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Clinical Report

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Levetiracetam-induced severe acute granulomatous interstitial nephritis

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Abstract
Granulomatous interstitial nephritis (GIN) is an uncommon cause of renal failure, which may be caused by drugs. Levetiracetam is an increasingly used anti-epileptic medication that is not known to cause renal toxicity in adults. To our knowledge, levetiracetam has not previously been reported as a cause of GIN. We report the case of a 69-year-old woman who developed haemodialysis-requiring acute renal failure after commencement of treatment with levetiracetam, which was shown to be GIN by renal biopsy. She made a complete recovery with cessation of levetiracetam and treatment with steroids.

Keywords: acute renal failure; granulomatous interstitial nephritis; levetiracetam

Introduction

Levetiracetam is an anti-epileptic drug used for the treatment of partial and generalized seizures. We report the case of a 69-year-old woman with previously normal renal function who developed acute granulomatous interstitial nephritis (GIN) requiring dialysis following levetiracetam consumption.

Case report

A 69-year-old woman with a background of early stage chronic lymphocytic leukaemia (CLL) was noted to have episodes of phrase repetition and instances of memory loss over 1 year. An electroencephalogram showed changes consistent with temporal lobe epilepsy. A magnetic resonance imaging showed mild deep white matter small vessel ischaemic changes with a small old infarct of the right caudate nucleus. She was commenced on carbamazepine. Six weeks later, she developed generalized erythematous macular rash (Figure 1A) and was admitted to hospital for wet dressings. A skin biopsy confirmed a lichenoid drug reaction and serological markers of vasculitis were negative. At this time, the patient had normal renal function as assessed by a serum creatinine of 49 mmol/L (0.55 mg/dL) and the absence of pyuria, haematuria (by urinary microscopy) or albuminuria on a spot urine assessment. Carbamazepine was discontinued and the patient was commenced on levetiracetam 500 mg twice a day and discharged home.

Fourteen days following commencement of levetiracetam, she presented with a 2-day history of severe oral mucositis and feeling generally unwell. On examination, she was afebrile and her blood pressure was 120/65 mmHg. She had severe mucosal ulceration affecting the tongue and mouth but sparing the conjunctiva. She had a widespread rash with areas of desquamation. Urinalysis demonstrated $+1$ protein only.

Initial laboratory evaluation revealed a serum urea of 37.1 mmol/L (103 mg/dL), creatinine of 393 mmol/L (4.44 mg/dL) and an elevated leucocyte count of 26.3×10^9/L ($26.3 \times 10^3/\mu$L), which were predominantly lymphocytes. The eosinophil count was normal. Urine microscopy showed $>100 \times 10^6$ leucocytes per litre and $<10 \times 10^6$ erythrocytes per litre. Urine culture grew *Klebsiella pneumoniae*. The urinary albumin: creatinine ratio was 47.6 mg/mmol (421.7 mg/g). A serological vasculitic screen was negative—in particular, the anti-nuclear anibody, extractable nuclear antibodies, double-stranded DNA antibody, anti-neutrophil cytoplasmic antibody and rheumatoid factor were all negative. Computed tomography (CT) of the urinary tract showed large kidneys (left measuring 13.5 cm and right 12.4 cm) with no hydronephrosis or hydroureter.

The patient was oliguric and the renal impairment did not respond to fluid resuscitation. She was treated with intravenous ceftriaxone for her urinary tract infection. Fluid overload, worsening azotaemia and metabolic acidosis required treatment with the commencement of haemodialysis via temporary venous catheter. A renal biopsy was performed which showed acute non-caseating granulomatous tubulointerstitial nephritis. The renal biopsy contained cortex and medulla with eight glomeruli, two of which were globally sclerosed. The viable glomeruli were normal. There was a diffuse active inflammation of the tubulointerstitium with non-necrotizing lymphohistiocytic giant cell granulomas as well as associated tubule destruction (Figure 1B and C). Ziehl Neelsen, auramine and periodic acid-Schiff stains were negative for mycobacterium and fungi. Herpes simplex virus staining was also negative. There was no evidence of

glomerulonephritis by routine light microscopic, immunofluorescence or electron microscopic examination.

She was initially treated with intravenous methylprednisolone daily (500 mg for 3 days) and the levetiracetam was replaced by sodium valproate 500 mg twice a day. Other more common causes of granulomatous interstitial disease were considered including tuberculosis, which was excluded with a negative urine culture and polymerase chain reaction (PCR). Sarcoidosis was also excluded with a CT scan of the chest and abdomen that did not reveal hilar lymphadenopathy or other features suggestive of sarcoidosis and a normal serum angiotensin-converting enzyme 35 U/L (8–52).

The oral mucositis was secondary to Herpes simplex virus as demonstrated on PCR of a swab of an oral lesion and was treated with acyclovir (dose adjusted for renal impairment, 250 mg intravenously for 3 days). She had panhypogammaglobulinaemia [IgG = 5.4 g/L (540 mg/dL), IgM <10 mg/L (10 mg/dL), IgA = 480 mg/L (48 mg/dL)] secondary to CLL and was given intravenous gammaglobulin (24 g daily over 3 days). Her hospital stay was further complicated by delirium and valproate was discontinued.

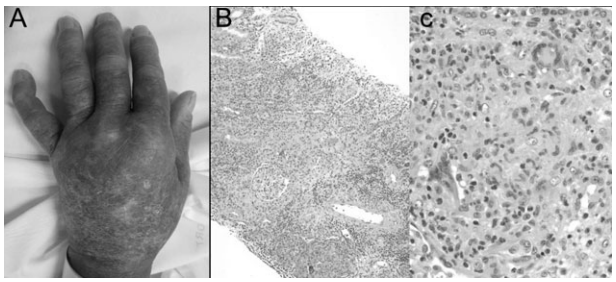

Fig. 1. Skin rash and renal histopathology. (**A**) Rash representative of that affecting the entire body after commencement of carbamazepine. (**B**) Renal biopsy [haematoxylin and eosin (H&E) stain ×250] showing diffuse active non-caseating granulomatous tubulointerstitial nephritis. (**C**) H&E stain (×400) demonstrating areas of GIN with lymphohistiocytic infiltrate and giant cells.

She had three haemodialysis treatments over 6 days and rapidly recovered renal function with increasing urine output and improved biochemistry (Figure 2). She had a course of oral prednisone commencing at 50 mg daily (1 mg/kg/day) that was withdrawn gradually over 3 months. Her renal function normalized and her current serum creatinine is 70 mmol/L (0.80 mg/dL).

Discussion

Renal toxicity secondary to levetiracetam has not previously been reported in adults although there is a single paediatric case report [1]. The most common side effects of levetiracetam in adults are somnolence, asthenia and dizziness [2]. Other side effects include depression and anxiety. It has high oral bioavailability and is excreted predominantly in the urine (93% after 48 h). Adjustment of the dose is required in renal impairment as its elimination is directly dependent on creatinine clearance [3].

Although tubulointerstitial nephritis is relatively common, GIN is rare, accounting for ~1% of diagnoses in native renal biopsies [4, 5]. The most common causes of GIN are sarcoidosis, drugs and infection, particularly tuberculosis [4]. Drugs implicated in cases of GIN are varied and include non-steroidal anti-inflammatory drugs, phenytoin, nitrofurantoin and vancomycin. GIN is also part of the tubulointerstitial nephritis and uveitis syndrome. GIN has been seen as a consequence of CLL with one case reporting leukaemic cells infiltrating the renal tissue with surrounding T cells and granuloma formation [6]. Our patient did not have leukaemic cells identified on renal biopsy.

This patient had renal failure requiring haemodialysis and a diagnosis of GIN confirmed by renal biopsy. She made a rapid recovery with withdrawal of levetiracetam and treatment with steroids. The outcome of patients with GIN is generally favourable [5] but some patients with an insidious

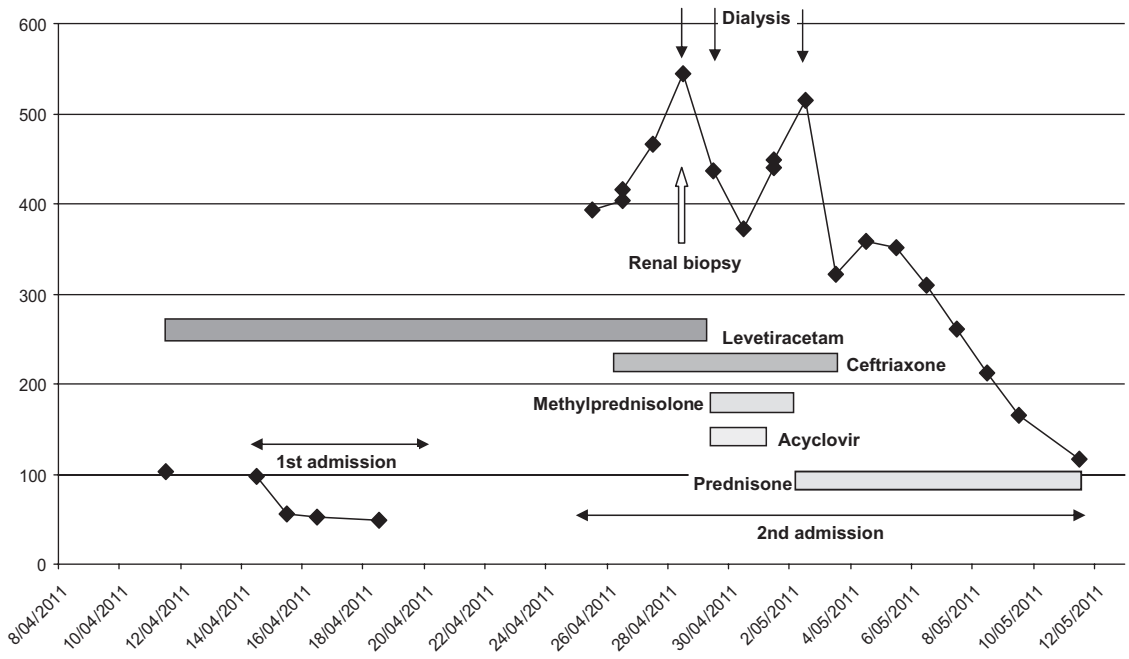

Fig. 2. Graph representing creatinine during course of disease. Timing of haemodialysis and commencement and cessation of all medications during disease course noted.

presentation may progress to end-stage renal failure. Steroids have been used at varying dosages but due to the infrequency of the disease, there are no defined treatment guidelines.

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Conflict of interest statement. None declared.

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