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BRIEF COMMUNICATION

‘A disease of disparity’: chronic kidney disease of unknown aetiology in endemic immigrant communities

Shriram Swaminathan[1] and Bobby Chacko [1,2]

[1]Nephrology and Transplantation Unit, John Hunter Hospital, and [2]School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia

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Correspondence
Bobby Chacko, Nephrology and Transplantation Unit, John Hunter Hospital, Newcastle, NSW 2310, Australia.
Email: bobby.chacko@health.nsw.gov.au

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Abstract

Chronic kidney disease (CKD) of unknown aetiology is a form of tubulointerstitial CKD in the absence of traditional and known predisposing risk factors. Since the early 2000s, there is an emerging trend in marginalised agricultural communities among workers exposed to occupational and environmental hazards. CKD of unknown aetiology has received significant attention in recent years and is becoming increasingly relevant to the Australian medical community with the growing migrant population, which this case-based communication illustrates.

A 23-year-old student presented to our emergency department with chest pain, fatigue and dyspnoea. This patient was originally from a rural farming village in Pakistan. His medical check in Pakistan 3 years ago was unremarkable. There was no other past medical history or family history of kidney disease, with no regular medications, including over the counter, alternative traditional herbal medications or recreational drug use. On examination, he was hypertensive at 200/100 mmHg with clinical features including hypertensive retinopathy with prominent vessels and patchy haemorrhage and right-sided isolated temporal field vision loss. He was otherwise euvolemic.

Initial pathology revealed advanced chronic kidney disease with creatinine 2779 μmol/L and urea 64.3 mmol/L and associated renal anaemia with haemoglobin 48 g/L. Despite this, he was relatively hypokalaemic at 4.0 mmol/L. Urine demonstrated moderate isomorphic haematuria and pyuria and a urine albumin–creatinine ratio of 478.8 mg/mmol. Management proceeded with urgent initiation of haemodialysis with a vascular access catheter and gradual reduction in urea over consecutive sessions.

During work-up, a glomerulonephritis screen was negative. Imaging revealed bilateral atrophic kidneys, suggesting end-stage disease, and therefore a biopsy was initially not undertaken as it would not change management. A heavy metal screen was not pursued, although there was no known significant heavy metal exposure.

However, after several weeks of haemodialysis, he developed fever of unknown origin and extensive work-up did not reveal a clear source. A renal biopsy was undertaken to rule out any possible contributing inflammatory nephritis. The biopsy revealed chronic tubulointerstitial nephritis (TIN) as the predominant pathology. Electron microscopy revealed marked chronic tubulointerstitial damage with dense lymphocytic infiltrates, while immunofluorescence was faintly positive for IgA only.

Discussion

Chronic kidney disease (CKD) of unknown aetiology is typically seen among tropical agricultural communities, with Sri Lanka and Central America two of the primary endemic areas.[1] The disease primarily impacts men aged 20–69 years in a 2:1 ratio compared with women.

In Australia, so far, there are few articles published describing the clinical and pathologic phenotype of CKD of unknown aetiology. Studies are limited but populations described include Aboriginal Australians in rural and regional communities. These populations often present with kidney failure without a clear or overt cause. Environmental factors proposed for CKD of unknown

Table 1 Demographics and proposed causes of chronic kidney disease (CKD) of unknown aetiology in Australia compared with endemic regions

	Mesoamerican nephropathy	Sri Lankan nephropathy	Uddanam nephropathy	CKD of unknown aetiology in Aboriginal Australians
Region	Rural areas of Central and South America	Northern Central districts including Anuradhapura	Central Indian states including Andhra Pradesh	Remote Western Australian communities
Demographic	Young men aged 20–50 years	Men slightly more predominant, aged 40–50 years	Young men aged 30–60 years	Further study required
Theorised risk factors	Hot tropical climates, physical exertion and recurrent dehydration	Heavy metal contamination of water, pesticides	Silica in groundwater, analgesic nephropathy, low water intake	Uranium and nitrate contamination of water sources
Occupational risk factors	Agricultural and industrial workers of numerous industries including sugarcane, cotton, corn, mining and construction	Rice farmers	Cashew, rice and coconut farmers	None known

aetiology in Aboriginal communities include uranium and nitrate contamination present in high concentrations of water sources in remote regions.[2] A summary of the typical demographic and features of CKD of unknown aetiology in endemic regions compared with CKD of unknown aetiology in Aboriginal communities can be found in Table 1 and highlight further areas of study necessary for understanding our population.

Other risk factors described in Australia have included cases of lead nephropathy in Queensland in the early 1900s,[3] as well as reduced proanthocyanidin intake among an elderly population group in Western Australia.[4] With an increasing immigrant population, we expect an emerging incidence and prevalence of this condition in Australia that warrants recognising the clinical and pathologic features.

Our case illustrates the typical presentation of CKD of unknown aetiology as a late presentation of end-stage chronic TIN with typically non-specific symptoms. Histologically, a study of 64 biopsies in Sri Lanka showed interstitial mononuclear infiltration as well as features of vascular disease including fibro intimal thickening and arteriolar hyalinosis.[5] Reviews of Mesoamerican nephropathy cases are also in keeping with this picture.[6]

Common causes of CKD in Australia include hypertension, diabetic nephropathy, obstructive uropathy and other glomerular diseases. However, TIN differs clinically from glomerular disease and this distinction is crucial for identifying CKD of unknown aetiology over other causes of CKD. Patients are usually not hypertensive in the early stages of disease and, unlike our case, heavy proteinuria is usually uncommon; however, there was biopsy-proven concurrent glomerular damage in our patient. Chronic TIN also typically have a hyperchloraemic metabolic acidosis out of proportion to renal dysfunction and can manifest with relative hypokalaemia and other electrolyte abnormalities, such as those seen in Fanconi syndrome.[7] The typical clinical and pathological features of chronic TIN as opposed to a glomerulonephritis are highlighted in Table 2.

The nature of CKD of unknown aetiology as a type of chronic TIN related to a variety of hypothesised causes therefore typically manifests with a late-stage presentation with non-specific clinical features but concerning serum markers of kidney and electrolyte dysfunction.

Table 2 Differentiating glomerular versus tubulointerstitial nephritis

	Chronic glomerulonephritis	Chronic tubulointerstitial nephritis
Clinical presentation	Variable, nephritic/nephrotic syndrome or acute renal failure over days to weeks	Deterioration of GFR with insidious onset
Proteinuria	Variable, including nephrotic range but typically >1 g	Typically low molecular weight protein <1 g/day
Urinary sediment	Haematuria, potential red cell casts	Inactive or sterile pyuria
Electrolytes and acid–base balance	Hyperkalaemia and metabolic acidosis proportionate to impaired GFR	Relative hypokalaemia, proximal or distal tubular acidosis, salt-wasting syndromes, Fanconi syndrome. Metabolic acidosis and bone and mineral disorder disproportionate to GFR
Fluid balance	Oedema, hypertension	Salt-sensitive hypertension, relative euvolemia
Other manifestations	Hypercoagulability in nephrotic syndrome	Anaemia at a relatively early stage of CKD (due to impaired tubular production of erythropoietin)

CKD, chronic kidney disease; GFR, glomerular filtration rate.

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Previously proposed theories for CKD of unknown aetiology have included heat exposure, pesticides, infection and water contamination with heavy metals. While several associations have been drawn, there are clear limitations in how we study the causes of CKD of unknown aetiology with heterogeneity of risk factors studied from region to region.

With respect to heat exposure and dehydration in extreme work environments, there is sparse evidence for serial acute kidney injuries or repeated moderate elevations in creatinine leading to long-term CKD.[8] An intervention study in El Salvador to improve working conditions with portable water reservoirs, shaded tents and scheduled rest periods showed a small and not statistically significant reduction in creatinine; however, there was great difficulty with follow up in the non-intervention control group.[9]

Similarly, while there are some links for pesticide exposure and acute kidney injury, there is no clear evidence for CKD of unknown aetiology epidemics, with the International Mesoamerican Nephropathy Workshop concluding it is an unlikely cause of CKD of unknown aetiology.[10] With respect to heavy metals, multiple reviews have found low levels of metals in the drinking water and/or urine in CKD of unknown aetiology populations, suggesting limited correlation.[11]

The question raised is whether CKD of unknown aetiology is instead a constellation of diagnoses with a similar presentation and histopathology or a multifactorial combination of insults without a single inciting event. Studies are primarily retrospective in nature and are subject to recall bias. Unfortunately, the nature of CKD of unknown aetiology as a typically late presentation of end-stage chronic TIN does not easily allow for prospective studies and randomised control trials. Therefore, there is a need to identify at-risk populations in an early stage of disease with early tubular biomarkers.

A study of 210 children in Nicaragua published in 2020 has looked at urinary biomarkers of tubular injury including Neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and interleukin-18 (IL-18).[12] Median urine NGAL, IL-18 and KIM-1 concentrations exceeded healthy reference values, with 19.5% of patients having urinary biomarker concentrations in the upper quartile for three or more biomarkers evaluated. Approximately 9% of the subjects already had a low estimated glomerular filtration rate (≤90 mL/min/1.73 m^2). A greater understanding of the potential role of these biomarkers may assist in providing a framework for screening processes in at-risk populations and allow early intervention and preventative public health policies.

Preventative management strategies on a population level focus on reducing heat stress and trying to identify potential exposure risk factors that can be mitigated. Supportive measures include the use of oral sodium bicarbonate as management for metabolic acidosis in Stages 4 and 5 CKD, as well as an interest in the role of uric acid in progressive disease due to the frequent presence of hyperuricaemia.[13] However, there is limited evidence for the role of uric acid lowering therapy in clinical trials for protection.[6]

In terms of the role of renin–angiotensin–aldosterone system (RAAS) blockers in CKD of unknown aetiology, there has previously been caution about their use, given concerns about volume depletion and dehydration.[6] However, the present case illustrates a patient who subsequently developed chronic hypertension with several vascular lesions that responded well to RAAS blockade, suggesting renin-mediated hypertension as a consequence of end-stage kidney disease. Given the long-term macrovascular complications of hypertension in a predominantly young population group, this would support its use in CKD of unknown aetiology patients who develop hypertension and in whom long-term chronic dehydration is less of a risk factor.

As the nature of CKD of unknown aetiology tends to be prevalent in rural parts of the world, this creates issues with access to haemodialysis centres often making peritoneal dialysis the preferred modality.[14] Transplantation would be ideal in an otherwise young population group; however, the risk of recurrence of CKD of unknown aetiology post-transplantation remains unknown, especially if underlying environmental tubular insults remain present. In an Aboriginal Australian population group, we see similar issues of both difficulty accessing dialysis but also lack of access to transplantation, with registry analysis showing Aboriginal Australian young adults having transplantation rates of only 56.2% compared with 89.3% in a non-Aboriginal equivalent group.[15]

We described the case of an Asian immigrant presenting with an unusual late-stage presentation of chronic TIN as part of an international spectrum of diseases in endemic countries. In Australia, CKD of unknown aetiology is rare but increasingly recognised, and applicable to late presentations among both an increasing immigrant population as well as the Aboriginal Australian population. The international issues of access to renal replacement therapy parallel a similar socioeconomic concern for the Australian population as well. Future areas of interest regarding biomarkers of early tubular injury may assist in generating large-scale occupational health surveillance programmes for improving detection and early clinical intervention in at-risk population groups.

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