What’s hiding behind IgA nephropathy?

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Clinical history:

A 31-year-old woman was admitted to the hospital for proteinuria, fatigue, edema of the hands, tinnitus and sudden hearing loss of the left ear.

Physical and laboratory examination revealed arterial hypertension, nephrotic proteinuria (5g/day) and microscopic hematuria. Kidney function was normal with a serum creatinine level of 73μmol/l (0.79mg/dl). Immunology was negative (ELISA testing – IgA, IgM, IgG, C3 and C4 complement, extractable nuclear antigen (ENA), anti-nuclear antibodies (ANA), ds-DNA antibodies, ANCA, rheuma factor). Audiometry showed hearing abnormalities.

In her family history, a father, uncle and sister suffer from IgA nephropathy (IgAN). She had no history of taking chronic medication or drug abuse.

A kidney biopsy was performed with a clinical diagnosis of IgAN or Alport syndrome.

Renal biopsy findings:

The biopsy sample for IF contained 3 glomeruli which showed strong positive staining for IgA in the mesangium. IgG, C3, and kappa, and lambda light chains showed weak similar staining pattern. Detection of IgM and C1q was negative.

In the paraffin embedded specimen there were 18 glomeruli, 2 of them were globally sclerotic. The remaining glomeruli had slight increase in the mesangial matrix with normal or mild increase of the mesangial cells. Three glomeruli showed segmental sclerotic lesions. No crescents were observed.

There were remarkable enlarged podocytes with foamy vacuolated cytoplasm.

The changes in the interstitium were unremarkable consisting from mild focal interstitial fibrosis and mild hyalinosis of arteriols. Small groups of foamy macrophages were identified in the interstitium.

In semi-thin toluidin blue stained section, rounded dark blue bodies were identified in the cytoplasm of podocytes. Numerous laminated bodies were seen in the podocytes and focally also in the endothelial cells during the ultrastructural evaluation. Simultaneously dense deposits in the mesangium were detected.
Diagnosis:
IgA nephropathy simultaneously with very suspicious Fabry disease.
Confirmation of Fabry disease by genetic testing was recommended.
Low $\alpha$-galactosidase A activity in plasma and leucocytes was confirmed and the heterozygous mutation of $\alpha$-Gal A gene was diagnosed.

Discussion:
IgA nephropathy:
IgA nephropathy is the most common primary glomerulonephritis. This renal disease is characterized by mesangial deposition and/or formation of IgG-IgA1, IgA1-IgA1 complexes (1). Moreover IgA deposits are frequently associated with complement components, mostly C3, C5 and properdin, less frequently with IgG and/or IgM deposits.
Aberantly glycosylated (deficiency of galactose in the hinge region of heavy chain) IgA1 can circulate as monomers or in self-aggregated forms. They can trigger an IgG autoimmune response forming IgG-IgA1 complexes or react with antigens and form true IgA1 complexes (2). Aberantly glycosylated IgA1 may be synthesized in response to a mucosal infection, and thus abnormalities in the mucosal response to common microbial and food antigens may be involved in production of galactose-deficient IgA1 (3). IgA1–containing immune complexes display high affinity for the extracellular matrix components fibronectin and type IV collagen in the mesangium, and preferentially bind and activate mesangial cells. Deposition of pathogenic immune complexes in the mesangium increase production of cytokines, macrophage migration inhibitory factor, growth factors, inducible nitric oxide synthase and renin (1). Recent data indicates that IgA1 glycosylation defects are inherited and constitutes a hereditable risk factor for IgAN. Kiryluk et al. proposed that inherited defect of IgA1 glycosylation is not sufficient to cause the disease (4). Additional environmental or genetic factors are probably required for renal injury, which is likely mediated by antiglycan antibody production and immune complex formation.
In the kidney biopsy samples, IgA nephropathy has very variable morphological features from almost normal morphology in light microscopy to diffuse proliferative crescentic GN and/or advanced sclerotic lesions. Several systems of subclassification of IgA nephropathy exist, first of all in effort to find some morphological features which can be useful in prediction of the disease progression. Recently, so-called Oxford classification has detected four pathological features (mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis) which predict renal outcome independently from all clinical indicators at the time of biopsy and during follow up (5). Now, multicenter study (Valiga) is in course to validate the Oxford Classification of IgA nephropathy in a large European cohort of patients.
**Fabry disease (FD):**

FD is an X-linked recessive lysosomal storage disorder. This enzymopathy is characterized by the deficient activity of α-galactosidase A which results in the accumulation of globotriaosylceramide in the lysosomes of the endothelium of various organs and also in other types of cells; in the kidneys mainly in podocytes. The disease is uncommon; the recent estimates of the frequency range from 1:40 000 to 1:117 000 births. More than 300 mutations α-galactosidase gene have been described, and most are family specific. About 5% of cases are sporadic. The clinical manifestations are variable and include skin lesions, corneal dystrophy, paresthesias and proteinuria. During adulthood heart disease, premature cerebrovascular accidents, and progressive renal disease occur. In females, there are highly variable levels of enzyme activity and, therefore, a broader range of clinical symptoms. Most females, contrary to the previous assumptions, are affected; in various studies, 12% of Fabry’s patients on dialysis are women. The diagnosis of FD in males can be confirmed by the demonstration of deficient enzyme activity in plasma, leucocytes, or cultured cells. Female carriers can exhibit normal level of enzyme activity, and therefore, an exclusion of carrier status can only be performed by mutational analysis.

In a kidney biopsy sample, the morphological feature which is leading to the first suspicion of FD, is represented by the swollen, finely vacuolated podocytes. These vacuoles look empty in light microscopy. However, in semi-thin sections embedded in epoxy resin the dark blue bodies are easily demonstrated. Ultrastructure demonstrates osmiophilic, lamellated bodies mainly in podocytes (myelin figures, “zebra” bodies). All renal cells can be affected.

In practice, these typical features are shown early in manifestation of FD. The situation becomes more difficult in cases with more advanced stages of FD with sclerotic glomeruli and morphological features of FSGS. Sometimes it can be very difficult to identify the inclusions without EM. Accumulation of lipids mimicking FD can be seen during long-term treatment with cationic amphiphilic drugs (chloroquine and amiodarone). The cellular inclusions are not infrequently considered almost identical with inclusions in FD (6, 7). Prof. Ferluga in his lecture (23rd ECP, Helsinki 2011) concluded that chloroquine-induced lipidosis in the kidney is not so rare as it appears according to limited literature and he showed specific curvilinear inclusions in podocytes, which are not present in FD.

There is no cure for FD. Survival is greatly reduced in males with classic FD. Treatment with recombinant α-galactosidase A is available and should be considered for eligible individuals, although the impact of enzyme replacement therapy on mortality is yet unknown. Enzyme replacement therapy is also suggested in males and female carriers with substantial non-renal manifestations.
The coexistence of IgA nephropathy and Fabry disease:
The coexistence of FD and immune disorders such as SLE, rheumatoid arthritis, IgAN and pauci-immune and immune complex-mediated necrotizing crescentic glomerulonephritis has been described in the literature (8).
The combination of FD and IgAN is rare. According to our knowledge, eight cases have been published. In addition to these data, we have another 2 cases in our renal biopsy register during past 10 years.

Patient’s follow-up
The patient has been treated with human α-galactosidase A replacement therapy and also antihypertensive drugs with diuretics. Her cardiac function and her blood pressure are in the normal range. Her kidney function is in the normal range with a serum creatinine level of 65 μmol/l (0.71 mg/dl). Proteinuria slightly decreased and peripheral edema disappeared. However she is still suffering from fatigue, paresthesia, tinnitus, and her hearing loss is worsening.
Her family members were tested, and in her mother, sister and aunt the diagnosis of FD was confirmed. Her two daughters (2 and 5-years old) has not been tested yet.

References: