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**Title:**

Acute myeloid leukaemia presenting with diabetes insipidus

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**Case:**

A 41-year-old male was referred to an endocrinologist for routine fertility review. He had a history of glucose-6-phosphate dehydrogenase deficiency. Examination revealed a BMI of 30 kg/m<sup>2</sup>, sparse facial, chest, axillary and pubic hair, preserved scalp hair, gynoid adipose distribution, bilateral gynaecomastia, small testicular volumes (12ml), a normal penis and intact visual fields. Investigations showed an undetectable total testosterone and inappropriately low gonadotropin levels, confirming a diagnosis of secondary hypogonadotropic hypogonadism. Other pituitary hormone tests were unremarkable. Magnetic resonance imaging (MRI) of the pituitary showed a 3mm Rathke's cleft cyst and preservation of the posterior pituitary bright spot (Figure 1A). He was commenced on HCG- $\alpha$  1500 U twice per week and five months later follitropin- $\alpha$  100 U. He had azoospermia at 3 months of follitropin therapy.

Eight months after the initial endocrine review he presented with a one month history of polydipsia and polyuria, estimated at 12 litres per day, with associated lethargy and easy bruising, but no headaches or visual changes. Serum sodium, osmolality, glucose and calcium were within normal limits, with a low urinary sodium and osmolality. He had persistent hypogonadotropic hypogonadism but no other pituitary hormone abnormalities; however a full blood count showed 28% circulating blasts. A bone marrow biopsy confirmed infiltration with 86% myeloblasts consistent with a diagnosis of acute myeloid leukaemia (AML) with inv(3)(q21.3q26.2) and monosomy 7.

A water deprivation test was performed to investigate the polyuria. Six hours into the test the patient remained polyuric despite more than 3% body weight loss and a serum osmolality of

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302 mosm/kg. His paired urine osmolality was 154 mosm/kg. After the administration of 4µg intravenous desmopressin his urine osmolality increased to 538 mosm/kg with a reduction in urine output and plateau in body weight (Table 1). A repeat pituitary MRI showed a slightly thickened pituitary stalk, stable Rathke's cyst, and absence of the pituitary bright spot (Figure 1 B). There was no clinical indication for lumbar puncture to investigate for central nervous system (CNS) involvement due to the absence of enhancing lesions or extramedullary lesions on imaging. Additionally this was unlikely to alter management given the standard induction chemotherapy regimen was already CNS penetrative. The diagnosis of central DI was determined to be associated with AML as investigations for inflammatory and infiltrative pathologies was negative. He was commenced on oral desmopressin with good effect. A surgical testicular sperm recovery attempt immediately prior to chemotherapy did not yield sperm. Two cycles of induction with high dose cytarabine in combination with idarubicin were required to obtain remission before he moved onto sibling allogeneic transplantation using busulphan and cyclophosphamide conditioning. Bone marrow examination at 30 and 100 days post-transplant revealed morphological and cytogenetic remission. All symptoms of DI resolved and desmopressin was ceased. Repeat MRI showed return of the posterior bright spot and a pituitary stalk of normal thickness. Biochemical hypogonadotropic hypogonadism persisted at this time but was uninterpretable in the context of systemic illness and recent chemotherapy.

**Discussion:**

DI is a rare complication of haematological malignancies. Central DI is believed to occur in 0.6%(1) of patients with leukaemia. The gene for anti-diuretic hormone is located at the cytogenetic location 20p13, however most reports describe patients with the combination of

AML and DI having cytogenetic aberrations  $\text{inv}(3)(\text{q}21.3\text{q}26.2)$  and monosomy 7 (2), with our patient's cytogenetics in keeping with this finding.

Outcomes appear to be worse in patients with AML and DI. AML with  $\text{inv}(3)(\text{q}21.3\text{q}26.2)$  accounts for 1.4% of AML(3) and is associated with thrombocytosis and trilineage dysplasia. A study of 31 patients with AML and DI classified patients based on the presence or absence of chromosome 7 aberrations(2) and found reduced survival in those with monosomy 7. Monosomy 7 is commonly seen as a secondary genetic lesion in patients with AML with  $\text{inv}(3)(\text{q}21.3\text{q}26.2)$  and is associated with an even poorer prognosis in this already poor prognostic group(4). One study suggests the presence of monosomy 7 in AML with  $\text{inv}(3)(\text{q}21.3\text{q}26.2)$  may also increase the risk of DI and may represent a unique disease (5) and patients affected may need surveillance for DI.

Pathogenic mechanisms proposed for the development of DI in AML include leukemic infiltration of the pituitary, interference with ADH synthesis, and abnormal thrombopoiesis influencing hormone levels. Leukemic infiltration was reported in 52 deceased patients with AML who had pituitary resection at autopsy (6). Twenty-four (46.1%) cases had peri-pituitary involvement but it is unclear if any of these cases had DI. In 1971 Miller described a patient with AML and concurrent DI, however autopsy findings showed bilateral infarcts in the supraoptic and paraventricular nuclei to be the cause of DI in that case (7). De la Chappelle noted two cases in 1987 that underwent autopsy (8). Monosomy 7 with leukemic infiltration was confirmed in one case. In 2012 Lin H et al reported a patient who had a relapse of AML post allogeneic bone marrow transplantation who also underwent resection of a 2cm sella mass for compressive symptoms (9). The patient had preoperative pituitary biochemistry

suggestive of anterior hypopituitarism but no DI. MRI showed posterior bright spot preservation suggestive of stored ADH, however histology revealed leukemic pituitary infiltration and positive immunohistochemically staining for myeloid leukemic markers. Pituitary imaging findings have been variable with less than 50% of cases of AML and DI having abnormal computed tomography or MRI in one series (2). While leukemic infiltration is a plausible mechanism, the data are inconclusive. The absence and re appearance of posterior bright spot and transient pituitary thickness on our patient's imaging corresponding with the onset of AML and subsequent disappearance of the known associated cytogenetic abnormality makes infiltration a potential explanation for DI. Despite an absence of confirmed AML CNS involvement this may have been borne out had more invasive investigations been performed. A case of DI and AML has been reported with radiological abnormalities suggestive of CNS involvement but subsequent absence of posterior hypophysis infiltration (10).

Given the increased frequency of cases with AML with  $inv(3)(q21.3q26.2)$  and DI, some authors have postulated that an ectopic virus integration (EV-1) site gene may play a role in pathogenesis. This gene is transcriptionally activated in AML with  $inv(3)(q21.3q26.2)$  (11). It encodes a 1051 amino acid that serves as a transcription factor. Overexpression of this factor is postulated to result in low levels of ADH (12). It also has direct implications for abnormal megakaryopoiesis(13), and given that 90% of ADH is bound to platelets, alteration in platelet number and quality could affect ADH levels or function. Keung described five cases of AML with  $inv(3)(q21.3q26.2)$  in consecutive cytogenetic studies of AML and myelodysplastic syndromes, two cases presented as sole abnormalities and three cases were associated with monosomy 7 (14). Only one case was associated with central DI. Our

patient's loss of posterior bright spot on imaging may support the hypothesis of an overexpressed transcription factor associated with AML affecting ADH synthesis, however a normal platelet count prior to commencement of chemotherapy make the pathogenesis of impaired ADH platelet binding unlikely.

Finally, our patient received gonadotropins treatments, two to three times per week with HCG and follitropin given 8 and 3 months preceding a diagnosis of AML respectively. Small embryonic-like stem cells are reported to express gonadotropin receptors that responded *in vivo* to gonadotropin stimulation (15) and pituitary-secreted gonadotropins may stimulate migration, adhesion and proliferation of established human leukemic cell lines (16), however to date there is no compelling evidence that pituitary gonadotropins are linked to development of hematopoietic malignancies.

#### Summary:

We present a patient with idiopathic hypogonadotrophic hypogonadism treated with gonadotropins who later developed DI and AML. To our knowledge it is the first reported case with this constellation of pathologies. It is unclear whether this is a chance association or if there are causative links, but is consistent with the increasing published association between DI and AML with  $inv(3)(q21.3q26.2)$  and chromosome 7 abnormalities. Potential pathogenic mechanisms in this case include direct posterior pituitary infiltration and over expression of transcription factors associated with AML affecting ADH synthesis. DI is a recognised association of haematological malignancies and should be considered in a patient presenting with polydipsia and polyuria.

Declaration of interest: no conflicts of interest to disclose

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Author contributions:

Dr Michele Bardin drafted the case report and performed the literature review. Associate Professor Chris Yates and Professor Robert McLachlan contributed to editing of the case report. Professor David Ritchie provided specialist haematology editorial input.

There are no conflicts of interest to disclose.


## References

1. Kimmel DW, O'Neill BP. Systemic cancer presenting as diabetes insipidus. Clinical and radiographic features of 11 patients with a review of metastatic-induced diabetes insipidus. *Cancer*. 1983;52(12):2355-8.
2. Harb A, Tan W, Wilding GE, Battiwalla M, Sait SN, Wang ES, et al. Acute myeloid leukemia and diabetes insipidus with monosomy 7. *Cancer Genet Cytogenet*. 2009;190(2):97-100.
3. Lugthart S, Groschel S, Beverloo HB, Kayser S, Valk PJ, van Zelderen-Bhola SL, et al. Clinical, molecular, and prognostic significance of WHO type inv(3)(q21q26.2)/t(3;3)(q21;q26.2) and various other 3q abnormalities in acute myeloid leukemia. *J Clin Oncol*. 2010;28(24):3890-8.
4. Anelli L, Pasciolla C, Zagaria A, Specchia G, Albano F. Monosomal karyotype in myeloid neoplasias: a literature review. *Onco Targets Ther*. 102017. p. 2163-71.
5. Chung HJ, Seo EJ, Kim KH, Jang S, Park CJ, Chi HS, et al. [Hematologic and clinical features of 3q21q26 syndrome: extremely poor prognosis and association with central diabetes insipidus]. *Korean J Lab Med*. 2007;27(2):133-8.
6. Masse SR, Wolk RW, Conklin RH. Peripituitary gland involvement in acute leukemia in adults. *Arch Pathol*. 1973;96(2):141-2.
7. Miller VI, Department of Pathology EUSoM, Atlanta, Ga., Campbell WG, Department of Pathology EUSoM, Atlanta, Ga., Department of Pathology EUSoM, Atlanta, Ga. 30322. Diabetes insipidus as a complication of leukemia: A case report with a literature review. *Cancer*. 2017;28(3):666-73.
8. de la Chapelle A, Lahtinen R. Monosomy 7 predisposes to diabetes insipidus in leukaemia and myelodysplastic syndrome. *Eur J Haematol*. 1987;39(5):404-11.

9. Lin HW, Shih SR, Yao M, Huang TS. Relapse of acute myeloid leukemia at the pituitary gland: a case report and review of literature. *Endocr Pathol.* 2012;23(3):172-6.
10. Kubota Y, Ichinohe T, Yoshimura M, Itamura H, Hisatomi T, Fukushima N, et al. Acute myeloid leukemia with t(3;8)(q26;q24) complicated by diabetes insipidus. *Ann Hematol.* 95. Germany2016. p. 653-5.
11. Ogawa S, Kurokawa M, Tanaka T, Mitani K, Inazawa J, Hangaishi A, et al. Structurally altered Evi-1 protein generated in the 3q21q26 syndrome. *Oncogene.* 1996;13(1):183-91.
12. Ma H, Yang J, Xiang B, Jia Y. Acute myeloid leukemia with monosomy 7, ectopic virus integration site-1 overexpression and central diabetes insipidus: A case report. *Oncol Lett.* 92015. p. 2459-62.
13. Jolkowska J, Witt M. The EVI-1 gene--its role in pathogenesis of human leukemias. *Leuk Res.* 2000;24(7):553-8.
14. Keung YK, Buss D, Powell BL, Pettenati M. Central diabetes insipidus and inv(3)(q21q26) and monosomy 7 in acute myeloid leukemia. *Cancer Genet Cytogenet.* 2002;136(1):78-81.
15. Mierzejewska K, Borkowska S, Suszynska E, Suszynska M, Poniewierska-Baran A, Maj M, et al. Hematopoietic stem/progenitor cells express several functional sex hormone receptors--novel evidence for a potential developmental link between hematopoiesis and primordial germ cells. *Stem Cells Dev.* 2015;24(8):927-37.
16. Abdelbaset-Ismail A, Borkowska S, Janowska-Wieczorek A, Tonn T, Rodriguez C, Moniuszko M, et al. Novel evidence that pituitary gonadotropins directly stimulate human leukemic cells--studies of myeloid cell lines and primary patient AML and CML cells. *Oncotarget.* 72016. p. 3033-46.

Table I:

13:45 4ug subcutaneous DDAVP



Time	0800	0900	1000	1100	1200	1300	1400	1500	1600
Weight (kg)	98.1	97.5	96.5	96.1	95.9	95.5	94.3	95.0	94.8
Urine Vol (ml)	500	450	750	150	450	350	250	50	100
Urine Na (mmol/L)	20	20	28	30	33	35	52	58	58
Urine Osm (mosm/kg)	110	123	122	132	143	154	247	491	538
Urine SG	<1.005	<1.005	<1.005	1.005	1.005	1.005	1.010	1.020	1.020
Serum Na (mmol/L)	142	143	148	148	144	145	144	150	145
Serum Osm (mosom/kg)	297	298	301	303	301	302	306	304	305
BP sitting	118/77	136/87	146/86	127/92	131/90	142/93	144/98	148/98	138/90
BP standing	121/85	121/84	132/91	120/87	120/88	127/86	128/87	132/93	148/98

Table 1: A controlled water deprivation test suggesting central diabetes insipidus with urinary concentration within 2.5 hours of DDAVP administration.

Figure 1:

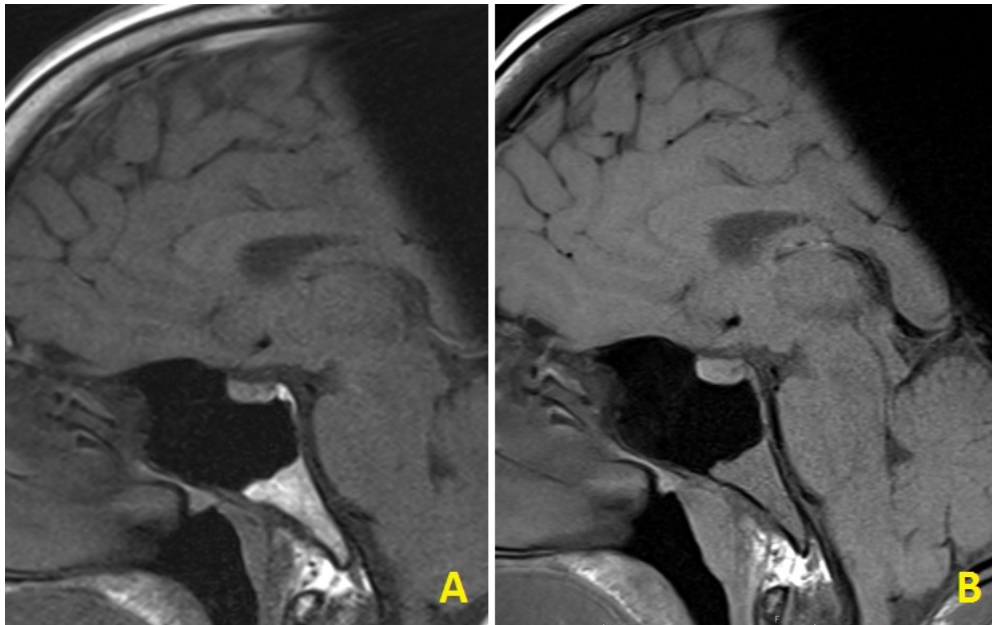


Figure 1: Sagittal magnetic resonance images of the pituitary: (A) 8 months prior to the diagnosis of AML with preservation of the posterior pituitary bright spot containing ADH. (B) At the time of the diagnosis of AML and DI with loss of the posterior bright spot and a slightly thickened pituitary stalk.

## Abstract:

A 41-year-old gentleman was diagnosed with hypogonadotropic hypogonadism managed with gonadotropins after routine fertility review. Eight months later he presented with new polydipsia and polyuria, lethargy, and easy bruising. A full blood count showed 28% circulating blasts. A bone marrow biopsy confirmed a diagnosis of acute myeloid leukaemia (AML) with  $inv(3)(q21.3q26.2)$  with additional monosomy 7. Central diabetes insipidus (DI) was diagnosed following a water deprivation test. Pituitary MRI showed a slightly thickened pituitary stalk, stable Rathke's cyst, and new absence of the pituitary bright spot. The patient was commenced on desmopressin and induction chemotherapy, subsequently requiring a bone marrow transplant. Bone marrow examination at 100 days post-transplant revealed cytogenetic remission. All symptoms of DI resolved and MRI showed return of the posterior bright spot and a pituitary stalk of normal thickness. Biochemical hypogonadotropic hypogonadism persisted but was uninterpretable in the context of systemic illness and recent chemotherapy. DI is a rare complication of haematological malignancies and the prevalence and pathophysiology of DI in this context are poorly understood. Pathogenic mechanisms proposed include leukemic infiltration of the pituitary, interference with ADH synthesis, and abnormal thrombopoiesis influencing hormone levels. Particular cytogenetic abnormalities such as  $inv(3)(q21.3q26.2)$  and monosomy 7 appear to be more commonly associated with DI and also appear to confer worse outcomes. Aetiologies in the literature remain elusive but as DI is a recognised association of haematological malignancies it should be considered in a patient presenting with polydipsia and polyuria.

(i) Title: Acute myeloid leukaemia presenting with diabetes insipidus: Case report and review of the literature.

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