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RESEARCH ARTICLE

Characteristics and treatment of acute myeloid neoplasms with cutaneous involvement in infants up to 6 months of age: A retrospective study

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Abstract

Background: Myeloid neoplasms account for 50% of cases of pediatric leukemias in infants. Approximately 25%–50% of patients with newborn leukemia have cutaneous extramedullary disease (EMD). In less than 10% of patients, aleukemic leukemia cutis or isolated extramedullary disease with cutaneous involvement (cEMD) occurs when skin lesions appear prior to bone marrow involvement and systemic symptoms. Interestingly, in acute myeloid leukemia with cutaneous EMD (AML-cEMD) and cEMD, spontaneous remissions have been reported.

Abbreviations: AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AML-cEMD, acute myeloid leukemia with cutaneous extramedullary disease; BMA, bone marrow aspirate; cEMD, isolated extramedullary disease with cutaneous involvement; CER-VD, Commission cantonale d'éthique sur la recherche de l'être humain, Vaud; ChCR, Childhood Cancer Registry; CI, confidence interval; CNS, central nervous system; COG, Children's Oncology Group; CRF, clinical report forms; DCOG, Dutch Childhood Oncology Group; DS, Down syndrome; EFS, event-free survival; EMD, extramedullary disease; HSCT, hematopoietic stem cell transplantation; IRB, institutional review board; OS, overall survival; TMD, transient myeloproliferative disease; TRM, treatment-related mortality; W&W, watch and wait.

Method: This is a multicentric retrospective cohort study aiming to describe characteristics, treatment, and outcome of infants with either cEMD or presence of cutaneous disease with involvement of the bone marrow (AML-cEMD). This study included patients born between 1990 and 2018 from Italy, the Netherlands, Switzerland, and the United States, diagnosed between 0 and 6 months of life with cEMD or AML-cEMD. Descriptive statistics, Fisher's exact test, Kaplan–Meier method, and log rank test were applied.

Results: The cohort consisted of $n = 50$ patients, including 42 AML-cEMD and eight cEMD patients. The most common genetic mutation found was a *KMT2A* rearrangement ($n = 26$, 52%). Overall 5-year event-free survival (EFS) and overall survival (OS) were 66% [confidence interval (CI): 51–78] and 75% [CI: 60–85], respectively. In two patients, complete spontaneous remission occurred without any therapy. Central nervous system (CNS) involvement was found in 25% of cEMD patients. No difference in outcomes was observed between the AML-cEMD and cEMD groups, but none of the latter patients included in the study died. *KMT2A* rearrangements were not associated with poorer prognosis.

Conclusion: In the largest cohort to date, our study describes the characteristics of infants with cutaneous involvement of myeloid neoplasms including cytomolecular findings and survival rates. Further prospective biologic and clinical studies of these infants with myeloid neoplasms will be required to individualize therapy for this rare patient population.

KEYWORDS
acute myeloid leukemia, aleukemic leukemia cutis, cutaneous infiltration, extramedullary disease, infants

1 | INTRODUCTION

Acute myeloid leukemia (AML) accounts for 50% of cases of pediatric leukemias in infants and 80% of cases in newborns.[1,2] Leukemia identified at birth is an even rarer event, representing less than 1% of pediatric leukemias, and thus being a challenge for any clinical or scientific investigation.[3] The etiology of leukemias in the first few months of life is not yet fully understood. Observations in infant twins with concordant leukemias, who share clonal *KMT2A* rearrangements, have provided evidence that the leukemogenic event originates in utero.[4,5] Bresters et al. also noted the presence of a chromosomal abnormality on chromosome band 11q23 (which is the location of the *KMT2A* gene) in 42% of AML cases diagnosed in the first 28 days of life from the Dutch cancer registry (1975–2000).[3] Other cytogenetic analyses identified are monosomy 7, trisomy 9, and several translocations, for example, t(8;16), t(9;18), t(9;11), and t(X;6).[6] These abnormalities are directly linked to prognostic factors, and some high- or low-risk mutations have been identified. For example, *KMT2A* rearrangements, which have contradictory prognostic significance in different studies. As some consider them high risk and treat them with intense treatment, while others describe cases with spontaneous remissions without any therapy.[7,8] Spontaneous remissions are also described with t(8;16) rearrangements and are in general linked with good prognostic significance.[9]

On a clinical level, leukemia is associated with pallor, lethargy, hepatosplenomegaly, petechiae, ecchymosis, anemia, leukocytosis, and leukemia cutis.[10] The latter can be defined as a cutaneous infiltration by neoplastic leukocytes (myeloid or lymphoid), resulting in clinically identifiable skin lesions. The mechanisms behind the cutaneous tropism is hypothesized to be related to an alteration in chemokines and receptors of blast cells, such as expression of CD56 in AML blasts, which permits the acquisition of skin-specific homing properties.[11,12] Approximately 25%–50% of patients with newborn leukemia have cutaneous leukemic infiltrates presenting as firm, papular, or nodular, red, blue, or purple lesions that can be solitary or extensive.[3,13,14]

In less than 10% of AML cases, skin lesions can occur prior to bone marrow involvement and systemic symptoms.[14] These cases have been termed either aleukemic leukemia cutis, primary extramedullary leukemia, isolated subcutaneous myelosarcoma, granulocytic sarcoma, or chloroma. In this manuscript, we will refer to them as isolated extramedullary disease with cutaneous involvement (cEMD). Few cases of cutaneous leukemia in infants less than 6 months of age have been described in the literature; therefore, the natural history of this presentation is not well understood.

Resnik and Brod's literature review of patients with newborn leukemias (AML and acute lymphoblastic leukemia [ALL]) with cutaneous infiltrations has suggested that cutaneous extramedullary disease (EMD) does not have prognostic value.[14] The reality is likely to be more complex: leukemia cutis is part of a heterogeneous group of diseases with protean clinical and pathologic manifestations and unclear prognostic implications that can in some cases even result in spontaneous resolution without the need for any therapy.[15–20] Identifying those patients for whom therapy is an unnecessary harm would be key for optimal care.[19] It is to be noted that patients with Down syndrome (DS), mosaicism 21, or solely a *GATA1* mutation can present with a different entity called transient myeloproliferative disease (TMD), which can also be present at birth and spontaneous remissions do occur in this group as well. Those patients were excluded from our study.

The main goal of this study was to describe a large number of infant AML-cEMD (acute myeloid leukemia with cutaneous extramedullary disease) and cEMD cases and describe their clinical characteristics, including diagnostic, therapeutic, prognosis, and their biological features, such as phenotype and molecular genetics.

2 | METHODS

2.1 | Patients and treatment

Eligibility criteria included diagnosis of AML-cEMD (i.e., bone marrow [BM] infiltration) or cEMD (i.e., no BM infiltration), diagnosed from birth to 6 months (=180 days) of life. To ensure more or less recent treatments, we included patients diagnosed between January 1, 1990 and October 1, 2018. Eligible patients were identified by direct communication with clinicians and researchers in Europe, as well as contacting clinical trial centers in Europe and North America. Patients with TMD, juvenile myelomonocytic leukemia (JML), or with DS (including mosaic forms) were excluded from the study. Treatment approaches were divided into two groups: chemotherapy (consolidation with/without hematopoietic stem cell transplantation [HSCT] depending on indication) and an observational approach (watch and wait [W&W]). The first group was further divided into two subgroups: short protocols, being less intense chemotherapy regimens and intensive protocols, being classical intensive AML chemotherapy blocks.

2.2 | Study design

This study was designed as a multicentric retrospective cohort study, with data collected in Italy, the Netherlands, Switzerland, and the United States through pre-established clinical report forms (CRFs). This CRF was developed based on a comprehensive literature review of previously published cases of infant AML-cEMD and cEMD, and consisted of multiple-choice questions and short open questions regarding clinical presentation, histopathology, immunophenotype, cytogenetic, and molecular biology studies with subdivisions (initial diagnosis, treatment, and follow-up). Approval by the ethics review board responsible for any research at the main study site (institutional review board [IRB]: Commission cantonale d'éthique sur la recherche de l'être humain [CER-VD]) was obtained (2018-02063, approved on August 15, 2019). For patients in Lausanne, Switzerland, data were collected from medical records after informed written consent could be obtained from legal guardians. For all other patients, several nationwide children's oncology registries were approached (Associazione Italiana Ematologia Oncologia Pediatrica [AIEOP], Dutch Childhood Oncology Group [DCOG], Childhood Cancer Registry [ChCR], Children's Oncology Group [COG]). Encoded data were shared with the main study site after signature of an IRB-validated data transfer agreement (DTA).

2.3 | Statistical analysis

Descriptive statistics were used to characterize cases, treatments, and outcomes. Ordinal and continuous data are presented in the form of descriptive statistics, as number of patients, median, mean, standard deviation, minimum, and maximum. Categorical data are presented using contingency tables with absolute and relative frequencies. Contingency tables were analyzed using Fisher's exact test, to identify possible significant associations between variables (patients' characteristics, treatment plan, or outcome). Event-free survival (EFS) was defined as the time from diagnosis to the date of first event (refractory disease, relapse, or death, whichever occurred first). Overall survival (OS) was defined as the time from diagnosis to death. EFS and OS curves were computed using the Kaplan–Meier method. If no event occurred during the follow-up period for a patient, data were censored at the time of last contact. Survival distribution function estimate and 95% confidence interval (CI) (log cumulative hazard transformation) were presented. Hall–Wellner confidence bands were represented on product-limit survival estimates graphs and extended to the last event times. Groups were compared using the log-rank test. Significance level was set to.05. Analyses were carried out using Statistical Analysis Software (SAS) version 9.4.

3 | RESULTS

3.1 | Patients' characteristics

Fifty-one patients were initially reported, but one case had to be excluded because of absence of sufficient proof of cutaneous infiltration. Baseline characteristics are summarized in Table 1. The median age at diagnosis was 74 days (range: 0–174 days), with an average at 75 days (standard deviation [SD] ± 52 days), whereas first symptoms appeared during the first month of life with a median age of 30 days (range: 0—115 days). Twenty-eight patients (56%) were male. Forty-two patients (84%) presented with AML-cEMD and $n = 8$ (16%) with cEMD (i.e., without BM infiltration). All patients with AML-cEMD were diagnosed by bone marrow aspirate (BMA), and those with cEMD by skin biopsy. In the dataset, cutaneous infiltrations were described as "present" in most of the cases ($n = 33$) without further details. The

TABLE 1 Patient's characteristics.

Characteristics	Cohort ($n = 50$)	AML-cEMD ($n = 42$)	cEMD ($n = 8$)
Age at diagnosis in days[a]			
0–90	31 (62%)	25 (60%)	6 (75%)
90–180	19 (38%)	17 (40%)	2 (25%)
Sex			
Female	22 (44%)	19 (45%)	3 (37.5%)
Male	28 (56%)	23 (55%)	5 (62.5%)
Country			
Italy	2 (4%)	1 (2%)	1 (12%)
Netherlands	7 (14%)	7 (17%)	0
Switzerland	12 (24%)	9 (21%)	3 (38%)
The United States	29 (58%)	25 (60%)	4 (50%)
CNS infiltration[b]			
Yes	18 (36%)	16 (38%)	2 (25%)
No	31 (62%)	25 (60%)	6 (75%)
Diagnosis			
AML-cEMD	42 (84%)		
cEMD	8 (16%)		
Genetic mutations			
KMT2A (11q23)	26 (52%)[c]	21 (50%)	5 (62.5%)[c]
t(10,11)	9[d]	8[d]	1
t(9;11)	5	3	2
t(11;19)	2	2	0
t(3;11)	1	1	0
t(11;17)	1[e]	1[e]	0
t(4;2;1;11)	2[d]	2[d]	0
t(6;11)	1	1	0
t(1;11)	2	1	1
t(2;11;17,6;10)	1	1	0
t(10;11;17)	1	1	0
t(8;18;11;10)	1	1	0
MOZ* fusions *(8p11)	6 (12%)	6 (14%)	0
MOZ-CBP t(8;16)	3	3	0
t(8;22)	2	2	0
t(8;17;16)	1	1	0
RBM15/MKL1 t(1;22)	2 (4%)	2 (5%)	0
Others	10 (20%)[e]	10 (24%)[e]	0
Unknown	4	4 (10%)	0
No mutation found	3	0	3 (37.5%)

Abbreviations: AML, acute myeloid leukemia; AML-cEMD, acute myeloid leukemia with cutaneous extramedullary disease; CBC, complete blood count; cEMD, isolated extramedullary disease with cutaneous involvement; CNS, central nervous system.

[a]Bold characters are used for subcategories for clarification purpose.

[b]Unknown for one patient.

[c]One patient had a confirmed *KMT2A* mutation via FISH, without further details known.

[d]One patient had 2 different *KMT2A* mutations, counted only once in the "*KMT2A* total" row.

[e]One patient had a *KMT2A* mutation and another additional mutation (*FTL3 ITD*).

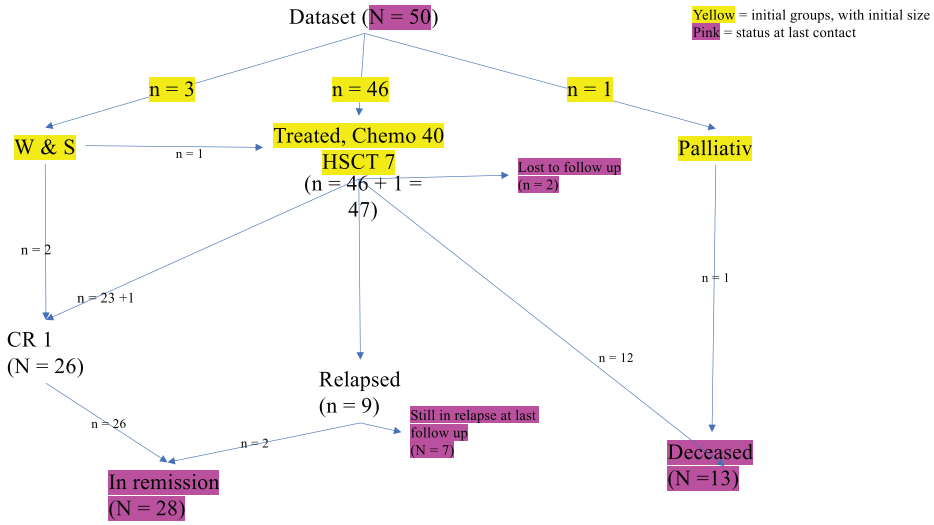

FIGURE 1 Flowchart of patients' treatment and outcome.

majority of patients with a more precise description had a blueberry muffin-like rash. Central nervous system (CNS) involvement was found in 18 (36%) patients. A *KMT2A* rearrangement was found in 26 patients (52%).

3.2 | Treatment characteristics

Almost all patients ($n = 46$, 92%) were treated immediately after diagnosis, $n = 3$ (6%) were followed by a W&W approach, and $n = 1$ (2%) patient proceeded directly to palliative care (Figure 1). W&W was used in one cEMD patient and two AML-cEMD patients, which were 8, 23 and 85 days old, respectively, at diagnosis. As for the treatment protocols,[21–25] 42 patients (91%) underwent intensive AML therapy and four (9%) a reduced intensity approach (used equally in both AML-cEMD and cEMD patients). Seven patients (14%) underwent first-line HSCT intensification after standard chemotherapy, with one of them after unsuccessful W&W and subsequent disease progression. Another patient received a second HSCT after relapse. The reason for first-line HSCT is known for five out of seven patients: four of them had a *KMT2A* mutation, which was categorized as poorer prognostic, and for the remaining one it was because of prolonged aplasia. Treatment choices followed genetic mutations, with the majority of the 42 patients receiving intensive therapy bearing *KMT2A* mutations ($n = 22$, 52%). The W&W approach was used on two patients without any mutation detected, and in one patient with a *KMT2A* mutation. HSCT as first line of treatment was mainly employed for patients with *KMT2A* mutations ($n = 4$ of 7, 57%).

3.3 | Outcome

Out of 50 patients at the time of data collection, 26 patients (52%) were in first complete remission (CR1), nine (18%) relapsed and are still alive (including seven [14%] who were still in relapse at last contact), 13 (26%) patients died (including six [12%] because of treatment-related mortality [TRM]), and two (4%) were lost to follow-up. With a median follow-up time of 6.4 years (range: 1.8–10.5), the estimated 5-year EFS and OS were 66% [CI: 51%—78%] and 75% [CI: 60%—85%], respectively (Figure 2).

For AML-cEMD and cEMD, the estimated 5-year EFS were 64% [CI: 47%—76%] and 83% [CI: 27%—98%] and the OS were 71% [CI: 54%—82%] and 100%, respectively, with no difference between AML-cEMD and cEMD in the probability of first event or death at any time point ($p = .25$ [EFS], and $p = .14$ [OS]) (Figure 3).

Regarding outcomes in patients with CNS involvement, all-cause mortality was 33% for patients with CNS involvement (six out of 18, including two TRM) and 19% for patients without CNS involvement (six out of 31, including three TRM) ($p = .23$). The relapse rate for CNS versus non-CNS patients was 11% (two of 18 patients) versus 22% (seven of 31 patients), respectively, with an odds ratio of 0.43 (exact 95% CI: 0.04–2.70). There was no significant association between CNS and relapse ($p = .45$, analysis done excluding the patients for whom CNS status was unknown). Their 5-year EFS (CNS vs. non-CNS) were 65% [CI: 38%—83%] and 69% [CI: 49%—83%] and OS were 65% [CI: 38%—83%] and 83% [CI: 63%—92%].

Patients with fatal outcomes ($n = 13$) had different types of mutations: seven patients had a *KMT2A* rearrangement (27% mortality among all *KMT2A* patients), one of them with a combined *FTL3 ITD* mutation. One patient had a *MOZ* fusion mutation (16% mortality among all *MOZ* patients). Two carried a *RBM15/MKL1* mutation (100% mortality). And for the remaining three observed deaths, two had unknown mutations and one another mutation. OS was similar in the *KMT2A* category to the non-*KMT2A* (Figure 4).

Regarding administered treatments, all patients undergoing a W&W approach are alive ($n = 3$), with two spontaneous remissions and one after treatment for disease progression (this patient carried a *KMT2A* mutation). Out of the 46 patients who were treated with chemotherapy after diagnosis, 23 (50%) were in CR1, nine (20%) relapsed but were alive, including seven (15%) who were still in relapse at last contact, 12 (26%) died including six (13%) TRM, and two (4%)

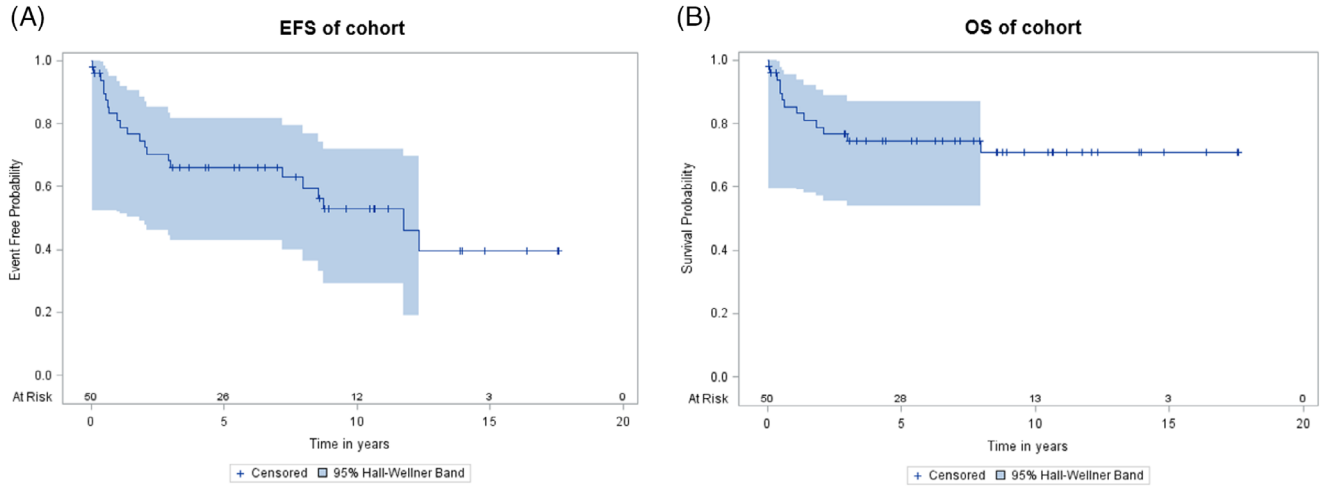

FIGURE 2 (A) Event-free survival (EFS) and (B) overall survival (OS) of entire cohort ($n = 50$).

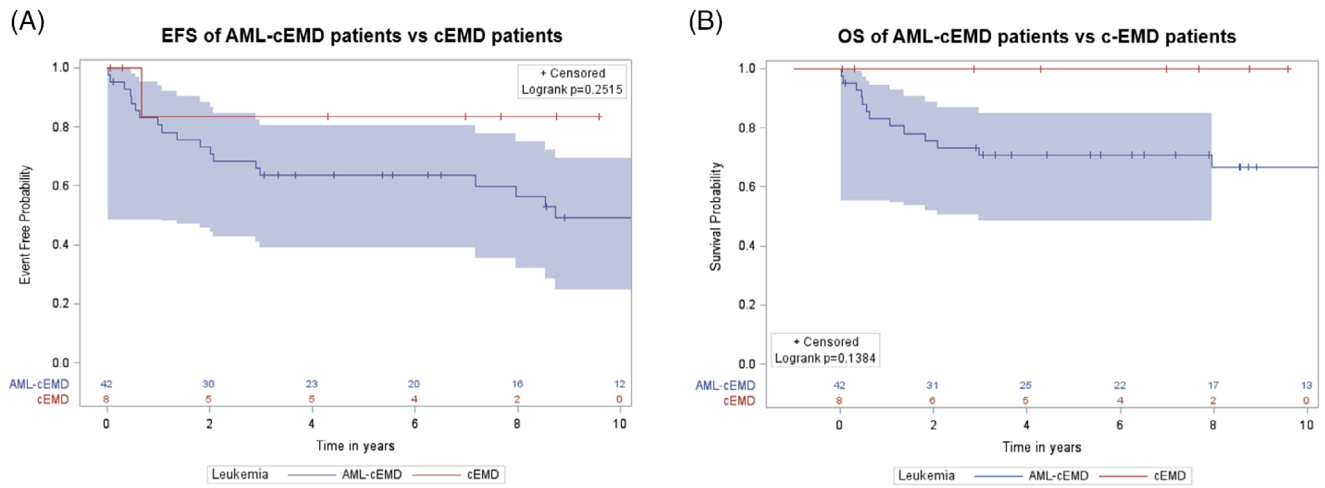

FIGURE 3 (A) Event-free survival (EFS) and (B) overall survival (OS) of AML-cEMD (acute myeloid leukemia with cutaneous extramedullary disease) patients (red) versus cEMD (isolated extramedullary disease with cutaneous involvement) patients (blue). Events and respectively deaths beyond the 10-year period were excluded from figures (but not from analysis).

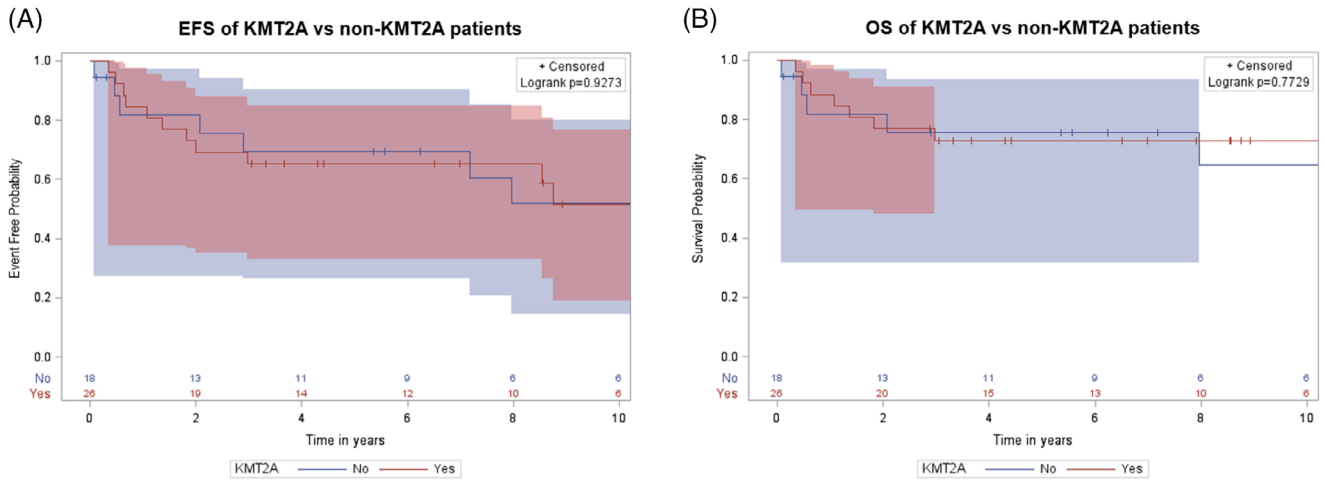

FIGURE 4 (A) Event-free survival (EFS) and (B) overall survival (OS) of *KMT2A* patients (red) versus non-*KMT2A* patients (blue); patients with unknown mutations were excluded. Events and respectively deaths beyond the 10-year period were excluded from figures (but not from analysis).

were lost to follow-up. Two patients of the $n = 7$ (29%) who needed an intensification with HSCT in first-line therapy died of HSCT complications, and one relapsed. For HSCT ($n = 7$) versus non-HSCT as first line of treatment ($n = 39$), 10-year EFS were 36% [CI: 1%−78%] and 56% [CI: 37%−71%] and OS were 43%[CI: 1%−85%] and 74% [CI: 57%−85%], respectively ($p = .83$ EFS, $p = .90$ OS; no difference between HSCT and non-HSCT in the probability of first event or death at any time point).

4 | DISCUSSION

In this large retrospective study, we aimed to describe patients with infant AML-cEMD and cEMD and provide information on clinical features, treatments, and outcomes. This study is unique by focusing on myeloid neoplasms only.

In our study, we noted a slight male predominance, a finding in agreement with what was reported in the Bresters et al. study.[3] CNS involvement was frequent (36%), with similar results described in studies on childhood AML.[26] Interestingly, patients with cEMD were also found to present with CNS involvement, suggesting that in the setting of a negative BMA clinicians should still search for CNS involvement.

Half of the patients had *KMT2A* rearrangements, which is more than what has been reported in the literature (37%–42%).[3,27] This variance could be due to a selection bias, but we feel it would be interesting to further explore whether a putative link exists between cutaneous infiltrates and *KMT2A* mutations. We found *KMT2A* rearrangements in 63% of cEMD patients.

Two main therapeutic strategies were employed to manage these children, that is, upfront chemotherapy versus a W&W approach. One of the main issues for clinicians facing these newborns and infants is to identify who will require therapy upfront and those for whom a W&S approach is reasonable and can lead to the avoidance of harmful and unnecessary therapy.[19,20] Our dataset included only three patients managed through a W&W approach. This clearly constitutes a limitation to the data interpretation and prohibits any conclusions on this topic. Nevertheless, it is of interest that patients with AML-cEMD and cEMD were offered this approach independently of *KMT2A* mutation status. In line with the current World Health Organization (WHO) classification on pediatric AML, current guidelines argue that those type of mutations are an indication for direct intensive treatment.[28,29] Regarding patients who received chemotherapy, they were mainly treated with intensive protocols regardless of their mutational background. As expected, patients with a *KMT2A* mutation were more likely to receive first-line HSCT, but the outcomes between patients treated with chemotherapy or HSCT were comparable in our study.

In our cohort, the 5-year OS was 75%. Zhang et al. described a survival rate of 44%, while Bresters et al. a survival of 23%.[3,30] Noteworthy, these studies included all types of leukemia (AML and ALL), with or without cutaneous infiltrations diagnosed within the first month of life. In those same studies, newborn ALL had a worse outcome than AML. Nonetheless, this could indicate that cutaneous infiltration could represent a favorable prognostic factor. This might be due to earlier disease detection by parents and/or pediatricians. A comparative study including a control group of infants with leukemias without cutaneous infiltration would be necessary to confirm this hypothesis.

We did not record any death in the cEMD subgroup. Unfortunately, the limited number of patients with cEMD included in the study precludes the possibility of observing a statistically significant difference.

In our study, CNS involvement seems to be associated with increased mortality (33% vs. 19% in non-CNS disease), although the difference was not statistically significant ($p = .23$). A study investigating CNS involvement in children with AML suggested that EFS might be more influenced by CNS involvement than OS, as shown by a higher relapse rate.[26]

KMT2A does not appear as a prognostic factor in our study, with similar mortality rates in patients with or without mutated *KMT2A*. Patients with *KMT2A* were more likely to undergo HSCT. It remains therefore difficult to exclude a role for *KMT2A* in the setting of AML-cEMD as a poor prognostic factor or indicator for more aggressive therapy. Interestingly, the patient with *KMT2A* rearrangement who was offered a W&W approach was the only one where this observational strategy failed. The role of a *KMT2A* rearrangement is widely discussed in pediatric leukemia literature: some classify it as conferring a high risk thus warranting pre-emptive therapy in the affected children.[30] Others including Jesudas et al. described patients with *KMT2A* rearrangements who made a full spontaneous recovery without therapy.[7,8] But the prognosis of patients with *KMT2A* rearrangements is largely dependent on their partner genes,[31] which could not be shown with our cohort size. Regarding other mutations found in our cohort, only one patient with *MOZ* fusion bearing a t(8;22) mutation died. This seems to agree with other studies describing *MOZ* fusions as a favorable prognostic factor with spontaneous remission occurrences present in neonates.[9]

The greatest limitation of this study was the potential for selection bias in the individuals included in the study. We collected patients through oncological databases (AIEOP, COG, ChCR, DCOG), which do not always represent the entire population of patients of the respective countries. Another limitation of this study was its retrospective nature and limited sample size. Evidently, retrospective studies are likely to be influenced by confounding factors and biases. Our study nonetheless constitutes the largest cohort reported to date on infant myeloid neoplasms with cutaneous infiltrates.

In conclusion, our study describes the characteristics of infants up to 6 months of age with cutaneous involvement of myeloid neoplasms including cytomolecular findings and survival rates. Further prospective biologic and clinical studies of these infants with myeloid neoplasms will be required to individualize therapy for this rare patient population.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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