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 euvoletic.

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. 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
aetiology in Aboriginal communities includes uranium and nitrate contamination present in high concentrations of water sources in remote regions. 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, as well as reduced proanthocyanidin intake among agricultural and industrial workers of numerous industries including sugarcane, cotton, corn, mining and construction. 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. Reviews of Mesoamerican nephropathy cases are also in keeping with this picture.

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 hyperchloremic 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. 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 1: Demographics and proposed causes of chronic kidney disease (CKD) of unknown aetiology in Australia compared with endemic regions |
|---------------------------------------------------------------|
| **Region** | **Mesoamerican nephropathy** | **Sri Lankan nephropathy** | **Uddanam nephropathy** | **CKD of unknown aetiology in Aboriginal Australians** |
|----------------|-----------------------------|---------------------------|---------------------|-----------------------------------------------|
| Demographic | Rural areas of Central and South America | Northern Central districts including Anuradhapura | Central Indian states including Andhra Pradesh | Remote Western Australian communities |
| Theorised risk factors | Young men aged 20–50 years | Men slightly more predominant, aged 40–50 years | Young men aged 30–60 years | Further study required |
| Occupational 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 |
| Rice farmers | | | Cashew, rice and coconut farmers | None known |

| Table 2: Differentiating glomerular versus tubulointerstitial nephritis |
|---------------------------------------------------------------|
| **Clinical presentation** | **Chronic glomerulonephritis** | **Chronic tubulointerstitial nephritis** |
|--------|----------------|----------------|
| 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.
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. 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.

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. 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.

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). 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 ($\leq 90$ 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. However, there is limited evidence for the role of uric acid lowering therapy in clinical trials for protection.

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. 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. 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.

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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References

1 Mendley S, Levin A, Correa-Rotter R, Joubert B, Whelan E, Curwin B et al. Chronic kidney diseases in agricultural communities: report from a workshop. *Kidney Int* 2019; 96: 1071–6.

2 Rajapakse J, Rainer-Smith S, Millar G, Grace P, Hutton A, Hoy W et al. Unsafe drinking water quality in remote Western Australian Aboriginal communities. *Geogr Res* 2018; 57: 178–88.

3 Weaver V, Fadrowski J, Jaar B. Global dimensions of chronic kidney disease of unknown etiology (CKDu): a modern era environmental and/or occupational nephropathy? *BMC Nephrol* 2013; 16: 145.

4 Ivey K, Lewis J, Lim W, Lim E, Hodgson J, Prince R. Associations of proanthocyanidin intake with renal function and clinical outcomes in elderly women. *PLoS One* 2013; 8: e71166.

5 Nanayakkara S, Komiya T, Ratnatunga N, Senevirathna S, Harada K, Hitomi T et al. Tubulointerstitial damage as the major pathological lesion in endemic chronic kidney disease among farmers in North Central Province of Sri Lanka. *Environ Health Prev Med* 2011; 17: 213–21.

6 Johnson R, Wesseling C, Newman L. Chronic kidney disease of unknown cause in agricultural communities. *N Engl J Med* 2019; 380: 1843–52.

7 Joyce E, Glasner P, Ranganathan S, Swiatecka-Urbano A. Tubulointerstitial nephritis: diagnosis, treatment, and monitoring. *Pediatr Nephrol* 2016; 32: 577–87.

8 Herath C, Jayasumana C, De Silva P, De Silva P, Siribaddana S, De Broe M. Kidney diseases in agricultural communities: a case against heat-stress nephropathy. *Kidney Int Rep* 2018; 3: 271–80.

9 Wegman D, Apelqvist J, Bottai M, Ekström U, García-Trabanino R, Glaser J et al. Intervention to diminish dehydration and kidney damage among sugarcane workers. *Scand J Work Environ Health* 2017; 44: 16–24.

10 Wegman D, Crowe J, Hogstedt C, Jakobsson K, Wesseling C, eds. *Mesoamerican Nephropathy: Report from the Second International Research Workshop on MeN; 2015 Nov 18–20; San José, Costa Rica. SALTRA: Heredia, Costa Rica; 2016.*

11 Pearce N, Caplin B. Let’s take the heat out of the CKDu debate: more evidence is needed. *Occup Environ Med* 2019; 76: 357–9.

12 Leibler J, Ramirez-Rubio O, Velázquez J, Pilarte D, Obeid W, Parikh C et al. Biomarkers of kidney injury among children in a high-risk region for chronic kidney disease of uncertain etiology. *Pediatr Nephrol* 2020; 36: 387–96.

13 Abraham G, Anupama P, Prasad N, Nzana V, Tiwari J, Mathew M. Dietary management in slowing down the progression of CKDu. *Indian J Nephrol* 2020; 30: 256–60.

14 Varughese S, Agarwal S, Raju T, Khanna T. Options of renal replacement therapy in CKDu. *Indian J Nephrol* 2020; 30: 261–3.

15 Chaturvedi S, Ullah S, LePage A, Hughes J. Rising incidence of end-stage kidney disease and poorer access to kidney transplant among Australian Aboriginal and Torres Strait Islander children and young adults. *Kidney Int Rep* 2021; 6: 1704–10.