Image Quiz 4

CLINICAL HISTORY:

A four month old, first born male child developed generalized body swelling and oliguria since one month (onset at three months of age).Antenatal period uneventful.
On examination: BP 140/98 mmHg, anasarca and mild ascites +

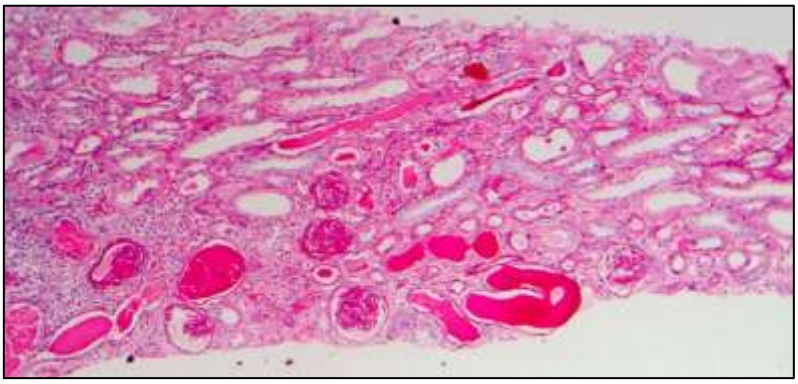
INVESTIGATIONS:

- Urine albumin 4+, granular casts + hyaline casts +, no RBC's.
- Serum creatinine 159.2 u mol/L (1.8 mg%).
- Serology for ANA, anti dsDNA, Viral markers- negative
- Serum complements C3 and C4- within normal limits, dyslipidemia +.

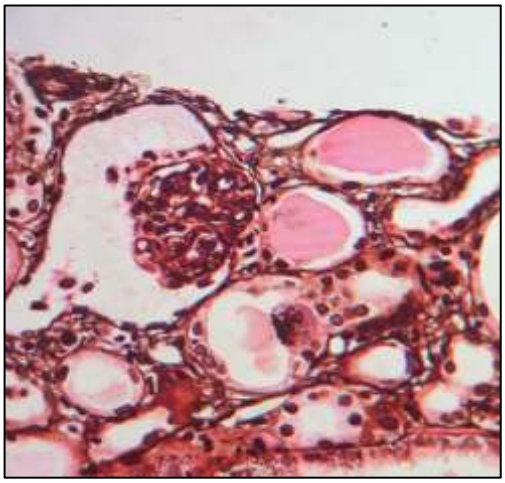
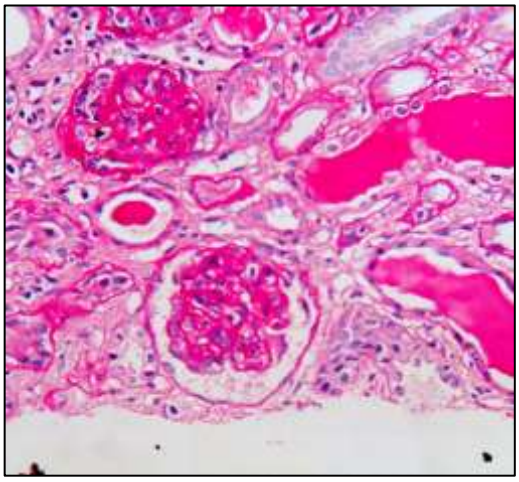
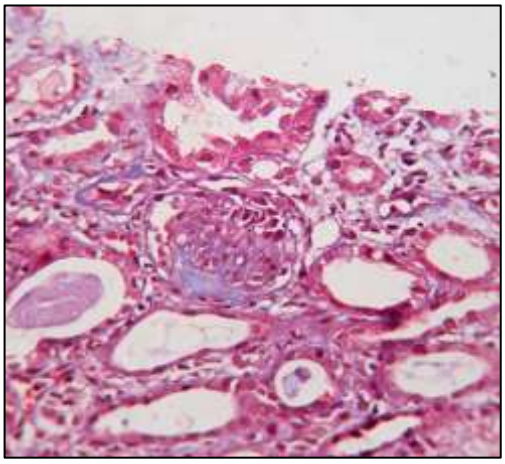
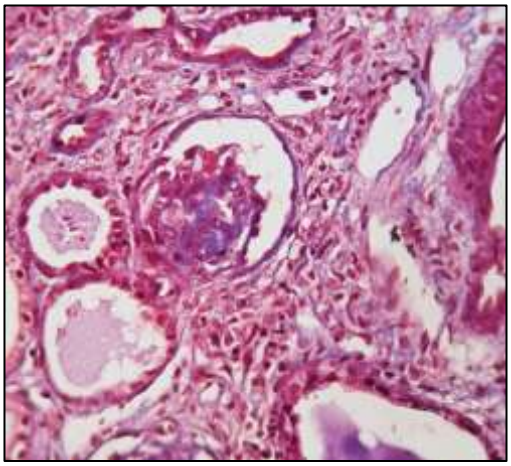
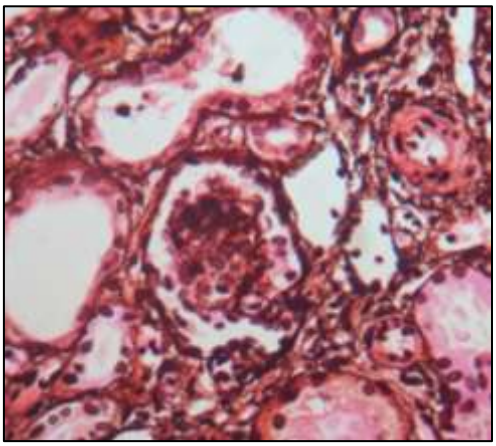
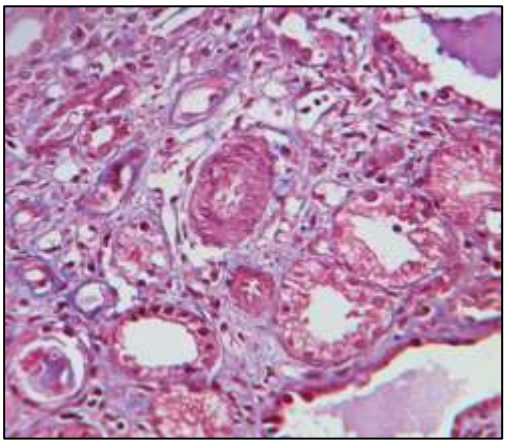
In a child presenting with nephrotic syndrome in first year of life with severe hypertension and renal dysfunction, a percutaneous renal biopsy was performed.

DIF studies were negative except for non-specific entrapment of IgM and C3.

MICROSCOPY:



Low power image of a PAS stained section showing a focus of tubular atrophy, interstitial fibrosis, chronic interstitial inflammation and several dilated tubules containing inspissated hyaline casts and glomeruli exhibiting varying degree of mesangial sclerosis.

Photomicrographs showing glomeruli exhibiting varying degree of mesagial sclerosis without significant increase in mesangial cellularity. The mesangial area in silver methenamine stained sections shows a peculiar “reticulated” appearance. Few glomerular tufts show a corona of hypertrophied podocytes forming pseudocrescent like structures. Vessels show hypertension related alterations.

DIAGNOSIS:

Diffuse Mesangial Sclerosis (DMS)

DISCUSSION:

The differential diagnosis of nephrotic syndrome in first year of life (NFYL) includes the congenital nephrotic syndrome of the Finnish type (CNF) , idiopathic nephrotic syndrome (including minimal change disease, mesangioproliferative glomerulonephritis & focal and segmental glomerular sclerosis) and diffuse mesangial sclerosis(DMS) [1].

DMS is a rare, usually isolated sporadic condition, but may also be related to heritable mutations of WT-1 *(with or without Denish Drash syndrome or Frasier syndrome)* [2], LAMB2 *(with or without Pierson syndrome or ocular abnormalities*) [3], PLCE1 [4], or NPHS1 [6]. Proteinuria in DMS develops after birth, most commonly between 4-12 months of age, however congenital nephrotic syndrome may also se seen in about 10% of patients with DMS ("French type CNS")[1]. As compared to CNF(Finnish type congenital nephrotic syndrome), placental abnormalities, premature delivery and low birth weight are rare in DMS, indicating that proteinuria develops after birth in these patients. Most patients present with severe hypertension and renal failure ensues rapidly, usually within 1-3 months.

Hsitopathological features of DMS are chracteristic and include diffuse increase in mesangial matrix, usually without significant increase in mesangial cellularity. Shrunken sclerotic glomeruli surrounded by a corona of hypertrophied podocytes are common. Podocyte hypertrophy and hyperplasia may resemble a crescent, however true crescents are rare in DMS. The mesangial sclerosis has a "spongy" or "reticulated" appearance , best appreciated in silver methenamine stained sections. The distributions of DMS lesions(at least in the early stages)is zonal with most severely affected glomeruli located in the

outer cortex . With disease progression, FSGS lesions , significant tubulointerstitial alterations (fibrosis, tubular atrophy and interstitial inflammation) develop. Immunofluoroscence findings are non specific and ulrastructural studies reflect changes associated with the proteinuric state.

Therapeutic amangement of DMS is similar to those for patients with CNF. The nephrotic syndrome in patients with genetic mutations is usually resistant to steroids or other immunosuppression and prognosis is guarded.However, two children with DMS associated with trucating mutations in PLCE1, responding to treatment with steroid/cyclosporine have been reported.[7] Most of mortalities are due to secondary infections.Other complications include growth retardation, delayed motor and mental development, hypothyroidism,thrombtic complications, and other mineral deficiencies (iron, Vitamin D etc.).Bilateral nephrectomy followed by dialysis support till the child is old enough for renal trasplantation is performed at few centres.Unlike CNF, recurrence of nephrotic syndrome , post transplant has not been descirbed for DMS.

REFERENCES:

1. Habib R. Nephrotic syndrome in the 1st year of life. Pediatr Nephrol. 1993 Aug;7(4):347-53.

2. Habib R et. al. The nephropathy associated with male pseudohermaphroditism and Wilms' tumor (Drash syndrome): a distinctive glomerular lesion--report of 10 cases. Clin Nephrol. 1985 Dec;24(6):269-78.

3. Denamur A et. al. Mother-to-Child Transmitted WT1 Splice-Site Mutation Is Responsible for Distinct Glomerular Diseases. JASN 1999;10:22219-23.

4. Zenker M et. al. Human laminin beta2 deficiency causes congenital nephrosis with mesangial sclerosis and distinct eye abnormalities. Hum Mol Genet. 2004 Nov 1;13(21):2625-32.

5. Gbadegesin R et. al. Mutations in PLCE1 are a major cause of isolated diffuse mesangial sclerosis (IDMS). Nephrol. Dial. Transplant. (2008) 23 (4): 1291-1297.

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7. Hinkes B, Wiggins RC, Gbadegesin R. Positional cloning uncovers mutations in PLCE1 responsible for a nephrotic syndrome variant that may be reversible. Nature Genetics 2006; 38: 1397 – 1405.

SUGGESTED FURTHER READING:

1. Orphanet article on DMS. http://www.orpha.net/data/patho/GB/uk-DMS.pdf

2. Nso Roca AP et. al. Evolutive study of children with diffuse mesangial sclerosis. Pediatr Nephrol. 2009 May;24(5):1013-9.

3. Baskin E et. al. Respiratory-chain deficiency presenting as diffuse mesangial sclerosis with NPHS3 mutation. Pediatr Nephrol. 2011 Jul;26(7):1157-61.

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6. Vats AN.Genetics of Idiopathic Nephrotic Syndrome. Indian J Pediatr 2005; 72 (9) : 777-783