC) and reactive myeloid infiltrates in the skin may be difficult to distinguish pathologically, sometimes even after an extensive immunohistochemical work-up. This poses a serious clinical dilemma, as the prognosis and treatment of either condition are markedly different. Although most reactive myeloid infiltrates require a simple course of corticosteroids before the symptoms regress, the development of LC may require chemotherapeutic or transplant-variant interventions. Erythroblast transformation specific regulated gene-1 (ERG) is a member of the erythroblast transformation specific family of transcription factors, which are downstream effectors of mitogenic signaling transduction pathways. ERG is a key regulator of cell proliferation, differentiation, angiogenesis, inflammation, and apoptosis and has recently been found to be overexpressed in acute myeloid and lymphoblastic leukemia. In this study, the authors aimed to explore the diagnostic utility of ERG immunohistochemistry in LC by comparing the frequency and expression level of ERG immunostain in 32 skin biopsies, 16 with LC and 16 with reactive leukocytic infiltrates. A significantly higher frequency of ERG positivity was detected in LC (13/16, 81.4%), compared with reactive conditions (0/16). In addition, the expression level of ERG in LC, calculated using H score (mean $\pm$ standard error of mean, 188 ± 24), was significantly higher than that in nonneoplastic leukocytic infiltrate (28 ± 8). Our results strongly suggest that ERG expression is potentially an extremely useful marker to distinguish between cases of LC from those of reactive myeloid infiltrates in the skin with a positive predictive value of 100% and negative predictive value of 84.2%.

Keywords

ERG; leukemia cutis; Sweet syndrome; neutrophilic dermatoses; immunohistochemistry

INTRODUCTION

Leukemia cutis (LC) is a nonspecific term defined as cutaneous infiltration by any type of leukemia, myeloid, or lymphoid, resulting in visible skin lesions. It has been reported in

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patients with acute myeloid leukemia (AML), myeloproliferative neoplasms (MPN), myelodysplastic syndrome (MDS), MDS/MPN, and also a range of mature and precursor lymphoid neoplasms.¹ Alternatively, it can be designated as myeloid sarcoma when leukemia of myeloid or monocytic lineage is present as a cutaneous tumor mass effacing the underlying tissue architecture.² Cutaneous involvement may develop in as many as 20%–70% of mature T-cell leukemias, 4%–20% of chronic lymphocytic leukemia/small lymphocytic lymphomas, 1% of precursor B or T-cell acute lymphoblastic leukemias (ALL), 15% of patients with AML, 10% of chronic myelomonocytic leukemias (CMML), and less frequently in MDS and MPN.^{1,3} The presence of LC often harbingers dissemination and progression of the disease and may be predictive of a grave prognosis and imminent death with 88% mortality within a year of diagnosis.¹ Thus, LC is one of the few diagnoses made primarily by dermatopathologists, which plays a critical role in acute management decisions that have a significant, measurable bearing on patient quality of life and survival, particularly when presented as the sole site of extramedullary proliferation or recurrence.⁴

Despite the gravity of this diagnosis, there are times when it may be quite difficult to make. Typically, this situation arises when the clinical differential diagnosis is nonclassic, when the morphologic features are not fully developed and when immunohistochemistry deviates from common patterns. Often in these cases, the diagnostic considerations are those of infiltrates consisting of reactive polymorphonuclear leukocytes, especially when there is a prominent left shift, and ranging from benign neutrophilic dermatoses to infection or traumatic inflammatory infiltrates. Therefore, a reliable immunohistochemical tool to assist with the differential diagnosis and subsequently guide clinical management is of the utmost importance.

Erythroblast transformation specific (ETS) regulated gene-1 (ERG) is a member of the ETS family of transcription factors, which are downstream effectors of mitogenic signaling transduction pathway.^{5–7} ERG is a key regulator of cell proliferation, differentiation, angiogenesis, inflammation, and apoptosis. Recently, ERG expression has been identified in CD34-positive stem cells and in the platelet and megakaryoblastic cell lineages. Overexpression of ERG has been detected in a subset of AML,^{5,7,8} acute megakaryoblastic leukemia,⁹ and ALL.¹⁰ Yet, no study has specifically investigated the utility of ERG as a potential immunohistochemical marker for LC. In this study, we aim to examine the immunoexpression of ERG in LC and a variety of nonneoplastic myeloid processes in the skin to explore the use of ERG immunohistochemistry in diagnosing LC.

MATERIALS AND METHODS

The study was conducted with the approval of the institutional review board. All patients included in this study were evaluated and treated at Memorial Sloan Kettering Cancer Center (New York, NY). Sixteen biopsies from 14 patients with a diagnosis of LC and 16 biopsies from 16 patients with reactive dermal and/or subcutaneous polymorphonuclear infiltrates were randomly retrieved from the pathology database of Memorial Sloan Kettering Cancer Center as LC and control cases. Antecedent bone marrow biopsies were available for all 14 patients with a diagnosis of LC and 9 of 16 patients with reactive leukocytic infiltrate (Tables 1 and 2). Additional immunophenotypic and cytogenetic data, when available, were

collected. All biopsies were fixed for 12–24 hours in 10% neutral-buffered formalin before tissue processing.

A monoclonal rabbit anti-human ERG antibody (clone EPR3864, concentration 23 µg/mL, Ventana Medical Systems Inc., Tucson, AZ) was used for immunohistochemistry on formalin-fixed paraffin-embedded tissue sections. The intensity of ERG immunolabeling within a leukocytic or leukemic infiltrate was classified on a scale of 1+ to 3+, with 1+ signifying weak staining, 2+ moderate, and 3+ strong intensity equal to that of internal endothelial cells (Fig. 1). The percentage of the infiltrate with the noted stain intensity was also recorded. A case was considered positive for ERG when moderate-to-strong nuclear staining (2+ to 3+) was identified in the leukocytic infiltrate. H scores, defined as the product of the percentage of tumor cells showing ERG labeling (0–100) multiplied by the labeling intensity (0–3), were calculated.¹¹ The review of histological slides and evaluation of immunostains were performed independently by the participating pathologists blinded to the diagnosis.

All statistical analyses were performed using the SPSS software 22.0 (IBM Corporation, New York, NY). The immunopositivity and H scores of ERG were compared between LC and reactive cases using the Fisher exact test and two-tailed Student *t* test, respectively. *P* values less than 0.05 were considered statistically significant.

RESULTS

Sixteen skin biopsies from 14 patients (4 females and 10 males) with a diagnosis of LC were included in this study. The average age at diagnosis was 50.1 years (standard error of mean, SEM = 4.8). Antecedent bone marrow biopsies were available to render a definite confirmative diagnosis of myeloid or lymphoid neoplasms in all cases, including 10 cases (71.4%) of AML, 1 case (0.7%) of MDS, refractory anemia with excessive blasts-2 (MDS, RAEB-2), 1 case (0.7%) of post-essential thrombocythemia myelofibrosis—accelerated phase, 1 case (0.7%) of T-ALL, and 1 case (0.7%) of biphenotypic acute leukemia (AML/T-ALL) (Table 1). Of the 16 biopsies from 14 patients with a diagnosis of LC, 13 biopsies (81.3%) from 11 patients (78.6%) were positive (2+ to 3+ intensity) for ERG in the leukemic dermal infiltrate (Table 1 and Fig. 2). On average, 84% of cells were positive for ERG (SEM = 6%; range, 30%–100%). Three cases of LC, including 2 cases with AML and 1 case with MDS-RAEB-2, were considered as negative for ERG with only focal or diffuse 1+ weak staining (Table 1, cases 1 to 3). The average H score for ERG in LC cases was 188 (SEM = 24; range, 2–300).

Sixteen patients (11 females and 5 males) with skin biopsies harboring a dermal and/or subcutaneous polymorpho-nuclear infiltrate were randomly selected as controls. The average age at diagnosis was 59.9 years (SEM = 2.9). The corresponding pathological diagnoses were Sweet or Sweet-like syndrome (n = 3; 18.8%), sterile neutrophilic dermatosis (n = 5; 31.3%), leukocytoclastic vasculitis (n = 2; 12.5%), pustular dermatitis or drug reaction (n = 2; 12.5%), inflamed ruptured cysts (n = 2; 12.5%), suppurative lobular panniculitis (n = 1; 6.3%), and dermal scar with inflammation (n = 1; 6.3%, Table 2). Antecedent bone marrow biopsies were performed in 9 patients for various reasons. A myeloid or lymphoid neoplasm

was detected in 4 patients, including 2 cases with AML, 1 case with MDS-RAEB, and 1 case with follicular lymphoma. None of the 16 biopsies harboring reactive neutrophilic infiltrates exhibited ERG-immunopositivity defined as moderate-to-strong ERG nuclear staining in the leukocytic infiltrate (Table 2 and Fig. 2). Among these cases, 3 showed complete absence of ERG immunostaining, whereas the remaining 13 exhibited focal to diffuse weak (1+) ERG labeling. The average H score was 26 (SEM = 8; range, 0–90).

Overall, LC cases were associated with a significantly higher frequency of ERG immunopositivity compared with the biopsies with reactive neutrophilic infiltrates (LC: 13/16, 81.3%; reactive: 0/16, 0%; Fisher exact test, $P < 0.001$), and also a significantly higher H score (LC: 188 ± 24 ; reactive: 28 ± 8 ; two-tailed Student t test, $P = 0.004$). The positive predictive value of ERG immunoreactivity to predict LC was 100%, whereas the negative predictive value was 84.1%.

DISCUSSION

LC is the infiltration of the skin by neoplastic leukocytes, myeloid, or lymphoid, resulting in visible skin lesions. LC most commonly occurs in patients with AML, a genetically heterogeneous group of hematologic malignancies characterized by the clonal proliferation of marrow-derived precursor cells involving bone marrow, peripheral blood, and/or extra-medullary tissues. Although LC may be seen in the context of various subtypes of AML, it is most commonly seen in AML with monocytic differentiation (13%) and myelomonocytic differentiation (10%–35%).^{12,13} LC may present concurrently with bone marrow disease, be the first sign of relapsed disease, or may rarely precede bone marrow involvement.¹⁴ Overall, LC in AML has a grave prognosis with 88% of patients dead within 1 year of diagnosis.¹ LC may also affect patients with myelodysplastic and/or MPN, including up to 10% of CMML.³ In general, the presence of LC is indicative of disease acceleration, transformation to AML, and shortened overall survival in patients with CMML.³

In this study, we have included a garden variety of reactive conditions that can be encountered frequently in our daily practice, e.g., Sweet or Sweet-like syndrome, sterile neutrophilic dermatosis, suppurative lobular panniculitis, pustular dermatitis, leukocytoclastic vasculitis, ruptured cysts, and scar, all of which harbored a dense neutrophil-predominant dermal infiltrate. Most conditions fall under the general category of neutrophilic dermatoses, a group of conditions that are characterized by an infiltration of mature polymorphonuclear leukocytes and a prompt clinical improvement after corticosteroid treatment.⁴ Currently, there is no consensus in the literature on which immunohistochemical markers should be used to reliably distinguish LC from reactive leukocytic infiltrates of the skin.^{1,13} Furthermore, LC may be negative for the easily visible blast markers CD34 and CD117. As an accurate distinction between LC and reactive leukocyte infiltrate is of the utmost importance when planning a patient's treatment, more sensitive and reliable diagnostic immunomarkers are needed to assist the pathologists to reach the correct diagnosis.¹⁵

ERG is a member of the ETS family of transcription factors, which are downstream effectors of mitogenic signaling transduction pathways.^{5–7} *ERG* is a potent oncogene, which plays a

key regulatory role in cell proliferation, differentiation, angiogenesis, inflammation, and apoptosis. Translocation involving *ERG* locus has been reported in multiple solid tumors, e.g., Ewing sarcoma and prostatic adenocarcinoma, and also hematopoietic malignancies, including AML and ALL.^{5,7,16} *ERG* is a crucial factor in normal and aberrant hematopoiesis. In normal hematopoiesis, *ERG* is required to maintain the number and functions of hematopoietic stem cells.^{6,16,17} A missense mutation in *ERG* causes thrombocytopenia, anemia, and a trend toward leukopenia, whereas force expression of *ERG* promotes megakaryopoiesis, induces an erythroid to megakaryoblastic phenotypic switch, and results in leukemia in multiple cell lines and mouse models.^{9,16,18} In 2004, Baldus et al were the first to link *ERG* amplification to a subset of AML. Using high-resolution bacterial artificial chromosome array-based comparative genomic hybridization, they demonstrated that the *ERG* gene is amplified to approximately 2.5-fold in AML with complex cytogenetics and abnormal chromosome 21.¹⁹ Subsequently, overexpression of *ERG* has been reported in a variety of hematopoietic disorders, including MDS,²⁰ AML,^{8,21,22} acute megakaryoblastic leukemia,⁹ and ALL.¹⁰ To date, *ERG* immunoreexpression has not been studied in other hematopoietic neoplasms, such as MDS, MDS/MPN, or mature T-cell and B-cell neoplasms. Overexpression of *ERG* activates RAS and Pim1 kinase pathways and induces a leukemic stem cell transcription program characteristic for AML in transgenic mouse models.⁵ More recently, multiple studies have shown that *ERG* is also a prognostic biomarker. Overexpression of *ERG* is an adverse prognostic factor in AML with normal cytogenetics^{8,21,22} and T-ALL.¹⁰ Yet, no one has investigated the potential utility of *ERG* as a diagnostic immunohistochemical marker in skin biopsies for LC. Our study is the first study to-date addressing this specific question. Despite the small number of cases included in this study, we have shown that *ERG* is a robust and specific immunomarker for LC with a sensitivity of 81.4%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 84.1%. A moderate-to-strong staining pattern of *ERG* in a dermal leukemic/leukocytic infiltrate is a useful clue to guide a pathologist toward the correct diagnosis of LC in challenging cases.

CONCLUSIONS

ERG expression is potentially a useful marker to distinguish between cases of LC and those of reactive myeloid infiltrates in the skin and should be included in the routine immunohistochemical work-up to diagnose LC.

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FIGURE 1.

Assessment of intensity of ERG immunohistochemistry staining. ERG is strongly positive in the nuclei of endothelial cells (E, arrows), which serves as internal positive control with 3+ (strong) stain intensity. ERG immunostains in neoplastic myeloid/lymphoid or reactive infiltrates are graded as follows: (1) negative (NEG, top left panel), defined as absence of staining; (2) 1+ (weak, top right panel), defined as visible faint nuclear staining; (3) 2+ (moderate, bottom left panel), in which significant nuclear staining is present but at level weaker than that of endothelial cells. Nuclear chromatin detail can still be appreciated at this level of intensity; and (4) 3+ (strong, bottom right panel) defined as strong uniform ERG positivity that masks the chromatin details at a level comparable to that of endothelial cells.

FIGURE 2.

ERG immunoexpression in skin biopsies for LC (A–C) and a reactive neutrophilic infiltrate (D, E). A punch skin biopsy from a patient with AML reveals a dense dermal and subcutaneous infiltrate (A) of immature myeloid precursor cells with intermediate-to-large nuclear size, vesicular chromatin, and occasional prominent nucleoli (B). (C) Immunohistochemical studies for ERG show diffuse moderate (2+) to strong (3+) staining in the leukemic infiltrate, comparable to that seen in endothelial cells (E, arrow). A skin biopsy with a diagnosis of ruptured follicular cyst (D) exhibits a marked neutrophilic infiltrate in the superficial and deep dermis (E). Weak (1+) immunolabeling for ERG is noted in the polymorphonuclear leukocytes (F).

TABLE 1

LC: Clinicopathological Features, Immunophenotype, and ERG Immunoeexpression Profile

	Age/Sex	ERG Immunostain (% of Cells)				H	BM Diagnosis
		NEG	1+	2+	3+	ERG*	
1	38/M	98	2	0	0	NEG	MDS (RAEB-2)
2	59/M	95	5	0	0	NEG	AML
3	36/M	0	100	0	0	NEG	AML
4	64/M	40	5	5	50	POS	AML with mutated <i>NPM1</i> and <i>FLT3-ITD</i>
5	61/M	0	30	60	10	POS	AML
6	82/F	10	0	70	20	POS	AML in the background of CMML-2
		5	5	80	10	POS	
		5	0	85	10	POS	
7	23/M	0	0	95	5	POS	AML
8	49/F	0	10	40	50	POS	AML
9	21/F	10	0	0	90	POS	AML
10	35/M	5	5	0	90	POS	AML with inv (16)
11	64/M	0	0	0	100	POS	Biphenotypic acute leukemia AML/T-ALL
12	71/F	0	0	0	100	POS	AML in the background of myelofibrosis
13	63/M	40	30	30	0	POS (focal)	Post-ET-myelofibrosis, accelerated phase
14	35/M	0	5	15	80	POS	T-ALL

	Cytogenetics	BM Blast (%)			Immunophenotype				
		BM Blast (%)	PB Blast (%)	CD43	CD34	CD117	CD68	Mur	MPO
1	Normal	18	4	POS	NEG	POS in BM and NEG in skin	POS	POS	NA
2	Normal	100	NA	POS	NEG	NEG	POS	POS	NEG
3	+8, +14	80	NA	POS	NEG	NEG	NA	POS	POS
4	<i>FLT3-ITD</i> mutation and <i>NPM1</i> (exon 12) mutation	53	25	POS	POS	POS	POS	NEG	POS in BM and NEG in skin
5	t(3;5)(q21;q13), del (3)	42	NA	POS	NEG	NEG	NA	NA	NA
6	<i>FLT3-TKD</i> mutation	88	22	NA	POS	POS	NA	NA	NA
7	+8, +21	87	74	NA	POS	POS	POS	NA	NEG
8	t(6;11)(q27;23)	20	0	NA	NEG	POS	NA	NA	NA

	Cytogenetics	Immunophenotype							
		BM Blast (%)	PB Blast (%)	CD43	CD34	CD117	CD68	Mur	MPO
9	del (5q), t(11) involving <i>MLL</i>	21	58	NA	POS	POS	NA	NA	NA
10	inv(16),+16, +8, +21	NA	NA	NA	NA	NA	NA	NA	NA
11	Complex (hypotetraploid)	85	0	NA	POS	POS in BM and NEG in skin	POS	NA	POS in BM and NEG in skin
12	Insufficient	90	85	NA	POS	POS	POS	NA	NA
13	<i>MPL</i> mutation +	7	0	NA	NA	Subset POS in BM and NEG in skin	NA	NA	NA
14	TCRβ and TCRg rearrangement, +8, <i>CDKN2A</i> (p16) deletion	87	74	NA	NEG	NEG	NA	NA	NA

* A positive ERG immunohistochemistry stain was defined as moderate-to-strong staining in 10% or above leukemic or leukocytic infiltrate.

BM, bone marrow; ET, essential thrombocythemia; FLT3-ITD, internal tandem duplication of the FLT3 gene; H, H score; MLL, myeloid/lymphoid or mixed-lineage leukemia; MPO, myeloperoxidase; Mur, muraminidase; NA, not available; NEG, negative; NPM, Nucleophosmin; PB, peripheral blood; POS, positive; TCR, T-cell receptor.

Table 2
Clinicopathological Features and ERG Immunorepression in Skin Biopsies With Reactive Leukocytic Infiltrate

Age/ Gender	Diagnosis	BM Diagnosis	ERG Immunostain (% of Cells)					ERG Immuno-Positivity	H Score
			NEG	1 +	2 +	3 +	4 +		
1	52/F	Heavily inflamed ruptured follicular cyst							
2	53/F	Ruptured cyst with suppurative and granulomatous dermatitis	N/A	95	5	0	0	NEG	5
3	54/M	Leukocytoclastic vasculitis							
4	66/F	Leukocytoclastic vasculitis	WNL, S/P BMT for APL	100	0	0	0	NEG	0
5	66/M	Pustular dermatitis	N/A	98	2	0	0	NEG	2
6	77/F	Pustular drug reaction	Metastatic adenocarcinoma	60	40	0	0	NEG	40
7	44/F	Scar with acute and chronic inflammation	N/A	100	0	0	0	NEG	0
8	60/M	Suppurative lobular panniculitis	N/A	70	30	0	0	NEG	30
9	65/M	Sterile neutrophilic dermatosis	AML, complex cytogenetics AML with <i>FLT3-ITD</i> mutation and <i>NPM1</i> (exon 12) mutation	98	2	0	0	NEG	2
10	67/F	Sterile neutrophilic dermatosis	MDS (RAEB)	50	50	0	0	NEG	50
11	35/F	Sterile neutrophilic dermatosis		100	0	0	0	NEG	0
12	48/F	Sterile neutrophilic dermatosis	WNL	10	90	0	0	NEG	90
13	69/F	Sterile neutrophilic dermatosis with left shift	N/A	20	80	0	0	NEG	80
14	69/M	Sweet syndrome	WNL, S/P BMT for AML	70	30	0	0	NEG	30
15	56/F	Sweet syndrome (histiocytoid)	Follicular lymphoma	100	0	0	0	NEG	0
16	77/F	Sweet-like drug reaction	N/A	30	70	0	0	NEG	70
			WNL	95	5	0	0	NEG	5

APL, acute promyelocytic leukemia with *t(15;17) PML-RARα*; BM, bone marrow; BMT, bone marrow transplant; FLT3-ITD, internal tandem duplication of the FLT3 gene; N/A, not available; NEG, negative; NPM, Nucleophosmin; S/P, status post; WNL, within normal limits.