Central diabetes insipidus as a manifestation of AML secondary to Temodar therapy for pancreatic neuroendocrine tumor

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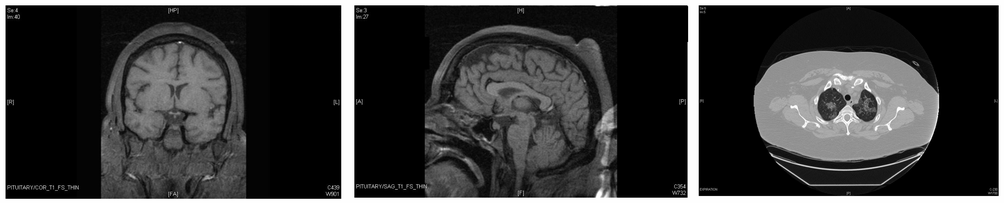
Introduction: Central diabetes insipidus (CDI), as a manifestation of acute myeloid leukemia, is rare, but has been noted in association with dysmegakaryopoiesis and chromosomes 3 abnormalities. Particularly in association with monosomy 7, the association is now considered to be more than fortuitous. A distinct mechanism has not been defined for the etiology of CDI, however it has been suggested that different cytogenetics may act through different disease processes to manifest in this rarely seen phenomenon. Our case illustrates a case of CDI with chromosome 3 abnormalities, in a patient who developed acute myelocytic leukemia following treatment with Temodar for a pancreatic neuroendocrine tumor.

Case: 35-year-old female, with past medical history of pancreatic neuroendocrine tumor (treated with a protracted course of Temodar), diabetes mellitus, hypertension, hyperlipidemia, and hypothyroidism, presented with progressive shortness of breath, and productive cough with subsequent treatment with antibiotics for a possible community-acquired pneumonia. RSV was eventually defined after CT revealed ground glass opacities and bronchoscopy washings grew the virus. Treatment was changed to ribavirin with resolution of RSV pneumonia. Also, on admission, acute kidney injury was present, and urine output was noted to be persistently greater than 8 L per day. Central diabetes insipidus was suspected. MRI of the brain with special attention to the pituitary was without abnormality, and a water deprivation test was inconclusive likely due to acute kidney injury. The patient was also noted to have a persistent leukocytosis with immature cells present in peripheral blood. A subsequent bone marrow examination revealed acute myelocytic leukemia, and cytogenetics on the bone marrow biopsy demonstrated inversion of 3 q and presence of 15% EV1 probe positivity. This mutation has been associated with thrombocytosis and dysmegakaryopoiesis, which has led to the suggestion of a platelet-mediated mechanism of CDI. The patient was started on induction chemotherapy with ARA C and Danourubicin, and subsequently she had notable improvement of her polyuria, along with resolution of hypernatremia, and acute kidney injury. 38% blasts on repeat bone marrow aspirate prompted re-induction with high dose Ara-C. She is currently in remission after 2 cycles of HIDAC and last bone marrow aspirate revealed normal cytogenetics with resolution of all features of diabetes insipidus.

A B C



Images A and B are sections from the patient's pituitary MRI and are without abnormality.
Image C is from the patients CT chest showing ground glass infiltrates

Discussion: Acute Myelogenous Leukemia is a relatively rare cancer, however approximately 10,000 new cases are diagnosed in the United States are each year with incidence greatly increasing after age 65 probably related to failure of innate DNA repair mechanisms with aging, in conjugation with the requirement of DNA fracture and chromosome reassembly for the occurrence of normal hematopoiesis. The majority of AML diagnoses occur de novo with secondary cases resulting from either transformation of pre-existing hematologic disorder or due to toxic exposure (chemotherapy, radiation, environmental toxins, etc). Often times, these secondary cases are more refractory to therapy. The World Health Organization classifies AML as a blast count of 20% or greater, further characterizing the disease by genetic and morphologic features categorizing it in one of the following four categories: AML with recurrent genetic abnormalities (category I), AML with multilineage dyplasia (category II), AML developing secondary to therapeutic intervention (category III), and AML not otherwise categorized (category IV). Our current case is representative of category III, and is most likely related to protracted use of Temodar.

AML most commonly presents with fatigue, however, rarely, central diabetes insipidus may manifest associated with certain cytogenetic abnormalities of chromosome 3 and monosomy 7. These cases are associated with poor prognosis as they are often refractory to chemotherapy. Two distinct mechanisms have been proposed to explain this uncommon presentation of AML. Cases of AML associated with dysmegakaryopoiesis and thrombocytosis along with certain cytogenetic abnormalities suggest a platelet mediated induction of CDI. Approximately 90% of circulating antidiuretic hormone is associated with platelets, and dysmegakaryopoiesis, along with elevated platelet count could be one possible explanation of this disease manifestation. This is thought to be secondary to inappropriate activation of the EVI-1 transcription factor. Other cases have reported imaging changes in the neurohypophysis suggesting that leukemic infiltration causing pituitary dysfunction represents another possible mechanism. One case described persistence of CDI after remission of AML further enforcing that disruption of the posterior pituitary resulted in CDI. Our case was without MRI imaging abnormality, however abnormalities of chromosome 3, dysmegakaryopoiesis, and thrombocytosis were present. Review of these cases suggest that rather than any single process, at least two separate mechanisms exist which lead to the development of CDI in AML.

In conclusion, regardless of mechanism, presence of CDI is a poor prognostic indicator when present in AML. While exact mechanisms of this presentation are not yet completely defined it is likely that different cytogenetic abnormalities result different processes to manifest CDI. Given the dismal outcome of patients presenting with CDI and AML a need for early initiation of aggressive therapeutic interventions would be suggested.

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