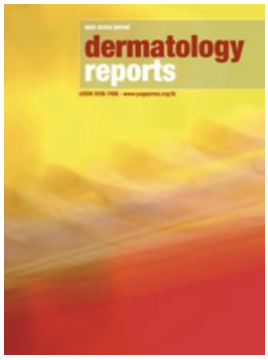

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A case of isolated cutaneous myeloid sarcoma preceding acute myeloid leukemia and literature review

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conducted the haematological treatment of the patient; APB performed a histologic examination on the biopsy specimen; IB and GG were responsible for the critical revising, manuscript editing, and supervision. All the authors have read and approved the final version of the manuscript and agreed to be held accountable for all aspects of the work.

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Abstract

Isolated Cutaneous Myeloid Sarcoma (icMS) and Aleukemic Leukemia Cutis (ALC) are cutaneous extramedullary manifestations of leukemia in which leukemic cells infiltrate the skin before they can be identified either in the peripheral blood or in the bone marrow. We report the case of a 67-year-old patient who presented with a rapidly developing cutaneous tumour and scaly, erythematous-squamous plaques. Isolated Cutaneous Myeloid Sarcoma was diagnosed which rapidly progressed to terminal-stage Acute Myeloid Leukemia (AML). To highlight the disease characteristics of the adult-onset icMS and ALC cases that preceded AML we additionally compiled the pertinent literature of case reports of these rare conditions. We identified n=15 previously published icMS/ALC cases with adequately detailed clinical data descriptions. We could confirm the medical experience that icMS/ALC patients have an overall worse prognosis. Moreover, we could identify FAB M5 AML subtype as a significant adverse prognosticator of these patients.

Introduction

Myeloid Sarcoma (MS), also referred to as chloroma, granulocytic sarcoma, or extramedullary myeloid tumor, is defined as an extramedullary tumour of proliferating myeloid blasts that infiltrate and destroy local tissue architecture.[1-3] MS can affect any organ or tissue in the body.[1,3] In a minority of cases (0,6-0,8%) MS may precede Bone Marrow (BM) and peripheral blood leukemia manifestations. Such cases with morphologically normal-appearing bone marrow at the time of extramedullary leukemia diagnosis have been termed Isolated MS (iMS).[1,3] However, the terminology of the cutaneous leukemia infiltrations is somehow more confusing as the terms leukemia cutis for Cutaneous MS (cMS) and Aleukemic Leukemia Cutis (ALC) for Isolated cMS (icMS) are also used in parallel depending on both the morphology of the lesions and the specialty background of the reporting physicians.[1,2]

Herein, we describe the case of an adult patient with an icMS rapidly progressing to terminal stage Acute Myeloid Leukemia (AML).[1,3] We additionally review the relevant literature to delineate the pertinent data on the clinical presentation and clinical evolution of adult-onset icMS or ALC cases that progressed to AML.

Case Report

A 67-year-old man with hypertension, dyslipidemia, and diabetes mellitus (on perindopril/amlodipine, simvastatin, and empagliflozin/metformin plus slow-release insulin) presented with one-month history of a rapidly growing, painless 9.5×10.0 cm large, ulcerated, purple-red skin tumor on the lower third of the right tibia and multiple, disseminated, slightly itchy, erythematous scaly plaques of up to about 2.0 cm in maximal diameter on the head, trunk and the extremities (Figure 1).

At admission, the routine laboratory tests (complete blood count, basic metabolic panel, lipoprotein panel, and blood clotting tests) were within normal limits. Punch biopsies from the tumor and from an erythematous plaque revealed a brisk dermal cell infiltrate separated by a distinct 'grenz zone' from hyperkeratotic, parakeratotic epidermis (Figure 2). The infiltrating cells were medium-sized blasts with convoluted nuclei and hyperchromatic nuclear membranes, characterized by myelomonocytic differentiation [MPO+, CD33+, CD68 (KP1)+, CLA-, CD163-, CD117-, CD34-, CD56-], consistent with the diagnosis of an MS.

At that time, no leukemia cells could be detected in the BM (aspiration probe and bone biopsy), and the cytogenetic analysis returned a normal 46XY karyotype; the conclusion was a diagnosis of icMS.

From this point on, the clinical state and the laboratory findings of the patient deteriorated rapidly and four weeks later, he had developed multiple, disseminated, poorly demarcated, asymptomatic nodules on the trunk and marked leukocytosis (~27.000 cells/μl, 70% blasts). At this point, the BM biopsy was repeated demonstrating an almost complete replacement of the tissue (representing 95% of the cells) by a clonal cell population with immunohistochemical, molecular, and cytogenetic features of an AML-Myelodysplasia-Related (AML-MR). Immunophenotypically the blast population was positive for HLA-DR, CD56, CD99, and PGM1, and negative for the CD3, CD117, CD20, MPO, CD34, TdT, CD138, glycophorin A. The test for the presence of FLT3 and NPM1 mutations was negative, and the cytogenetic study revealed a complex karyotype, with no defining genetic abnormalities. Of note, the detected -7q and +8 aberrations have been associated with unfavorable and indeterminate prognosis, respectively.[4,5] A Positron Emission Tomography (PET) scan demonstrated an extensive leukemic infiltration of different organs (lymph nodes,

spleen, axial skeleton, pelvis bones, multiple cutaneous foci). Induction therapy with cytarabine and idarubicin was started; however, the patient developed severe complications (febrile neutropenia, nasal bleeding, supraventricular arrhythmias, and respiratory tract infection with isolation of *Acinetobacter baumanii*) and passed away on day 14 after treatment initiation, only six weeks after the confirmation of icMS diagnosis.

Discussion

A rapidly enlarging cutaneous tumor in a 67-year-old patient in combination with disseminated erythemato-squamous plaques raised the suspicion of an underlying haematological malignancy and led to the diagnosis of an icMS, which eventually evolved to a rapidly fatal AML-MR.

To highlight the clinical characteristics of leukemic skin infiltrations preceding the manifestation of AML in adult (older than 18 years) patients we searched the databases PubMed and Scopus for icMS or ALC cases reports (for details of search strategy and data analysis, see Supplementary Material 1). We identified fourteen publications that reported n=15 adequately documented cases (Supplementary Material 2 - Supplementary Table 1).[6-19] Table 1 summarizes the pertinent demographic, clinical, and laboratory findings of these patients.

Compared to all adult MS, patients with AML-related icMS/ALC tend to be older (mean age at diagnosis: 64.7 *vs* 48-58 years) and contrary to overall androtropism of adult-onset MS affects equally both sexes.[3]-Typical AML-associated icMS/ALC cases presented with multiple, disseminated, asymptomatic, and monomorhous plaques or/and nodules, that correspond to a cutaneous-subcutaneous, brisk infiltrate of atypical mononuclear cells separated by a ‘grenz’ zone from a largely uninvolved epidermis.

The mean and median times from the onset of the skin lesions to the diagnosis of icMS/ALC were 18.5 (Standard Error, SE: 6.3) and 8.0 (SE: 2.2) weeks, and from the icMS/ALC diagnosis to the confirmation of systemic disease 70.5 (SE: 24.6) and 12 (SE: 20) weeks (Kaplan-Meier method) respectively. The mean and median survival times after the icMS/ALC diagnosis were 90.0 (SE: 27.8) and 44.0 (SE: 7.5) weeks (Supplementary Material 2 - Supplementary Figure 1A) with a survival probability of 43% (6/16 patients) at one year after the icMS diagnosis (Supplementary Material 2 - Supplementary Table 2).

Considering the substantial variability of the survival time after icMS diagnosis, patients with AML of the FAB M5-subtype(s) had a significantly worse prognosis, compared to cases of icMS that preceded AML of the rest of subtypes (Supplementary Material 2 - Supplementary Figure 1B; p=0.022, Mantel-Cox test; Supplementary Material 2 - Supplementary Table 3).

Notably, AML of M4 and M5 subtypes were additionally found to be associated with an increased relapse rate in the patients undergoing allogeneic stem cell transplantation.[20]

The management of AML-associated icMS/ALC remains challenging. There is still no consensus on the treatment and AML therapeutic protocols are generally recommended.[3] Of note, there has been no apparent progress in the management of this condition in the last decades as highlighted by the comparison of the outcomes of cases published before and after 2010. Neither the time spent from the first clinical signs to the confirmation of icMS/ALC diagnosis (Z=0.000, p=1.000; runs test) nor the survival of the patients after the icMS/ALC diagnosis (Z=-0.724, p=0.469) differed between the patients of the two groups.

Conclusions

In conclusion, the diagnosis of icMS/ALC remains intriguing, partly due to the rarity of this condition and partly to its morphological variability. However, the unfavorable outcome and the failure to record progress in survival through the years highlights the need to shorten the lag time between the initial evaluation of cutaneous findings and the final haemato-pathological diagnosis confirmation through clinical agility of the consulting dermatologists and interdisciplinary collaboration.

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Figure 1. Isolated cutaneous myeloid sarcoma. **A,B)** Well-demarcated, purple-red, ulcerated tumor (right tibia). **C)** Disseminated, slightly infiltrated erythematous scaly plaques (trunk).

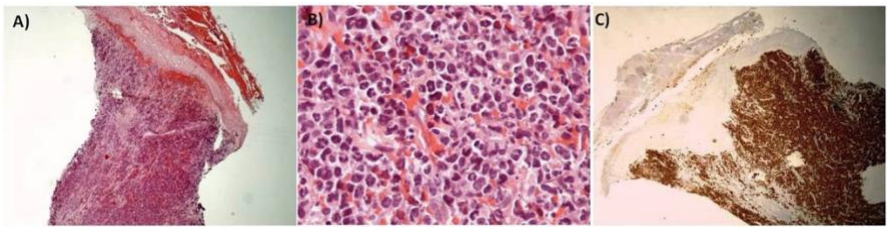

Figure 2. Isolated cutaneous myeloid sarcoma: histopathologic findings of the tumor (right tibia). **A)** Dense and diffuse neoplastic cell infiltration of the dermis (hematoxylin-eosin; x40). **B)** Medium-sized neoplastic cell clone with atypical, folded, hyperchromatic nuclei (hematoxylin-eosin; x600). **C)** The neoplastic cells were MPO+ (DAB staining; x40).

Table 1. Core demographic and disease data of adult patients with primary Cutaneous Myeloid Sarcoma that preceded the development of Acute Myeloid Leukemia: number of cases/number of cases with available information (% of cases with available information).

Patient	**Sex**	Male	8[a] (50%)[b]
		Female	8 (50%)
	Age [years]	Mean [Range]	64.7 [43-84]
icMS/ALC	Features of skin lesions	Multiple	13 (93%)
		Papules/nodules/tumors	
			12 (86%)
		Plaques /patches	8 (57%)
	Localization of skin lesions	Head-neck	4 (29%)
		Trunk	12 (86%)
		Extremities	12 (86%)
	Symptoms/findings	Asymptomatic	8/12[c] (67%)
		Pruritus	4/12 (33%)
	Time to diagnosis in weeks	Mean [Range]	18.5 [4-56]
	Histology of cutaneous lesions	Uninvolved epidermis	6/6 (100%)
		Grenz zone	5/5 (100%)
		Diffuse dermis infiltrate	13/13 (100%)
	Immunophenotype	$CD43^+$	8/8 (100%)
		$CD68^+$	13/14 (93%)
		MPO^+	8/10 (80%)
		$CD3^+$	0/5 (0%)
		$CD20^+$	0/5 (0%)
		$CD34^+$	1/5 (20%)
		$CD30^+$	0/6 (0%)
AML	Time from icMS/ALC to AML diagnosis in weeks	Mean [Range]	70.5 [2-320]
	Subtype (FAB)	M1	2/16 (12,5%)
		M2	2/16 (12,5%)
		M4	3/16 (19%)
		M5(a/b)	9/16 (56%)
	Outcome	Alive at last FU	1/16 (6%)
		Survival in weeks[d]: Mean [Range]	90.0 [2-400]

[a]Number of cases;

[b]% of cases with available information;

[c]number of cases/number of cases with available information (corresponding %);

[d]from the time of icMS/ALC diagnosis, Kaplan-Meier method;

icMS, Isolated Cutaneous Myeloid Sarcoma; ALC, Aleukemic Leukemia Cutis; AML, Acute Myeloid Leukemia

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

Supplementary Material 2.

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).

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

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.

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).

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’.