Dermatology Reports

Isolated cutaneous myeloid sarcoma preceding acute myeloid leukemia: a case report and literature review

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SUPPLEMENTARY MATERIAL

Supplementary Material 1. Methodology of literature review and data analysis.

Literature search

The aim of this literature review was to compile reported information regarding adult-onset AML, *i.e.,* published reports of adult patients with isolated cutaneous myeloid sarcoma (icMS) or aleukemic leukemia cutis (ALC) as the earliest manifestation of acute myeloid leukemia (AML), in order to highlight the disease characteristics of these rare conditions and contribute to their clinical recognizability. The study specifically focused on cases where cutaneous leukemia infiltration was confirmed, and no diagnosis of acute myeloid leukemia (AML) could be established through blood or bone marrow examinations. A search of the databases PubMed and Scopus from January 1985 to December 2022 was conducted to identify English-language publications reporting adult patients (older than 18 years) with 'specific' skin involvement in the course of AML. The search terms used included: primary OR isolated myeloid sarcoma skin OR primary OR isolated granulocytic sarcoma skin OR primary OR isolated chloroma skin OR aleukemic leukemia cutis. In line with the definition of the 'aleukemic' skin involvement, the initial output of N=251 publications was subsequently searched after the exclusion of the duplicates (N=37) in a two-step procedure, initially by title/abstract (N=111) and subsequently by text content for reports of cases of cutaneous MS/ALC preceding adult-onset AML (N=103), *i.e.*, cases in which the AML could first be diagnosed in the peripheral blood and/or the bone marrow distinctly after the confirmation of the skin involvement.

Only reports with adequate descriptions of the clinical data were included; studies that just mentioned icMS or ALC without detailed clinical information were not considered in this review. Literature retrieval and data extraction were conducted by two authors independently (KM and SG), and data were compiled using descriptive statistics. A total of 14 publications were identified that reported 15 cases fulfilling the inclusion criteria of this study.

Statistical analysis

Descriptive statistics, Mann-Whitney U test, runs test [cutoff: median] for time series, Kaplan-Meier times-to-events evaluations with Log Rank (Mantel-Cox) test, and Cox proportional hazard models were calculated with the statistical package SPSS (IBM, Chicago IL, USA) and were interpreted at probability level $p<0.05$.

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[6]	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 promiment.	CD14+ CD33+ CD43+ CD68+ CD163+ MPO+ CD34- CKIT- TdT-
2	Barzilai et al., 2002[7]	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[8]	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[9]	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[9]	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[10]	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[11]	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 conspicious 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[12]	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[13]	76/F	multiple	Erythematous maculonodular	Disseminated	Trunk, extremities	Pruritus	Absent	56	N/A	Auer bodies	Chloroacetate esterase+
10	Iitani et al., 2009[14]	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[15]	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[16]	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[17]	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[18]	79/F	multiple	Nodules, erythematous	Disseminated	Trunck, 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[19]	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.

		Acute myeloid leukemia (AML)						
				Laboratory			Outcome	
Patient	Reference	AML subtype (WHO/FAB)[d]	Time from icMS to AML [weeks][e]	Blood	BM cytology	BM cell markers	Outcome / time to outcome [weeks][f]	Details
1	Azari-Yaam et al., 2020[6]	ACUTE MONOCYTIC LEUKEMIA / M5	2	Hb 9 g/dL WBC 146 × 10^9/L PLT 94 × 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[7]	N/A / M5	72	N/A	Monocytic infiltrate	N/A	Death / 80	Disseminated disease
3	Benez et al., 2001[8]	N/A / M5b	28	7% blasts	40% blasts	N/A	Alive / 44	In chemotherapy without remission
4	Breccia et al., 2004[9]	N/A / M2	152	N/A	N/A	HLA-DR− CD34− CD33+ CD15+	Death / 156	N/A
5	Breccia et al., 2004[9]	N/A /M2	176	N/A	N/A	Not determined	Death / 180	N/A
6	De Coninck et al., 1986[10]	N/A / M4	12	WBC 144000/mm3, blasts 63%	N/A	MPO+ esterase enzymes+	Death / 17	Generalized bleedings
7	Di Palma et al., 1993[11]	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[12]	N/A / M5	28	Leukemic blast cells	Leukemic blast cells	N/A	Death / 28	Disseminated disease
9	Hainsworth et al, 1987[13]	N/A / M4	0	Hb 6 g/dL WBC 28x10^3 PLT 158x10^3	Auer bodies	Chloroacetate esterase+	Death / 64	Rapid decline of patient's condition
10	Iitani et al., 2009[14]	N/A / M5	7	Hb 100g/L PLT 212x10^3 WBC 2,9X10^3 (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[15]	N/A / M4	140	Blasts	AML-M4	N/A	Death / 168	N/A
12	Narvaez Moreno et al., 2015[16]	N/A / M1	320	N/A	BM: blasts without maturation (AML FAB M1)	N/A	Death / 400	N/A
13	Rallis et al., 2008[17]	AML NOS / M5a	4	7% blasts	35% blasts	N/A	Death / 36	Pancytopenia
14	Takahashi et al., 2015[18]	N/A / M5a	8	27% blasts	94% blasts	N/A	Death / 8.3	Dyspnea, renal failure and DIC
15	Wilkins et al., 2004[19]	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 (*Acinetobacter baumanii*)

[a]Time after symptoms' onset to icMS/ALC diagnosis; [b]+, expressed by icMS/ALC cells; -, not expressed; [c]N/A, 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

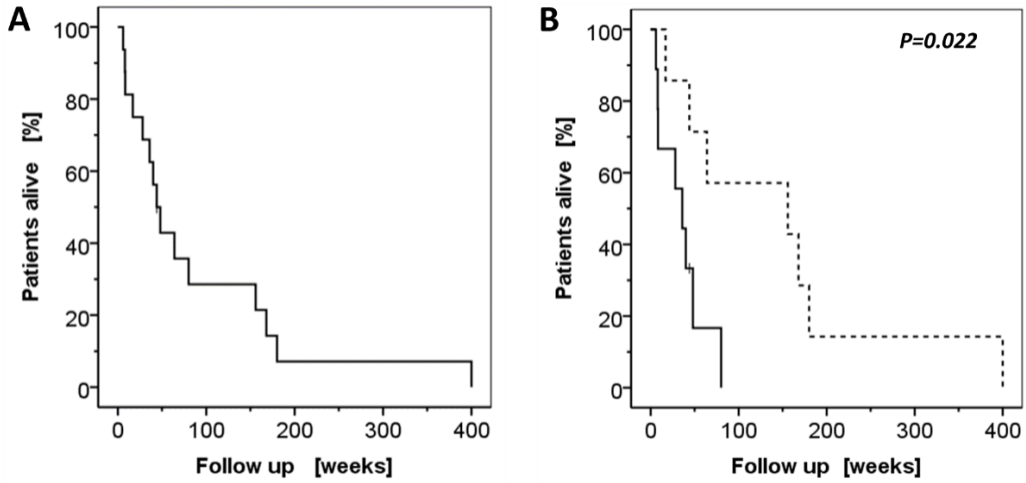
N, number of patients still alive at corresponding time point; S.E., standard error of the estimate.

Supplementary Table 3. Time 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	-

[a]Data not available for four cases; [b]probability 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. **A**) All patients (n=16 patients); **B**) comparison of patients with acute myeloid leukemia (AML) FAB subtype(s) M5 (n=9; solid line) *vs*. the rest of FAB subtypes (n=7, dashed line). Perpendicular bars in **A**) and **B**) indicate the last information, 'patient alive'.



P=comparison of the two levels according to Log Rank (Mantel-Cox) test.

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