

Supplementary Table 1a. Core demographic, clinical, and laboratory data of adult patients with Isolated Cutaneous Myeloid Sarcoma (icMS)/ Aleukemic Leukemia Cutis (ALC) preceding Acute Myeloid Leukemia (AML).

| Patient | Reference | Age/sex | Isolated cutaneous myeloid sarcoma (icMS) / aleukemic leukemia cutis (ALC) | | | | | | | | | |
|---------|-------------------------|---------|--|---|-----------------------------|--------------------------------------|----------------|-------------------------|-----------------------------------|---|---|--|
| | | | Cutaneous lesions | | Localization of the lesions | | Other findings | | Time to icMS [weeks] ^a | Skin pathology | | |
| | | | Number | Morphology | Distribution | Regions affected | Symptoms | Extracutaneous findings | | Histology | Cytology | CD markers ^b |
| 1 | Azari-Yaam et al., 2020 | 46/M | multiple | Non-tender raised erythematous patches (<15 cm), satellite erythematous papules | Disseminated | Face, neck, trunk, upper extremities | Pruritus | Absent | 4 | Epidermis: normal. Grenz zone: N/A. Dermis: diffuse infiltration. Subcutis: diffuse infiltration with perivascular and periadnexal accentuation. | Mononuclear cells with large, folded nuclei, small nucleoli, and a moderate amount of amphophilic cytoplasm. Mitoses: not prominent. | CD14+ CD33+ CD43+ CD68+ CD163+ MPO+ CD34- CKIT- TdT- |
| 2 | Barzilai et al., 2002 | 75/F | multiple | Erythematous, violaceous, and flesh-colored infiltrated plaques and nodules | Confined | Extremities | Pruritus | Absent | 8 | Epidermis: N/A. Grenz zone: N/A. Dermis: diffuse infiltrate. Subcutis: N/A. | Large cells with abundant amphophilic cytoplasm. Mitoses: few. | CD43+ CD68+ |
| 3 | Benez et al., 2001 | 62/F | multiple | Erythematous slightly infiltrated maculae with a brown hue | Disseminated | Trunk, extremities | Asymptomatic | Absent | 24 | Epidermis: N/A. Grenz zone: N/A. Dermis: infiltration by parallel strands of atypical cells. Subcutis: N/A | Mononuclear cells with hyperchromatic nucleoli, surrounded by a rim of faintly basophilic cytoplasm. Mitoses: N/A. | CD43+ CD68+ lysozyme+ chloroacetate esterase+ MPO+ |
| 4 | Breccia et al., 2004 | 70/F | N/A ^c | N/A | N/A | N/A | N/A | | N/A | N/A | Blastic myeloid cells (no morphologic evidence of granulocytic differentiation) | MPO+ CD68+ |
| 5 | Breccia et al., 2004 | 84/M | N/A | N/A | N/A | N/A | N/A | | N/A | N/A | Blastic myeloid cells (no morphologic evidence of granulocytic differentiation) | CD43+ CD45+ MPO+ CD68R+ |
| 6 | De Coninck et al., 1986 | 57/M | multiple | Erythroderma | Disseminated | Trunk, extremities | Asymptomatic | Absent | 4 | Epidermis: intact. Grenz zone: yes. Dermis: dense infiltration. Subcutis: dense infiltration with perivascular and periadnexal accentuation. | Mononuclear cells with an admixture of some granulocytic cells. The nuclei were irregularly shaped and contained nucleoli. Mitoses: N/A. | a-naphthyl acetate esterase chain+ Leder stain+ PAS stain- |
| 7 | Di Palma et al., 1993 | 59/M | solitary | Nodule | Confined | Left arm | Asymptomatic | Absent | N/A | Epidermis: intact. Grenz zone: N/A. Dermis: infiltration by tumour cells mostly single or arranged in cord-like structures surrounded by loose myxoid tissue. Subcutis (and underlying skeletal muscle): infiltrated. | Uniform, round to oval, immature cells with scanty cytoplasm and vesicular nuclei with fine chromatin and well-defined nuclear membrane and conspicuous nucleoli, surrounded by abundant myxoid stroma. No eosinophilic | CD45+ CD68(KP1)+ lysozyme+ vimentin+ Mac387+ CD45RA- CD45RO- CD3- CD20- CD30- CD7- CD8- CD19- CD22- S100- EMA- |

| | | | | | | | | | | | | |
|----|----------------------------|------|----------|---|--------------|------------------------------|--------------|--------|-----|--|--|--|
| | | | | | | | | | | | granulocytes. Mitoses: frequent. | |
| 8 | Gil-Mateo et al., 1997 | 50/F | multiple | Erythematous brownish nodules, confluent, some ulcerated; edematous erythematous infiltrated plaque | Disseminated | Trunk, extremities, forehead | Pruritus | Absent | 4 | Epidermis: normal. Grenz zone: yes. Dermis: dense monomorphous cellular infiltrate. Subcutis: dense monomorphous cellular infiltrate with perivascular and periadnexal accentuation. | Cells with large kidney-shaped or oval nucleus with one or more conspicuous nucleoli, and abundant pale, slightly eosinophilic cytoplasm. Mitoses: atypical present. | CD43+ CD68+ CD4+ CD45RO+ CD15+ lysozyme+ CD20- CD3- CD30- chloroacetate esterase chains- |
| 9 | Hainsworth et al, 1987 | 76/F | multiple | Erythematous maculonodular | Disseminated | Trunk, extremities | Pruritus | Absent | 56 | N/A | Auer bodies | Chloroacetate esterase+ |
| 10 | Iitani et al.,2009 | 81/M | multiple | Violaceous nodules | Disseminated | Groin, trunk, limbs | Asymptomatic | Absent | 8 | Epidermis: N/A. Grenz zone: N/A. Dermis: dense infiltrate. Subcutaneous tissue: dense infiltrate. | Mononuclear. Mitoses: scant, atypical. | LCA+ CD68+ MPO+ |
| 11 | Mansoor et al., 2010 | 43/M | multiple | Nodules | Disseminated | Abdomen, back, legs | N/A | N/A | 16 | Epidermis: uninvolved. Grenz zone: N/A. Dermis: sheets of immature cells separating collagen bundles. Subcutis: Infiltration by sheets of immature cells with perivascular and periadnexal accentuation. | Round tumour cells with vesicular nuclei and prominent nucleoli and abundant, granular cytoplasm. Mitoses: numerous. | CD43+ CD45+ CD68+ MPO+ CD3- CD20- CD30- CD34- |
| 12 | Narvaez Moreno et al, 2015 | 52/F | multiple | Nodules, pale-red | Confined | Abdomen | Asymptomatic | Absent | N/A | Epidermis: N/A. Grenz zone: yes. Dermis: brisk infiltration. Subcutis: N/A. | Atypical mononuclear cells. Mitoses: high mitotic index (Ki67 50%). | MPO+ CD43+ CD117+ Bcl-2+ CD3- CD10- CD20- CD2- CD30 - CD34- CD56- CD68- TdT- |
| 13 | Rallis et al., 2008 | 78/M | multiple | Pink to skin-colored firm papules and bruise nodules | Disseminated | Trunk, extremities | Asymptomatic | Absent | 4 | Epidermis: N/A. Grenz zone: N/A. Dermis: full-thickness infiltration. Subcutaneous: N/A. | Large atypical mononuclear cells. Mitoses: N/A. | CD34+ CD56+ CD68+ MPO- CD4- CD5- |
| 14 | Takahashi et al., 2015 | 79/F | multiple | Nodules, erythematous | Disseminated | Trunk, extremities | N/A | N/A | 8 | Epidermis: N/A. Grenz zone: yes. Dermis: dense infiltration. Subcutis: N/A. | Monomorphous, medium- sized atypical monocytic cells with distorted round oval nuclei and scant cytoplasm; small number of eosinophilic myelocytes. Mitoses: N/A. | CD68 (clone KP1)+ MIB1+ MPO- CD30- CD34- LCA- naphthol AS- D chloroacetate esterase- |
| 15 | Wilkins et al.,2004 | 56/F | multiple | Plaques, violaceous infiltrated (right cheek) and multiple raised brown (trunk) | Disseminated | Right cheek, trunk | Asymptomatic | Absent | 52 | Epidermis: N/A. Grenz zone: N/A. Dermis: diffuse infiltration with perivascular accentuation. Subcutis: N/A. | Monotonous population of medium sized blast cells with convoluted nuclei, a fine chromatin pattern and moderate amounts of pale blue cytoplasm. Mitoses: N/A. | CD43+ CD68+ absence of B-/T- cell markers lysozyme- neutrophil elastase-CD15-Mac 387- |

| | | | | | | | | | | | | |
|----|--------------|------|----------|---|--------------|--|--------------|--------|---|---|---|--|
| 16 | Present case | 67/M | multiple | Solitary purple-red ulcerated tumour and scattered, multiple erythematous scaly plaques | Disseminated | Tumour: right tibia; plaques: head, trunk, extremities | Asymptomatic | Absent | 4 | Epidermis: hyperkeratosis, parakeratosis and spongiosis. Grenz zone: yes. Dermis: diffuse infiltration. Subcutis: N/A | Medium sized blast cells with folded nuclei, atypic deep coloured nuclear membrane. Mitoses: frequent (Ki67~70%). | MPO+ CD33+ CD68+ CD79a+ CD4+/- CD30+/- CLA- CD163- CD117- CD34- CD207- CD56- CD2- CD3- CD5- CD7- CD8- CD19- CD20- CD21- CD23- CD31- CD35- CD57- PAX- CD1a- ALK- TIA1- granzyme B- perforin- MART1- MelanA- S100- pankeratin- chromogranin- synaptophysin- LANA1(HHV8)- |
|----|--------------|------|----------|---|--------------|--|--------------|--------|---|---|---|--|

Supplementary Table 1b. Acute Myeloid Leukemia (AML) core data and outcomes.

| Patient | Reference | Acute myeloid leukemia (AML) | | | | | Outcome | |
|---------|-------------------------|------------------------------------|--|--|---|--|--|--|
| | | AML subtype (WHO/FAB) ^d | Time from icMS to AML [weeks] ^e | Laboratory | | | Outcome / time to outcome [weeks] ^f | Details |
| | | | | Blood | BM cytology | BM cell markers | | |
| 1 | Azari-Yaam et al., 2020 | ACUTE MONOCYTIC LEUKEMIA / M5 | 2 | Hb 9 g/dL WBC $146 \times 10^9/L$ PLT $94 \times 10^9/L$ | 95% blasts | CD4 (62% dim), CD38 (65%), CD11b (97%), CD15 (65%), CD33 (61%), CD1a (42%), HLA-DR (85% dim) | Death / 40 | Cardiopulmonary arrest. Autopsy: multiorgan leukemic infiltration. |
| 2 | Barzilai et al., 2002 | N/A / M5 | 72 | NNN N/AN/A /A | Monocytic infiltrate | N/A | Death / 80 | Disseminated disease |
| 3 | Benez et al., 2001 | N/A / M5b | 28 | 7% blasts | 40% blasts | N/A | Alive / 44 | In chemotherapy without remission |
| 4 | Breccia et al., 2004 | N/A / M2 | 152 | N/A | N/A | HLA-DR- CD34- CD33+ CD15+ | Death / 156 | N/A |
| 5 | Breccia et al., 2004 | N/A / M2 | 176 | N/A | N/A | Not determined | Death / 180 | N/A |
| 6 | De Coninck et al., 1986 | N/A / M4 | 12 | WBC 144000/mm ³ , blasts 63% | N/A | MPO+ esterase enzymes+ | Death / 17 | Generalized bleedings |
| 7 | Di Palma et al., 1993 | N/A / M1 | 8 | N/A | Extensive infiltration by atypical immature myeloid cells | N/A | Death / 44 | N/A |
| 8 | Gil-Mateo et al., 1997 | N/A / M5 | 28 | Leukemic blast cells | Leukemic blast cells | N/A | Death / 28 | Disseminated disease |
| 9 | Hainsworth et al., 1987 | N/A / M4 | 0 | Hb 6 g/dL WBC 28×10^3 PLT 158×10^3 | Auer bodies | Chloroacetate esterase+ | Death / 64 | Rapid decline of patient's condition |
| 10 | Itani et al., 2009 | N/A / M5 | 7 | Hb 100g/L PLT 212×10^3 WBC $2,9 \times 10^3$ (with 0,12 POLY, 0,38 LYM, 0,10 atypical LYM, 0,40 MONO) ESR 83 mm/h). One | N/A | N/A | Death / 8 | N/A |

| | | | | | | | | | |
|----|-----------------------------|---------------|-----|--|--|--|-------------|--|--|
| | | | | week later: WBC 3.6 x 10 ³ (with 0.07 POLY, 0.30 LYM) | | | | | |
| 11 | Mansoor et al., 2010 | N/A / M4 | 140 | Blasts | AML-M4 | N/A | Death / 168 | N/A | |
| 12 | Narvaez Moreno et al., 2015 | N/A / M1 | 320 | N/A | BM: blasts without maturation (AML FAB M1) | N/A | Death / 400 | N/A | |
| 13 | Rallis et al., 2008 | AML NOS / M5a | 4 | 7% blasts | 35% blasts | N/A | Death / 36 | Pancytopenia | |
| 14 | Takahashi et al., 2015 | N/A / M5a | 8 | 27% blasts | 94% blasts | N/A | Death / 8.3 | Dyspnea, renal failure and DIC | |
| 15 | Wilkins et al., 2004 | N/A / M5 | 44 | N/A | N/A | N/A | Death / 48 | N/A | |
| 16 | Present case, 2021 | AML MR / M5 | 4 | Leukocytosis (~27.000 / µl with 70% blast cells) | 95% blasts | HLA DR+ CD56+ CD99+ PGM1+ CD3- c-kit- CD20- MPO- CD34- TdT- CD138- glycophorinA- | Death / 6 | Neutropenia, nasal bleeding, supraventricular arrhythmia, and lower respiratory tract infection (<i>Acinetobacter baumannii</i>) | |

after symptoms' onset to icMS/ALC diagnosis

^b +: expressed by icMS/ALC cells; -: not expressed

^c N/A: Information not available

^d Classification as provided in the source publication

^e Time from icMS/ALC diagnosis to confirmation of (systemic) AML

^f Time from icMS/ALC diagnosis to last follow up information /outcome

Supplementary Table 2. Probability of survival (estimate) as a function of time after Isolated Cutaneous Myeloid Sarcoma (icMS)/ Aleukemic Leukemia Cutis (ALC) diagnosis (survival in weeks): all (n=16) patients. Kaplan-Meier method.

| Survival | N | Estimate | S.E. |
|----------|----|----------|-------|
| 12 | 13 | 0.813 | 0.098 |
| 24 | 12 | 0.750 | 0.108 |
| 36 | 10 | 0.625 | 0.121 |
| 48 | 6 | 0.429 | 0.126 |

N: Number of patients still alive at corresponding time point.

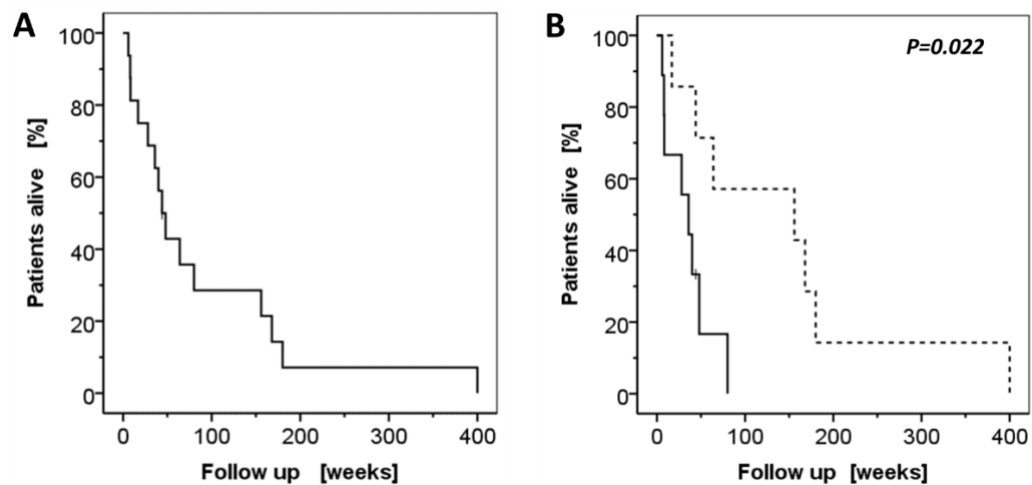
S.E.: standard error of the Estimate.

Supplementary Table 3. Times between clinical events according to Acute Myeloid Leukemia (AML) subtypes: comparison of Isolated Cutaneous Myeloid Sarcoma (icMS) cases preceding AML of FAB M5 subtypes vs icMS preceding FAB non-M5 AML (Kaplan-Meier method with Mantel-Cox test).

| Time intervals | AML of FAB M5 subtype | No. cases | Mean time±S.E. [weeks] | p ^b |
|------------------------------------|-----------------------|-----------------|------------------------|----------------|
| First symptoms to icMS diagnosis | No | 3 | 25.3±15.7 | 0.367 |
| | Yes | 9 | 16.0±6.9 | |
| | All | 12 ^a | 18.5±6.3 | - |
| icMS diagnosis to AML confirmation | No | 7 | 115.4±44.5 | 0.077 |
| | Yes | 9 | 25.2±9.3 | |
| | All | 16 | 70.5±24.6 | - |
| Survival after icMS diagnosis | No | 7 | 147.0±48.8 | 0.022 |
| | Yes | 9 | 35.4±9.2 | |
| | All | 16 | 90.0±27.8 | - |

^aData not available for four cases.

^bProbability for accepting the null hypothesis (Mantel-Cox test)



Supplementary Figure 1. Probability of survival as a function of follow-up time after Isolated Cutaneous Myeloid Sarcoma (icMS)/Aleukemic Leukemia Cutis (ALC) diagnosis. Panel (A): all patients (n=16 patients). Panel (B): comparison of patients with Acute Myeloid Leukemia (AML) FAB subtype(s) M5 (n=9; solid line) vs rest FAB subtypes (n=7, dashed line). Insert: p-value for the comparison of the two levels according to Log Rank (Mantel-Cox) test. Perpendicular bars in Panels (A) and (B) indicate the last information ‘patient alive’.

References

1. Azari-Yaam A, Safavi M, Ghanadan A. Aleukemia cutis: clinicopathological and molecular investigation of two cases. *J Cutan Pathol* 2020;47:747-54.
2. Barzilai A, Lyakhovitsky A, Goldberg I, et al. Aleukemic monocytic leukemia cutis. *Cutis* 2002;69:301-4.
3. Benez A, Metzger S, Metzler G, Fierlbeck G. Aleukemic leukemia cutis presenting as benign-appearing exanthema. *Acta Derm Venereol* 2001;81:45-7.
4. Breccia M, Mandelli F, Petti MC, et al. Clinico-pathological characteristics of myeloid sarcoma at diagnosis and during follow-up: report of 12 cases from a single institution. *Leuk Res* 2004;28:1165-9.
5. De Coninck A, De Hou MF, Peters O, et al. Aleukemic leukemia cutis. An unusual presentation of acute myelomonocytic leukemia. *Dermatologica* 1986;172:272-5.
6. Di Palma S, Feudale E. Granulocytic sarcoma with myxoid stroma. Report of a case. *Tumori* 1993;79:71-3.
7. Gil-Mateo MP, Miquel FJ, Piris MA, et al. Aleukemic “leukemia cutis” of monocytic lineage. *J Am Acad Dermatol* 1997;36:837-40.

8. Hainsworth JD, Greco FA. Unrecognized leukemia cutis. *South Med J* 1987;80:663-4.
9. Iitani MM, Abe R, Yanagi T, et al. Aleukemic leukemia cutis with extensive bone involvement. *J Am Acad Dermatol* 2010;63:539-41.
10. Mansoor S, Din N, Azam M, Jamshed A. Generalized Cutaneous Granulocytic Sarcoma with Joint Involvement. *J Coll Physicians Surg Pak* 2010;20:339-40.
11. Narváez-Moreno B, Pereyra-Rodríguez JJ, Pulpillo-Ruiz A, et al. Acute myeloid leukemia 7 years after aleukemic leukemia cutis. *Int J Dermatol* 2015;54:459-61.
12. Rallis E, Stavropoulou E, Michalakeas I, et al. Monoblastic sarcoma cutis preceding acute monoblastic leukemia. *Am J Hematol* 2009;84:590-1.
13. Takahashi A, Nakajima K, Togitani K, et al. Spontaneous remission of aleukemic cutaneous myeloid sarcoma followed by crisis of acute monoblastic leukemia. *J Dermatol* 2016;43:452-3.
14. Wilkins R, Janes S. Aleukaemic leukaemia cutis: case report and review of the literature. *Clin Lab Haematol* 2004;26:73-5.