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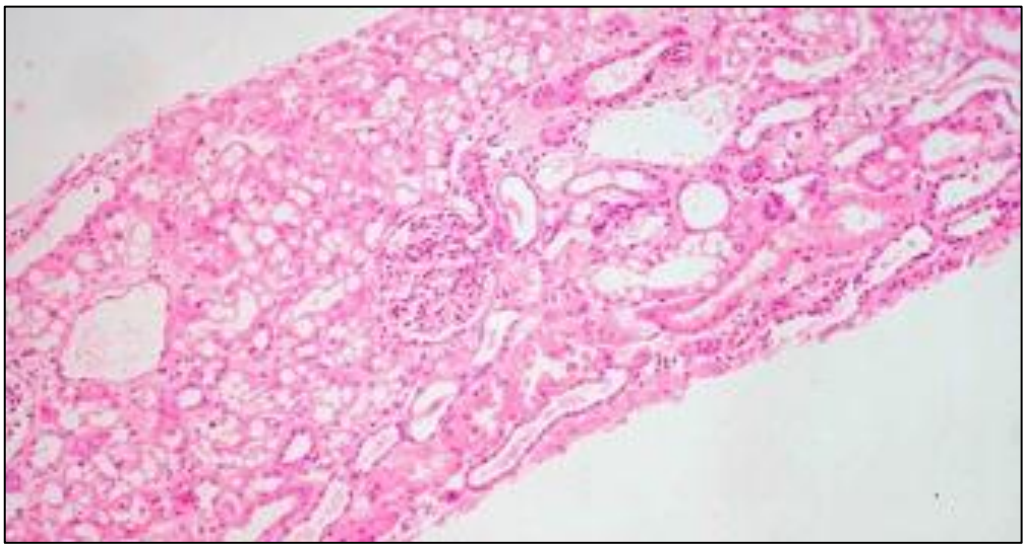
Image Quiz 3

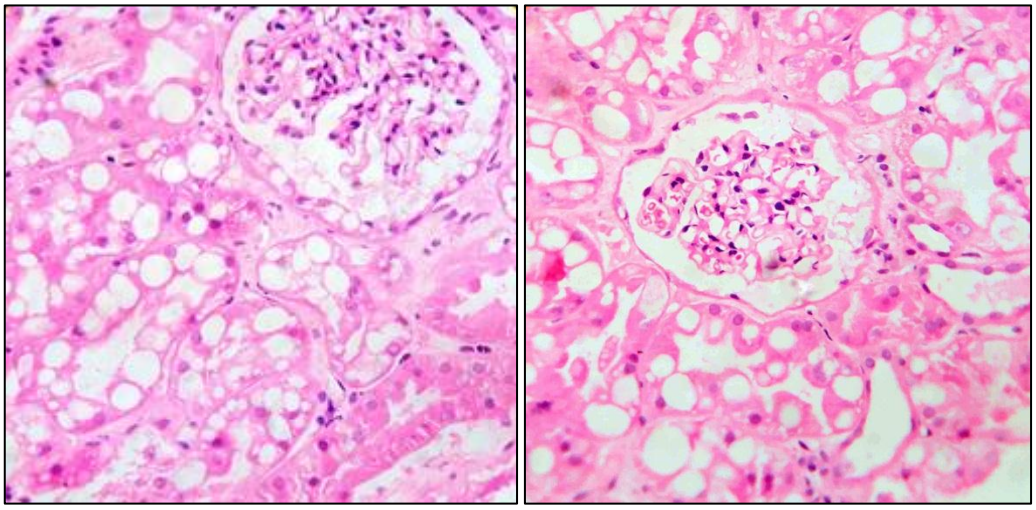
CASE HISTORY:

A 32 year old female underwent renal transplantation for ESRD secondary to IgA nephropathy, brother (age 36 years) being the donor: Haploidentical, crossmatch negative. Baseline creatinine at discharge was 1.1 mg% (97.2 u mol/L) on triple immunosuppresion (Tacrolimus, Wysolone and MMF). Three weeks later she presented with rise in serum creatinine to 2.6 mg% (229.8 u mol/L). On examination: BP-160/98 mmHg, graft tenderness- absent.
Other investigations: Urine albumin- trace, RBC - occasional, WBC 4-5/hpf, Epithelial cells 3-4/hpf. Serum Tacrolimus level: 12 ng/mL. She received an empirical pulse of i.v steroids with non-resolution of graft dysfunction.
A renal allograft biosy was performed, with clinical differentials of ATN /AMR/ calcineurin inhibitor toxicity.
Stain for C4d (by IHC technique) was negative. No immune deposits were seen on immuofluoroscence examination. Representative light microscopic images are provided:

MICROSCOPIC EXAMINATION:



Low magnification image showing prominent vacuolization in tubular epitheilal cell cytopalsm. Significant interstiital inflammation is not seen.



Higher magnification reveals large unevenly sized vacuoles diffusely involving the proximal tubular cytoplasm. The glomeruli appear realtively unremarkable without evidence of significant glomerulitis

FURTHER COURSE:

History revealed that patient was prescribed diuretics (thiazides) for hypertension detected by his treating physician, which were inadvertently administered in high doses for past one week.

Investigations revealed:

- Hypokalaemia : serum potassium 2.3 mmol/l, and hypomagnesemia 0.6 mmol/l
- Spot urine Pottasium/Creatinine ratio:17 mmol/g
- ABG analysis showed features of uncompensated metabolic alkalosis (pH 7.5, paCO2 45 mmHg, HCO^{-3} 27 m Eq/L)
- Plasma renin activity and aldosterone levels were within reference ranges.

Patient was given potassium supplementation and thiazides were replaced by ACE inhibitors. Dose of Tacrolimus was reduced (considering the elevated drug levels and suspecting it to be contributory factor in hypertension).

Serum creatinine settled to 1.2 mg% and serum potassium levels reached a value of 3.5 mmol/l after one week of initiation of treatment.

DIAGNOSIS:

- **Hypokalemic nephropathy**, possibly secondary to inadvertent diuretic abuse with features of acute uncompensated metabolic alkalosis.

DISCUSSION:

Vacuolar change in tubular epithelial cytoplasm can be seen in several conditions [1]

- **Hydropic change** is a fine and diffuse vacuolar clearing of the cytoplasm of the proximal tubular epithelium seen in :
  a. Patients treated with hypertonic solutions such as sucrose solutions, mannitol, high molecular-weight dextrans, radio-opaque contrast material, or intravenous immunoglobulin (IVIg).
  b. acute calcineurin inhibitor toxicity often referred to as *isometric or isotonic vacuolization*. The vacuolation seen by light microscopy is a reflection of distended lysosomes, and dilated endoplasmic reticulum.
- **Hypokalemic nephropathy**: In contrast to the fine vacuoles seen in hydropic change, the vacuoles in hypokalemic nephropathy are much coarser, larger and irregular. The brush border is generally well preserved.
- **Fatty change,** the cytoplasm is filled with fine, small, clear vacuoles best seen at the base of the proximal tubular epithelium. Stains to demonstrate fat must be performed on the frozen sections as lipid is lost during preparation of paraffin sections. This is noted in :
  a. Severe proteinuric states or the nephrotic syndrome with hyperlipidemia and hyperlipiduria.
  b. Patients with Reye's syndrome [2] and phosphorus or carbon tetrachloride poisoning [3]
  c. In patients without significant proteinuria, prominent cytoplasmic vacuolization (and interstitial foam cells) raise the suspicion of Alport's disease.

Hypokalemic nephropathy, also called kaleopenic nephropathy is characterized histologically by various-sized, empty cytoplasmic vacuoles in the renal tubular epithelium. This vacuolation is caused by both expansion of the extracellular spaces with ballooning of the basal lateral cell membranes and cytoplasmic vacuole formation. The condition can be induced by any acute or chronic loss of potassium (including both renal and non-renal causes). The clinical findings are reversible by potassium administration.

Key points to remember are:

1. Hypokalemia can lead to a renal concentrating defect leading to polyuria and polydipsia- Diabetes insipidus
2. Long standing potassium loss may lead to tubulointerstitial disease, proteinuria and renal cysts
3. There is also impairment of renal angiogenesis, evidenced by progressive capillary loss, reduced endothelial cell proliferation, and loss of VEGF expression [4-7]

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