# Chronic kidney disease from polyvinylpyrrolidone deposition in persons with intravenous drug use

Running head: PVP deposition in the kidney from IV drug use

Ida V. Stalund MD[1,2], Heidi Grønseth MD[1], Finn P. Reinholt MD PhD[3], Einar Svarstad MD PhD[2], Hans-Peter Marti MD Dr. Med[2,4], Sabine Leh MD PhD[1,2]

[1]Department of Pathology, Haukeland University Hospital, Bergen, Norway

[2]Department of Clinical Medicine, University of Bergen, Bergen, Norway

[3]Department of Pathology, Oslo University Hospital, Oslo, Norway

[4]Department of Medicine, Haukeland University Hospital, Bergen, Norway

Corresponding author:

Ida Viken Stalund, MD

Department of Pathology

Haukeland University Hospital

Post Box 1

5021 Bergen

Norway

Email 1: ida.viken.stalund@helse-bergen.no

Email 2: ida.stalund@uib.no

Phone: +47 48265169

Abstract word count: 288 words.

Manuscript word count: 3181 words

Number of figures: 4

Number of tables: 2

## Abstract

Background and objectives: Persons with intravenous drug use have a higher risk of developing chronic kidney disease (CKD) compared to the general population. In Norway, deposits of polyvinylpyrrolidone (PVP) have been observed in kidney biopsies taken from persons with opioid addiction and intravenous drug use since 2009. PVP is an excipient commonly used in pharmaceuticals, and the PVP deposits observed in these patients were caused by intravenous injection of a specific oral methadone syrup containing very high molecular weight PVP. Here, we present the clinicopathological findings from 28 patients with CKD associated with PVP deposition in the kidney.

Design, setting, participants and measurements: The 28 patients and their kidney biopsies were included when PVP deposition was recognized, either retrospectively or at the time of diagnostic evaluation. Biopsies were taken between 2009 and 2016. We collected laboratory parameters and clinical data from digital patient charts. For each kidney biopsy, the glomerular volume, extent of PVP deposition, and tubulointerstitial area with tubular atrophy were assessed quantitatively.

Results: All patients (mean age 37 years) had CKD (mean eGFR 33 mL/min/1.73 $m^2$) and normal urine protein or non-nephrotic range proteinuria. Biopsies showed moderate to severe tubular atrophy (mean extent 65%) and interstitial infiltrates of vacuolated macrophages containing PVP (mean share of biopsy area 1.5%). Underperfused and ischemic glomeruli were common findings. In 22 samples, ultrastructural investigation revealed PVP-containing vacuoles in the mesangial or endothelial cells of glomeruli. At the last follow-up, most patients had stable or improved eGFR. Two patients had developed kidney failure and underwent hemodialysis.

Conclusions: Intravenous injection of a specific oral methadone syrup caused PVP deposition in the kidney in persons with opioid addiction and intravenous drug use. Kidney biopsy findings suggested an association between PVP-deposition and tubular atrophy.

## Introduction

Intravenous (IV) drug use is associated with a wide range of diseases, including chronic kidney disease (CKD) (1, 2). The risk of CKD in this patient group is due in part to effects of the drugs themselves (3), and in part to co-morbidities associated with IV drug use, such as soft tissue infections (4, 5), chronic viral infections (6), and episodes of rhabdomyolysis (7). Common histopathologic diagnoses are glomerulopathies (e.g. membranoproliferative glomerulonephritis), amyloidosis, acute interstitial nephritis, and acute tubular necrosis (3, 8).

Starting in 2009, pathology departments in Norway received biopsies from patients with opioid addiction and IV drug use showing deposits of polyvinylpyrrolidone (PVP) (9-12), a common excipient in pharmaceuticals (13). Moderate and high molecular weight PVP is exclusively utilized in oral and topical medications (13), as it may accumulate in the body if injected (14, 15). In most countries, the use of moderate and high molecular weight PVP in parenteral medication ended in the late 1970s (16) when it was recognized that extensive PVP deposition could cause severe organ dysfunction (17-19). However, cases of CKD resulting from PVP deposition have rarely been reported (20, 21).

In this case series, we present the clinicopathological findings from 28 patients with PVP deposition in the kidney and CKD. The PVP deposited in these patients originated from intravenous use of a specific oral methadone syrup marketed as an opioid substitution drug in Norway and several other countries from 2007 to 2014 (22). Intravenous use of oral opioid substitution drugs is widespread among persons with IV drug use (23) and the drugs are also shared and sold on to others (24). In this specific methadone syrup, very high molecular weight PVP was added as a thickener with the aim of preventing unintended intravenous use (11, 22). Unfortunately, the higher viscosity did not have the intended effect, and injection of the methadone syrup caused PVP deposition in various organs, including the kidneys, in some cases with detrimental clinical consequences (11, 12).

This study aims to describe the clinical, light microscopy and ultrastructural findings in a series of patients with PVP deposition in the kidney, and to alert both clinicians and pathologists to this diagnostic possibility in the context of CKD, opioid addiction, and IV drug use.

## Materials and methods

### Patients

Twenty-eight kidney biopsies taken between 2009 and 2016 showing PVP deposition were included continuously or retrospectively following primary or second opinion diagnostic evaluation. Biopsies were obtained from four pathology departments in Norway: Haukeland University Hospital, Oslo University Hospital, St. Olav's University Hospital, and Førde Hospital. PVP-deposition was defined as the presence of macrophages with intracytoplasmatic vacuoles displaying the following staining properties: light blue in the hematoxylin and eosin (H&E) stain, red in the Congo stain, and grey or black in the Periodic Acid Silver-Methenamine stain (PASM) (Figure 1) (17). Vacuole content should not be birefringent in Congo red stain or any other stain (17).

*Figure 1 approximately here*

Patient clinical and demographic data were collected from pathology referral forms, digital patient charts (medical records), and/or the Norwegian Renal Registry. Follow-up data were collected in May 2019. Proteinuria was assessed by albumin to creatinine ratio (ACR) or protein to creatinine ratio (PCR), depending on which were available. For one patient, proteinuria was assessed by strip test evaluation. Proteinuria was graded as; normal to mildly increased (< 30 mg/g (ACR) or <150 mg/g (PCR)), moderately increased (30 – 300 mg/g (ACR) or 150 – 500 mg/g (PCR)) or severely increased (>300 mg/g (ACR) or > 500 mg/g (PCR)) (25). In four cases, there was a discrepancy between ACR and PCR levels. In these cases, proteinuria was graded according to the parameter showing the highest level. The diagnosis of CKD was defined as > 3 months of abnormalities in kidney function

documented as GFR <60 ml/min/1.73 $m^2$ or albuminuria (25). Progression of CKD was categorized as slow progression (decrease in eGFR of 1 – 3 ml/min/1.73 $m^2$ per year), or fast progression (decrease in eGFR > 3 ml/min/1.73 $m^2$ per year) (25, 26).

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 27687). REK approved exemption from the consent requirement for the use of information and biological material gathered in healthcare services. The study was performed in adherence to the Declaration of Helsinki.

## Methods of measurement

As part of the original diagnostic evaluation, formalin-fixed, paraffin-embedded biopsies were routinely stained with H&E, Congo red, Periodic Acid-Schiff (PAS), trichrome, and PASM. The following immunohistochemical panel was used: IgG, IgA, IgM, C1q, and C3c. Immunohistochemical evaluation of macrophages with CD68 was performed in eight cases. Tissue for electron microscopy (EM) from 27 of the 28 cases was fixed and processed according to standard procedure at each hospital. Available slides were scanned with ScanScope® XT (Aperio) at ×40 magnification (resolution 0.25 µm/pixel). We viewed and annotated the virtual slides in ImageScope 12.

The total number of assessable glomeruli (defined as > 25% of the capillary tuft visible) were counted, as well as the number of glomeruli with necrosis, segmental glomerulosclerosis (SGS), global glomerulosclerosis (GGS), crescents, underperfused glomeruli and ischemic glomeruli. An underperfused glomerulus was defined as a glomerulus with a collapsed capillary tuft. An ischemic glomerulus was defined as a glomerulus with a collapsed capillary tuft and periglomerular fibrosis in at least 50% of the glomerular circumference with involvement of the tubular pole (27). We measured the tuft area of each non-sclerotic glomerulus using the annotation pen tool in ImageScope 12. The glomerular tuft volume was calculated using the Weibel-Gomez formula: $V_{glom} = \frac{{A_{glom}}^{1.5} * 1.38}{1.01}$ (28).

An atrophic tubule was defined as a tubule with thickened basement membranes and/or a reduction in tubule diameter (29). We quantified the tubulointerstitial area affected by tubular atrophy (TA) by point counting using a square test lattice with 100 µm between test lines applied to PAS-stained calibrated digital slides. The extent of TA was expressed as the percentage of points hitting cortical tubulointerstitial areas with TA, out of the total number of points hitting cortical tubulointerstitial tissue.

Arteriosclerosis was graded 0 – 2 by the extent of intimal thickening compared to the thickness of the media (30). Arteriolohyalinosis was graded 0-3 representing increasing severity according to the Banff aah score (29, 31).

PVP-containing vacuoles were noted present or absent in the interstitium, glomeruli and tubular epithelium. The extent of PVP deposition was expressed as the percentage of the total biopsy area occupied by PVP-containing vacuoles, as measured using the pen tool in Aperio ImageScope. We used sections stained with Congo red stain, H&E stain or PAS, depending on which sections were available or which were most easily interpreted.

By EM, PVP-containing vacuoles were noted present in glomerular cells if they met all of the following criteria (17, 20, 32): 1. At least three round/oval vacuoles of similar size present in a single cell; 2. Vacuole content has low to intermediate electron density and low granularity; 3. Vacuole profile diameter 0.3 – 1.5 µm; 4. Vacuoles are not collocated with osmiophilic material making the structure suspicious of lipofuscin.

## Statistical analyses

Statistical analyses were performed using SPSS for Windows, version 24. Central tendency for continuous variables was reported as mean (standard deviation (SD) or range). We performed correlation analyses using the Spearman's rank correlation coefficient for nonparametric data. Statistical significance was assumed at a P-value $< 0.05$.

# Results

## Demographics, comorbidities and clinical kidney parameters at the time of biopsy

Summarized clinical data are available in Table 1. This case series included 28 adults. All had a history of opioid addiction and IV drug use, and 27 (96%) of them received treatment with opioid substitution drugs. Hepatitis B and C virus positivity was common. None of the patients were HIV positive. Six patients were receiving treatment for hypertension, and two patients had diabetes mellitus type 2.

*Table 1 approximately here*

For 27 of 28 patients, indication for biopsy was kidney disease with reduced eGFR. For one patient with previously diagnosed systemic lupus erythematosus, indication for biopsy was CKD with newly discovered proteinuria. At the time of biopsy, 22 patients (79 %) had CKD, two patients (7 %) had acute kidney injury on CKD and three patients (11 %) had newly discovered kidney disease. The last patient had reduced eGFR, but pre-biopsy duration is unknown to us.

## Pathology features

Pathological features are summarized in Table 2.

### *Tubulointerstitial findings*

The most prominent histological finding was the widespread TA (Figure 2a). Areas with atrophic tubules showed extended interstitium with varying degrees of fibrosis. PVP-containing macrophages, singular or clustered, were dispersed in the interstitium, mainly in areas affected by TA (Figure 2a-c). In some biopsies, extensive aggregates of PVP-containing macrophages displaced tubules in larger areas. In rare incidences, we also found PVP-containing vacuoles within the tubular epithelium. The

extent of PVP deposition compared to the extent of TA varied between biopsies (Figure 2b-c), and we could not find a significant correlation between these two parameters.

No case showed amyloid deposition and except for the PVP-containing macrophages, there was little or no tubulointerstitial inflammation.

*Figure 2 and table 2 approximately here*

### *Glomerular findings*

The most striking finding in the glomerular compartment was the many underperfused (Figure 2d) and ischemic glomeruli. Glomerular volume varied greatly both within and between biopsies. Mean glomerular volume was 2.3 * $10^6$ $\mu m^3$ (SD = 1.7, 95% CI 2.2—2.4), indicating a low mean glomerular volume compared to the normal value of 2.6 * $10^6$ $\mu m^3$ (SD = 1.00) reported by Denic et al. (33). In 22 cases, we observed PVP-containing vacuoles in glomeruli by light microscopy, which in some cases corresponded to a higher number of macrophages (Figure 2e-f).

Clinically significant immunopathological findings with corresponding electron dense deposits were present in only two biopsies. One of these was from a patient with previously diagnosed systemic lupus erythematosus, and showed a mesangioproliferative lupus nephritis with secondary segmental sclerosis (Class III). The second biopsy showed a mesangioproliferative immune-complex glomerulonephritis. No case showed evidence of glomerular disease associated with IV drug use, such as subepithelial electron dense deposits or membranous or membranoproliferative patterns.

### *Vascular findings*

Arterial vessels did not show PVP deposits. Arteriosclerosis and/or arteriolohyalinosis was present in 27 of 28 cases, and moderate to severe vascular sclerosis was common. We could not find a correlation between severity of vascular sclerosis and the extent of TA or the share of underperfused or ischemic glomeruli.

### *EM findings*

In 22 of 27 biopsies examined by EM, we observed cells in glomeruli with vacuoles that met our criteria for PVP-containing vacuoles (Figure 3a-c). All 22 biopsies revealed vacuolated mesangial cells, and 11 of them showed vacuolated endothelial cells. There were often numerous vacuoles in a single cell, occupying much of the cytoplasm and frequently making indentations in the nucleus. Some vacuoles contained granular electron-dense material along the vacuoles' limiting membrane. The ultrastructural appearance of vacuoles in interstitial macrophages was similar, but considerably larger vacuoles were common (Figure 3d). In podocytes, vacuoles were typically fewer in each cell, more variable in size and collocated with osmiophilic material suspicious of lipofuscin (Figure 3e). Hence, we could not separate these from lipid-filled vacuoles with certainty.

*Figure 3 approximately here*

## Further development and patient outcome

While the first biopsy in this study was performed in 2009, the deposits observed were not recognized as PVP until 2013 (Figure 4). The methadone product that was the likely source of PVP in these patients was retracted from the market in Norway and the European Union in 2014 (22). After 2016, we know of no new cases of kidney PVP deposition.

*Figure 4 approximately here*

Most patients in this study received follow-up at a nephrology outpatient clinic, and we have follow-up data for 26 patients (mean observation time 4.8 years (SD = 2.4, range 1.3 – 9.1)). In 23 of 26 patients (88 %), eGFR had slowly declined (8 %), stabilized (31 %) or improved (50 %), but normalization was not observed. Only three patients (12 %) had a rapid decline in eGFR, one of whom had lupus nephritis. The other two patients had developed kidney failure requiring hemodialysis. Both had concomitant chronic soft tissue infections and osteomyelitis. Six patients were deceased by the time of the last follow-up. One patient, who had biopsy proven PVP deposition in several organs, died with multiple organ failure and kidney failure with ongoing hemodialysis. One

patient died from injuries caused by violence, and two likely died from overdoses. The cause of death for the two remaining patients is unknown to us

## Discussion

This series of 28 cases is a systematic description of the clinicopathological findings in patients with kidney PVP deposition after injection of a specific oral methadone syrup containing high molecular weight PVP as an excipient. All patients had CKD with absent or low-grade proteinuria, and all had a history of opioid addiction and IV drug use. The main biopsy findings were moderate to severe TA associated with infiltrates of PVP-containing macrophages, highlighting a likely causal role of PVP deposits in the development of CKD in these patients. This case series is unique in describing PVP deposition in the kidneys in the context of CKD, opioid addiction and IV drug use, and may serve to raise awareness among both clinicians and pathologists regarding this diagnostic possibility.

PVP is considered an inert substance; it is not absorbed from the gastrointestinal tract, nor is it enzymatically degraded (34). If administered parenterally, the only mechanism of elimination is through glomerular filtration, which is progressively ineffective with increasing molecular weight of the PVP molecules (14). In the kidney, circulating PVP molecules enter the interstitium via the post-glomerular capillaries (35). We hypothesize the following pathogenesis of CKD in these patients: the PVP deposits increase the distance between the post-glomerular capillaries and the tubules leading to an inadequate supply of nutrients and oxygen. This causes an initial acute and later chronic tubular epithelial cell damage, and eventually leads to a decreased glomerular filtration rate via altered tubuloglomerular feedback (36). The frequent observation of underperfused glomeruli in our cases and the reduced mean glomerular volume would be consistent with such a mechanism.

It should be noted that biopsy samples with similar extent of TA showed markedly different extent of PVP-deposition, and that no significant correlation between the extent of PVP deposition and the extent of TA was found. One possible explanation for lack of correlation may be that there is a

potential redistribution of PVP from the kidney to other tissues (14). Such a mechanism may also explain the improvement in kidney function observed in several patients after they ceased injecting the methadone syrup.

The pronounced arteriosclerosis could be an alternative explanation or contributing factor for both TA and glomerular underperfusion and ischemia. However, arteriosclerosis is a common finding in persons with illicit drug use as shown in an autopsy study by Buettner et al. on a cohort with similar age and gender distribution (37). Although arteriosclerosis was pronounced, Buettner et al. reported interstitial fibrosis and TA > 10% in only 16 % of cases, while all our cases showed a significantly higher proportion of TA. Likewise, we could not find a correlation between vascular sclerosis and TA or glomerular underperfusion. Glomerulonephritides with significant nephron loss as an alternative explanation for the observed tubular atrophy could be excluded. These observations taken together support the notion that PVP deposition was central in the development of TA in our patients.

CKD in concurrence with PVP deposition in the kidney has so far only been reported in two case reports from 1968 and 1972 (20, 21). The PVP deposits in these cases originated from repeated injections of parenteral medication containing moderate molecular weight PVP. Similar to our cases, the biopsies in these reports showed tubular atrophy, large interstitial accumulations of macrophages with PVP-containing vacuoles, as well as glomerular deposits. However, in contrast to our findings, the case report by Grunfeld et al. described vacuolated tubular epithelial cells as a main finding, and found most of the glomerular PVP deposits residing in the podocytes (20). While our biopsies did show vacuolated podocytes, we were not able to distinguish these from lipid-filled vacuoles, which is a common finding in kidney biopsies (38). The differences in findings between the case reported by Grunfeld et al. and the cases in this study could be due to the much lower molecular weight of the PVP previously used in parenteral medication (16, 20), which allows partial glomerular filtration and possibly reabsorption by the tubular epithelium (14). The lower molecular weight might also explain why CKD from PVP deposition has rarely been reported.

The methadone syrup linked to our cases was marketed in six European countries between 2007 and 2014 (22). However, moderate molecular weight PVP is still used as an excipient in several opioid substitution drugs and other oral medications with addictive properties, both in Europe and the US (11, 22, 39). Frequent injection of such medications may lead to some level of accumulation of PVP(34). The question remains whether our cases are isolated incidents, or if PVP deposition is under-reported due to milder disease in cases exposed to PVP with lower molecular weight. Deposition of a lipid-like material in kidney biopsies from patients with IV drug use has been described in four case reports (40-43). Three of these described a total of seven patients with pathological findings that differ from our cases in that the deposits were primarily located in the glomeruli, and that most patients presented with nephrotic syndrome (40-42). We therefore suspect that an excipient other than PVP caused the glomerular changes in these cases. Finally, a case report from Germany described two patients in a methadone substitution program who were biopsied in 2012 (43). These cases were very similar to ours in both their clinical presentation and the localization of the deposits in both glomeruli and the interstitium. The deposits could therefore very well correspond to PVP deposits. However, the authors of this report did not state whether they had investigated this possibility. Nevertheless, all four of these reports linked the deposits observed to injection of opioid substitution drugs and other oral medications with addictive properties, and their excipients (40-43).

Our study has some limitations. Biopsies and patients were included in the study only when PVP deposits were recognized, which means that individual biopsies might have escaped detection. Furthermore, detailed data such as amount of medication injected and time between PVP exposure and kidney biopsy were not available to us. Our study benefits from the relatively large number of cases, but could still be underpowered to detect significant correlations. Furthermore, we were not able to investigate any of the biopsies with lipid stains, as fresh frozen tissue was not available to us.

In conclusion, intravenous use of a specific oral methadone syrup has caused PVP deposition in the kidney in persons with opioid addiction and IV drug use. Clinicopathological findings suggest an association between PVP deposition, TA and CKD. This specific methadone syrup containing high molecular weight PVP is no longer marketed, but moderate molecular weight PVP is an excipient in several opioid substitution drugs and other medications with addictive properties. As injection of oral medication is widespread among persons with IV drug use (39), it is likely that cases with deposits of excipients such as PVP are under-diagnosed and under-reported, as are kidney diseases in general in this patient group (44).

## Disclosures

All authors declare that they have no disclosures to report.


## Funding

The Western Norway Health Authority funded this study (grant number 912001).

## Acknowledgements

We thank the Departments of Pathology at Førde Hospital, St.Olavs Hospital, and Oslo University Hospital for sharing their cases with us. We also thank Brynhild Haugen, Jean Stain and Tina Straus Dahl, Kidney Biopsy Laboratory, Department of Pathology at Haukeland University Hospital Bergen for excellent technical assistance. We are indebted to Erik Heyerdahl Strøm, Oslo University Hospital for professional advice. Data from this study was presented as an oral presentation at the American Society of Nephrology's Kidney Week 2019 on November 8, 2019, in Washington DC. Ida Viken Stalund is a PhD candidate funded by The Western Norway Health Authority, and the current communication will be a part of her degree. The funding body had no role in the design of the study, collection, analysis, and interpretation of data or in writing the manuscript.

## References


1. Novick, T, Liu, Y, Alvanzo, A, Zonderman, AB, Evans, MK, Crews, DC: Lifetime Cocaine and Opiate Use and Chronic Kidney Disease. *Am J Nephrol,* 44**:** 447-453, 2016 10.1159/000452348
2. Perneger, TV, Klag, MJ, Whelton, PK: Recreational drug use: a neglected risk factor for end-stage renal disease. *Am J Kidney Dis,* 38**:** 49-56, 2001 10.1053/ajkd.2001.25181
3. Mansoor, K, Kheetan, M, Shahnawaz, S, Shapiro, AP, Patton-Tackett, E, Dial, L, Rankin, G, Santhanam, P, Tzamaloukas, AH, Nadasdy, T, Shapiro, JI, Khitan, ZJ: Systematic review of nephrotoxicity of drugs of abuse, 2005-2016. *BMC Nephrol,* 18**:** 379, 2017 10.1186/s12882-017-0794-0
4. Scott, JK, Taylor, DM, Dudley, CRK: Intravenous drug users who require dialysis: causes of renal failure and outcomes. *Clin Kidney J,* 11**:** 270-274, 2018 10.1093/ckj/sfx090
5. Manner, I, Sagedal, S, Roger, M, Os, I: Renal amyloidosis in intravenous heroin addicts with nephrotic syndrome and renal failure. *Clin Nephrol,* 72**:** 224-228, 2009 10.5414/cnp72224
6. Ozkok, A, Yildiz, A: Hepatitis C virus associated glomerulopathies. *World J Gastroenterol,* 20**:** 7544-7554, 2014 10.3748/wjg.v20.i24.7544
7. Hing Yim, CL, Wong, EWW, Jellie, LJ, Lim, AKH: Illicit drug use and acute kidney injury in patients admitted to hospital with rhabdomyolysis. *Intern Med J*, 2019 10.1111/imj.14266
8. do Sameiro Faria, M, Sampaio, S, Faria, V, Carvalho, E: Nephropathy associated with heroin abuse in Caucasian patients. *Nephrol Dial Transplant,* 18**:** 2308-2313, 2003 10.1093/ndt/gfg369
9. Kaur, P, Bergrem, A, Gerlyng, P, Reims, HM, Leh, S, Valeur, J: A methadone user with anaemia, skeletal pain and altered appearance. *Tidsskr Nor Laegeforen,* 136**:** 925-929, 2016 10.4045/tidsskr.15.0692
10. Kristoffersen, AH, Bjanes, TK, Jordal, S, Leh, S, Leh, F, Svarstad, E: Polyvinylpyrrolidone induced artefactual prolongation of activated partial thromboplastin times in intravenous drug users with renal failure. *Journal of thrombosis and haemostasis : JTH,* 14**:** 936-939, 2016 10.1111/jth.13299
11. Leh, F, Stalund, IV, Bjanes, TK, Ohldieck, C, Svarstad, E, Leh, S: Polyvinylpyrrolidone deposition disease in patients with intravenous opioid use: a case series. *Hum Pathol,* 116**:** 102-111, 2021 10.1016/j.humpath.2021.07.009
12. Stalund, IV, Riise, GN, Leh, F, Bjanes, TK, Riise, L, Svarstad, E, Leh, S: Case Report: Polyvinylpyrrolidone deposition disease from repeated injection of opioid substitution drugs: report of a case with a fatal outcome. *F1000Res,* 10**:** 300, 2021 10.12688/f1000research.51927.2
13. Buehler, V: *Polyvinylpyrrolidone Excipients for Pharmaceuticals: Povidone, Crospovidone and Copovidone,* Berlin, Springer, 2005.
14. Ravin, HA, Seligman, AM, Fine, J: Polyvinyl pyrrolidone as a plasma expander: studies on its excretion, distribution and metabolism. *N Engl J Med,* 247**:** 921-929, 1952 10.1056/NEJM195212112472403
15. Altemeier, WA, Schiff, L, Galle, A, Giuseffi, J, Freiman, D, Mindrum, G, Braunstein, H: Physiological and pathological effects of long-term polyvinylpyrrolidone retention. *AMA Arch Surg,* 69**:** 308-314, 1954
16. Robinson, BV, Sullivan, FM, Borzelleca, JF, Schwarz, SL: *PVP - A Critical Review of the Kinetics and Toxicology of Polyvinylpyrrolidone (Povidone),* Michigan, Lewis Publishers, 1990.
17. Reske-Nielsen, E, Bojsen-Moller, M, Vetner, M, Hansen, JC: Polyvinylpyrrolidone-storage disease. Light microscopical, ultrastructural and chemical verification. *Acta Pathol Microbiol Scand A,* 84**:** 397-405, 1976
18. Edelmann, U, Johansen, P, Pedersen, AB, Christensen, M, Hau, C: [PVP storage as the cause of specific organ symptoms]. *Ugeskr Laeger,* 139**:** 2309-2312, 1977
19. Christensen, M, Johansen, P, Hau, C: Storage of polyvinylpyrrolidone (PVP) in tissues following long-term treatment with a PVP-containing vasopressin preparation. *Acta Med Scand,* 204**:** 295-298, 1978 10.1111/j.0954-6820.1978.tb08442.x

20. Grunfeld, JP, de, MH, Berry, JP, Reveillaud, RJ: [Apropos of a case of thesaurismosis due to polyvinylpyrrolidone with predominant renal localization]. *J Urol Nephrol (Paris),* 74**:** 656-666, 1968
21. Bert, JM, Balmes, JL, Cayrol, B, Bali, JP, Pages, A, Baldet, P: [Case of thesaurismosis caused by polyvinylpyrrolidone (P.V.P.)]. *Sem Hop,* 48**:** 1809-1816, 1972
22. European Medicines Agency: Assessment report for methadone medicinal products for oral use containing povidone, 2014 http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Methadone/Position_provided_by_CMDh/WC500170689.pdf
23. Bretteville-Jensen, AL, Lillehagen, M, Gjersing, L, Andreas, JB: Illicit use of opioid substitution drugs: prevalence, user characteristics, and the association with non-fatal overdoses. *Drug Alcohol Depend,* 147**:** 89-96, 2015 10.1016/j.drugalcdep.2014.12.002
24. Johnson, B, Richert, T: Diversion of methadone and buprenorphine by patients in opioid substitution treatment in Sweden: prevalence estimates and risk factors. *Int J Drug Policy,* 26**:** 183-190, 2015 10.1016/j.drugpo.2014.10.003
25. Kidney Disease Improving Global Outcomes: KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, 2013 https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf
26. Rosansky, SJ, Glassock, RJ: Is a decline in estimated GFR an appropriate surrogate end point for renoprotection drug trials? *Kidney Int,* 85**:** 723-727, 2014 10.1038/ki.2013.506
27. Jenkins, J, Brodsky, SV, Satoskar, AA, Nadasdy, G, Nadasdy, T: The relevance of periglomerular fibrosis in the evaluation of routine needle core renal biopsies. *Arch Pathol Lab Med,* 135**:** 117-122, 2011 10.1043/2009-0484-OAR1.1
28. Samuel, T, Hoy, WE, Douglas-Denton, R, Hughson, MD, Bertram, JF: Applicability of the glomerular size distribution coefficient in assessing human glomerular volume: the Weibel and Gomez method revisited. *J Anat,* 210**:** 578-582, 2007 10.1111/j.1469-7580.2007.00715.x
29. Roufosse, C, Simmonds, N, Clahsen-van Groningen, M, Haas, M, Henriksen, KJ, Horsfield, C, Loupy, A, Mengel, M, Perkowska-Ptasinska, A, Rabant, M, Racusen, LC, Solez, K, Becker, JU: A 2018 Reference Guide to the Banff Classification of Renal Allograft Pathology. *Transplantation,* 102**:** 1795-1814, 2018 10.1097/TP.0000000000002366
30. Working Group of the International Ig A Nephropathy Network, Renal Pathology Society, Roberts, IS, Cook, HT, Troyanov, S, Alpers, CE, Amore, A, Barratt, J, Berthoux, F, Bonsib, S, Bruijn, JA, Cattran, DC, Coppo, R, D'Agati, V, D'Amico, G, Emancipator, S, Emma, F, Feehally, J, Ferrario, F, Fervenza, FC, Florquin, S, Fogo, A, Geddes, CC, Groene, HJ, Haas, M, Herzenberg, AM, Hill, PA, Hogg, RJ, Hsu, SI, Jennette, JC, Joh, K, Julian, BA, Kawamura, T, Lai, FM, Li, LS, Li, PK, Liu, ZH, Mackinnon, B, Mezzano, S, Schena, FP, Tomino, Y, Walker, PD, Wang, H, Weening, JJ, Yoshikawa, N, Zhang, H: The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. *Kidney Int,* 76**:** 546-556, 2009 10.1038/ki.2009.168
31. Solez, K, Colvin, RB, Racusen, LC, Haas, M, Sis, B, Mengel, M, Halloran, PF, Baldwin, W, Banfi, G, Collins, AB, Cosio, F, David, DS, Drachenberg, C, Einecke, G, Fogo, AB, Gibson, IW, Glotz, D, Iskandar, SS, Kraus, E, Lerut, E, Mannon, RB, Mihatsch, M, Nankivell, BJ, Nickeleit, V, Papadimitriou, JC, Randhawa, P, Regele, H, Renaudin, K, Roberts, I, Seron, D, Smith, RN, Valente, M: Banff 07 classification of renal allograft pathology: updates and future directions. *Am J Transplant,* 8**:** 753-760, 2008 10.1111/j.1600-6143.2008.02159.x
32. Hübner, G: [Electron microscopic studies on so-called collidon nephrosis. (A contribution to the problem of the tubular uptake of the substance)]. *Beitr Pathol Anat,* 126**:** 1-28, 1962
33. Denic, A, Mathew, J, Nagineni, VV, Thompson, RH, Leibovich, BC, Lerman, LO, Lieske, JC, Alexander, MP, Augustine, JJ, Kremers, WK, Rule, AD: Clinical and Pathology Findings Associate Consistently with Larger Glomerular Volume. *J Am Soc Nephrol,* 29**:** 1960-1969, 2018 10.1681/asn.2017121305
34. Wessel, W, Schoog, M, Winkler, E: Polyvinylpyrrolidone (PVP), its diagnostic, therapeutic and technical application and consequences thereof. *Arzneimittelforschung,* 21**:** 1468-1482, 1971

35. Gartner, K, Vogel, G, Ulbrich, M: [Studies on the penetration of macromolecules (polyvinylpyrrolidone) through glomerular and postglomerular capillaries into the urine and kidney lymph, and on the extent of extravascular circulation of 131-I-albumin in the kidney interstitium]. *Pflugers Arch Gesamte Physiol Menschen Tiere,* 298**:** 305-321, 1968
36. Schnermann, J: Homer W. Smith Award lecture. The juxtaglomerular apparatus: from anatomical peculiarity to physiological relevance. *J Am Soc Nephrol,* 14**:** 1681-1694, 2003 10.1097/01.asn.0000069221.69551.30
37. Buettner, M, Toennes, SW, Buettner, S, Bickel, M, Allwinn, R, Geiger, H, Bratzke, H, Amann, K, Jung, O: Nephropathy in illicit drug abusers: a postmortem analysis. *Am J Kidney Dis,* 63**:** 945-953, 2014 10.1053/j.ajkd.2014.01.428
38. Ogawa-Akiyama, A, Sugiyama, H, Kitagawa, M, Tanaka, K, Kano, Y, Mise, K, Otaka, N, Tanabe, K, Morinaga, H, Kinomura, M, Uchida, HA, Wada, J: Podocyte autophagy is associated with foot process effacement and proteinuria in patients with minimal change nephrotic syndrome. *PLoS One,* 15**:** e0228337, 2020 10.1371/journal.pone.0228337
39. McLean, S, Patel, R, Bruno, R: Injection of Pharmaceuticals Designed for Oral Use: Harms Experienced and Effective Harm Reduction Through Filtration. *Curr Top Behav Neurosci,* 34**:** 77-98, 2017 10.1007/7854_2016_470
40. Lynn, KL, Pickering, W, Gardner, J, Bailey, RR, Robson, RA: Intravenous drug use and glomerular deposition of lipid-like material. *Nephron,* 80**:** 274-276, 1998 10.1159/000045186
41. Lim, AK, Dowling, JP, Kanellis, J: Glomerular lipid deposition: a clue to illicit intravenous drug use. *Nephrology (Carlton),* 14**:** 358-359, 2009 10.1111/j.1440-1797.2009.01133.x
42. Mohan, J, Nybo, CJ, Vegsundvag, J, Roald, B, Liem, YS: Nephrotic syndrome and pulmonary hypertension as complications of intravenous drug abuse. *Apmis,* 128**:** 506-510, 2020 10.1111/apm.13065
43. Porubsky, S, Kuppe, C, Maier, T, Birk, HW, Wornle, M, Moeller, MJ, Floege, J, Grone, HJ: Renal lipidosis in patients enrolled in a methadone substitution program. *Arch Pathol Lab Med,* 138**:** 689-693, 2014 10.5858/arpa.2013-0075-CR
44. Pendergraft, WF, III, Herlitz, LC, Thornley-Brown, D, Rosner, M, Niles, JL: Nephrotoxic Effects of Common and Emerging Drugs of Abuse. *Clin J Am Soc Nephrol*, 2014 10.2215/cjn.00360114

# Tables

*Table 1: Demographics, comorbidities, clinical kidney parameters at the time of biopsy.*

| Characteristic | Value |
|---|---|
| Age at time of biopsy | 37 (SD 6, range 23 - 52) |
| Male sex | 22 (79 %) |
| HBV positive | 16 (57 %) |
| HCV positive | 26 (93 %) |
| Proteinuria [a] | |
| No/mild | 18 (64 %) |
| Moderate | 9 (32 %) |
| Severe | 1 (4 %) |
| Hematuria present [b] | 4 (14 %) |
| Serum creatinine (mg/dL) | 2.45 (SD 0.70, range 1.25 - 4.32) |
| eGFR (mL/min/1.73m$^2$) | 33 (SD 11, range 14 - 58) |

*Values represent frequency (percentage) or mean (SD, Range). HBV, hepatitis B virus (seropositivity); HCV, hepatitis C virus (seropositivity); eGFR, estimated glomerular filtration rate (calculated by the CKD-EPI formula).*

*[a] Based on measurements of albumin/creatinine ratio or protein/creatinine ratio. Graded according to the KDIGO guidelines (25). [b] Based on strip test evaluation.*

*Table 2: Pathology findings*

| Characteristic | Value |
|---|---|
| Extent of tubular atrophy (%) | 65 (SD 20, range 34 - 92) |
| Extent of PVP deposition (%) | 1.5 (SD 2.0, range 0.05 - 9.1) |
| Number of glomeruli | 24 (SD 12, range 4 - 53) |
| Underperfused (%) | 51 (SD 20, range 0 - 86) |
| Ischemic (%) | 20 (SD 16, range 0 - 61) |
| Globally sclerosed (%) | 8 (SD 11, range 0 - 50) |
| Arteriosclerosis [a] | |
| 0 | 8 (29 %) |
| 1 | 2 (7 %) |
| 2 | 18 (64 %) |
| Arteriolohyalinosis [b] | |
| 0 | 9 (32 %) |
| 1 | 7 (25 %) |
| 2 | 4 (14 %) |
| 3 | 8 (29 %) |

*Values represent frequency (percentage) or mean (SD, range). TA, tubular atrophy; PVP, polyvinylpyrrolidone*

[a] Graded as suggested by Roberts et al (30) (0 – No intimal thickening. 1 – Intima thickened to less than the thickness of the media. 2 – Intima thickened to more than the thickness of the media). [b] Graded according to the Banff aah score (29, 31) (0

– no hyaline arteriolar thickening. 1 – hyaline deposits in only one arteriole. 2 – hyaline deposits in more than one arteriole. 3 – hyaline deposits with circumferential involvement, independent of the number of arterioles involved).

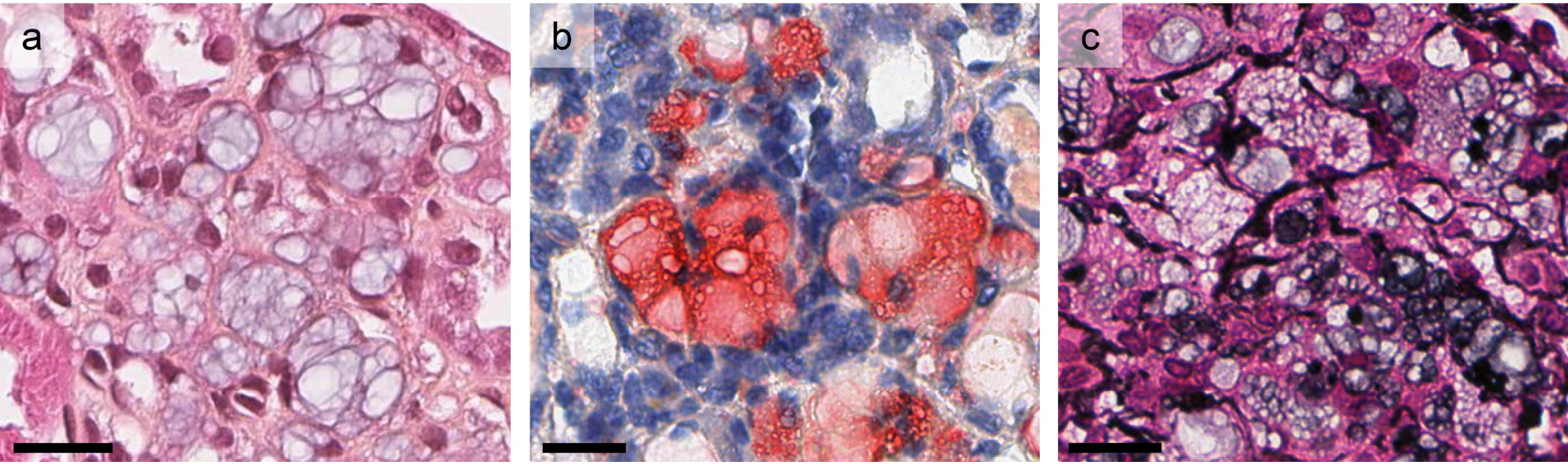
## Figure legends

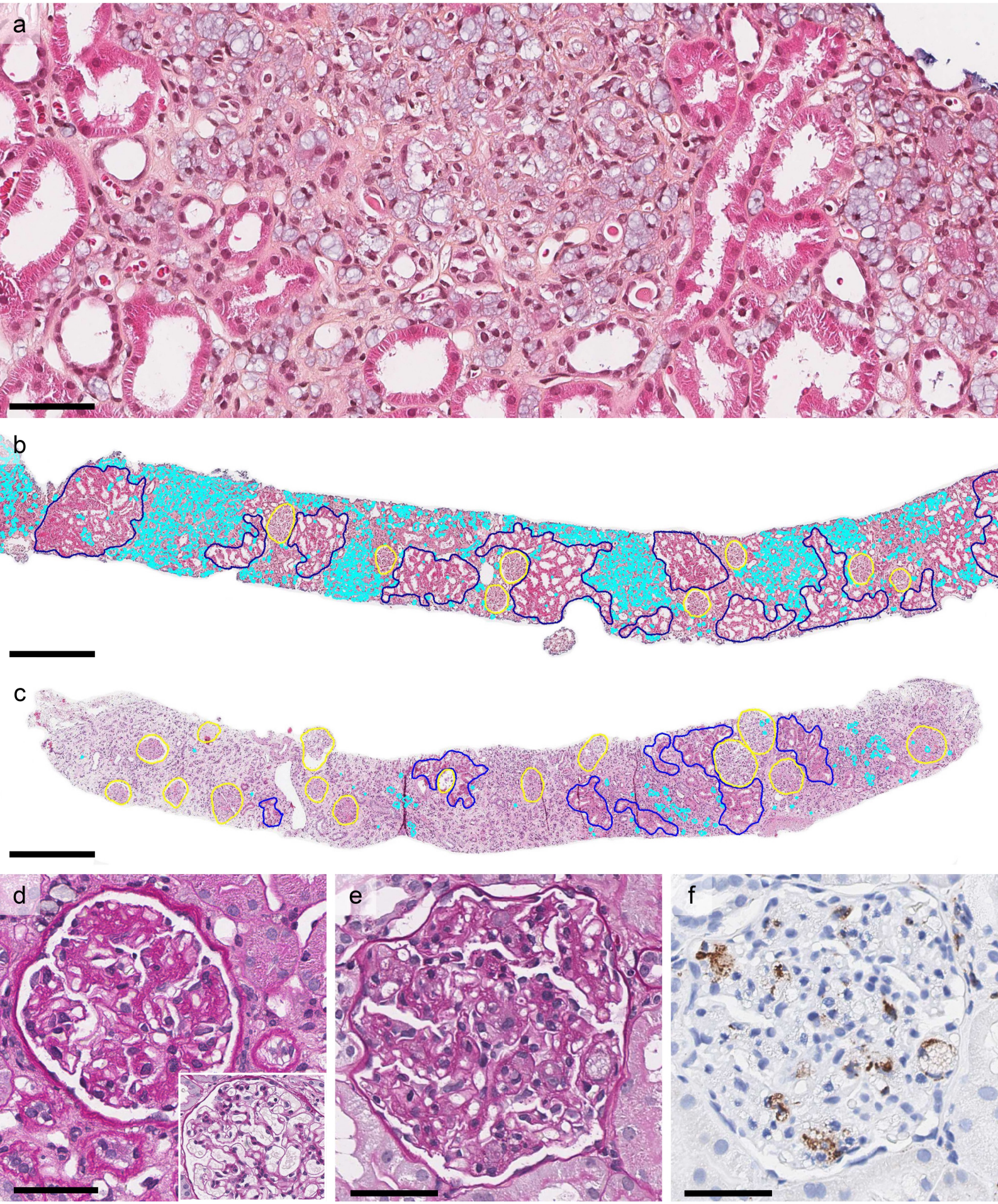
*Figure 1: Staining characteristics for polyvinylpyrrolidone (PVP) deposited in tissue. Scale bars 20 µm. a: Light blue in Hematoxylin & Eosin (H&E). b: Red in Congo red stain, though not birefringent in polarizing light. c: Grey or black in Periodic Silver-Methenamine stain (PASM).*

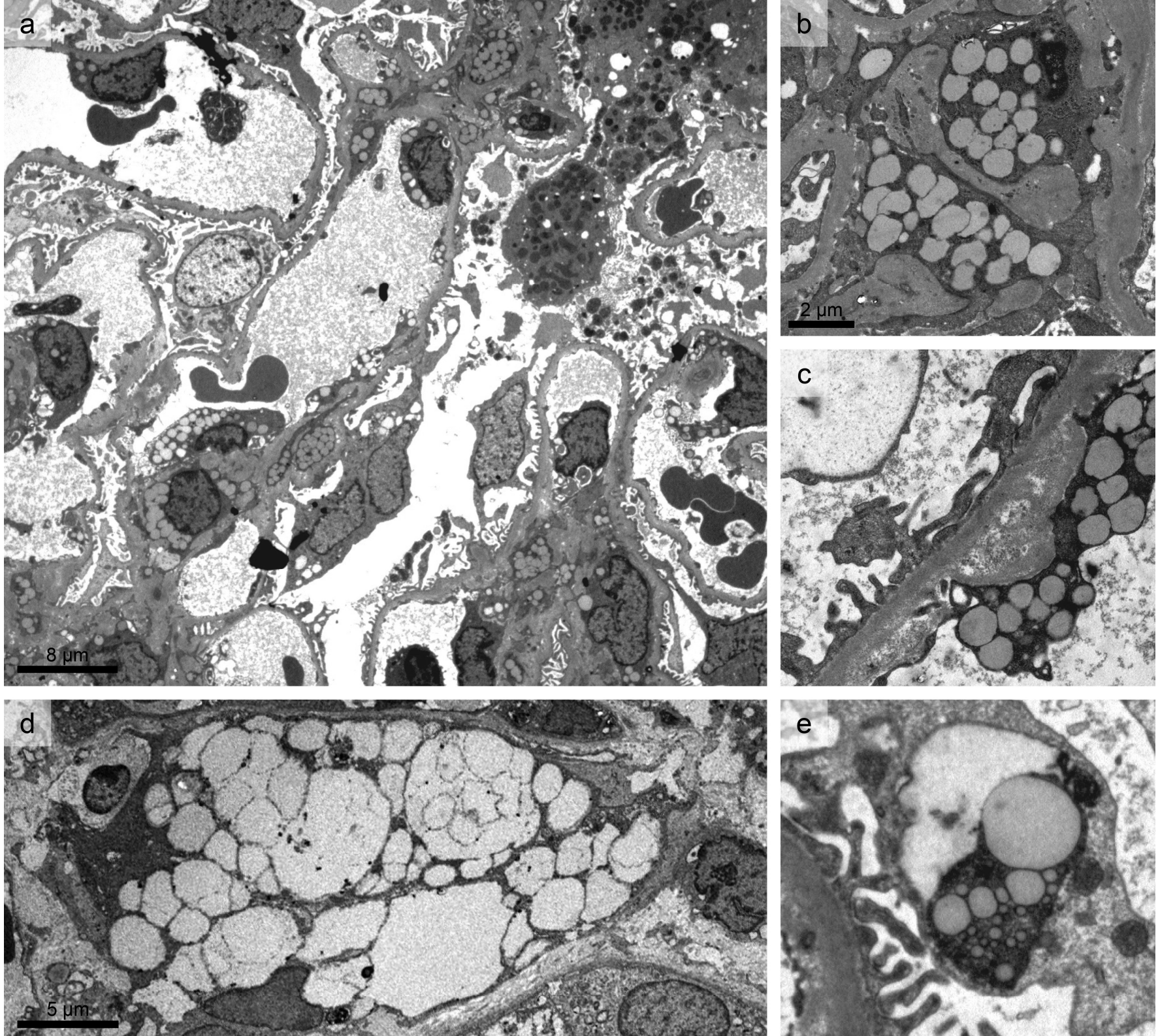
*Figure 2: Tubulointerstitial and glomerular findings in biopsies with polyvinylpyrrolidone (PVP) deposits. a: Abrupt transition from an area with tubular atrophy (TA) to more normal looking tubules. There is a dense infiltrate of PVP-containing macrophages in the extended interstitium (Hematoxylin & Eosin (H&E) with saffron), scale bar 50 µm. b-c: Whole biopsy micrographs (H&E), scale bars 500 µm. To illustrate the distribution, PVP-containing vacuoles are encircled with turquoise, glomeruli with yellow and normal tubulointerstitial areas with blue. b: The infiltrates of PVP-containing macrophages and areas with TA are largely overlapping. c: As in b, the infiltrates of PVP-containing macrophage are localized in areas with TA, but TA is more extensive and the PVP deposition markedly less extensive than in b. d-f: Glomerular findings, scale bars 50 µm. d: Underperfused glomerulus (Periodic Acid-Schiff (PAS)). The capillary tuft is collapsed with wrinkling of the basement membranes. Inset: Normal glomerulus for comparison. e: Glomerulus with PVP deposits (PAS). PVP-containing vacuoles appear to be located in the extended mesangium. f: Glomerulus (same as in e) with higher number of CD68-positive macrophages corresponding to PVP deposits in e.*

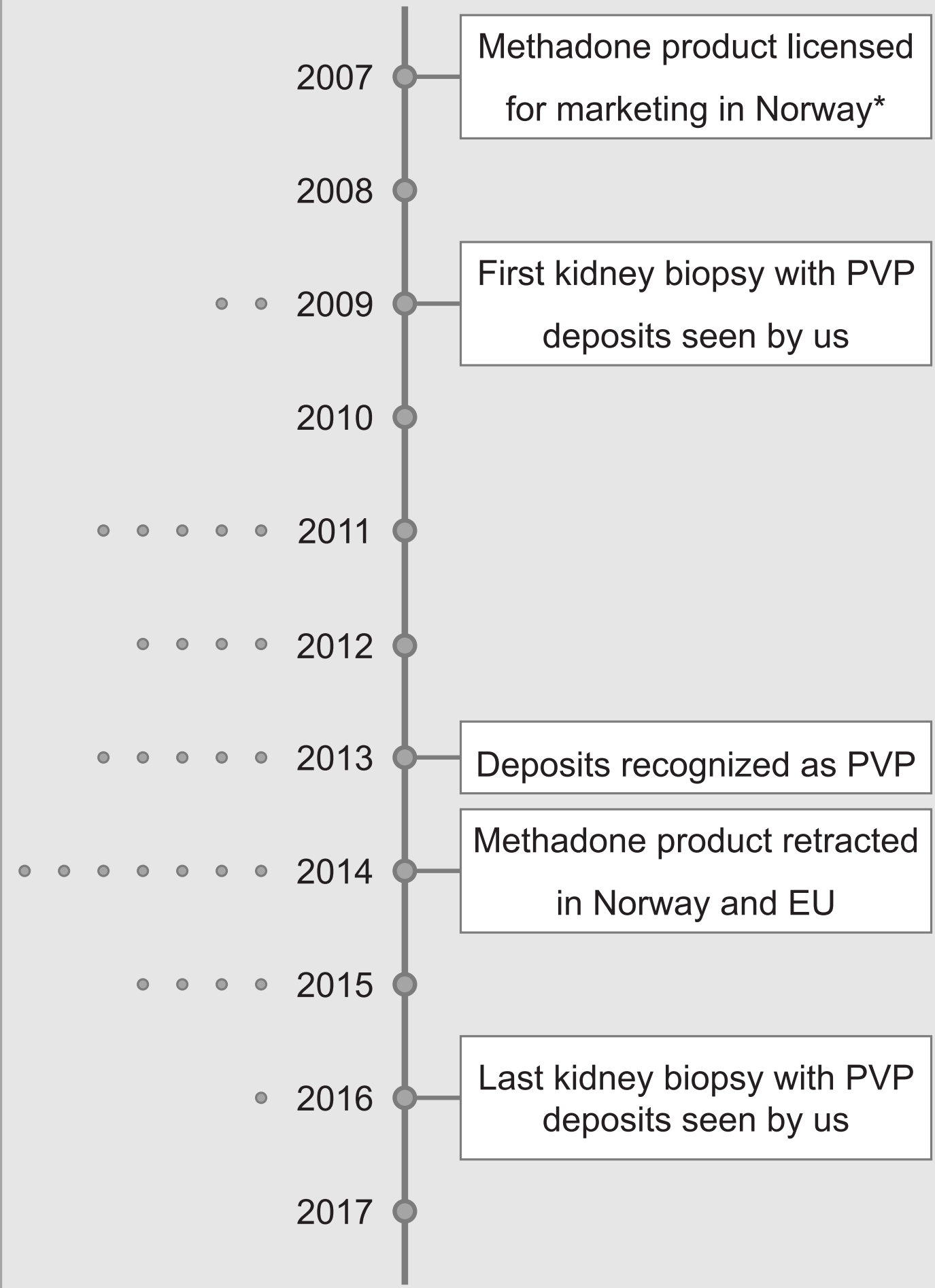
*Figure 3: Electron microscopy (EM) findings in biopsies with polyvinylpyrrolidone (PVP) deposits. a: Overview showing extended mesangial areas with vacuolated cells. b: Cells in the mesangium containing multiple vacuoles. Vacuole content has low to intermediate electron density and low-grade granularity. Vacuole profile diameter typically 0.3 – 1.5 µm. Some vacuoles have granular electron dense material along the limiting membrane. c: Vacuolated endothelial cells. Vacuole appearance as described under b. d: Macrophage in the interstitium distended by multiple vacuoles. Vacuole profile diameter up to 5 µm. e: Vacuolated podocyte. The vacuoles' appearance is similar to those in the mesangial and endothelial cells. However, the vacuoles are fewer with larger variation in size and collocated with osmiophilic material suspicious of lipofuscin.*

*Figure 4: Timeline from the start of the marketing license in Norway for the methadone product containing high molecular weight polyvinylpyrrolidone (PVP). The number of observed kidney biopsies showing polyvinylpyrrolidone (PVP) deposits for each year is shown to the left with each point representing one kidney biopsy. *Start of marketing license for five other European countries in 2010.*


a
b
c


a
b
c
d
e
f


a
8 µm
b
2 µm
c
d
5 µm
e


2007
Methadone product licensed for marketing in Norway*
2008
2009
First kidney biopsy with PVP deposits seen by us
2010
2011
2012
2013
Deposits recognized as PVP
2014
Methadone product retracted in Norway and EU
2015
2016
Last kidney biopsy with PVP deposits seen by us
2017