Progressive Renal Failure in a 24-Year-Old Man

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A 20-year-old man presented to the emergency department (ED) with a 3- to 4-week history of worsening dyspnea upon exertion, lower extremity edema, weakness, anorexia, and vomiting. He also reported that, over the last 4 years, he would have intermittent painless hematuria several times per year, not always associated with activity. Six months prior to admission, he reported a decreased visual acuity, as well as difficulty hearing, needing to turn up the volume on his mobile devices. He has not seen a physician since age 16 years when he needed a physical for school and reported no antecedent illnesses. He had tested negative for COVID-19 on 2 occasions and was not vaccinated against COVID-19.

Physical Examination

Upon presentation, he was afebrile and had a normal pulse of 84 beats/min, increased respiration rate of 20 breaths/min, increased blood pressure of 154/88 mmHg, and an oxygen saturation of 94% on room air. No jugular vein distention was noted. His heart sounds were normal with an S1/S2 without rub, and his lungs had rales 1/3 on both sides.

A hepatojugular reflux was elicited, without abdominal ascites. Extremities had 3+ edema to the mid-thigh with pitting. Results of a neurological examination were within normal limits, but his cranial nerves were not tested.

A chest radiography scan was conducted, results of which revealed evidence of pulmonary edema (Figure). Results of an electrocardiogram showed a normal sinus rhythm without ST-T changes.

Laboratory Testing

Results were significant for a low sodium level of 126 mEq/L, a high potassium level of 6.5 mEq/L, a low chloride level of 96 mEq/L, and a low total carbon dioxide level of 12 mEq/L. The following values were also elevated in this patient: anion gap, 18 mEq/L; blood urea nitrogen, 175 mg/dL; creatinine, 14.7 mg/dL; phosphorous, 10.7 mg/dL.

Results of an arterial blood gases test showed acidosis with a pH level of 7.22/21/58/10/88% on room air. Results of a urinalysis showed a normal urine specific gravity of 1.015, a normal pH level of 7.0, an abnormal 3+ protein level, an abnormal 4+ red blood cell count, and a significantly elevated level of red blood cells per high powered field of more than 50.

What is the first order of treatment for this patient?

A. Diuresis with loop diuretics
B. Hemodialysis, ultrafiltration
C. Continuous renal replacement therapy (CRRT)
D. Conservative care

What other testing should be done?

A. Echocardiogram to assess for left ventricular systolic function
B. 24-hour urinalysis for protein and creatinine clearance
C. Detailed family history
D. All of the above

A detailed family history obtained at presentation revealed moderate hearing loss in several relatives, including first-degree cousins, but none reported in his immediate family—mother, father, and 2 sisters.

Of note, the patient was held back from sports at age 14 years because he had had hypertension and mild proteinuria, although it was never quantitated. He had required corrective lenses since age 5 years because of myopia.

A 24-hour urinalysis showed a total volume of 350 ml/24 hrs, 3226 mg protein/24 hrs, and creatinine clearance of 4 mL/min. Results of an echocardiography scan showed normal left ventricular systolic function (50%-55%), concentric left ventricular heart function, and mild to moderate mitral regurgitation.

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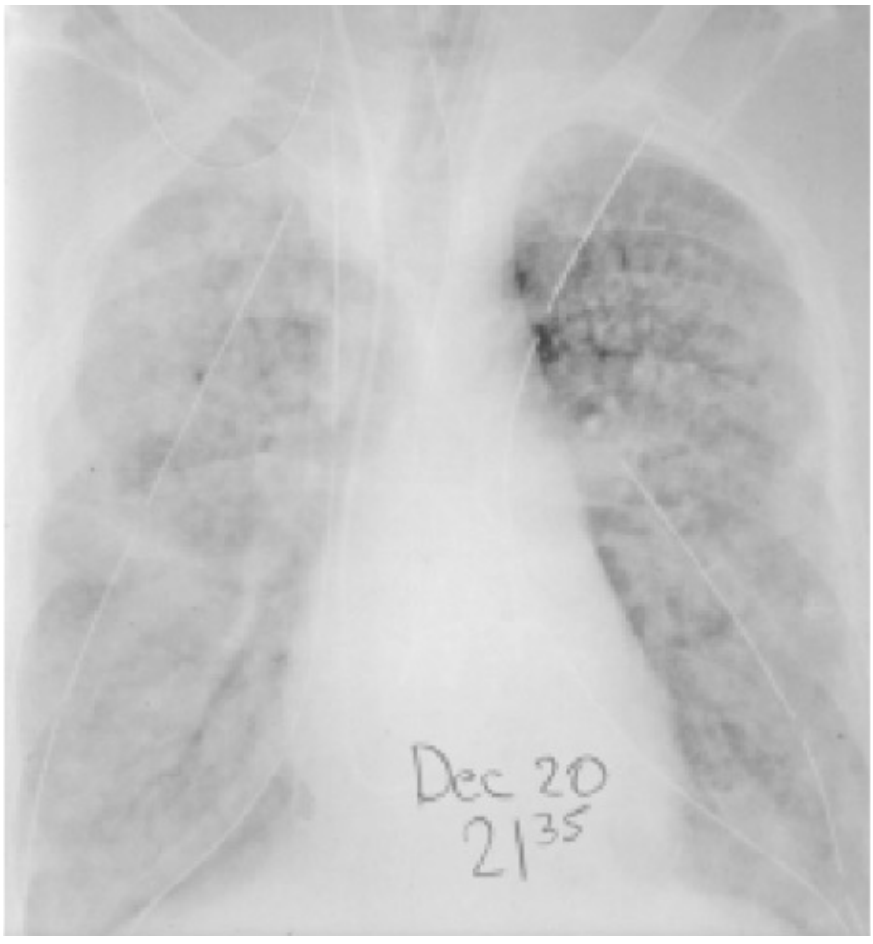

Figure. Results of a chest radiography scan showed pulmonary edema.

There was no bloodwork conducted prior to this ED visit. The last urinalysis was conducted at age 14 years, results of which showed 1+ protein and 1+ red blood cells. Results of a renal ultrasonography scan showed atrophic kidneys, with the left at 6.3 cm in length (reference range, 10-12 cm), the right at 6.9 cm in length, and thinned cortices. No hydronephrosis was noted.

What would be in the differential diagnosis for advanced, probable end-stage renal disease in this young man?

A. Rapidly progressing glomerulonephritis
B. Hereditary nephritis (Alport syndrome)
C. Immunoglobin A (IgA) nephropathy (Berger disease)
D. Acute tubular necrosis
E. All of the above
F. A, B, and C

A, B, and C are the best answers, as acute tubular necrosis (answer D) is unlikely to cause this level of chronic kidney disease (CKD), small atrophic kidneys, and advanced renal disease. We still need to consider other glomerular diseases in a young man, and the glomerular panel—including C3, C4, antinuclear antibodies, anti-neutrophil cytoplasmic autoantibodies, and antiglomerular basement membrane—returned results within normal limits. With the family history and personal history of some ocular and hearing issues, hereditary nephritis (HN) should be considered. IgA nephropathy can also present in the setting of advanced renal disease (especially if it is crescenteric), but IgA nephropathy usually does not present with hearing and visual issues early in life. CKD can, in general, present with hearing loss.[1]

Discussion

HN—otherwise known as Alport syndrome—is a rare genetic disorder collagen synthesis, affecting the basement membranes in several systems, including renal, auditory, and visual. Defects in synthesis of collagen-IV genes, particularly *COL4A3, COL4A4,* and *COL4A5*, account for the clinical findings seen in HN. HN is an X-linked, autosomal recessive or dominant disorder and carries significant risk for renal failure and end-stage renal disease (ESRD), sensorineural deafness, and eye abnormalities.[2]

When considering genetic testing, *COL4A3–COL4A5*, which affects the structure or function of a collagen-IV α-chain, can confirm a diagnosis of HN. When noted, other family members should be tested to determine their level of risk for HN. ESRD can be predicted with genetic testing as well, since hemizygous men with *COL4A5* have a 90% risk of ESRD by age 40 years, while women with a heterozygous *COL4A5* variant have up to a 30% likelihood of having ESRD by age 60 years.3 HN inheritance patterns include X-linked, autosomal recessive, and autosomal dominant means. About 80% of HN cases are X-linked type due to mutations in *COL4A5* found on the X-chromosome.[3] Autosomal recessive inheritance accounts for about 15% of individuals, related to mutations in both the alleles of either *COL4A3* or *COL4A4*.[4]

Both ocular and vestibular abnormalities should be a clue to thinking about this disease, especially in younger patients, and diagnosis and intervention may help alleviate progression to CKD. Ocular issues such as lenticonus, corneal opacities, fleck retinopathies, and temporal retinal thinning have been described and can lead to cataracts.[5] Early detection of these conditions should prompt physicians to think of HN as well. As far as auditory or

sensorineural hearing loss, progressive bilateral high-frequency sensorineural hearing loss is commonly found in patients with HN. This is usually detected in school for children who later develop HN.[6]

What type of biopsy (if any) would be helpful in this patient?

A. Kidney biopsy
B. Skin biopsy
C. None of the above
D. Both A and B

A tissue diagnosis for HN can come from renal or skin biopsies, but there are pros and cons to both. In a kidney biopsy specimen, finding a longitudinal splitting of the lamina densa of the GBM is diagnostic but may not be present in younger patients. Attenuation of the GBM is seen in young men with X-linked HN, women with X-linked HN, young men and women with autosomal recessive HN, and all patients with autosomal dominant HN.[7] A skin biopsy can diagnose suspected X-linked HN. This looks for a monoclonal antibody against the α-5(IV) chain. If this is absent in a man, a diagnosis of X-linked HN can be made, and if it is normally expressed, then an alternate diagnosis may be present, including variants of HN. In these cases, a renal biopsy may be warranted.[8]

True or False: Since there is no real treatment for HN, diagnosis with invasive biopsy is not needed.

A. True
B. False
C. Unsure

Treatment and management

As with many other renal diseases, modification of the renin-angiotensin-aldosterone axis leads to potential benefits in slowing the progression of CKD. In a 2020 study, Yamamura and colleagues examined renal survival in patients taking and not taking renin-angiotensin-aldosterone system inhibitor (RAASi) therapy.[9] The median renal survival period of patients in this cohort was 35 years; the onset of ESRD in patients not taking RAASi was age 28 years, whereas in patients taking RAASi, the median age of onset was about age 50 years.[9] With uncontrolled hypertension also contributing to declines in renal function, targeting aggressive blood pressure management is warranted. This may require additional agents in combination with RAASi. Even with progression slowed, ESRD remains a likely outcome. Therefore, other therapeutic options are essential for managing HN. These therapies can target areas such as:

- Reducing proteinuria, adjunctive to the use of RAASi
- Reducing tubular protein toxicity
- Reducing tubulointerstitial fibrosis

The CARDINAL trial examined bardoxolone, a semisynthetic drug that activates nuclear factor erythroid 2-related factor 2 (Nrf2).[10] Nrf2 is important in expressing genes related to oxidative stress and inflammation. In this study, treatment with bardoxolone showed significant improvement in kidney function vs placebo the intent-to-treat population. This equated to a 7 to 8 mL/min improvement in estimated glomerular filtration rate (eGFR).[10] Bardoxolone also demonstrated a significant improvement in eGFR a month after the medication was stopped.10 In 2021, bardoxolone is being submitted to the US Food and Drug Administration for potential treatment of CKD caused by HN.

Patient outcome

He was started on dialysis and emergent hemodialysis for fluid overload and uremia. A renal biopsy was performed, results of which confirmed significant tubulointerstitial disease and fibrosis, as well as pathological findings consistent with HN. Once stable, the patient was converted to home hemodialysis and was referred for renal transplant evaluation.

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