

Diabetes Insipidus as Presenting Manifestation of Waldenstrom's Macroglobulinemia

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Abstract

Nephrogenic diabetes insipidus (DI) is characterized by inability of the kidney to concentrate urine due to diminished renal response to vasopressin. We report a patient with diabetes insipidus and hyperviscosity as presenting manifestations of Waldenstrom's macroglobulinemia. After two treatments with plasmapheresis, serum viscosity normalized and the ability to concentrate urine, polyuria, and polydipsia improved. With ongoing chemoimmunotherapy, he has not had a recurrence of DI. Although rare, nephrogenic DI is a complication of hematologic disorders such as Waldenstrom's macroglobulinemia, multiple myeloma and sickle cell anemia.

Keywords: Diabetes insipidus; Waldenstrom's macroglobulinemia

Introduction

Nephrogenic diabetes insipidus (DI) is a syndrome in which the urinary concentrating ability of the kidney is reduced because of diminished renal response to vasopressin. In contrast to central DI, hypothalamic and pituitary gland function are intact and the release of vasopressin in response to stimuli is normal. Urinary concentration requires both the generation of a hypertonic medullary interstitium via active sodium chloride reabsorption by the water-impermeable ascending limb of the loop of Henle, as well as passive reab-

sorption of water in the collecting duct via aquaporin water channels. Insertion of aquaporins into the luminal membrane of collecting duct cells is stimulated by the interaction of circulating vasopressin with the vasopressin receptor on the apical surface of the collecting duct cells [1]. Nephrogenic DI occurs either as a result of inherited abnormalities in the vasopressin receptor or the aquaporins or acquired dysfunction from medications such as lithium or illnesses such as hypercalcemia. We report a case in which nephrogenic DI occurred in the setting of Waldenstrom's macroglobulinemia (WM).

Case Report

A 58-year old male with chronic hepatitis C infection and type II diabetes with neuropathy had two hospitalizations within one month for polyuria, polydipsia, nocturia, hyperglycemia, confusion, and short term memory loss. He reported gradually worsening generalized weakness, dark/blurred vision upon standing up, exertional dyspnea, forgetfulness, and a 13 kg unintentional weight loss. On physical examination, he had mottled appearing skin and dilated retinal veins on fundoscopic exam. On initial presentation he was admitted to the intensive care unit with hyperosmolar non-ketotic acidosis with hyperglycemia (678 mg/dL), elevated creatinine (1.79 mg/dL), and an anion gap of 13.5. After aggressive intravenous volume repletion and intravenous insulin, his blood glucose levels improved, but his 5 L daily polyuria persisted.

One week later, he was re-admitted with similar symptoms and hyperglycemia (453 mg/dL) despite taking increased doses of insulin. After improved glycemic control (90 to 222 mg/dL), the polyuria and polydipsia persisted. Additional laboratory studies included serum sodium 148 mmol/L, creatinine 1.49 mg/dL, and serum osmolality 330 mOsm/kg H₂O (normal range, 275 - 290). Serum vasopressin was 17.0 pg/mL (normal range, 1.0 to 13.3). He was diagnosed with nephrogenic DI based on the appropriately elevated serum vasopressin level and the minimal increase in urinary osmolality after administration of DDAVP (Table 1). The hematology service was consulted because of "slug-

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Table 1. Timeline of Serum and Urine Osmolality and Sodium, IgM, and Viscosity

	Pre-treatment	Fluid Restriction	Before DDAVP	After DDAVP	After 1st Plasma-pheresis	After 2nd Plasma-pheresis	After 4 cycles BDR
Serum osmolality (mOsm/kg H ₂ O)	330	323	332			321	314
Serum sodium (mmol/L)	148	151	151			138	137
Serum Glucose (mg/dL)	352	148	163			400	386
Urine osmolality (mOsm/kg H ₂ O)	188	159	222	234		330	863
Urine sodium (mmol/L)	45	37	54	61			
IgM (mg/dL)	2080					1560	287
Viscosity (centiPoise)	> 20				2.7	1.7	1.6

DDAVP: vasopressin; BDR: bendamustine, bortezomib, and rituximab.

gish" blood flow noted during phlebotomy.

The complete blood count was remarkable for hemoglobin of 9.4 g/dL (normal range, 13.5 - 18.0). Serum viscosity was > 20.0 CentiPoise (normal range, 1.4 - 1.8). Cryoglobulins were present with a cryocrit of 33%. He had a monoclonal IgM kappa gammopathy. The quantitative IgM concentration was 2,080 mg/dL (normal range, 46 - 304), with reciprocal suppression of IgG and a normal IgA concentration. Serum free light chains were normal. Hepatitis serologies were positive for hepatitis C antibody and hepatitis C RNA was 4,298,780 IU/mL. A bone marrow biopsy showed well-defined discrete aggregates of predominantly small lymphoid cells with round regular nuclear contours comprising 10% of the cellularity, staining for LCA with a prominent component of cells staining for CD20. CD138-positive plasma cells were present in clusters rimming the lymphoid aggregates, comprising 10-15% of cellularity, and exhibiting monoclonal staining for kappa light chain. The findings were in keeping with lymphoplasmacytic lymphoma. Of note, no evidence of amyloidosis was detected.

The patient underwent plasmapheresis for two consecutive days, with improvement of serum viscosity to 2.7 and 1.7 centiPoise after one and two sessions, respectively, and reduction of his IgM from 2080 mg/dL to 1560 mg/dL after two sessions. His mental status, polyuria, and polydipsia improve after plasmapheresis with a reduction of daily urine volume of 1,650 mL. Urine osmolality increased to 330 mOsm/kg H₂O with a serum osmolality 321 mOsm/kg H₂O and serum sodium 140 mmol/L (Table 1). After 4 cycles of bendamustine, dexamethasone and rituximab chemimmunotherapy over 4 months, his IgM dropped to 287 mg/dL and he did not have any evidence of DI [2].

Discussion

The major presenting symptom of our patient with WM was polyuria/polydipsia due to nephrogenic diabetes insipidus. He was diagnosed with WM due to his IgM kappa gammopathy, elevated quantitative IgM, and his bone marrow biopsy and flow cytometry. DI was demonstrated by persistent low urine osmolality despite fluid deprivation and nephrogenic DI determined by the failure to respond to vasopressin. While renal impairment may have contributed to the concentrating defect, the rapid improvement in urinary concentrating ability with plasmapheresis despite an unchanged estimated GFR excludes renal failure as a major contributor. Remarkably, the low urine osmolality and polyuria both improved within days of initiation of plasmapheresis and normalization of serum viscosity. After four cycles of chemotherapy, the kidney maintained its ability to concentrate urine.

The increased serum viscosity was likely a combination of WM and cryoglobulinemia related to his hepatitis C. In a summary of newly diagnosed patients with WM at

the Dana-Farber Cancer Institute, the upper range for serum viscosity was 7.2 cP [3, 4]; our patient had a serum viscosity of > 20 cP. Cryoglobulinemia can cause an exaggerated temperature-dependent elevation of serum viscosity, as is the case in this report [5]. However, cryoglobulin complex formation should not readily occur in the medulla of the kidney, which is at core body temperature, and therefore should not impact the ability to concentrate urine. In the presence of cryoglobulinemia, serum IgM levels can be underestimated if a warm bath collection is not used [3]. In our case, a warm bath collection was not performed, although the tube was kept at body temperature during the transport to the lab. This may contribute to the discrepancy between the IgM level and serum viscosity.

Renal failure in WM is rare. Classically, WM causes renal failure by intracapillary monoclonal deposition, lymphoplasmacytic infiltration of the interstitium, or amyloidosis. Additionally, WM has been associated with a diverse range of nephropathies, including immunotactoid and non-amyloid fibrillary glomerulopathy, distal renal tubular acidosis, and DI [6-8]. A previous case report noted WM causing DI, but response to vasopressin suggested central DI [6].

While hematologic disorders usually do not cause DI, there is an association between kappa-light chain multiple myeloma and nephrogenic DI [9-11]. Two case reports have reported nephrogenic DI in the setting of renal tubular acidosis (RTA) [9, 10]. This process is likely related to tubular toxicity of filtered light chains. Nephrogenic DI occurring in the amyloidoses has been reported and attributed to amyloid deposition in the peri-collecting duct tissue [12-14]. Histologic evidence of AA was reported in one series and the type of amyloidosis was not reported in the second case report.

Some literature reports DI in hypergammaglobulinemia. In one large series of patients with Sjogren's Syndrome, three patients with polyclonal IgG levels (2,224 mg/dL) had nephrogenic DI and distal RTA [15]. Another case report demonstrated distal RTA and nephrogenic DI in a patient with a polyclonal hypergammaglobulinemia [16]. Since it can occur in polyclonal gammopathy, DI in immunoglobulin-secreting hematologic malignancies is unlikely the result of activity of antibody binding site. A proposed mechanism postulates that tubular dysfunction allows delivery of proteolysis-resistant light chains to the loop of Henle, resulting in impairment in concentration of urine [9]. This does not explain DI in our case as IgM cannot be filtered by the glomeruli and the patient's serum free light chains were normal.

Local ischemia in the medulla can lead to nephrogenic DI. In sickle cell disease, sickling erythrocytes are thought to cause ischemia and micro-infarcts in the medulla, causing distortions of the vasa recta and maximum urine osmolality in water-deprived adults between 400 and 500 mOsm/kg H₂O [17]. We speculate that severe hyperviscosity could cause local ischemia in the vasa recta, impairing its function, and affecting generation of the medullary concentrating

gradient. This is supported by rapid improvement of DI with plasmapheresis and normalization of serum viscosity.

Conclusion

Nephrogenic diabetes insipidus may be the presenting manifestation of Waldenstrom's macroglobulinemia. In our patient, we attribute the DI to hyperviscosity-related impairment in the generation of medullary concentration. The DI resolved rapidly with plasmapheresis.

Disclosures

No conflicts of interest to report.

References

1. Agre P, Kozono D. Aquaporin water channels: molecular mechanisms for human diseases. *FEBS Lett.* 2003;555(1):72-78.
2. Treon SP, Ioakimidis L, Soumerai JD, Patterson CJ, Sheehy P, Nelson M, Willen M, et al. Primary therapy of Waldenstrom macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. *J Clin Oncol.* 2009;27(23):3830-3835.
3. Treon SP. How I treat Waldenstrom macroglobulinemia. *Blood.* 2009;114(12):2375-2385.
4. Treon SP, Branagan AR, Ioakimidis L, Soumerai JD, Patterson CJ, Turnbull B, Wasi P, et al. Long-term outcomes to fludarabine and rituximab in Waldenstrom macroglobulinemia. *Blood.* 2009;113(16):3673-3678.
5. Stone MJ, Bogen SA. Evidence-based focused review of management of hyperviscosity syndrome. *Blood.* 2012;119(10):2205-2208.
6. Chelazzi G. [A case of Waldenstrom's macroglobulinemia complicated by diabetes insipidus]. *Minerva Med.* 1975;66(10):455-469.
7. Audard V, Georges B, Vanhille P, Toly C, Deroure B, Fakhouri F, Cuvelier R, et al. Renal lesions associated with IgM-secreting monoclonal proliferations: revisiting the disease spectrum. *Clin J Am Soc Nephrol.* 2008;3(5):1339-1349.
8. Feringa HH, Ardestani A, Gnanaraj J. Distal renal tubular acidosis in lymphoplasmacytic lymphoma Waldenstrom's macroglobulinemia: a case report. *Cases J.* 2009;2:7198.
9. Hoorn EJ, Zietse R. Combined renal tubular acidosis and diabetes insipidus in hematological disease. *Nat Clin Pract Nephrol.* 2007;3(3):171-175.
10. Minemura K, Ichikawa K, Itoh N, Suzuki N, Hara M, Shigematsu S, Kobayashi H, et al. IgA-kappa type multiple myeloma affecting proximal and distal renal tubules. *Intern Med.* 2001;40(9):931-935.
11. Goranov S, Hristova I, Pencheva K. Nephrogenic diabetes insipidus--prodromal phase of multiple myeloma. *Folia Med (Plovdiv)* 1994; 36(2): 63-6.
12. Neugarten J, Gallo GR, Buxbaum J, Katz LA, Rubenstein J, Baldwin DS. Amyloidosis in subcutaneous heroin abusers ("skin poppers' amyloidosis"). *Am J Med.* 1986;81(4):635-640.
13. Asmundsson P, Snaedal J. Persistent water diuresis in renal amyloidosis. A case report. *Scand J Urol Nephrol.* 1981;15(1):77-79.
14. Carone FA, Epstein FH. Nephrogenic diabetes insipidus caused by amyloid disease. Evidence in man of the role of the collecting ducts in concentrating urine. *Am J Med.* 1960;29:539-544.
15. Ren H, Wang WM, Chen XN, Zhang W, Pan XX, Wang XL, Lin Y, et al. Renal involvement and followup of 130 patients with primary Sjogren's syndrome. *J Rheumatol.* 2008;35(2):278-284.
16. Spruce BA, Baylis PH, Kerr DN, Morley AR. Idiopathic hypergammaglobulinaemia associated with nephrogenic diabetes insipidus and distal renal tubular acidosis. *Postgrad Med J.* 1984;60(705):493-494.
17. Pham PT, Pham PC, Wilkinson AH, Lew SQ. Renal abnormalities in sickle cell disease. *Kidney Int.* 2000;57(1):1-8.