Histologic and Immunohistologic Characterization of Skin Localization of Myeloid Disorders

A Study of 173 Cases

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Abstract

A retrospective analysis of 173 skin biopsy specimens of myeloid leukemia cutis (MLC) was performed to determine histologic and immunophenotypic criteria that could distinguish the varied myeloid disorders from one another. For the study, 11 relevant histologic items were scored and 12 antigens were studied (CD68 [KP1], CD163, CD14, CD4, myeloperoxidase [MPO], CD33, CD117, CD34, CD56, MIB-1, CD303, and CD123).

Underlying myeloid disorders were essentially acute myeloid leukemias (65.3%), chronic myelomonocytic leukemias (11.0%), and refractory anemia (10.4%). Skin lesions were de novo in 7.5%, concurrent in 26.6%, and subsequent in 60.7%.

Several morphologic characteristics (density, size of tumor cells, inflammatory background) were statistically useful in distinguishing between varied myeloid disorders. De novo MLCs displayed a specific morphologic profile.

Association of CD68, CD33, and MPO could diagnose 100% of the cases of MLC. However, the immunohistochemical panel could not distinguish between the varied underlying myeloid disorders, with the exception that CD123 was particularly powerful in recognizing chronic myelomonocytic leukemia and also permitted reclassification of 4 cases as blastic plasmacytoid dendritic cell neoplasm.

The term leukemia cutis usually refers to a skin infiltration by lymphoid or myeloid malignancy. When tumor cells are identified as myeloid cells, other terms can be found in the literature such as chloroma, myeloid sarcoma, and granulocytic sarcoma, which all signify extramedullary localization of a myelomonocytic malignancy. Most of these myeloid disorders represent acute myeloid leukemias (AMLs), particularly those of monocytic differentiation. However, other myeloid disorders, less frequently represented as chronic myelomonocytic leukemia (CMML), refractory anemia (RA), and myeloproliferative syndrome (MPS), may also involve the skin at the time of their blastic transformation. In this report, we use the generic term myeloid leukemia cutis (MLC) because this term seems most appropriate, as morphologic and immunohistologic criteria have not been identified to distinguish the varied underlying myeloid disorders. Patients with myeloid malignancies, particularly AML, often have various skin pathologies1 such as viral or fungi infections, drug reaction, vasculitis, or purpuric or hemorrhagic phenomena due to thrombopenia.

Distinguishing tumoral infiltrates from nonmalignant manifestations requires skin biopsy and a pathologist able to recognize leukemia cutis and use an immunohistochemical panel to verify its presence. The prevalence of skin involvement in myeloid malignancies is estimated around 3%.2 While clinical and pathologic diagnosis is readily made when the MLC occurs after the diagnosis of leukemia has been established, patients who initially have skin
manifestations, so-called aleukemic leukemia cutis, can be difficult to identify.\textsuperscript{2}

The aims of the present study, based on the largest series ever published in the literature of 173 cases of MLC, were first to determine minimal histologic and immunophenotypic criteria for MLC and second to identify pathologic characteristics that distinguish the varied myeloid disorders from one another.

**Materials and Methods**

**Case Selection**

Cases diagnosed as MLC on skin biopsy were selected from the database of the French Study Group of Cutaneous Lymphomas (FSGCL) and also, as myeloid disorders are not systematically included by the FSGCL, from the databases of 9 centers, all members of the FSGCL and willing to participate in the study (Dijon, Bordeaux, Lille, Clermont-Ferrand, Paris-Necker, Montpellier, Paris-Cr\'eteil, Paris-Bobigny, Paris-Cochin, all in France). Databases were searched between 1992 and 2008. Cases were considered eligible for the study when slides and blocks of the biopsies were available. Based on these criteria, 173 cases were selected for the study.

**Clinical Data**

Clinical data included sex, age, chronology, and clinical description of the skin lesions (number, size, types [plaque, papule, nodule, and tumor], color, purpuric features, and localization). Because this was a retrospective study, myeloid malignancies had been classified in the varied centers according to the French-American-British classification,\textsuperscript{3,4} so we kept this classification for the study. The different disorders were initially diagnosed as AML (subtypes AML-0 to AML-6), CMML, RA, MPS (subtypes, chronic myeloid leukemia [CML], essential thrombocythemia [ET], polycythemia vera [PV], and chronic eosinophilic syndrome [CES]), and extramedullary myeloid sarcoma.

**Histologic Data**

For each case, paraffin blocks were available with H&E and Giemsa stains. All cases were reviewed by 2 pathologists (C.B. and T.P.) to first confirm the diagnosis and second to choose the spots for the tissue microarray (TMA) blocks.

Items for morphologic analysis were the following at low magnification: patterns, including few scattered tumor cells, nodular (perivascular and/or periadnexal), diffuse with or without a grenz zone, presence of single file arrangement, and granuloma annulare–like pattern; density of the tumor-cell infiltrate scored as weak (score 1), medium (score 2), or dense (score 3); epidermal infiltration; fat tissue infiltration; presence of reactive-cell background (lymphocytes, epithelioid or multinucleated histiocytes, granulocytes, eosinophils, or mast cells); and density of reactive-cell background judged as low (\(\leq 10\%\)) or high (\(>10\%\)). At high magnification, the morphologic analysis included the following: tumor cell size, small (<2 times the size of a lymphocyte), medium (between 2 and 4 times the size of a lymphocyte), or large (>4 times the size of a lymphocyte); monomorphous or polymorphous pattern of the tumor cells infiltrate; presence of kidney-shaped nuclei; mitotic index; and apoptosis.

**Immunohistochemical Data**

Five TMA blocks were built with 2 core biopsies from each of the 173 genuine blocks. Twelve antibodies were tested: CD68 (KP1), CD163, CD14, CD4, myeloperoxidase (MPO), CD33, CD117, CD34, CD56, MIB-1, CD303, and CD123. Sources of the antibodies were as follows: CD68, MPO, CD117, and MIB-1, DAKO, Glostrup, Denmark; CD164, CD14, CD34, CD33, and CD56, Ménarini Diagnostics, Rungis, France; CD34, Coulter/Immunotech, Luminyn, France; CD123, Clinisciences, Montrouge, France; CD303, Dendritics, Lyon, France. For the cases positive for CD123 and/or CD303, additional immunostaining was performed with TCL1 (Mickael Teitell, MD, PhD, UCLA, Los Angeles, CA), CD2AP (Teresa Marafioti, MD, PhD, John Radcliffe Hospital, Oxford, England), and granzyme B (3 complementary markers of plasmacytoid dendritic cells).

Immunohistochemical analysis was performed using a BenchMark Ventana automate (Ventana Medical Systems, Illick, France).

For each antibody, the TMA slides were scanned (Aperio scanner, Vista, CA) followed by semiquantitative analysis (laboratory version 8.0, Aperio). For each spot, the staining was interpreted as negative (0; no stained cells), positive homogeneous (1; \(>90\%\) stained cells), or positive heterogeneous (2; \(\leq 90\%\) stained cells), except for MIB-1, for which 4 groups were done: 0, \(< 5\%\); 1, 6\% to 33\%; 2, 34\% to 66\%; and 3, 67\% to 100\%.

With our TMA blocks, around 38\% of the immunostaining was not interpretable because both spots of each case were lost. This is a little higher than TMA results published, essentially because skin punch biopsy specimens were too tiny to allow more than 2 spots.

**Statistical Analyses**

Bilateral tests between the different types of myeloid disorders (AML, de novo AML, CMML, RA, and MPS) were performed by using the \(\chi^2\) test or the Fisher exact test (Stata 8.0, STATA, College Station, TX) when more than 20\% of the theoretical enrollments were lower than 5. A threshold of 5\% was considered as significant.
Results

Patients

The sex ratio showed a male predominance, with 101 males and 72 females (1.4:1). The median age was 62 years, ranging from 1 month to 88 years. The chronology of the skin lesions is summarized in Table 1. For 13 cases (7.5%), the skin lesions were de novo with no underlying myeloid disorder; for 46 patients (26.6%), the skin lesions were concurrent with the diagnosis of the myeloid disorder; and for 105 patients (60.7%), the skin lesions were subsequent to the myeloid disorder and considered as skin relapse. For 9 patients (5.2%), the chronology of the lesions was unknown.

The type of the underlying myeloid disorder was known for 163 patients and classified according to the French-American-British system. The repartition of the different types of myeloid disorder is summarized in Table 2. There were 113 AMLs, 19 chronic CMMLs, 18 RAs, 5 CMLs, 3 PVs, 1 ET, 1 CES, and 3 extramedullary myeloid sarcomas (other than skin). For cases of CMML, data concerning the subtypes (CMML-1, <5% blasts; CMML-2, 5%-19% blasts) were not provided.

For 162 patients, clinical data for the skin lesions were known. The skin lesions were solitary in about 23% of the cases and multiple in about 77% (Image 1). All parts of the body could be involved (face, skull, trunk, and limbs). In about 85% of the cases, the lesions were infiltrated, displaying a nodule and/or a papule, and flat in about 15%. Most of the lesions were reddish and/or violaceous nodules. In 2 cases, the lesions were “itchy” and painful in 1 case. Vascular changes were rare: ecchymotic, 1 case; purpuric, 2 cases; and livedoid, 1 case. In 1 case, the lesions were hyperkeratotic and in 1 case, erysipelo.

Lack of follow-up for many of the cases did not allow studying survival curves of the varied cohorts.

Table 1
Chronology of 173 Skin Lesions

<table>
<thead>
<tr>
<th>Chronology</th>
<th>No. (%) of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>De novo; no underlying myeloid disorder</td>
<td>13 (7.5)</td>
</tr>
<tr>
<td>Concurrent with diagnosis of myeloid disorder</td>
<td>46 (26.6)</td>
</tr>
<tr>
<td>After diagnosis of myeloid disorder</td>
<td>105 (60.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (5.2)</td>
</tr>
</tbody>
</table>

Table 2
Distribution of 173 Cases of Myeloid Disorders

<table>
<thead>
<tr>
<th>Myeloid Disorder</th>
<th>No. (%) of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute myeloid leukemia</td>
<td>113 (65.3)</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia</td>
<td>19 (11.0)</td>
</tr>
<tr>
<td>Refractory anemia</td>
<td>18 (10.4)</td>
</tr>
<tr>
<td>Myeloproliferative syndrome</td>
<td>10 (5.8)</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>5</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>3</td>
</tr>
<tr>
<td>Essential thrombocytopenia</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophilic syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Extramedullary granulocytic sarcoma</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (5.8)</td>
</tr>
</tbody>
</table>

Histopathologic Results

Global results are given for the 173 cases, regardless of the subtypes of myeloid disorders. More details are given in Table 3. Results and discrepancies between the subtypes are given and discussed later.

Morphologic analysis at low magnification showed a diffuse pattern in 52.0% (90/173) with presence of a grenz zone in 85.0% (147/173) of the cases. A nodular pattern was observed in 56.1% (97/173). In 12.1% (21/173) of the cases, a mixed nodular and diffuse pattern was observed in the same biopsy specimen. Single file cells were observed in 17.9% (31/173). A granuloma annulare–like pattern was observed in 4.6% (8/173), with an “onion bulb” pattern in 1 case.

Table 3
Histologic Results and Statistical Correlations

<table>
<thead>
<tr>
<th>Histologic Criteria</th>
<th>All Cases (n = 173)</th>
<th>All (n = 113)</th>
<th>Types 1 and 2 (n = 21)</th>
<th>Types 4 and 5 (n = 63)</th>
<th>CMML (n = 19)</th>
<th>RA (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse pattern</td>
<td>63 (56.1)</td>
<td>9 (43)</td>
<td>39 (62)</td>
<td>7 (37)</td>
<td>10 (56)</td>
<td>.12</td>
</tr>
<tr>
<td>Nodular pattern</td>
<td>61 (54.0)</td>
<td>12 (57)</td>
<td>31 (49)</td>
<td>12 (63)</td>
<td>12 (67)</td>
<td>.5</td>
</tr>
<tr>
<td>Single file cells</td>
<td>24 (12.9)</td>
<td>2 (10)</td>
<td>16 (25)</td>
<td>3 (18)</td>
<td>1 (6)</td>
<td>.8</td>
</tr>
<tr>
<td>Tumor cell density</td>
<td>9 (5.7)</td>
<td>5 (28)</td>
<td>4 (24)</td>
<td>2 (11)</td>
<td>1 (6)</td>
<td>.07</td>
</tr>
<tr>
<td>Tumor cell size</td>
<td>4 (2.3)</td>
<td>2 (11)</td>
<td>2 (11)</td>
<td>1 (6)</td>
<td>1 (6)</td>
<td>.033</td>
</tr>
<tr>
<td>Kidney-shaped cells</td>
<td>12 (6.9)</td>
<td>5 (4.4)</td>
<td>7 (6)</td>
<td>10 (16)</td>
<td>14 (25)</td>
<td>.9</td>
</tr>
<tr>
<td>Mitoses (&gt;3/10 fields ×400)</td>
<td>34 (19.7)</td>
<td>20 (17.7)</td>
<td>15 (24)</td>
<td>4 (21)</td>
<td>3 (17)</td>
<td>.091</td>
</tr>
<tr>
<td>Inflammatory background</td>
<td>55 (31.8)</td>
<td>33 (20)</td>
<td>21 (33)</td>
<td>6 (32)</td>
<td>7 (39)</td>
<td>.1</td>
</tr>
<tr>
<td>Inflammatory background components</td>
<td>76 (43.9)</td>
<td>37 (23)</td>
<td>16 (25)</td>
<td>9 (47)</td>
<td>10 (56)</td>
<td>.023</td>
</tr>
</tbody>
</table>

| AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; RA, refractory anemia. * Data are given as number (percentage) or number/total (percentage).
the lesion was made of very rare perivascular blast cells, and in 1 case it was made of a single dermal nodule. An epidermal ulceration was seen in 5 cases but without features of epidermotropism in the remaining epidermis. Fat tissue was present in 68.2% (118/173) and was infiltrated in 84.7% of these cases (100/118).

Morphologic analysis at high magnification showed that the skin tumors were made of blastic or immature myeloid tumor cells. These cells were small in 9.2% (16/173), medium-sized in 50.9% (88/173), and large in 9.8% (17/173) of the cases [Image 4]. Small and medium-sized cells were mixed in 12.1% (21/173) of the cases. Medium-sized and large cells were mixed in 17.3% (30/173) of the cases. Only 1 case displayed an admixture of small and large cells. Kidney-shaped nuclei were observed in 6.9% (12/173). Apoptotic bodies were seen in 31.8% (55/173) of the cases. In 80.3% (139/173) of the cases, mitoses were rare or absent (<3 mitoses per ×400 field). Inflammatory cells were seen in only 43.9% (76/173). In most of these cases, the inflammatory background contained mast cells and/or lymphocytes, but sometimes it was made of neutrophils, eosinophils, or epithelioid histiocytes. In 2 cases, the inflammatory background was made of multinucleated histiocytes. In 8 cases, the inflammatory background harbored eosinophils.

Immunohistochemical Results

The mean frequency of available data for the 12 antibodies was 70%. Global results of immunohistochemical analysis are given in Table 4. We studied 4 antigens considered as monocytic markers: CD68, CD163, CD14, and CD4. CD68 [Image 5A] was positive in 97.4%, CD163 in 52%, CD14 in 35.2%, and CD4 in 61.1%. We studied 3 antigens considered as myeloid markers: MPO, CD33, and CD117.
### Table 4
Immunohistochemical Results and Statistical Correlations

<table>
<thead>
<tr>
<th>Antibody</th>
<th>All Cases (n = 173)</th>
<th>AML Types 1 and 2 (n = 21)</th>
<th>Types 4 and 5 (n = 63)</th>
<th>CMML (n = 19)</th>
<th>RA (n = 18)</th>
<th>AML/CMML</th>
<th>AML Types 1-2/4-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD68</td>
<td>148/152 (97.4)</td>
<td>93/95 (98)</td>
<td>53/54 (98)</td>
<td>17/19 (94)</td>
<td>17/17 (100)</td>
<td>.4</td>
<td>.3</td>
</tr>
<tr>
<td>CD163</td>
<td>49/95 (52)</td>
<td>30/62 (48)</td>
<td>22/37 (59)</td>
<td>6/9 (67)</td>
<td>9/13 (69)</td>
<td>.5</td>
<td>.038</td>
</tr>
<tr>
<td>CD14</td>
<td>38/108 (35.2)</td>
<td>24/74 (32)</td>
<td>19/44 (43)</td>
<td>3/8 (37)</td>
<td>8/14 (57)</td>
<td>1</td>
<td>.072</td>
</tr>
<tr>
<td>CD4</td>
<td>7/126 (61.1)</td>
<td>49/79 (62)</td>
<td>29/44 (66)</td>
<td>14/18 (78)</td>
<td>5/14 (36)</td>
<td>.2</td>
<td>.2</td>
</tr>
<tr>
<td>MPO</td>
<td>95/152 (62.5)</td>
<td>60/98 (61)</td>
<td>32/55 (58)</td>
<td>9/18 (50)</td>
<td>11/16 (69)</td>
<td>.4</td>
<td>.17</td>
</tr>
<tr>
<td>CD33</td>
<td>66/71 (93)</td>
<td>66/51 (93)</td>
<td>40/49 (100)</td>
<td>12/16 (75)</td>
<td>13/14 (93)</td>
<td>.055</td>
<td>.003</td>
</tr>
<tr>
<td>CD117</td>
<td>36/120 (30.0)</td>
<td>22/76 (29)</td>
<td>11/40 (27)</td>
<td>3/14 (21)</td>
<td>4/15 (27)</td>
<td>.7</td>
<td>.3</td>
</tr>
<tr>
<td>CD34</td>
<td>7/147 (4.8)</td>
<td>5/92 (5)</td>
<td>1/51 (2)</td>
<td>2/17 (12)</td>
<td>0/18 (0)</td>
<td>.3</td>
<td>1</td>
</tr>
<tr>
<td>CD56</td>
<td>22/119 (18.5)</td>
<td>14/72 (19)</td>
<td>6/40 (15)</td>
<td>1/14 (7)</td>
<td>1/14 (7)</td>
<td>1</td>
<td>.7</td>
</tr>
<tr>
<td>MIB-1</td>
<td>&lt;5%</td>
<td>41/115 (35.7)</td>
<td>28/74 (38)</td>
<td>15/42 (36)</td>
<td>6/14 (43)</td>
<td>4/15 (27)</td>
<td>.8</td>
</tr>
<tr>
<td></td>
<td>5%-33%</td>
<td>40/74 (54)</td>
<td>58/74 (78)</td>
<td>24/42 (57)</td>
<td>5/14 (36)</td>
<td>9/15 (60)</td>
<td>.7</td>
</tr>
<tr>
<td></td>
<td>&gt;67%</td>
<td>5/115 (4.3)</td>
<td>1/14 (7)</td>
<td>1/14 (7)</td>
<td>2/15 (13)</td>
<td>.011</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>-67%</td>
<td>7/115 (6.1)</td>
<td>1/14 (7)</td>
<td>2/14 (14)</td>
<td>0/15 (0)</td>
<td>.077</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>CD123</td>
<td>1/23 (8.7)</td>
<td>5/80 (6)</td>
<td>3/48 (7)</td>
<td>5/17 (29)</td>
<td>.7</td>
<td>.3</td>
</tr>
<tr>
<td></td>
<td>CD303</td>
<td>4/124 (3.2)</td>
<td>1/81 (1)</td>
<td>1/48 (2)</td>
<td>2/16 (13)</td>
<td>1</td>
<td>.7</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MPO, myeloperoxidase; RA, refractory anemia.

* Data are given as number positive/number tested (percentage).

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**Image 5** Immunostaining on tissue microarrays. **A**, CD68 (×100). **B**, Myeloperoxidase (×100). **C**, CD33 (×100).
disorders. But no features of so-called leukemic vasculitis reported by Seckin et al. were observed. These masqueraders can be added to those already reported, which include unique facial erythema, vesiculobullous lesions,7 papular exanthema,9,10 and cutaneous localized hyperpigmentation.11 In addition to the aforementioned cases, one of our cases of CML manifested with a unique large ulcerated tumor of the forehead simulating a solid tumor.

Genetic data were available for around half of our cases. Various karyotypic abnormalities were found, but in a significant percentage of these cases (16%), aneuploidy (loss or gain) of chromosome 8 was found. These data confirm the results of a preceding study, which showed a statistical correlation ($P < .0001$).2

Most often, the infiltrative pattern was diffuse and of medium density, sparing epidermis and involving fat tissue. However, morphologic features could vary depending on the underlying myeloid disorder. Single filing of cells was found in 31 cases (38%), consisting predominantly of monocytic AML (AML-4 and AML-5; Table 3). Conversely, they were very rare in RA. An inflammatory background was present in around half of the cases. In about 7% of the cases, the background was made of neutrophils, with or without leukocytoclasis, simulating neutrophilic dermatosis (Sweet syndrome). As in skin lymphomas and, particularly, in mycosis fungoides, granulomatous features can be found in MLC. In 8 cases, we found a granuloma annulare–like pattern with collagen changes, and in 2 cases of AML-4, we found a background rich in giant and multinucleated cells.

MPO was positive in 62.5%, CD33 in 93%, and CD117 in 30.0%. CD34, which is considered a marker of undifferentiated blast cells was positive in only 4.8% of the cases. CD56, which is widely used as a natural killer cell marker, was positive in 18.5% of the cases. The mitotic index was predominantly low; in 90.0% of the cases, MIB-1 was less than 33% of positive cells. We studied 2 plasmacytid dendritic cells markers: CD123 and CD303. CD123 was positive in 8.7% (11 cases) and CD303 in 3.2% (4 cases).

Genetic Data

Cyto genetic data were available for 83 patients. They were normal in 43% of the cases (36/83) and displayed complex abnormalities in 20% (17/83). Aneuploidy of chromosome 8 was present in 16% of the AMLs (13/83). The translocation t(15-17) was present in 1 of the 2 AML-3 cases, associated with trisomy 8. Two cases of AML-4 displayed an inversion of chromosome 16.

Discussion

Clinical data for this series of 173 cases of MLCs confirmed data in recent reports. There was a slight male predominance (1.4:1) and no peak of age. The median age was 62 years. AML cases with monocytic predominance (AML-4 and AML-5) were overrepresented in the skin (40%) compared with the blood (10%). Skin lesions were usually multiple at the time of diagnosis (75%), with no site of predilection. They were generally papulonodular and reddish and/or violaceous. Pain and pruritus were rarely reported. Some cases in this series manifested with an unusual vascular change, misdirecting the clinical diagnosis toward vasculitis or coagulation disorders. But no features of so-called leukemic vasculitis reported by Seckin et al. were observed. These masqueraders can be added to those already reported, which include unique facial erythema, vesiculobullous lesions, papular exanthema, and cutaneous localized hyperpigmentation. In addition to the aforementioned cases, one of our cases of CML manifested with a unique large ulcerated tumor of the forehead simulating a solid tumor.

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in a case of de novo AML. In 8 cases, the inflammatory background contained eosinophils, but this finding did not correlate with the underlying disorder. In 2 cases, eosinophils were very dense; these cases were 1 RA and 1 PV. Curiously, in the case of CES, eosinophils were present but not so dense.

**Morphologic Discrepancies Between Underlying Myeloid Disorders**

Cytomorphologic study of our large series of MLCs could highlight discrepancies between cases of AML-1 and AML-2 and of AML-4 and AML-5 (Table 3). AMLs with monocytic differentiation were made of denser infiltrate ($P = .011$). Tumor cells were generally larger in AML-4 and AML-5 ($P = .033$) with some very rare exceptions. One case of AML-5 was made of small cells simulating an undifferentiated leukemia. Kidney-shaped nuclei were present in 12 cases of our series. As in the series of Kaddu et al, we found more kidney-shaped nuclei in AML-4 and AML-5 (n = 5), but interestingly, we also found this type of cells in 3 cases of CMML and 3 cases of RA. No differences were seen between AML-1 and AML-2 and AML-4 and AML-5 when focusing on the infiltrative pattern, the number of mitoses, the presence of apoptotic bodies, or the inflammatory background.

Comparisons between cases of AML, CMML, and RA (Table 3) did not show any differences in the pattern, the density, or the size of tumor cells. However, the presence of an inflammatory background occurred significantly more frequently in CMML and RA ($P = .023$). In around 50% of cases of CMML and RA, there was an inflammatory background, predominantly constituted of lymphocytes and/or mast cells.

![Image 8](Image8.png) Numerous eosinophils in a case of refractory anemia (H&E, x400).

**De Novo MLCs Show a Specific Histologic Phenotype**

The 173 cases of this study were divided into 3 groups depending on the chronology of skin lesion onset: de novo, concurrent, and subsequent. In the de novo group ($n = 13$), MLC occurred without any myeloid underlying disorder known or clinically suspected. In the concurrent group ($n = 46$), skin lesions were found at the time of the myeloid disorder diagnosis. In the subsequent group ($n = 105$), skin lesions appeared during the life time of the disease. For 9 patients, data were not provided. The de novo group represented about 8% of the cases. There were 7 males and 6 females. The youngest patient was a newborn child (congenital AML), and the oldest patient was 86 years old. For 4 patients, the skin diagnosis led to the discovery of circulating blast cells in the following days. For 1 patient, the delay between the skin diagnosis and the spread of the disease was 1 month. For 1 other patient, it was 9 months. For 6 of these 13 patients, the data were not provided. In 5 patients, the subtype of AML was determined later and corresponded to AML-4 and AML-5. For the 7 other patients, it has never been determined. Skin lesions were multiple nodules in 11 cases (85%) and solitary nodules in 2 cases (15%).

Significant morphologic discrepancies were observed between the de novo group and the non–de novo group (concurrent and subsequent groups together) (Table 5). Cases of the de novo group were significantly associated with a diffuse pattern ($P = .016$), a high dense infiltrate ($P = .006$), large cells ($P = .004$), and a high mitotic index ($P = .019$). The presence of apoptotic bodies and the absence of inflammatory background were also predominant criteria but not statistically significant.

MLC of the de novo group of our study corresponds to the so-called aleukemic leukemia, an expression frequently used in the literature. In a series of leukemia cutis published in 1984, Su et al found, as we did, 7% of “aleukemic” lesions. It can occur at any age. The disease may be strictly localized to the skin, even relapses, but generally, hematologic spread occurs, with variable delay. Although a delay of 7 years has been reported, it is generally less than 1 year. Some exceptional cases of spontaneous regression have been reported in newborn children. Our de novo group also corresponds to the so-called myeloid sarcoma. Myeloid sarcoma is defined as an extrahematopoietic myeloid leukemia. It can occur in every organ of the body, but in the large series of myeloid sarcoma from Pileri et al skin forms represented the most common manifestation in 28% of all their cases. It has been suggested that this particular de novo group could represent a subtype of myeloid leukemia in which blast cells displayed specific properties such as skin homing properties. Our results support that idea, showing a morphologic profile statistically different from the group of concurrent and subsequent myeloid leukemia. Unfortunately, impact on survival could not be studied because of lack of follow-up data.
**Table 5**

<table>
<thead>
<tr>
<th>Morphologic Criteria</th>
<th>De Novo (n = 13)</th>
<th>Concurrent and Subsequent (n = 151)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse pattern</td>
<td>11 (85)</td>
<td>75/150 (50.0)</td>
<td>.016</td>
</tr>
<tr>
<td>High density (score 3)</td>
<td>8 (62)</td>
<td>35 (23.2)</td>
<td>.006</td>
</tr>
<tr>
<td>Large cells (score 3)</td>
<td>5 (38)</td>
<td>11 (7.3)</td>
<td>.004</td>
</tr>
<tr>
<td>Mitoses (&gt;3/10 fields x400)</td>
<td>6 (46)</td>
<td>28 (18.6)</td>
<td>.019</td>
</tr>
<tr>
<td>Apoptotic bodies</td>
<td>8 (62)</td>
<td>42 (27.8)</td>
<td>.024</td>
</tr>
<tr>
<td>Inflammatory background</td>
<td>1 (8)</td>
<td>26 (17.2)</td>
<td>.7</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) or number/total (percentage).*

**Does the Immunohistochemical Panel Allow Diagnosis of MLC and Distinction of Types of Myeloid Disorders?**

We chose the panel of antibodies according to the specificity of the antigens and also their property to work on paraffin sections.

CD34 and CD117 are used in routine cytometry analyses as markers of myeloid stem cells, and CD34 is frequently expressed by blood or bone marrow myeloid blasts. In our study, CD34 was positive in only about 5% and CD117 in about 30%. These results are close to those published in skin series and confirm that these 2 markers are irrelevant for the diagnosis of MLC. Although Pileri et al. found CD117 useful for the diagnosis in a series of myeloid sarcomas, in our study, CD117 was useful only for detecting mast cells. Distinguishing mast cells from blast cells was quite easy because the staining was stronger and granular in mast cells. Concerning the discrepancy between the expression of CD34 in the skin and bone marrow or blood, several explanations have been proposed in the literature. Although it has been suggested that blast cells in the skin could have lost their CD34 expression, the most likely explanation is the difference in sensitivity between cytometric and immunohistochemical techniques.

CD68 is commonly used by pathologists for the detection of histiomonocytic cells. It is the most sensitive antigen in MLC, with rates of positivity between 94% and 100% reported in the literature. In our study, it was positive in about 97%, independent of the type of underlying myeloid disorder. This result highlights the lack of specificity of CD68 for distinguishing MLC with monocytic differentiation from the other types. Among all cases tested for CD68, only 4 were negative; 2 of them were positive for MPO, and 1 was negative for MPO but positive for CD33. For the last one, MPO and CD33 studies could not be performed. The 3 other monocytic markers, CD163, CD14, and CD4, seemed to be more specific. CD163 was globally positive for about 52% of the cases; however, when focusing on tumor of monocytic differentiation, it was positive in about 59% of AML-4 and AML-5 cases and about 67% of CMML cases, while it was positive in only 25% of AML-1 and AML-2 cases. CD14 was globally positive in about 35% but was positive in about 43% of AML-4 and AML-5 cases and in about 37% of CMML cases, while it was positive in only about 10% of AML-1 and AML-2 cases. CD4 was globally positive in about 61% of the cases but was positive in about 66% of AML-4 and AML-5 cases and in about 78% of CMML cases, while it was positive in only about 46% of AML-1 and AML-2 cases. These results confirm that none of these monocytic markers can reliably distinguish monocytic differentiation from the myeloid differentiation.

MPO and CD33 are considered myeloid markers. In this study, MPO was globally positive in about 62% of the cases. It was positive in about 78% of AML-1 and AML-2 cases, while it was positive in about 58% of AML-4 and AML-5 cases and in about 50% of CMML cases. These results show that it is sensitive for AML of granulocytic differentiation, but not specific. Unexpectedly, CD33 was statistically more powerful (P = .003) for a monocytic origin because it was positive in only about 71% of AML-1 and AML-2 cases, whereas it was positive in 100% of AML-4 and AML-5 cases.

CD56 was globally positive in about 18% of the cases. This result is in accordance with the median rate of CD56 expression in AML, which is around 20%. There is no difference between skin and blood AML. In our series, CD56 seems more frequently expressed in AML-4 and AML-5 and CMML than in AML-1 and AML-2.

Among the cases expressing CD56, 16 cases were CD56+ and CD4+ Image 9. Thus, there is a strong association between these 2 antigens because about 85% of CD56+ MLC expressed CD4. For these 16 cases, the underlying disorder was AML in 11 cases, CMML in 3 cases, and RA in 1 case. For the remaining case, the underlying disease was unknown. Among these 16 CD4+/CD56+ cases, 2 cases could be reclassified as blastic plasmacytoid dendritic cell neoplasms (BPDCNs). They were morphologically typical, and the tumor cells strongly expressed the PDC markers CD123, CD303, TCL1, and CD2AP, while MPO and granzyme B were negative. The first patient was a 72-year-old man. In 1998, he had skin lesions associated with splenic and lymph node infiltration. Skin lesions were purpuric plaques of the
and 4 were varied AMLs. Differences of CD123 expression between the CMML group (5/16 [29%]) and the AML group (5/80 [6%]) were statistically significant \((P = .011; \text{Table 4})\) before the reclassification of 4 cases into BPDCN. The difference was much more significant after reclassification because 4 of the 5 cases of AML were actually reclassified as BPDCN. After reclassification, only 1 case of CD123+ AML remained. In this case, the positive cells were mature PDCs. These results show the powerful interest in PDC markers in distinguishing AML from CMML and also support a putative relationship between PDCs and CMML.

Previous studies on BPDCN underlined the association with CMML.30-34 According to the different series, 5% to 20% of the cases of BPDCN occur in patients with CMML.33 In BPDCN, PDCs are considered as immature (blastic); however, tumoral accumulation of mature PDCs has also been reported in patients with myeloid disorders, particularly CMML.34-37 In these cases, accumulation or proliferation of mature PDCs can be found in bone marrow, lymph nodes, and skin. According to Orazi et al,38 mature PDC nodules should be found in bone marrow biopsies of 20% of CMML cases. It is not clear whether the presence and accumulation of these mature PDCs should be considered as reactive or tumoral. CMML is a strange and ill-understood disease harboring features of myeloproliferative and myelodysplastic syndromes. It does not display recurrent genetic abnormalities. In the current definition of CMML, the blastic component is made of myeloid and monocytic blasts. Maybe it is also made of PDC blasts, but this has to be demonstrated. In our patients, skin lesions were made of an admixture of blast cells, inflammatory cells, and mature PDCs. However, it was difficult to tell face, skull, and chest. Tumor cells were MPO– and CD68+. The diagnosis at that time was undifferentiated leukemia. He died 1 year later. The second patient was a 71-year-old woman. In 2006, she had violaceous skin nodules. A leukemic phase was found, and a diagnosis of AML-5 was made. She died several months later.

Besides these 2 CD4+/CD56+ cases reclassified as BPDCN, 2 other cases have been reclassified as BPDCN; however, they were CD4+/CD56−. CD56 is not mandatory for the diagnosis of BPDCN, and several CD56− cases have been reported in the literature.27 These 2 other cases were also morphologically typical and strongly expressed the PDC markers CD123, CD303, TCL1, and CD2AP. Of the 2 patients, 1 was a 75-year-old man monitored for a CMML for 5 years when, in 1999, he had disseminated skin plaques. Tumor cells were MPO−, CD68+, and granzyme B−. He was treated with cytarabine. Eleven months later, he was still alive, but after that, no follow-up has been provided. The other patient was an 84-year-old man. He was treated for AML-5 when skin lesions appeared. The follow-up was unknown.

Besides these 4 cases of BPDCN strongly expressing both CD123 and CD303 (score 1, >90%), heterogeneous expression (score 2, <90%) of these PDC markers was also detected in 10 other cases Image 10A and Image 10B. In these 10 cases, cells also expressed TCL1 Image 10D and CD2AP and, contrary to BPDCN, they corresponded morphologically more to mature PDC than blastic PDC. Furthermore, they expressed granzyme B Image 10C, which is classically expressed in mature PDC28 but not in blastic PDC.29 Seven cases were positive for CD123 alone, 1 case was positive for CD303 alone, and 2 cases were positive for both. It is interesting that half of the cases were CMMLs, 1 was a myelodysplastic syndrome, and 4 were varied AMLs. Differences of CD123 expression between the CMML group (5/16 [29%]) and the AML group (5/80 [6%]) were statistically significant \((P = .011; \text{Table 4})\) before the reclassification of 4 cases into BPDCN. The difference was much more significant after reclassification because 4 of the 5 cases of AML were actually reclassified as BPDCN. After reclassification, only 1 case of CD123+ AML remained. In this case, the positive cells were mature PDCs. These results show the powerful interest in PDC markers in distinguishing AML form CMML and also support a putative relationship between PDCs and CMML.
whether the cells expressing PDC markers were tumor cells or associated reactive mature PDCs. The study by Vermi et al.\textsuperscript{35} supports the first hypothesis by demonstrating by the fluorescence in situ hybridization technique in lymph nodes that the mature PDC component was clonal, displaying the same genetic abnormality as monocytic blasts.

Concerning the group of de novo MLCs (13 cases), in contrast with morphologic study, no immunohistochemical characteristics were observed. All cases were positive for CD68 and none for CD34. Eight cases were negative for MPO. Among the CD68+/MPO− cases, 2 were CD4+ and CD56+ but CD123− and CD303−. So none of the cases reclassified as BPDCN were in this group. Unexpectedly, while the mitotic index was a morphologic distinguishing criterion between de novo and non–de novo AMLs ($P = .019$), MIB-1 was not ($P = .5$).

**Chronic MPSs Cannot Be Distinguished From Other Underlying Myeloid Disorders**

For 10 patients in the series, the underlying disorder was chronic MPS: 5 cases of CML, 3 cases of PV, 1 case of ET, and 1 case of CES. Four of five cases of CML and 1 of 3 cases of PV were transformed into AML at the time of skin lesions. For the 3 remaining cases (1 CML, 1 PV, and 1 ET) skin lesions were considered as the onset of the acute transformation (blastic crisis), and no specific skin lesions were seen during the chronic phases of the diseases. Furthermore, no specific morphologic features such as presence of erythroblasts.

or megakaryocytes reflecting the chronic underlying diseases were seen. So, morphologically speaking, no histologic criteria were found permitting the distinction of the underlying disorders. Concerning the phenotype, all cases expressed MPO and CD68.

Conclusion

In this work focusing on retrospective diagnosis of skin localization of myeloid disorders, 173 cases diagnosed in 9 centers of the FSGCL between 1992 and 2008 were morphologically and immunohistochemically studied. Even if in the large majority (65%) the underlying disorders were AMLs (and half of these of monocytic differentiation), it is noteworthy that CMML (11%), RA (10%), and also MPS (6%) can also present skin localization. Distinguishing these varied disorders on skin biopsy is not so easy, particularly when these disorders are unknown at the time of the skin lesion, which happens in 8% of the cases. Hence, the generic term of myeloid leukemia cutis seems appropriate to report this kind of lesion. In this study, we have shown that morphologic and phenotypic study may help in distinguishing varied types of AMLs and also in recognizing CMML. This study particularly highlights the implication of PDCs. BPDCNs may be misdiagnosed without appropriate immunohistochemical analysis, even in patients known to have AML or CMML because BPDCN can complicate the evolution of these diseases. Accumulation or proliferation of mature PDCs is shown to be a hallmark of CMML. This phenomenon was observed in around 25% of our cases of CMML. The pathogenesis of this phenomenon is not clear. A common progenitor may be at the origin of the disease unless PDCs are part of the reactive background and have only their physiologic role of secreting α-interferon under the control of cytokines secreted by tumor cells. This likely represents an interesting topic for further studies.

Immunohistochemical analysis is an essential tool in the diagnosis of MLC. Several algorithms in the literature have emphasized the role of CD68 and MPO. The present study shows that CD33 is an additional interesting tool in the panel. This likely represents an interesting topic for further studies.

References


