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Case Report

Progressive renal failure due to renal infiltration by BK polyomavirus and leukaemic cells: which is the culprit?

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Renal infiltration with leukaemic cells is a common finding in patients suffering with chronic lymphocytic leukaemia (CLL) but rarely does it lead to significant renal dysfunction. Similarly, BK nephropathy is a recognized cause of graft failure in renal transplant recipients but rarely causes significant disease in native kidneys. In the few reports where leukaemic infiltration of the kidney has led to significant renal impairment, the pathological process causing renal dysfunction is not identified on biopsy. In these cases, it is unclear whether BK polyomavirus (BKV) nephropathy has been excluded. We describe a case of dual pathologies in a patient with Binet stage C CLL and deteriorating renal function where renal biopsy reveals leukaemic infiltration of the kidney occurring alongside BKV nephropathy. The relative importance of each pathology in relation to the rapid decline to end-stage renal failure remains unclear, but the presence of both pathologies appears to impart a poor prognosis. Additionally, we describe the novel histological finding of loss of tubular integrity resulting in tubular infiltration and occlusion by leukaemic cells. It is possible that the patient with advanced CLL is at particular risk of BK activation, and the presence of BK nephropathy may compromise tubular integrity allowing leukaemic cell infiltration and obstruction of tubules. This case bares remarkable resemblance to the first and only other report of its kind in the literature. It is not clear how available immunocytochemistry for polyoma infection is outside transplant centres, and it is possible that BK nephropathy is being under-diagnosed in patients with CLL in the context of declining renal function. At present, the combination of BKV nephropathy and leukaemic infiltration represents a management conundrum and the prognosis is poor. Further research is required in order to better understand the pathological process and therefore develop management strategies.

Keywords: acute kidney injury; BK nephropathy; BKV nephropathy; chronic lymphocytic leukaemia; native kidney

Case history

A 72-year-old gentleman with a history of Binet stage C chronic lymphocytic leukaemia (CLL), hypogammaglobulinaemia and bronchiectasis was referred to our Renal Unit in April 2009 with deteriorating renal function. He was diagnosed with CLL in 1990 and had since received multiple courses of chemotherapy. His disease had become refractory to chlorambucil, fludarabine and cyclophosphamide, but in November 2008 he responded to alemtuzuimab and methyl prednisolone. Lymph node biopsy in March 2009 revealed low-grade disease. He received regular intra-venous immunoglobulin (IvIg) replacement for hypogammaglobulinaemia despite which he developed bronchiectasis, for which he received periodic treatment with ciprofloxacin. His renal function had remained stable and normal throughout this period.

Between March and April 2009 his serum creatinine rose from 111 to 207 μmol/L. At this time his regular medications included lansoprazole 30 mg once daily, aciclovir 400 mg three times daily, allopurinol 100 mg once daily and co-trimoxazole 480 mg once daily. Aciclovir, allopurinol and co-trimoxazole were immediately discontinued. By August 2009 his creatinine was 410 μmol/L, and in September 2009 it had risen to 647 μmol/L.

Examination revealed a regular pulse with a rate of 70 bpm and a blood pressure of 136/70 mm Hg. He was afebrile and euvolaemic. He had an ejection systolic murmur, axillary and cervical lymphadenopathy and a palpable spleen 5 cm below the left costal margin. Remaining systemic examination was unremarkable. Serum ANA and ANCA were negative, though urinary Bence Jones proteins were present and serum free light chains were elevated (Table 1). We proceeded to renal biopsy.

Preliminary H&E sections showed renal cortex infiltrated by sheets of monotonous lymphoid cells that appeared to spare the tubules (Figure 1). There was severe tubular atrophy with the tubular epithelial cells having

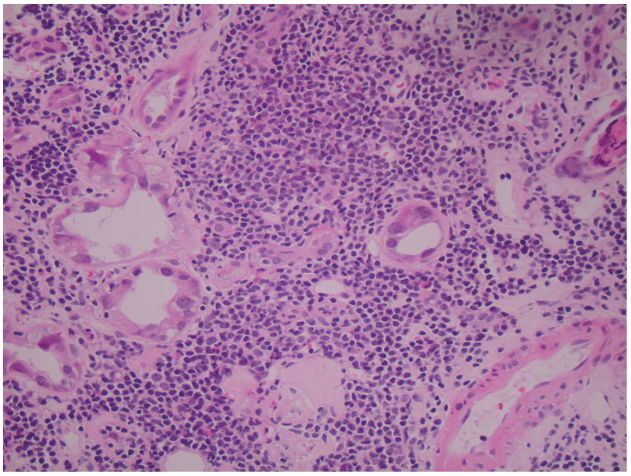

Fig. 1. H/E section showing sheets of lymphocytes that mostly spare the tubules. The tubules have atypical nuclei. ×200 original magnification.

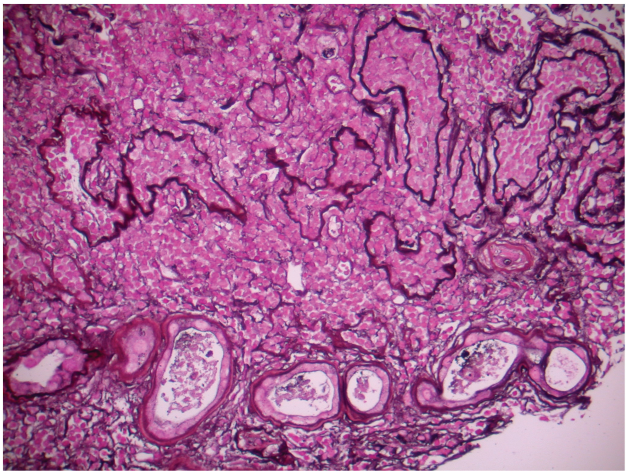

Fig. 3. A diffuse lymphoid infiltrate overruns and occludes tubules lacking epithelial cells. Tubules lined by residual epithelial cells with atypical nuclei are present in the lower half of the picture. Jones stain, ×200 original magnification.

atypical, often hyperchromatic and enlarged nuclei. Some had areas of nuclear pallor and vacuolation. Condensed chromatin surrounding the pallor was very rare. This together with focal loss of tubular epithelial cells and renal failure raised the possibility of viral infection. Immunocytochemistry with an antibody to SV40 large T antigen (Oncogene Research Products) for polyoma showed frequent nuclear staining (Figure 2). Subsequent stains highlighted tubules showing frequent intact tubular basement membranes with total loss of epithelial cells and replacement by lymphocytes (Figure 3). Infrequent granular and hyaline casts were present. Interstitial fibrosis was present but not of major degree. Fourteen out of 17 glomeruli were sclerosed, with one collapsed and two normal glomeruli. Congo red was negative. No immune deposits were seen and there was no evidence of myeloma. Electron microscopy confirmed the absence of cast nephropathy.

Pulse methyl prednisolone was given as interim treatment in an attempt to salvage renal function. Following proven polyoma infection, his management was switched to IvIg and targeted BK virus treatment with ciprofloxacin. The evidence base for treatment of native kidney BK polyomavirus (BKV) nephropathy is largely extrapolated from studies involving immunosuppressed patients and relies heavily on reducing immunosuppression. Additionally, however, some 'targeted' therapies have been shown to reduce BK viral load though the impact on patient outcome is unclear. Such agents include leflunomide, quinolones, IvIg and cidofovir. Leflunomide has additional immunosuppressive properties, and the antiviral cidofovir is nephrotoxic. IvIg was therefore used alongside ciprofloxacin in an attempt to reduce viral load. Despite this, his renal function continued to deteriorate and he unfortunately progressed to end-stage renal failure, requiring regular haemodialysis. Subsequently, his CLL relapsed and he succumbed to the illness.

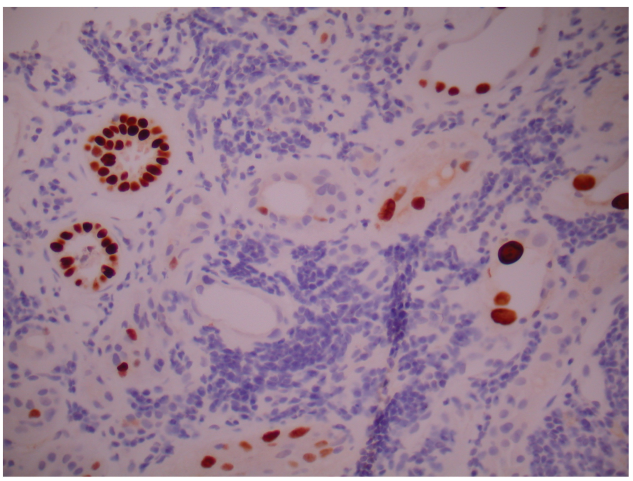

Fig. 2. Immunocytochemical staining for polyoma showing staining of both enlarged, atypical and normal tubular epithelial nuclei. ×200 original magnification.

Discussion

BKV occurs ubiquitously as an asymptomatic infection that occurs in childhood and leads to lifelong persistence in the kidney [1]. BKV has long been recognized as an important cause of transplant nephropathy in renal transplant recipients. It is not generally known to cause native kidney nephropathy. In this case, the biopsy satisfies the criteria for the diagnosis of BKV nephropathy.

CLL has been associated with multiple mechanisms of acute kidney injury (AKI) including obstructive uropathy, acute uric acid nephropathy, tumour lysis syndrome, haemolysis, amyloid, light chain nephropathy, cryoglobulinaemia and glomerulopathies. Though a large proportion of patients with CLL will have significant renal infiltration (60–90%) [3,4], rarely does this result in renal impairment and the infiltrate characteristically spares the tubules. Literature review reveals 11 cases of AKI in patients with CLL where biopsy has excluded all of the aforementioned causes of renal impairment leading their authors to the conclusion that CLL infiltration itself was the cause of the disease. Direct involvement of the tubules by infiltra-

Table 1. Table of Results

Haematology	Hb 8.8 g/dL, WBC 69.5 × 10^9/L, PLT 117 × 10^9/L
Serum biochemistry	Urea 35.5 mmol/L, Na 135 mmol/L, K 5.3 mmol/L, Creatinine 646 mmol/L, Adj Ca 2.14 mmol/L, Phosphate 1.79 mmol/L, Urate 0.62 mmol/L, CRP 35 mg/L, Alb 32 g/L, Bili 15 µmol/L, ALP 60 IU/L, AST 23 IU/L
Urine biochemistry	PCR 37 mg/mmol, Bence Jones protein positive 0.09 g/L lambda light chain
Immunology	ANA negative, ANCA negative Complement C3 1.29 g/L, C4 0.16 g/L within normal range
Serum virology	HIV Ag/Ab not detected, Hep B surface antigen not detected, Hep C antibody not detected JC DNA genome copies: 1.77E + 6 gc/mL> JC virus PCR: JC virus DNA detected BK virus DNA genome copies: 5.35E + 6 gc/mL BK virus PCR: BK virus detected
Urine virology	JC DNA genome copies: 2.20E + 9 gc/mL JC virus PCR (nested): JC virus DNA detected BK DNA genome copies: 1.09E + 10 gc/mL BK virus PCR (nested): BK virus DNA detected

tion of the epithelial cells was commented on once by Tucker *et al.* where mild infiltration was seen [5]. Minor infiltration also appears to be present in the images presented by Boudville and Saggi [6,7]. Interestingly, the biopsies rarely indicated a direct mechanism of renal dysfunction other than the hypothesis that heavy infiltration leads to compression of tubules and microvasculature leading to ischaemia. There is no evidence of staining for BKV in any of these reports.

Here we report the additional novel finding of tubular infiltration and obstruction of the lumena by leukaemic cells further implicating CLL as the direct cause of renal dysfunction (Figure 2). Polyoma infection causes tubular epithelial damage with loss of epithelial cells and denudation of the basement membrane. It may well be that this enables the leukaemic cells to infiltrate along the residual lumena of the tubules.

This is only the second case reported whereby renal biopsy revealed the highly unusual finding of polyomavirus occurring alongside CLL infiltration [6]. In transplants, the changes may only be seen in the medulla and may be focal without nuclear abnormality or inclusions [2]. In our experience, tubular nuclear atypia is easier to identify than nuclear inclusions, with immunocytochemistry identifying many more abnormal nuclei than are seen on H&E sections. In the absence of staining, the subtle histological changes consistent with polyoma infection may well be missed and therefore BKV nephropathy under-diagnosed. It is not clear how available immunocytochemistry for polyoma is outside transplant centres, and it is possible that polyoma infection, particularly in the immunocompromised patient, including those with CLL, is more common than has been reported. In this cohort of patients, serum and urinary BK PCR represents a non-invasive investigation that may be beneficial in establishing polyoma infection [2].

There is remarkable similarity between these two cases with both patients having Binet stage C disease, hypogammaglobulinaemia and bronchiectasis. Such a biopsy finding poses a management conundrum. On the one hand, treating CLL infiltration of the kidney with further immunosuppression has in the past been met with varying degrees of success. Irradiation of the infiltrated kidney has also proved beneficial in one case. Conversely, however, the management of BKV nephropathy, at least in transplanted kidneys, relies heavily on reducing immunosuppression with the addition of targeted anti-viral therapy, though the benefit of the latter remains unclear [2].

Unfortunately, both cases of leukaemic infiltration and BKV nephropathy reported to date resulted in the relentless march towards end-stage renal failure. The relative contribution of either pathology to the deterioration in renal function remains unclear. Given that a large proportion of patients with CLL will have normal renal function despite renal infiltration on biopsy, it is reasonable to speculate that the presence of CLL infiltration in both of these cases is less significant than the presence of BK virus. Contrary to this, 5 of the 11 previously documented renal injuries put down to CLL based on biopsy findings did indeed respond to aggressive chemotherapy. These two cases do suggest, however, that the presence of both pathologies imparts a poor prognosis. With this in mind, it is appropriate that in the population of patients with CLL, deterioration in renal function should be aggressively and rapidly investigated and the presence of BK virus confirmed or excluded.

Conflict of interest statement. None declared.

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