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Diabetes Insipidus as an Initial Presentation of Myelodysplastic Syndrome: Diagnosis with Single-Nucleotide Polymorphism Array-Based Karyotyping

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Myelodysplastic syndrome (MDS) is a group of clonal hematopoietic diseases characterized by cytopenia, dysplasia and increased risk of development to acute myeloid leukemia (AML). Unfavorable cytogenetic changes such as complex karyotypes or chromosome 7 anomalies are predictive of the progression to AML and poor prognosis. Central diabetes insipidus (CDI) is the result of a deficiency of arginine vasopressin, and its major causes are idiopathic, primary or secondary tumors, neurosurgery and trauma. Importantly, CDI is a rare complication of MDS. To date, only 5 cases of MDS co-occurring with CDI have been reported; 3 of 5 had cytogenetic abnormalities uncovered by metaphase cytogenetics and 3 of 5 evolved to AML. Here, we describe a 74-year-old woman who presented with CDI as her initial symptom of MDS and eventually progressed to AML. The metaphase cytogenetics, combined with the single-nucleotide polymorphism array (SNP-A)-based karyotyping, with superiority in resolution and detecting copy number variation, revealed a complex karyotype that included monosomy of chromosome 7, deletion of 20q, and absence of heterogeneity (AOH) in more than one chromosome. To the best of our knowledge, this is the first case report of MDS co-occurring with CDI with numerous cytogenetic abnormalities revealed by the SNP-A-based karyotyping. Our case supports that the cytogenetic abnormalities may be associated with the clinical features and the prognosis of MDS co-occurring with CDI. The SNP-A-based karyotyping is helpful in revealing more subtle cytogenetic abnormalities and unveiling their roles in the pathogenesis of MDS.

Keywords: cytogenetics; diabetes insipidus; karyotype; myelodysplastic syndrome; single-nucleotide polymorphism array
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Introduction

Diabetes insipidus (DI) is categorized as central DI (CDI) and nephrogenic DI. CDI is the result of a deficiency of arginine vasopressin (AVP), which is also known as antidiuretic hormone (ADH) (Makaryus and McFarlane 2006), and nephrogenic DI is related to inadequate sensitivity of the kidney or nephron to ADH. The most common causes of CDI are idiopathic DI, primary or secondary tumors, neurosurgery and trauma. Hematologic malignancy complicated by CDI is very rare. Acute myeloid leukemia (AML) with DI was first reported in 1980's (de la Chapelle and Lahtinen 1987), but the underlying mechanism remains unclear. Leukemic infiltration of the pituitary or hypothalamus, leukostasis, thrombosis, infection, hemorrhage, pituitary stalk/gland necrosis or partial necrosis of the hypothalamus may be factors responsible for its etiology. Recently, cytogenetic changes, including partial or complete deletion of chromosome 7 and structural abnormality of chromosome 3q have been reported in AML with CDI (Chuang et al. 2015).

Here, we report a 74-year-old woman who presented with polyuria, hypernatremia and disturbed consciousness. After detailed evaluation, a diagnosis of myelodysplastic syndrome (MDS) with CDI was established. Only 5 MDS cases with CDI have been reported in the literature to date (Keung et al. 2002; Kollen et al. 2003; Nakamura et al. 2004; Sano et al. 2010; Chuang et al. 2015). To our knowl-

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edge, ours is the first reported case of newly diagnosed MDS presenting as CDI with numerous cytogenetic abnormalities revealed by single-nucleotide polymorphism array (SNP-A)-based karyotyping.

Case Presentation

A 74-year-old female presented for emergent medical care with a 2-month history of polyuria and a 5-day history of new-onset fever and cough. Two months prior to presentation, she experienced polyuria, polydipsia, and increased fatigue but did not seek any medical consultation. Five days prior to presentation, the above symptoms worsened, and she developed fever and disturbance of consciousness. Her past medical history included venous thrombosis in the lower left extremity 4 months prior that was treated with warfarin for less than 3 months without regular monitoring. She had lost 4 kilograms of body weight over the past 2 months. On admission, her physical examination revealed a body temperature of 38°C, a pale face and dehydrated skin and mucosa. Rales were noticed in both lungs. There was no hepatosplenomegaly or lymphadenopathy. No neurological deficits were found.

Laboratory studies revealed the following: white blood cell count, 16.05×10^9/L; hemoglobin, 79 g/L; platelets, 416×10^9/L; neutrophils, 71%; blasts 2%; Serum sodium, 160.1 mmol/L (normal range, 137-147 mmol/L); albumin, 28.9 g/L (normal range, 35-55 g/L); globulin, 43.2 g/L (normal range, 19-34 g/L); and lactic dehydrogenase 536 IU/L (normal range, 180-220 IU/L). After hospitalization, her pulmonary infection and fever was well controlled with Micafungin and Piperacillin/Tazobactam based on her sputum culture and sensitivity test. However, her urine output was remarkable at 6 to 7 liters in 24 hours with a urine specific gravity of 1.003 (normal range, 1.010-1.025). Urine and plasma osmolalities were 137 mOsm/kg (normal range, 50-1,200 mOsm/kg) and 390 mOsm/kg (normal range, 275-305 mOsm/kg), respectively. These findings strongly suggested the presence of DI. Her levels of thyroid-stimulating hormone (TSH), prolactin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were normal. Her morning cortisol level and 24-hour cortisol output were normal. A water deprivation and vasopressin test was performed, and the results were consistent with the diagnosis of CDI. T1-weighted magnetic resonance imaging (MRI) did not reveal any attenuation of the physiological high density (so called "bright spot") of the neurohypophysis or empty sella. Oral desmopressin was initiated at 50 mg twice daily, and her symptoms of polyuria and polydipsia promptly improved.

The patient provided consent for use of her medical record and samples for clinical and research purposes, and the examination was performed in accordance with both the ethics committee of West China Hospital and the Helsinki Declaration. The patient's bone marrow aspirate revealed prominent dysplasia of the erythroid, myeloid and megakaryocyte lineage with 5.5% blasts. Bone marrow biopsy demonstrated hypercellularity with increased immature myeloid cells and mild to moderate myelofibrosis. Flow cytometry analysis showed that myeloid blasts were positive for CD34, HLA-DR, CD117, CD13 and CD113. Standard molecular genetic analysis showed negative results for the breakpoint cluster region-Abl tyrosine kinase (BCR-ABL), runt related transcription factor 1-runt related transcription factor 1 translocated to 1 (AML1-ETO), core-binding factor β-myosin heavy chain 11 (CBFβ-MYH11), transcription factor 3-pre B cell leukemia homeobox 1 (E2A-PBX1), mixed-lineage leukemia-AF4/FMR2 family member 1 (MLL-AF4), promyelocytic leukemia-retinoic acid receptor alpha (PML-RaRα) and ets variant 6-runt related transcription factor 1 (TEL-AML1) fusion genes. The patient was also negative for mutation at codon 617 of the Janus kinase 2 (JAK2V617), fms related tyrosine kinase 3 internal tandem duplications (FLT-ITD), CCAAT/enhancer binding protein alpha (CEBPα), KIT proto-oncogene receptor tyrosine kinase (c-Kit) and nucleophosmin (NPM-1) mutations. Real-time polymerase chain reaction (PCR) results were also negative for ecotropic virus integration site-1 (EVI-1) gene expression. Karyotype analysis of metaphase chromosomes showed a complex karyotype of 46,XX, t(1;4;20)(q12;q25;q11.2), del(5)(q15),-6,der(19)t(6;19)(p12;p12) in only 10 mitoses, possibly due to the myelofibrosis. To confirm the karyotype and broaden the scope of karyotyping, SNP-A-based analysis was performed using the Affymetrix Gene Chip Mapping 750K Assay kit and Gene Chip Scan 3000D ×V.2 (affymetrix, Santa Clara, CA). Interestingly, SNP-A-based karyotyping revealed a more complex karyotype (shown in Fig. 1, Table 1) that included monosomy of chromosome 7, losses of 5q and 20q, which have been commonly identified in MDS, and several short lesions were recognized as absence of heterogeneity (AOH) of uncertain significance. In light of the above findings, a diagnosis of myelodysplastic syndrome, refractory anemia with excess blasts-1 (MDS-RAEB1) with a complex karyotype was established. Because of her compromised performance status, examination of her cerebrospinal fluid was not performed at that time.

After several weeks of supportive care and antibiotic therapy for a pulmonary infection, the patient was advised to begin hypomethylating therapy; however, she opted to receive best supportive care with desmopressin maintenance. She developed pancytopenia and progressed to AML 2 months later and finally died of a severe infection.

Discussion

MDS is a group of clonal hematopoietic stem cell diseases characterized by cytopenia, dysplasia and increased risk of development to AML (Vardiman et al. 2009). Although DI in AML patients has been recognized since the 1980s, DI as the only presenting symptom of MDS has rarely been reported. To the best of our knowledge, only 5 cases of MDS with DI have been reported (Keung et al. 2002; Kollen et al. 2003; Nakamura et al. 2004; Sano et al.

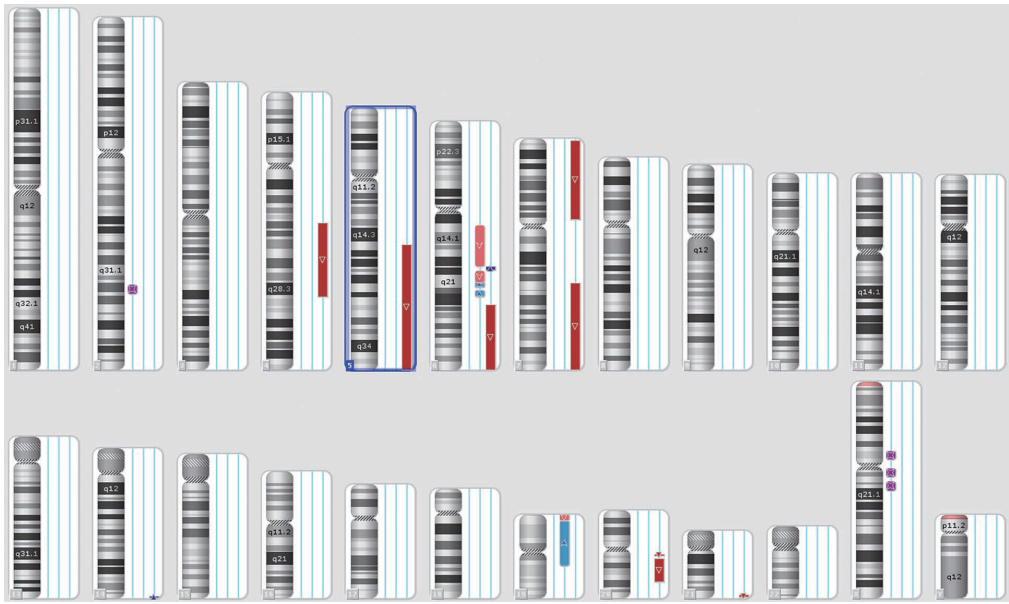

Fig. 1. SNP-A-based karyotyping of the present MDS patient.
Blue indicates gains ≥ 400 Kb; red indicates losses ≥ 400 Kb; purple indicates absence of heterogeneity > 5 Mb.

Table 1. List of the SNP-A-based karyotyping analysis in this patient.

chromosome abnormality	copy number state	Size (Kb)	Significance	Related genes	Location
Loss (5q15-qter)	1	85,784	Abnormalities in MDS	NPM1, EGR1, APC, RPS14, miR-145, miR-146a	94,931,476-180,715,096
Loss (7q22.1-qter)	1	59,470		Neutrophil migration gene; ASNS (asparagine synthetase gene) in 7q21.3-q22.1; ACHE (acetyl cholinesterase); EPO (erythropoietin), PLANH1 (plasminogen activator inhibitor 1) in 7q22; and MET in 7q31.2-31.3	99,649,905-159,119,707
Loss (20q11.22-q13.2)	1.17	18,785		IDI, BCL2L1, ZNF217, BCAS1, topoisomerase 1 (TPO1-), phospholipase C (PLC1), hepatocyte factor nuclear 4 (HNF4) and adenosine desaminase (ADA), Fusion of ASXL1 and TSHZ2 in ider (20q), U2AF1mut overrepresented in MDS with del(20q)	33,994,869-52,779,999
Loss (4q22.1-q31.1)	1.13	48,140	Reported in RAEB, RARS, CMML and RAEB-2	TET2 (4q24) related to MDS/MPN	91,670,808-139,811,079
complex abnormality 6q	1-3	90,378	Loss 6q and Gain 6q have been reported in MDS and sAML patients	PTP4A1(6q12) is highly expressed in AML; Promoter of DDX43(6q13) is hypomethylation in CML; Methylation of CASP8AP2 (6q15) affects the treatment of ALL; DLL1 is associated with leukemia	71,601,341-170,914,297
Loss (7p11.2-pter)	1	53,805	Reported in RARS, RAEB-T, RCMD and sAML patients	Absence of NT5C3 (7p14.3) is associated with hemolytic anemia; IKZF1 (7p12.2) is associated with ALL	1,201,675-55,006,261
Gain (19p13.3-q13.12)	2.3	34,019	Gain(19p) has been reported in AML	STXBP2(19p13.2) is associated with Hemophagocytic Lymphohistiocytosis Familial	2,123,365-36,142,392
Gain (14q32.33)	3	500	Polymorphism in copy number variation	no report on disease-related genes	106,251,486-106,751,178
Loss (19p13.3)	1	1,862	no reports in blood diseases of the acquired CNV	Fusion of TCF3 (19p13.3) and PBX1 (1q23.3) is associated with ALL	260,911-2,123,364
Loss (21q22.3)	1	1,269		ITGB2 (21q22.3) is associated with leukocyte adhesion defects	45,690,635-46,959,141
AOH (2q32.1-q32.2)	2	6,412	reported in the normal human UPD database and no reports in blood diseases with the acquired UPDs	SLC40A1 (2q32.2) is associated with Hemochromatosis type 4	184,406,776-190,818,878
AOH (Xp11.21-p11.23)	2	10,500		ALAS2 (Xp11.21) is associated with X-linked sideroblastic anemia	47,726,921-58,227,320
AOH (Xq11.1-q13)	2	6,128		MIR223 (Xq12) has been reported to be a key gene for the function and differentiation of myeloid cells	62,036,670-68,164,510
AOH (Xq13.2-q21.1)	2	6,304		ABCB7(Xq13.3) is associated with Sideroblastic anemia ATRX(Xq21.1) is associated with Alpha-thalassemia and myelodysplasia syndrome, somatic.	71,811,554-78,115,982

AOH, absence of heterogeneity; RARS, refractory anemia with ring sideroblasts; RAEB-T, refractory anemia with excess blasts in transformation; sAML, secondary AML; RCMD, refractory cytopenia with multilineage dysplasia; UPD, uniparental disomy.

Table 2. Reported cases of MDS patients associated with DI.

Reference	Age/ Gender	WBC (10^9/L)	Hb g/dL	Plt (10^9/L)	% blast in BM	Imaging	Cytogenetics	Treatment of MDS	Outcome of MDS	Treatment & Outcome of DI	Initial diagnosis	Time to AML
(Chuang et al. 2015)	53 male	6.1	9.4	26	16%	no "bright spot"	normal	idarubicin＋ ARA-c umbilical cord blood transplantation	CR	DDAVP maintenance	RAEB-2	> 18 months
(Keung et al. 2002)	31 male	8.8	13.8	206	20%	NA	inv(3)(q21q26),-7	Allogeneic transplantation	Died of infection	Controlled by DDAVP	RAEB-2	NA
(Kollen et al. 2003)	6 male	19	7.9	70	6%	normal	-7	allogeneic transplant	CR	released from DDAVP after transplantation	RAEB-1	NA
(Nakamura et al. 2004)	60 female	1.7	NA	55	1%	attenuate "bright spot"	normal	daunorubicin+ ARA-c	CR after 2 course	released from DDAVP after CR	RCMD	2 months
(Sano et al. 2010)	73 male	2.34	7.2	43	1% (PB)	no "bright spot" enhancive hypothalamus	-7q31	Supportive & control of DI	Died	Controlled by DDAVP＋ fludrocortisone	MDS-U	3 months

NA, data not available; BM, bone marrow; PB, peripheral blood; CR, complete remission; ARA-c, arabinosylcytosine; RCMD, refractory cytopenia with multilineage dysplasia; MDS-U, myelodysplastic syndrome, unclassifiable.

2010; Chuang et al. 2015) and this is the first report of a case of MDS co-existing with CDI, with numerous cytogenetic abnormalities detected by the SNP-A-based analysis. Table 2 presents a review of the 5 cases of MDS with DI described in the literature, including the complete blood counts, blast percentages, cytogenetic features, imaging, treatments and outcomes.

The mechanism of MDS/AML with DI is uncertain. Leukemic infiltration of the pituitary gland or hypothalamus, leukostasis, thrombosis, infection, and hemorrhage may be contributing factors to its etiology. Muller et al. (2002) found that as many as 50% of AML patients showed evidence of pituitary infiltration with leukemia cells at autopsy; however, very few of them had coexisting DI. Further investigation of the molecular pathogenesis of MDS/AML complicated by DI is warranted. Our patient had a 2-month history of polyuria and polydipsia without any symptoms of infection. After admission, her pulmonary infection was well controlled but CDI did not improve. Therefore, the contribution of the pulmonary infection to her CDI is less likely.

Partial or complete monosomy of chromosome 7, detected in 3 out of 5 reported cases, the most commonly reported chromosome abnormality in MDS/AML with DI, may affect the neutrophil migration gene located in the 7q22 gene region and result in the absence of gp130 on neutrophils. This abnormality may lead to increased susceptibility to infection and may be associated with DI, as it impairs the migratory and chemotactic functions of neutrophils (Keung et al. 2002; Harb et al. 2009; Cull et al. 2014). The altered glycosylation of neutrophils and possibly thrombocytes may directly affect ADH release by influencing the modulation of pre-pro-vasopressin into active ADH. Different glycosylation of neutrophils and thrombocytes may also lead to competition at the level of ADH receptors, which contain predicted sites for glycosylation (Kollen et al. 2003). The presence of monosomy 7, a novel finding, was identified in our case by the SNP-A-based analysis. Harb et al. (2009) have found that the outcomes of patients with AML with monosomy 7 and DI was significantly worse than those of patients with monosomy 7 but without DI.

Interestingly, the patient in our report had a deletion of the chromosomal region 20q. Chromosome 20 contains genes responsible for the production of ADH, oxytocin, and their carrier proteins (Ye et al. 2005; Katz et al. 2013). Autosomal dominant neurohypophyseal diabetes insipidus (ADNDI) is caused by a mutation in the arginine vasopressin (AVP-NPII) gene located on chromosome 20. But the AVP-NPII gene is located on chromosome 20p13 encoding for the precursor protein of AVP. At present, there have been no reports related to 20q and DI. The chromosome alteration 20q- has been commonly reported in MDS, but only one AML patient with DI and monosomy 20 has been described (Katz et al. 2013). Therefore, It is of interest to examine the link between DI with MDS and 20q-. Our case is the first report of an MDS patient with DI carrying 20q- and -7 with CDI. Further research is needed to evaluate the connection between chromosomal alterations other than chromosome 7 and 3q abnormalities in MDS with DI.

Previous reports have suggested an association between AML, DI and thrombocytosis. Cull et al. (2014) have described 5 cases of AML with DI with a median platelet count of 407×10^9/L, and the median platelet count for MDS with DI has been reported to be 80×10^9/L (Table 1). Our patient was not found to have any abnormality of the 3q locus or aberrant EVI gene expression. However, she presented with an elevated platelet count on admission and had a remarkable history of deep venous thrombosis 4 months before admission, which may have partly contributed to her central DI. It is uncommon for AML or MDS patients to have a normal or high platelet count. An associ-

ation between thrombocytosis and structural abnormalities at chromosome locus 3q has been well described in the "3q21q26 syndrome". In this syndrome, the EVI-1 gene is rearranged, resulting in an abnormally active fusion protein that appears to drive leukemogenesis and dysmegakaryopoiesis (Keung et al. 2002).

The prognosis of MDS with DI is very poor based on its similar cytogenetic abnormality as those observed in AML with DI, which usually indicating a rapid transition to AML and resistance to regular chemotherapy (Cull et al. 2014). The generally accepted strategy for MDS/AML patients with DI is to control the DI and initiate chemotherapy followed by allogeneic hematopoietic stem cell transplantation. DI symptoms could subside once the underlying MDS were cured, or the patient may require permanent desamine-8-D-arginine vasopressin (DDAVP) maintenance. In the 5 reported cases of MDS with CDI, 3 patients were treated with allogeneic hematopoietic stem cell transplantation and 2 achieved complete remission (CR) for MDS, 1 died from transplantation related infection. One of the 5 patients achieved CR after 2 courses of induction and was released from DDAVP. The one with advanced age was given supportive therapy and died of AML transformation.

By combining SNP-based microarray analysis with metaphase cytogenetics (MC), we uncovered additional MDS-associated cytogenetic abnormalities and some changes of unknown significance in this MDS patient with DI, especially those associated with monosomy 7 and AOH. Considering the small size of AOH and absence of germline controls in our patient, it is difficult to judge the AOH from somatic or germline (Maciejewski et al. 2009). Until now, we have been unable to associate AOH with MDS and DI. According to some authors, combined SNP-A karyotyping with routine MC in MDS improved the cytogenetic detection of del(5q), monosomy 7, del(7q), trisomy 8 and del(20q) (Makishima et al. 2010). The significant diagnostic and prognostic contributions of SNP-A-detected defects in MDS and related diseases underscore the utility of SNP-A when combined with MC in hematologic malignancies (Tiu et al. 2011). In our case, monosomy 7 was not found by MC, but detected by the SNP-A-based karyotyping. Recent whole-exon sequencing (WES) and expression analysis of both cases with deletions and those with an apparently normal diploid chromosome 7 have demonstrated the various associations of the loss of heterogeneity (LOH) of 7q with or without concomitant mutations in genes located in the 7q region with patient prognosis (Hosono et al. 2014). The SNP-A analysis achieves superb resolution and can detect copy number-neutral AOH or LOH, thereby overcoming shortcomings such as fewer mitoses, myelofibrosis in MC or fluorescence in situ hybridization (FISH). Thus, application of this technique to assess MDS patients with DI will help us to further elucidate the pathogenesis of MDS and DI.

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Conflict of Interest

The authors declare no conflict of interest.

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