

LSUHSC-S Renal Pathology Consultative Services Interesting Case

Case Study #: 7
10/19/09 Answers

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Clinical History:

26 year old Caucasian female presented with worsening renal function, edema, creatinine of 1.52, and albumin of 3.4.

Delivered a baby girl 8 months prior to presentation, at which time the patient developed ARF secondary to NSAIDs.

Case courtesy of Dr. M.L. Larroque, MD

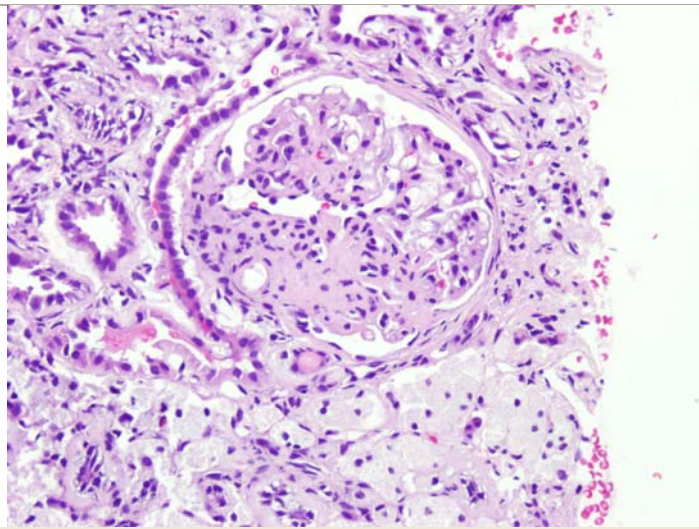


Figure 1: H&E stain shows a glomerulus with a segmental sclerotic lesion.

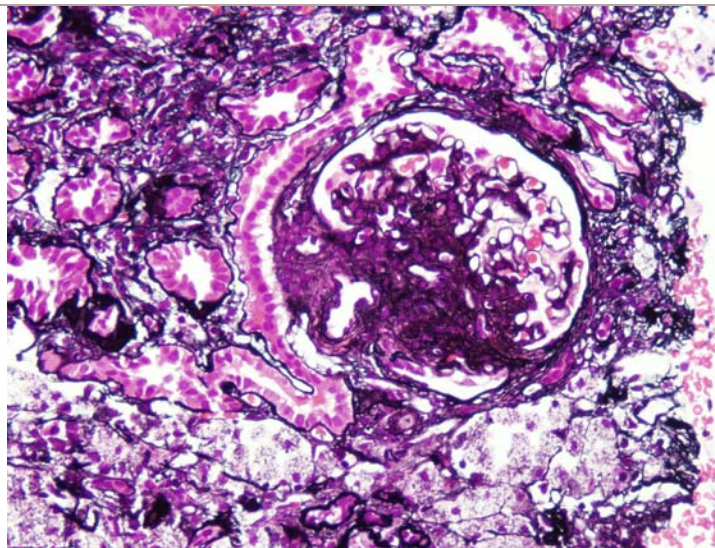


Figure 2: JM Silver stain reveals a segmental sclerotic lesion

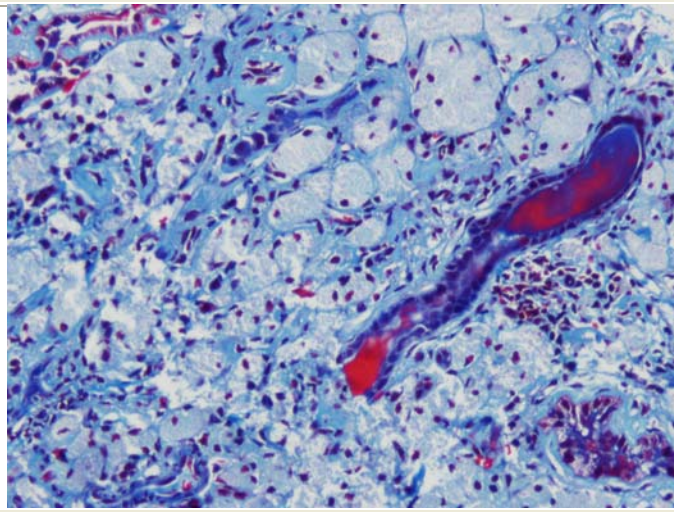


Figure 3: Masson's trichrome highlights the presence of interstitial foam cells.

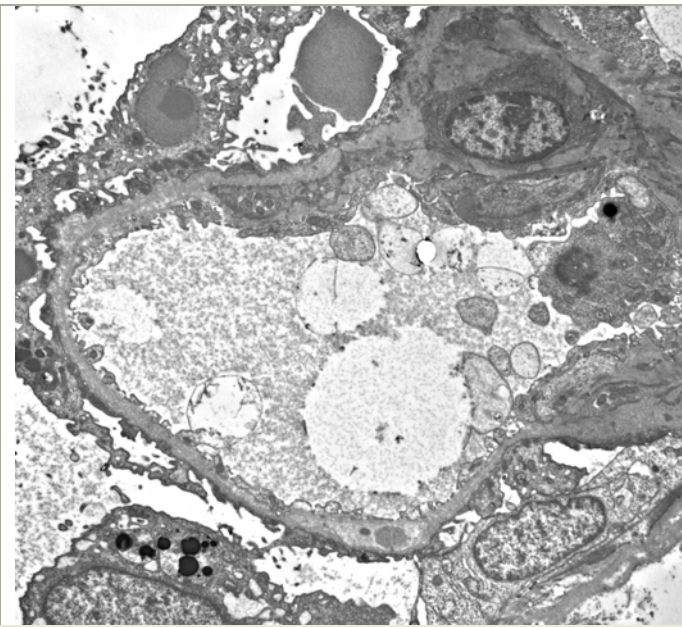


Figure 4: EM demonstrates diffuse effacement of podocyte foot processes. In addition, basement membrane (BM) attenuation alternating with areas of BM thickening and electron dense granulations are identified.

Question:

1. What additional clinical history would be of interest in this case?

A family history of hereditary nephritis was present in this patient. In general, a clinical history of bilateral high-tone sensorineural deafness, ocular abnormalities, and hematuria would also be helpful.

2. What is your diagnosis based on the LM and EM findings?

LM shows a glomerulus with a segmental sclerotic lesion. On EM, diffuse effacement of podocyte foot processes is identified. In addition, basement membrane (BM) attenuation alternating with areas of BM thickening and electron dense granulations are seen. These findings are characteristic of Hereditary nephritis, also known as Alport's syndrome.

3. What genetic abnormalities are commonly involved in this entity?

In 1927, Cecil A. Alport described 3 generations of a family with combinations of progressive hereditary nephritis and deafness. Hematuria is the most common presenting symptom, and that males are affected more severely than females. In most patients, the disease is inherited as an X-linked trait; however, some families have AR and AD forms.

Alport's syndrome is caused by mutations in the genes encoding alpha-3, alpha-4, or alpha-5 chains of type IV collagen of the basement membranes.

Three genetic forms of Alport's syndrome exist:

- a) XLAS, which results from mutations in the *COL4A5* gene and accounts for 85% of cases
- b) ARAS, which is caused by mutations in either the *COL4A3* or the *COL4A4* gene and is responsible for approximately 10-15% of cases
- c) ADAS, which is caused by mutations in either the *COL4A3* or the *COL4A4* gene and is rare.

4. What prognosis is expected for this disease?

Renal prognosis depends on the kind of mutation. Approximately 90% of patients with Alport's syndrome develop ESRD by age 40 years. Prognosis in females with XLAS is usually benign, with only 12% developing ESRD by age 40 years and 30% by age 60 years.

This patient with significant glomerulosclerosis already present at age 26 will likely be in the 12% group with early onset of renal failure.

References:

Van der Loop FT, Heidet L, Timmer ED, et al. Autosomal dominant Alport syndrome caused by a *COL4A3* splice site mutation. *Kidney Int.* Nov 2000; 58(5):1870-5.

Kashtan CE. Alport syndrome and thin glomerular basement membrane disease. *J Am Soc Nephrol.* Sep 1998; 9(9):1736-50.

Flinter F. Alport's syndrome. *J Med Genet.* Apr 1997; 34(4):326-30.

Heidet L, Cai Y, Guicharnaud L, et al. Glomerular expression of type IV collagen chains in normal and X-linked Alport syndrome kidneys. *Am J Pathol.* Jun 2000; 156(6):1901-10.

Jais JP, Knebelmann B, Giatras I, et al. X-linked Alport syndrome: natural history in 195 families and genotype-phenotype correlations in males. *J Am Soc Nephrol.* Apr 2000; 11(4):649-57.

Meleg-Smith S, Magliato S, Cheles M, et al. X-linked Alport syndrome in females. *Hum Pathol.* Apr 1998; 29(4):404-8.