

Acute myeloid leukemia with monosomy 7, ectopic virus integration site-1 overexpression and central diabetes insipidus: A case report

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Abstract. Central diabetes insipidus (DI) is a rare complication in patients with acute myeloid leukemia (AML), typically occurring in patients with abnormalities of chromosomes 3 or 7. The association between AML with monosomy 7 and DI has been described in a number of studies; however, DI has been rarely reported in cases of ectopic virus integration site-1 (*EVII*)-positive AML with monosomy 7. The current study reports a case of AML with monosomy 7 and *EVII* overexpression, with central DI as the initial symptom. The patient was an 18-year-old female who presented with polyuria and polydipsia. Bone marrow aspiration revealed 83.5% myeloperoxidase-positive blasts without trilineage myelodysplasia. The karyotype was 45,XX,-7, and the patient presented monosomy 7 and *EVII* overexpression (-7/*EVII*⁺) without 3q aberration. Treatment with induction therapy was unsuccessful. To the best of our knowledge, this is the second case of DI-AML with -7/*EVII*⁺ and without a 3q aberration. The possible mechanisms associated with *EVII*, monosomy 7 and DI were investigated.

Introduction

Acute myeloid leukemia (AML) represents a group of myeloid neoplasms characterized by the accumulation of myeloblasts in the bone marrow and/or blood (1). Central diabetes insipidus (DI) is a rare complication observed in <0.6% of patients with AML (2,3), which typically occurs in patients with abnormalities in chromosomes 3 or 7 (4-7). Central DI is a condition characterized by extreme thirst and excessive urination, that is caused by a deficiency of antidiuretic hormone (ADH) (8). A number of case

studies have described an association between DI and AML with monosomy 7 (4,6,7,9,10); however, DI has been rarely reported in cases of ectopic virus integration site-1 (*EVII*)-positive AML with monosomy 7. The *EVII* gene is located on chromosome 3q26 and encodes a 1,051-amino acid DNA-binding phosphoprotein, which functions as a transcription factor (11,12). Groschel *et al* (13) reported that *EVII* overexpression is observed in 10.7% AML patients. The present study reports the case of an 18-year-old female suffering from AML with monosomy 7 and *EVII* overexpression (-7/*EVII*⁺) without 3q aberration, who presented with central DI as the initial symptom. In addition, the present study investigated the possible mechanisms associated with *EVII*, monosomy 7 and DI.

Case report

In December 2012, an 18-year-old female presented at West China Hospital (Chengdu, China) with complaints of fatigue, ecchymosis, polyuria and polydipsia lasting for two months. A physical examination performed upon admission revealed dry skin, indicating dehydration. A complete blood count revealed a white cell count of 151.93x10⁹/l, with 84% peripheral blasts, a hemoglobin level of 80 g/l and a platelet count of 139x10⁹/l. In addition, electrolyte tests identified a serum sodium level of 162.4 mmol/l (indicating the presence of hypernatremia), serum osmolality level of 342 mOsm/kg and urine osmolality level of 128 mOsm/kg. Magnetic resonance imaging of the brain revealed mild thickening of the pituitary stalk (Fig. 1), while cerebrospinal analysis was negative for leukemia. Central DI was suspected, and the patient was administered desmopressin acetate tablets (2 mg; Minirin; Ferring International Center SA, Saint-Prex, Switzerland) orally, three times a day. The polyuria, polydipsia and dry skin resolved, with normalization of serum sodium and serum osmolality levels. Bone marrow smear tests indicated a morphological diagnosis of AML with 83.5% blasts (Fig. 2). Cytochemical staining was negative for peroxidase and positive for periodic acid-Schiff (Baso Diagnostics Inc., Zhuhai, Taiwan). Flow cytometric analysis revealed 88% blasts in the total nucleated cell population expressing cluster of differentiation (CD) 34, human leukocyte antigen (HLA)-DR, CD13, CD117 and CD123 (data not shown), and a diagnosis of AML with minimal differentiation [French-American-British

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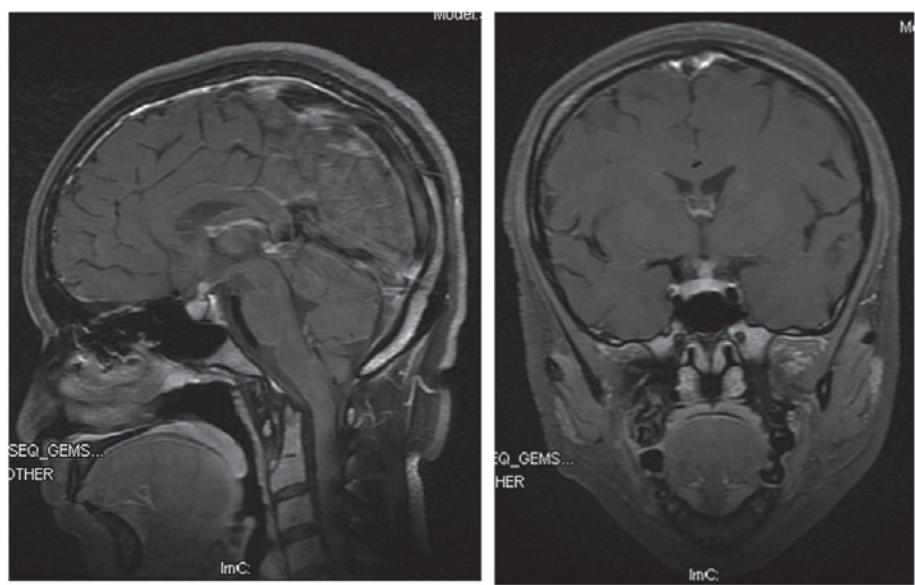


Figure 1. Magnetic resonance imaging of the brain (sagittal and coronal scans) revealed a thickened pituitary stalk.

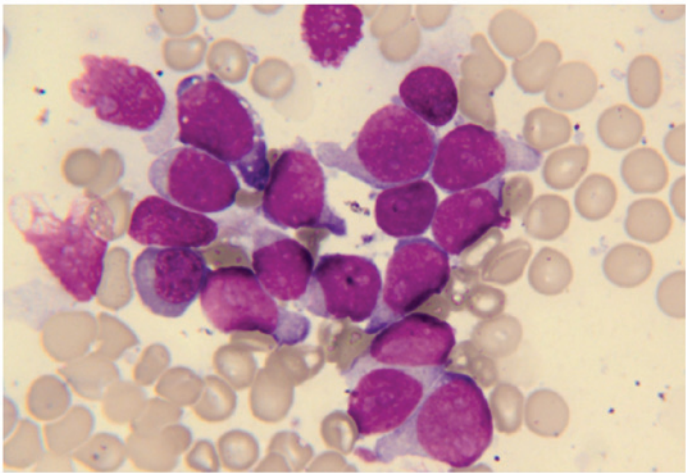


Figure 2. Bone marrow smear test revealed the presence of a high number of myeloblasts, which indicates the diagnosis of acute myeloid leukemia.

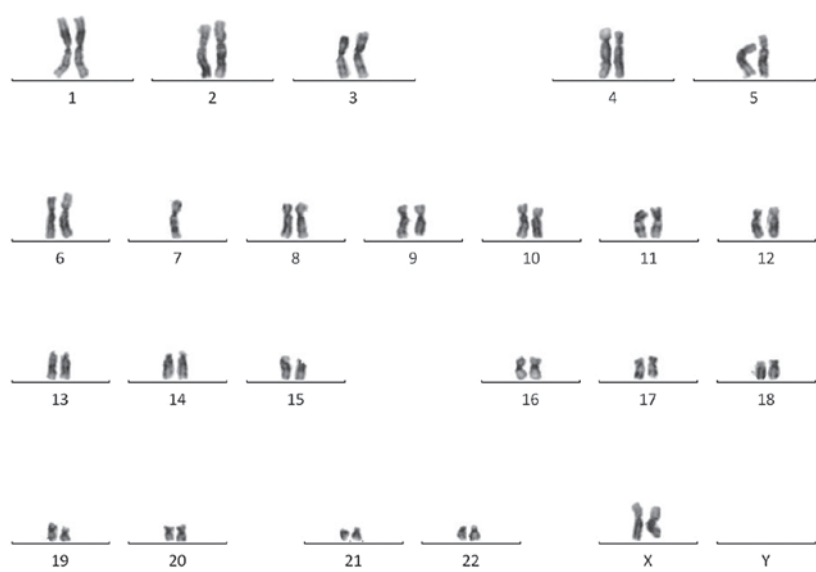


Figure 3. Karyotype of G-banded subclone with monosomy 7.

classification, AML-M0 (14)] was determined. Trilineage dysplasia was unremarkable, while a cytogenetic analysis revealed a monosomy karyotype, 45,XX,-7 (Fig. 3). The patient was screened for fusion genes, revealing that *EVII* and T-cell leukemia homeobox 1 were positive, whereas *FLT3/ITD*, *C-KIT D816V*, nucleophosmin and CCAAT/enhancer binding protein α were negative. Furthermore, the patient had a family history of acute lymphocytic leukemia (pre-B), since the patient's father had been diagnosed with the disease at West China Hospital one year before the present diagnosis. Cytogenetic analysis and genetic screening of the bone marrow of the patient's father was performed to identify whether a common oncogene was present, however the results were unremarkable.

Subsequently, the patient was subjected to an initial cycle of induction chemotherapy with daunorubicin (45 mg/m², days 1-3) and cytarabine (200 mg/d, days 1-7); however, remission was not achieved. A second cycle of induction chemotherapy was administered using the FLAG regimen (50 mg fludarabine, days 1-5; 2 g cytarabine, days 1-5; 300 μ g granulocyte colony-stimulating factor, days 0-15) with no response. Treatment with arsenic trioxide (10 mg, days 1-21) and lenalidomide (10 mg, days 1-21) also produced no response. Without improvement or significant deterioration, the patient's platelet count remained high (83x10⁹/l - 194x10⁹/l) following chemotherapy. Due to the refractoriness to chemotherapy and the high risk associated with transplantation, the patient was reluctant to undergo allogeneic stem-cell transplantation, despite her sibling being an HLA match. Therefore, the patient continued to take desmopressin acetate tablets, and palliative care with low-dose cytarabine and supportive treatment were administered. However, the patient succumbed to a severe pulmonary infection 8 months after diagnosis.

Discussion

AML associated with DI (DI-AML) rarely occurs. The association between DI-AML and cytogenetic aberrations has been reported in a number of studies (1-3). The most common aberrations are monosomy 7 and 3q alterations. Montecucco *et al* (15) and de la Chapelle *et al* (9) reported that 77% of DI-AML cases were associated with monosomy 7q and 44% of cases were associated with 3q alterations. In addition, Piccin *et al* (16) reviewed previously published reports of DI-AML, revealing that all 76 cases had acquired monosomy 7. The finding of the aforementioned studies indicate that monosomy 7q alterations may be a common 'chromosomal determinant' for DI-AML onset. DI-AML patients with 3q aberrations have a number of common characteristics, including age (29-52 years), normal or high platelet count, hyperleukocytosis, trilineage myelodysplasia, no central nervous system involvement, failure to respond to first-line treatment or early relapse, and poor prognosis (17,18). These features are termed 3q21q26 syndrome. The findings of the current study are consistent with such features, with the exception of trilineage myelodysplasia and 3q aberration. However, the patient also demonstrated *EVII* overexpression and monosomy-7 (-7/*EVII*⁺), consistent with one of the two cases reported by Piccin (15). To the best of our knowledge, this is the second case of DI-AML with -7/*EVII*⁺ without a 3q aberration.

The *EVII* gene is located on 3q26 and codes for a 1,051-amino acid DNA-binding phosphoprotein, which

functions as a transcription factor (11,12). Groschel *et al* (13) demonstrated that *EVII*⁺ is associated with specific chromosome abnormalities, including inv(3)/t(3;3), monosomy 7 and 11q23 translocations. *EVII*⁺ was detected in 21/23 AML patients with inv(3)/t(3;3) and in 33/38 AML patients with monosomy 7. The role of *EVII* remains unclear; however, inappropriate *EVII* activation, in combination with other undefined genetic alterations, are hypothesized to result in low levels of antidiuretic hormone (ADH) (18). As ~90% of circulating ADH is associated with platelets, it is postulated that platelet ADH originates in the hypothalamus and that chromosome 3 abnormalities are associated with dysthrombopoiesis, which may result in alterations in ADH levels or function (7,19,20). However, this does not explain why DI-AML patients without 3q alterations exhibit aberrations in ADH levels or function.

In the present study, the patient exhibited no cytogenetic evidence of chromosome 3 abnormalities. Curley *et al* (21) reported a case of DI-AML with t(3;3)(q21;q26) and monosomy 7 that presented *EVII* overexpression at the onset; however, *EVII* overexpression was not detected upon AML relapse and DI did not recur. This indicates that *EVII* overexpression may be involved in the development of DI in AML patients. The prognosis of DI-AML is poor and patient survival, regardless of karyotype, is extremely low compared with a similar cohort of AML patients without DI. Monosomy 7 separates the disease into two entities (7). Patients with monosomy 7 tend to have a poorer complete remission (CR) rate and outcome compared with patients with other aberrations (7). Gröschel *et al* (13) reported that 31/33 patients with -7/*EVII*⁺ AML failed to achieve CR following the first induction therapy, and 31 patients succumbed to the disease after a median period of 8.6 months. All patients with -7/*EVII*⁺ AML had a poor survival rate [two-year relapse-free survival (RFS), 0%; two-year overall survival, 0%]. Additionally, patients with *EVII*⁺ AML who received allogeneic stem cell transplantation during the first CR had significantly improved five-year RFS (33±10% vs. 0%) (13). The response to treatment and survival time in the present study are similar to the results of the study by Groschel *et al* (13).

In the current study, the case of an AML patient with monosomy 7 and *EVII* overexpression, who exhibited central DI as the initial symptom, was presented. Treatment with induction therapy was unsuccessful. This case suggests that the presence of -7/*EVII*⁺ may be involved in the development of DI-AML, which is a rare syndrome, and indicates an extremely poor prognosis. The association between *EVII* overexpression and poor prognosis of AML requires further investigation and thus, the establishment of aggressive treatment approaches, including stem cell transplantation, and novel clinical trials are required.

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