

CASE OF THE MONTH JULY 2023

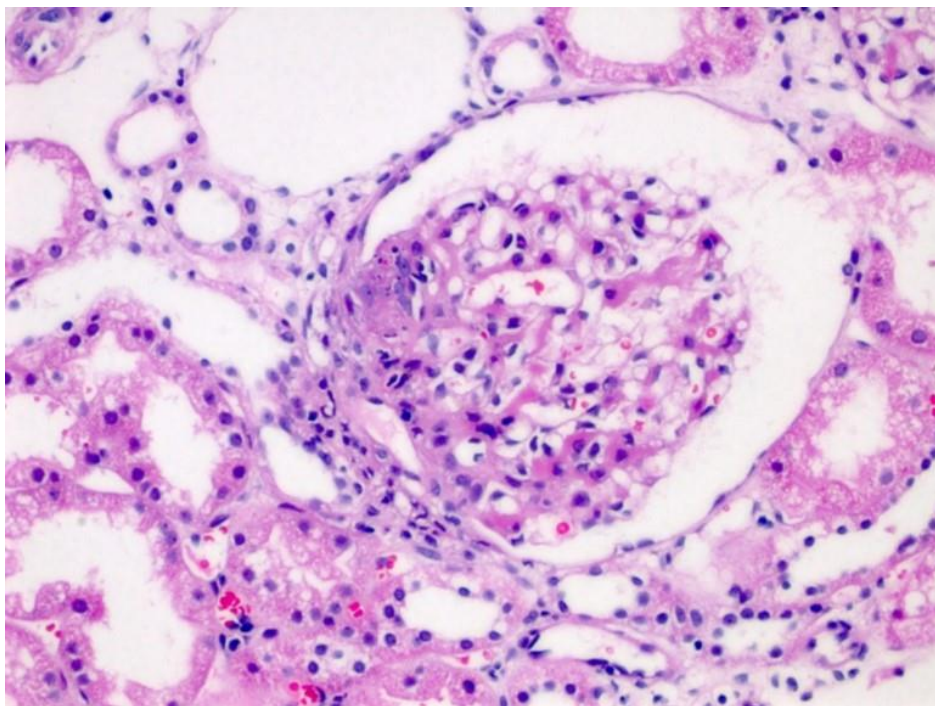
Contributed by Dr Shaila Khubchandani, Mumbai

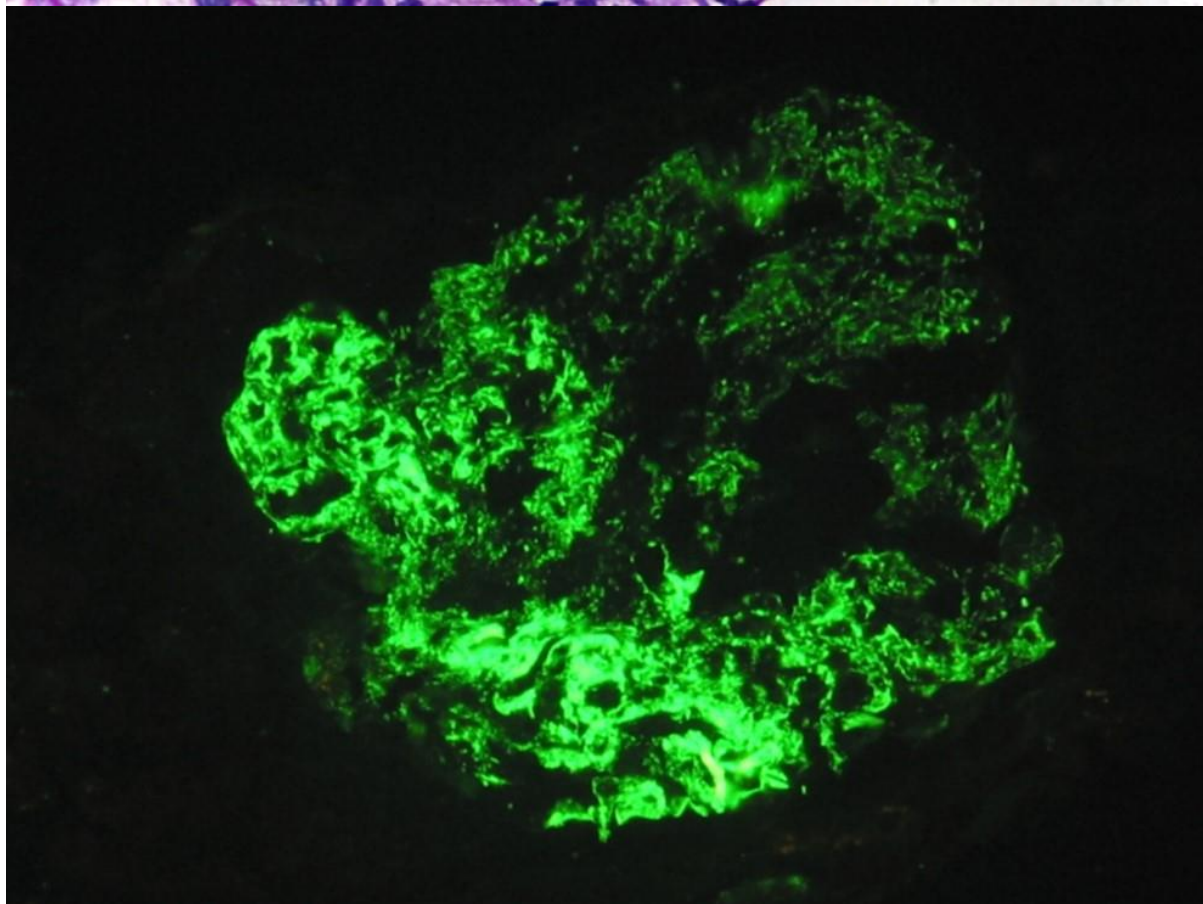
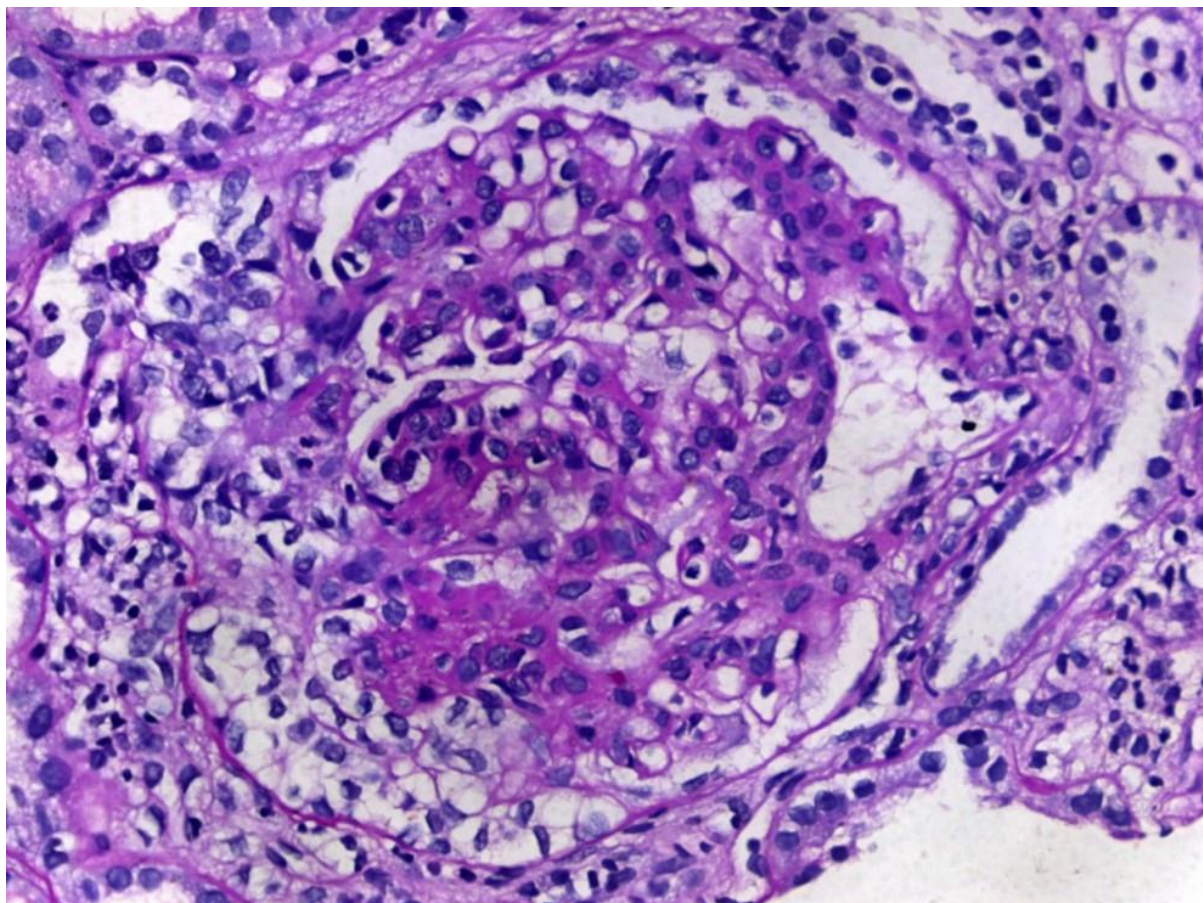
HISTORY:

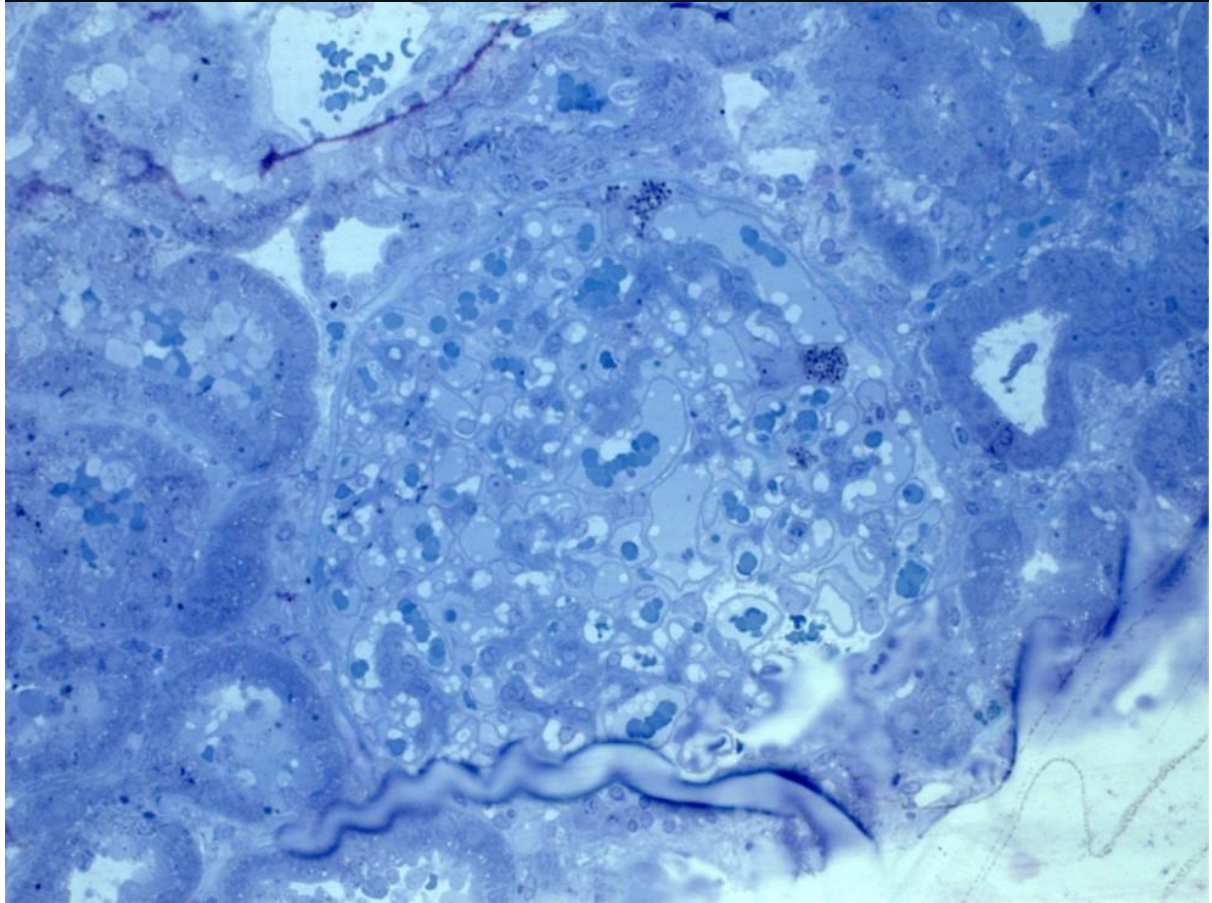
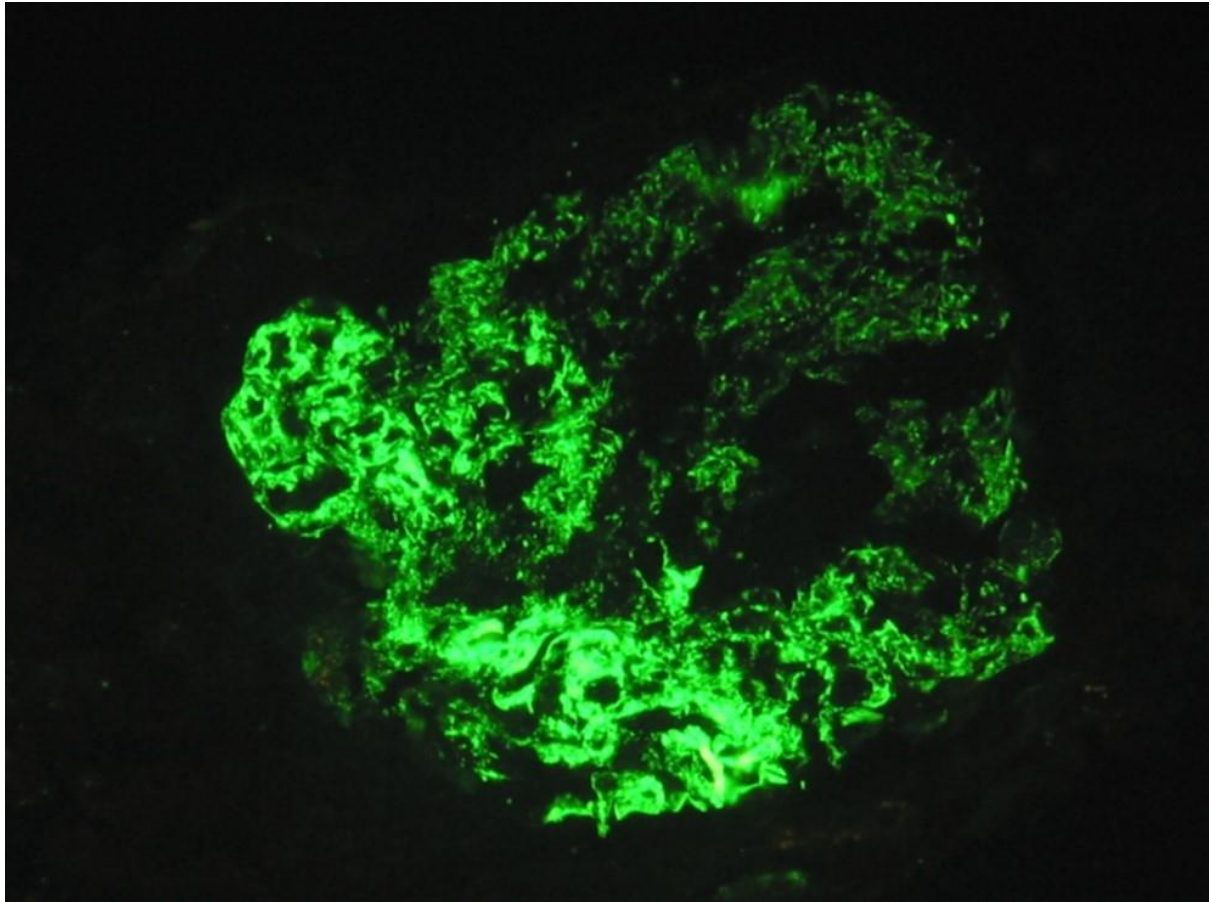
A 30-year-old lady diagnosed to have SLE eight years ago was placed on tapering doses of steroid, hydroxychloroquine 200 mgs twice a day and calcium. All her follow up visits till date were uneventful.

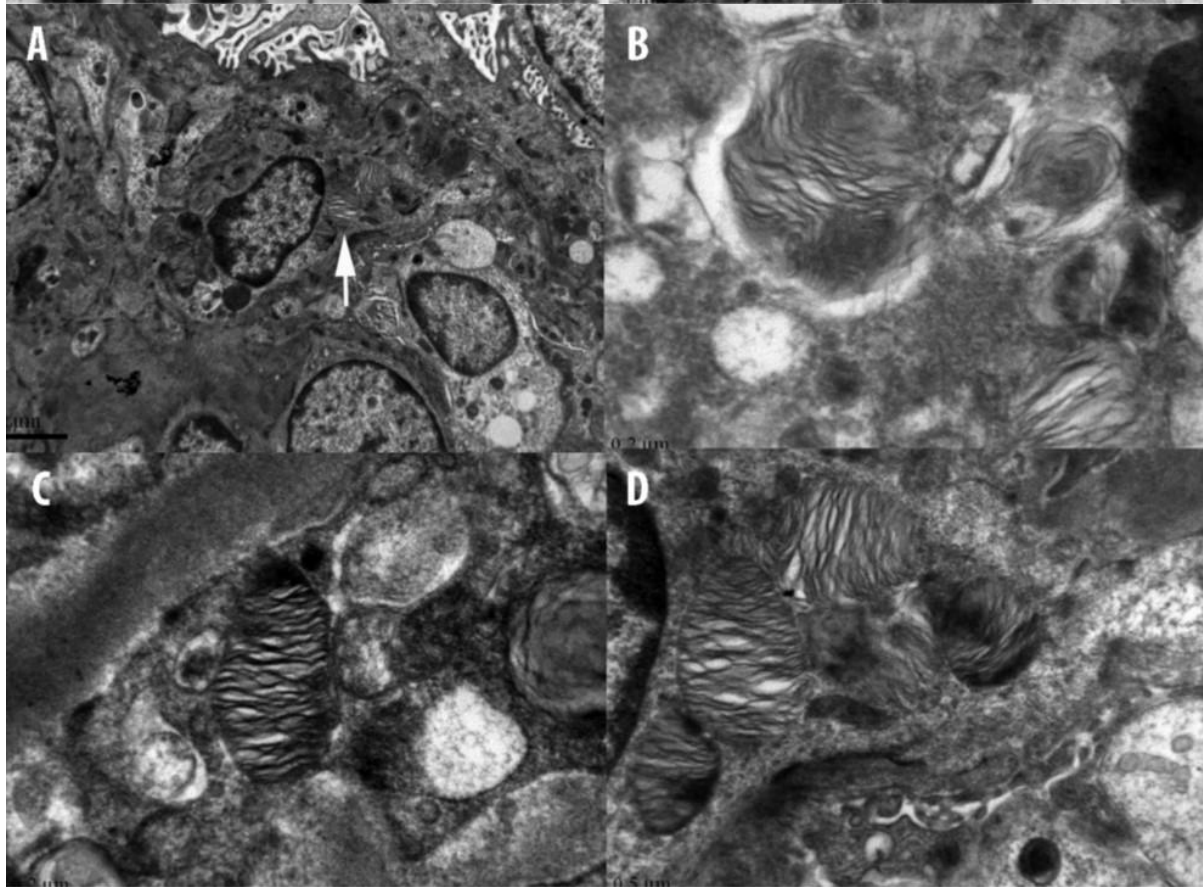
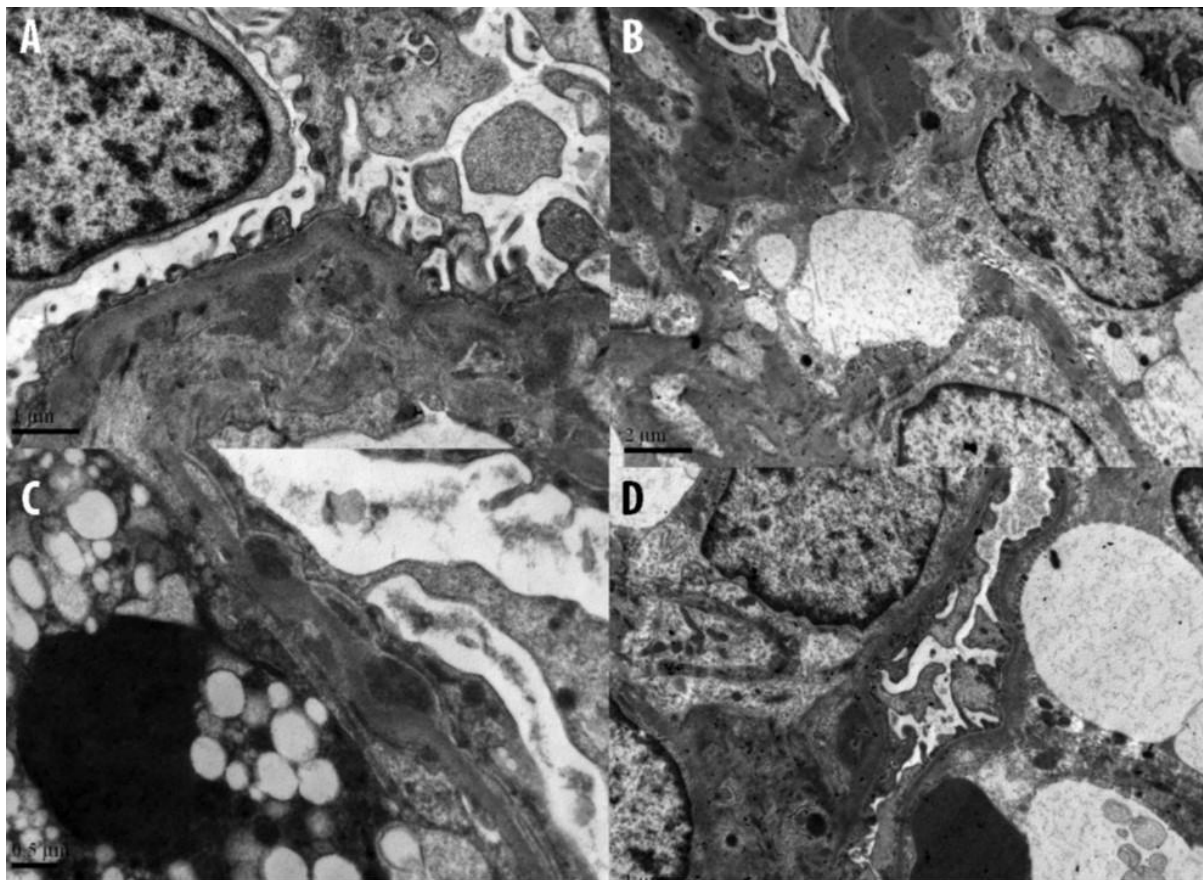
This time she presented with a "renal flare "and her joint pains had worsened. The urine examination revealed active sediment, (albumin ++, 3-5 RBC's/high power fields(hpf) and 4-5 WBC's/hpf). She was anemic (Hb7 gm/dl) and the red blood cells revealed microcytosis, hypochromasia with anisocytosis. The 24-hour urine albumin was 3.5 gm. The BUN/ Creatinine were 40 and 1.05 mg respectively. The uric acid was raised to 7.11 mg %. The total proteins were 5.2gm% and albumin was 2.7gm%. The globulins were 2.5 gm%. The complement levels were low. All the other tests were within normal limits and the C reactive protein was negative. A kidney biopsy was performed to evaluate the renal disease and steroids were reintroduced. The hydroxychloroquine and calcium supplements were continued.

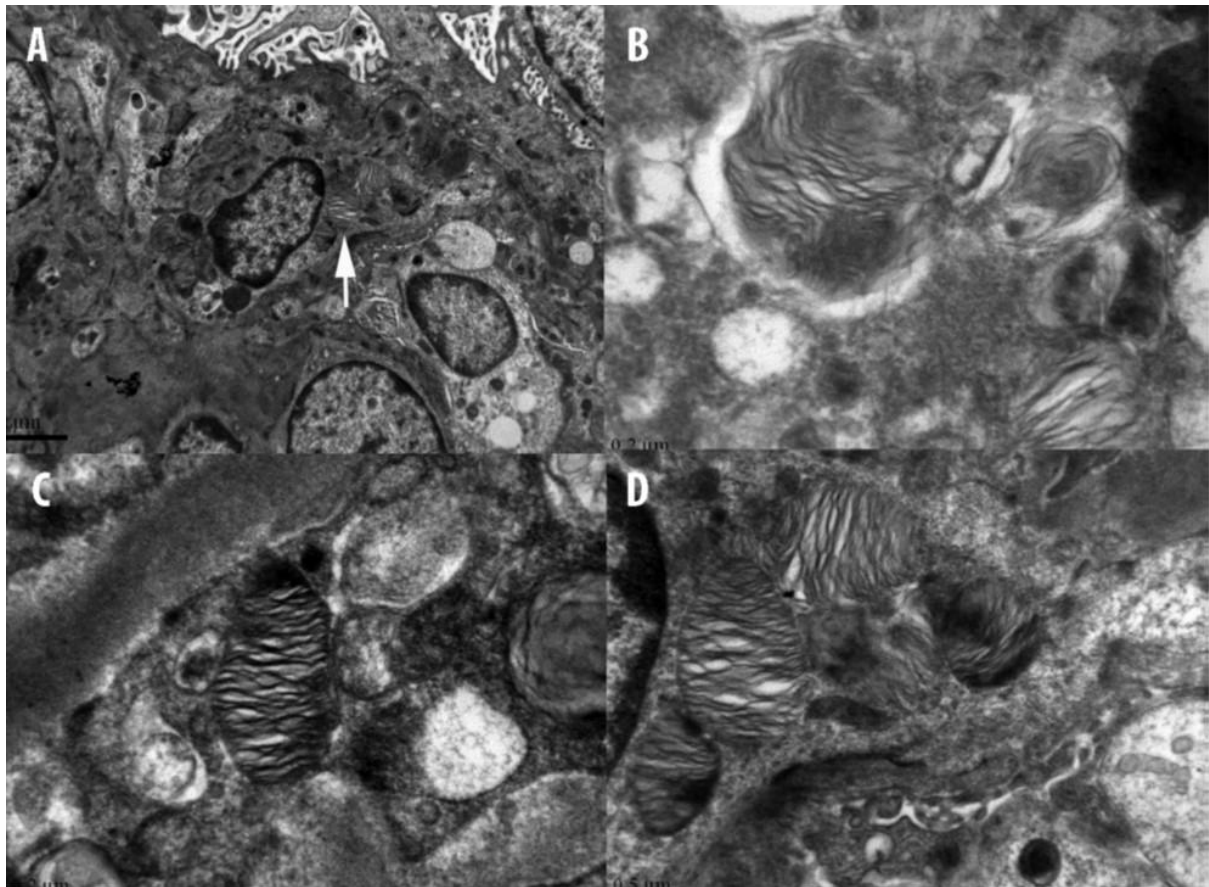
Within two days she also developed chest pain. The ECG was unremarkable but the 2D ECHO revealed cardiomyopathy, moderate impairment of left ventricular function and pericardial effusion.











DIAGNOSIS:

HYDROXYCHLOROQUINE INDUCED PHOSPHOLIPIDOSIS IN A CASE OF SLE

Systemic lupus erythematosus, (SLE) the archetypical systemic disease having a proclivity to evolve over time frequently manifests with Lupus nephritis. These patients receive steroids, immunosuppressive agents, anti-hypertensives and anti-malarial medications (chloroquine and hydroxychloroquine). The latter has been used for treatment of SLE since 1630. They are known to improve disease control, reduce accrual damage and produce a beneficial effect on survival. SLE also has other rather protean manifestations which may overlap with Fabry disease. The latter is a well characterized phospholipidosis with renal phenotype, having an X-linked inheritance occurring due to inactivation of the lysosomal enzyme alpha galactosidase. Rarely both diseases have been known to coexist and infrequently SLE patients (on treatment) can masquerade as Fabry disease.

The electron dense multilamellated myelin like figures (Zebra like bodies) resulting as an accumulation of phospholipid material are the hall mark of Fabry disease. Renal involvement

of Fabry disease is characterized by glycolipid deposits mainly in podocytes. They are also seen in mesangial, endothelial, tubular epithelial cells, vascular endothelial cells of capillaries, veins, arteries and vascular smooth muscle cells. No increase in cellularity or immune deposit is observed. All other primary renal lipidoses have different morphologic appearances. Very rarely Niemann-Pick disease may show whorled myelin like figures restricted mainly to the podocytes. Almost identical zebra bodies have been observed in association with drugs commonly chloroquine, amiodarone, aminoglycosides, laxatives and silicon albeit the former two are the commonest. Though the deposits are almost identical, a subtle difference exists between the two phospholipidosis. The classic zebra bodies are uniformly numerous in Fabry's disease. Iatrogenic chloroquine phospholipidosis may reveal additional small round homogenous dense granular inclusions in the endothelial, mesangial and tubular cell mitochondria. Few reports also describe the presence of curvilinear bodies like those seen in ceroid lipofuscinosis and histiocytic inclusions within the podocytes and endothelial cells in this condition. These latter two were however not seen in the case associated with phospholipidosis induced due to hydroxychloroquine. Chloroquine is a weak base that becomes concentrated within lysosomes and then inhibits key lysosomal enzymes including alpha galactosidase, cathepsin, acid hydroxylase and phospholipases. Chloroquine and Hydroxychloroquine have very similar chemical structure. It is hence possible that both have analogous modes of action resulting in almost identical phospholipidosis. The adverse effects of hydroxyl chloroquine

occur mainly in patients receiving high doses of the drug or those who have renal impairment. It is probably for this reason that values of the alpha galactosidase enzyme levels may be altered resulting in the mistaken diagnosis of Fabry disease. It is therefore important to confirm the diagnosis of Fabry disease only after enzyme studies and mutational analysis of alpha galactosidase A gene. Genetic analysis also helps to detect female carriers who have normal enzyme activity due to unequal X chromosome activation.

This case confirms that scrupulous clinical evaluation, routine investigations and appropriate follow up do help to piece the jigsaw puzzle in most cases and affect correct care to the patients.

It also warns us against various "dangerous mimics" and favours diagnostic frugality of Occam's Razor over Hickman's dictum.