Reviewer's report

Title: Chronic kidney disease, severe renal vascular involvement and two distinct kidney neoplasias: on the spectrum of kidney involvement in MELAS syndrome.

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Reviewer: michael hughson

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The authors describe a patient with MELAS syndrome due to the common 3243 A>G mitochondrial mutation who developed severe renal impairment and nephrotic syndrome following unilateral nephrectomy. I believe the article meets the journal requirements for a case report as it presents new findings in an uncommon genetic disease, and the findings have implications for the development of sclerosing renal disease in the general population. I have questions regarding the pathologic findings and their description and suggest moderately extensive revision.

1. Some very vague terms are used for the pathology of the kidney that should be changed to more specific pathologic diagnoses or processes.
   a. The terms renal vascular involvement and renal vascular damage are used. This could mean any type of vascular pathology. The authors illustrate intimal fibrosis of arcuate and interlobular arteries with a wedge-shaped area of interstitial fibrosis and tubular atrophy that appears to extend to the renal capsule. The vascular pathology should be referred to as intimal fibrosis and the glomerular changes as glomerular obsolescence with the glomerular and vascular changes being of the type associated with benign arteriolonephrosclerosis. It might be mentioned that while arteriolonephrosclerosis is characteristic of benign hypertension, it is often seen in elderly individuals who have never been known to be hypertensive. It can also be noted that some people working in the field (Richard Tracy among others) suggest that the vascular changes precede hypertension.
   b. Figure 4 shows a hyaline arteriolosclerosis involving two arterioles. This should be noted in the description of the pathology and should be referred to as hyaline arteriolosclerosis. The illustration of focal segmental glomerulosclerosis
(FSGS) is not very convincing. A better illustration is needed if it can be provided.

2. I do not believe that the findings warrant the conclusion that there are two neoplasms. An oncocytoform is clearly described and illustrated. What is being diagnosed as a chromophobe carcinoma consists of a 0.5 cm lesion. I doubt that any lesion that small could be considered a chromophobe carcinoma. Unless monosomies of multiple chromosomes characteristic of chromophobe carcinoma could be demonstrated, it would probably be best to consider the lesion a tumoral focus of tubular oncycytosis and a precursor of another oncocytoform.

3. It is mentioned that kidney involvement is "protean". I do not know what this means. Most of the reports on the kidney disease of MELAS syndrome describe FSGS.

4. Under conclusions:
   a. Second paragraph. The unusual feature of this case is the severe arteriolonephrosclerosis occurring without hypertension and the deterioration in renal function and development of nephrotic range proteinuria shortly after nephrectomy for a renal tumor.
   b. The authors refer to steroid resistant FSGS and later to a lack of steroid sensitivity in FSGS. FSGS is virtually always steroid resistant. Do the authors mean steroid sensitive and resistant nephrotic syndrome.

5. The parallel with 5/6th nephrectomy is well taken. As the authors state, the report seems to be an example of a unilateral nephrectomy associated nephrotic syndrome owing to hyperperfusion occurring on a background of severe arteriolonephrosclerosis. The oncocytoform may be the result of the intrinsic mitochondrial mutation combined with the tendency for neoplasms, including oncocytoforms, to develop in chronically diseased kidneys.

The title of the paper needs to be changed to reflect the comments.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests