Another Case of Mitochondriopathy Manifesting as Inherited Tubulointerstitial Nephropathy without Other Symptomatic Organ Involvement

To the Editor We read with great interest the case report of Buglioni *et al.*,[1] and report a similar one.

A 27-year-old man presented with mild kidney impairment (creatinine serum level 1.6 mg/dl, estimated glomereular filtration rate 55 ml/min per 1.73 m^2) and low-grade proteinuria (0.25 g/d) without hematuria or leucocyturia. Workup revealed high creatinine kinase levels (700 UI/L, N < 200) and an HbA1C level of 6.2%. Renal ultrasound showed normal-sized kidneys. A kidney biopsy specimen showed mild, nonspecific, chronic tubulointerstitial nephritis by light microscopy and an absence of immune deposits by immunofluorescence.

The patient's family history was positive. His 23-year old sister had been diagnosed with type 2 diabetes with microalbuminuria, and his mother had developed gestational diabetes at age 32 years (Figure 1) with normal kidney function. Autosomal dominant tubulo-interstitial kidney disease (ADTKD)—TCF2 mutations were ruled out in the patient. Next-generation sequencing of the entire mitochondrial genome was then performed on a urine sample, showing an m.3243A>G point mutation in the mitochondrial-encoded *MTTL1* gene, the most common cause of mitochondrial disease. Patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome have a highly variable phenotype, ranging from isolated diabetes and deafness to mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (OMIM #540000).[2] In MELAS syndrome, kidney involvement in rare and is usually associated with a focal segmental glomerulosclerosis pattern of injury. The m.3243A>G heteroplasmy was 31% and 88% in the patient's blood and urine samples, respectively,

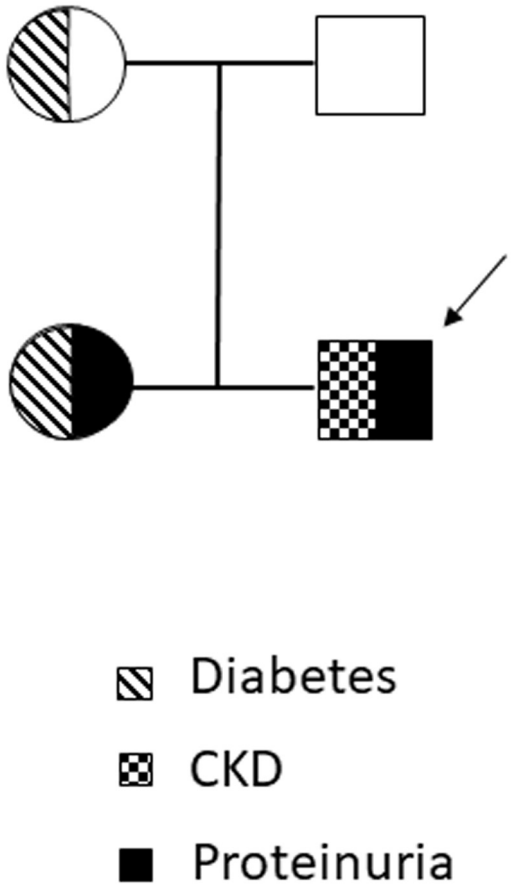

Figure 1. Patient's family tree. CKD, chronic kidney disease.

and 19% in his sister's blood sample. Urinary epithelium shows the most consistent mutation load for initial diagnosis.[3]

Both cases highlight the clinical relevance of including mitochondrial diseases in the differential diagnosis of tubulo-interstitial disease in young patients, even with no or mild extrarenal manifestations.

1. Buglioni A, Hasadsri L, Nasr SH, et al. Mitochondriopathy manifesting as inherited tubulointerstitial nephropathy without symptomatic other organ involvement. *Kidney Int Rep.* 2021;6:2514–2518.
2. Schijvens AM, van de Kar NC, Bootsma-Robroeks CM, et al. Mitochondrial disease and the kidney with a special focus on CoQ_{10} deficiency. *Kidney Int Rep.* 2020;5:2146–2159.
3. Whittaker RG, Blackwood JK, Alston CL, et al. Urine heteroplasmy is the best predictor of clinical outcome in the m.3243A>G mtDNA mutation. *Neurology.* 2009;72:568–569.

Valentine Gillion[1], Arnaud Devresse[1], Nathalie Demoulin[1] and Karin Dahan[1,2]

[1]Department of Nephrology, Cliniques Universitaires Saint-Luc, Brussels, Belgium; and [2]Center of Human Genetics, Institut de Pathologie et de Génétique, Gosselies, Belgium

Correspondence: Valentine Gillion, Cliniques Universitaires Saint-Luc, 10 Avenue Hippocrate, 1200 Brussels, Belgium. E-mail: valentine.gillion@uclouvain.be

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Minimal Change Disease Associated With Durvalumab

To the Editor: At present, minimal change disease (MCD) caused by PD-L1 inhibitors has not been reported. We have reported the first case of MCD caused by a PD-L1 inhibitor, durvalumab. A 75-year-old Asian man who developed nephrotic syndrome after 4 cycles of durvalumab administration for non–small cell lung cancer (NSCLC) was diagnosed with MCD by kidney biopsy. Complete remission (CR) was achieved soon after administration of prednisolone (PSL) (see Supplementary Material, Case Presentation and Supplementary Figures S1 and S2).

In the present case, MCD was thought to be caused by durvalumab rather than NSCLC, because proteinuria was observed soon after durvalumab administration, MCD was dramatically improved by administration of PSL, and disease activity of MCD and NSCLC are not consistent.[1] Although most cases of renal immune-related adverse effects (irAEs) present with interstitial nephritis,[2] rare cases of MCD by CTLA-4 inhibitors and PD-1 inhibitors have been reported (Table 1). The mechanism by which durvalumab causes MCD is assumed to be enhanced effects of T-cell–derived humoral factors[2] and direct impairment of the glomerular filtration barrier via activation of CD80 in podocytes.[3]

As treatment, most patients were treated well with PSL 1 to 2 mg/kg per day and tapered off over 6 to 26 weeks. If renal irAEs are grade 2 or lower and if renal

Table 1. Summary of published reports of minimal change disease associated with immune checkpoint inhibitors

	Authors, year	Age	Sex	Disease	ICPIs	Cr (baseline) (mg/dl)	Cr (worst) (mg/dl)	Proteinuria (pretreatment) (g/d)	Proteinuria (posttreatment) (g/d)	Treatment (/d)	Taper (days)	Outcome	Rechallenge
No Rechallenge	Bickel *et al.*, 2016	62	M	Mesothelioma	Pembrolizumab	GFR 90	GFR 27	19	0	PSL 1 mg/kg	70	CR	
	Kidd and Gizaw, 2016	55	M	Melanoma	Ipilimumab	1.2	5.2	9	NA	PSL 2 mg/kg	NA	CR	
	Kitchlu *et al.*, 2017	43	M	Hodgkin lymphoma	Pembrolizumab	0.76	3.93	10.3	3.1	PSL 2 mg/kg	180	PR	
	Goo *et al.*, 2018	40	M	Hodgkin lymphoma	SHR-1210 (anti–PD-1)	0.77	NA	30	0.18	PSL 1 mg/kg	56	CR	
	Izzedine *et al.*, 2019	NA	NA	Melanoma	Pembrolizumab	GFR 90	GFR 28	6	NA	PSL (NA) mg	NA	ESRD	
	Izzedine *et al.*, 2019	NA	NA	Ileal NETs	Pembrolizumab	NA	1.65	3.5	NA	No treatment	NA	SD	
	E. Vaughan *et al.*, 2020	57	M	Tongue squamous cell carcinoma	Nivolumab	0.79	2.29	2.1	NA	PSL 75 mg	NA	SD	
Rechallenge	Kitchlu *et al.*, 2017	45	M	Melanoma	Ipilimumab	0.68	0.8	9.5	0.39	PSL 1 mg/kg	120	CR	Recurrence without PSL
	Saito *et al.*, 2019	79	M	Lung adenocarcinoma	Pembrolizumab	NA	NA	13.8	0	PSL 40 mg → 10 mg	56	CR	No recurrence with PSL 10 mg/d
	Glutsh *et al.*, 2019	68	M	Melanoma	Pembrolizumab	normal	2.86	19	0.33	PSL 100 mg	42	CR	Recurrence without PSL

CR, complete remission; ESRD, end-stage renal disease; GFR, glomerular filtration rate; ICPIs, immune checkpoint inhibitors; M, male; NA, not available, NETs, neuroendocrine tumors; PD-1, programmed death–1; PR, partial response; PSL, prednisolone; SD, stable disease.