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CASE REPORT

Histopathology of congestive nephropathy: a case description and literature review

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Abstract

Congestive nephropathy is an underappreciated manifestation of cardiorenal syndrome and is characterized by a potentially reversible kidney dysfunction caused by a reduced renal venous outflow secondary to right-sided heart failure or intra-abdominal hypertension. To date, the histological diagnostic criteria for congestive nephropathy have not been defined. We herein report a case of acute renal dysfunction following cardiac allograft failure and present a review of the relevant literature to elucidate the current understanding of the disease. Our case demonstrated that congestion-driven nephropathy may be histopathologically characterized by markedly dilated veins and peritubular capillaries, focally accentuated low-grade acute tubular damage, small areas of interstitial fibrosis, and tubular atrophy on a background of normal glomeruli and predominantly normal tubular cell differentiation.

Keywords Acute heart failure; Acute kidney injury; Cardiorenal syndrome; Worsening renal function

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Introduction

Heart failure (HF) and abnormal kidney function frequently coexist, and are commonly referred to as cardiorenal syndrome (CRS). Up to 60% of patients admitted with acute HF have an estimated glomerular filtration rate (eGFR) of $<$60 mL/min/1.73 m^2, which corresponds to moderate-to-severely reduced kidney function or kidney failure.[1] Chronic kidney disease (CKD) is considered as one of the most important risk factors for mortality in HF, with the risk increasing incrementally with lower baseline eGFR.[2] CKD has also been recognized as one of the main risk factors for the development of HF, particularly HF with preserved ejection fraction.[3] While well-recognized as a burden to both individuals and the healthcare system, the underlying mechanisms of CRS remain poorly understood. Current data suggest that venous congestion, arterial underfilling, neurohormonal activation, and inflammation are contributory to the intense sodium retention and diuretic resistance observed with the condition.[4] Congestive nephropathy is a potentially reversible subtype of CRS, wherein increased renal interstitial pressure secondary to right-sided HF or intra-abdominal hypertension results in intrinsic renal compartment syndrome, causing transiently reduced renal perfusion pressure and renal function.[5] We herein contribute to the limited body of literature on the histopathology of congestive nephropathy, and present the case of a patient with impaired kidney function following cardiac allograft rejection, who fully recovered with heart re-transplantation.

Case Report

A 23-year-old man with a history of hypoplastic left heart syndrome and heart transplantation (HTx) shortly after birth presented to the emergency department with progressive dyspnoea. On examination, 3+ pitting oedema of the lower

limbs with warm extremities were noted, with a blood pressure of 109/64 mmHg, and a heart rate of 86 beats per minute. Laboratory tests showed elevated B-type natriuretic peptide (373 pg/mL) and raised serum creatinine levels (1.4 mg/dL; baseline level, 1.1 mg/dL). Echocardiography revealed acceptable left ventricular function (fractional shortening 27%), but a *de novo* severe right ventricular dysfunction (tricuspid annular plane systolic excursion, 8 mm) with moderate-to-severe tricuspid regurgitation, dilated inferior vena cava, pleural effusion, and ascites, indicative of right-sided HF (*Figure* S1). Segmental pulmonary embolism was excluded on computed tomography pulmonary angiogram. Corticosteroid and intravenous immunoglobulin therapy were initiated due to suspected acute allograft rejection, while a combination of diuretics (loop and thiazide diuretics, and aldosterone antagonist) was administered for congestion relief. Serial paracentesis was performed for recurrent ascites. Signs of acute HF was demonstrated on cardiac catheterization, including severe venous congestion and elevated biventricular filling pressures. A diagnosis of progressive cardiac allograft vasculopathy without option for coronary intervention was made. Based on findings of ISHLT (International Society for Heart and Lung Transplantation) grading 1R (mild) acute cellular rejection on endomyocardial biopsy, and the detection of *de novo* human leukocyte antigen antibodies (lack of donor HLA typing), immunoadsorption and rituximab therapy were initiated to treat for possible acute humoral rejection. Despite treatment, no improvement in HF status was observed. The patient was thus listed as a candidate for heart re-transplantation. Ultimately, the reason for the acute rejection and formation of *de novo* human leukocyte antigen antibodies remained unclear. Notably, no signs of chronic HF were observed in the preceding months.

A concurrent and progressive decline in kidney function was noted. At the time of nephrology referral, his serum creatinine was 2.6 mg/dL (eGFR 33 mL/min/1.73 m^2). Urine microscopy showed bland sediment with normal albuminuria, alongside normal tubular stress and injury biomarker (dickkopf-3 and kidney injury molecule-1, respectively) levels. Doppler analysis demonstrated a monophasic intrarenal venous flow (IRVF) pattern, corresponding to a markedly elevated renal venous stasis index of 0.68 (see the supporting information for definition and rationale), and an elevated renal resistive index of 0.84, indicative of severe renal venous congestion and reduced renal parenchymal perfusion, respectively. Autoimmune workup for anti-neutrophil cytoplasm and anti-glomerular basement membrane antibodies was negative. Kidney biopsy was performed to determine the extent of acute and chronic nephron damage and for prognostication of renal outcome after heart re-transplantation to determine the need for concurrent kidney transplantation. Unexpectedly, normal glomeruli and predominantly normal tubular cell differentiation were observed (*Figure 1A–C*), alongside focally accentuated low-grade acute tubular damage and small areas of interstitial fibrosis and tubular atrophy (IFTA) (*Figure 1C,D*). Notably, markedly dilated peritubular veins and capillaries were seen (*Figure 1D,E*). Immunohistochemical staining for SV40 viral antigen for BK virus nephropathy was negative.

Given the distinct histopathological findings suggestive of haemodynamically mediated congestive nephropathy, a decision was made to proceed with urgent heart-only re-transplantation. During the course of his ICU stay, improvement in kidney function was observed, implying improved renal perfusion pressure caused by effective decongestion and noradrenaline treatment. In the post-transplant period, he experienced two episodes of acute kidney injury owing to the surgery itself and to transiently elevated tacrolimus trough levels. His kidney function recovered to near baseline (pre-HF) levels at approximately 3 months post-transplantation. Doppler analysis further showed improvement in renal congestion (pulsatile IRVF pattern) and parenchymal perfusion status.

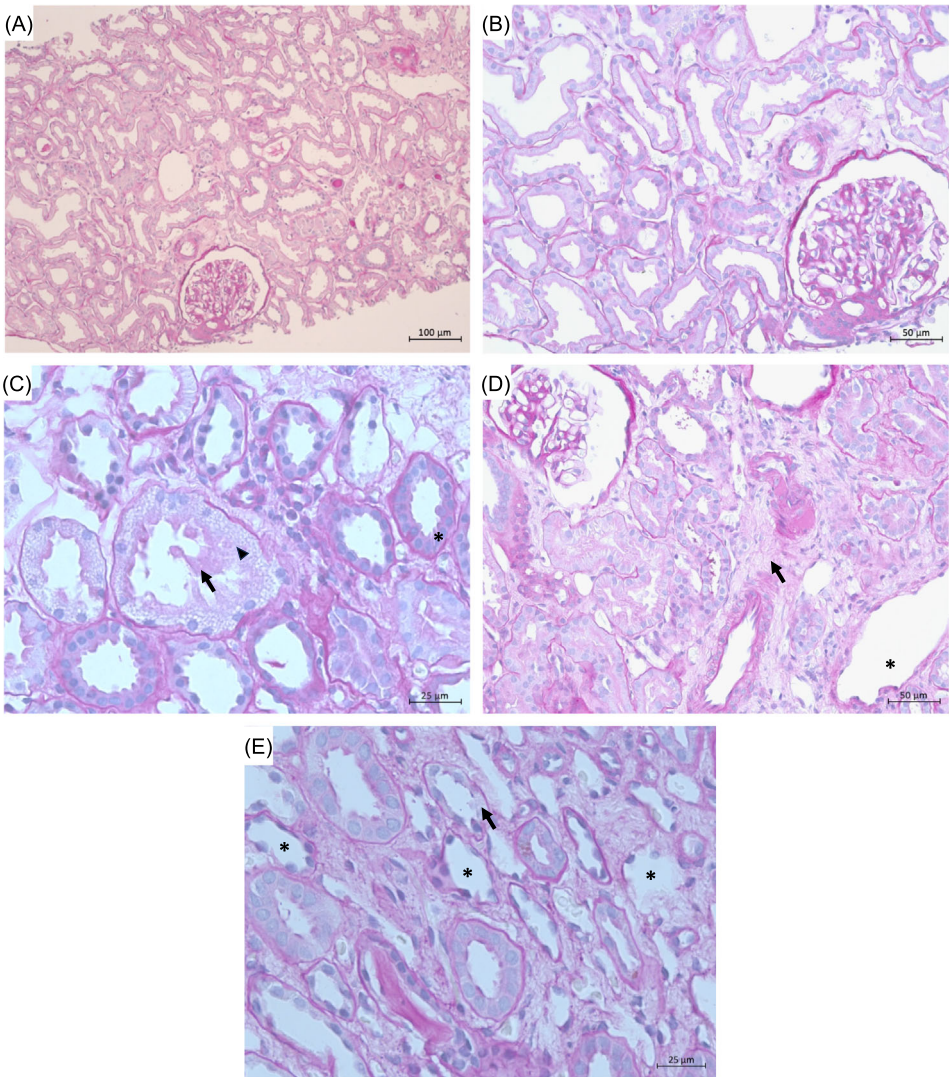
Discussion

There is growing consensus that rises in serum creatinine in the context of acute HF may be largely functional and congestion-driven, rather than a reflection of morphologically detectable tubular injury, and may thus be considered a clinically benign phenotype.[6,7] Our predominant findings of dilated peritubular capillaries on histopathology, normal urinalysis results on a background of markedly reduced eGFR, and severely congested renal venous flow identified on Doppler supported the diagnosis of congestive nephropathy.

The development of congestive nephropathy has been proposed to stem from an increase in venous congestion or intra-abdominal pressure, leading to tissue oedema and raised renal interstitial hydrostatic pressure.[5] With the limited expansion capacity of the renal capsule, vessels and tubules become compressed, resulting in transiently reduced renal perfusion pressure and, thus, reduced GFR. Subsequent tissue hypoxia, and the resultant activation of the systemic inflammatory response, may exacerbate abnormal kidney function. However, the role of long-standing congestion in kidney fibrosis remains a matter of controversy; whether our findings of IFTA were the result of recurrent acute tubular injury or persistent venous congestion remains unclear. Further exploration is therefore warranted.

To date, the histological diagnostic criteria for congestive nephropathy have not been defined due to the lack of biopsy samples with diagnosed congestive CRS. To our knowledge, our paper represents the third human case report involving the histopathological assessment of congestive nephropathy

Figure 1 Representative histopathological findings of our patient with congestive nephropathy. (A) Normal kidney parenchyma (10× magnification). (B) Normal glomerulus (20× magnification). (C) Tubular cells with normal tubular differentiation (asterisk), as well as acute injury with focal shedding of degenerating epithelial cells into the lumen (arrow) and cytoplasmic vacuolization (arrowhead) (40× magnification). (D) Mild interstitial extracellular matrix accumulation (arrow) and dilated vein (asterisk) (20× magnification). (E) Chronic tubular damage with relatively small tubular diameter, flat epithelium, and broad basement membrane (arrow), amongst dilated peritubular capillaries (asterisk) (40× magnification). All images were PAS-stained and were viewed using low-power light microscopy.



(*Table* S1). While animal studies have been instrumental in exploring the underlying mechanisms of this disease, models of isolated congestion have yet been established, and the long-term effects of congestion on the renal parenchyma remain unknown (*Table* S1). Most animal studies focus on glomerular and tubular damage secondary to an abrupt increase in venous pressure. In contrast, chronic venous congestion, as usually observed in CRS patients, predominantly manifests as interstitial oedema and tubular dysfunction with associated morphometric lesions. We acknowledge that the histological findings of our patient were non-specific, and a follow-up biopsy, which was not performed due to ethical reasons, may have allowed for more accurate characterization of congestive nephropathy. Patients listed for HTx represent a distinct cohort for the study of congestive nephropathy, as kidney biopsies are performed in selected cases for prognosis, wherein patients with reversible kidney damage are segregated from those with severe IFTA and advanced CKD to guide the indications for heart-only or combined heart-kidney transplantation. Notably, case series studies have reported the lack of correlation of GFR and proteinuria with the degree of IFTA on biopsy, as well as the limited predictive value of IFTA for

post-HTx renal outcomes.[8,9] We postulate that such observations may have been the manifestations of unrecognized congestive nephropathy.

In conclusion, our case of acute congestive nephropathy contributes to the current understanding of the disease, and confirms the short-term reversible nature of this subtype of CRS. Our findings may serve as the benchmark for future research in defining the histological criteria for congestive nephropathy, and in evaluating the utility of renal venous Doppler ultrasonography as a non-invasive diagnostic approach to improve the clinical classification of CRS.

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Conflict of interest

FH-S, JR, JN, SS, CX, H-WB, and H-JG declare no competing interests.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Clinical course of our 23-year-old patient with severe cardiorenal syndrome secondary to cardiac allograft failure.

Table S1. Relevant animal and human studies with histopathology reports of renal dysfunction due to venous congestion or elevated intra-abdominal pressure.

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