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Residual Renal Function: A Double-Edged Sword

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Keywords
Cardiovascular risk · Nephrotic syndrome · Pharmacologic nephrectomy · Residual renal function

Abstract
Introduction: Nephrotic syndrome may persist despite end-stage kidney disease and result in dyslipidaemia, thrombosis and a significantly increased cardiovascular risk. Treatment of refractory nephrotic syndrome includes surgical bilateral nephrectomy, renal artery embolization and pharmacologic nephrectomy. ***Case Presentation:*** We present a case of a haemodialysis patient with refractory nephrotic syndrome who underwent pharmacologic nephrectomy. The procedure decreased the patient's cardiovascular risk and enabled the patient to become a candidate for kidney transplantation. ***Conclusion:*** In certain situations residual renal function may be harmful. In such instances, nephrectomy should be considered. Pharmacologic nephrectomy using nephrotoxic drugs is a non-invasive approach with least potential complications.

Introduction

Residual renal function in dialysis patients is beneficial since it is associated with lower mortality [1]; however, in patients with massive proteinuria, residual renal function is not desirable due to major complications derived from nephrotic syndrome (NS), particularly increased cardiovascular risk. Medical termination of renal function is needed in some cases. We report a case of a young dialysis patient with persistent NS in whom "medical nephrectomy" was induced by the synergistic nephrotoxic action of indomethacin and losartan, resulting in significant improvement of his lipid and anaemia status.

Case Report

A 37-year-old Caucasian male presented to his general practitioner with eyelid and lower extremities oedema and stage 1 arterial hypertension. His previous medical history, as well as family history, was unremarkable. Initial laboratory tests revealed a mildly reduced glomerular filtration rate (eGFR CKD EPI 88.9 mL/min/1.73 m^2), a spot urine sample positive for proteins, as well as 3–7 erythrocytes in urine sediment. He was referred to a nephrologist where further evaluation showed an increased erythrocyte sedimentation rate (60 mm/h), dyslipidaemia (total cholesterol 16 mmol/L, LDL cholesterol 12.5 mmol/L, triglycerides 2.03 mmol/L), hypoalbuminemia (20.5 g/L), hypogammaglobulinemia (3.2 g/L), and severe proteinuria of 15–16 g/24 h. Other laboratory analysis, were all negative or within the normal range. Screening for HIV and hepatitis B and C was negative. Renal ultrasound detected normal kidney morphology. Due to NS, the patient underwent renal biopsy. The histopathology was consistent with primary focal segmental glomerulosclerosis (FSGS) – perihilar type. Within the next 2 years, he received a number of immunosuppressants including steroids as first-line treatment, followed by cyclosporine, mycophenolate mofetil, cyclophosphamide combined with plasmapheresis, together with angiotensin II receptor

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Table 1. Pharmacological nephrectomy protocol

	Losartan daily dose, mg	Indomethacin daily dose, mg	Number of weekly HD sessions*	Additional medications
Week 1	150	150	7	Pantoprazole 2×40 mg
Week 2	150	150	5	Pantoprazole 2×40 mg
Week 3–4	100	100	3	Pantoprazole 2×40 mg
Week 5–6	100	75	3	Pantoprazole 2×40 mg
Week 7–8	100	50	3	Pantoprazole 2×40 mg
Week 9–10	100	25	3	Pantoprazole 2×40 mg
Week 11 and onwards	100	0	3	/

*During the first 2 weeks ultrafiltration during HD sessions was combined with limited fluid intake in order to maintain patient's body weight below dry weight.

blocker (ARB) due to allergy to ACE inhibitor, mineralocorticoid receptor antagonist, statin, diuretic and occasional infusions of 20% albumins, osteoporosis and thrombosis prophylaxis. However, not even partial remission was accomplished with any of the aforementioned drugs. Namely, NS persisted with proteinuria of up to 47 g/24 h. He was not interested in the rituximab trial. FSGS genetic testing was performed with negative results. At that point, his kidney function started to deteriorate (eGFR CKD EPI 64.6 mL/min/1.73 m^2) together with the development of mild normocytic normochromic anaemia (haemoglobin 105 g/L). A trial of lipid apheresis was started, however, with no effect since proteinuria remained around 20 g/24 h. The patient's anaemia deepened and demanded high doses of EPO and parenteral iron. After excluding bleeding and other potential causes, we concluded that NS led to significant urinary loss of both endo and exogenous EPO and transferrin. His kidney function continued to decline and three and a half years after the first presentation, he started with haemodialysis (HD). The patient had residual diuresis of 1 L, his blood pressure was well controlled, lower extremity oedema were not as severe as before, anasarca was no longer present, he was generally feeling better and attended the HD clinic only twice weekly and was able to work. However, his proteinuria remained 20 g/24 h, serum albumin levels were 20 g/L, gamma globulins were 3 g/L, and anaemia was difficult to treat and demanded high doses of EPO. He was unfit for consideration of kidney transplantation. He had severe dyslipidaemia despite maximal dose of atorvastatin and incipient atherosclerotic plaques of abdominal aorta and right common iliac artery. The patient refused to accept doctors' explanations of the harmful effect of his residual renal function and his increased cardiovascular risk. The crucial moment happened when we explained to him the importance of high lipoprotein(a) [Lp(a)] level of 453 nmol/L (N <75 nmol/L). At this point, the patient began to understand the severity of his cardiovascular risk and started to collaborate. The number of weekly HD sessions was increased to 3; however, this approach did not result in a decrease in residual urine volume over the following months. Medical termination of renal function was suggested. He was presented with 3 options: bilateral renal artery occlusion, pharmacological nephrectomy, and bilateral surgical nephrectomy. After consultations, the patient opted for pharmacological nephrectomy. We decided to try a protocol with high doses of NSAID and supramaximal dose of ARB due to allergy to ACEi (Table 1). He was admitted to the hospital in order to achieve better monitoring of urine output and body weight variations and limit fluid intake in the hospital. The effect on daily diuresis was seen immediately (Fig. 1): on the very first day after the start of the procedure, the patient became and remained oligoanuric with maximal daily urine volume of 300 mL. No hypotension episodes occurred, his serum albumins and immunoglobulin levels increased, lipid status normalized, Lp(a) levels ameliorated, lower doses of EPO were needed (Fig. 1). His cardiovascular risk decreased substantially. Pretransplantation work up was started since the patient was willing to undergo cadaveric kidney transplantation despite the possibility of FSGS recurrence in renal allograft.

Discussion

Some patients retain significant amount of residual diuresis despite the initiation of dialysis. For the majority of dialysis patients, this residual renal function is beneficial and should be preserved as long as possible [1]. However, in patients with nephrotic-range proteinuria residual diuresis is actually harmful since it results in dyslipidaemia despite diet and cholesterol-lowering medications, risk of thrombosis as well as cardiovascular events due to enhanced atherosclerosis. Lp(a) is plasma lipoprotein associated with increased cardiovascular risk independently of low-density lipoproteins and is elevated in patients with NS and difficult to treat [2–4]. NS remission causes a dramatic decrease in Lp(a) concentration [3]. Additionally, urinary loss of EPO has been shown to cause EPO-deficiency anaemia in NS [5].

In order to prevent cardiovascular complications, achieve better control of anaemia and improve the patient's nutritional and overall status and make the patient fit for possible kidney transplantation, one should consider nephrectomy. In our case, we decided to apply pharmacological one with losartan and indomethacin. The concomitant use of ARB and NSAID synergistically results in deterioration of renal function

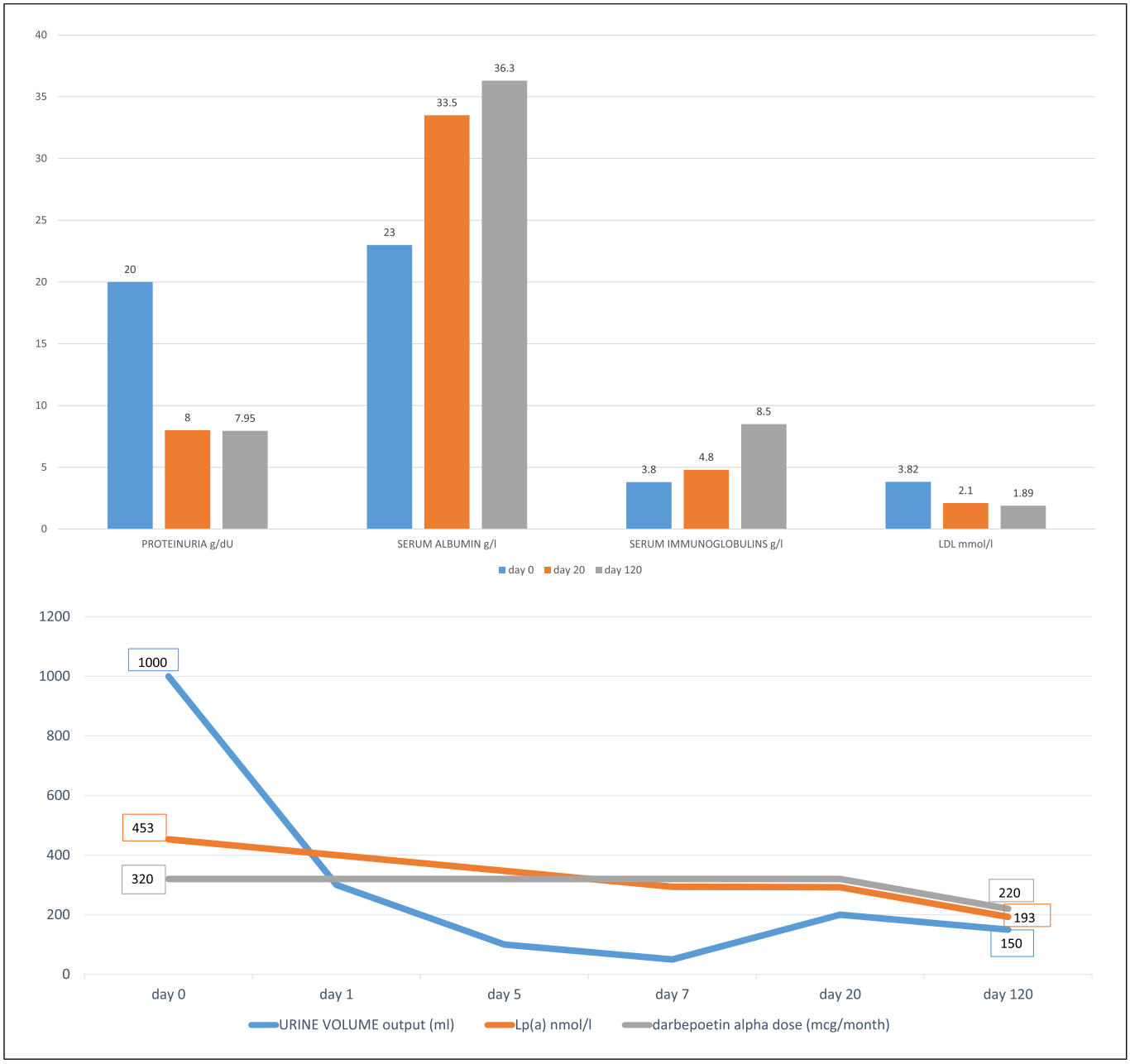

Fig. 1. Patient's clinical course.

[6–8]. The renal effect of losartan and indomethacin is usually reversible once the drugs are stopped. However, in dialysis patients with chronic renal lesions, prolonged administration of these drugs might result in definite anuria. Other options for the treatment of refractory NS include surgical bilateral nephrectomy which is the most effective strategy to suppress renal function but is a major procedure with substantial morbidity and mortality [9]. Another way to suppress renal function is renal artery embolization. However, this is an invasive procedure with potential complications such as haematoma, thrombosis, arterial dissection, peripheral embolization, renal abscess formation, and major post-embolization syndromes with shock and fatal outcomes [10]. Pharmacologic nephrectomy using nephrotoxic drugs is a non-invasive approach with fewer potential complications than the two aforementioned procedures. In our patient, the synergistic effect of NSAID and ARB in

combination with daily HD and ultrafiltration to retain the patient's body weight below dry weight resulted in permanent "medical nephrectomy" and consequent reduction in cardiovascular and other added risks. This case could be used as an example showing that residual diuresis is not always beneficial; in patients with resistant NS, it is associated with high cardiovascular risk and in such situations consideration of medical nephrectomy should be made promptly.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.K.Š.: concept and design of the paper, acquisition of the data, interpretation of the data, draft of the article, final approval of the version to be published, and agreement to be accountable for all aspects of the work; M.F.P.: acquisition of the data, interpretation of the data, revision of the manuscript, final approval of the version to be published, and agreement to be accountable for all aspects of the work; B.J.: interpretation of the data, revision of the manuscript, final approval of the version to be published, and agreement to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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