

CLINICAL REPORT

Cutaneous Myeloid Sarcoma: Natural History and Biology of an Uncommon Manifestation of Acute Myeloid Leukemia

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We conducted a retrospective study of patients with cutaneous myeloid sarcoma, from 2 tertiary care institutions. Eighty-three patients presented, with a mean age of 52 years. Diagnosis of myeloid sarcoma in the skin was difficult due to the low frequency of myeloperoxidase and/or CD34⁺ cases (56% and 19% of tested cases, respectively). Seventy-one of the 83 patients (86%) had ≥ 1 bone marrow biopsy. Twenty-eight (39%) had acute myeloid leukemia with monocytic differentiation. Twenty-three had other *de novo* acute myeloid leukemia subtypes. Thirteen patients had other myeloid neoplasms, of which 4 ultimately progressed to an acute myeloid leukemia. Seven had no bone marrow malignancy. Ninety-eight percent of the patients received chemotherapy, and approximately 89% died of causes related to their disease. Cutaneous myeloid sarcoma in most cases represents an aggressive manifestation of acute myeloid leukemia. Diagnosis can be challenging due to lack of myeloblast-associated antigen expression in many cases, and difficulty in distinguishing monocyte-lineage blasts from neoplastic and non-neoplastic mature monocytes. *Key words: cutaneous myeloid sarcoma; chloroma; myeloid sarcoma; monoclastic sarcoma.*

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The World Health Organization defines myeloid sarcoma as “a tumor mass consisting of myeloid blasts with or without maturation occurring at an anatomical site other than the bone marrow” (1). Although the skin is identified as a common site of involvement of myeloid sarcoma, studies of cutaneous myeloid sarcoma (CMS) are relatively lacking. A large study consisting of cases presenting in the skin is desirable to evaluate the demographic, clinical, and histopathologic properties of CMS, and the potential impact of the microanatomy and cytokine milieu of the skin in the presentation of cutaneous leukemias.

We report the results of a retrospective study of 83 patients presenting with CMS over a 19-year period at 2 tertiary care institutions in the Midwest United States. We emphasize the demographics, clinical presentation, and pathologic workup of these patients, and their response to therapy.

METHODS

The study was performed with the joint approval of the Institutional Review Boards of the Saint Louis University and Washington University Schools of Medicine.

Search parameters

A search of the electronic databases of the Department of Dermatology, Division of Dermatopathology, Saint Louis University, and the Section of Anatomic and Molecular Pathology, Department of Pathology and Immunology, Washington University, was performed. Typical patient demographic data was collected (date of birth, gender, and race) along with dermatological information regarding lesion size, morphology, and anatomic site. In addition, data concerning other anatomic sites of involvement, patient treatment regimen, clinical course, and survival status were also recorded.

The study also describes the bone marrow in comparison with the cutaneous involvement of myeloid blasts. This was accomplished by including bone marrow aspirate immunohistochemistry, histochemistry, flow cytometry, phenotype of the myeloid leukemia by flow cytometry, marrow cellularity, myeloid:erythroid ratio, myeloid blast cell percentage, along with enzyme cytochemical analysis results. Whenever available, karyotype, fluorescence-*in-situ*-hybridization, and the results of molecular genetic testing were also included.

Chart review

The charts of all patients were reviewed for evaluation of the following parameters: age at initial presentation, gender, race, site(s) of involvement, clinical description of lesion(s), temporal relationship of CMS to acute myeloid leukemia (AML) (i.e. did the diagnosis of CMS precede, coincide, or follow the diagnosis of AML), therapy, and outcome. For patients who were evaluated at Saint Louis University or Washington University and treated elsewhere, additional clinical follow-up was obtained from the referring clinicians.

Pathologic review

In all patients, the diagnostic biopsies of the skin, bone marrow, and other sites of involvement were reviewed for all available cases. Notes were made of the histopathologic features, immunohistochemistry, and flow cytometry of all tested cases.

Statistical analysis

The patient demographics, cutaneous lesion presentation characteristics, dermatopathologic findings, and bone marrow characteristics of patients with CMS were described using frequencies (%) for categorical level variables and measures of central tendency (means \pm standard deviation (SD)) for continuous level variables.

Additionally comparisons were made to identify if the characteristics vary between length of time from diagnosis of AML, age, race, site of involvement, number of lesions, and other important factors. Chi-square analysis, independent samples *t*-test, and analysis of variance between groups (ANOVA) were utilized to analyze the data. All analyses were defined as statistically significant when $\alpha < 0.05$. SPSS software, version 16 (Chicago, Illinois) was used for the analysis.

RESULTS

Eighty-three patients were identified in the search of the laboratory information systems of both institutions. Although CMS has a male predominance (50 males and 33 females, $p = 0.62$). The vast majority of patients were white (86% of patients), and a wide age range was identified, with age at onset of cutaneous disease range between 2 weeks–89 years old. The lesions were discrete in all cases, and most often were described as papules, nodules, or plaques. They presented most commonly on the torso (39% of cases), followed by the upper extremities (24%), lower extremities (21%), and head and neck (16%). In 34 cases the patients had a diagnosis of bone marrow-based AML and a sufficient clinical history allowed a temporal relationship to be established between the two diagnoses. CMS preceded the bone marrow diagnosis of AML in 6 (18%) cases, followed it in 15 (44%), and was coincident with the diagnosis of AML in the bone marrow (defined as occurring within 2 weeks of the bone marrow diagnosis) in 13 (38%). Most patients had disease limited to the skin and bone marrow; however, 18/83 (22%) of the patients experienced involvement of sites outside the skin and bone marrow, most commonly the central nervous system (6 cases) and lymph nodes (6 cases). Other sites of involvement included the gastrointestinal tract, liver, and lung (3 patients each), and the spleen, oral mucosa, and testes (2 patients each). Fifteen patients had involvement of the bone marrow by an AML with monocytic differentiation (French-American-British classification of AML (FAB): M4 or M5). Using the “registry” with 83 cases of CMS, the one-year mortality status was determined for 59 (or 71.1%) of cases. Of these 59 cases, 86.4% were deceased one-year after the diagnosis date. Of the patients who died during the observed period, the mean number of survival days after the diagnosis date was 227 ± 319 (range 14–1,561, median 64, 25–75% 31–275). The death date was unknown for one of the 51 cases known to be deceased. The mean age at CMS diagnosis was 54.9 ± 20 years, based on 75 cases with known age at CMS diagnosis.

Women were younger than men at age of diagnosis (49.5 vs 58.4), but this was not statistically significant ($p = 0.062$). No difference was observed in age at diagnosis by race (white vs. black vs. other). The possible association between patient age at diagnosis and survival days was explored by calculating the Pearson correlation coefficient. Among the 51 patients who were deceased, there was no correlation between age at diagnosis and survival days (correlation coefficient of 0.012, $p = 0.993$). The registry includes 18 cases who survived for > 1 year. Among these 18 cases, the mean age at diagnosis was 51.6 ± 22 among the 17 subjects with known age information. 61% of survivors were male; 61% were Caucasian. There was no statistically significant difference between mean age at diagnosis ($p = 0.352$) or gender ($p = 0.800$) between one-year survivors and deceased cases. When examined for survival at the 60-day mark, the same results persisted: no differences were seen between mean age at diagnosis or gender. Four patients were autopsied, all of whom had noncutaneous sites of involvement which had not been detected antemortem.

The skin lesions had a variable microscopic appearance. The overlying epidermis was essentially unremarkable in all cases. In all cases the malignant cells involved the superficial and deep dermis. The cells comprising the infiltrate were clearly identifiable as blasts in most cases by their immature cytomorphology, abundant mitotic activity, dispersed nuclear chromatin with nucleoli, and scattered apoptotic cells. This cytomorphology was a particularly important consideration for cases in which the infiltrate was relatively subtle and/or predominantly perivascular and could simulate a benign process inflammatory skin disorder. Eleven cases demonstrated extension of blasts through the dermis into the underlying subcutis. In most cases the pattern of infiltration was perivascular, periadnexal, and interstitial, with relative preservation of the microanatomy of the dermis (Fig. 1). In contrast, 20 cases demonstrated an overall pattern of diffuse involvement, with destruction of the normal microanatomic features of the dermis (Fig. 2). In a statistical comparison of cases with diffuse growth versus others, there were no significant differences regarding survival, and the demographic and phenotypic properties of both groups were similar.

Due to the retrospective nature of this study, in which the cases were initially reviewed by a large number of hematopathologists and dermatopathologists, the diagnostic approach to the skin biopsies was highly variable. The myeloid lineage of all cases was subsequently established by us (2). Cases initially presenting in the bone marrow with secondary involvement of the skin frequently had a minimal workup, since the differential diagnosis was very limited. Nineteen cases with involved skin biopsies and a prior bone marrow diagnosis of AML were evaluated by a hematoxylin

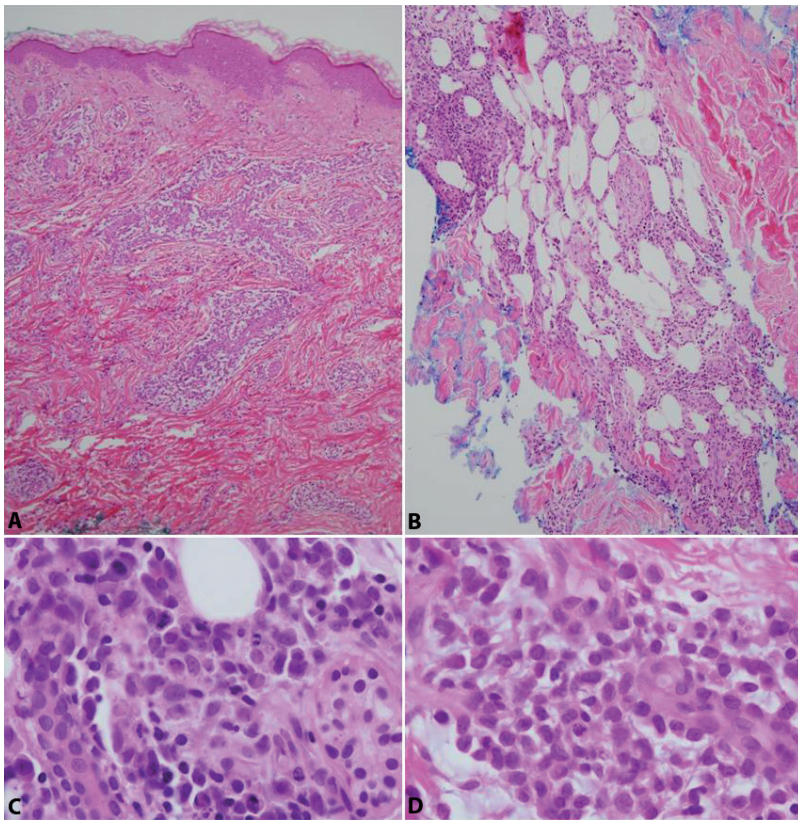


Fig. 1. Myeloid sarcoma, example of a case (A) with focal architecture, characterized by periadnexal, perivascular, and perifollicular growth with sparing of dermal microanatomic structures, and (B) extension into the subcutaneous fat (H&E, original magnifications $\times 200$). (C, D) Blasts are large with high nuclear: cytoplasmic ratio, dispersed nuclear chromatin, and prominent nucleoli; mitoses are prominent (H&E, original magnification $\times 400$).

and eosin-stained section without additional studies. In an additional 19 patients, evaluated by a hematoxylin and eosin-stained section and a chloroacetate esterase (Leder) stained section, the blasts were Leder negative. The remaining cases had immunohistochemistry analysis as part of their workup, including lysozyme (positive in 14/14[100%] of tested cases), myeloperoxidase (20/36, 56%), CD68 (14/14, 100%), and

particularly in patients presenting with skin lesions, includes blastic plasmacytoid dendritic cell neoplasm (formerly referred to as blastic natural killer cell lymphoma and agranular CD4⁺/CD56⁺ hematodermic neoplasm). In such patients, a more extensive immunohistochemical workup may be warranted, and the clinical history may be critical. All 3 patients with CD4⁺/CD56⁺ blasts had a prior history of AML (2 with acute myelomonocytic

CD34 (3/16, 19%). A comprehensive list of antibodies reviewed in this study is listed in Table SI (available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1458>). Of note, several cases demonstrated aberrant expression of markers of other lineages, which is a well-known phenomenon in AML but may lead to an erroneous diagnosis, particularly in patients with a limited immunohistochemical workup and/or lack of clinical history. Aberrant expression of B-lymphoid-related antigens was rare, limited to CD20 expression in one of 20 tested cases. This unusual finding has been previously noted in AML (3) Aberrant expression of T- and NK-cell antigens was more frequent. CD5 expression was noted in 1 of 2 tested cases, which has been reported in rare cases of AML (4). CD7 was positive in 1 of 5 tested cases; however the diagnosis of T-cell lymphoma was not of diagnostic concern based on the absence of expression of other T-cell associated antigens, and the supporting clinical history. CD56 was expressed in 5 of 6 tested cases, and in 3 of these cases was coexpressed with CD4 (Fig. S1; available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1458>). The differential diagnosis for such cases,

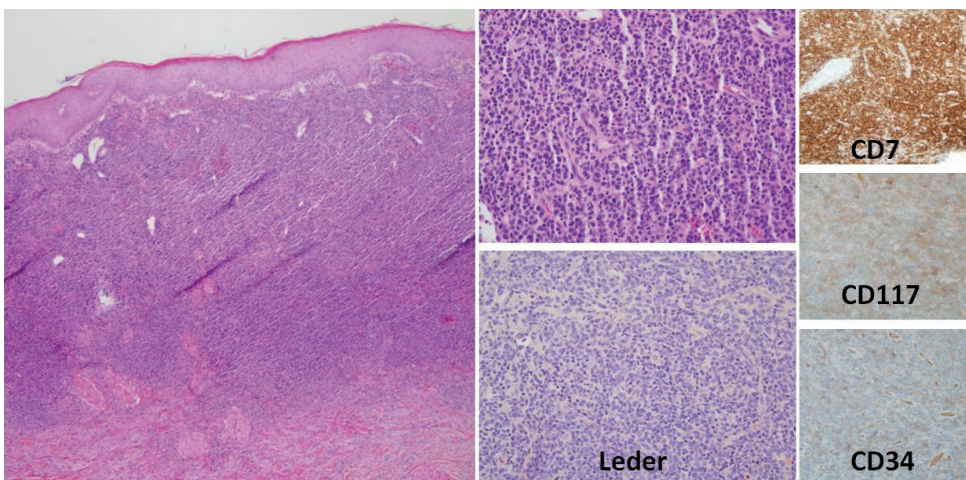


Fig. 2. Myeloid sarcoma; example of a case with diffuse growth, characterized by destruction of dermal microanatomic structures (hematoxylin and eosin, original magnifications $\times 200$, $\times 400$). Leder histochemistry is negative in blasts (original magnification $\times 400$). Immunohistochemistry ($\times 400$) demonstrates the blasts to express CD7, CD117, and CD34 (partial).

leukemia, one with relapsed acute AML in which the original material could not be reviewed) and had blasts which also expressed lysozyme and CD68. Although rare CD68⁺ cases of blastic plasmacytoid dendritic cell neoplasm have been reported in the literature, lysozyme expression is indicative of myeloid origin for the malignant cells.

Of the 83 patients 71 (85%) had at least one bone marrow biopsy available for review. Twenty-nine patients (41%) had an AML with monocytic differentiation (15 acute myelomonocytic leukemias [FAB: M4], 14 acute monoblastic/ monocytic leukemias [FAB: M5]). Thirty-five patients had other AML subtypes. Many AML cases could not be further subclassified because 1) a disease-defining cytogenetic abnormality was not present and 2) enzyme cytochemical analysis of the blasts was not performed. Thirteen patients had myeloproliferative neoplasms, myelodysplastic syndromes, or overlap diseases (5 cases of chronic myelomonocytic leukemia), of which 5 ultimately progressed to an AML. Seven patients had no evidence of bone marrow involvement by a malignancy. A comprehensive list of bone marrow diagnoses is listed in Table II (available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1458>). Cytogenetic and/or molecular genetic results were abnormal in 23/29 (79%) of tested individuals and revealed the following: 2 patients with loss of chromosome 7, 2 patients with loss of the long arm of chromosome 7, 7 patients with trisomy of chromosome 8, and 5 patients with abnormalities of chromosome 11q23 involving the mixed lineage leukemia (MLL) locus. Nine patients had multiple nonspecific structural and/or numerical chromosomal abnormalities. Five patients had normal conventional cytogenetic analysis. Fluorescence *in situ*-hybridization confirmed the findings of *MLL* rearrangement in 4 patients and trisomy of chromosome 8 in 4 patients, and revealed low-level abnormal loss of the *RUNX1* (formerly known as *AML1*) locus in one patient with normal conventional cytogenetics.

Due to the retrospective nature of the specimens, analysis of the degree of phenotypic concordance between the skin and bone marrow specimens is limited. However, the available data support that the blast immunophenotype is retained at both sites (Tables I and II), both in cases with flow cytometric analysis of the bone marrow and in cases with immunohistochemical analysis of the bone marrow. In addition, there was only one case with discordant CD117 immunohistochemistry, a case of AML derived from prior chronic myelomonocytic leukemia.

DISCUSSION

The skin is one of the most common sites of involvement by myeloid sarcoma. The mechanism responsible for the

Table I. Reactivity for selected immunohistochemistry in skin biopsies by bone marrow diagnostic group

Diagnosis	Lysozyme		Myeloperoxidase		CD68	
	Positive	Negative	Positive	Negative	Positive	Negative
M0	0	0	0	1	0	0
M1	1	0	1	0	0	0
M2	2	0	0	0	0	0
M4	5	0	3	4	2	0
M5	3	0	1	3	2	0
M7	0	0	0	1	0	0
CMML	3	0	2	0	1	0
MDS	1	0	3	0	0	0
JMML	1	0	1	0	0	0
Unknown	12	1	8	5	9	0
Unclassifiable	0	0	0	3	0	0
Total	28	1	19	17	14	0

CMML: chronic myelomonocytic leukemia; MDS: myelodysplastic syndrome; JMML: juvenile myelomonocytic leukemia.

migration of myeloid blasts to the skin is poorly understood, but is hypothesized to be the result of the expression of chemokine receptors and adhesion molecules by the blasts and various cell types residing in the skin (5). The mechanism of preferential migration of blasts to the skin rather than to other extramedullary sites is likewise

Table II. Concordance between skin and bone marrow blast phenotypes

Antibody	Bone marrow diagnosis	Skin result	Bone marrow result
<i>Concordant skin immunohistochemistry/bone marrow flow cytometry</i>			
CD4	M4	+	+
CD4	M4	+	+
CD5	M4	+	+
CD33	M5	+	+
CD34	M4	-	-
CD34	M4	-	-
CD34	M5	+	+
CD34	M5	-	-
CD34	M4	+	+
CD56	M5	+	+
CD56	M4	+	+
CD56	M4	+	+
CD117	M4	+	+
CD117	M0	-	-
<i>Discordant skin immunohistochemistry/bone marrow flow cytometry</i>			
CD4	M4	+	-
CD34	AML ex CMML	-	+
CD34	M6a	-	+
CD117	AML ex CMML	-	+
<i>Concordant skin immunohistochemistry/bone marrow immunohistochemistry</i>			
CD3	M4	-	-
CD4	M4	+	+
CD7	M4	-	-
CD8	M4	-	-
CD20	M4	-	-
CD30	M4	-	-
CD34	M4	-	-
CD34	AML NOS	-	-
CD56	M4	+	+
CD56	M5	+	+
CD68	M2	+	+

AML: acute myeloid leukemia; CMML: chronic myelomonocytic leukemia; NOS: nitric oxide synthase.

unknown, but may be related to the similarity of certain features of the microanatomies of both sites, such as the rich microvascular background and similar percentage of type III collagen and other intermediate filaments.

Despite the frequency of involvement of the skin by AML, large studies of CMS are relatively few. To our knowledge, 9 previous studies have appeared in the peer-reviewed English language medical literature within the last 20 years (6–14), none of which fully address all major questions regarding clinical and pathologic features, molecular genetic findings, and outcome in CMS.

In our study, CMS is identified as predominantly affecting the elderly, although a broad age range is present. This is also reflected in the medical literature (6–14). Like us, most series reported a male predominance, although the study of Kaddu et al. (11) reports a predominance of females. Information about risk of cutaneous disease based on ethnicity is relatively lacking, probably due to a relative paucity of cases reported from North America. In our study, the vast majority of patients were Caucasian. Lesions are usually multiple and are described as papules, plaques, and/or nodules. The torso is most commonly involved, although a wide range of body sites has been reported. Our data show that the distribution of lesions favors the upper body. In all series in which an appropriate level of detail was provided (7–14), the most common bone marrow diagnosis was AML, and cases with myelomonocytic or monoblastic/monocytic differentiation were prominently represented. When reported, CMS was noted to follow the initial bone marrow diagnosis (6, 12, 13), though most patients eventually have bone marrow involvement. The pattern of skin involvement has been described previously (8, 9, 11–13), and Benet et al. (13) describe that cases initially presenting in the skin have a predilection for diffuse architecture, “high dense infiltrate”, large cells, and high mitotic index compared to cases with secondary involvement of the skin. This finding was not observed in our cases. The reason for this is uncertain, but may involve timing of the biopsy (longer-standing lesions would presumably have a larger number of malignant cells), preferential biopsy of the center vs. the leading edge of a lesion, or some other factor. Moreover, the clinical significance of differentiating the *de novo* vs. secondary cases (which could, of course, have been resolved on clinical grounds) is likely of little consequence in our patients, since survival for patients in our series was almost uniformly poor; patients do not appear to have benefitted from recent innovations in chemotherapeutic regimens or bone marrow transplant, as previous studies performed over a decade ago have demonstrated similar findings (8, 11).

Genetic mutations are not widely reported in cases of AML with skin involvement, and are postulated to be similar to the commonly occurring cytogenetic findings in AMLs occurring in other sites. Notably, a

high percentage of cases in our series had abnormal conventional cytogenetic findings. In 25% of cases, there were multiple numerical and/or structural abnormalities, suggestive of evolution of an aggressive clone. Of the cases, 25% had trisomy of chromosome 8, a finding identified in myeloid sarcomas involving the skin (14) and other sites.

Numerous studies emphasize the challenges in diagnosing CMS. In large part, this is due to the historic and ongoing problems in distinguishing non-neoplastic from neoplastic monocytes and their precursors and the relative insensitivity of antibodies such as CD34 and CD117 in identifying blasts in the skin. These are, of course, related concepts, since the highest percentage of cases in all studies, including ours, represent involvement of the skin by AML with monocytic differentiation, either acute myelomonocytic leukemia (FAB: M4) or acute monoblastic/monocytic leukemia (FAB: M5). It is thus important to identify a battery of immunohistochemical markers which distinguish AMLs involving the skin from other diseases. In addition, it may be of interest to identify those markers which successfully identify cases with monocytic differentiation, for several reasons: patients with acute monocytic leukemia may have a more aggressive disease course, although this is controversial and not uniformly seen in all studies (15–19); AMLs with monocytic differentiation may harbor rearrangements involving the *MLL* gene, many of which, with the prominent exception of the translocation t(9;11), have been associated with a more aggressive disease course; and perhaps most importantly for diagnostic purposes, it may be important to the diagnostician to determine if reactivity for a given marker is sufficiently specific to identify cases having monocytic differentiation.

In our patients, the antibodies which were most sensitive in detecting cases of CMS, but were unhelpful in distinguishing AMLs with monocytic differentiation from others and were performed in a sufficient number of cases to be assessed were CD43, CD68, and lysozyme. CD43, although highly sensitive, has a broad range of expression, including granulocytes, T cells, and some malignant B cells (20). Lysozyme, although very sensitive for the detection of myeloid disease, is relatively nonspecific for distinction of malignancies with monocytic differentiation (e.g. M4, M5, chronic myelomonocytic leukemia (CMML)) from other leukemias without monocytic differentiation (e.g. M1, M2). Myeloperoxidase is frequently negative due to the high frequency of AML with monocytic differentiation. CD68 is reportedly similar to lysozyme in sensitivity, and is similarly nonspecific for distinction of malignancies with monocytic differentiation (e.g. M4, M5 CMML) from other leukemias without monocytic differentiation (e.g. M1, M2). We conclude that none of the antibodies studied by us is sufficiently specific,

either alone or in combination, to distinguish AMLs with monocytic differentiation from other AMLs, although CD43, lysozyme, and CD68 are most sensitive in differentiating CMS from other disorders.

Also of interest is whether the blast phenotype is concordant between the bone marrow and skin populations, or whether there is a high rate of phenotypic discordance, as has been previously reported (14). Notably, the earlier study of Cronin et al. (14) does not include bone marrow immunohistochemistry, which was often employed in our cases in lieu of or in addition to flow cytometry. Due to the retrospective nature of this study, complete and uniform immunophenotypic analysis of all cases was not performed. However, our data show that the blast phenotype as assessed by immunohistochemistry is highly consistent between sites. Four discordant cases were identified by flow cytometry comparing flow cytometry of the bone marrow and immunohistochemistry of the skin. These differences thus may more likely represent differences in the techniques such as antibody sensitivities rather than a true discrepant phenotype between the skin and bone marrow blasts.

To summarize, CMS is an uncommon malignancy which in most cases represents an aggressive manifestation of AML. Diagnosis can be challenging due to the lack of myeloblast-associated antigen expression in many cases, and the difficulty in distinguishing monocyte-lineage blasts from neoplastic and non-neoplastic mature monocytes, and aberrant expression of CD7 and/ or CD56. However, the combination of highly sensitive (CD43 and lysozyme) and more specific (myeloperoxidase, CD68, CD117, and CD34) antibodies can aid in the identification of suspected cases. There are additional antibodies that are more specific and sensitive for use in the setting of a suspected CMS (2). Interestingly, the blast phenotype is usually concordant between the bone marrow and skin populations. Cytogenetic abnormalities were detected in a high percentage of cases, consistent with the aggressive behavior of this disease. The vast majority of patients died of disease within one year of diagnosis. As the clinical data show, the majority of patients with this disorder have a prior or concomitant history of AML. Thus, diagnosis of CMS is multidisciplinary in many cases and is greatly facilitated by the clinical history.

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