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Renal Transplantation in Pure Autonomic Failure

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INTRODUCTION

Pure autonomic failure (PAF) is a rare disorder of the autonomic nervous system that often presents in the sixth decade of life. PAF is thought to result from the deposition of α-synuclein in autonomic ganglia and peripheral autonomic nerves, whereas the central nervous system remains unaffected.[1] Patients usually present with orthostatic intolerance (because of orthostatic hypotension [OH]) and approximately 50% also have supine hypertension.[2] The latter may cause left ventricular hypertrophy and chronic kidney disease (CKD), which may complicate the management of OH.[3,4]

We report the case of a 69-y-old gentleman with PAF who developed end-stage renal disease necessitating peritoneal disease (PD) and transplantation. His OH was well controlled on PD but substantially worsened following deceased donor renal transplantation. This resulted from profound volume depletion secondary to the restoration of euvolemia as unrecognized hypervolemia had been masking orthostatic symptoms while on dialysis. We describe the investigation, treatment, and subsequent outcome and discuss the pathophysiology. This, to the best of our knowledge, is the first report of renal transplantation in a patient with documented PAF.

CASE PRESENTATION

A 69-y-old gentleman was referred to the renal service with nephrotic range proteinuria and progressive CKD in 2016. Hypertension had been diagnosed 13 y previously, and he had begun to experience severe orthostatic intolerance, frequently when upright, postprandially, and after exertion.

He developed CKD 2 y after his initial symptoms. Renal histology was consistent with secondary focal segmental glomerulosclerosis (FSGS). PD was commenced upon progression to end-stage renal disease (ESRD). He dialyzed for 4 y, during which symptoms of OH became less incapacitating. He was taking Midodrine 2.5 mg in the morning and afternoon for OH, and Amlodipine 5 mg nocte to reduce supine hypertension.

He was referred to London in 2017, after he started PD, for further autonomic investigations. He reported dizziness while upright, and also after food, alcohol, and exercise (especially going uphill) and in hot weather. He fainted intermittently. He had occasional palpitations. There was no ankle edema or peripheral vascular pooling. He could break into a cold sweat without shivering. He was increasingly fatigued especially with exertion and without coat-hanger headache. There were no urinary symptoms. He was constipated. On examination, there were no neurological features. Table 1 outlines the specialized autonomic testing,[5] that confirmed autonomic failure with sympathetic vasoconstrictor and cardiac parasympathetic impairment. He had marked OH, enhanced with stimuli that cause vasodilatation such as food and exertion. He also had substantial supine hypertension. There were no neurological features, which was consistent with a diagnosis of PAF.

The combination of autonomic symptoms and CKD prompted consideration of various diagnoses causing or contributing to autonomic failure. With the duration and progression, Lyme disease and amyloidosis were considered unlikely. Ganglionic acetylcholine receptor antibody level was not elevated, excluding autoimmune autonomic impairment. Nerve conduction studies, extractable nuclear antigen

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Written informed consent was obtained from the patient for this case report.

Z.U.A. was part of the MDT team who managed the patient in the in and outpatient setting. He conducted the literature review on the topic, coined the idea of writing the case report, drafted the article, critically reviewed it, and approved the final version for submission. A.R. conducted literature review, drafted the article, prepared the figures and tables, critically reviewed the article, and approved the final version before submission. N.D.G. was lead consultant who managed the patient's pretransplant out patient management. She helped in drafting the article, and critically reviewing it approving it for final submission. E.H. was heavily involved in managing the neurological condition of the patient both as an in and out patient and was part of the MDT team. She helped in drafting the article, critically reviewing it, and approving it for final submission. C.M. is Emeritus Professor of Neurovascular Medicine, Queen Square Institute of Neurology, University College London. He and his team were involved in diagnosing and advising on autonomic management. He contributed to editing/revising the article and reviewed/approved the final version before resubmission. A.C. contributed to the paper's conception, helped in drafting the article, contributed to the literature review, critically reviewed the article after each iteration, and approved it before submission.

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TABLE 1.

Specialized autonomic testing (details of which are referenced[5]), that confirmed autonomic failure and lead to a diagnosis of PAF

Autonomic investigations	Results
Supine and standing BP	Supine 200/105 fell to 120/70 on standing
Head up tilt test	Supine BP 253/164 dropped to 165/97 without symptoms
Liquid meal test	On tilt hypotension exacerbated to 93/55 on tilt and with visual symptoms
Supine graded exercise	A fall in BP as opposed to normal rise when exerting while flat 15 min after exercise BP was 127/82, lower than when standing before exercise
Plasma catecholamine levels (adrenaline and noradrenaline)	Subnormal when supine,with amodest rise (considering the postural BP drop) when upright
Plasma dopamine levels	Normal and not elevated
24 h automated BP and HR autonomic profile summary	Mean daytime supine BP 178/104 h 79 bpm Mean night time BP 196/105, HR 70 Highest supine BP 240/134 Postmeal BP while sitting 100/69, HR 85 Exertion BP 92/61, HR 86 when symptomatic

BP, blood pressure; HR, heart rate; PAF, pure autonomic failure.

antibodies, serum-free light chains, transthyretin, Lyme serology, celiac screen, and antineuronal antibodies were all normal. Magnetic resonance imaging of the brain and spinal cord was unremarkable.

Work up for kidney transplantation was commenced. An echocardiogram revealed mildly reduced left ventricular systolic function (ejection fraction of 50%) and moderate left ventricular hypertrophy. A myocardial perfusion (MIBI) scan was suggestive of inducible ischemia in the anteroseptal and inferior regions. A coronary angiogram excluded significant coronary artery stenosis. He was placed on the deceased donor transplant waiting list.

In 2020, 4 y after commencing dialysis, he received a deceased donor renal transplant from a 59-y-old male with no prior medical history. The HLA mismatch was 1:1:1. Midodrine and Amlodipine were discontinued before surgery. On the day of surgery, his weight was 73 kg, his lying blood pressure was 130/90 mm Hg with no orthostatic drop, and he had no edema. The surgery was uncomplicated. Induction immunosuppression was with Basiliximab and Methylprednisolone. Maintenance immunosuppression was with tacrolimus, mycophenolate mofetil, and prednisolone. He had primary graft function and was normotensive at this point.

The patient developed polyuria from the sixth postoperative day. He began rapidly to lose weight (Figure 1) and developed a progressive postural drop in systolic and diastolic blood pressure. After 3 d, supine blood pressure was 170/90 and fell to 130/60 when upright, with a further fall after 7, 8, and 9 d to 103/59, 100/57, and 87/52, respectively, when standing.

Investigations indicated excellent graft function (creatinine 90 μmol/L at 2 wk posttransplantation); mildly elevated serum calcium (in keeping with known secondary hyperparathyroidism that settled a few days into transplantation); normal urea and electrolytes, serum albumin, white cell count, C-reactive protein, and morning cortisol level. Tacrolimus levels were between 8 and 12 ng/mL. There were no clinical signs of infection. A transthoracic echocardiogram indicated an ejection fraction of 50% but with no significant valvular disease. An electrocardiogram showed normal sinus rhythm.

The patient had a profound weight loss of 23 kg over a 3-wk period. A computed tomogram of the thorax, abdomen, and pelvis showed no evidence of malignancy. Bone scan and myeloma screen were normal.

Our patient after successful transplant surgery initially developed marked orthostatic intolerance and was unable to lift his head from the pillow. To reduce OH and symptoms of orthostatic intolerance that probably were contributory, a combination of nonpharmacological measures and drugs as used in PAF were initiated.[6] The former included maintaining a fluid intake of 2–3 L/d, increased dietary salt intake, head elevation, avoiding lying supine, lower limb compression stockings, abdominal binders, daily physiotherapy, and a Thera-bike to aid reconditioning. The pharmacological therapies and the possible mechanisms of their benefit are summarized in Table 2.[7-11] There were no adverse effects to the medications.

He gradually improved with a combination of measures and in due course could walk short distances with a frame at 4 mo posttransplantation. Graft function remained excellent. Twenty months posttransplantation, he continues to have postural symptoms and his features of PAF have been unaffected by a successful renal transplant. He remains on the listed medications. He is now able to ride a static bike and is far more mobile.

DISCUSSION

Orthostatic hypotension in PAF manifests with symptoms of cerebral hypoperfusion, that include lightheadedness and syncope.[12] An adapted cerebral autoregulatory response may develop over time and some become less symptomatic despie an orthostatic BP fall. This may have been the case in our patient before transplantation 12 y after the onset of PAF, as he was relatively free of symptoms on a small (2.5 mg bd) dose of Midodrine. Patients with autonomic failure, including PAF, often have nocturnal polyuria secondary to supine hypertension, accounting for their being more symptomatic on waking in the morning when their body weight is lower, and accounting for their beneficial response to nocturnal Desmopressin.[13] We hypothesize that a significant factor contributing to improvement in his orthostatic symptoms was progression to ESRD and subsequent control of fluid balance through dialysis, which prevented hypovolemia secondary to supine hypertension. There may have been a degree of intravascular

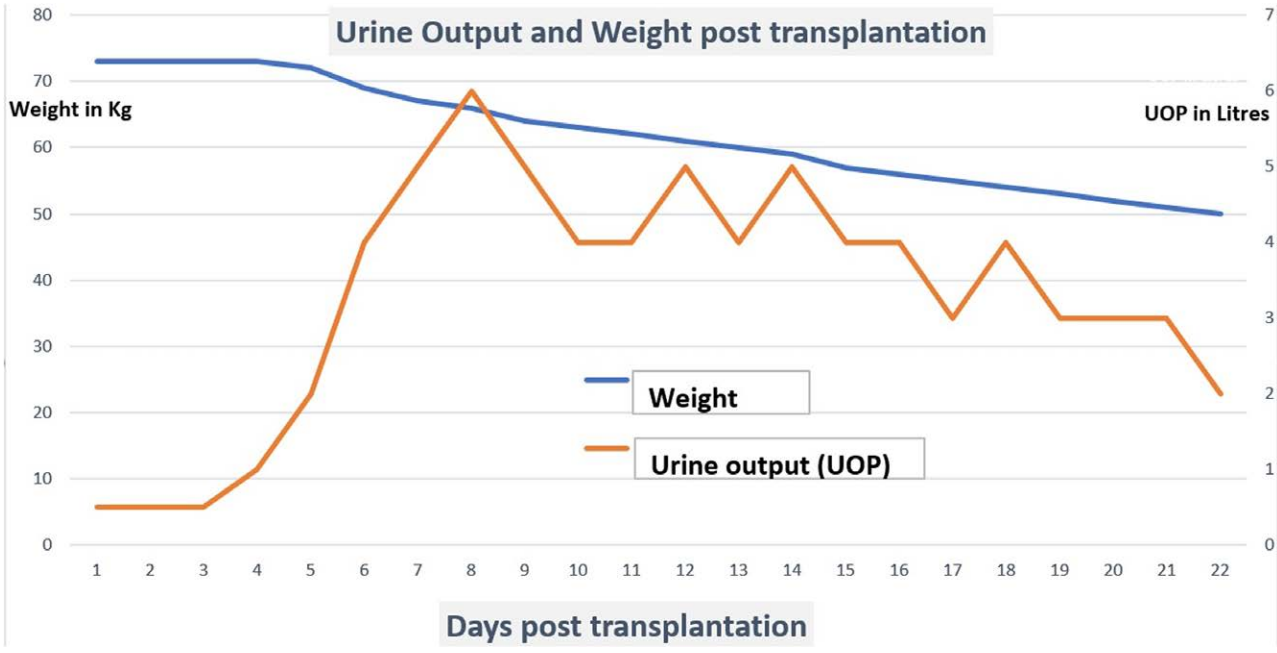

FIGURE 1. A line graph showing changes in urine output and weight after kidney transplantation. UOP, urine output.

hypervolemia, reducing OH and thus orthostatic intolerance. The restoration of normal renal function by successful transplantation and the resulting reversal of body fluid homeostasis without affecting the key autonomic abnormalities in PAF are likely to explain the rapid weight loss and the recurrence of marked OH.

Post-renal transplant tubular dysfunction is common and can manifest initially as polyuria, electrolytes abnormalities, and renal tubular acidosis.[14] These tend to improve with time as they usually are because of acute tubular necrosis and calcineurin inhibitor toxicity. Our patient had post-transplant polyuria from days 6 to 18. Metabolic acidosis and hypokalemia resolved early in the posttransplant phase. His symptoms of OH initially were probably because of volume depletion from polyuria. In the absence of renal failure, patients with PAF have nocturnal pressure natriuresis because of supine hypertension, and a substantial overnight weight loss, causing a greater orthostatic blood pressure fall on waking.[13,15] With renal failure, despite the regular dialysis, our patient was likely to have had a degree of intravascular fluid retention/hypervolemia that is likely to have buffered the BP fall when upright, and especially after vasodilatory stimuli such as food and exertion. The successful renal transplantation and initial post transplant polyuria were the likely reason for orthostatic symptoms initially worsening, and persisting even after resolution of the polyuric phase.

Patients with PAF may develop CKD that may be secondary to repeated episodes of hypotension, reduced renal perfusion, impaired renal autoregulation because of autonomic failure, and supine hypertension.[3,4] The pathophysiology causing supine hypertension is not fully understood but is probably because of impaired baroreceptor function and adrenergic

TABLE 2.

Pharmacological interventions used after renal transplantation with a brief description of their mechanisms of action and relevant publications

Medication	Class of drug	Mechanism of action	Route of administration	Postoperative day started	Dose at discharge
Fludrocortisone	Corticosteroid (mineralocorticoid)	Increases renal sodium and water reabsorption thereby expanding intravascular blood volume	Oral	13	100 µg BID (0800 and 1400 h)
Midodrine	α_1-adrenoreceptor agonist	Peripheral vasoconstriction.[7]	Oral	15	10 mg thrice daily (0600, 1200, and 1800 h)
Pyridostigmine	Acetylcholinesterase inhibitor	Potentiates neurotransmission through autonomic ganglia.[8]	Oral	32	60 mg thrice daily (0600, 1200, and 1800 h)
Desmopressin (DDAVP)	Vasopressin analogue	Promotes fluid retention by increasing water permeability in the distal tubule of the kidney, thereby expanding intravascular blood volume.[9]	Intranasal	35	20 µg once daily (2200 h)
Octreotide	Somatostatin analogue	Prevents postprandial hypotension by inhibiting vasodilatatory gut peptides, and reducing splanchnic vasculature pooling.[10]	Subcutaneous	35	25 µg sc thrice daily before meals (0600, 1200, and 1800 h)
Droxidopa	Synthetic amino acid analogue and prrecursor of noradrenaline	Converted by dopa-decarboxylase to noradrenaline, which increases vascular tone.[11]	Oral	Started after 6 mo	200 mg orally once daily

receptor sensitivity.[1] The finding of FSGS at native renal biopsy suggests that supine hypertension may have contributed to our patient's primary renal disease. This was unlikely to be primary FSGS due an absence of overt nephrotic syndrome. Most secondary causes were excluded by history and renal imaging, and genetic tests were also negative. Renal histopathology demonstrated extensive global glomerulosclerosis, tubular atrophy, interstitial fibrosis, and severe arteriosclerosis likely in keeping with hypertensive renal damage. This also was in keeping with longstanding history of hypertension, diagnosed in 2003 with poor control caused by off and on orthostatic symptoms.

Our patient did not have sensory-motor neurological features that separate PAF from other causes of autonomic failure. He developed symptoms of OH in 2007 when his glomerular filtration rate was 50 mL/min. His NCS and EMG were normal and thus not consistent with uremic neuropathy. Uremic neuropathy classically affects the sensory system first with gradual involvement of the motor system. This was not so in our patient. Renal transplantation has been reported to reverse uremic sympathetic and parasympathetic autonomic dysfunction simultaneously and at a relatively early stage; however, his symptoms persisted many months after transplantation, which does not favor uremic neuropathy.[16]

Autonomic dysfunction contributes to intradialytic hypotension (IDH) experienced by many during hemodialysis and which increases cardiovascular mortality.[17,18] We hypothesize that patients with PAF may be particularly susceptible to and symptomatic from IDH, although there are no published data to support this. Repeated episodes of IDH may result in clinicians increasing their patient's dry weight, believing them to be hypovolaemic, promoting intravascular hypervolemia, and thus mitigating the symptoms of IDH. A retrospective study of patients with familial dysautonomia, a neurodegenerative disease characterized by autonomic and sensory dysfunction and thus different from PAF, reported poor dialysis tolerability.[19] However, a report in 2 patients with familial dysautonomia described improvement in supine hypertension in response to antihypertensive agents and quality of life after transplantation, as compared with when these patients were on hemodialysis.[20] The medications used to treat orthostatic symptoms in our patient are not believed to have altered the metabolism of transplant immunosuppressants.

In summary, we report the first case of renal transplantation in a patient with PAF. Symptoms of OH in PAF, especially when previously on PD, may acutely worsen following renal transplantation by restoring euvolemia when previously hypervolemic. Improvement in quality of life is a key goal of transplantation. Because of the disabling nature of the complications, we observed initially in our patient after transplantation, we recommend that those with PAF are forewarned of this possibility. It is important that other contributory causes of OH are ruled out. Treatment should include both pharmacological and nonpharmacological measures. Anticipation of this condition posttransplant, that restores renal function but does not affect the underlying pathophysiology in PAF (for which there is no cure), informs all the early introduction of treatment measures especially immediately posttransplantation, and is crucial in preventing deterioration in such patients.

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