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NEPHROGENIC DIABETES INSIPIDUS ASSOCIATED WITH TEMOZOLOMIDE THERAPY IN A PATIENT WITH GRADE IV ASTROCYTOMA

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ABSTRACT

Temozolomide (TMZ), an alkylating agent used in glioblastoma multiforme and anaplastic astrocytoma treatment, is generally associated with side effects like myelosuppression and nausea. This case report describes a rare occurrence of nephrogenic diabetes insipidus (NDI) in a 45-year-old male with grade IV astrocytoma undergoing TMZ therapy. Following TMZ discontinuation due to haematological toxicity, the patient developed significant polyuria and hypernatremia. Central diabetes insipidus was initially suspected, but limited improvement with desmopressin and normal endocrine investigations suggested renal involvement. The diagnosis of partial NDI was made and linked to TMZ-induced acute tubulointerstitial nephropathy (ATN). Despite symptom onset coinciding with TMZ administration, recovery was delayed after discontinuation, implicating possible lasting tubular damage. Although the precise pathogenesis remains uncertain, it may involve TMZ-induced renal tubule inflammation, affecting aquaporin-2 expression and water retention. In this case, management of NDI included adequate intravenous hydration, oral fluid restriction, and progressive resolution of polyuria without the need for diuretic or non-steroidal anti-inflammatory drug. This case emphasizes the need for vigilance regarding renal complications, particularly NDI, in patients receiving TMZ, warranting careful monitoring of electrolytes, renal function and diuresis to ensure prompt identification and management of this rare but serious side effect.

KEYWORDS

Nephrogenic diabetes insipidus, temozolomide, tubulointerstitial nephritis

LEARNING POINTS

- Temozolomide can in rare cases cause diabetes insipidus and, even more exceptionally, nephrogenic diabetes insipidus.
- The resolution of nephrogenic diabetes insipidus following the discontinuation of a high-intensity regimen is promising, and patients should not be denied temozolomide due to this complication.

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INTRODUCTION

Diabetes insipidus (DI) is characterized by hypotonic polyuria (urine output > 50 ml/kg/day) associated with polydipsia (fluid intake > 3 litre/day) and nocturia[1]. DI can be of central origin due to insufficient synthesis of arginine vasopressin (AVP), nephrogenic when kidneys fail to respond to AVP, or gestational, caused by placental vasopressinase-mediated destruction of AVP[2]. Nephrogenic DI (NDI) may result from genetic mutations affecting AVP receptors (AVPR2) or aquaporin (AQP2), or may be acquired secondary to electrolyte disturbances (hypercalcemia, hypokalaemia) or nephrotoxic medications (including lithium, cisplatin, foscarnet, and amphotericin B)[1,2]. Temozolomide (TMZ) is an alkylating agent that crosses the blood-brain barrier, widely used in combination with radiotherapy for newly diagnosed glioblastoma multiforme and anaplastic astrocytoma[3]. Common adverse effects of TMZ include fatigue, myelosuppression, nausea, and skin rash[3,4]. We report a rare case of NDI occurring in a patient treated with TMZ for grade IV astrocytoma, notably characterized by delayed symptom resolution following TMZ discontinuation, suggesting persistent renal tubular injury.

CASE DESCRIPTION

A 45-year-old Caucasian male was followed for a grade IV astrocytoma (6 mm, right parietal location), resected in October 2024. He subsequently received adjuvant radiotherapy (60 Gy over 30 sessions) targeting the right fronto-parietal postoperative cavity with an anatomical safety margin while sparing the pituitary gland, from November to December 2024. Postoperative magnetic resonance imaging (MRI) demonstrated satisfactory resection of the enhancing portion of the right parietal tumour lesion. He also received daily TMZ therapy at 75 mg/m^2, discontinued due to hematologic toxicity at day 42. Additionally, the patient was taking levetiracetam at a dose of 750 mg twice daily. A corticosteroid therapy regimen consisting of solumedrol was initiated at 16 mg o.d., gradually tapered to 8 mg once daily by 13 October 2024 and discontinued on 16 October 2024. Due to grade 3 lymphopenia, he also received prophylactic sulfamethoxazole/trimethoprim at 800/160 mg three times per week, from 12 December 2024 until 30 December 2024. In January 2025, he presented with complaints of blurred vision, dizziness, diplopia, and fatigue. Physical examination showed moderate tachycardia, mild epigastric tenderness and scattered petechiae, but no clinical signs of dehydration. Ophthalmological examination was normal, including normal oculomotor cranial nerve assessment. Laboratory investigations revealed severe pancytopenia with haemoglobin at 9.5 g/dl (normal range: 13.5–17.5 g/dl), platelets at 13,000/mm^3 (normal range: 150,000–450,000/mm^3), neutrophils at 510/mm^3 (normal range: 1500–7500/mm^3), eosinophils at 40/mm^3 (normal range: < 500/mm^3), and elevated C-reactive protein at 27 mg/l (normal range < 5 mg/l). The patient reported intense thirst from 31 December 2024, subsequently developing polyuria and nocturia with daily fluid intake of 4–5 l/day compared to his baseline of 2–2.5 l/day. Fasting blood glucose levels were normal, excluding diabetes mellitus. Urinary osmolality of 258 mOsm/kg supported this finding. Serum creatinine rose slightly (1.38 mg/dl versus baseline 1.23 mg/dl; N< 0.7 mg/dl), initially attributed to polyuria-induced dehydration. Initial investigations for central insipidus diabetes revealed a normal hypothalamic-pituitary axis (FSH/LH/PRL/GH/ACTH) and normal cerebral MRI, especially no pituitary gland abnormalities. Intravenous hydration (5% dextrose solution) and oral fluid restriction were initiated. Intravenous desmopressin dosage was progressively increased up to 2 µg every 6 hours, achieving partial polyuria reduction (persisting at 4–5 l/day). Serum creatinine initially improved (1.13 mg/dl) before rising again (1.24 mg/dl at day 9) after switching to intranasal desmopressin on January 14 *(Fig. 1)*. Sample urine analysis shows slight tubular proteinuria protein-to-creatinine ratio (0.43 g/g creatinine), with slight microscopic haematuria without leukocyturia (white blood

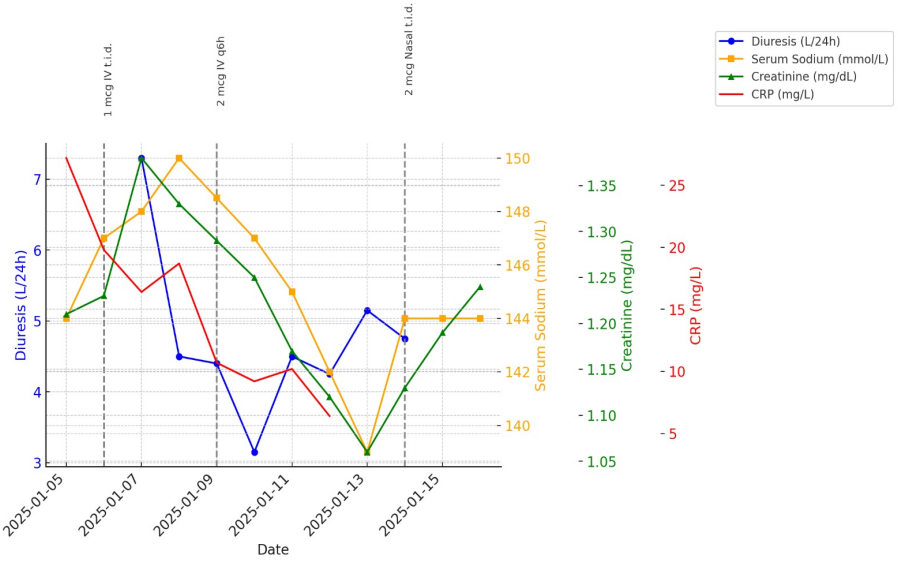


Figure 1. Evolution of diuresis, serum sodium, serum creatinine, and C-reactive protein during hospitalization, with initiation of intravenous desmopressin and fluid restriction indicated on January 6, 2025.

Abbreviations: CRP, C-reactive protein; q6h, every six hours; t.i.d., three times a day.

cells <8/µl – N < 25/µl), haematuria (25 red blood cells/µl – N < 25/µl) suggesting TMZ-induced ATN. Sodium levels initially increased before progressively normalizing under desmopressin (0.02 mg t.i.d.). Despite these interventions, residual polyuria persisted. The partial response to desmopressin, the lack of improvement despite hydration, and the concurrent ATN strongly suggested TMZ-induced nephropathy associated with partial NDI. Neither renal biopsy nor copeptin dosage was performed. Slow but continuous clinical improvement supported this hypothesis, and eventually there was a return to baseline fluid intake and urine output (~2.5 l/day).

DISCUSSION

The present case highlights NDI as a rare complication of TMZ treatment. Although central DI linked to TMZ has occasionally been reported, association with NDI remains very uncommon[3,4]. To date, only two cases of TMZ-associated NDI have been reported in the literature[3,5]. In our patient, polyuria began shortly after TMZ initiation, approximately three weeks following the start of treatment, which aligns with similar timelines described in the literature[5]. The persistence of polyuria despite adequate desmopressin administration and normal endocrine evaluation strongly suggested renal involvement. The hypothesis of hypophysitis or hypopituitarism induced by radiotherapy was quickly ruled out, given that the doses received by the pituitary during treatment were much lower than those described in the literature (mean dose 30 Gy, dose max 45 Gy) *(Fig. 2)*[6,7]. The precise pathophysiological mechanism underlying TMZ-associated NDI remains uncertain due to the limited number of reported cases. To date, only one biopsy-proven case of TMZ-induced ATN associated with NDI has been documented[3]. It demonstrated significant renal interstitial inflammation, possibly explaining the impaired renal concentrating ability observed clinically. Although TMZ-specific renal injury mechanisms are poorly defined, insights from nephrotoxicity induced by other alkylating agents suggest a potential direct cytotoxic effect on renal tubular cells, resulting in tubulointerstitial inflammation and impaired AQP2 expression or membrane localization[3,8]. Cisplatin-induced nephrotoxicity typically involves apoptosis and necrosis of tubular epithelial cells, mechanisms closely linked to inflammation and oxidative stress, contributing significantly to renal dysfunction[8]. However, direct histological confirmation through renal biopsy was not obtained in our patient, limiting definitive conclusions about the specific renal pathology.

Delayed recovery from symptoms following TMZ discontinuation may reflect prolonged renal tubular injury, as drug-induced nephrogenic diabetes insipidus may persist several weeks after discontinuation[9]. Management of NDI primarily involves TMZ discontinuation. In our patient, this measure alone did not provide immediate symptom resolution. Therefore, management was reinforced with intravenous hydration, oral fluid restriction, and incremental desmopressin administration. Clinical improvement occurred progressively alongside with renal injury resolution, supporting the hypothesis of TMZ-induced tubular dysfunction. In previously reported cases of drug-induced NDI, adjunctive therapy involving thiazide diuretics or amiloride has been beneficial, resulting in significant clinical improvement, notably in polyuria reduction and electrolyte management, although response rates vary individually[9]. Moreover, our patient also received concomitant trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis due to significant lymphopenia. A similar clinical scenario previously documented described NDI with ATN in a patient treated concurrently with TMZ and TMP/SMX, suggesting a possible additive nephrotoxic effect. In that case, symptoms progressively resolved following discontinuation of both drugs and supportive measures, emphasizing caution when these agents are combined due to overlapping nephrotoxic potentials[3]. Given the potential severity and rarity of TMZ-

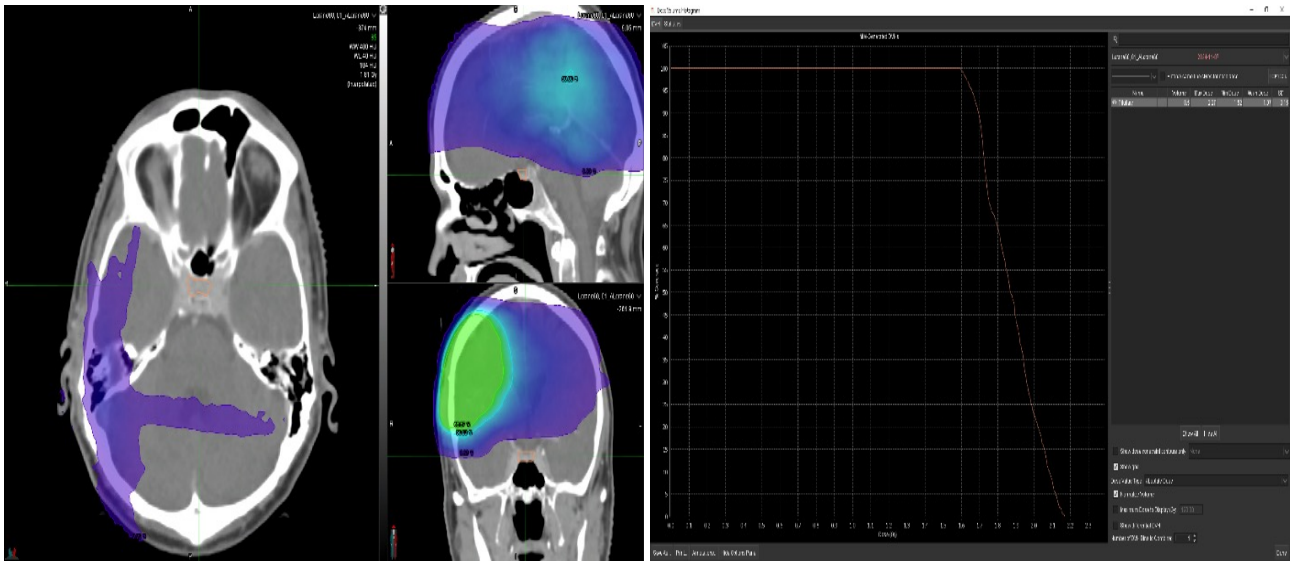


Figure 2. Planned radiotherapy treatment centred on the pituitary gland (dark blue, light blue, and green clouds represent doses of 5 Gy, 30 Gy, and 40 Gy, respectively). Dose-volume histogram representing the radiation dose received as a function of pituitary gland volume.

induced NDI, heightened vigilance regarding renal function monitoring and careful assessment of urinary output is recommended, particularly when TMZ is administered concurrently with other nephrotoxic medications. This case underscores the importance of early recognition and intervention to prevent severe electrolyte disturbances and renal complications.

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