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Acute myeloid leukemia with central diabetes insipidus

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ABSTRACT

While acute myeloid leukemia (AML) is the most common type of acute leukemia in adulthood, the constellation of AML associated with central diabetes insipidus (CDI) is rare and typically occurs in patients with chromosome 3 or 7 abnormalities. This subgroup of AML is associated with a poor clinical outcome.

In this report, we present a young woman with AML and concurrent CDI in the presence of inversion(3)(q21q26). The AML was refractory to the induction therapy "7 + 3". Afterwards, the patient underwent allogenic stem cell transplantation (alloHSCT) and is still remaining in complete remission (CR) from AML as well as CDI 440 days after alloHSCT.

Subsequently, in the largest study concerning patients with AML and CDI reported so far, we discuss additional cases from the literature. We demonstrated that patients with AML and CDI belong to the adverse prognostic group and clearly benefit from alloHSCT.

1. Introduction

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adulthood with a yearly incidence of approximately 20,000 newly diagnosed patients in the United States and 18,000 in Europe [1,2]. The constellation of AML and central diabetes insipidus (CDI) is extremely rare with currently about 100 published case reports worldwide. While the first description of leukemia related CDI dates back to 1970 [3] and the earliest publication of AML with CDI was released in 1984 [4], the underlying pathomechanism still remains unknown. Common characteristics of patients who suffered from AML with CDI were associations to monosomy 7 and inversion(3)(q21q26) and an overall poor response to (chemo)therapy resulting in poor outcomes.

Here, we report a young woman who suffered from AML with CDI and is still remaining in complete remission (CR) from AML as well as CDI 440 days after allogenic hematopoietic stem cell transplantation (alloHSCT). Furthermore, we review 50 previously reported cases of myeloid malignancies with CDI with a focus on cytogenetics as well as therapy and desmopressin response. To the best of our knowledge, this is the most comprehensive analysis of AML with CDI.

2. Case presentation

A 28-year-old Caucasian woman (height 163 cm, weight 96,3 kg) presented to her primary care physician in January 2017 with progressive fatigue, exertional dyspnoea, polyuria, and polydipsia (8–10 l/day). Except for a general paleness, the physical examination did not show any remarkable findings. The CBC displayed a bicytopenia with WBC of 4.6×10^3/µl, hemoglobin of 5.6 g/dl and platelet count of 54×10^3/µl. No blasts were observed in peripheral blood smears. Of note, megakaryoblastic fragments were detected in peripheral blood.

Bone marrow aspiration and biopsy revealed an unusual histological constellation: On the one hand CD34 and CD33 positive blasts were present in 20–30% of the bone marrow, fulfilling the criteria of acute myeloid leukemia. Additionally proliferating, atypical megakaryocytes in a hypercellular marrow could be detected. On the other hand, a prominent myelofibrosis (grade II) was diagnosed (Fig. 1). In summary, these findings led to the diagnosis of acute megakaryoblastic leukemia (AML-M7).

Cytogenetic analysis revealed an inversion(3)(q21q26) in 9/10 metaphases. Fluorescence in situ hybridization (FISH) confirmed the inversion and also demonstrated MECOM (=EVI-1) gene

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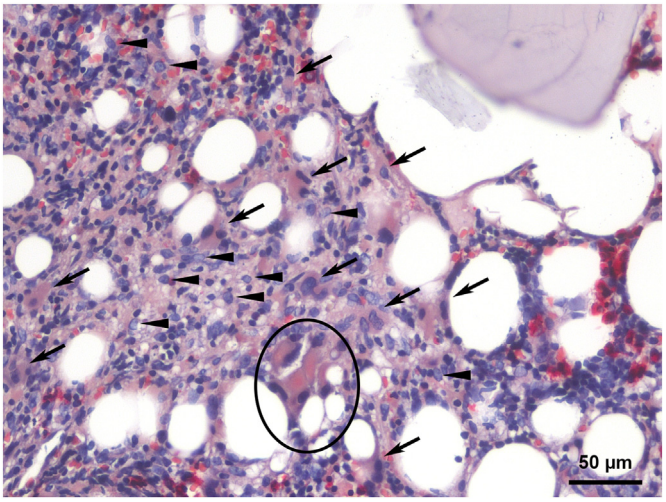

Fig. 1. Chloroacetate esterase stained section of a bone marrow trephine biopsy at initial diagnosis (original magnification 200×): The severe marrow fibrosis leads to partial crush artefacts of the bone marrow cells. The hematopoiesis is severely dysplastic with a proliferation of small atypical megakaryocytes with non-lobulated or bilobed nuclei which are singly dispersed (arrows) or grouped (circle). Blast cells are diffusely intermingled and show delicate chromatin as well as narrow cytoplasmatic rims (well preserved blasts marked with arrowheads).

rearrangement in 39% of cells. Molecular genetic studies were negative for FLT3-ITD, NPM1, IDH, and CEBRA mutations. HemaVision® Multiplex RT-PCR test (DNA Diagnostic, Denmark) including 39 typical AML translocations was also negative. Due to a positive family history of myeloid malignancies (the patient's grandmother died of MDS), we ruled out a germline inversion(3)(q21q26) in the course of genetic counselling by analysis of lymphocytes during the neutropenia with blast clearance in peripheral blood.

Pre-existing medical conditions were polycystic ovary syndrome and hypothyroidism requiring thyroid hormone replacement. Since our patient displayed typical clinical symptoms of diabetes insipidus (DI) like extreme thirst and excretion of an excessive amount of diluted urine, endocrinology service was consulted confirming the diagnosis of CDI. Treatment with desmopressin (DDAVP) resulted in rapid improvement of DI symptoms. Cerebral MRI was performed, which showed normal findings of the pituitary gland. In addition, a hypophysis insufficiency was excluded. Copeptin, that comprises the C-terminal part of the AVP precursor (CT-proAVP), as surrogate marker for arginine vasopressin release, was within the reference range (7.62 pmol/l; ref. range 0.81–28.2). (Although it is necessary to take into account, that the test could not be performed appropriately due to the clinical intolerability of the required 8 hour dehydration.)

Subsequently, the patient was subjected to an initial course of standard induction chemotherapy comprising daunorubicin (60 mg/m^2, days 2–4) and cytarabine (100 mg/m^2, days 1–7) in February 2017. Day 14 bone marrow examination revealed blast persistence with 60% residual blasts.

We did not administer a second induction therapy but directly made provisions for alloHSCT. After a conditioning chemotherapy with fludarabine, amsacrine, treosulfan, cytarabine and cyclophosphamide (FLAMSA protocol [5]) we transplanted peripheral blood stem cells from an unrelated donor with a 10/12 HLA match. One day before the transplantation, upper gastrointestinal bleeding and sepsis occurred. The patient had to be transferred to the ICU, where sepsis therapy including mechanical ventilation followed over the course of two weeks. As a result of therapy related comorbidities, acute cutaneous and intestinal graft-versus-host reactions grade III–IV occurred.

Currently, our patient remains in hematological and cytogenetic CR over 650 days post-transplantation with consistently complete (100%) donor chimerism. In conjunction with the complete AML remission, our patient's CDI resolved completely and desmopressin treatment was discontinued stepwise.

3. Materials and methods

We performed a comprehensive search of relevant published case reports in the PubMed database. Restrictions were made on the publication language (English only) and age (children aged under 18 years were excluded). A final update of the search was conducted in May 2018.

The Venn diagram demonstrating the proportions of cytogenetic findings (Fig. 1) was generated using an online tool by Whitehead Institute for Biomedical Research, Cambridge (http://jura.wi.mit.edu/bioc/tools/venn.php).

Kaplan-Meier curves were plotted for both groups, AML patients with CDI either receiving an alloHSCT or being treated with other therapies, and they were compared with a log-rank test using GraphPad Prism 5.03 software. In the group of patients who were treated with other therapy options, those patients who were treated by best supportive care only were excluded from analysis.

4. Review of literature

The coincidence of CDI with AML is extremely rare and has been described in just about 100 cases worldwide whereas to the best of our knowledge 50 cases in 31 publications were sufficiently evaluated clinically and, for the most part, cytogenetically to be feasible for our review of literature analysis (Table 1). About 50 cases from earlier publications [3,6–8] were excluded for various reasons; mostly for the frequent absence of differentiation between AML and ALL, the lack of cytogenetical analyses as well as major differences in leukemia treatment regimes.

While we focused our review of literature on adults over 16 years, 9 children with childhood myeloid malignancies were reported to have suffered from CDI [9–17]. In close resemblance to adult cases, the majority of juvenile cases (8/9) were also AMLs, with 1 of 9 children being diagnosed with MDS. CDI was also mostly occurring as a presenting feature (7/9 cases) and associated with Monosomy 7 (3/9 cases), in one case additionally with inversion(3)(q21q26), with the limitation of only 5 cytogenetically analyzed cases. Furthermore, the paediatric cases also had a poor disease remission rate of 22% and low survival rates [9].

Altogether 51 adult patients with myeloid malignancies were included (50 cases from 31 publications and the patient from our case report). Hence, this is the largest study concerning patients with AML and CDI reported so far.

The median age at diagnosis of adult patients who suffered from a myeloid malignancy with CDI was 48 years (range between 16 and 74 years) with 58.8% being female. 88.2% of the patients (45/51) were diagnosed with an AML; among these there were two cases of secondary AML [4,18], one case of aplastic anemia with transformation to AML [19] and two cases of MDS with transformation to AML [4,20]. 9.8% of the patients were diagnosed with MDS (5/51) and one patient suffered a CMML-2 [21].

Cytogenetical analysis was performed in 80.4% (41/51) (Fig. 1) with monosomy 7 being the most prevalent aberration with 75.6% (31/41); in one further case a deletion of the half of the long arm of chromosome 7 (del7q22) could be detected [22]. The second most frequent detected chromosomal aberration with 46.3% (19/41) was inversion(3)(q21q26). Chromosome 3 aberrations were detected in 54.8% (17/31) of patients with monosomy 7; 38.7% (12/31) had other cytogenetic aberrations and chromosome 3 aberrations, whereas only two patients with a normal karyotype harboured a chromosome 3 anomaly, one of them is subject of this report. In 19.5% (8/41) neither of both

Table 1
Review of literature with characteristics of previously described AML cases associated with DI.

Reference	Age (y)/ sex	Type of myeloid malignancy	Cytogenetics		Onset of DI	Desmopressin response	Imaging abnormalities (MRI)	Therapy			Outcome		
			Monosomy 7	Inversion(3) (q21q26)				Chemotherapy	Remission sustained	HSCT	Survival from diagnosis	Persistence of DI after CR	Cause of death
Arabi et al. [46]	46/F	AML-M7	NR	NR	At diagnosis	Yes	NR	7 + 3	No	NA	2 weeks	NA	Pulmonary failure
Baron et al. [21]	69/ M	CMML-2	No	No	At relapse	NR	Yes	Azacitidine 7 + 3 with i.t. MTX	NR NR	No	< 6 months	NA	Sepsis
Breccia et al. [47]	29/F	AML-M5a	Yes	Yes	At diagnosis	Yes	No	7 + 3	NR	No	1 month	NA	Severe lung infection
	44/ M	AML-M1	Yes	Yes	At diagnosis	Yes	No	7 + 3	No	No	1 month	NA	Severe infection
Castagnola et al. [18]	37/F	Secondary AML-M2	NR	NR	At diagnosis	Yes	No (CT)	6-TG	No	No	1 month	NA	NR
	63/F	AML-M2	NR	NR	At diagnosis	Yes	No (CT)	High dose Ara-C	No	No	1 month	NA	NR
	63/F	AML-M2	Yes	No	At diagnosis	Yes	No (CT)	Ara-C + 6-TG	No	No	4 months	NA	NR
	48/F	AML-M2	No	No	At diagnosis	Yes	No (CT)	Ida, Ara-C, Eto	No	No	20 months	NA	NR
	43/F	AML-M4	Yes	Yes	At diagnosis	Yes	No	Ida, Ara-C, Eto	No	No	8 months	NA	NR
Cull et al. [19]	37/F	AML	Yes	No	At diagnosis	Yes	No	7 + 3 Mitoxantrone/Eto/Ara-C/ PSC833; topotecan/Ara-C	No No	Yes	< 6 months	NA	Refractory disease
	48/ M	AML	No	Yes	At diagnosis	Yes	Yes	7 + 3; Reinduction (Ara-C) Busulfan/fludarabine	No Yes	Yes	8 months	NR	Septic shock
	60/ M	AML	Yes	Yes	At diagnosis	Yes	No	E1900 + high-dose dauno Reinduction: Dauno/Ara-C	No Yes	No	2 months	NR	*Aspergillus* pneumonia
	42/F	AA transformed to AML	Yes	Yes	At diagnosis	Yes	No	7 + 3	Nadir BMB NP	No	1 month	NR	Pneumonia
	59/F	AML	Yes	No	At diagnosis	Yes	Yes	7 + 3 Decitabine/6-TG; Busulfan/fludarabine	No Yes	Yes	Alive (12 months after HSCT)	No	NA
Curley et al. [41]	42/ M	AML	Yes	Yes	At diagnosis	Yes	No	7 + 3 Reinduction Big ICE; CP + full body irradiation	No No	Yes	< 1 year	No	Progressive AML (relapse on day +88)
de la Chapelle [22]	52/F	MDS transformed to AML	Yes	NR	1 year after diagnosis	Yes	NR	No	NA	NA	22 months	NA	Progressive AML
	57/ M	AML-M2	Yes	NR	2 months before diagnosis	Yes	NR	Yes	No	No	6 months	NA	Progressive AML
	51/ M	AML-M2	Yes	NR	At diagnosis	Yes	NR	Yes	No	No	8 months	NA	Progressive AML
	53/F	AML-M2	No but del (7)(q22)	NR	2 months after diagnosis	Yes	NR	Yes	No	No	4 months	NA	Progressive AML
Dilek et al. [30]	40/ M	AML-M4	NR	NR	At diagnosis	Yes	Yes	7 + 3	No	No	42 day	NA	Sepsis
	16/ M	AML-M4	NR	NR	At diagnosis	NR	No	No	No	No	2 days after admission	NA	Intracranial bleeding

(*continued on next page*)

Table 1 (*continued*)

Reference	Age (y)/ sex	Type of myeloid malignancy	Cytogenetics		Onset of DI	Desmopressin response	Imaging abnormalities (MRI)	Therapy			Outcome		
			Monosomy 7	Inversion(3) (q21q26)				Chemotherapy	Remission sustained	HSCT	Survival from diagnosis	Persistence of DI after CR	Cause of death
Dy et al. [48]	44/F	AML	NR	NR	At relapse	Yes	No	Chemotherapy	Yes	Yes	NR	NR	NA
	52/F	AML	Yes	Yes	At relapse	Yes	No	NR	NA	Yes (prior)	1 month	NR	Sepsis
Eibl et al. [39]	28/F	AML-M0	Yes	No	At diagnosis	Yes	No	7 + 3 c-HAM FLAG	No No Yes	Yes	CR 13 months after HSCT	No	NA
Harb et al. [25]	52/ M	MDS transformed to AML	Yes	No	At diagnosis	Yes	No	After transformation into AML: 7 + 3	No	No	12 months	NA	Transformation into AML
	48/ M	AML	No	No	At diagnosis	Yes	Yes	Arsenic trioxide/Ara-C/Ida; Eto/cytoxan; Ara-C/gemtuzumab ozogamicin; Fludarabine/melphalan	No No Yes	Yes	< 12 months	Yes	Chronic lung GVHD and progressive respiratory failure
Harrup et al. [26]	69/F	AML	No	No	At diagnosis	Yes	Yes	Hydroxyurea, BSC	NA	No	Few months	NA	Infection, progressive disease
La Starza et al. [38]	48/ M	AML_M1	Yes	Yes	At diagnosis	Yes	No	Ida, Ara-C, VP16 with MTX and Ara-C i.t.	Yes	No but autologous at relapse (no CR)	9 months	NR	NR
Lawrie et al. [37]	20/F	AML	Yes	Yes	At diagnosis	Yes	No (CT)	Dauno/Ara-C/Eto	NR	No	5 weeks	NR	Sepsis
Lavabre-Bertrand et al. [49]	39/F	AML-M2	Yes	Yes	At diagnosis	Yes	No (CT)	Cytarabin + dauno	No	No	6 months	NA	NR
	38/ M	AML-M2	Yes	Yes	At diagnosis	Yes	No (CT)	Rubidazone + Ara-C Amsacrine, Ara-C, vindesin, thioguanin, cyclophosphamid	No No	No	8 months	NA	NR
	42/F	AML-M2	Yes	Yes	At diagnosis	Yes	No (CT)	Rubidazone + cytarabine; Amsacrine, Ara-C, vindesin, thioguanin, cyclophosphamid	No No	No	14 months	NA	NR
Keung et al. [50]	31/ M	AML	Yes	Yes	At diagnosis	Yes	No	High dose Ara-C, mitoxantrone, L-asparaginase High dose CP + total body radiation	No Yes	Yes	8 months	NR	Pneumonia
Ma et al. [27]	18/F	AML-M0	Yes	Yes	At diagnosis	Yes	Yes	7 + 3 FLAG	No No	No	8 months	NA	Severe pulmonary infection
Mozersky et al. [33]	61/ M	AML	Yes	No	At diagnosis	Yes	No	Ara-C and dauno	CR	No	Unknown, patient discharged on day 69, no follow-up	NR	NA
Muller et al. [20]	31/F	MDS transformed to AML	Yes	Yes	At diagnosis	Not tested	Yes	Ara-C, VP-16, Ida FLAG-Ida	No Yes	Yes	CR 16 months after HSCT	No	NA
Nakamura et al. [23]	60/F	MDS	No	No	At diagnosis	Minor improvement	Yes	At transformation to AML: 7 + 3	Yes	No	Alive (2 years after diagnosis)	No	NA
Nieboer et al. [34]	52/F	AML	No	No	At diagnosis	Yes	NR	7 + 3	CR	No	Few months	NR	NR

(*continued on next page*)

Table 1 (*continued*)

Reference	Age (y)/ sex	Type of myeloid malignancy	Cytogenetics		Onset of DI	Desmopressin response	Imaging abnormalities (MRI)	Therapy			Outcome		
			Monosomy 7	Inversion(3) (q21q26)				Chemotherapy	Remission sustained	HSCT	Survival from diagnosis	Persistence of DI after CR	Cause of death
Otrock et al. [28]	53/F	AML-M2	Yes	No	At diagnosis	Yes	Yes	7 + 3	No	No	45 days	NA	Pulmonary aspergillosis
Pagano et al. [35]	NR/ M	AML	NR	NR	At diagnosis	Yes	NR	7 + 3; Consolidation	CR	Yes	CR 9 months after HSCT	No	NA
Piccin et al. [31]	27/ M	AML-M6	Yes	NR but EVI-1 gene overexpression	At diagnosis	NR	Yes	Ida, Eto, Ara-C Mitoxantrone, Ara-C FLAG-GCSF	No No	Yes	< 6 months	NA	Interstitial pneumonia
	51/F	AML-M6	No	NR but EVI-1 gene overexpression	At diagnosis	NR	Yes	Ida, Eto, Ara-C Mitoxantrone, Ara-C FLAG-GCSF Busulfan, CP	No No Yes	No	< 6 months	NR	Relapse with septicemia
Puolakka et al. [4]	57/ M	secondary AML	Yes	NR	At diagnosis	Yes	Yes (CT)	Ara-C, 6-TG, dauno	No	No	7 months	NA	Infection
	52/F	MDS transformed to AML	Yes	NR	1 year after diagnosis	Yes	Yes (CT)	No (patient refused therapy)	NA	No	< 2 years	NA	Progressive AML
Ra'anani et al. [32]	37/ M	AML-M2	No	No	At relapse	Yes	Yes	Ara-C, amsacrine	NR	No	34 days	NA	Disseminated fungaemia
Sano et al. [24]	73/ M	MDS	No	No	2 months before diagnosis	No (Pitressin was used), responded to fludrocortisone	Yes (hypothalamus)	Methylprednisolone	NR	No	< 6 months	NA	Progressive AML
Slater et al. [29]	51/F	AML-M1	Yes	Yes	At diagnosis	Yes	Yes (CT)	Adriamycin, Ara-C, 6-TG	No	No	6 weeks	NA	Sepsis in progressive AML
Sonmez et al. [51]	26/ M	AML	Yes	Yes	At diagnosis	Yes	No	7 + 3 Salvage treatment regime	No Yes	Yes	CR but follow up only 3 months	Yes	NA
Sun et al. [52]	74/F	MDS-RAEB1	Yes	No	At diagnosis	Yes	No	No, BSC	NA	NA	< 6 months	NA	Severe infection
Yen et al. [36]	28/F	AML	NR	NR	At diagnosis	NR	No	Induction therapy with high dose Ara-C	CR	No but autologous	< 6 months	NR	Sepsis in progressive AML

Abbreviations: "7 + 3": seven days of cytarabine and three days of an anthracycline antibiotic or an anthracenedione (most often daunorubicin); 6-TG: 6-thioguanin; AA: aplastic anemia; Ara-C: cytarabine; BMB: bone marrow biopsy; BSC: best supportive care C = central; CP: cyclophosphamide; Dauno: daunorubicin; Eto: etoposide; F: female; FLAG: fludarabine + high-dose cytarabine + G-CSF [53]; GCSF: Granulocyte-Colony Stimulating Factor; HSCT: hematopoietic stem cell transplantation; Ida: idarubicine; i.t.: intrathecal administration, M: male; NR: not reported; NA: not applicable; NP: not performed.

abnormalities was detected.

Regarding the onset of CDI in relation to the time of diagnosis of the myeloid malignancy, the vast majority of patients (88.2%; 45/51) suffered from CDI approximately (± 2 months) at the time of diagnosis of their myeloid malignancy. Two patients developed CDI one year after being diagnosed with a myeloid malignancy and 4 patients developed CDI as one of the first relapse symptoms.

For 90.2% (46/51) of the cases the response to a vasopressin analog (mostly desmopressin) was documented: 95.7% of the patients showed a significant improvement of CDI symptoms upon desmopressin treatment, whereas one patient showed only a minor improvement [23] and one patient did not improve with a vasopressin analog but responded to fludrocortisone [24].

Brain imaging (mostly MRI) was performed in 86.3% (44/51) of the cases with 61.4% (27/44) of the patients having no abnormalities with the limitation of 8 patients being evaluated by CT imaging only with a known lower sensitivity for detection of abnormalities in the pituitary region. In 38.6% (17/44) of cases, the presence of an MRI and/or CT abnormality could be detected. Pathologic imaging findings were mainly the loss of the posterior pituitary bright spot [19–21,25] or a nodular thickening/attenuation of the pituitary stalk [23,26–29]. Rarer findings were the detection of an infundibular mass [30], detection of an empty sella [4,31], detection of an infiltrative process in suprasellar region [32] or symmetrically enhanced lesions in the hypothalamus [24].

A precise assessment of induction chemotherapy response was possible for 39 cases (76.4%). An induction therapy with either an anthracycline (mostly daunorubicin) plus cytarabine (“7 + 3”) or high dose cytarabine led to an initial complete remission (CR) with blast clearance in 15.4% (6/39) of all reported cases [23,33–37], whereas 69.2% (27/39) AMLs were primarily resistant. Two patients received an alternative induction therapy (high-dose daunorubicin or 6-TG) and also did not show a disease remission. Three patients received best supportive care and one patient died two days after diagnosis from an accident.

Overall 64.7% (33/51) of all reported patients with AML and DI were treated with other therapy options than alloHSCT, mainly by different chemotherapy combinations [36,38]. Two patients (3.9%) were treated with high dose chemotherapy and autologous stem cell transplantation (autoHSCT) [36,38]. The outcome of this patient group was extremely poor with only 5 patients being alive 12 months after diagnosis. In 22 of 33 cases the causes of death were documented. The patients deceased mainly from severe infections (50%; 11/22), refractory AML (27.3%; 6/22), a combination of both (18.1%; 4/22) as well as rarer events like intracranial bleeding or pulmonary failure.

23.5% (12/51) of all reported patients with AML and CDI underwent alloHSCT. Of 12 patients who were treated by alloHSCT, three patients were reported to be alive and in CR 12 months post-transplantation [19,20,39]. Another case was reported to be alive and in CR 9 months after alloHSCT [35] and one further patient had a CR after alloHSCT but was lost to follow-up. Causes of death after alloHSCT were refractory AML (n = 2), infectious complications (n = 3) and in one case a chronic lung GVHD with progressive respiratory failure.

The 1-year survival rate of all documented AML patients with CDI regardless of the chosen therapeutic option was 20.3%. Compared to patients who were treated with other therapy options than alloHSCT - mainly chemotherapy, but also two cases of autoHSCT - patients who underwent an alloHSCT had a clearly better prognosis with 40% survivors 12 months after AML diagnosis while in the group of patients who were treated with other therapy options the 1-year survival rate amounts only 10% (Fig. 2). The median overall survival (OS) was 6 months for the entire cohort, with patients receiving an alloHSCT surviving significantly longer with 13 months, whereas the median OS for patients who were treated with other therapy options was only 3 months (p = 0.0013). The hazard ratio for death in the alloHSCT group versus the group of patients receiving other therapies was 0.3154 (95% CI, 0.156–0.6375) (Fig. 3).

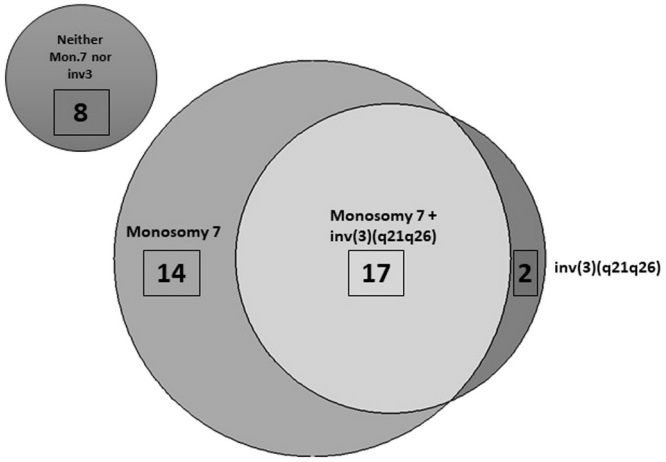

Fig. 2. Proportions of most prevalent cytogenetic findings in patients with AML and CDI.

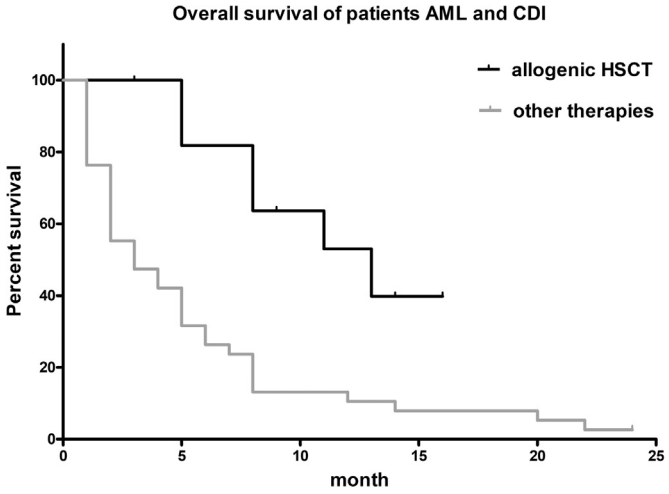

Fig. 3. Kaplan-Meier overall survival of patients with AML with CDI who either received an alloHSCT (black) or were treated with other therapies (grey).

For only 9 cases of AML with CDI an evaluation of the status of CDI after a reached CR was documented. While 2 patients continued to suffer from CDI with desmopressin dependence after reaching a CR, the other 7 cases including our patient could discontinue with desmopressin after CR since there were no signs of a persisting CDI.

5. Discussion

AML presenting together with CDI is a rare condition with a poor clinical outcome and an unclear pathomechanism. The constellation of AML with CDI is often referred to characteristic feature of “3q21q26 syndrome”. It is noteworthy that our literature analysis shows that although the inversion(3)(q21q26) is a frequent aberration, it does not appear to be an essential and single cause for AML with CDI, because in about half of reported patients with AML and CDI this aberration could not be detected. One of the repeatedly shared hypothesis for a possible pathomechanism concerning the inversion(3)(q21q26) is its involvement in overexpression of the nuclear transcription factor EVI1 [40]. The assumption is, that the interaction of EVI1 with other dysregulated, undefined genes may lead to a reduction and/or impairment of vasopressin (ADH) [41]. However, an experimental evidence for this putative interaction is lacking.

Monosomy 7 and inversion(3)(q21q26) were observed in 75.6% and

46.3% respectively while the frequency of the two aberrations in general AML patient populations is reported to be substantially lower with 3% and 1% respectively [42]. Our patient presented with an inversion (3)(q21q26) only, supporting the approach that this cytogenetical change is contributing to the development of DI with an unknown pathophysiological link. But on the other hand, still 17.8% of reported cases of AML with CDI had neither of those aberrations.

Our report contradicts the previously described associations between AML, CDI, and thrombocytosis in patients with chromosome 3q21q26 abnormalities. The second most common explanatory approach for a possible pathomechanism of AML with 3q21q26 abnormalities is the observation that AML patients with 3q21q26 aberrations frequently show a dysthrombopoeitic phenotype. Since 90% of peripheral ADH is platelet-bound [43], it is assumed that the abnormal platelets would limit the circulating ADH-levels resulting in CDI [37]. However, in our case the platelet count was decreased to $54 \times 10^3/\mu l$. Interestingly, megakaryoblastic fragments originating from small atypical megakaryocytes in bone marrow (Fig. 1) could be detected in our patients' peripheral blood. One possible explanation for the previously reported frequently elevated platelets in AML patients with CDI might be, that the elevated platelet counts in older reports could be caused by technical 'artefacts' originated by use of impedance counters. Impedance counters count platelets by the change in impedance they produce during the passage through an electric field. The degree of change is proportional to the volume of the cell. Platelets are separated from erythrocytes by size, the cut-off being 30 fl. Cell fragments are spuriously counted as platelets. Thus, falsely elevated automated platelet counts may occur due to megakaryoblastic fragments that were seen in peripheral blood smear at time of diagnosis of our patient.

CDI onset is variable but usually occurs as a presenting feature of myeloid malignancies. In the majority of cases no imaging findings by MRI or CT could be detected. A positive family history of myeloid malignancies was documented in 2 of 30 cases: The grandmother of our patient deceased from MDS; Lawrie et al. reported a case of a mother and daughter with AML and CDI harbouring the same cytogenetic abnormalities (monosomy 7 and inversion(3)(q21q26)) [37]. However, currently there is no clear evidence for hereditability.

According to the current international recommendations for AML management, either of the frequent cytogenetic aberrations of AML patients with CDI, monosomy 7 as well as inversion(3)(q21q26), are classified as adverse prognostic factors [44]. The 1-year survival rate for AML patients belonging to the adverse genetic risk group is approximately 25% [45], whereas the 1-year survival rate of all documented AML patients with CDI regardless of the chosen therapeutic option was 20.3%.

Under the restriction of comparing data of a prospective large study with restricted retrospective data and limited follow-up times, according to our survival analysis it does not appear that an AML-associated CDI has a clear additional poor prognostic implication. This seems to contradict another publication by Harb et al. who hypothesized that patients with AML, monosomy 7 and CDI had a significantly worse outcome than patients with monosomy 7 but without CDI. The demonstration was performed based on CR rates [25], here, we compare OS rates, which is the more valid and reliable factor to estimate the patient's outcome.

As expected, since widely demonstrated for AML of the adverse prognostic group, there is a clear need for intensive upfront therapy approaches. After an intensive induction therapy, if possible an alloHSCT in the first CR appears to be the most favourable therapeutic option for this unique patient-group. Our patient clearly benefited from the promptly performed alloHSCT, remains in CR with consistently complete (100%) donor chimerism over 1-year post-transplantation and subsequently no evidence of CDI.

Our analyses are based on case reports and are retrospective. We cannot rule out the bias that only patients with initially higher performance status underwent alloHSCT. Therefore, the data should be interpreted with caution.

References

[1] American Cancer Society, Cancer Facts and Figures, American Cancer Society, Atlanta, 2017.
[2] AML Global Portal., Disease overview. http://www.amlglobalportal.com/disease-overview. Last access: November 2016., AML Global Portal.
[3] M. Boga, L. Halmy, P. Rutkai, Diabetes insipidus occurring with acute leukaemia, Haematologia (Budapest) 4 (1970) 235–239.
[4] K. Puolakka, T. Korhonen, R. Lahtinen, Diabetes insipidus in preleukaemic phase of acute myeloid leukaemia in 2 patients with empty sella turcica. A report of 2 cases, Scand. J. Haematol. 32 (1984) 364–366.
[5] C. Schmid, M. Schleuning, G. Ledderose, J. Tischer, H.J. Kolb, Sequential regimen of chemotherapy, reduced-intensity conditioning for allogeneic stem-cell transplantation, and prophylactic donor lymphocyte transfusion in high-risk acute myeloid leukemia and myelodysplastic syndrome, J. Clin. Oncol. 23 (2005) 5675–5687.
[6] V.I. Miller, W.G. Campbell Jr., Diabetes insipidus as a complication of leukemia. A case report with a literature reviews, Cancer 28 (1971) 666–673.
[7] C. Montecucco, M. Cazzola, E. Ascari, Diabetes insipidus in the preleukaemic phase of acute non-lymphocytic leukaemia. A monosomy 7-associated condition? Scand. J. Haematol. 33 (1984) 326–327.
[8] D. Juan, S.D. Hsu, J. Hunter, Case report of vasopressin-responsive diabetes insipidus associated with chronic myelogenous leukemia, Cancer 56 (1985) 1468–1469.
[9] P. Surapolchai, S.Y. Ha, G.C. Chan, et al., Central diabetes insipidus: an unusual complication in a child with juvenile myelomonocytic leukemia and monosomy 7, J. Pediatr. Hematol. Oncol. 35 (2013) e84–e87.
[10] M.C. Joseph, S.E. Levin, Leukaemia and diabetes insipidus; case report, with unexpected effect of cortisone, Br. Med. J. 1 (1956) 1328–1331.
[11] S. Roy 3rd, W.W. Johnson, Diabetes insipidus in a child with erythromyelocytic leukemia, Am. J. Dis. Child. 119 (1970) 82–85.
[12] G.E. Bergman, H.J. Baluarte, J.L. Naiman, Letter: diabetes insipidus as a presenting manifestation of acute myelogenous leukemia, J. Pediatr. 88 (1976) 355.
[13] U. Betkerur, A. Shende, P. Lanzkowsky, Acute myeloblastic leukemia presenting with diabetes insipidus, Am J Med Sci 273 (1977) 325–327.
[14] D.J. Kanabar, D.R. Betts, B. Gibbons, J.E. Kingston, O.B. Eden, Monosomy 7, diabetes insipidus and acute myeloid leukemia in childhood, Pediatr. Hematol. Oncol. 11 (1994) 111–114.
[15] H.A. Frangoul, D.W. Shaw, D. Hawkins, J. Park, Diabetes insipidus as a presenting symptom of acute myelogenous leukemia, J. Pediatr. Hematol. Oncol. 22 (2000) 457–459.
[16] W. Wossmann, A. Borkhardt, R. Gossen, F.J. Gobel, A. Reiter, Acute myeloid leukemia presenting with diabetes insipidus, Eur. J. Pediatr. 161 (2002) 161–162.
[17] W.J. Kollen, L.M. Ball, P. Snijder, S.L. van Zelderen-Bhola, R.M. Egeler, Diabetes insipidus in a child with a monosomy-7 associated myelodysplastic syndrome and neurofibromatosis I, Med. Pediatr. Oncol. 40 (2003) 257–259.
[18] C. Castagnola, E. Morra, P. Bernasconi, et al., Acute myeloid leukemia and diabetes insipidus: results in 5 patients, Acta Haematol. 93 (1995) 1–4.
[19] E.H. Cull, J.M. Watts, M.S. Tallman, et al., Acute myeloid leukemia presenting with panhypopituitarism or diabetes insipidus: a case series with molecular genetic analysis and review of the literature, Leuk. Lymphoma 55 (2014) 2125–2129.
[20] C.I. Muller, M. Engelhardt, J. Laubenberger, et al., Myelodysplastic syndrome in transformation to acute myeloid leukemia presenting with diabetes insipidus: due to pituitary infiltration association with abnormalities of chromosomes 3 and 7, Eur. J. Haematol. 69 (2002) 115–119.
[21] M. Baron, K. Maloum, D. Roos-Weil, Central diabetes insipidus revealing neuromeningeal localization of chronic myelomonocytic leukaemia, Br. J. Haematol. 164 (2014) 314.
[22] A. de la Chapelle, R. Lahtinen, Monosomy 7 predisposes to diabetes insipidus in leukaemia and myelodysplastic syndrome, Eur. J. Haematol. 39 (1987) 404–411.
[23] F. Nakamura, Y. Kishimoto, T. Handa, Y. Arai, K. Mitani, Myelodysplastic syndrome with central diabetes insipidus manifesting hypodipsic hypernatremia and dehydration, Am. J. Hematol. 75 (2004) 213–216.
[24] S. Sano, K. Yamagami, T. Morikawa, K. Yoshioka, Myelodysplastic syndrome complicated by central diabetes insipidus and cerebral salt wasting syndrome with peculiar change in magnetic resonance images, Intern. Med. 49 (2010) 161–165.
[25] A. Harb, W. Tan, G.E. Wilding, et al., Acute myeloid leukemia and diabetes insipidus with monosomy 7, Cancer Genet. Cytogenet. 190 (2009) 97–100.
[26] R. Harrup, M. Pham, G. McInerney, Acute myeloid leukemia with diabetes insipidus and hypophyseal infiltration, Asia Pac. J. Clin. Oncol. 12 (2016) e350–e351.
[27] H. Ma, J. Yang, B. Xiang, Y. Jia, Acute myeloid leukemia with monosomy 7, ectopic virus integration site-1 overexpression and central diabetes insipidus: a case report, Oncol. Lett. 9 (2015) 2459–2462.
[28] Z.K. Otrock, I. Salti, M. Merheb, A.T. Taher, Diabetes insipidus and thrombocytosis as the presenting symptoms of acute myeloblastic leukemia with monosomy 7, Am. J. Hematol. 81 (2006) 152–153.
[29] S.E. Slater, P.K. Maccallum, F. Birjandi, B. Gibbons, T.A. Lister, Acute myelogenous leukemia (AML) and diabetes insipidus (DI): further association with monosomy 7, Hematol. Oncol. 10 (1992) 221–223.
[30] I. Dilek, A. Uysal, T. Demirer, et al., Acute myeloblastic leukemia associated with hyperleukocytosis and diabetes insipidus, Leuk. Lymphoma 30 (1998) 657–660.
[31] A. Piccin, R. Raimondi, S. Laspina, et al., Erythroleukaemia, diabetes insipidus and hypophyseal damage: two case reports, Leuk. Res. 31 (2007) 1135–1139.

[32] P. Ra'anani, O. Shpilberg, M. Berezin, I. Ben-Bassat, Acute leukemia relapse presenting as central diabetes insipidus, Cancer 73 (1994) 2312–2316.
[33] R.P. Mozersky, V.K. Bahl, D. Meisner, H. Patel, Diabetes insipidus, acute myelogenous leukemia, and monosomy 7, J. Am. Osteopath. Assoc. 96 (1996) 116–118.
[34] P. Nieboer, E. Vellenga, R. Adriaanse, A.A. van de Loosdrecht, Central diabetes insipidus preceding acute myeloid leukemia with t(3;12)(q26;p12), Neth. J. Med. 56 (2000) 45–47.
[35] L. Pagano, M.T. Voso, S. Sica, G. Leone, Recovery from diabetes insipidus associated with AML after a BMT conditioning regimen including busulfan, Bone Marrow Transplant. 11 (1993) 175–176.
[36] C.C. Yen, C.H. Tzeng, J.H. Liu, et al., Acute myelomonocytic leukemia preceded by secondary amenorrhea and presenting with central diabetes insipidus: a case report, Zhonghua Yi Xue Za Zhi (Taipei) 60 (1997) 213–218.
[37] A. Lawrie, D.A. Stevenson, T.N. Doig, M.A. Vickers, D.J. Culligan, Acute myeloid leukemia presenting in a mother and daughter pair with the identical acquired karyotypic abnormality consisting of inversion 3q21q26 and monosomy 7: a review of possible mechanisms, Cancer Gene Ther. 205 (2012) 599–602.
[38] R. La Starza, D. Falzetti, C. Fania, et al., 3q aberration and monosomy 7 in ANLL presenting with high platelet count and diabetes insipidus, Haematologica 79 (1994) 356–359.
[39] M. Eibl, H.W. Auner, W. Zinke-Cerwenka, et al., High-risk AML complicated by pulmonary aspergillosis: successful treatment with nonmyeloablative stem cell transplantation and long-term administration of voriconazole, Ann. Hematol. 83 (2004) 133–136.
[40] K. Suzukawa, E. Parganas, A. Gajjar, et al., Identification of a breakpoint cluster region 3′ of the ribophorin I gene at 3q21 associated with the transcriptional activation of the EVI1 gene in acute myelogenous leukemias with inv(3)(q21q26), Blood 84 (1994) 2681–2688.
[41] C. Curley, G. Kennedy, A. Haughton, et al., Acute myeloid leukemia, the 3q21q26 syndrome and diabetes insipidus: a case presentation, Asia Pac. J. Clin. Oncol. 6 (2010) 77–79.
[42] E. Papaemmanuil, M. Gerstung, L. Bullinger, et al., Genomic classification and prognosis in acute myeloid leukemia, N. Engl. J. Med. 374 (2016) 2209–2221.
[43] S.S. Nussey, V.T. Ang, D.H. Bevan, J.S. Jenkins, Human platelet arginine vasopressin, Clin. Endocrinol. 24 (1986) 427–433.
[44] H. Dohner, E. Estey, D. Grimwade, et al., Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel, Blood 129 (2017) 424–447.
[45] C. Rollig, M. Bornhauser, C. Thiede, et al., Long-term prognosis of acute myeloid leukemia according to the new genetic risk classification of the European LeukemiaNet recommendations: evaluation of the proposed reporting system, J. Clin. Oncol. 29 (2011) 2758–2765.
[46] Y. Arabi, M. Varterasian, Acquired central diabetes insipidus complicating acute megakaryocytic leukemia, Am. J. Hematol. 52 (1996) 241.
[47] M. Breccia, M.C. Petti, E. Ottaviani, et al., Diabetes insipidus as first manifestation of acute myeloid leukaemia with EVI-1-positive, 3q21q26 syndrome and T cell-line antigen expression: what is the EVI-1 gene role? Br. J. Haematol. 118 (2002) 438–441.
[48] P. Dy, P. Chua, J. Kelly, S. Liebman, Central diabetes insipidus in the setting of acute myelogenous leukemia, Am. J. Kidney Dis. 60 (2012) 998–1001.
[49] T. Lavabre-Bertrand, P. Bourquard, J. Chiesa, et al., Diabetes insipidus revealing acute myelogenous leukaemia with a high platelet count, monosomy 7 and abnormalities of chromosome 3: a new entity? Eur. J. Haematol. 66 (2001) 66–69.
[50] Y.K. Keung, D. Buss, B.L. Powell, M. Pettenati, Central diabetes insipidus and inv(3)(q21q26) and monosomy 7 in acute myeloid leukemia, Cancer Genet. Cytogenet. 136 (2002) 78–81.
[51] M. Sonmez, N. Erkut, T.S. Tat, et al., Can a high platelet count be responsible for diabetes insipidus in acute myelogenous leukemia with monosomy 7 and inversion 3 (q21q26)? Int. J. Hematol. 90 (2009) 273–274.
[52] R. Sun, C. Wang, X. Zhong, Y. Wu, Diabetes insipidus as an initial presentation of myelodysplastic syndrome: diagnosis with single-nucleotide polymorphism array-based karyotyping, Tohoku J. Exp. Med. 238 (2016) 305–310.
[53] G. Visani, P. Tosi, P.L. Zinzani, et al., FLAG (fludarabine + high-dose cytarabine + G-CSF): an effective and tolerable protocol for the treatment of 'poor risk' acute myeloid leukemias, Leukemia 8 (1994) 1842–1846.