A CASE OF FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FHH) PRESENTING AS BILE CAST NEPHROPATHY.

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INTRODUCTION

- Familial hypocalciuric hypercalcemia (FHH) is a rare autosomal dominant condition. It occurs as a result of mutations in the calcium-sensing receptor gene (CASR) that lead to decreased receptor activity.
- It is inherited in an autosomal dominant fashion with near-complete penetrance, but variable expressivity.
- Most persons with FHH are asymptomatic. Symptoms of hypercalcemia, if present, are less severe than in primary hyperparathyroidism.

CASE REPORT

- A 19 year old male, Engineering student from Bangalore, with history of recurrent pancreatitis since 2016, presented with history of pain abdomen, nausea and vomiting and reduced urine output for 4 days.
- Patient appeared icteric and features of volume overload were present. Urine analysis showed bile casts. Laboratory evaluation showed deranged renal functions (Urea- 271 mg/dl Creatinine – 9.42mg/dl) , Direct hyperbilirubinemia(Total bilirubin – 25 mg/dl, Direct bilirubin 12.02 mg/dl), with raised liver enzymes (AST – 264 U/L, ALT- 214 U/L), raised pancreatic enzyme levels.
- Serum calcium was in the normal range (9.1mg/dl) with normal phosphorous (4.09mg/dl) and raised serum PTH (221 pg/ml).
- He required 2 sessions of hemodialysis in view of anuria, which was later withheld with improving urine output.
- MRCP ruled out structural abnormalities. History of raised PTH during previous episodes of Pancreatitis. Hyperparathyroidism was suspected.
- No parathyroid adenoma on Sestamibi T99m scan.
- 24 hour Urinary calcium excretion was 50mg. Calcium/Creatinine excretion ratio was 0.009.
- As pancreatitis subsided, Obstructive jaundice and AKI improved, with improvement in urine output.
- Diagnosis of FHH was made taking in view clinical presentation, 24 hour urinary calcium and Ca/Cr Excretion ratio values.
- Patient was initiated on Cinacalcet; No further episodes of pancreatitis in 4 months of follow up.
- Present Calcium – 9.3mg/dl, Creatinine – 0.8mg/dl.

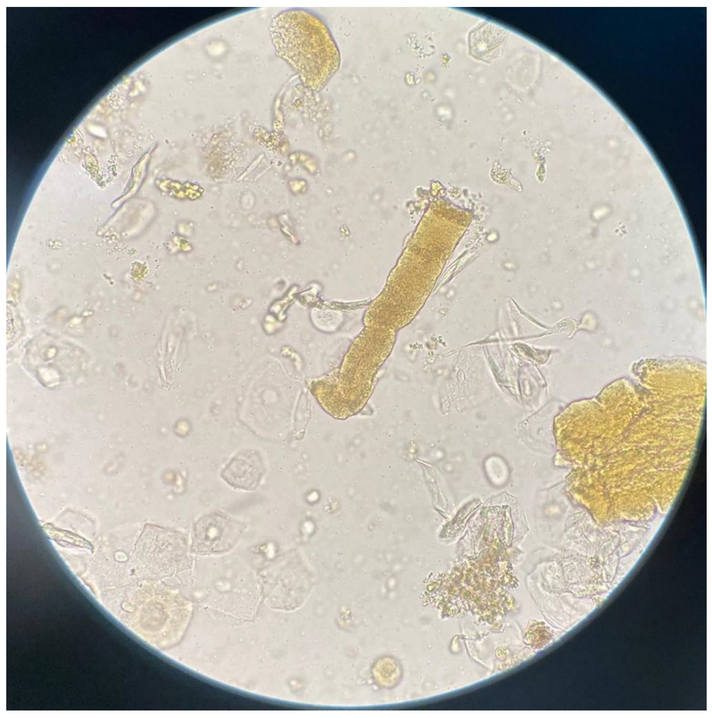

FIG 1: URINE MICROSCOPY SHOWING BILE CAST

DISCUSSION

- FHH is a rare, lifelong, benign condition caused by an inactivating mutation, most frequently in the CASR gene and less commonly in the GNA11 and AP2S1 genes, leading to a general Calcium hyposensitivity, compensatory hypercalcemia, and hypocalciuria.
- CaSR, a G protein–coupled receptor, is expressed primarily in the parathyroid glands, C cells of the thyroid, and kidney. It is also found in the gut, pancreas, and bone.
- Elevations in serum calcium concentration stimulate the CaSR, which promotes calcitonin production and urinary calcium excretion while suppressing the synthesis and secretion of parathyroid hormone (PTH), thereby lowering the calcium concentration.
- In FHH, there is a heterozygous loss-of-function mutation in the CASR gene causing reduced ability of the CaSR to sense or respond to elevated calcium concentrations. This causes tubular resorption of calcium and failure of PTH response, resulting in hypercalcemia, relative hypocalciuria, and inappropriately high serum PTH concentrations.
- More than 99% of the filtered calcium gets reabsorbed despite the presence of hypercalcemia.
- In FHH, the 24 hours urinary calcium excretion is less than 100 mg/24 hours.
- The Ca/Cr excretion ratio is very low. It is calculated as follows:

$$[UCa \times SCr] / [SCa \times UCr]$$

where UCa is the urinary calcium concentration, SCr is the serum creatinine, SCa is the serum calcium concentration, and UCr is the urinary creatinine concentration, all in mg/dl.

- Patients with a Ca/Cr ratio of 0.020 or less should be tested for mutations in CaSR gene.
- Subtotal parathyroidectomy in FHH is virtually always followed by persistent hypercalcemia, and this treatment is not recommended.
- Calcimimetics are allosteric modulators of CaSR that make the mutant receptor more sensitive to serum calcium levels. This increased sensitivity results in a reduction of PTH and serum calcium levels. Cinacalcet is currently the only drug in this class approved for human use.

CONCLUSION

- Patient presented with pancreatitis with rapidly progressive renal failure with bile cast nephropathy. On the background of recurrent pancreatitis with normal calcium levels and raised PTH, Hypercalcemia mediated pancreatitis was suspected.
- In view of calcium creatinine excretion ratio of 0.09, diagnosis of Familial hypocalciuric hypercalcemia was made. Patient was initiated on Cinacalcet.