NPM1 and FLT3-TKD mutations are enriched in patients with leukemia cutis

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Abstract

Leukemia cutis (LC) is a dermatologic manifestation of leukemia. Its clinical implications for the patient and the biological mechanism behind the manifestation of LC are unknown. The oncology community is increasingly utilizing mutations to classify a number of malignancies to prognosticate outcomes and to choose targeted therapies. A single-center, retrospective analysis of dermatopathology cases with a diagnosis of leukemia cutis was performed. Patients with genetic testing using the Columbia Combined Cancer Panel (a targeted sequencing protocol of 467 genes) or Genoptix (targeted sequencing protocol of 44 genes) were identified. The frequency of the presence of genetic mutations in LC patients was compared to AML patients from the COSMIC (Catalogue of Somatic Mutations in Cancer) database. Twenty nine cases were confirmed to have leukemia cutis, 22 of which had acute myeloid leukemia (AML). Genetic testing was available in 11 patients. Twelve different mutations were observed with particular enrichment for *NPM1* and *FLT3-TKD*. Our original hypothesis was that patients with LC would display a distinct mutation profile. Ultimately, the distribution of mutations observed in our cohort of LC patients largely reflects the mutational profile seen in AML patients in general.

Keywords: leukemia cutis, genetics, dermatooncology, cutaneous oncology, leukemia, acute myelogenous leukemia, NPM1, FLT3-TKD

Introduction

Leukemia cutis (LC) is a cutaneous disorder characterized by nonspecific skin lesions and pathologically defined by the associated leukemic infiltrates [1]. Leukemia cutis most commonly presents as one or many violaceous, red-brown, or hemorrhagic papules, nodules, or plaques of varying sizes [2]. Although LC is usually observed following the diagnosis of a leukemia, it can infrequently occur prior to any evidence of bone marrow infiltration [3,4]. Currently, diagnosis of LC is based on the morphologic pattern of skin infiltration, the cytologic features, and the immunophenotype of the tumor cells [2]. Leukemia cutis is most commonly seen in acute myeloid leukemia (AML) and believed to portend a poor prognosis in that disease [2,5]. Although LC is frequently biopsied, genetic studies are not usually performed, in contrast to the extensive genetic evaluation that is performed on a patient's bone marrow or peripheral blood leukemia cells [6]. In hematologic malignancies, detection of genetic lesions is important for classification, prognostic stratification, and monitoring of a variety of cancers. In a progressive shift, cancers are increasingly being categorized by genetic characteristics instead of morphologic changes [7, 8]. Given the emphasis in new AML categorization schema on molecular abnormalities, further data are needed to understand the relationship between leukemia cutis and current genetic-based AML classifications and prognostic predictions [9].

An estimated 3-8% of patients with AML have leukemia cutis [5, 10]. Leukemia cutis is also observed in other types of leukemia including chronic myelogenous leukemia [11]. Patients with myelodysplastic syndrome may develop LC, suggesting progression to AML [1]. The pathophysiology resulting in LC is hypothesized to relate to altered chemokine receptors and adhesion molecules leading to migration of leukemic cells to the skin [12, 13]. As the leukemic cells of LC are believed to originate from the bone marrow, it is likely that the molecular abnormalities seen in the skin mirror those in the marrow; however, notably there have been reports of discordant findings between the two sites in limited cases [14, 15]. No consistent demographic or clinical differences between leukemic patients who do or do not develop LC have been observed; those studied include age, sex, white blood cell count, or other hematologic parameters [15].

Few studies have investigated specific genetic mutations in patients with LC. In early studies, Falini and colleagues evaluated myeloid sarcoma (cutaneous presentation of which is commonly referred to as leukemia cutis), reporting nucleophosmin 1 (*NPM1*) mutation in 26 of 181 (14%) tested samples [16]. Falini's study is of limited utility as samples were taken from sites other than the skin [16]. Aberrations of *NPM1* are one of the most common mutations found in AML [17]. Ansari-Lari et al. similarly tested cutaneous and non-cutaneous myeloid sarcoma samples for Fms-like tyrosine kinase 3 (*FLT3*) mutations, another common mutation seen in AML [18], and found three of 20 (15%) had tandem duplications (ITD), [19]. Thus far, only Luskin et al. have specifically investigated leukemia cutis [20]. Using targeted sequencing of the bone marrow, Luskin and colleagues found *NPM1* mutations in 22 of 48 (46%) patients with LC [20]. Chromosome 8 abnormalities, including trisomy 8 and translocation t(8;21) are suspected to be found in higher proportions of patients with LC based on review of the literature [5, 21, 22]. Other reported abnormalities include del(16q) [23], t(8;17) [24], t(8;16) [25], and t(1;11) [26]. Chromosomal abnormalities inv(16) and t(9;11) have been reported to be associated with extramedullary disease, in general [27]. Historically, LC has been believed to be associated with poor prognosis. However, modern assessment of patients with leukemia cutis in the context of genetic abnormalities and modern treatments has yielded mixed results [28, 29].

An increasing number of patients diagnosed with leukemia are routinely tested for cancer-associated mutations given their prognostic value and role in therapeutic decision making [7, 30]. This change in practice toward expanded genetic testing provides the opportunity to investigate the association of particular mutations with relatively rare manifestations of cancer, such as LC. In this study, we conducted a single-center retrospective analysis of patients with LC whose bone marrow was tested for genetic mutations. We hypothesized that a distinct subset of mutations would be found in patients with LC.

Methods

We searched Columbia University Irving Medical Center dermatopathology reports from August 2007 to October 2017 for the terms "leukemia cutis" and "leukemia." These reports were initially screened for the diagnosis of leukemia cutis or the description of leukemic cells infiltrating the dermis or epidermis. A dermatopathologist then reviewed the pathology slides of all selected cases and independently confirmed the diagnosis of leukemia cutis as defined by leukemic cells infiltrating the dermis or epidermis. Equivocal cases in which few leukemic cells were present in an inflammatory infiltrate with another more likely clinical diagnosis were excluded. Charts of identified cases were reviewed for Columbia Combined Cancer Panel testing (see below). Only patients with the diagnosis of leukemia were included in genetic analysis as the evaluation for patients with other hematologic malignancies such as lymphoma is not comparable. All leukemia cases were confirmed through review of diagnostic material with an oncologist. The presence of monocytic features was determined by a combination of morphology and immunophenotypic analysis as appropriate by a

Table 1. *Age and oncologic diagnosis of studied cohort.*

	Initial Cohort *n* = 29	Cohort with genetic testing *n* = 11
Age		
Median Age at Cancer Diagnosis (Range)	59 (0 - 82)	66 (26 - 82)
Median Age at Leukemia Cutis Diagnosis (Range)	60 (0 - 82)	66 (26 - 82)
Median Number of Months from Cancer to Leukemia Cutis Diagnosis (Range)	10 (1 - 138)	6 (1-26)
Number Patients with Age < 60 yo at Cancer Diagnosis	13 (45%)	4 (36%)
Number Patients with Age ≥ 60 yo at Cancer Diagnosis	16 (55%)	7 (64%)
Oncologic Diagnosis		
Acute Myeloid Leukemia	22 (76%)	11 (100%)
Myelodysplasia	5 (17.2%)	-
Chronic Myelogenous Leukemia	1 (3.4%)	-
Juvenile Myelomonocytic Leukemia	1 (3.4%)	-

hematopathologist. Redundant cases were excluded.

The Columbia Combined Cancer Panel, developed by the Molecular Pathology Laboratory of Columbia University, is a targeted sequencing protocol of 467 genes performed on DNA purified from tumor (bone marrow in the case of leukemic patients) using Custom Agilent SureSelect capture and Illumina HiSeq 2500 sequencing (San Diego, CA). These sequences were evaluated for single nucleotide variants and small insertions and deletions. Actionable mutations were confirmed by Sanger sequencing. Internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations in Fms-like tyrosine kinase 3 (FLT3) were analyzed by polymerase chain reaction (PCR) and fluorescent fragment size analysis in the Molecular Pathology Laboratory of Columbia University, ARUP Laboratories (Salt Lake City, UT), or Genoptix (Carlsbad, CA). As the Comprehensive Cancer Panel was not available prior to 2014, mutational analysis was performed at Genoptix in several patients. Genomic DNA was isolated from bone marrow aspirates or peripheral blood and the DNA sequence of targeted regions of 44 genes commonly mutated in myeloid malignancies was determined using next-generation sequencing (NGS) technology.

Extensive clinical data including age at diagnosis, months since diagnosis, status at last follow-up, karyotype, and fluorescence in situ hybridization (FISH) analysis were collected upon chart review. Patients were risk stratified by the WHO Classification of Myeloid Neoplasms and Acute Leukemias and the European Leukemia Net guidelines [7, 31]. The Institutional Review Board of Columbia University Medical Center approved this research.

Results

A total of 206 cases with the term "leukemia" or "leukemia cutis" in the dermatopathology report were identified. Upon review of the pathology slides, 29 were confirmed to have leukemia cutis, 22 of which had acute myeloid leukemia (AML), 5 had

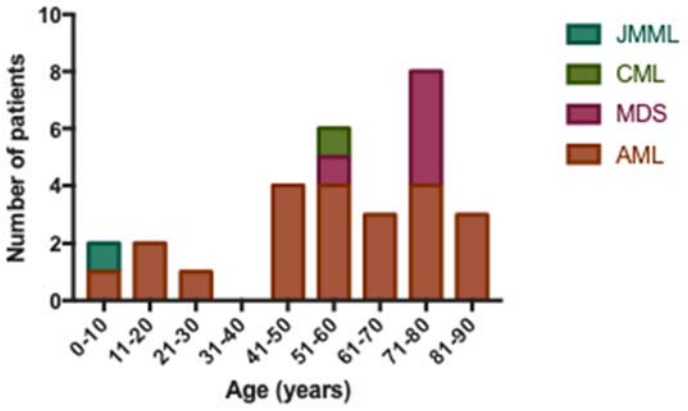

Figure 1. *Age at diagnosis of leukemia cutis by decade. JMML: Juvenile Myelomonocytic Leukemia; CML: Chronic Myelogenous Leukemia; MDS: Myelodysplasia; AML: Acute Myeloid Leukemia.*

Table 2. *Genetics of patients with leukemia cutis and acute myeloid leukemia.*

Patient	WHO Classification	Monocytic Morphology	Mutations Present*	Karyotype
10	AML without differentiation	Not Present	NPM1; FLT3-ITD†	Normal
11	AML with minimal differentiation	Not Present	NPM1; FLT3-TKD; IDH1; DNMT3A†	Normal
12	Acute monocytic leukemia	Present	U2AF1	Normal
13	Acute myelomonoctyic leukemia	Present	NRAS	46,XY,t(11;19)(q23;q13.1){24}
14	AML, NOS	Not Present	NPM1; FLT3-TKD	Normal
15	AML with mutated NPM1	Present	NPM1	Normal
16	AML, NOS	Not Present	U2AF1	56,XY,+3,+6,+8,+8,+13,+14,+19,+21,+1\ R\2mar{20}
17	AML, NOS	Not Present	FLT3-ITD/TKD; RUNX1; WT1	Normal
18	AML with mutated NPM1	Not Present	NPM1; CEPBA; TET2; TET2	Normal
19	AML with mutated RUNX1	Present	FLT3-TKD; RUNX1	Normal
22	AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A	Not Present	FLT3-TKD; STAG2; IDH1	46,XX,t(9;11)(p21;q23){13}/46, idem,ins(14;?)(q11.2;?){4}/47, idem,+der(9)t(9;11)(p21;q23){3} /48,idem,+X,+6{1}

**Information on mutations attained from Columbia Comprehensive Cancer Panel (CCP). See Methods section for more details.*
†CCP was not available at the time of diagnosis of these patients. Information attained through Genoptix screening.
Abbreviations: WHO: World Health Organization, AML: acute myeloid leukemia, NOS: not otherwise specified, NPM1: nucleophosmin 1, RUNX1: runt-related transcription factor 1, MLLT3: myeloid/lymphoid or mixed-lineage leukemia translocated to chromosome 3, KMT2A: histone-lysine N-methyltransferase 2A, FLT3: fms related Tyrosine Kinase 3, ITD: internal tandem duplication, TKD: tyrosine kinase domain, IDH1: isocitrate dehydrogenase 1, DNTM3A: DNA (cytosine-5)-methyltransferase 3A, U2AF1: U2 small nuclear RNA auxiliary factor 1, NRAS: neuroblastoma RAS viral oncogene homolog, WT1: Wilms tumor 1, CEPBA: CCAAT enhancer-binding protein alpha, TET2: tet methylcytosine dioxygenase 2, STAG2: stromal antigen 2.

myelodysplasia (MDS), one had chronic myelogenous leukemia (CML), and one had juvenile myelomonocytic leukemia (JMML), (**Table 1**). Eleven other patients were identified with abnormal infiltrates on pathology preliminarily consistent with leukemia cutis, but their underlying malignancy was found to be a lymphoma and therefore those cases were excluded. Age at diagnosis of the primary cancer varied from 0 to 82 years with a median age of 59 years. Median age of LC diagnosis was one year later at 60 years. (**Table 1**, **Figure 1**)

Genetic testing or karyotype analysis was available in most patients with AML. Eleven patients underwent genetic testing; 9 were tested using the Columbia Combined Cancer Panel and two using Genoptix testing (**Table 2**). Twelve different mutations were observed with particular enrichment for *NPM1* mutation (45% of patients) and *FLT3-TKD* (45% of patients). One patient had a *FLT3-TKD* mutation with *NPM1* and one had *FLT3-ITD* with *NPM1*. Frequencies of mutations observed (by patient) as compared to those values reported in the literature are shown in **Table 3**. As shown, other mutations were only present in one-to-two patients (**Table 2**).

The majority of patients had normal karyotypes with only three of 11 patients exhibiting an abnormal karyotype. Two patients had complex karyotypes, including the presence of trisomy 8. The third patient has t(11;19)(q23;q13.1), (**Table 2**).

The median overall survival of all patients in this study was 9 months. The European Leukemia Net guidelines provide genetic and morphologic criteria by which to stratify patients with AML into adverse, intermediate and favorable risk categories [31]. Of the 21 patients with AML and LC, 11 belonged to the adverse risk category (with a median survival of 9 months), 5 to the intermediate risk category (median

survival 8 months), and 5 to the favorable risk category (median survival 12 months), (**Figure 2**). There was no statistically significant difference in survival between the adverse, intermediate, and favorable risk categories by log-rank test.

Discussion

In this study, we performed an unbiased examination of potential mutations associated with LC using a retrospective analysis of cases at Columbia University Irving Medical Center. This study identified a predominance of *NPM1* and *FLT3-TKD* mutations. This study is one of the most comprehensive investigations into LC-associated mutations to date given our mutation panel screened for over 460 cancer-associated genes. We show in **Table 3** the frequencies of mutations as compared to those that have been reported for the general AML population and find that the distribution of mutations in patients with LC largely reflects the mutational profile seen in AML patients in general.

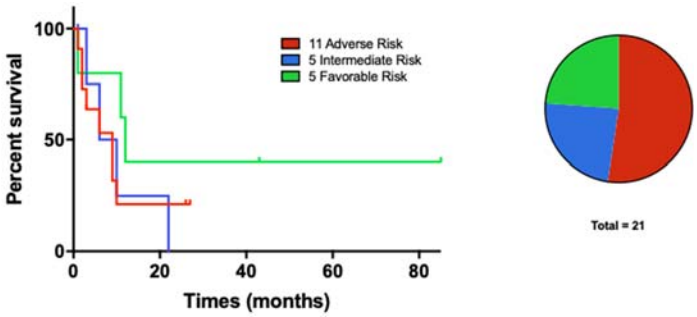

Figure 2. *Kaplan-Meier curves of patients with acute myeloid leukemia and leukemia cutis classified into risk categories by European Leukemia Net (ELN) Guidelines. The European Leukemia Net guidelines provide genetic and morphologic criteria by which to stratify patients with AML into adverse, intermediate and favorable risk categories. Kaplan-Meier curves measure the proportion of patients alive at a certain time after diagnosis. Each line represents a group of patients followed over time (months). The start time is defined by date of biopsy of leukemia cutis. Up-ticks on the line demonstrate when a patient was lost to follow up. Step-wise decrease in the line indicates a patient death. The y-value of the line demonstrates the percent of patients still alive after x-value of months. The pie-chart is a graphical representation of the proportion of patients in each ELN group. This Kaplan-Meier curve demonstrates that patients categorized into the "Favorable Risk – green line" group survived longer than the patients categorized into the "Adverse Risk – red line" and "Intermediate Risk – blue line" groups. The majority of patients were categorized into the "Adverse Risk" group. These results were not statistically significant by logrank test for trend, χ^2 (1, N = 21) = 1.145, P=0.28. Note: One patient with AML was excluded from this analysis as bone marrow aspirate was not available for appropriate ELN classification. AML: Acute Myeloid Leukemia.*

Our study is consistent with Luskin and colleagues' finding of *NPM-1* and its likely association with LC [20]. This is especially relevant as LC has previously been associated with a poor prognosis, whereas *NPM-1* is considered a positive prognostic indicator in some circumstances [32]. Interestingly, of the 5 patients with an *NPM1* mutation, only one patient had AML with monocytic features in contrast to

Table 3. *Frequency of mutations seen in cohort with leukemia cutis and acute myeloid leukemia compared to database of samples with acute myeloid leukemia.*

	Frequency observed in LC, N=11	Frequency reported in samples with AML COSMIC*, N=68,863 - 948
Mutation		
NPM1	45%	31.7%
FLT3-TKD	45%	23.6%
FLT3-ITD	18%	18.7%
IDH1	18%	6.4%
RUNX1	18%	7.6%
U2AF1	18%	2.5%
NRAS	9%	13.2%
WT1	9%	9.0%
CEBPA	9%	9.6%
TET2	9%	12.4%
STAG2	9%	3.8%
DNMT3A	9%	18.7%

**COSMIC (Catalogue of Somatic Mutations in Cancer) is a database cataloguing somatic mutations in human cancers, Forbes, S. A., et al. [35].*

Abbreviations: LC – leukemia cutis, AML – acute myeloid leukemia, NOS – not otherwise specified, NPM1 – nucleophosmin 1, RUNX1 – runt-related transcription factor 1, MLLT3 – myeloid/lymphoid or mixed-lineage leukemia translocated to chromosome 3, KMT2A – histone-lysine N-methyltransferase 2A, FLT3 – fms related Tyrosine Kinase 3, ITD – internal tandem duplication, TKD – tyrosine kinase domain, IDH1 – isocitrate dehydrogenase 1, DNTM3A – DNA (cytosine-5)-methyltransferase 3A, U2AF1 – U2 small nuclear RNA auxiliary factor 1, NRAS – neuroblastoma RAS viral oncogene homolog, WT1 – Wilms tumor 1, CEPBA – CCAAT enhancer-binding protein alpha, TET2 – tet methylcytosine dioxygenase 2, STAG2 – stromal antigen 2.

previous studies suggesting a higher monocytic predominance in LC [20].

FLT3-TKD was also found to have increased predominance in patients with LC in this cohort. *FLT3-TKD* has been studied less than its more common counterpart, *FLT3-ITD*. Ansari-Lari et al. previously found *FLT3-ITD* mutations to be associated with extramedullary manifestations of AML but not specifically limited to the skin [19]. *FLT3-ITD* mutations are associated with a worse prognosis whereas *FLT3-TKD* mutations are of unclear significance [33].

The overall median survival of our patient series was low at 9 months. A recent retrospective study combining data from newly diagnosed AML patients who were treated in 11 clinical trials calculated a median overall survival of 1.035 years [28]. Previous small reports suggest that leukemia cutis may be associated with a poor prognosis, but results are mixed [2]. One study observed a 7.6 month overall survival for patients with leukemia cutis and AML [34]. Ganzel and colleagues, however, demonstrate that after adjusting for known prognostic risk factors such as older age, high white blood cell count, and cytogenetic risk factors, the presence of extramedullary disease did not have prognostic significance [28]. In contrast, Wang and co-authors found that patients with AML and LC as compared to those without LC had a hazard ratio of 2.06 for leukemia-specific death, after controlling for similar risk factors as Ganzel [29]. We did not find a statistical difference between the known prognostic risk factor-based predictions and the overall survival in our cohort. However, after risk-stratifying our patients with LC by European Leukemia Net criteria, the favorable risk group had a non-significantly increased overall survival (12 months) compared to the adverse (9 months) and intermediate risk categories (8 months). These results likely did not achieve significance owing to the small study population.

Our study is limited by its small, single-center, and retrospective nature. AML patients were not prospectively monitored for leukemia cutis and thus we may have missed a number of patients with AML who did not have a diagnostic biopsy of their leukemia cutis performed. Additionally, our analysis is limited by the small number of available cases with both diagnostic biopsies demonstrating leukemia cutis and with genetic testing. Our lack of genetic studies on the biopsy samples themselves may also have led us to miss a gene potentially associated with LC not seen in the bone marrow. A study comparing the mutations seen in the bone marrow versus the skin biopsy would also further aid in elucidating the mechanism by which leukemic cells travel to the skin and would be an interesting future project. Reassuringly, however, our results are consistent with previous studies that show *NPM1* and *FLT3* are prevalent mutations in AML patients with extramedullary disease [16, 19, 20]. Although *NPM1* and *FLT3* are among the most studied mutations in AML [16-18], the mutational panel utilized here included a large number of cancer-associated genes not necessarily specific to AML; thus, our findings are unlikely to be biased towards identifying genes only tested in AML. Additionally, the large number of genes included (over 450 genes) in our panel lessens the likelihood of missing a particular gene.

Conclusion

The mutational profile of the bone marrow of patients with AML and LC is largely similar to that of patients with AML in the literature. To further the understanding of the biologic mechanisms underlying the manifestation of LC, future studies should focus on understanding the molecular architecture of the LC lesions themselves. Alternatively, given that patients with AML more commonly manifest LC, further investigation into what is unique in terms of AML patients' mutational profiles as compared to patients with other types of leukemias is warranted.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Longacre TA, Smoller BR. Leukemia cutis. Analysis of 50 biopsy-proven cases with an emphasis on occurrence in myelodysplastic syndromes. *Am J Clin Pathol*. 1993;100:276–84. [PMID: 8379536].
2. Cho-Vega JH, Medeiros LJ, Prieto VG, Vega F. Leukemia cutis. *Am J Clin Pathol*. 2008;129:130–42. [PMID: 18089498].
3. Su WPD, Buechner SA, Li C-Y. Clinicopathologic correlations in leukemia cutis. *J Am Acad Dermatol*. Elsevier; 1984;11:121–8. [PMID: 6736347].
4. Gru AA, Coughlin CC, Schapiro ML, et al. Pediatric aleukemic leukemia cutis: report of three cases and review of the literature. *Am J Dermatopathol*. 2015;37:477–84. [PMID: 25148106].
5. Agis H, Weltermann A, Fonatsch C, et al. A comparative study on demographic, hematological, and cytogenetic findings and prognosis in acute myeloid leukemia with and without leukemia cutis. *Ann Hematol*. 2002;81:90–5. [PMID: 11907789].
6. Desch JK, Smoller BR. The spectrum of cutaneous disease in leukemias. *J Cutan Pathol*. 1993;20:407–10. [PMID: 8300925].
7. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391–405. [PMID: 27069254].
8. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*. 2010;116:354–65. [PMID: 20385793].
9. Li AW, Yin ES, Stahl M, et al. The skin as a window to the blood: Cutaneous manifestations of myeloid malignancies. *Blood Rev*. 2017;31:370–88. [PMID: 28732587].
10. Shaikh BS, Frantz E, Lookingbill DP. Histologically proven leukemia cutis carries a poor prognosis in acute nonlymphocytic leukemia. *Cutis*. 1987;39:57–60. [PMID: 3802911].
11. Ansell JE, Bhawan J, Pechet L. Leukemia cutis in blastic transformation of chronic myelocytic leukemia: TdT positive blasts and response to vincristine and prednisone. *J Cutan Pathol*. 1980;7:302–9. [PMID: 6933170].
12. Chang H, Brandwein J, yi Q-L, et al. Extramedullary infiltrates of AML are associated with CD56 expression, 11q23 abnormalities and inferior clinical outcome. *Leuk Res*. 2004;28:1007–11. [PMID: 15289011].
13. Campbell JJ, Haraldsen G, Pan J, et al. The chemokine receptor CCR4 in vascular recognition by cutaneous but not intestinal memory T cells. *Nature*. 1999;400:776–80. [PMID: 10466728].
14. Murphy MJ. Molecular testing of leukemia cutis. *J Cutan Pathol*. 2012;40:286–8. [PMID: 23167505].
15. Pileri SA, Ascani S, Cox MC, et al. Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. *Leukemia*. 2006;21:340–50. [PMID: 17170724].
16. Falini B, Lenze D, Hasserjian R, et al. Cytoplasmic mutated nucleophosmin (NPM) defines the molecular status of a significant fraction of myeloid sarcomas. *Leukemia*. 2007;21:1566–70. [PMID: 17443224].
17. Falini B, Mecucci C, Tiacci E, et al. Cytoplasmic nucleophosmin in acute myelogenous leukemia with a normal karyotype. *N Engl J Med*. 2005;352:254–66. [PMID: 15659725].
18. Carow CE, Levenstein M, Kaufmann SH, et al. Expression of the hematopoietic growth factor receptor FLT3 (STK- 1/Flk2) in human leukemias. *Blood*. 1996;87:1089–96. [PMID: 8562934].
19. Ansari-Lari MA, Yang C-F, Tinawi-Aljundi R, et al. FLT3 mutations in myeloid sarcoma. *Br J Haematol*. 2004;126:785–91. [PMID: 15352981].
20. Luskin MR, Huen AO, Brooks SA, et al. NPM1 mutation is associated with leukemia cutis in acute myeloid leukemia with monocytic features. *Haematologica*. 2015;100:e412–4. [PMID: 26113416].
21. Sen F, Zhang XX, Prieto VG, Shea CR, Qumsiyeh MB. Increased incidence of trisomy 8 in acute myeloid leukemia with skin infiltration (leukemia cutis). *Diagn Mol Pathol*. 2000;9:190–4. [PMID: 11129442].
22. Baer MR, Barcos M, Farrell H, Raza A, Preisler HD. Acute myelogenous leukemia with leukemia cutis. Eighteen cases seen between 1969 and 1986. *Cancer*. 1989;63:2192–200. [PMID: 2785843].
23. Dachary D, Bernard P, Lacombe F, et al. Acute myeloid leukemia with marrow hypereosinophilia and chromosome 16 abnormality. *Cancer Genet Cytogenet*. 1986;20:241–6. [PMID: 3455867].
24. Miura I, Nishinari T, Hashimoto K, et al. Translocation (8;17)(p21;q21), a possible variant of t(15;17), in acute promyelocytic leukemia. *Cancer Genet Cytogenet*. 1994;72:75–7. [PMID: 8111744].
25. Bernstein R, Pinto MR, Spector I, Macdougall LG. A unique 8;16 translocation in two infants with poorly differentiated monoblastic leukemia. *Cancer Genet Cytogenet*. 1987;24:213–20. [PMID: 3466674].
26. Douet-Guilbert N, Morel F, Le Bris M-J, et al. Rearrangement of MLL in a patient with congenital acute monoblastic leukemia and granulocytic sarcoma associated with a t(1;11)(p36;q23) translocation. *Leuk Lymphoma*. 2009;46:143–6. [PMID: 15621793].
27. Byrd JC, Edenfield WJ, Shields DJ, Dawson NA. Extramedullary myeloid cell tumors in acute nonlymphocytic leukemia: a clinical review. *J Clin Oncol*. 1995;13:1800–16. [PMID: 7602369].
28. Ganzel C, Manola J, Douer D, et al. Extramedullary disease in adult acute myeloid leukemia is common but lacks independent significance: Analysis of patients in ECOG-ACRIN Cancer Research Group Trials, 1980-2008. *J Clin Oncol*. 2016;34:3544–53. [PMID: 27573652].
29. Wang CX, Pusic I, Anadkat MJ. Association of leukemia cutis with survival in acute myeloid leukemia. *JAMA Dermatol*. 2019;155:826–32. [PMID: 30969325].
30. Tallman MS, Wang ES, Altman JK, et al. Acute Myeloid Leukemia, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2019;17:721–49. [PMID: 31200351].
31. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129:424–47. [PMID: 27895058].
32. Döhner H, Gaidzik VI. Impact of genetic features on treatment decisions in AML. *Hematology Am Soc Hematol Educ Program*. 2011;2011:36–42. [PMID: 22160010].
33. Patnaik MM. The importance of FLT3 mutational analysis in acute myeloid leukemia. *Leuk Lymphoma*. 2018;59:2273–86. [PMID: 29164965].
34. Kaddu S, Zenahlik P, Beham-Schmid C, Kerl H, Cerroni L. Specific cutaneous infiltrates in patients with myelogenous leukemia: a clinicopathologic study of 26 patients with assessment of diagnostic criteria. *J Am Acad Dermatol*. 1999;40:966–78. [PMID: 10365929].
35. Forbes S, Beare D, Boutselakis H. COSMIC: somatic cancer genetics at high-resolution. *Nucleic Acids Res*. 2017;45:D777–D783. [PMID: 27899578].