KI REPORTS
KIReports.org
CLINICAL RESEARCH

Spectrum of Kidney Biopsy Findings Associated With Methamphetamine Use

Hae Yoon Grace Choung[1], Cynthia C. Nast[1], Mark Haas[1], Mercury Lin[1], Michifumi Yamashita[1] and Jean Hou[1]

[1]Department of Pathology and Laboratory Medicine, Cedars Sinai Medical Center, Los Angeles, California, USA

Introduction: Methamphetamine (METH) is one of the most used drugs of abuse worldwide. However, there are few reports and series examining the toxic kidney effects of METH, and associated histopathological changes are not well-described.

Methods: We retrospectively identified 112 patients with a history significant for METH abuse, of whom 62 were using METH-only and 60 were using METH plus other drugs of abuse.

Results: In the METH-only cohort, the mean age was 41 years (interquartile range [IQR]: 33–49) and most (76%) were male. Almost all cases (97%) showed evidence of kidney dysfunction at the time of biopsy. Of the cases, 65% had proteinuria, of which 53% were nephrotic range and 10% had nephrotic syndrome. The most common biopsy diagnosis was acute tubular necrosis (ATN) (66%), of which 19% had myoglobin casts; followed by focal segmental glomerulosclerosis (FSGS) in 53% (not otherwise specified [NOS] in 76% and collapsing FSGS [cFSGS] in 18%). Biopsy findings also include tubulointerstitial nephritis (TIN) (37%), thrombotic microangiopathy (TMA) (24%), and diabetic glomerulosclerosis (DG) (31%). Glomerulonephritis (GN) was identified in one-third of cases, the most common of which were infection-related GN (IRGN) (15%) and IgA nephropathy (IgAN) (11%). Of those with GN, 64% had underlying infection. Of interest, there was increased association for myoglobinuric ATN in those with concurrent ethanol-abuse ($P = 0.002$). Moreover, the METH-only patients were more likely to have DG compared to those with multiple substance-use ($P = 0.01$). More than half of the patients demonstrated at least moderate to severe tubulointerstitial scarring and marked hypertensive vascular disease.

Conclusion: Most patients with METH-use present with acute kidney injury (AKI) and often have proteinuria associated with a wide spectrum of renal pathology.

Kidney Int Rep (2024) **9,** 2180–2188; https://doi.org/10.1016/j.ekir.2024.04.049
KEYWORDS: acute renal failure; chronic kidney disease; drug misuse; methamphetamine; public health; rhabdomyolysis
© 2024 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Recreational illicit drug use has been a significant chronic public health problem in the United States and has increased in recent years.[1,2] METH is a highly addictive psycho-active stimulant and one of the most misused drugs worldwide. It is a synthetic derivative of amphetamine, which is available as a prescription medication for treatment of attention-deficit/hyperactivity disorder or narcolepsy but is most frequently produced illegally using over-the-counter medications such as pseudoephedrine to create the popular street drug "crystal meth." Use of illicit or misuse of drugs is commonly associated with kidney failure, which is well-described in the setting of cocaine and opiate use[3-10]; however, the toxic kidney effects of METH are infrequently reported and not well-understood.[11-13] At our institution, we have noticed an increase in kidney biopsies from patients with AKI in the setting of METH use. However, the kidney histopathological changes of METH use have not been well-described. This retrospective study seeks to characterize METH-related kidney pathologic findings and is one of the first and largest kidney biopsy series describing renal pathology specifically associated with METH use.

METHODS

We retrospectively reviewed all native kidney biopsies accessioned at Cedars Sinai Medical Center between January 1, 2013 and December 31, 2023. The eligibility criterion was all native kidney biopsies from adult patients (aged >18 years) with a history significant for

Correspondence: Hae Yoon Grace Choung, Department of Pathology, Cedars Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, California 90048, USA. E-mail: haeyoon.choung@cshs.org

Received 28 March 2024; revised 16 April 2024; accepted 23 April 2024; published online 1 May 2024

METH use, defined as use sufficient for the treating physician to consider METH use as possible etiology for the patient's presenting symptoms with or without a current positive toxicology result. Cases were divided into 2 groups, namely METH-only and METH plus use of other illicit drugs.

Demographic and clinical information at the time of biopsy were collected from electronic medical records and referral forms from the submitting physicians, if available. Collected data included: age; sex; biopsy diagnosis; history of any infections, autoimmune diseases, neoplasms, other additional illicit drug (e.g., opiates, cocaine) or alcohol misuse; and laboratory parameters including serum creatinine, proteinuria, urinalysis, and urine toxicology. All kidney biopsies were processed using standard techniques for light microscopy, immunofluorescence, and electron microscopy; and were interpreted by 1 of 6 renal pathologists.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY). Continuous variables were expressed as median and IQRs whereas categorical variables were shown as frequency (%). To compare continuous values between groups, we performed *t* test and Mann-Whitney *U* test depending on the distribution of the variables. To compare categorical differences, we used Fisher exact test. This study was approved by the Institutional Review Board at Cedars Sinai (STUDY 00002729).

RESULTS

From January 2013 to December 2023, 112 patients with a history significant for METH use underwent native kidney biopsy. Of those patients, 12.5% ($n = 14$) were also using cocaine, 8% ($n = 9$) were using heroin, and 18% ($n = 20$) were using marijuana. Approximately 19% ($n = 21$) had a concurrent history of alcohol misuse. Of the 26 patients with urine toxicology screen available, 85% ($n = 22$) were positive, of which 50% ($n = 11$) were positive for METH-only, 36% ($n = 8$) for METH and other drugs, 4.5% ($n = 1$) for cocaine only, and 4.5% ($n = 1$) for opioid only. Excluding those with known concurrent cocaine, opioid, and/or marijuana use, and alcohol misuse, 62 patients were reportedly using only METH (Table 1). The mean age in this cohort was 41 years (IQR: 33–49) and most were male ($n = 47$; 76%).

Clinically, almost all patients demonstrated evidence of kidney dysfunction at the time biopsy ($n = 60$; 97%) (Table 1). A large proportion ($n = 40$; 65%) presented with proteinuria, of which 53% were nephrotic range and 10% with nephrotic syndrome; 27% ($n = 17$) had hematuria. The median serum creatinine was 5.1 mg/dl (IQR: 2.5–7.8). There were no significant demographic, comorbidity, or laboratory differences in those who used METH-only or METH plus other substances, although there was a trend to more infections in the METH-only cohort.

Table 1. Demographic and clinical characteristics of patients with METH-use undergoing renal biopsy

Characteristic	METH-use alone ($n = 62$) median (IQR) or *n* (%)	METH with other drugs of abuse ($n = 50$) median (IQR) or *n* (%)	*P*-value[a]
Age (yr)	41 (33–49)	40 (32–48)	0.6
Female	15 (24)	10 (20)	0.7
Male	47 (76)	40 (80)	
Diabetes	20 (32)	10 (20)	0.2
Hypertension	34 (55)	23 (46)	0.4
Malignant HTN	11 (18)	14 (28)	0.3
Cardiomyopathy/HF	13 (21)	7 (14)	0.5
Infections	34 (55)	18 (36)	0.06
Serum creatinine (mg/dl)	5.1 (2.5–7.8)	4.4 (2.7–7.3)	0.7
Hematuria	17 (27)	18 (36)	0.4
Proteinuria	40 (65)	32 (64)	1.0
Nephrotic range proteinuria without nephrotic syndrome	21 (34)	11 (22)	0.2
Nephrotic syndrome	4 (6.5)	7 (14)	0.2

HF, heart failure; HTN, hypertension; IQR, interquartile range; METH, methamphetamine.
[a]$P < 0.05$.

Comorbid conditions in those using METH-only included diabetes in 32% of patients ($n = 20$). Hypertension (HTN) was common and diagnosed in 55% ($n = 34$). Eleven patients (18%) had malignant HTN at presentation. Approximately one-fifth of the cases ($n = 13$) had heart failure or cardiomyopathy. Infection was present in 55% ($n = 34$), one-third of which were associated with more than 1 infectious agent (Table 2). Of those cases with an identifiable bacterial organism reported, there were 8 *Staphylococcus spp.*, 4 of which were methicillin-resistant *Staphylococcus aureus*; 5 were *Treponema pallidum*; 1 was *Streptococcus pneumoniae*; 1 *Klebsiella pneumoniae*; and 1 *Pseudomonas aeruginosa*. Of the 20 patients with viral infections, 12 had HIV (1 with concurrent hepatitis B virus and 1 with COVID-19), 6 hepatitis C virus, 2 hepatitis B virus, and 2 COVID-19. One HIV-positive patient had a fungal pneumonia due to Pneumocystis. Although an identifiable bacterial organism could not be found in most cases of METH plus other substances, the types of infections were overall similar in the patients using METH with and without additional misuse of other substances.

The most common biopsy diagnosis (Figure 1, Table 3) in those using METH with or without other substances was ATN (72% and 66%, respectively), of which 25% and 19%, respectively had myoglobin casts.

Table 2. Infections in patients with METH-use, *n* (%)

Infections	METH-use alone ($n = 34$)[a]	METH with other drugs of abuse ($n = 20$)[a]	*P*-value[b]
Bacterial	23 (68)	15 (75)	1.0
Staphylococcus spp.	8 (24)		
MRSA	4 (50)		
MSSA	2 (25)		
Unknown	2 (25)		
Streptococcus pneumoniae	1 (3)		
Klebsiella pneumoniae	1 (3)		
Pseudomonas aeruginosa	1 (3)		
Treponema pallidum	5 (15)	1 (5)	0.4
Unknown/unreported	7 (21)	14 (70)	
Viral	20 (59)	9 (45)	0.4
HCV	6 (18)	6 (30)	0.3
HBV	2 (6)	1 (5)	1.0
HIV	12 (35)	3 (15)	0.1
COVID	2 (6)	0 (0)	0.5
Site of bacterial infection			
Cellulitis	5 (15)	5 (25)	0.4
Sepsis	7 (20)	1 (5)	0.2
Endocarditis	4 (12)	2 (10)	1.0
UTI	4 (12)	3 (15)	1.0
PNA	3 (9)	4 (20)	0.4
Osteomyelitis	1 (3)	1 (5)	1.0

HBV, hepatitis B virus; HCV, hepatitis C virus; METH, methamphetamine; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PNA, pneumonia; UTI, urinary tract infection.
[a]Patients may have more than 1 infection.
[b]$P < 0.05$

The most frequent glomerular finding in both cohorts and second most common biopsy finding overall was FSGS (Figure 2), in the METH-only cohort present in 53% ($n = 33$), with NOS being the most common variant (76%, $n = 25$) followed by cFSGS (18%, $n = 6$). In the METH-only patients, additional findings included TIN (37%, $n = 23$), TMA (24%, $n = 15$), DG (31%, $n = 19$), IRGN (15%, $n = 9$), and IgAN (11%, $n = 7$). Of patients with TIN 48% had acute TIN (AIN), 9% had chronic active TIN, and 26% had chronic inactive TIN. All cases of AIN, chronic active TIN, and chronic inactive TIN had mononuclear leukocytic infiltrates consisting of predominantly lymphocytes with nearly half of them containing admixed eosinophils. Of these, 17% ($n = 4$) had features of active pyelonephritis (characterized by prominent interstitial neutrophils, neutrophilic tubulitis, and neutrophilic casts), 1 of which was associated with numerous interstitial eosinophils suggestive of superimposed hypersensitivity-type drug-induced reaction. All of the TMA cases were acute and involved blood vessels (93% arterioles, 73% arteries, and 67% both). Acute changes of TMA included a combination of endothelial cell swelling (87%), mucointimal edema (80%), fibrin thrombi (67%), and fragmented red blood cells (40%). One biopsy showed glomerular involvement in the form of subendothelial widening by electron lucent flocculent material and early double contour formation. TMA biopsies had chronic changes in 53%, characterized by severe luminal narrowing with onion skin-type intimal fibrosis. Among those with DG, 84% showed at least segmental glomerular mesangial matrix nodules whereas 16% had only diffuse DG.

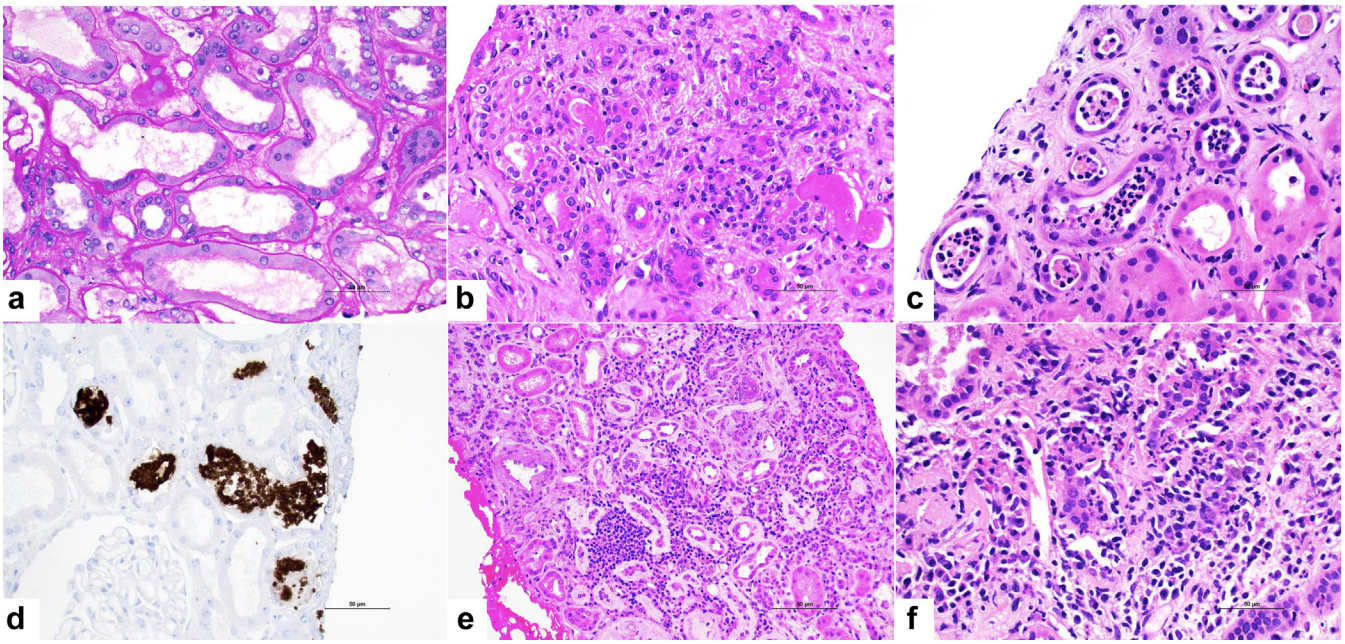

Figure 1. (a) Acute tubular necrosis. Proximal tubules show marked cytoplasmic simplification and loss of brush borders (Periodic acid-Schiff, ×400). (b) Acute tubulointerstitial nephritis (H&E, ×400). (c) Acute pyelonephritis with intraluminal neutrophil casts (H&E, ×400). (d) Acute tubular necrosis with myoglobin casts by immunohistochemistry (×400). (e) Chronic tubulointerstitial nephritis (H&E, ×200). (f) Acute and chronic pyelonephritis. Cortex shows interstitial inflammatory infiltrates consisting of lymphocytes, plasma cells, and intermixed neutrophils with prominent neutrophilic tubulitis (Jones, methenamine silver, ×400). H&E, hematoxylin and eosin stain.

Table 3. Renal biopsy findings in 112 patients with history of METH-use

METH-use alone ($n = 62$)[a]	METH with other drugs of abuse ($n = 50$)[a]
ATN (41)	ATN (36)
Myoglobin (8)	Myoglobin (9)
Focal segmental glomerulosclerosis (33)	Focal segmental glomerulosclerosis (21)
NOS (25)	NOS (17)
Collapsing (6)	Collapsing (2)
Tip (1)	Tip (1)
Perihilar (1)	Perihilar (1)
TIN (23)	TIN (18)
AIN (11)	AIN (3)
Chronic active TIN (2)	Chronic active TIN (5)
CIN (6)	CIN (7)
Pyelonephritis (4)	Pyelonephritis (3)
Granulomatous TIN (1)	Plasma-cell rich TIN (1)
TMA (15)	TMA (16)
Vascular TMA (14)	Vascular TMA (15)
Vascular & glomerular (1)	Vascular & glomerular (1)
Diabetic glomerulosclerosis (19)	Diabetic glomerulosclerosis (5)
IRGN (9)	IRGN (7)
C3-dominant (8)	C3-dominant (6)
IgA-dominant (1)	IgA-dominant (1)
IgA nephropathy (7)	IgA nephropathy (6)
Glomerulomegaly (5)	Glomerulomegaly (5)
Lupus or lupus-like nephritis (2)	Lupus nephritis (5)
Membranous nephropathy	Membranous nephropathy
PLA2R-positive (2)	PLA2R-negative (1)
Amyloidosis (1)	Amyloidosis (4)
AA (1)	AA (3)
	AL-lambda (1)
ANCA-associated pauci-immune GN (1)	ANCA-associated pauci-immune GN (2)
IC-mediated GN NOS (1)	IC-mediated GN NOS (2)
	Cryoglobulinemic GN (1)

AIN, acute tubulointerstitial nephritis; ANCA, antineutrophil cytoplasmic antibody; ATN, acute tubular necrosis; CIN, chronic tubulointerstitial nephritis; GN, glomerulonephritis; IRGN, infection-related GN; METH, methamphetamine; NOS, not otherwise specified; PLA2R, phospholipase A2 receptor; TIN, tubulointerstitial nephritis; TMA, thrombotic microangiopathy.
[a]Patients in these categories could have more than 1 coexistent renal disease.

Comparisons between those with METH-only versus METH plus other illicit drug use showed statistically significant increased association for myoglobinuric ATN in those with concurrent alcohol misuse ($P = 0.002$). Malignant HTN presented more often with concurrent cocaine use ($P = 0.01$). Although pathologic changes of TMA were seen in higher frequency with cocaine, it did not reach statistical significance ($P = 0.59$). Of note, none of the cases with cocaine use had cFSGS. All 8 patients with cFSGS were seen with METH-only (80%) or METH with marijuana (20%) and were accompanied by pathologic features of TMA in 2 cases. cFSGS occurred in the clinical setting of lupus nephritis in 1 patient, and infections in 5 patients (most had multiple infections; 3 had HIV). The *APOL1* risk allele status of the 8 patients with collapsing glomerulopathy is unknown; 50% of these patients were of African ancestry. Interestingly, the METH-only patients were more likely to have DG than patients with multiple substance-use ($P = 0.01$).

Biopsies from METH-only patients with IRGN showed endocapillary hypercellularity in 56% (83% associated with infiltrating neutrophils); 44% were additionally with mesangial hypercellularity; and 22% with active crescents, which involved less than 25% of glomeruli. The remaining 44% showed features of remote or inactive IRGN, including weak mesangial C3 deposits and rare to occasional subepithelial hump-shaped deposits undergoing various stages of resolution without associated glomerular inflammation. Only 1 case of IRGN was IgA-dominant and associated with methicillin-susceptible *Staphylococcus aureus* tricuspid valve endocarditis. Most of the cases (71%) with IgAN did not have significant proliferative features (e.g., no mesangial or endocapillary hypercellularity, or crescents). The remaining 29% ($n = 2$) had crescents involving 25% or less of sampled glomeruli, 1 of which also had endocapillary hypercellularity. None of the IgAN cases had known liver or gastrointestinal disease. Two patients had lupus or lupus-like nephritis, of which 1 was class III + V and 1 was class I. One case of immune complex (IC)-mediated GN NOS had mesangial hypercellularity without other proliferative changes.

Compared to the METH-only cohort, IRGN cases in the METH plus other illicit drug use group had more proliferative changes. Specifically, 71% had endocapillary (exudative) hypercellularity and 43% had active crescents, though the differences were not statistically significant ($P = 0.6$ for both). Of the 3 cases with active crescents, 2 had concurrent positive antineutrophil cytoplasmic antibodies (ANCAs) (1 had 27% crescents with perinuclear ANCA and 1 had 86% crescents with an unreported ANCA type). Neither patient was using cocaine or opioids (1 had concurrent alcohol-use whereas the other patient was using marijuana and nonsteroidal antiinflammatory drugs) and did not have endocarditis at the time of biopsy. The remaining case was an IgA-dominant IRGN with 10% crescents in the setting of hepatitis C virus and tricuspid valve endocarditis (organism was not reported). Similar to the METH-only group, the METH plus other drug use cohort did not show significant proliferative features in other IC-mediated GNs (e.g., IgAN, lupus nephritis, or IC-mediated GN NOS). Of IgAN cases in the METH plus other substance use, 33% had mesangial hypercellularity, 1 of which also had less than 25% active crescents. One additional IgAN case had crescents involving 28% of glomeruli. However, given the lack of significant endocapillary or mesangial hypercellularity, it was suspected that the active crescents may be secondary to an underlying ANCA related to cocaine use rather than IgAN.

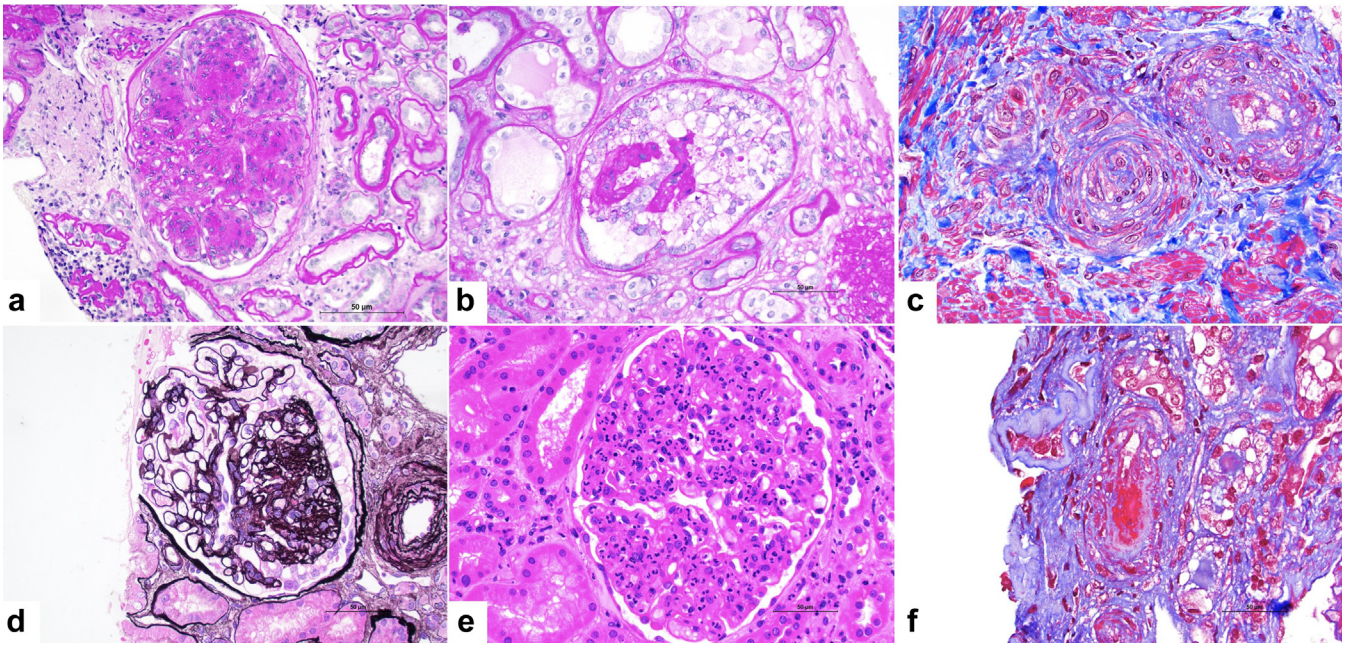

Figure 2. (a) Nodular diabetic glomerulosclerosis (PAS, ×400). (b) Collapsing glomerulopathy in the setting of thrombotic microangiopathy (PAS, ×400). (c) Vascular thrombotic microangiopathy with onion-skin type intimal fibrosis and endothelial cell swelling (Trichrome, ×400). (d) Focal segmental glomerulosclerosis in a patient with malignant hypertension and vascular thrombotic microangiopathy (Jones methenamine silver, ×400). (e) Infection-related glomerulonephritis with abundant endocapillary neutrophils (H&E, ×400). (f) Vascular thrombotic microangiopathy. An artery is occluded by a fibrin thrombus (Trichrome, ×400). H&E, hematoxylin and eosin stain; PAS, periodic acid-schiff.

Although most of those in the METH plus other illicit drug use cohort with IgAN did not have underlying liver or gastrointestinal disease, 1 case was associated with alcohol-related cirrhosis. There was more lupus nephritis ($n = 5$) in the METH plus other drugs group. However, the majority were not significantly active (3 were class V and 1 was class II). Only 1 case had active class IV, which was attributable to diffuse endocapillary hypercellularity without crescents. One of the class V lupus nephritis cases had 33% crescents with necrotizing arteritis, which was thought to be separate from the lupus nephritis and possibly related to ANCA (despite the reported negative serology) in the context of tricuspid valve endocarditis and heroin use.

Approximately 56% ($n = 35$) of METH-only cases had moderate to severe tubulointerstitial scarring. Chronic vascular changes included 55% ($n = 34$) with arteriosclerosis, of which 71% ($n = 24$) were moderate to severe; and 50% ($n = 31$) with arteriolosclerosis, 71% ($n = 22$) of which were moderate to severe. The median global glomerulosclerosis was 23% (IQR: 8%–47%). These chronic changes were slightly higher than those with METH plus other substance use but did not reach statistical significance.

DISCUSSION

Herein, we describe kidney biopsy findings associated with METH-use with and without additional substance use or misuse, which revealed a wide spectrum of pathologies. Almost all cases (97%) showed evidence of kidney dysfunction at the time of biopsy. The most common findings were tubulointerstitial-related, notably ATN, of which nearly one-fifth were accompanied by myoglobin casts. This correlates with case reports and studies documenting AKI and rhabdomyolysis in the setting of METH intoxication.[14–17] One study identified myoglobin associated ATN in up to 77% of autopsy cases positive for METH.[17] Mechanisms that lead to ATN are multifactorial, including volume depletion and increased sympathomimetic activity resulting in vasoconstriction, hemodynamic instability, and ischemic injury. Nontraumatic rhabdomyolysis due to METH occurs in the setting of hyperthermia, extreme physical exertion, volume depletion, and direct toxic effects to myocytes.[14,18] The pathomechanism of rhabdomyolysis-induced AKI is thought to be triggered by precipitation of myoglobin in Tamm-Horsfall protein in tubules, which causes luminal obstruction, lipid peroxidation, and epithelial cell damage.[19] Noteworthy was the increased incidence of myoglobin-related ATN in cases with concurrent alcohol misuse, which itself has been linked to rhabdomyolysis through multiple processes including acute intoxication-induced muscle compression and injury related to prolonged immobilization and long-term electrolyte imbalances from chronic misuse.[20–22] Given these considerations, it would be reasonable to assume

that ingestion of alcohol with illicit drugs such as METH may have a synergistic effect in the development of rhabdomyolysis-related ATN.

TIN was also frequent in this cohort. Rare studies of AIN associated with amphetamine and a chemically similar drug phentermine have suggested that a hypersensitivity reaction may develop in some individuals.[23,24] It is worth mentioning that approximately 68% of our METH-only cases with TIN had a concurrent infection. Other than the 4 cases of pyelonephritis and 1 granulomatous TIN in the setting of *Mycobacterium avium* complex infection, the remaining were AIN and/or chronic inactive TIN of unspecified etiology. Although it is possible that METH itself (or an adulterant) may have elicited a hypersensitivity response in some of these cases, the possibilities that the AIN or chronic inactive TIN were either secondary to the infection itself or to antibiotic or antiviral medications cannot be excluded. Moreover, given the stigma associated with drug-use, it is possible that a proportion of the METH-only cohort may have underreported using other illicit drugs[25,26] such as marijuana, heroin, or cocaine, all of which have been associated with TIN.[27]

Similar to the few published case reports and series,[11,13,28,29] malignant HTN and vascular TMA were a common finding. One study, from South Africa, of kidney histopathologic changes related to METH-use found hypertensive changes in 50% ($n = 12$) and pathologic features of malignant HTN in 25% ($n = 6$).[13] Although hypertensive change was not the main diagnostic finding in our cohort's biopsies, up to 55% of the METH-only cohort did have underlying arteriosclerosis and arteriolosclerosis with more than half demonstrating moderate to severe luminal narrowing. Moreover, 24% of these patients had vascular TMA typical of the changes seen in malignant HTN. It is not surprising that vascular pathology is prominent, given the shared mechanism with potent sympathomimetics such as cocaine. Catecholamine excess and release of endothelin-1 leading to potent vasoconstriction, hypoperfusion, ischemia, and endothelial injury have been postulated to be potential causes of METH-related vascular disease.[30-33] METHs have also been shown to induce expression of tissue factor on endothelial cell surface, which increases the activation of coagulation pathways resulting in clot formation.[34] These mechanisms may explain cases of METH-associated renal cortical necrosis and ischemic infarctions involving other organs such as the heart, intestine, and brain.[12,35-39]

Proteinuria was identified in 65% of METH-only patients, likely attributable to glomerular pathology which was most frequently FSGS and DG. The majority (85%, $n = 29$) of FSGS lesions were secondary FSGS, of which NOS-type was the most common (86%, $n = 25$) followed by those with collapsing features (14%, $n = 4$). The high incidence of secondary FSGS is not surprising given that a majority of biopsies had >1 diagnosis; more than two-thirds were associated with at least moderate to severe chronic tubulointerstitial changes. The most common findings associated with secondary FSGS were TMA (43%) followed by TIN (33%) and DG (31%). Of the FSGS cases with collapsing features, 3 were attributed to HIV and 1 to TMA. The remaining 4 patients with FSGS were idiopathic or primary (defined by nephrotic syndrome with extensive podocyte foot process effacement), and comprised of tip ($n = 1$), collapsing ($n = 2$), and NOS-type ($n = 1$), with the caveat that genetic assessment and a full viral panel including parvovirus were not done.

DG was common in this cohort and could be a consequence of inadequate diabetes self-management. This observation appears supported by studies that have found a high incidence of hyperglycemia and diabetic ketoacidosis in diabetics who use METH.[40,41] Interestingly, DG was more prominent in the METH-only group compared to those with METH plus other drugs of abuse, despite similarities in the frequency of diabetes in both groups. It is unclear why this is the case given that all illicit drugs are linked with adverse self-management behaviors that result in increased hospital admissions for diabetic ketoacidosis and other morbidities such as cerebrovascular accident and myocardial infarction.[42] One possible explanation may be related to METH-induced abnormalities in glucose metabolism and insulin resistance secondary to increased sympathetic nervous system activity.[41] Other possibilities include METH-users high consumption of sugar-rich beverages, which has been reported in multiple studies in association with dental caries typical of long-term METH abuse and over time could increase the risk of diabetes.[43,44] More studies are needed to understand potential associations between diabetes and substance misuse.

GN was identified in one-third of METH-only cases. Jones and Rayner[13] found in their cohort mesangiocapillary GN (also known as membranoproliferative GN) in 58% ($n = 14$) of patients. All had IgM and C3 deposits with some also demonstrating variable staining for IgG ($n = 9$) and IgA ($n = 7$). Except for 1 case of HIV, the remaining cases of mesangiocapillary GN did not have an identifiable infectious agent, though the authors proposed chronic antigenemia related to prolonged exposure to infectious agents as a possible explanation. An underlying clinical history of infection was found in 64% ($n = 14$) of our GN cases, thus supporting this hypothesis. The most common GN was

IRGN (15%) followed by IgAN (11%), lupus or lupus-like nephritis (3%), IC-mediated GN NOS (2%), and antiphospholipase A2 receptor–associated membranous nephropathy (2%). Approximately 43% (3/7) of IgAN had concomitant infections: 1 associated with endocarditis, 1 with a urinary tract infection, and 1 with syphilis. One case with lupus nephritis was also associated with COVID-19 infection and another case of IC-mediated GN NOS was positive for hepatitis B virus surface antigen. None of the antiphospholipase A2 receptor–associated membranous nephropathy lupus-like nephritis cases were associated with an identifiable infection. Of interest, given the significant presence of diabetes and DG in our cohort with history of METH abuse, a higher frequency of IgA-dominant IRGN was expected. However, we identified only 1 case that had IgA-dominant IRGN. A possible explanation for the low incidence of IgA-dominant IRGN could be the limited sample size and relatively younger age in our cohort of METH users compared to the older population (average 60 years) described in patients with IgA-dominant IRGN.[45]

Drugs of abuse, including METH, are often accompanied by infections due to increased exposure to microbial pathogens and drug-mediated immunomodulatory effects.[46] Moreover, infections have been linked to autoimmunity, possibly explaining the multiple reports of IC-mediated or autoimmune related GNs that develop in the setting of infection.[47-55] Of note, 1 case in our METH-only cohort had an ANCA-associated crescentic GN in the setting of multiple infections (syphilis and HIV). Rare reports of vasculitis in the setting of METH use have been described, 1 of which was positive for antimyeloperoxidase antibodies.[56-58] However, in those cases, blood vessels were involved without crescents and were not associated with any known infection. The single case of endocarditis in our cohort was not accompanied with crescentic GN.

Our study has several limitations, including the retrospective nature of the study; and limited clinical data available, such as the duration of METH-use, the absence of toxicology results for a large proportion of cases, and lack of *APOL1* genotyping in those with cFSGS. Moreover, it is possible that some of the patients in the METH-only cohort may have underreported additional illicit drug-use.

In summary, although clinical presentations of METH use are commonly AKI and/or proteinuria, there is a wide spectrum of METH-associated kidney pathology. The most common pathologic finding is ATN (especially associated with myoglobin casts), as well as TMA, TIN, FSGS, and DG. GN is also prominent in this cohort and commonly associated with underlying infection. A substantial proportion of our cohort demonstrated marked chronic changes in the form of at least moderate to severe tubulointerstitial scarring and marked hypertensive vascular disease. Noteworthy are the increased frequency of myoglobin-related ATN in cases with concurrent alcohol misuse and the significant presence of DG in the METH-only group, both which have not been reported previously in any biopsy-based study or case report.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This research was performed under approval of the Cedars Sinai Institutional Review Board (STUDY 00002729) and all ethical principles and guidelines for the protection of human subjects were followed. This study has been granted an exemption from requiring written informed consent by the Institutional Review Board at Cedars Sinai.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

HYC and JH contributed the research idea and study design. HYC, CN, MH, ML, MY, and JH did data acquisition. HYC and JH did data analysis/interpretation. HYC performed the statistical analysis. JH and CN provided supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature, if appropriate.

REFERENCES

1. Chomchai C, Chomchai S. Global patterns of methamphetamine use. *Curr Opin Psychiatry*. 2015;28:269–274. https://doi.org/10.1097/YCO.0000000000000168
2. Han B, Compton WM, Jones CM, Einstein EB, Volkow ND. Methamphetamine use, methamphetamine use disorder, and associated overdose deaths among US adults. *JAMA Psychiatr*. 2021;78:1329–1342. https://doi.org/10.1001/jamapsychiatry.2021.2588
3. Goel N, Pullman JM, Coco M. Cocaine and kidney injury: a kaleidoscope of pathology. *Clin Kidney J*. 2014;7:513–517. https://doi.org/10.1093/ckj/sfu092

4. Filho J, Ogawa MY, de Souza Andrade TH, et al. Spectrum of acute kidney injury associated with cocaine use: report of three cases. *BMC Nephrol*. 2019;20:99. https://doi.org/10.1186/s12882-019-1279-0
5. Sethi S. The changing spectrum of heroin-associated kidney disease. *Clin J Am Soc Nephrol*. 2018;13:975–976. https://doi.org/10.2215/CJN.06080518
6. Cunningham EE, Zielezny MA, Venuto RC. Heroin-associated nephropathy. A nationwide problem. *JAMA*. 1983;250:2935–2936. https://doi.org/10.1001/jama.1983.03340210033020
7. Dettmeyer R, Wessling B, Madea B. Heroin associated nephropathy-a post-mortem study. *Forensic Sci Int*. 1998;95:109–116. https://doi.org/10.1016/s0379-0738(98)00082-6
8. Friedman EA, Rao TK, Nicastri AD. Heroin-associated nephropathy. *Nephron*. 1974;13:421–426. https://doi.org/10.1159/000180420
9. Lan X, Rao TK, Chander PN, Skorecki K, Singhal PC. Apolipoprotein L1 (APOL1) Variants (Vs) a possible link between Heroin-associated Nephropathy (HAN) and HIV-associated Nephropathy (HIVAN). *Front Microbiol*. 2015;6:571. https://doi.org/10.3389/fmicb.2015.00571
10. Llach F, Descoeudres C, Massry SG. Heroin associated nephropathy: clinical and histological studies in 19 patients. *Clin Nephrol*. 1979;11:7–12.
11. Baradhi KM, Pathireddy S, Bose S, Aeddula NR. Methamphetamine (N-methylamphetamine)-induced renal disease: underevaluated cause of end-stage renal disease (ESRD). *BMJ Case Rep*. 2019;12:e230288. https://doi.org/10.1136/bcr-2019-230288
12. Gupta A, Kuperman M, Shah S, N-methylamphetamine. ("Crystal Meth")-associated acute renal cortical necrosis. *Kidney Int Rep*. 2018;3:1473–1476. https://doi.org/10.1016/j.ekir.2018.07.003
13. Jones E, Rayner B. Renal biopsy findings in methamphetamine users. *J Hypertens*. 2015;33:E489-E489. https://doi.org/10.1097/01.hjh.0000468928.42863.25
14. Chansaengpetch N, Worasuwannarak W, Worawichawong S. Methamphetamine-induced profound rhabdomyolysis and myoglobin cast nephropathy: a case report and a literature review. *J Forensic Leg Med*. 2023;96:102530. https://doi.org/10.1016/j.jflm.2023.102530
15. Isoardi KZ, Mudge DW, Harris K, Dimeski G, Buckley NA. Methamphetamine intoxication and acute kidney injury: a prospective observational case series. *Nephrol (Carlton)*. 2020;25:758–764. https://doi.org/10.1111/nep.13762
16. Nicol JJ, Yarema MC, Jones GR, et al. Deaths from exposure to paramethoxymethamphetamine in Alberta and British Columbia, Canada: a case series. *CMAJ Open*. 2015;3:E83–E90. https://doi.org/10.9778/cmajo.20140070
17. Ishigami A, Tokunaga I, Gotohda T, Kubo S-i. Immunohistochemical study of myoglobin and oxidative injury-related markers in the kidney of methamphetamine abusers. *Leg Med (Tokyo)*. 2003;5:42–48. https://doi.org/10.1016/s1344-6223(03)00005-1
18. Campbell GA, Rosner MH. The agony of ecstasy: MDMA (3,4-methylenedioxymethamphetamine) and the kidney. *Clin J Am Soc Nephrol*. 2008;3:1852–1860. https://doi.org/10.2215/CJN.02080508
19. Godrati S, Pezeshgi A, Valizadeh R, Kellner SJ, Radfar SR. Acute and delayed nephropathy due to methamphetamine abuse. *J Nephropathol*. 2020;9:e22-e22. https://doi.org/10.34172/jnp.2020.22
20. Hewitt SM, Winter RJ. Rhabdomyolysis following acute alcohol intoxication. *J Accid Emerg Med*. 1995;12:143–144. https://doi.org/10.1136/emj.12.2.143
21. Qiu LL, Nalin P, Huffman Q, Sneed JB, Renshaw S, Hartman SW. Nontraumatic rhabdomyolysis with long-term alcohol intoxication. *J Am Board Fam Pract*. 2004;17:54–58. https://doi.org/10.3122/jabfm.17.1.54
22. Richards JR, Johnson EB, Stark RW, Derlet RW. Methamphetamine abuse and rhabdomyolysis in the ED: a 5-year study. *Am J Emerg Med*. 1999;17:681–685. https://doi.org/10.1016/s0735-6757(99)90159-6
23. Foley RJ, Kapatkin K, Verani R, Weinman EJ. Amphetamine-induced acute renal failure. *South Med J*. 1984;77:258–260. https://doi.org/10.1097/00007611-198402000-00035
24. Shao EX, Wilson GJ, Ranganathan D. Phentermine induced acute interstitial nephritis. *BMJ Case Rep*. 2017;2017. https://doi.org/10.1136/bcr-2017-219452
25. Muncan B, Walters SM, Ezell J, Ompad DC. "They look at us like junkies": influences of drug use stigma on the healthcare engagement of people who inject drugs in New York City. *Harm Reduct J*. 2020;17:53. https://doi.org/10.1186/s12954-020-00399-8
26. Luoma JB, Twohig MP, Waltz T, et al. An investigation of stigma in individuals receiving treatment for substance abuse. *Addict Behav*. 2007;32:1331–1346. https://doi.org/10.1016/j.addbeh.2006.09.008
27. Mansoor K, Kheetan M, Shahnawaz S, et al. Systematic review of nephrotoxicity of drugs of abuse, 2005-2016. *BMC Nephrol*. 2017;18:379. https://doi.org/10.1186/s12882-017-0794-0
28. Ruderman I, Finlay M, Barbour T. The perfect storm. *Kidney Int*. 2017;92:267. https://doi.org/10.1016/j.kint.2017.03.049
29. Jones ES, Rayner BL. Hypertension, end-stage renal disease and mesangiocapillary glomerulonephritis in methamphetamine users. *S Afr Med J*. 2015;105:199–201. https://doi.org/10.7196/samj.8731
30. Fleckenstein AE, Volz TJ, Riddle EL, Gibb JW, Hanson GR. New insights into the mechanism of action of amphetamines. *Annu Rev Pharmacol Toxicol*. 2007;47:681–698. https://doi.org/10.1146/annurev.pharmtox.47.120505.105140
31. Broadley KJ. The vascular effects of trace amines and amphetamines. *Pharmacol Ther*. 2010;125:363–375. https://doi.org/10.1016/j.pharmthera.2009.11.005
32. Jaffe JA, Kimmel PL. Chronic nephropathies of cocaine and heroin abuse: a critical review. *Clin J Am Soc Nephrol*. 2006;1:655–667. https://doi.org/10.2215/CJN.00300106
33. Seo JW, Jones SM, Hostetter TA, Iliff JJ, West GA. Methamphetamine induces the release of endothelin. *J Neurosci Res*. 2016;94:170–178. https://doi.org/10.1002/jnr.23697
34. Gebhard C, Breitenstein A, Akhmedov A, et al. Amphetamines induce tissue factor and impair tissue factor pathway inhibitor: role of dopamine receptor type 4. *Eur Heart J*. 2010;31:1780–1791. https://doi.org/10.1093/eurheartj/ehp598
35. Khokhar S, Garcia D, Thirumaran R. A rare case of renal infarction due to heroin and amphetamine abuse: case

report. *BMC Nephrol*. 2022;23:28. https://doi.org/10.1186/s12882-021-02642-1

36. Attaran H. Fatal small intestinal ischemia due to methamphetamine intoxication: report of a case with autopsy results. *Acta Med Iran*. 2017;55:344–347.
37. Johnson TD, Berenson MM. Methamphetamine-induced ischemic colitis. *J Clin Gastroenterol*. 1991;13:687–689. https://doi.org/10.1097/00004836-199112000-00015
38. Schürer S, Klingel K, Sandri M, et al. Clinical characteristics, histopathological features, and clinical outcome of methamphetamine-associated cardiomyopathy. *JACC Heart Fail*. 2017;5:435–445. https://doi.org/10.1016/j.jchf.2017.02.017
39. Ho EL, Josephson SA, Lee HS, Smith WS. Cerebrovascular complications of methamphetamine abuse. *Neurocrit Care*. 2009;10:295–305. https://doi.org/10.1007/s12028-008-9177-5
40. Gilbert JD, Byard RW. Fatal diabetic ketoacidosis-a potential complication of MDMA (ecstasy) use. *J Forensic Sci*. 2018;63:939–941. https://doi.org/10.1111/1556-4029.13602
41. Lewis D, van den Heuvel C, Kenneally M, Byard RW. Methamphetamine use and the risk of diabetic ketoacidosis. *Med Sci Law*. 2022;62:39–42. https://doi.org/10.1177/00258024211020936
42. Pastor A, Conn J, MacIsaac RJ, Bonomo Y. Alcohol and illicit drug use in people with diabetes. *Lancet Diabetes Endocrinol*. 2020;8:239–248. https://doi.org/10.1016/S2213-8587(19)30410-3
43. Murphy DA, Harrell L, Fintzy R, Vitero S, Gutierrez A, Shetty V. Soda consumption among methamphetamine users in the USA: impact on Oral Health. *Oral Hlth Prev Dent*. 2016;14:227–234. https://doi.org/10.3290/j.ohpd.a35620
44. Morio KA, Marshall TA, Qian F, Morgan TA. Comparing diet, oral hygiene and caries status of adult methamphetamine users and nonusers - a pilot study. *J Am Dent Assoc*. 2008;139:171–176. https://doi.org/10.14219/jada.archive.2008.0133
45. Nasr SH, D'Agati VD. IgA-dominant postinfectious glomerulonephritis: a new twist on an old disease. *Nephron Clin Pract*. 2011;119:c18–c25; discussion c26. https://doi.org/10.1159/000324180
46. Friedman H, Pross S, Klein TW. Addictive drugs and their relationship with infectious diseases. *FEMS Immunol Med Microbiol*. 2006;47:330–342. https://doi.org/10.1111/j.1574-695X.2006.00097.x
47. Milroy CM, Parai JL. The histopathology of drugs of abuse. *Histopathology*. 2011;59:579–593. https://doi.org/10.1111/j.1365-2559.2010.03728.x
48. Gordon RJ, Lowy FD. Bacterial infections in drug users. *N Engl J Med*. 2005;353:1945–1954. https://doi.org/10.1056/NEJMra042823
49. Couser WG, Johnson RJ. Theetiology of glomerulonephritis: roles of infection and autoimmunity. *Kidney Int*. 2014;86:905–914. https://doi.org/10.1038/ki.2014.49
50. Sethi S, D'Costa MR, Hermann SM, Nasr SH, Fervenza FC. Immune-complex glomerulonephritis after COVID-19 infection. *Kidney Int Rep*. 2021;6:1170–1173. https://doi.org/10.1016/j.ekir.2021.02.002
51. Alawieh R, Satoskar A, Obole E, Hebert L, Ayoub I. Infection-related glomerulonephritis mimicking lupus nephritis. *Clin Nephrol*. 2020;94:212–214. https://doi.org/10.5414/CN110202
52. Prema KSJ, Kurien A. Incidence of anti-glomerular basement membrane disease during the COVID-19 pandemic. *Clin Kidney J*. 2022;15:180–181. https://doi.org/10.1093/ckj/sfab204
53. Haas M, Kaul S, Eustace JA. HIV-associated immune complex glomerulonephritis with "lupus-like" features: a clinicopathologic study of 14 cases. *Kidney Int*. 2005;67:1381–1390. https://doi.org/10.1111/j.1523-1755.2005.00215.x
54. Rollino C, Vischini G, Coppo R. IgA nephropathy and infections. *J Nephrol*. 2016;29:463–468. https://doi.org/10.1007/s40620-016-0265-x
55. Rodriguez-Iturbe B. Autoimmunity in acute poststreptococcal GN: a neglected aspect of the disease. *J Am Soc Nephrol*. 2021;32:534–542. https://doi.org/10.1681/ASN.2020081228
56. Bingham C, Beaman M, Nicholls AJ, Anthony PP. Necrotizing renal vasculopathy resulting in chronic renal failure after ingestion of methamphetamine and 3,4-methylenedioxymethamphetamine ('ecstasy'). *Nephrol Dial Transplant*. 1998;13:2654–2655. https://doi.org/10.1093/ndt/13.10.2654
57. Sánchez JAR, Arreguin YL. MPO ANCA-associated vasculitis in a patient with a history of methamphetamine abuse. *Nephrol Dial Transplant*. 2023;38. https://doi.org/10.1093/ndt/gfad063c_6949
58. Chamarthi G, Lee Loy J, Koratala A. Methamphetamine-induced renal pseudovasculitis: suspicion is the key. *Clin Case Rep*. 2019;7:381–382. https://doi.org/10.1002/ccr3.1976