Myelodysplastic syndrome presenting with central diabetes insipidus is associated with monosomy 7, visible or hidden: report of two cases and literature review

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Case Report

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Abstract

Background

Central diabetes insipidus (CDI) is a rare complication of myelodysplastic syndrome (MDS). Although the cytogenetic features of patients with MDS and CDI are not clear, CDI in acute myeloid leukemia (AML) patients is associated with chromosome 7 and/or 3 anomalies.

Case presentation

In this report, we describe two patients with MDS and concurrent CDI, and in one of them, CDI was the first manifestation. Metaphase cytogenetics (MC) revealed monosomy 7 in one patient. We found monosomy 7 as well as numerous cytogenetic abnormalities in the other patient using single-nucleotide polymorphism array (SNP-A) karyotyping, while their MC did not uncover monosomy 7. In this manuscript we also reviewed reported DI-MDS cases to summarize the relationship between DI-MDS and karyotype and to explore the best treatment strategy of DI-MDS.

Conclusions

DI-MDS is closely related to monosomy 7. Allogeneic hematopoietic cell transplantation may be the only effective treatment to DI-MDS. The SNP-A-based karyotyping is helpful to reveal subtle cytogenetic abnormalities and unveil their roles in the clinical features of MDS.

Background

Diabetes insipidus (DI) can be caused by either deficiency of antidiuretic hormone (ADH), which is known as central DI (CDI), or inadequate sensitivity of the kidney to ADH, which is known as nephrogenic DI. CDI is rare in cases of hematological malignancy but can be the initial manifestation of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) [1–4]. The mechanism of CDI occurs in AML and MDS is largely unknown. While AML and MDS with DI (DI-AML and DI-MDS) have been reported to be closely related with cytogenetic abnormalities, including partial or complete deletion of chromosome 7 and structural abnormalities of chromosome 3 [4–8]. In this report, we describe two patients with MDS and CDI. Monosomy 7 were founded in both cases by metaphase cytogenetics (MC) or single-nucleotide polymorphism array (SNP-A)-based karyotyping. In addition, we reviewed all the reported DI-MDS in the literature, in order to provide experience for the diagnosis and treatment of similar patients.

Case Presentation

Case 1

A 43-year-old man presented with a 6-month history of polydipsia and polyuria. His urine output was 3.5 to 6 liters per day with a urine specific gravity of 1.003 (normal range, 1.010–1.025). His serum sodium was 150.4 mmol/L (normal range, 137–147 mmol/L), urine osmolality was 146 mOsm/kg (normal range, 50–1,200 mOsm/kg) and plasma osmolality was 320 mOsm/kg (normal range, 275–305 mOsm/kg). Thyroid-stimulating hormone (TSH) was elevated at 6.72 mU/L (normal range, 0.27–4.2 mU/L), and prolactin was 23.64 ng/mL (normal range, 4.60–21.40 ng/mL). The levels of other pituitary hormones, testosterone and the morning cortisol level were normal. Magnetic resonance imaging (MRI) revealed a slightly thickened pituitary stalk and a small nodule in the left pituitary. The water deprivation and vasopressin test supported the diagnosis of CDI. The patient was started on desmopressin and showed improvement in his symptoms.

The complete blood count (CBC) showed a white blood cell count (WBC) of $2.81 \times 10^9/L$, hemoglobin of 111 g/L, and platelet count of $34 \times 10^9/L$. His bone marrow aspirate revealed dysplasia of the erythroid lineage with 6.5% myeloblasts. Flow cytometry and bone marrow biopsy demonstrated MDS. Standard molecular genetic analysis showed a single mutation of CEBPA, whereas FLT3-ITD, NPM1, C-kit, IDH1, IDH2, DNMT3A, PHF6, TET2, ASXL1, and EVI1 were negative. Karyotype analysis of metaphase chromosomes showed a karyotype of 47, XY, +8 [10]. To confirm the karyotype and broaden the scope of karyotyping, an SNP-A-based analysis was performed using the Affymetrix Gene Chip Mapping 750K Assay kit and Gene Chip Scan 300D×V.2 (Affymetrix, Santa Clara, CA). Interestingly, SNP-A-based karyotyping revealed a complex karyotype (Fig. 1, Table 1) that included monosomy 7, 12p- and trisomy 8, which are common in myeloid malignancy, especially in MDS, and 4 short lesions were recognized as an absence of heterogeneity (AOH) of uncertain significance. Thus, a diagnosis of MDS with excess blasts-1 (MDS-EB1) was established. The patient underwent an allogeneic hematopoietic cell transplantation (HCT), and oral desmopressin was tapered down to discontinuation. He achieved complete remission 11 months after the transplant with no evidence of recurrent DI.

Table 1
List of the SNP-A-based karyotyping findings for Case 1

Chromosome abnormality	Copy number state	Size (Kb)	Significance	Location
LossMosaic (7p22.3-q36.3) ×1–2	1.5	159,076	Abnormalities in myeloid malignancies esp. in MDS	43,376 – 159,119,707
GainMosaic (8p23.3-q24.3) ×2–3	2.3	145,471		158,048–145,629,232
LossMosaic (12p13.2-p13.1) ×2–3	1.5	1,951	Reported in MDS-RAEB2	11,197,813 – 13,148,969
Gain(15q12.3)	3	414	Polymorphism in copy number variation	32,029,692 – 32,444,043
UPD (3p21.31-p21.1)	2	8,455	Reported in the normal human UPD database	45,843,438 – 54,298,805
UPD (20q11.21-q11.23)	2	6,643	and no reports in blood diseases with the	29,501,306 – 36,153,360
Gain (5p12p11)	3	1,100	acquired UPDs	45,288,800 – 46,389,261
UPD, uniparental disomy.				

Case 2

A 40-year-old female presented with a 5-month history of dizziness and weakness. The CBC showed a WBC of $1.16 \times 10^9/L$, hemoglobin of 63 g/L, and platelet count of $51 \times 10^9/L$. Bone marrow aspirate and flow cytometry analysis indicated MDS-RAEB1. Karyotype analysis revealed a complex karyotype of 46, XX, t (3; 3) (q21; q26) [2]/45, idem, -7[4]/45, idem, der (4) (1; 4) (q25; p16), -7[11]/46, XX [3] (Fig. 2). Fluorescence in situ hybridization (FISH) of 5p15.2/5q33-34, 7p11.1-q11.1/7q31, 8p11.1-q11.1, 20q12, 17p13.1 revealed a signal loss of 7p11.1-q11.1/7q31, which indicated -7. Real-time fluorescence quantitative polymerase chain reaction revealed overexpression of EVI1 (EVI1/ABL1 = 95.21%). After hospitalization, the patient complained of newly developed polydipsia and polyuria, and her urine output was 3 to 7 liters per day with a urine specific gravity of 1.003 (normal range, 1.010–1.025). Her serum sodium and urine sodium were 152.5 mmol/L (normal range, 137–147 mmol/L) and 177.3 mmol/24h (normal range, 130–261 mmol/24h), respectively. An MRI of her brain showed a normal pituitary gland. The endocrinology service was consulted, and CDI was the diagnosis. She was started on oral desmopressin with improvement.

Subsequently, the patient was subjected to two cycles of decitabine-based chemotherapy without response, and progressed to AML quickly. She underwent HCT, but remission was still not achieved. Interestingly, her symptoms of polydipsia and polyuria disappeared for more than 1 month after HCT and reappeared when the blasts increased. The patient progressed to AML and finally died 8 months after the transplant.

Discussion And Conclusions

Here we reported two cases of DI-MDS with monosomy 7. In our case 1, CDI was the initial manifestation of MDS, which might have led to misdiagnosis or delayed treatment. MDS associated with DI has rarely been reported. To our knowledge, only five MDS cases with CDI have been reported till now [4, 6, 7, 9, 10]. The information of reported DI-MDS cases was summarized in Table 2.

Table 2
Characteristics of five reported cases with MDS and CDI

Reference	Age (years)	MDS subtype	Partial/complete deletion of chromosome 7	MRI abnormal	Treatment of MDS	Outcome of CDI	Time to AML (months)	OS (months)
4	74	RAEB 1	Yes	No	Supportive care	Controlled by desmopressin	2	2
6	6	RAEB 1	Yes	No	Allo-HCT	Controlled by desmopressin and cured after HCT	No	NA
7	53	RAEB 2	No (Normal karyotype)	Nodular lesion on pituitary stalk & absent of posterior “bright spot” of neurohypophysis on T1-weighted MRI	Chemotherapy and Allo-HCT	Controlled by desmopressin and need for desmopressin persists after allo-HCT	No	18+
9	60	MDS-MLD	No (Normal karyotype)	Attenuation of “bright spot”	Chemotherapy	Recovered after chemotherapy	1	NA
10	73	NA	Yes	Absent of posterior “bright spot” & symmetrical enhancing lesions in the hypothalamus	NA	Temporary controlled by desmopressin	3	3
MDS: myelodysplastic syndrome; CDI: central diabetes insipidus; MRI: magnetic resonance imaging; NA: not available; AML: acute myeloid leukemia; OS: overall survival; RAEB: refractory anemia with excess blasts; Allo-HCT: allogeneic hematopoietic cell transplant; MDS-MLD: MDS with multilineage dysplasia.								

Although the reason for why DI occurs in MDS is unclear, the co-occurrence of AML and DI has several possible explanations. For instance, leukemic infiltration of the pituitary gland or hypothalamus, leukostasis, thrombosis, hemorrhage and infection have been presumed as causes. In our case 1, the MRI revealed a slightly thickened pituitary stalk and a small nodule in his left pituitary, which may indicate a pituitary infiltration. It is worth noting that the WBCs of both patients were lower than normal, which makes leukostasis unlikely.

The chromosomal anomalies we identified were closely related to AML/MDS with DI. Partial or complete monosomy of chromosome 7, which is the most commonly reported chromosome abnormality in DI-AML, was detected in both cases by MC analysis or SNP-based microarray; this abnormality was also found in 3 out of 5 reported cases of MDS with DI [4, 6, 10]. One possible explanation for this correlation is that monosomy 7 may affect expression of the neutrophil migration gene located on the 7q22 gene region. This impairs the migratory and chemotactic functions of neutrophils and may be related to blast infiltration of the pituitary gland in these patients [11, 12].

A few studies have suggested the prognosis of DI-AML to be poor [1, 8, 13]. It is reasonable to suspect a poor prognosis for DI-MDS based on the similar cytogenetic abnormality in DI-AML. In all three reported DI-MDS who didn't perform allogeneic HCT, progression to AML occurred within three months [4, 9, 10]. In our case 2, despite being treated with decitabine, rapid progression to AML occurred. These results suggest allogeneic HCT may be the only effective therapy for DI-MDS and should be performed as soon as possible. In all reported cases and our cases, the symptoms of polydipsia and polyuria could be controlled by desmopressin [4, 6, 7, 9, 10]. Desmopressin was no longer needed after MDS were well controlled in our case 1 and two reported cases [6, 9]. However, need for desmopressin persisted even after allogeneic HCT in one case [7]. Both of our cases showed fluctuation of the severity of DI with MDS status. Thus, it would be worthwhile to investigate how MDS status influences the incidence or severity of DI in the milieu of fewer blasts.

Cytogenetic aberrations have important diagnostic, prognostic and therapeutic roles in MDS. However, the “false normal karyotype” of MC analysis often occurs because of the lack of metaphase nuclei in MDS. FISH and SNP-A-based karyotyping don't rely on metaphase nuclei, while FISH is limited to detection of the known lesions. SNP-A-based karyotyping can reveal unbalanced defects in as few as 10% of cells [14], thus to identify cryptic abnormalities that are below the resolution of MC analysis. Meanwhile, SNP-A-based karyotyping can identify segmental uniparental disomy (UPD) that is undetectable by MC or FISH. Tiu et al. reported that SNP-A-based karyotyping

detected chromosomal defects in 54% of MDS with normal MC results, and the presence and number of new SNP-A detected lesions, including UPD, are independent predictors of overall and event-free survival [15]. Recently, Yang Ou et al. reported the presence of UPD was an independent prognostic factor in MDS patients with normal karyotype [16]. Makishima H. et al. revealed that combined SNP-A karyotyping with routine MC in MDS improved the cytogenetic detection of monosomy 7, del (7q), del (5q), del (20q) and trisomy 8 [17]. By combining SNP-A-based karyotyping with MC, we uncovered additional cytogenetic abnormalities in our case 1, especially those associated with monosomy 7 and AOH. It is difficult to judge the AOH from somatic or germline cells because of the absence of germline controls for our patients. Until now, we have been unable to associate AOH with DI-MDS. In our case 1, monosomy 7 was not found by MC but was detected by the SNP-A-based karyotyping. These results indicate that the significance of a “normal karyotype” in reported DI-MDS cases may need to be reconsidered. The SNP-A analysis achieved superb resolution and can detect UPD, which overcomes the technical limitations of MC or FISH, such as the need for metaphase nuclei, hypocellularity, incompetence in unknown lesions and relatively low resolution. Thus, application of this technique to assess MDS patients with DI will help us to further elucidate the pathogenesis of DI-MDS.

Abbreviations

CDI: Central diabetes insipidus; MDS: Myelodysplastic syndrome; AML: Acute myeloid leukemia; MC: Metaphase cytogenetics; SNP-A: Single-nucleotide polymorphism array; TSH: Thyroid-stimulating hormone; MRI: Magnetic resonance imaging; CBC: Complete blood count; WBC: white blood cell count; AOH: absence of heterogeneity; MDS-EB1: MDS with excess blasts-1; HCT: hematopoietic cell transplantation; UPD: uniparental disomy.

Declarations

Ethics approval and consent to participate: this study was approved by the scientific ethical committee of our hospital.

Consent for publication: Not applicable.

Availability of data and materials: All relevant data and material is included in this publication.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: YY, YW and TL prepared the manuscript, YY, TL, TD and YW provided medical care to the patients. All authors provided revisions and feedback on the manuscript draft. All authors read and approved the final manuscript.

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Figures

Figure 1

(A) SNP-A-based karyotyping of case 1. Blue indicates gains ≥ 400 Kb; red indicates losses ≥ 400 Kb; purple indicates absence of heterogeneity > 5 Mb. (B) Metaphase cytogenetics of case 1 showing trisomy 8. (C) Bone marrow smear showing blast cells.

Figure 2

Metaphase cytogenetics of case 2 revealed a karyotype including (A) 46, XX, t (3; 3) (q21; q26), (B) 45, idem, -7 and (C) 45, idem, der (4) (1; 4) (q25; p16), -7.