

Renal Arcuate Vein Microthrombi-Associated AKI

Andrew Redfern,* Huda Mahmoud,* Tom McCulloch,[†] Adam Shardlow,* Matthew Hall,[‡] Catherine Byrne,[‡] and Nicholas M. Selby*[§]

Abstract

Backgrounds and objectives This report describes six patients with AKI stages 2–3 (median admission creatinine level, 2.75 mg/dl [range, 1.58–5.44 mg/dl]), hematuria (five with hemoproteinuria), and unremarkable imaging with an unusual and unexplained histologic diagnosis on renal biopsy.

Design, setting, participants, & measurements The patients were young adults who presented to two neighboring United Kingdom nephrology centers over a 40-month period (between July 2010 and November 2013). Four were male, and the median age was 22.5 years (range, 18–27 years). Their principal symptoms were flank pain or lower back pain. All had consumed alcohol in the days leading up to admission.

Results Renal biopsy demonstrated microthrombi in the renal arcuate veins with a corresponding stereotypical, localized inflammatory infiltrate at the corticomedullary junction. All patients recovered to baseline renal function with supportive care (median, 17 days; range, 6–60 days), and none required RRT. To date, additional investigations have not revealed an underlying cause for these histopathologic changes. Investigations have included screening for thrombophilic tendencies, renal vein Doppler ultrasonographic studies, and testing for recreational drugs and alcohol (including liquid chromatography–mass spectrometry of urine) to look for so-called designer drugs. Inquiries to the United Kingdom National Poisons Information Centre have identified no other cases with similar presentation or histologic findings.

Conclusions Increased awareness and additional study of future cases may lead to a greater understanding of the underlying pathophysiologic mechanisms that caused AKI in these patients.

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Introduction

Over a 40-month period, a series of patients have presented to two neighboring United Kingdom nephrology units with a previously unrecognized clinical-pathologic entity causing AKI. The histologic findings on renal biopsy are distinctive and not widely reported as a cause of AKI or otherwise, while certain prominent clinical features may help to distinguish this entity from other causes of AKI. These observations have implications for clinical practice and may also have a public health message. We report the clinical features of these cases, present the histologic findings, and discuss their potential relevance.

Case Histories

Case 1 (August 2011)

An 18-year-old woman presented to the emergency department after 3 days of vomiting associated with central abdominal and bilateral flank pain. She also reported a reduction in urine volume. The patient was normally fit and well and did not take regular medication. Symptoms started 2 days after a social event during which she consumed at least a moderate amount of alcohol. She had taken two naproxen tablets in response to her symptoms but no other medication; she reported no use of illicit drugs. At presentation her vital

signs were normal except for a tympanic temperature of 37.7°C. Examination demonstrated tenderness in the central abdomen and left flank.

Initial bloods tests revealed a serum creatinine level of 2.6 mg/dl. Urinalysis demonstrated protein (1+) and blood (4+). Results of a pregnancy test and midstream culture were both negative. Findings on chest radiography, abdominal radiography, and renal ultrasonography were also unremarkable. Subsequently a complete immunology screen was performed; results of tests for antinuclear antibodies (ANA), ANCA, anti-glomerular basement membrane antibodies, and anti-double-stranded DNA antibodies were negative, while C3 and C4 levels were normal. Renal function continued to deteriorate despite supportive care, so a renal biopsy was performed on day 4 of her admission.

Case 2 (July 2013)

A 23-year-old man presented to the emergency department with coryzal symptoms, a dull pain in his lower back, and severe left flank pain that developed over a 4-day period immediately after his return from holiday in Ibiza. During his holiday he had consumed more than his usual 25 units of alcohol per week, but he reported no recreational drug use. He had attended

*Department of Renal Medicine, Royal Derby Hospital, Derby, United Kingdom;

[†]Department of Histopathology, Nottingham

University Hospitals, Nottingham, United Kingdom;

[‡]Department of Renal Medicine, Nottingham City Hospital, Nottingham University Hospitals, Nottingham, United Kingdom; and

[§]Division of Medical Science and Graduate Entry Medicine, School of Medicine, University of Nottingham, Nottingham, United Kingdom

Correspondence: Dr.

Nicholas Selby, Department of Renal Medicine, Royal Derby Hospital, Uttoxeter Road, Derby, DE22 3NE, UK. Email: nicholas.selby@nottingham.ac.uk

an emergency primary care center 48 hours before admission and had been prescribed trimethoprim, although the patient had taken only two tablets. He took no additional prescribed or proprietary medications and had no significant past medical history. His vital signs were within normal limits and the only positive finding on examination was left flank tenderness.

Initial serum creatinine level was 3.17 mg/dl, and urinalysis was positive for blood only (1+). Abdominal computed tomography demonstrated normal unenhanced appearances of both kidneys and no renal tract calculi. He was catheterized in the emergency department and intravenous fluids were commenced. Subsequent immunologic screen and urine culture were normal. The patient's renal function failed to improve with supportive measures. A renal biopsy was performed on day 3.

Case 3 (August 2013)

A 24-year-old woman presented to the hospital after 3 days of nausea and vomiting associated with bilateral flank pain and lower back pain. The patient had mild asthma and hay fever but was normally fit and well; she was taking oral contraceptives. She had been prescribed trimethoprim by a primary care physician 1 day before admission but had taken only one dose. The patient reported that 2 days before symptom onset she had consumed four or five alcoholic cocktails during the course of one evening; this patient also reported no recreational drug use. Positive findings on examination were a tympanic temperature of 37.5°C and marked bilateral renal angle tenderness.

Initial blood results showed severe impairment of renal function, with a serum creatinine level of 5.44 mg/dl. Urinalysis was positive for leukocytes (1+), protein (1+), and blood (1+). Initial concern about a vascular etiology for her symptoms prompted abdominal computed tomography with contrast, which demonstrated normal structure and perfusion of both kidneys. Because the differential diagnosis also included rapidly progressive GN, pulsed methylprednisolone was started empirically. By the following day, the patient's serum creatinine level had fallen rapidly to 2.83 mg/dl, and methylprednisolone was discontinued after the first dose. A subsequent immunologic screen (including ANCA) was normal except for a raised ANA titer (1:320). However, the patient's serum creatinine level did not fully return to normal, remaining at 1.52 mg/dl on day 4. Thus, a renal biopsy was performed.

Case 4 (November 2013)

A 27-year-old man presented to hospital after 2 days of feeling generally unwell with bilateral flank pain, nausea, and vomiting. In the 2 weeks before symptom onset he had attended several social events, including the celebration of his engagement, and had consumed alcohol in a variety of different forms. His medical background included musculoskeletal back pain, mild asthma, and a previous episode of cellulitis. He did not take any regular medication other than occasional nonsteroidal anti-inflammatory drugs (NSAIDs); in fact, before admission he had taken two proprietary analgesic tablets that he had purchased during a previous trip to Turkey (Minoset Plus, containing paracetamol, caffeine, and propyphenazone). Observations were within normal limits and the examination was unremarkable except for bilateral flank tenderness.

On admission, serum creatinine was 2.26 mg/dl. Urine dip revealed blood (3+) and protein (1+). An immunology screen revealed no abnormalities, and findings on renal ultrasonography were normal. Urine and plasma were sent for complete toxicology assessment, including liquid chromatography–mass spectrometry, which did not detect standard drugs of abuse or any designer drugs/legal highs. In addition, alcohol gas chromatography of urine did not detect any atypical alcohols. The patient's creatinine level rose to 3.97 mg/dl, and an ultrasound-guided renal biopsy was performed on day 2 of admission.

Case 5 (February 2012)

A 22-year-old man presented to the emergency department after a deliberate, mixed overdose while intoxicated with alcohol. The patient estimated that he had taken twenty 500-mg paracetamol tablets, an unknown quantity of zopiclone, and "large amounts of alcohol," including >300 ml of vodka. The patient presented at the emergency department immediately after the overdose. Initial blood tests demonstrated a serum creatinine level of 0.71 mg/dl, with paracetamol and salicylate levels within the normal range, after which he was discharged home.

He returned to the emergency department with intermittent right-sided flank pain 3 days later. His serum creatinine level was 1.58 mg/dl. Urinalysis showed blood (3+) and protein (1+). Computed tomography of the abdomen, performed because of the flank pain, showed no urinary tract stones and normal unenhanced appearances of the kidneys. He was referred to nephrology and after a progressive rise in his serum creatinine he underwent renal biopsy on day 5.

Case 6 (July 2010)

A 21-year-old man was admitted with vomiting and bilateral loin pain. He had no previous past medical problems. He had taken eight ibuprofen tablets over the course of several days before admission because of toothache. He drank approximately 25 units of alcohol per week, but a more detailed history of alcohol consumption prior to symptom onset was not taken. He regularly attended the gym and took glucosamine, amino acid, creatine, and pure protein supplements daily. He admitted prior use of mephedrone and cocaine but had not taken these substances within the 3 months before admission.

His serum creatinine level at presentation was 7.82 mg/dl. Urine dip was positive for blood (3+) and protein (1+). A toxicology screen was not performed. He was initially treated with intravenous fluids and intravenous methylprednisolone and underwent a renal biopsy on day 2 of admission. Subsequently, immunology and virology screens were unremarkable.

Clinical and biochemical features of the six cases are summarized in Table 1.

Histopathologic Findings

All renal biopsies were reported by the same specialist renal histopathologist (T.A.M.). Histopathology allowed initial recognition of cases. Additional cases were then retrospectively collated from a database of renal biopsy specimens from both centers maintained at the Department of Histopathology, Nottingham University Hospitals.

Table 1. Summary of demographic data, clinical and renal biochemical parameters.

Case	Age (yr)	Sex	Location	Occupation	Clinical Presentation	Alcohol (Time Consumed before Presentation)	Baseline Creatinine (mg/dl)	BUN on Admission (mg/dl)	Admission Creatinine (mg/dl)
1	18	Female	Derby	Administrative work	2 d bilateral flank pain	"Moderate amount of alcohol" (2 d)	—	22.97	2.6
2	23	Male	Ibiza	Builder	4 d severe left flank pain and dull back pain	>25 units of alcohol (4 d)	—	23.81	2.9
3	24	Female	Matlock	Doctor	3 d of bilateral lower back pain	4–5 cocktails (about 5–10 units) (2 d)	—	38.1	5.44
4	27	Male	Derby	Engineer	2 d of bilateral flank pain	8–12 units of beer (over 2 wk)	1.09	22.41	2.62
5	22	Male	Nottingham	Student	3 d of right-sided flank pain	About 24 units of vodka (3 d)	0.71	29.13	1.58
6	21	Male	Nottingham	Unknown	1 d of bilateral loin pain	About 25 units of alcohol (unknown)	—	44.54	5.21

Modification of Diet and Renal Disease formula was used to estimate the GFR. The creatinine conversion equation is $\text{mg/dl} \times 88.4 = \mu\text{mol/L}$. The urea conversion equation used is $\text{mg/dl} \times 0.357 = \mu\text{mol/L}$. RBC, red blood cells; PCR, protein-to-creatinine ratio; CRP, C-reactive protein; CK, creatine kinase; NSAIDs, nonsteroidal anti-inflammatory drugs.

^aExpressed as urine dipstick result, followed in parentheses by the automated urine microscopy result. The urine microscopy did not show casts or crystals in any of the cases.

All the biopsy specimens had material taken for light microscopy, immunofluorescence, and electron microscopy. The light sample contained cortex and medulla in all cases except case 6, which contained cortex only. The light samples contained between 9 and 25 glomeruli (mean, 16). The immunofluorescence samples contained glomeruli in all cases (range, 5–16; mean, 10) except case 2. The electron microscopy samples contained glomeruli in all cases (mean, 7; range, 2–15) but case 1.

In each case the findings on biopsy were similar and were largely based on the findings on light microscopy: There was interstitial inflammation concentrated at the corticomedullary junction (CMJ) and associated with well defined microthrombi in the renal arcuate veins in five of the six biopsy specimens (Figures 1 and 2). The biopsy specimen for case 2 was the only one in which microthrombi were not seen, but CMJ inflammation with extravasated thrombus material was present. The thrombus material appeared to consist mainly of fibrin and inflammatory cells with scanty platelets and red cells (Figure 3). In some cases, nonthrombosed arcuate or interlobular venous radicals were dilated with margination and adhesion of inflammatory cells to the endothelium. This was associated with focal inflammation

of the venous wall, accumulation of thrombus material, and disruption of the endothelial lining with subsequent extravasation of the thrombus material. This was associated with the presence of a rather stereotypical and unusual inflammatory reaction at the CMJ characterized by edema, inflammation, and a reactive fibroblastic proliferation. Mononuclear cells, neutrophil polymorphs, and, in particular, eosinophils were present (Figure 4).

The interlobular cortical venous radicals showed dilation secondary to the thrombosed arcuate venous system and also showed very minor focal thrombi and leukocyte endothelial adhesion. Peritubular capillaries contained leukocytes in two cases. There was accompanying interstitial cortical edema but very little inflammation. Features of acute tubular injury, specifically loss of the brush border and epithelial cell flattening, were seen in some proximal tubular profiles in three cases, but there was no evidence of myoglobin deposition in any of the four cases tested. More severe evidence of acute tubular injury, such as cytoplasmic or cell sloughing, was not apparent; neither was there evidence of tubulointerstitial nephritis.

The medulla showed occasional foci of mixed inflammatory cells, similar to those seen at the CMJ. The vasa

Table 1. (Continued)

Peak Creatinine (mg/dl)	Final Creatinine (mg/dl)	Final eGFR ml/min/1.73 m ²	Urine Dipstick (Urine Microscopy) ^a	Urine PCR (mg/mmol)	Time to Renal Recovery (d)	CRP (mg/L)	CK (U/L)	Bicarbonate (mEq/L)	Medications before Admission
4.33	0.85	>90	Hemoproteinuria (leukocytes 1, RBC 0, epithelial cells 2)	103	12	47	–	16	Naproxen
3.17	1.09	>90	Hematuria (leukocytes 4, RBC 3, epithelial cells 0)	19	17	47	–	26	Trimethoprim
5.44	0.77	>90	Hemoproteinuria (leukocytes 1, RBC 0, epithelial cells 0)	56	6	68	57	19	Trimethoprim, oral contraceptive pill
3.97	1.1	>90	Hemoproteinuria (leukocytes 18, RBC 15, epithelial cells 16)	–	31	12	207	16	Minoset plus NSAIDs
2.71	1.01	>90	Hemoproteinuria (leukocytes 18, RBC 3, epithelial cells 9)	123	18	43	–	31	Paracetamol, zopiclone
7.82	1.03	>90	Hemoproteinuria (leukocytes 58, RBC 13, epithelial cells 28)	44	61	62	130	29	Ibuprofen, glucosamine, protein/creatinine supplements

recta in the outer medulla also contained mononuclear cells, but thrombi were not seen in the vasa recta.

In case 4, all features except intravascular thrombus were visible on light microscopy; however, a well defined thrombus in an arcuate vein (containing IgM, IgG, and complement) was seen in the sample submitted for immunofluorescence. Aside from this case the findings at immunofluorescence and electron microscopy did not add further significant information.

In summary, the features in all cases suggested *in situ* formation of thrombus, mainly consisting of fibrin and inflammatory cells, in the arcuate venous system, with a thrombophlebitic component leading to extravasation of thrombus material at the CMJ and thence a brisk and histologically characteristic localized inflammatory response. Secondary features of cortical edema and mild acute tubular injury were present as a consequence of this process but no alternative causes of AKI were identified.

Subsequent Progress

All patients were treated supportively and all achieved complete recovery of renal function, with a median time to recovery of 17 days (range, 6–60 days). None of the patients have had any further episodes. The final creatinine results ranged from 0.77 to 1.1 mg/dl, corresponding to an eGFR >90 ml/min per 1.73 m² in all patients (Table 1). On follow-up, all patients had documented resolution of hemoproteinuria and normal BP. In cases 1 and 6, further

investigations were performed after the results of the renal biopsy were known: Renal vein Doppler ultrasonography revealed normal renal vessels, and thrombophilic tendencies were excluded (Table 2). Case 4 was the only patient to have detailed toxicology screening, which was negative. Further examination of the cases has not revealed any connections between the patients and in each case the alcohol was consumed in different locations with no obvious geographic relationship. Inquiries made to the National Poisons Information Centre did not identify any reports of other cases with similar presentation or histologic findings.

Discussion

We describe a series of patients who were identified after developing AKI associated with an unexplained pathologic finding of renal arcuate venous microthrombi with associated localized inflammatory response. During the same time period, we also treated two further patients with the same clinical picture of AKI, flank pain, and hemoproteinuria after the ingestion of alcohol but who did not undergo renal biopsy (because renal function rapidly returned to baseline). A systematic review (over a 3-month period) has revealed only one previous case report that described histologic findings of any similarity, in that instance in the setting of ecstasy (MDMA) use (1). That case also had similarities in some of the clinical features; the patient experienced bilateral loin pain and urinalysis demonstrated hemoproteinuria. The vasoactive properties of

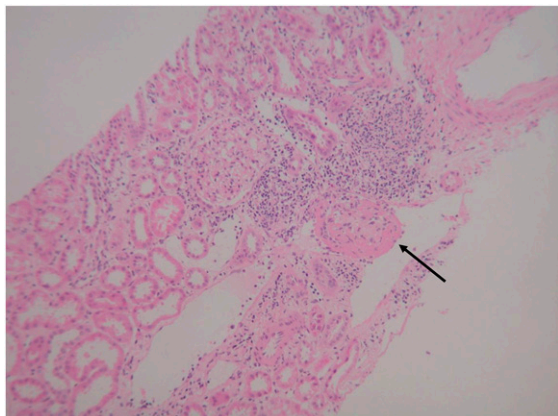


Figure 1. | Microthrombus Identified in Renal Arcuate Vein at Corticomedullary Junction. Intermediate-power view of corticomedullary junction with dilated arcuate veins, one of which shows a fragment of thrombus (arrow) (case 3). Note the localized inflammatory reaction showing close relationship to the thrombosed vessel. Arcuate artery seen top right, x100 (Hematoxylin and stain).

MDMA, hyperthermia, and dehydration were suggested as possible causative factors. A recent case series documenting AKI in users of a synthetic cannabinoid (SPICE) also described flank pain as a predominant presenting symptom, although the histologic findings on renal biopsy were different and displayed classic features of acute tubular necrosis (2). One further report of AKI in a young patient who presented with flank pain was associated with mephedrone ingestion, but in that case no renal biopsy was performed (3).

In our series, presenting symptoms had obvious similarities. Affected patients were young, healthy adults who had generally consumed moderate to large amounts of alcohol in the days before presentation. This differs from most patients who sustain AKI, who tend to be elderly and comorbid (4). Presentation with flank pain and lower back pain was also notable. This led to patients undergoing a variety of

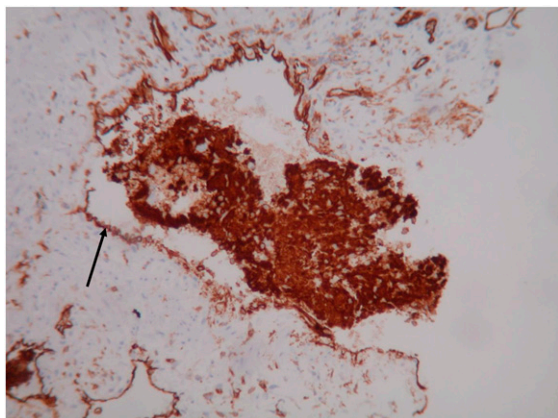


Figure 2. | Microthrombus and Arcuate Vein Endothelium stained with CD31. Immunohistochemical staining for the endothelial marker CD31 shows the thrombus (heavily stained because of the presence of CD31-positive platelets) within an arcuate vein whose endothelium also stained strongly for the antibody (arrow). This is the same case as for Figure 1 but from another vein, x200 (Immunohistochemistry).

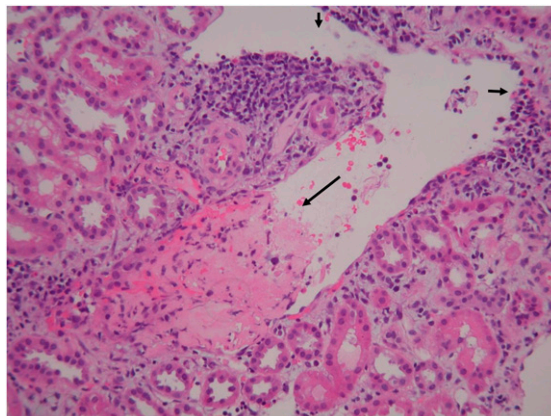


Figure 3. | Dilated Renal Arcuate Venous Radical Containing Microthrombus Material. High-power view of a dilated interlobular vein containing thrombus composed mainly of fibrin (long arrow) with some red cells and inflammatory cells. Marginating mononuclear cells can be seen top and right (short arrows) (case 1), x200 (Hematoxylin and stain).

investigations, including abdominal computed tomography (sometimes with intravenous contrast material) and treatment for other conditions (with antibiotics or steroids) prior to the diagnosis being made.

An increased awareness of this condition may aid in the diagnosis in other similar cases and is relevant to other specialists in addition to nephrologists (*e.g.*, urologists, emergency medicine physicians, acute-care physicians, general practitioners) to whom these patients may present.

It seems likely that the observed pathologic changes were responsible for both the AKI and the symptoms of flank pain, as evidenced by the resultant cortical edema and dilation of the cortical venous system. However, it is less clear as to why arcuate vein microthrombi should occur. This entity appears distinct from renal vein thrombosis, which almost always occurs in the setting of nephrotic

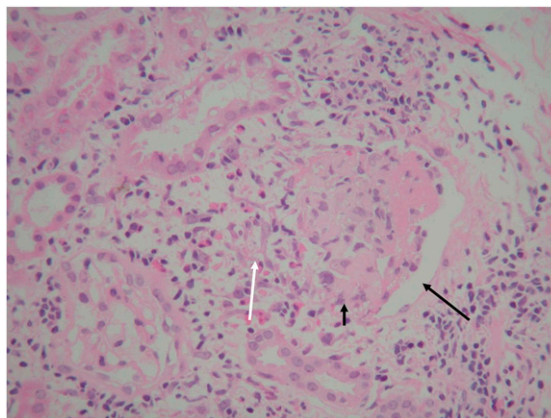


Figure 4. | Inflammatory Response in the Interstitium Secondary to Ruptured Arcuate Venous Radical Containing Microthrombus. Small venous radical (long black arrow) containing thrombus with destruction of the endothelial lining (short black arrow) and secondary inflammatory reaction (white arrow), including fibroblastic proliferation and presence of eosinophils, x200 (hematoxylin and stain).

Table 2. Summary of radiologic, biochemical, and microbiology parameters

Case	Renal Imaging	Immunology	Microbiology	Toxicology	Coagulation	Low-Grade Temperature?
1	US Right 10 cm, left 10.9 cm venous flow Normal	Negative	MSU negative Virology negative	Not performed	Within normal range	Yes
2	US right 10.6 cm, left 11.3cm	Negative except low IgM levels	MSU negative Virology negative ASO negative	Not performed	Within normal range	Yes
3	US right 10.7 cm, left 10.8 cm Contrast-enhanced CT showing normal renal perfusion and normal arterial and venous anatomy	Negative except ANA titer 1:320	MSU negative Virology negative ASO negative	Not performed	Within normal range	Yes
4	Normal-sized kidneys on CT	Negative	MSU negative Virology negative	Negative urine and serum specimens	Within normal range	No
5	Normal-sized kidneys on CT	Not performed	MSU negative Virology negative	Not performed	Within normal range	No
6	US right 12.5 cm, left 12.4 cm Resistive index, 10.4 Normal venous flow	Negative	MSU negative Virology negative	Not performed	Within normal range	Yes

US, ultrasonography; CT, computed tomography; ANA, antinuclear antibody; MSU, midstream urine; ASO, antistreptococcal O.

syndrome or malignancy and in its chronic form is often clinically silent; the acute form requires bilateral renal infarction to induce renal failure (5). Although CMJ nephrons are generally considered most susceptible to changes in perfusion in terms of both tissue oxygenation and alterations in regional blood flow (6), prerenal factors are unlikely to be the sole cause because the patients were not shocked or particularly dehydrated. In addition, with an isolated prerenal etiology it would be expected that the histologic changes that we observed would have been seen in previous biopsy series. Virchow’s triad comprises three factors that predispose to thrombus formation: endothelial injury, hypercoagulability, and abnormal blood flow (stasis/turbulence). Although the hemodynamic characteristics of the CMJ may contribute to the latter, it would seem more likely that an additional insult was present to cause the localized thrombus formation that we observed. Indeed, the presence of marginating mononuclear cells with adherence to the local endothelium in these vessels would suggest additional, perhaps more specific factors, although there was no evidence of an immunologic-mediated process.

While we can speculate about possible additional factors, the demographic characteristics of the patients are particularly suggestive. Similarities to previous case reports mean that recreational drug use, taken intentionally or possibly introduced without patients’ knowledge, should be considered as a potential etiologic factor; this would explain why we have not seen the condition in older adults. However, there was no evidence of this in the one patient who underwent extensive toxicology screening, and all of the six persistently denied this, despite direct questioning (as did the other two patients who did not undergo renal biopsy, one of whom also had a negative recreational drug screen). A unifying feature in our series was the use of alcohol before symptom onset, and although dehydration as a result of alcohol use may have been a contributing factor there is no obvious reason why ethanol use in isolation should result in the observed pathophysiology. An alternative possibility is the ingestion of illegally produced alcohol, which may contain substitutes for ethanol (methanol, isopropanol, or other alcohols found in cleaning fluids or nail remover) plus a variety of contaminants; the United Kingdom has seen an increase in this problem since 2005 (7). Some, but not all, of the patients had taken additional medications, including NSAIDs (three patients, who took the drugs in response to the pain), antibiotics (two patients), and protein supplements (one patient), but there was no unifying agent. NSAIDs in particular may affect intrarenal hemodynamics and may have been a contributory factor; again, however, it is difficult to attribute all of the findings to this. Therefore, we can speculate, the cause of the AKI associated with arcuate vein microthrombi in our patients at present remains uncertain.

These cases have some clinical implications. Because of the uncertain etiology, any young patients presenting with AKI and similar clinical features should have detailed toxicology testing on admission in both urine and blood for atypical alcohols and recreational drugs, including so called legal highs (8). Osmolar and anion gap should routinely be calculated, while urine and serum samples should be saved for further testing if required at a later date. There is also a strong argument for pursuing a histologic diagnosis in similar cases, particularly when renal function is slow to

recover, in order to differentiate from other conditions that would require alternative treatment.

Finally, we are uncertain about the incidence of this condition or how widespread it is, particularly if some cases have previously gone undiagnosed, in the absence of renal biopsy, for example, or biopsy samples that do not include the CMJ. This requires further investigation, especially in view of the demographic characteristics of the patients and possible associations with exogenous substances, which if borne out would require a public health approach to prevention. Further identification and characterization of additional cases with similar clinical and histologic findings may help clarify this.

In conclusion, we describe a previously unreported cause of AKI associated with renal arcuate vein microthrombi that occurred in young persons with certain unifying clinical features. Increased awareness and additional testing of future cases may improve understanding of the underlying pathophysiologic mechanisms of injury.

Disclosures

N.S. has received consultation fees for AbbVie and Pfizer.

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