Subacute Biventricular Heart Failure due to New Onset Nephrotic Syndrome

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Introduction

The isolated entities of heart failure and nephrotic syndrome (NS) commonly present with overlapping symptoms. Lesser known is the role systemic inflammation and urinary protein loss from nephrotic syndrome plays in the development of heart failure. Providers should be aware of the pathophysiology of nephrotic syndrome and its potential as a precipitant of subacute heart failure.

Case Presentation

A 56-year-old female with a past medical history of unspecified kidney disease presented with generalized edema to the mid-sternum. Symptoms included orthopnea, paroxysmal nocturnal dyspnea, decreased urine output, and dark urine. She denied chest pain or palpitations at any point in her life.

On physical exam, blood pressure was 134/88 mmHg. Heart sounds were distant and pulmonary crackles were present bilaterally.

Laboratory values were significant for albumin of 1.7, total protein of 5.8, and massive proteinuria of 15.98 g/day by random protein to creatinine ratio. BNP was 2817 pg/mL and troponin levels were within normal limits. Creatinine was 1.51 mg/dL with an unknown baseline and BUN 33.

EKG was low voltage but without ST changes. Her chest X-ray showed bilateral pleural effusions and pulmonary edema.

Resolution of Case

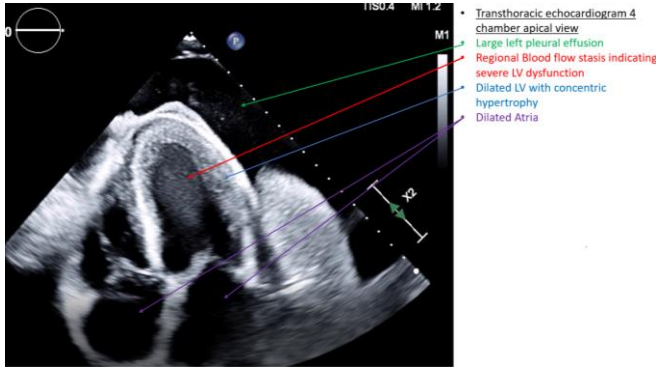
Milrinone was required to aid diuresis, but after euvolemia was achieved, right heart catheterization revealed mildly elevated right atrial and right ventricular pressures (RA 12/12/11 and RV 39/12/11), normal pulmonary artery pressure (34/15/24), and PCWP < 12 mm Hg.

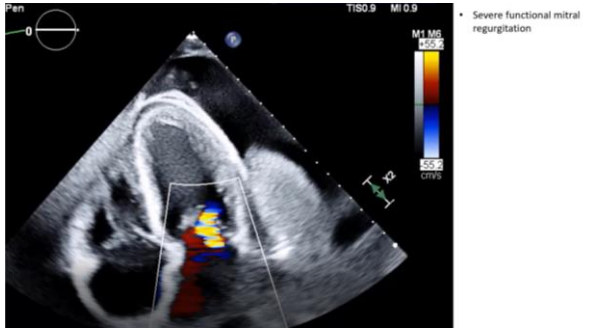
Metoprolol succinate 12.5 BID and lisinopril 5 mg daily were started, after which proteinuria decreased to 9.61 g/day and she was able to be discharged to subacute physical rehabilitation. Prior to endomyocardial biopsy or cardiac MRI, the patient passed suddenly of a PEA arrest.

Diagnostic Studies, Imaging & Case Outcome

- Transthoracic echocardiogram
- EF 25% with severe global hypokinesis of bilateral ventricles
- Severe pulmonary hypertension with pulmonary systolic pressure of 62-62 mm Hg
- Moderate concentric left ventricular hypertrophy
- Moderate to severe functional mitral regurgitation
- Moderate pericardial effusion without evidence of increased intrapericardial pressure
- Large left and right pleural effusions.

Renal biopsy revealed diabetic nephropathy and HbA1c of 7.9% confirmed new diagnosis of likely longstanding diabetes mellitus.





Discussion

A theoretical link between NS and ischemic cardiomyopathy exists because NS causes hyperlipidemia which increases the risk of atherosclerosis.[1,2] A causal relationship between NS and heart failure is not agreed upon, and children with focal segmental glomerular sclerosis develop heart failure without coronary artery disease.[3]

Our patient had no signs or history of ischemia. Furthermore, she presented with biventricular hypokinesis, which would have required multiple right and left coronary artery ischemic events, and in the presence of renal failure, we would expect a persistently elevated troponin. Therefore, we propose a non-ischemic, causal mechanism of subacute heart failure in our patient presenting with NS.

Severe nephrotic syndrome causes impaired intestinal absorption, protein wasting, and inflammatory activation.[3,4] Malnutrition causes sarcomeric lengthening and ultimately dilated cardiomyopathy.[8] Inflammation, specifically elevated TNF-alpha, has anti-inotropic effects on cardiomyocytes and leads to progressive ventricular dilation and cardiomyopathy over a chronic time period.[5]

In a mouse model, Moreira-Rodrigues et al. linked systemic inflammation due to NS with the development of dilated cardiomyopathy. Following puromycin aminonucleoside (PAN) injection, a protein that induces massive proteinuria and reduces GFR without impacting de novo protein synthesis, mice exhibited both skeletal and cardiac muscle atrophy without fibrosis. TNF levels were elevated after only days and left ventricular cardiac function was impaired in both contraction and relaxation.[3] Cardiac atrophy was accompanied by decreased gene and protein expression of SERCA2a, the main protein involved in sarcoplasmic reticulum calcium reuptake.[3]

Through one mechanism or another, NS is causally related to heart failure. We propose that the systemic inflammation and proteinuria causing malnutrition were the causes of her subacute heart failure. The treatment of our patient consisted of aggressive diuresis and eventually the addition of an ACE inhibitor aimed at improving urinary protein loss and reducing afterload. Although more research is needed to further elucidate NS as a cause of heart failure, treatment aimed at NS may have lasting impacts on improving patients' cardiac function.

References

1. Ordoñez JD, Hiatt RA, Killebrew EJ, Fireman BH. The increased risk of coronary heart disease associated with nephrotic syndrome. *Kidney Int*. 1993;44(3):638-642. doi:10.1038/ki.1993.292
2. Vaziri ND. Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences. *Kidney Int*. 2016;90(1):41-52. doi:10.1016/j.kint.2016.02.026
3. Moreira-Rodrigues M, Roncon-Albuquerque R Jr, Henriques-Coelho T, et al. Cardiac remodeling and dysfunction in nephrotic syndrome. *Kidney Int*. 2007;71(12):1240-1248. doi:10.1038/sj.ki.5002204
4. De sain-van der Velden MG, de Meer K, Kulik W *et al.* Nephrotic proteinuria has no net effect on total body protein synthesis measurements with (13)C valine. Am J Kidney Dis 2000; 35: 1149-1154
5. Torre-Amione G, Kapadia S, Lee J et al. Expression and functional significance of tumor necrosis factor receptors in human myocardium. Circulation 1995; 92: 1487-1493