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MORNING REPORT

NEPHROTIC SYNDROME AS AN UNDERRECOGNIZED RISK FACTOR FOR CORONARY ARTERY DISEASE (CAD)

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A 47-year-old woman with insulin-dependent type 2 diabetes, hypertension, and active tobacco use presented with an inferior ST-elevation myocardial infarction (STEMI) complicated by complete heart block (CHB) and hypotension progressing to cardiogenic shock. She received appropriate medical management in the field per advanced cardiac life support guidelines, was urgently started on a dopamine infusion and subsequently required transcutaneous pacing before being intubated.

An acute ST-elevation myocardial infarction (STEMI) is an event in which transmural myocardial ischemia results in myocardial injury or necrosis, leading to ST-segment elevation on electrocardiogram of at least 1 mm in two consecutive extremity leads or at least 2 mm in two consecutive precordial leads. Our patient developed an unstable bradyarrhythmia as a result of her infarction and rapidly progressed to profound cardiogenic shock requiring vasopressor agents and pacing to maintain hemodynamics. Her prolonged hypotension markedly raises concern for her risk of developing significant end organ damage. This inferior STEMI will naturally require urgent revascularization based on STEMI treatment protocols.

Her coronary angiogram revealed severe three-vessel coronary artery disease (CAD), including a fully occluded proximal right coronary artery (RCA) consistent with the culprit lesion for her inferior STEMI and resultant CHB. She underwent successful percutaneous coronary intervention with the placement of one drug-eluting stent, and she rapidly returned to normal sinus rhythm following reperfusion. With normalization of her heart rhythm her blood pressure improved and she was titrated off the dopamine infusion. She was admitted to the intensive care unit and rapidly extubated.

Complications of myocardial infarction (MI) are common, and include cardiogenic shock, arrhythmias, congestive heart failure, and pericarditis. Delayed cardiac mechanical complications include ventricular free wall rupture, interventricular septum rupture, and acute mitral regurgitation. Non-cardiac complications include acute kidney injury, which is common after MI and is well known to be associated with both short and long-term elevated mortality.[1] Along with her underlying comorbid conditions, and also considering the contrast agent load from her catheterization, our patient's risk of post-STEMI kidney injury is significant.

Her subsequent TTE was notable for acute systolic heart failure; her left ventricular ejection fraction was 40-45% with accompanying akinetic inferior and inferolateral cardiac walls, consistent with her complete RCA occlusion. Her hospital course was further complicated by acute kidney injury with azotemia. Her creatinine on arrival was 2.87 mg/dL (Baseline 0.8 mg/dL), which remained persistently elevated post reperfusion, peaking at 3.62 mg/dL. Her urinalysis was notable for large blood and >500 mg/dL of protein. Urine microscopy showed one muddy brown cast. She continued to produce appropriate urine in the hospital and had no dialysis indications.

In the clinical context of a late presenting STEMI complicated by cardiogenic shock, this kidney injury was consistent with acute tubular necrosis (ATN). ATN is a syndrome of intrinsic acute renal injury that is secondary to ischemic or toxic insults and is a common cause of acute renal failure in hospitalized patients. Decreased blood supply results in necrosis of tubules leading to renal injury. Brown, granular casts seen in the urine of our patient supported this diagnosis. There was a possible contributing concurrent element of contrast-induced nephropathy from her PCI that was difficult to precisely tease out from her underlying ATN.

In reviewing prior urine studies done as part of her outpatient diabetes care several years preceding her STEMI, we discovered a trend of significant proteinuria, which had not been added to her problem list. Old urinalyses were notable for nephrotic range proteinuria

continued on page 2

MORNING REPORT *(continued from page 1)*

approximating 8 grams of protein in her urine daily, far exceeding the criteria for nephrotic syndrome (NS). Her albumin had been concurrently low (<2.5 g/dL) and she also had significant dyslipidemia; her most recent lipid panel was notable for total cholesterol of 258 mg/dL and LDL of 153 mg/dL. This progressively worsening dyslipidemia correlated with the progression of her proteinuria over time.

Nephrotic syndrome consists of peripheral edema, heavy proteinuria, and hypoalbuminemia, often with hyperlipidemia. The syndrome can be due to intrinsic renal disease,(e.g., membranous nephropathy, focal segmental glomerulosclerosis) or secondary to an underlying medical condition (e.g. type 2 diabetes mellitus, systemic lupus erythematosus). Management of NS is limited by a lack of clear guidelines, with treatment often consisting of sodium restriction, fluid restriction, and diuretics. The role for renal biopsy in diagnosing nephrotic syndrome remains unclear.

The most likely etiology of her NS was thought to be her longstanding poorly controlled diabetes. Her hemoglobin A1C had been above 11% for many years. Complement studies were within normal limits, both her serum and urine protein electrophoresis were unremarkable, and an infectious work-up including HIV, hepatitis B, and hepatitis C was negative. The case for diabetic nephropathy was thought to be strong and renal biopsy was deferred.

The question arose as to why this relatively young and thin female (BMI 24) developed such profound ischemic heart disease. While she had several obvious risk factors for CAD including diabetes mellitus and active tobacco use, the severity of her three vessel disease culminating in a life threatening STEMI raised the question of whether her persistently undiagnosed nephrotic syndrome could have been contributing to her extensive heart disease.

Patients with NS have long been assumed to be at increased risk for atherosclerosis and heart disease because of NS-associated hyperlipidemia and hypertension, as well as the intermittent use of steroids in therapy. One retrospective chart review with age matched controls demonstrated that patients with NS were at increased risk of CAD, however this research excluded diabetics, making it less relevant to our patient.[2] A post-mortem pathologic analysis of the coronary arteries in 20 patients with nephrotic syndrome showed significantly more coronary luminal narrowing by atherosclerotic plaques compared to controls.[3] Primarily in the pediatric domain, several case reports have been published of children with premature coronary atherosclerosis thought to be secondary to underlying nephrotic syndrome.[4,5] Thrombosis represents another possible etiology for CAD among patients with NS, as a result of the hypercoagulable state stemming from imbalances in the coagulation cascade, the loss of antithrombin III in the urine, and an overall milieu of increased platelet activation and aggregation.[6] While no official guideline recommendation exists, many providers treat the subsequent dyslipidemia in nephrotic syndrome with lipid lowering medications to reduce the risk of coronary disease.[4]

During her hospitalization our patient was initiated on a guideline-directed medical therapy package for coronary artery disease and heart failure including dual-antiplatelet therapy (aspirin and clopidrogel), a beta-blocker (carvedilol), a high intensity statin (atorvastatin), and isosorbide dinitrate. An inhibitor of the renin-angiotensin-aldosterone system was not initiated due to her poor renal function, which failed to return to her baseline. She was instructed to follow a sodium and fluid restricted diet, and was discharged in stable condition with persistent kidney injury, with plan for outpatient follow up.

This case highlights the importance of reconciling patients' known comorbid conditions but also remaining curious to unexpected diseases or unexpected severity of presentations.

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