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Pemetrexed-Induced Nephrogenic Diabetes Insipidus

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Abstract

Pemetrexed is an approved anti-metabolite agent, now widely used for treating locally advanced or metastatic non-squamous, non-small cell lung cancer. Although no electrolyte abnormalities are described in the prescribing information for this drug, several case reports have noted nephrogenic diabetes insipidus with associated acute kidney injury. We present a case of nephrogenic diabetes insipidus without severely reduced kidney function and propose a mechanism for the isolated finding. Severe hyponatremia can lead to encephalopathy and osmotic demyelination, and our report highlights the importance of careful monitoring of electrolytes and kidney function in patients with lung cancer receiving pemetrexed.

Index Words

Nephrogenic diabetes insipidus; drug toxicity; proton coupled folate transporters; pemetrexed; adverse drug reaction

Pemetrexed is an anti-folate, anti-metabolite agent, first approved in 2004 by the US Food and Drug Administration in combination with cisplatin for non-resectable pleural mesotheliomas.¹ With additional clinical trial data demonstrating efficacy for treatment of locally advanced or metastatic non-squamous, non-small cell lung cancer, approved indications for its use have expanded.²

Pemetrexed is eliminated almost entirely through the urine by both tubular secretion and glomerular filtration in the original drug form.^{2,3} The largest clinical trial, comprised of 862 participants in the pemetrexed treatment arm, did not report clinically significant increases in acute kidney injury (AKI) or electrolyte abnormalities.⁴ However, several case reports of AKI have surfaced in the kidney and oncology literature.^{5–9} In 2 such cases, accompanying nephrogenic diabetes insipidus was also noted, with the authors suggesting that the modest to severe AKI may have led to distal tubular injury sufficient to explain the nephrogenic diabetes insipidus.^{10,11}

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We report a case of nephrogenic diabetes insipidus without evidence of severely reduced kidney function in a patient with metastatic lung adenocarcinoma. We also discuss a potential mechanism for selective distal tubule toxicity of pemetrexed that could result in nephrogenic diabetes insipidus even in the absence of AKI.

Case Report

A 36 year-old-man was diagnosed with stage IV adenocarcinoma of the lung with diffuse osseous metastases that was initially treated with erlotinib 150 mg/d. With disease progression, his chemotherapy regimen was switched to a combination of carboplatin 572.5 mg/m² (target area under the curve, 6 mg min/mL), pemetrexed 500 mg/m², and bevacizumab 15 mg/kg.^{12,13} Two days after his third cycle of chemotherapy, he experienced copious, watery, non-bloody diarrhea. He had accompanying mucositis with poor oral intake and was admitted for further evaluation. On admission, his vital signs were normal except for tachycardia.

Within 24 hours, the patient's serum sodium rose from 138 to 158 mmol/L; serum creatinine, from 1.3 mg/dL to 1.7 mg/dL (estimated glomerular filtration of 69 ml/min/1.73 m² and 50 ml/min/1.73m², respectively, as calculated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation¹⁴). All other electrolytes were within reference range, as shown in Table 1. He was judged to be volume depleted, and received 10L of intravenous (IV) 0.9% saline over 48 hours. After confirmation of the absence of *C. difficile* or *E. coli* infection, loperamide and opium tincture were prescribed as symptomatic treatments.

With saline repletion, the patient's serum creatinine returned to baseline (1.1–1.2 mg/dL; eGFR, 77–85 ml/min/1.73 m²) by hospital day 4; however serum sodium continued to rise to 163 mmol/L. Despite administration of between 5–7L/day of IV 5% dextrose water, his serum sodium remained between 145–163 mmol/L over the next 3 days.

On hospital day 9, the nephrology service was consulted. Placement of a Foley catheter demonstrated that the patient's urine output was >400 mL/hr, raising the possibility of diabetes insipidus. Magnetic resonance imaging (MRI) with and without contrast did not show evidence of brain metastases. On hospital day 10, after discontinuation of IV fluids for 6 hours, a 12-hour water deprivation test was performed (Figure 1). Despite a rising serum sodium (from 143 to 146 mmol/L) and serum osmolality (294 to 303mOsm/Kg), urine output remained at 300–400 mL/hr and urine osmolality remained dilute (99mOsm/kg). With administration of 4 mcg IV desmopressin, urine osmolality rose only slightly to 132mOsm/kg and urine output remained at 175ml/hr for the next 4 hours.

Since urine osmolality remained below plasma osmolality during the entire water deprivation test and administration of desmopressin increased urine osmolality by less than 35%–40%, a diagnosis of partial nephrogenic diabetes insipidus was made.¹⁵

With gradual improvement in his mucositis, the patient was able to better keep with up with fluid losses, such that IV 5% dextrose water and desmopressin was withdrawn. His urine

output also started to decrease, likely due to the waning effect of pemetrexed. One week post discharge, his serum sodium was normal with improvement in polyuria.

Given these adverse effects, he did not restart pemetrexed therapy and was given erlotinib and bevacizumab for his fourth cycle of chemotherapy. He did not experience recurrence of diabetes insipidus or other electrolyte abnormalities.

Discussion

Hallmarks of diabetes insipidus are large urine volume ($>2\text{--}3.5\text{L}$ in 24 hours) with low urine osmolality (less than 300mOsm/kg). Serum osmolality $>300\text{mOsm/kg}$ after 6.5 hours of water deprivation and urine osmolality less than serum osmolality have been used in initial experiments to distinguish diabetes insipidus from primary polydipsia.¹⁶ An incomplete rise in urine osmolality ($<50\%$) after administration of desmopressin confirms nephrogenic diabetes insipidus (while a complete response suggests central diabetes insipidus). Table 2 presents common causes and proposed mechanisms for nephrogenic diabetes insipidus.

Pemetrexed was released in 2004 and now occupies 40%–70% of the market share for first-line and maintenance therapy for non-small cell lung cancer.¹⁷ The most common kidney-related side effect of pemetrexed is AKI: a 1%–5% incidence of “creatinine elevation” is noted in the drug’s package insert but a higher incidence has recently been reported in a case series, in which 24% of 46 patients receiving long-term therapy developed AKI.¹⁸ In one patient with severe AKI during single-agent pemetrexed use, physicians used thymidine in combination with hemodialysis and reported resolution of the AKI.⁵

Less commonly, electrolyte abnormalities have been reported, including nephrogenic diabetes insipidus. One case described a patient with non-small cell lung cancer who showed AKI beginning with the first cycle of pemetrexed therapy, with serum creatinine rising and ultimately peaking at 3.4 mg/dL (eGFR , 19ml/min/1.73 m^2).¹⁰ After 3 cycles of pemetrexed therapy, he developed nephrogenic diabetes insipidus, based on hypernatremia, low specific gravity, and urine sodium, normal hypothalamic-pituitary MRI, and only partial response to polyuria with desmopressin. Kidney biopsy specimen showed interstitial fibrosis and acute tubular necrosis. One other case report describes development of nephrogenic diabetes insipidus in conjunction with at least modest AKI (peak serum creatinine, 3.4mg/dL ; eGFR , 20ml/min/1.73m^2).¹¹

In our case, the patient had recovered from a mild rise in serum creatinine but developed persistent, significant hypernatremia despite large volumes of IV free water administration. His mucositis and accompanying diarrhea not only heightened the severity of hypernatremia by potentiating free water loss but also likely unmasked an underlying nephrogenic diabetes insipidus, which the patient may have otherwise been able to avoid by increasing his water intake to keep up with thirst.

Pemetrexed is secreted from the renal tubules by organic anion transporters (OATs), specifically OAT3 and OAT4.¹⁹ This transport is especially enhanced at an acidic pH.²⁰ Other drugs transported by OATs are thought to induce tubular injury via influx of these substances in proximal renal tubular epithelial cells, increasing intracellular concentration.

Especially in the presence of other drugs transported via a similar mechanism (such as nonsteroidal anti-inflammatory drugs and cisplatin), tubular injury would be magnified, presumably due to competitive inhibition of pemetrexed efflux across the apical membrane.²¹ Our patient was also prescribed carboplatin, which unlike cisplatin, is excreted unchanged in the kidneys and is not directly nephrotoxic.²² Furthermore, while there is an association with electrolyte derangements (potassium and magnesium wasting) with cisplatin, and to a lesser degree, with carboplatin, neither drug alone has been associated with nephrogenic diabetes insipidus.^{23–25}

However, putative mechanism of pemetrexed-induced kidney injury does not explain the accompanying nephrogenic diabetes insipidus. While nephrogenic diabetes insipidus can accompany modest to severe AKI (Table 2), this is rare.²⁶ Moreover, our patient developed nephrogenic diabetes insipidus after a rapid fall in serum creatinine, presumably due to prerenal azotemia with reversal by extracellular fluid repletion. One potential mechanism for the reported pemetrexed-associated nephrogenic diabetes insipidus is that apical or basolateral folate carriers may transport pemetrexed into principal cells of the collecting duct.²⁷ In addition to OAT receptors, folic acid transporters (namely the proton-coupled folate transporter [PCFT, SLC46A1,2,3]), are also implicated in the transport of pemetrexed into cells.²⁸ Proton-coupled folate receptors are selectively expressed; a recent analysis of different nephron segments suggested that SLC46A1,2,3 in rat kidney showed selective, modest expression in the collecting duct, the site of origin for nephrogenic diabetes insipidus.²⁹ In preclinical studies, 11 of 12 dogs treated with varied doses of pemetrexed (5 to 25 mg/kg) for 9 months suffered mild tubular hypertrophy, mainly in the cortex. No significant serum electrolyte abnormalities were noted. Polydipsia or polyuria were not observed (V. Reddy, personal communication, Sep 2015).

In summary, we report a case of pemetrexed-induced nephrogenic diabetes insipidus in the absence of AKI. Care should be taken to monitor electrolytes and kidney function while patients receive pemetrexed. Clinical trials do not always include a sufficient number of patients to detect more rare side effects of drugs,³⁰ particularly ones that may require a confluence of other clinical syndromes (eg, mucositis and diarrhea). Phase IV information on drug toxicities, whether reported in the form of aggregated case reports or to the US Food and Drug Administration's Adverse Event Reporting System, is crucial to constructing a complete side effect profile of medications.

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Figure 1. Serum osmolality, urine osmolality and serum sodium during a 12-hour water deprivation test. Intravenous desmopressin of 4 mcg was administered at t=0.

Table 1

Baseline serum and urine electrolytes

	Baseline	24 hours later
Serum Electrolytes		
Sodium, mmol/L	138	158
Potassium, mmol/L	3.5	3.0
Chloride, mmol/L	103	132
Carbon dioxide, mmol/L	20	17
Urea Nitrogen, mg/dL	12	6
Calcium, mg/dL	7.3	7.2
Magnesium, mg/dL	2.1	1.8
Phosphorous, mg/dL	1.6	1.0
Creatinine, mg/dL	1.3	1.7
Urine Electrolytes		
Glucose	Negative	Negative

Note: Conversion factors for units: serum urea nitrogen in mg/dL to mmol/L, $\times 0.357$; calcium in mg/dL to mmol/L, $\times 0.2495$; phosphorus in mg/dL to mmol/L, $\times 0.3229$; creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$.

Table 2

Common causes and proposed mechanisms of nephrogenic diabetes insipidus

Etiology	Mechanism
Drugs	
Lithium	Accumulates in principal cells of the collecting duct through apical entry via the epithelial sodium channel (ENaC), and inhibits glycogen synthase kinase type 3beta, which in turn inhibits apical translocation of aquaporin-2 channels ²⁷
Ifosfamide	Damages proximal tubular cells and induces renal glucosuria, which leads to free water loss ²⁸
Cidofovir	Unclear, postulated to be due to phosphorylated metabolites which interact with interact with vasopressin intracellular kinases downstream of the vasopressin 2 receptor ²⁹
Foscarnet	Decrease in urea transport affecting the countercurrent mechanism and ability to concentrate urine ³⁰
Osmotic or Electrolyte disturbances	
Hyperglycemia, or osmotic load from high protein feeding or mannitol infusion	A non-reabsorbed solute in the tubular lumen leads to relatively larger loss of free water ³¹
Hypercalcemia	A. Inhibition of Na ⁺ /K ⁺ /2Cl ⁻ (sodium/potassium/chloride cotransporter), increasing free water losses due to loss of the counter-current gradient; ³² B. Activation of the calcium sensing receptor, reducing ADH sensitivity ³³
Hypokalemia	Downregulation of aquaporin-2 ³⁴
Other	
Genetic (X-linked)	A defect in the V2 receptor gene; V2 receptors are responsible for ADH binding in collecting tubule and endothelial cells ³⁵
Genetic (Autosomal recessive)	A defect in aquaporin-2 water channels ³⁶
Pregnancy	Vasopressinase (i.e. ADH cleaving enzyme) production by the placenta ³⁷
Acute kidney injury (especially post-obstructive)	Obstruction interferes with formation of the hyperosmotic medulla; other mechanisms of AKI may lead to requirement for increased solute excretion in functioning nephrons ²¹
Sickle cell anemia	Sickling in vasa recta and repetitive oxidative damage, leading to a hyperosmotic medulla ³⁸

Abbreviations: ADH, antidiuretic hormone; AKI, acute kidney injury.