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Collapsing Glomerulopathy Associated With Hydrophilic Polymer Emboli

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INTRODUCTION

Hydrophilic polymer is a synthetic, biodegradable coating applied to various intravascular devices and vascular grafts to reduce friction between instruments and endothelium, in an effort to prevent vasospasm and thrombosis.[1,2] However, the hydrophilic polymer itself can dislodge from these devices resulting in downstream ischemic complications involving brain, heart, lungs, kidneys, gastrointestinal tract, or skin.[1–9,S1–S9] To date, 3 cases of hydrophilic polymer emboli have been reported to involve the kidneys, but none has been associated with collapsing glomerulopathy.[4,S1,S6] Here, we report the first case of collapsing glomerulopathy temporally related to renal embolization by hydrophilic polymer.

CASE PRESENTATION

A 71-year-old white man with history of hypertension, bioprosthetic aortic valve replacement (February 2015), ascending aortic dissection (September 2015), and obstructive sleep apnea was found to have descending aortic dissection on surveillance computed tomography (CT) scan of the chest in April 2018. He underwent staged vascular repairs that included a carotid to subclavian bypass and thoracic endovascular aortic repair with iliac stenting. During the procedure, 7-French and 9-French Pinnacle Introducer sheaths (Terumo Medical, Somerset, NJ) were inserted into the right femoral artery, thoracic aorta, and left subclavian artery. His preoperative laboratory results showed serum creatinines ranging from 0.8 to 1.0 mg/dl, with a urinalysis negative for protein by dipstick. Two days following the surgery, his creatinine rose to 1.8 mg/dl, prompting discontinuation of hydrochlorothiazide and losartan. His serum creatinine peaked at 3.9 mg/dl on April 19, 2018, and he was discharged with a serum creatinine of 2.7 mg/dl on April 22, 2018, and was told to follow up with a nephrologist. In May, he had a serum creatinine of 2.36 mg/dl with urine protein-to-creatinine ratio of 1118 mg/g. In June, he had a serum creatinine of 2.18 mg/dl with urine protein-to-creatinine ratio of 6974 mg/g. Given the persistent renal dysfunction and worsening proteinuria, a kidney biopsy was performed on July 16, 2018. At that time, physical examination showed an overweight man with body mass index of 28.3 kg/m^2 and blood pressure of 136/76 mm Hg and no edema. He had no skin rash, livedo, or peripheral cyanosis. His neurologic, cardiac, and lung examinations were unremarkable.

The patient had no history of HIV or recent infection, and he did not take any nephrotoxic medications. Specifically, there was no history of exposure to bisphosphonates or interferon. Results of other laboratory tests were negative, including antinuclear antibody, antineutrophil cytoplasmic antibody, HIV, cytomegalovirus (CMV) and parvovirus serology, and serum protein electrophoresis. Complement studies were not performed.

Kidney biopsy contained 2 cores with 31 glomeruli, 2 of which were globally sclerotic. Three glomeruli, arranged in zonal distribution, showed segmental to global wrinkling and collapse of the glomerular basement membranes, with hypertrophy and hyperplasia of the overlying glomerular epithelial cells (Figure 1). The remaining glomeruli were normal in size and appeared unremarkable. Proximal tubules showed focal cytoplasmic lipid vacuoles and protein resorption droplets. In addition, there were tubular microcysts distended by proteinaceous casts. Mild tubular atrophy and interstitial fibrosis occupied 10% to 15% of the cortex. Vessels showed mild arterial intimal sclerosis and arteriolar hyalinosis. Several small interlobular arteries and arterioles were completely occluded by nonpolarizable foreign material (Figure 2), which appeared weakly eosinophilic,

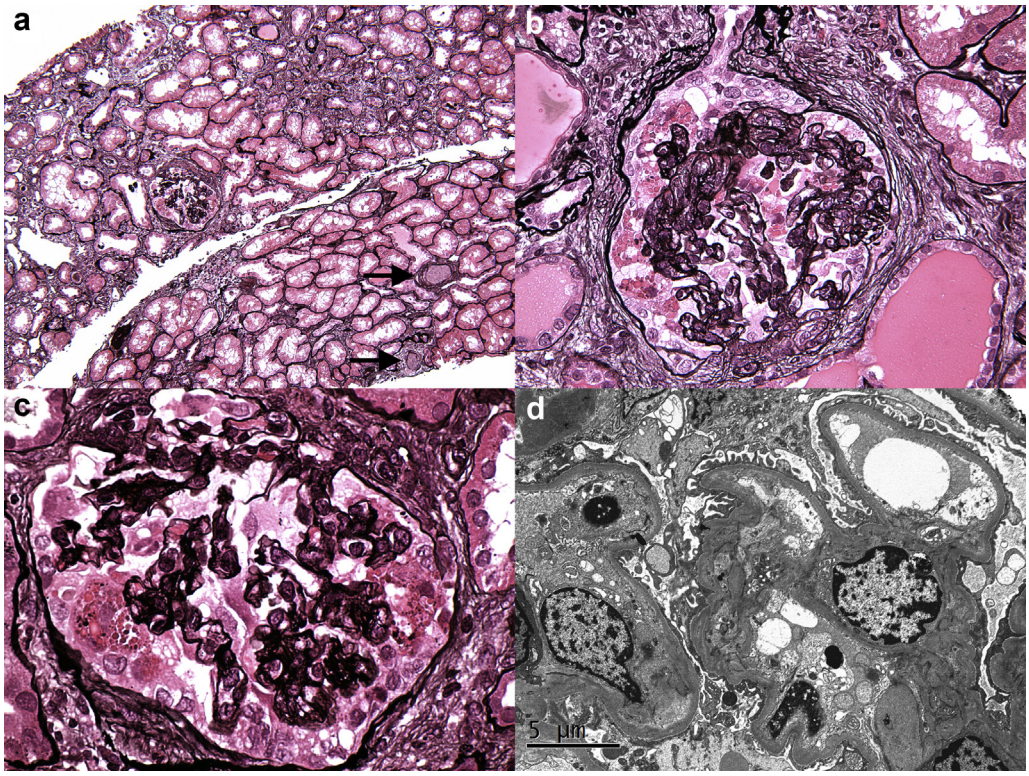

Figure 1. (a) A low-power view shows a characteristic glomerulus with global wrinkling and collapse of glomerular capillary walls with overlying glomerular epithelial cell hyperplasia diagnostic of collapsing glomerulopathy in a zonal distribution. Multiple emboli (arrows) are present in arterioles and small arteries (Jones methenamine silver, original magnification ×100). (b,c) Higher-power views illustrate the features of collapsing glomerulopathy. Overlying epithelial cells contain numerous intracytoplasmic hyaline droplets (Jones methenamine silver, original magnification ×400, ×600). (d) A representative electron micrograph illustrates segmental foot process effacement (original magnification ×6000).

periodic acid–Schiff (PAS)-negative, largely silver-negative with speckled granular positivity, and light blue-gray on trichrome stain. One of these vessels was recanalized, and the foreign material was associated with a giant cell reaction. The tissue received for immunofluorescence contained only medulla; therefore, salvage immunofluorescence was performed on pronase-digested paraffin sections for IgG, IgM, IgA, C3, C1, fibrinogen, albumin, and kappa (κ) and lambda (λ) light chains. Twenty-nine glomeruli were sampled and 4 showed 1 to 2+ segmental to global tuft staining for IgM and C3 (1–2+ intensity, on a scale of 0–4). There was 1+ droplet staining for albumin in the distribution of proximal tubular protein resorption droplets. One glomerulus was available for ultrastructural examination. Podocytes showed approximately 40% foot process effacement and there were no electron-dense deposits or endothelial tubuloreticular inclusions (Figure 1d). No foreign material was present in the corresponding toluidine blue–stained thick sections.

Diagnosis

A diagnosis of collapsing glomerulopathy was rendered. Given the temporal correlation and the zonal distribution of the collapsing lesions with hydrophilic polymer emboli in adjacent vessels, collapsing glomerulopathy was favored to be secondary to acute vascular occlusion by hydrophilic polymer material.

Clinical Follow-up

The patient was treated supportively, without immunosuppression. One month following the biopsy, the patient continued to have fatigue and mild edema. The patient had a serum creatinine of 2.94 mg/dl, albumin of 4.1 g/dl, and urine protein-to-creatinine ratio improved to 2.5 g/g.

DISCUSSION

The kidneys receive approximately 20% to 25% of cardiac output through the renal arteries and their branches, making them particularly susceptible to ischemic injury from thromboembolic or other occlusive phenomena, such as trauma or iatrogenic causes. Hydrophilic polymer coating is applied to various medical devices, including vascular catheters, grafts, and guidewires to reduce vasospasm and risk of thrombosis from endothelial injury.[1] However, complications related to embolization of hydrophilic polymers have been reported to affect multiple organs,

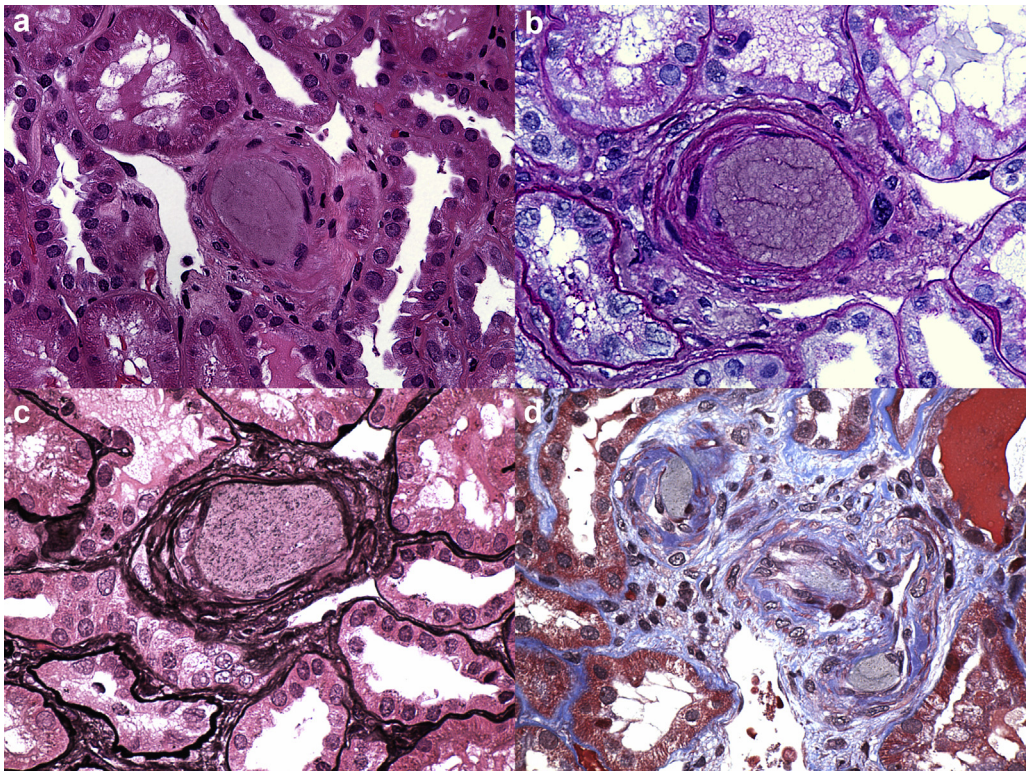

Figure 2. Hydrophilic polymer embolus stained weakly eosinophilic with hematoxylin-eosin stain (a, original magnification ×400); negative with periodic acid–Schiff (PAS) stain (b, original magnification ×600); largely negative with Jones methenamine silver stain (c, original magnification ×600), except for some speckled silver positivity within the embolus; and light blue-gray with Masson trichrome stain (d, original magnification ×600).

including brain, heart, lung, kidney, gastrointestinal tract, and skin.[1–9,S1–S9] The precise composition of emboli is difficult to ascertain in individual cases due to the large number of instruments used in surgical procedures. However, polyvinylpyrrolidone has been implicated in some studies.[S8,S9]

To date, only 3 cases of hydrophilic polymer emboli to the kidneys have been reported (Table 1). All patients had a history of prior intravascular procedures involving vessels proximal to the renal artery. Two patients had history of abdominal aortic aneurysm repair, with polymer emboli involving a native kidney in 1 patient, and an allograft in the other.[S1,S6] Another patient, with an allograft anastomosed to the right external iliac artery, had a history of stenting of the right common iliac artery.[4] The intravascular procedures occurred as long as 5 months before clinical presentation with signs or symptoms of embolization.[4] Although results of urinalysis were not provided for 2 of these patients, the patient with polymer emboli in a native kidney presented with nephrotic range proteinuria (5 g/d).[S6] In this patient, a renal biopsy showed focal segmental glomerulosclerosis, not otherwise specified. The other 2 patients had polymer emboli in the hilar region with ischemic changes and foreign body giant cell reaction.[4,S1] The acute kidney injury resolved in 2 patients, with available follow-up information.[4,S1]

Table 1. Reported cases of polymer emboli in the kidneys

Author (Year)	Age	Sex	Native/allograft kidney	Preceding invasive procedures	Serum creatinine at presentation (mg/dl)	Proteinuria at presentation (g/g or g/d)	Pathology	Follow-up post-biopsy
Sequeira *et al.* (2013)[S1]	59	F	Allograft	Renal artery angioplasty; coronary artery angioplasty; AAA repair	2.3	NA	Foreign body giant cell reaction; coexisting acute cellular rejection	Resolution of AKI
Chen *et al.* (2015)[4]	42	F	Allograft	Common iliac artery stent; coronary artery angioplasty	Hemodialysis	NA	Ischemic change	Resolution of AKI
Arend (2016)[S6]	76	M	Native	AAA repair	3.6	≥ 5	FSGS, NOS	Creatinine 2.5 mg/dl at discharge; proteinuria 5 g
Current case	71	M	Native	Repair of aortic dissection	3.9	6.97	Collapsing glomerulopathy	Proteinuria 2.5 g/g; creatinine 2.94 mg/dl at 1 mo

AAA, abdominal aortic aneurysm; AKI, acute kidney injury; F, female; FSGS, NOS, focal segmental glomerulosclerosis, not otherwise specified; M, male; NA, not available.

Clinical and morphologic manifestation of arterial occlusion differs depending on the embolic material and location of occlusion. Because the kidneys have collaterals only in the subcapsular area and medulla, an occlusion at the level of the renal artery results in a cortical coagulative necrosis, most severely affecting proximal tubular cells, with a relative sparing of medulla and the subcapsular area. This relative sparing likely accounts for the so-called "rim sign," which refers to 1- to 3-mm iso- or hyperintense subcapsular enhancement on contrast-enhanced CT or magnetic resonance imaging.[S10] Clinically, patients typically present with acute flank pain, and possibly hypertension, which may be renovascular owing to acute renin release.[S11,S12] Serum creatinine is often elevated, possibly with hematuria or proteinuria; however, serum creatinine may be within normal range in patients with adequate renal function in the contralateral kidney.[S12]

Although experience with hydrophilic polymer emboli is limited, they most commonly involve smaller arteries and arterioles. Differential diagnosis includes other causes of embolization to intrarenal vessels, the most common of which is atheromatous emboli. Atheroemboli classically show cholesterol clefts, associated with red blood cells, fibrin, and other inflammatory cells, including multinucleated giant cell reaction. In later stages, the cholesterol emboli are incorporated into the intima, with intimal fibrosis or recanalization.

Glomerular lesions associated with atheromatous emboli include ischemic changes with wrinkling and retraction of glomerular basement membranes, segmental sclerosis, or collapsing glomerulopathy, distributed in a zonal fashion.[S13] Of note, patients with significant proteinuria, especially if nephrotic range, are more likely to have focal segmental sclerosis or collapsing glomerulopathy.[S13] Accordingly, both the patient with polymer emboli and focal segmental sclerosis reported by Arend,[S6] and our patient with collapsing glomerulopathy had nephrotic range proteinuria. Other causes of collapsing glomerulopathy, including viral etiology, including CMV, Epstein-Barr virus, and parvovirus, and medications, such as bisphosphonates or interferon, were excluded in our patient. Furthermore, his race makes the presence of APOL1 pathogenic variants unlikely.

The pathomechanism of collapsing glomerulopathy in the setting of acute ischemia is not fully understood. As early as 1998, Meehan *et al.*[S14] noted the morphologic similarity between ischemic glomeruli and collapsing glomerulopathy, as well as the relatively high frequency of associated chronic vascular lesions in allografts with collapsing glomerulopathy. In addition, collapsing glomerulopathy has been noted to occur in acute antibody-mediated rejection, thrombotic microangiopathy, and atheroembolization.[S13,S15,S16] A role of ischemia in the pathogenesis of collapsing lesions is also supported by a distinct zonal distribution of collapsing lesions seen in some cases.[S16] Hypothetically, acute and complete occlusion of afferent arteriole may lead to a global collapse of glomerular tuft, resulting in a widespread ischemic injury to podocytes and upregulation of hypoxia-inducible factors resulting in proliferation of visceral and parietal epithelial cells.[S17,S18] In contrast, a partial occlusion may not trigger sufficient hypoxic signal for epithelial cells to proliferate. Furthermore, the etiology of collapsing lesions in both native and transplant kidneys can be multifactorial.[S19]

Differential diagnosis of foreign body emboli also includes starch particles, which may become lodged in glomeruli or peritubular capillaries of the renal allograft after pulsatile machine perfusion (Table 2).[S20,S21] These starch particles measure 10 to 30 μm in diameter, are not visible on hematoxylin-eosin and trichrome stains, stain strongly positive with PAS, and show "Maltese-cross" birefringence when polarized.[S20] These particles likely originate from surgical gloves and are of no clinical significance.[S20] In i.v. drug abusers, emboli from various exogenous materials, such as cellulose, starch, and talc, can occur. Because

Table 2. Conditions considered in differential diagnosis of polymer emboli in the kidneys and their histologic features

	Shape and staining characteristics with H&E	PAS positivity	Birefringence under polarized light	Other staining characteristics
Polymer emboli	Serpentine, round, eosinophilic	No	No	Speckled positivity with silver stain, rare giant cell reaction
Atheroemboli	Cleft or needle shaped, not visible by H&E	No	No	Often surrounded by giant cells or fibrin, can be embedded in intima
Starch particles	Round, 10–30 μm, not visible by H&E	Yes, strongly	Yes with "Maltese-cross" appearance	Does not stain with trichrome
Cellulose	Needle shaped	Yes	Yes	Silver positive
Talc	Needle shaped, unstained	No	Yes	
Amyloid	Amorphous, pale eosinophilic, typically deposited in vessel wall	Yes, weakly	No	Congo red positive
Immune thrombi	Round highly eosinophilic	Yes	No	Can be associated with vasculitis
Pooled serum	Amorphous, pale and conforms to lumen	No	No	

H&E, hematoxylin and eosin; PAS, periodic acid–Schiff.

Table 3. Teaching points

Hydrophilic polymer emboli also should be considered in a differential diagnosis whenever clinical history is suggestive for atheromatous emboli.
Careful examination of the biopsy is necessary to identify hydrophilic polymer emboli due to its focal nature.
Identification of ischemia, which may be caused by atheromatous or hydrophilic polymer emboli, as a cause of secondary collapsing glomerulopathy, is crucial to avoid unnecessary immunosuppression.

these materials are typically injected in veins, they are most commonly seen in the lungs and are only rarely encountered in the kidneys at autopsy.[S22] These materials can be distinguished from each other by their morphology, as talc is PAS-negative (unlike cellulose and starch), and cellulose lacks the "Maltese-cross" appearance of starch under polarized light.[S23,S24] Although both hydrophilic polymer and talc are PAS-negative, talc is distinguished by its typical needle shape, which contrasts with the round or serpentine appearance of polymer material.[S23,S24] Last, their lack of staining with the panel of antisera used in routine immunofluorescence, their granular appearance, speckled silver positivity, and Congo red negativity distinguish the polymer material from vascular amyloid deposits, immune thrombi (such as due to cryoglobulinemia or crystalglobulinemia) or pooled serum.

In summary, we report the first case of collapsing glomerulopathy associated with hydrophilic polymer emboli. Clinical history of endovascular procedure and a zonal distribution of glomerular lesions, ranging from ischemic changes, segmental sclerosis, or collapsing glomerulopathy, should alert pathologists to search not only for atheromatous emboli, but for hydrophilic polymers, which can be easily overlooked as artifact (Table 3). These polymers in turn should be distinguished from other foreign materials. Their proper identification is essential to assign an ischemic etiology for the collapsing glomerulopathy and avoid inappropriate treatment with immunosuppressive agents, as typically given for primary collapsing glomerulopathy.[S25]

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary References.

Supplementary material is linked to the online version of the paper at www.kireports.org.

REFERENCES

1. Mehta RI, Mehta RI, Solis OE, et al. Hydrophilic polymer emboli: an under-recognized iatrogenic cause of ischemia and infarct. *Mod Pathol*. 2010;23:921–930.
2. Mehta RI, Mehta RI. Polymer-induced central nervous system complications following vascular procedures:spectrum of iatrogenic injuries and review of outcomes. *Hum Pathol*. 2016;53:178–190.
3. Chavez JA, Chen W, Frankel WL, et al. Hydrophilic polymer-associated ischemic enterocolitis. *Am J Surg Pathol*. 2017;41:271–276.
4. Chen CL, Chen NC, Wang JS. Acute hydrophilic-polymer nephropathy and acute renal failure. *N Engl J Med*. 2015;372:1775–1776.
5. Kozak M, Adams DR, Ioffreda MD, et al. Sterile inflammation associated with transradial catheterization and hydrophilic sheaths. *Catheter Cardiovasc Interv*. 2003;59:207–213.
6. Mehta RI, Mehta RI, Choi JM, et al. Hydrophilic polymer embolism and associated vasculopathy of the lung: prevalence in a retrospective autopsy study. *Hum Pathol*. 2015;46:191–201.
7. Mehta RI, Mehta RI, Fishbein MC, et al. Intravascular polymer material after coil embolization of a giant cerebral aneurysm. *Hum Pathol*. 2009;40:1803–1807.
8. Rosen LE, Singh RI, Mahon B. Myocardial hydrophilic polymer emboli following cardiac catheterization: a case report and literature review. *Cardiovasc Pathol*. 2014;23:175–177.
9. Sado D, Witherow F. Sterile granuloma formation following radial artery facilitated coronary catheterization. *Catheter Cardiovasc Interv*. 2009;74:606.