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Hydrophilic polymer embolism and associated vasculopathy of the lung: Prevalence in a retrospective autopsy study

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Abstract

Hydrophilic polymers are commonly applied as surface coatings on vascular devices and have been shown to dissociate during endovascular use, causing hydrophilic polymer embolism (HPE). Adverse effects related to this phenomenon have been recognized and reported. The prevalence of this complication is unknown. We conducted a retrospective study to determine the prevalence of HPE among hospital autopsies over a 29-month period. Postmortem tissue was histologically evaluated for the presence, location(s) and extent of HPE. HPE findings were correlated with documented clinical and laboratory data and patient outcome. Of 136 hospital autopsies examined, 18 (13%) showed evidence of HPE involving the lungs (n = 18), heart (n = 1) or central nervous system (n = 1). Localized pulmonary HPE was seen in 12 patients (9%). Multifocal pulmonary HPE was found in 6 patients (4%) and was associated with clinical vasculitis (33%; P < .0001), suspected pulmonary ischemia (50%; P = .008), coagulopathy (67%; P = .002), and constitutional disease (83%; P = .01). Within affected lung, associated histopathologic changes included occlusive intravascular or perivascular inflammation (89%), intravascular fibrous response (56%), microthrombus formation (44%), vasculitis (28%), and/or pulmonary microinfarction (28%). Statistically significant differences in hospital days (P = .008) and number of vascular interventions (P = .01) were noted between affected and unaffected patients. We conclude that HPE is an underdiagnosed phenomenon with primary involvement of the lungs, where secondary vascular changes are common. Additional studies may be needed to clarify risks and to identify preventative strategies for this iatrogenic complication of catheterizations and “minimally invasive” endovascular techniques.

Keywords

catheterization; drug delivery vehicle; endovascular procedure; HPE; hydrophilic polymer embolism; iatrogenic complication; vasculopathy

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Introduction

Hydrophilic polymers are increasingly used for biomedical applications. Enhanced lubrication and biocompatibility, made possible by hydrophilic coats on cardiovascular and neurointerventional devices, allow for less invasive approaches for common endovascular procedures [1-3]. The advent of drug-eluting polymers additionally allows for sustained, targeted release of intravascular drugs which improve therapeutic efficacy and compliance, while reducing systemic drug toxicities. With advanced nano-technologies and evolution of bioengineered insertable and implantable “smart devices”, manufacturers will continue to incorporate this material on new and emerging vascular devices [4-6].

Despite their technological advances, polymer coating materials have been shown to dissociate from device surfaces during endovascular manipulation [7-16], or following implantation in patients [9]. These foreign materials may then deposit in unexpected locations within the body. Recent studies conducted by our group document morbidity and mortality attributable to embolization of polymer particles within the bloodstream [12,13]. Thus, Hydrophilic Polymer Embolism (HPE), a term we introduced in 2010, has recently been established as a potentially fatal iatrogenic disease [13], although its frequency in populations at risk has not been clear.

While vascular devices undergo friction, durability, and particulate trials required by the United States Food and Drug Administration (USP XXII sec 788) [17], risks associated with intravascular polymer applications are not fully recognized by the medical community [12,13,18,19]. To date, the clinicopathological effects associated with HPE in patients have not been systematically evaluated. The recent observation of widespread polymer microemboli in a new fatal case prompted us to perform a retrospective analysis at a tertiary care hospital. Herein, we report the frequency of this condition and analyze associated pulmonary vascular changes in affected patients who died in a hospital setting and underwent autopsy.

Materials and Methods

Autopsy Material and Tissue Processing

During a 29-month interval, from January 1, 2010 to May 30, 2012, 2766 patients died at the University of Maryland, Baltimore, Medical System. Of the total deaths, 198 in-hospital autopsy requests were made during this period. Of these, 54 fetal, stillborn, or infant pediatric autopsies were excluded from this study; slides were unavailable in our files on 6 cases; 2 cases consisted of gross examination only. Corresponding tissue slides for the remaining 136 cases were evaluated.

During routine autopsies, standard blocking protocols were used, with expanded organ sectioning utilized in cases with prominent gross pathology (e.g., infarction or hemorrhage) or restricted autopsies. Autopsy blocks ranged from 10-71 (mean, 36 total blocks), per case. Overall mean per organ (and range in sampled organs) were: 10 from the central nervous system (range: 11-38); 6 from the lungs (range: 4-20); 6 from the heart (range: 3-29); 2 from

the gastrointestinal tract (range: 1-5); 2 from the genitourinary organs (range: 2-4); 1 from the liver (range: 1-5); 1 from vertebral bone (range: 1-2); 1 from skin (range: 1-3); 1 from muscle and peripheral nerve (range: 1-2); and 1 from aorta (range: 1-4). Tissue blocks were processed per standard protocol, including formalin fixation (5-10 days duration), paraffin embedment, 5- μ m thick sectioning, and hematoxylin and eosin (H&E) staining.

Quantification of Polymer Emboli and Autopsy Diagnoses

Autopsy cases were routinely diagnosed by attending staff pathologists at the University of Maryland Medical Center, and were retrospectively re-reviewed by an autopsy pathologist who was blinded to demographic and clinical information. Slides were scanned by light microscopy (200X and 600X) and in some cases were additionally evaluated on serial step cuts and special staining [13,20,21]. Localized HPE was defined by polymer deposition within a single organ, whereas multifocal HPE was defined by widespread involvement of both lungs and/or spread to multiple organ systems. HPE-positive cases were re-reviewed by a senior autopsy pathologist to confirm presence of foreign polymer materials. Alternate diagnoses were ruled out on histologic evaluation conducted by an autopsy pathologist with expertise on vascular diseases.

Clinical Data and Hospital Course

Demographic and clinical data were collected from electronic medical records by a co-investigator who was blinded to autopsy results. Age, sex, previous medical history, and drug habits were noted from admission notes. Inpatient vascular procedures, clinical signs, symptoms and clinically suspected cause of death were determined by review of inpatient and death notes originating during the final month of life. Number and duration of admissions during the final year of life were also tabulated. Post-admission laboratory values were recorded from inpatient flowsheets.

Associated Factors and Statistical Analysis

To investigate factors associated with a diagnosis of HPE, several demographic, clinical, laboratory and pathology variables were examined. The number of percutaneous vascular interventions incorporating polymer coated catheters and devices during the final month of life were tabulated. Numbers of tissue blocks evaluated at autopsy were additionally analyzed. Two-group comparisons were made among patients with HPE (multifocal, localized, or all) and without HPE. Statistical analysis was performed using JMP software (Cory, NC, USA). Categorical variables were compared using the Chi-squared (Pearson) test. Continuous variables were compared using ANOVA one-way test. A *P* value of less than 0.05 was considered to indicate statistical significance.

Results

Patient Autopsies

A total of 4794 tissue slides originating from 136 adult and adolescent hospital autopsies were evaluated (patient age range, 10-96 years; 53% male). Per autopsy consent, 85 cases were unrestricted autopsies; 26 cases excluded examination of the head; 19 cases consisted

only of chest examination; 4 autopsies were limited to examination of the heart, abdomen, pancreas, or liver only; while 2 cases were limited to examination of the brain.

Of 136 autopsy cases examined, 18 cases (13%) showed histologic evidence of HPE. One decedent had multifocal, systemic evidence of HPE with widespread involvement of the lungs, heart and central nervous system; 5 decedents had multifocal intrapulmonary HPE with involvement of all lobes; 12 decedents had only rare HPE with localized involvement of 1 or more lobes of lung (Table 1). Affected patients included 13 men, 4 women, and 1 adolescent male (age range, 16-73 years) who had no documented heritable coagulopathies or history of active drug use. Additional demographical information is detailed in Table 2. No statistically significant differences in mean age or number of autopsy tissue blocks evaluated were found between affected and unaffected patients (Table 3).

Quantification of Polymer Emboli and Associated Tissue Reactions

On histologic examination, occlusive polymer emboli were non-refractile, nonpolarizable, lamellated, and finely granular and basophilic on H&E stain (Figs. 1 and 2) [13]; and were red on Congo Red and Mucicarmine stains (Fig. 2G and 2H, respectively) [20], and blue on Masson trichrome stain (Fig. 2I) [13,20,21]. Affected vessels numbered from 1 to greater than 200 per case, and ranged from 7 μm – 1.3 mm in diameter (mean: \sim 100 μm). Concordance of findings among reviewers was high (>90%). Anatomical distribution of HPE for each case is delineated in Table 1; preferential involvement was noted within the lungs. Associated pulmonary intravascular and/or perivascular inflammation was present in 16 decedents (89%) (Figs. 1 and 2) [9,11-14], including macrophages (16 cases, 89%) (Fig. 1C and D); foreign body giant cell reaction (11 cases, 61%) (Figs. 1E); neutrophils (12 cases, 67%); and rare eosinophils (5 cases, 28%). Additional associated tissue changes included intravascular fibrous reaction in 10 cases (Masson Trichrome) (56%) (Figs. 1F); microthrombus formation in 8 cases (44%) (Fig. 1G); fibrinoid vascular necrosis in 6 cases (33%); giant cell or granulomatous vasculitis in 5 cases (28%) (Fig. 2B); internal elastic damage in 5 cases (elastic stain) (28%); and intravascular and/or perivascular neutrophilic collection in 3 cases (17%) (Fig. 2C). Associated hemorrhagic microinfarcts were also found (5 cases, 28%) [13]. Heterogeneous vascular reactions to polymer emboli were frequently observed (Fig. 2A-E). Punctate intravascular calcification was associated with luminal fibrous reaction in two cases (alizarin red). No definite tissue reactions were observed in two cases. On original autopsies, evidence of HPE was recorded only in 3 patients (17%), having been overlooked in the majority of affected decedents (83%).

Clinical Presentation

Clinical signs, symptoms, and suspected patient diagnoses are shown in Tables 2 and 3. Suspected pulmonary embolism (PE) was documented in a greater proportion of patients with HPE, compared to those without HPE ($P = 0.006$); likewise, pulmonary infarcts were identified more commonly on routine autopsies ($P < 0.001$). Concurrent saddle thromboembolus was identified in one patient who had known deep venous thrombosis (case 15); another patient who died acutely from PE had widespread pulmonary HPE and rare intravascular plant material of unclear origin (case 6); and 1 patient had concurrent septic emboli (case 5) (Table 2). The remaining 15 patients with HPE showed no

cholesterol, fat, or thrombo-emboli, or other significant polarizable or non-polarizable embolic sources on histopathologic evaluation, although bone marrow microemboli were incidentally found within the lungs of 6 patients who underwent attempted resuscitation prior to death. Although clinical suspicion of thromboembolic stroke was not more prevalent among affected patients, focal embolic cerebral infarcts were incidentally found in a greater proportion of patients, relative to those without HPE ($P = 0.03$) (Table 3). Patients with multifocal HPE were more likely to exhibit clinical evidence of vasculitis, ischemia and/or infarction, and constitutional disease, relative to those with localized or no HPE (Table 3).

Conditions of Hospitalization

Patients with HPE had undergone a significantly greater number of percutaneous vascular procedures incorporating polymer-coated devices, relative to patients with no HPE ($P = 0.01$), and had longer hospitalizations before death ($P = 0.008$) (Table 2). One affected patient had undergone insertion of a Cook Spectrum Glide central venous catheter (CVC) (Cook, Bloomington, IN), only [11]. In the remaining patients, definite causative device(s) could not be determined retrospectively [13]. However, continuous veno-venous hemofiltration was noted among a greater proportion of patients with HPE, relative to those without HPE ($P = 0.001$). Patients with multifocal HPE had additionally undergone placement of arterial lines, peripherally inserted central catheters, hemodialysis, cardiac catheterization and/or extracorporeal membrane oxygenation (ECMO) (Table 2).

Discussion

Hydrophilic coating materials are widely used on medical devices and have revolutionized catheterization and endovascular devices and techniques. Despite their numerous unique advantages, these substances occasionally dissociate from device surfaces and deposit within the bloodstream, thereby embolizing distally during clinical use [13]. Intracerebral polymer microemboli were first described by Barnwell et al following use of infusion microcatheters (Target Therapeutics, Fremont, CA) [7]. Subsequent reports illustrated localized polymer reactions at dermal access sites following transcutaneous cardiovascular procedures (Cook, Bloomington, IN) [8,9]. Recent studies further demonstrate polymer microembolism due to diverse procedures and illustrate potential for distal inflammatory and/or ischemic parenchymal damage within the vital organs, including the lungs [11,13], brain [7,12,13], heart [14, 16], kidney [15], liver (Mehta, unpublished observation) and lower limb [13]. Notably, foreign polymer materials have been documented also in peripheral arteriovenous grafts following dialysis as well as in explanted organs originating from patients who underwent invasive monitoring prior to transplantation [13,15]. The overall frequency of HPE in populations at risk, however, is not previously reported.

We performed a histopathological analysis to assess how commonly polymer microparticle embolism is detected among adolescent and adult hospital decedents. In this retrospective 29-month autopsy study of 136 patients, we identify a prevalence rate of 13%. Most affected patients showed only localized arterial deposits within peripheral lung (9%); however, multifocal pulmonary parenchymal involvement was found in 6 patients (4%). Associated microvascular injuries were commonly found, including inflammatory and/or fibrous

response, with vascular occlusion and occasional microinfarcts involving areas of peripheral lung. The diverse patterns of vascular damage were consistent with iatrogenic polymeric reactions elicited in experimental animal models [21,22].

HPE Vasculopathy: Potential Clinical Implications & Limitations of the Current Study

We speculated previously that ischemia and infarction due to HPE are clinically under-recognized [12-13]. Moreover, growing evidence suggests that clinical sequelae attributable to HPE may be highly disparate [11-16], depending on organ and degree of involvement, among several other device and patient-related factors. The clinicopathological effects associated with HPE, however, have not yet been systematically evaluated.

In this study, we illustrate preferential HPE involvement within the distal pulmonary vasculature, wherein the body naturally filters systemic venous blood. To our knowledge, only 6 prior cases of pulmonary HPE have been reported in the literature [11,13]. One was that of a 22-year-old woman, reported by our group [13], who developed pulmonary infarction and death following central catheterization (device unknown). Another was the case of a 34-year-old woman, reported by Allan et al [11], who developed lung abscesses and vasculitis after central catheterization (Cook, Bloomington, IN) [11]. Sequelae in both patients were due to vascular damage and obstruction resulting from pulmonary HPE. The latter patient was found to have elevated p-antineutrophil cytoplasmic antibody (p-ANCA) and C-reactive protein in the setting of active Crohn colitis, and multiple lung wedge resections were required to determine the etiology of her transient pulmonary disease.

Herein, we report 18 additional cases of pulmonary HPE, including 6 (33%) with multifocal lung involvement. Among these, HPE appeared to be incidental in 14 patients (78%); however, widespread pulmonary HPE directly contributed to death of at least 1 patient (5%). Notably, this patient developed multiple symptoms following uneventful catheterization that were unexplainable at the time of her demise (case 1). She experienced an unusual constellation of findings including suspected PE (pulmonary computed tomography angiogram negative) and vasculitis (p-ANCA positive), with subsequent coagulopathy, lymphadenopathy and systemic inflammatory response disease (SIRS) [additional post-admission laboratory values: elevated CRP, ESR, leukocytes, PT, PTT, D-dimer, fibrin split products; low fibrinogen]. In the absence of other etiologies, the terminal findings were attributed to a syndromic effect resulting from widespread pulmonary HPE. In the remaining patients (17%), HPE may have contributed to morbidity, although definitively affects could not be evaluated due to comorbid disease.

This descriptive study sheds new light regarding the phenomenon of HPE in a select patient population; however, several limitations exist: Extensive tissue sampling of vital organs is currently necessary to confirm presence and distribution of HPE. In autopsy patients, controlling for confounding variables is a limitation to accurate assessment of iatrogenic injuries [23]. Because only limited representative tissues can be sampled retrospectively at autopsy, and because polymer materials gradually biodegrade, the frequency and burden recorded in these patients are likely underestimated. Although this study provides important new data, the true prevalence and significance of HPE cannot be accurately assessed by conventional diagnostic modalities.

Polymer surface coatings have been in wide clinical use for over two decades, suggesting that the complication of polymer embolization has gone undetected “under the radar” for several years. A heightened clinical awareness is necessary for premortem diagnosis of this iatrogenic phenomenon. Given the widespread use of polymer coatings and millions of catheterizations and endovascular procedures performed annually worldwide, morbidity associated with HPE is likely underrecognized. Although the current study highlights the utility of autopsies in this modern era of advanced procedures [24,25], additional investigations and novel diagnostic techniques (e.g., new serum tests) may be needed for additional clinical characterization of this vascular phenomenon. Ultimately, a better understanding of hydrophilic polymer embolism and associated vascular effects may lead to safer and more efficient methods of targeted drug and device delivery, and more importantly, to improved outcomes following catheterizations and “minimally invasive” endovascular procedures.

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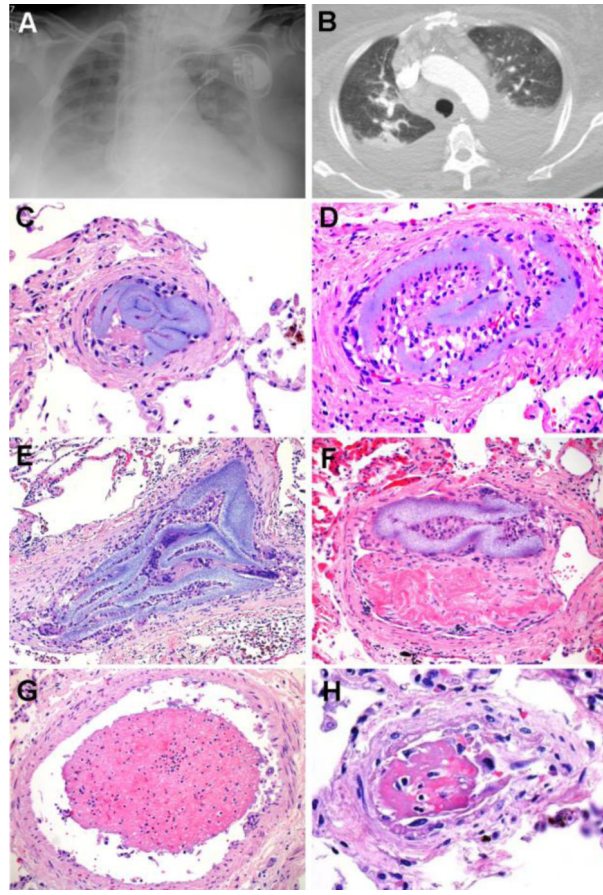


Figure 1. Summary, Patient 1

A 73-year-old woman with hypertrophic cardiomyopathy, sinus node dysfunction, hypertension, diabetes mellitus type 2 and chronic renal disease presented with pulmonary edema. Cardiac enzymes were negative; BNP and creatinine were elevated. Initially, the patient was improving with diuresis, intravenous fluids and dialysis. After admission, a CVC was placed and broad-spectrum antibiotics were administered for suspected pneumonia. The patient's respiratory symptoms subsequently worsened; however, transthoracic echocardiography and right and left cardiac catheterization revealed no definite cardiac etiology for her symptoms. During her hospitalization, she developed suspected PE, elevated ESR, p-ANCA+ vasculitis, coagulopathy of unknown cause, and prominent mediastinal lymphadenopathy. Chest X-Ray (A) and pulmonary CT angiography (B) showed pleural effusions and areas of pulmonary consolidation, with no evidence of PE. Despite multiple negative cultures, the patient developed multiple organ dysfunction syndrome and suspected sepsis, progressing to death. Autopsy, performed 1 month after admission, failed to reveal any natural etiology for her terminal symptoms. Retrospective histopathological analysis, however, showed multifocal HPE involving the bilateral peripheral pulmonary arteries (C-F), as well as the heart and central nervous system (not shown). Intravascular histiocytes (D), giant cells (E), and fibrous reaction (F) were associated with HPE. Adjacent vessels showed microthrombus formation (G) and areas of vascular injury (H). The cause of death was retrospectively attributed to widespread pulmonary HPE in the setting of hypertrophic cardiomyopathy [C-H: H&E, original magnification 600X].

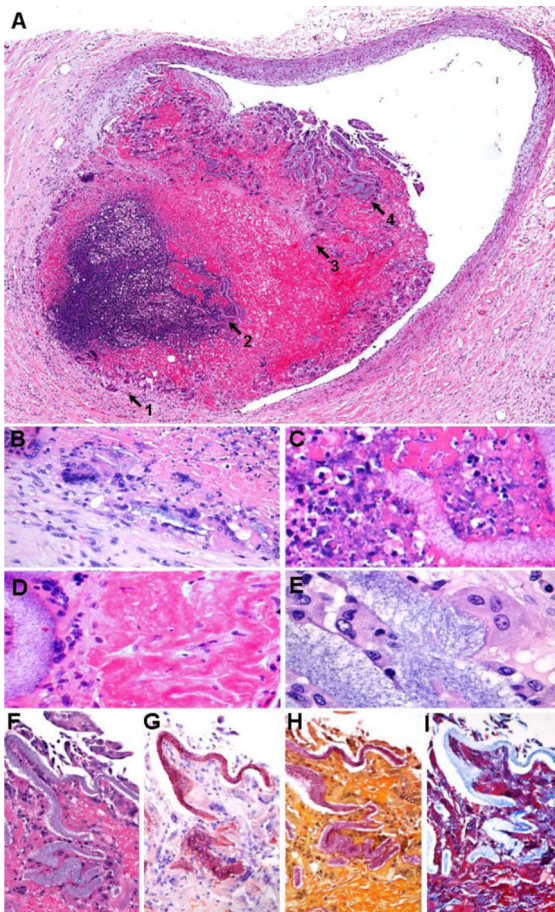


Figure 2. Summary, HPE Vasculopathy

Heterogeneous reactions (A) elicited by intravascular polymer include foreign body giant cell vasculitis (arrow 1), intravascular microabscess formation (arrow 2); intravascular fibrous reaction (arrow 3); and histiocytic response (arrow 4) (magnified in panels B-E, respectively); high-power microscopy further demonstrates lamellated strips of foreign granular material, consistent with polymer [A-F: H&E; G: Congo Red; H: Mucicarmine; H: Masson Trichrome; A: 200X; B-I: 400X].

Table 1
Disease burden and anatomical distribution of HPE in 18 patients with Multifocal or Localized involvement.

Case	Multifocal HPE (n=6)						Localized HPE (n=12)						18 ^a						
	1	2	3	4	5	6	7 ^a	8 ^a	9	10	11	12 ^a		13	14	15	16	17	
Anatomical Region																			
LUNGS																			
Right upper lobe	++	++	++	+++	+++	++	0	0	+	+	+	0	+	0	0	+	+	0	
Right middle lobe	++	++	+	++	+++	++	+	+	++	0	0	0	+	0	0	0	0	+	
Right lower lobe	++	++	+++	++	+++	++	+	+	0	0	0	0	+	0	0	0	0	+	
Left upper lobe	+++	+++	++	+++	++	++	+	+	+	+	+	0	+	0	0	0	0	0	
Left lower lobe	++	+++	++	+++	++	++	+	+	0	0	0	+	0	+	+	0	0	0	
HEART	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
BRAIN																			
Cerebral cortex	++	0	0	0	0	0	N/A	N/A	0	0	0	N/A	0	0	0	0	0	0	N/A
White matter	++	0	0	0	0	0	N/A	N/A	0	0	0	N/A	0	0	0	0	0	0	N/A
Subcortical nuclei	++	0	0	0	0	0	N/A	N/A	0	0	0	N/A	0	0	0	0	0	0	N/A
Leptomeninges	++	0	0	0	0	0	N/A	N/A	0	0	0	N/A	0	0	0	0	0	0	N/A
Cerebellum	+	0	0	0	0	0	N/A	N/A	0	0	0	N/A	0	0	0	0	0	0	N/A
Brainstem	+	0	0	0	0	0	N/A	N/A	0	0	0	N/A	0	0	0	0	0	0	N/A
SPINAL CORD	+	0	0	0	0	0	N/A	N/A	0	0	0	N/A	0	0	0	0	0	0	N/A
Number of Vessels with HPE Mean = ~70 (Range: 25 – over 200) Mean = ~7 (Range: 1 – 10)																			
Size of Vessels with HPE Mean = ~100 µm (Range: 7 µm – 1.3 mm) Mean = ~100 µm (Range: 13 µm – 370 µm)																			

Semiquantitative scores: 0, none; +, sparse (1-5); ++, moderate (6-10); +++, common (11-15); +++++, widespread (>15)

Abbreviations: HPE, hydrophilic polymer emboli; N/A, not available

^aCentral nervous system examination was excluded on restricted autopsy

Table 2

Summary of comorbidities, recent procedures, and clinicopathological course in 18 patients with Multifocal or Localized HPE.

Case	Age Sex	Comorbid Conditions and → Suspected Contributing Procedure(s)	Documented Clinical Cause of Death	Documented Cause(s) of Death on Original Autopsy	Documented Signs and Diagnoses (Final Month of Life)	Findings on Retrospective CP Review
Multifocal HPE (n=6)						
1	73F	Hypertrophic cardiomyopathy; HTN; DM; CKD requiring HD → Hemodialysis; CVVH; Cardiac cath; CVC	Cardiac insufficiency	Per clinical history, probable cardiac insufficiency	<ul style="list-style-type: none"> ■ Possible pneumonia ■ Pulmonary embolism ■ Vasculitis (p-ANCA +) ■ Lymphadenopathy ■ Sepsis with DIC, MODS 	^a Multiorgan failure; Widespread HPE; Hypertrophic cardiomyopathy
2	65M	Aortic stenosis requiring prior valve replacement; A. fib; HTN; DM; Recent cardioversion complicated by <i>Clostridium difficile</i> colitis → CVC	Respiratory insufficiency	Respiratory failure/DIC	<ul style="list-style-type: none"> ■ Possible pneumonia ■ Hemoptysis ■ Decubitus ulcer ■ Sepsis with DIC, MODS 	^a Multiorgan failure; DIC; HPE; Scattered pulmonary and cerebral infarcts
3	64M	HTN; DM; CKD; A. fib; Ischemic cardiomyopathy; recent OHT (on immunosuppressive therapy) → CVC; ECMO; Hemodialysis; CVVH	Septic shock	Pneumonia; Septic shock; Peripheral pulmonary emboli noted	<ul style="list-style-type: none"> ■ Mediastinitis ■ Groin infection ■ Pneumonia ■ Pulmonary embolism ■ Upper GI bleed ■ Acute PEA + SVT ■ Septic shock with MODS 	^{a,b} Septic shock; Pneumonia; Pulmonary HPE; Pulmonary microinfarct
4	69M	CAD; prior CABG; HL; recent MVA w/ Brown Sequard syndrome complicated by empyema and sepsis → CVC	Sepsis; leptomeningitis; brainstem infarcts	Sepsis; leptomeningitis; brainstem infarcts	<ul style="list-style-type: none"> ■ Leptomeningitis ■ Embolic stroke ■ A fib with RVR ■ DVT ■ Septic shock with DIC, MODS 	Sepsis; Leptomeningitis; Brainstem infarcts; Pulmonary HPE
5	41M	Remote h/o aortic dissection s/p repair; HTN; hepatitis C; osteogenesis imperfecta; Presented to ED with acute diarrhea → CVC; Arterial Line; Hemodialysis	Septic shock; embolic stroke	Multiple embolic infarcts involving lungs, brain, kidneys, liver, spleen	<ul style="list-style-type: none"> ■ Vasculitis (p-ANCA –) ■ Embolic stroke ■ Septic shock with DIC, MODS ■ Anoxic brain injury 	^c Multiple embolic infarcts involving lungs, brain, kidneys, liver, spleen secondary to septic emboli; Pulmonary HPE
6	59M	Abdominal liposarcoma requiring recent colectomy → PICC; CVC; Arterial line	Acute Pulmonary embolism	Acute pulmonary embolism due to foreign material	<ul style="list-style-type: none"> ■ Pulmonary embolism ■ Sudden death 	^{a,b,d} Acute pulmonary embolism due to foreign material
Localized HPE (n=12)						
7	57F	h/o breast CA; dilated cardiomyopathy; PFO; HTN; CKD; A. fib requiring	Nonischemic cardiomyopathy	Multiorgan failure associated with cardiomyopathy	<ul style="list-style-type: none"> ■ Pulmonary embolism ■ Pneumonia ■ A fib with RVR ■ DVT 	Multiorgan failure; Cardiomyopathy; Pulmonary HPE

Case Age Sex	Comorbid Conditions and → Suspected Contributing Procedure(s)	Documented Clinical Cause of Death	Documented Cause(s) of Death on Original Autopsy	Documented Signs and Diagnoses (Final Month of Life)	Findings on Retrospective CP Review
8 21F	warfarin; Admitted for cellulitis requiring IV Ab warfarin; Admitted for cellulitis requiring IV Ab → CVC ; Cardiac Cath	Pneumonia; sepsis; Cor pulmonale	Pneumonia; sepsis; DAD; Cor pulmonale	<ul style="list-style-type: none"> ■ SIRS/shock with DIC, MODS ■ Pneumonia ■ Pulmonary embolism ■ Septic shock ■ Coagulopathy with DIC, MODS 	^b Pneumonia; sepsis; DAD; Cor pulmonale; Pulmonary HPE
9 55M	Aortic regurgitation; aortic aneurysm; HTN; HL; CHF; Admitted for aortic valve replacement → Cardiac Bypass	Acute PEA	Acute PEA; Anoxic brain injury	<ul style="list-style-type: none"> ■ Acute PEA ■ Anoxic brain injury 	Acute PEA; Pulmonary HPE; Anoxic brain injury
10 65M	Rectal CA s/p recent resection; CAD; HTN; HL; Recent pneumonia requiring IV Ab → CVC ; Arterial line	Acute pneumonia	Acute pneumonia	<ul style="list-style-type: none"> ■ Resolving perineal wound ■ Acute pneumonia ■ Acute hypoxemia ■ Acute PEA 	Acute pneumonia; Pulmonary HPE
11 61M	h/o CVA; MI; HTN; HL; CKD; Admitted for upper GI bleed/newly diagnosed signet ring CA (gastric) → CVC	Hemorrhagic shock; signet ring CA	Hemorrhagic shock; signet ring CA	<ul style="list-style-type: none"> ■ GI hemorrhage/signet ring CA ■ Hemorrhagic shock ■ ARDS ■ MODS 	Hemorrhagic shock; Signet ring CA; Pulmonary HPE
12 16M	Anomalous left coronary artery requiring surgical repair → ECMO ; Swan-Ganz	Acute cardiac tamponade; Pneumonia	Acute cardiac tamponade; Pneumonia	<ul style="list-style-type: none"> ■ Pulmonary hemorrhage ■ Pneumonia ■ Pulmonary embolism ■ Septic shock with MODS 	Cardiac tamponade; Pneumonia; Pulmonary HPE
13 60M	h/o CAD; DM; HL; ESRD on HD; Aortic stenosis; Schizophrenia; Admitted for acute MI → Hemodialysis ; CVC ; IVC Filter	Cardiogenic shock	Cardiogenic shock	<ul style="list-style-type: none"> ■ Cardiogenic shock ■ Pneumonia ■ DVT ■ MODS ■ Upper GI bleed 	Cardiogenic shock; Pulmonary HPE
14 47F	Rheumatoid arthritis; nonischemic cardiomyopathy; Admitted for CHF → CVC ; CVVH	Nonischemic cardiomyopathy	Nonischemic cardiomyopathy; Pneumonia	<ul style="list-style-type: none"> ■ Cardiogenic shock ■ MODS 	Nonischemic cardiomyopathy; Pneumonia; Pulmonary HPE
15 61M	COPD; esophageal ulcers; recent admission for cysturethroscopy; Readmitted for syncope → CVC ; Pulmonary Angiography	Pulmonary thromboembolism	Pulmonary thromboembolism	<ul style="list-style-type: none"> ■ Pulmonary thromboembolism 	^b Pulmonary thromboembolism; Pulmonary HPE

Case Age Sex	Comorbid Conditions and → Suspected Contributing Procedure(s)	Documented Clinical Cause of Death	Documented Cause(s) of Death on Original Autopsy	Documented Signs and Diagnoses (Final Month of Life)	Findings on Retrospective CP Review
16 48M	h/o Fournier's gangrene admitted for debridement → CVC	Septic shock	Septic shock; acute pulmonary hemorrhage	<ul style="list-style-type: none"> ■ Pneumonia ■ Pulmonary Embolism ■ Urinary tract infection ■ Gastrointestinal bleed ■ Possible DVT ■ Septic shock with MODS 	<i>b</i> Septic shock, Acute pulmonary hemorrhage; PNA; Pulmonary HPE
17 35M	HTN; CAD; HL; Admitted for acute type A aortic dissection → ECMO	Acute aortic dissection	Acute aortic dissection	<ul style="list-style-type: none"> ■ Acute MI ■ Acute aortic dissection ■ Anoxic brain injury ■ Cardiac tamponade ■ MODS 	Acute aortic dissection; Scattered cerebral infarcts; Pulmonary HPE
18 71M	h/o CAD; A. Fib; HL; PVD; Recent cardiac cath/stenting Recent lower extremity vascular bypass surgery → CVC; Lower Extremity Bypass; CVVH	Septic shock; CHF	Septic shock; CHF	<ul style="list-style-type: none"> ■ Septic shock ■ Rhabdomyolysis ■ Small bowel ischemia ■ MODS 	Septic shock; CHF Pulmonary HPE

Abbreviations: A, Fib, atrial fibrillation; B/L, bilateral; CA, adenocarcinoma; CABG, coronary artery bypass graft; CAD, coronary artery disease; cardiac cath, cardiac catheterization; CKD, chronic kidney disease; CP, clinicopathological; CVA, cerebral vascular accident; CVC, central venous catheterization; CVVH, continuous veno-venous hemofiltration; DIC, disseminated intravascular coagulation; DM, diabetes mellitus type II; DVT, deep venous thrombosis; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; HD, hemodialysis; HL, hyperlipidemia; h/o, history of; HPE, hydrophilic polymer emboli; HTN, hypertension; HL, hyperlipidemia; IV Ab, intravenous antibiotics; IVH, intravenous hydration; LAD, lymphadenopathy; MI, myocardial infarction; MODS, multiple organ dysfunction syndrome; OHT, orthotopic heart transplantation; PE, pulmonary embolism; PEA, pulseless electrical activity; PFO, patent foramen ovale; PICC, peripherally inserted central catheter; PNA, bronchopneumonia; R., right; RUL., right upper lobe of lung; RUQ, right upper quadrant; RVR, rapid ventricular response; SIRS, systemic inflammatory response syndrome; s/p, status post; SVT, supraventricular tachycardia; VSD, ventricular septal defect.

^a HPE may have been a primary cause of morbidity

^b "Rule out pulmonary embolism" specified on autopsy request

^c Scattered septic emboli were present, along with multifocal HPE

^d Mechanism of death is inconclusive (in addition to HPE, rare intravascular plant material is identified)

Table 3

Documented demographic, clinical, and laboratory or pathology findings in 136 patients without or with (all, multifocal, or localized) HPE.

	No HPE (n=118)	All HPE (n=18)	Multifocal HPE (n=6)	Local HPE (n=12)	P value ^d	
					All HPE	Local HPE
Demographic Data						
Age (years, mean)	56 ± 14	54 ± 17	62	50	0.66	
Sex (% male)	53	78	83	75	0.07	
Hospital days (mean, current admission)	26	46	56	42	0.008*	0.09
ICU days (mean, current admission)	13	25	39	19	0.01*	0.40
Total admissions (mean, prior year)	2	2	2	2	0.99	
Vascular procedures (mean)						
Total vascular interventions	4 ± 3.5	7 ± 5.5	8	6	0.01*	0.08
Left heart/arterial interventions	2 ± 1.3	2 ± 1.8	2	2	0.16	0.40
Right heart/venous interventions	3 ± 2.6	5 ± 3.6	6	4	0.008*	0.07
Central catheters	2 ± 1.7	3 ± 1.7	3	3	0.03*	0.14
Other right heart and venous	2 ± 1.0	2 ± 1.9	3	2	0.05	0.02*
Autopsy tissue blocks examined (mean)						
Total blocks	34 ± 14	41 ± 10	40	42	0.06	
Lung blocks	6 ± 3	7 ± 3	7	7	0.16	
Heart blocks	6 ± 5	7 ± 3	8	6	0.88	
Central nervous system blocks	10 ± 8	10 ± 7	9	11	0.74	
Clinical Sign or Symptom Prior to Death^d						
Constitutional symptoms ^b	46 (39%)	14 (78%)	6 (100%)	8 (67%)	0.002*	0.003*
Multiple organ dysfunction syndrome (MODS)	20 (17%)	14 (78%)	5 (83%)	9 (75%)	<0.0001*	<0.0001*
SIRS/sepsis	38 (32%)	10 (56%)	5 (83%)	5 (42%)	0.054	0.01*
Suspected pulmonary embolism	14 (12%)	8 (44%)	3 (50%)	5 (42%)	0.006*	0.008*
Thrombo/embolic stroke	19 (16%)	3 (17%)	2 (33%)	1 (8%)	0.95	0.005*

	No HPE (n=118)	All HPE (n=18)	Multifocal HPE (n=6)	Local HPE (n=12)	P value ^d	
					All HPE	Local HPE
Suspected vasculitis	1 (1%)	2 (11%)	2 (33%)	0 (0%)	0.006*	<0.0001*
Lymphadenopathy	20 (17%)	2 (11%)	2 (33%)	0 (0%)	0.53	
Acute cardiac arrhythmia/PEA	24 (20%)	2 (11%)	0 (0%)	2 (17%)	0.35	
Laboratory or Pathology Finding^{d,ss}						
Leukocytosis	94 (80%)	18 (100%)	6 (100%)	12 (100%)	0.035*	
↑ D-dimer ↑ fibrin split products ↓ fibrinogen	20 (17%)	6 (33%)	4 (67%)	2 (17%)	0.10	0.002*
Acute pulmonary infarct(s)	5 (4%)	5 (28%)	3 (50%)	2 (17%)	<0.0001*	<0.0001*
Acute focal cerebral infarct(s)	8 (7%)	4 (22%)	3 (50%)	1 (8%)	0.03*	0.0002
↑ Erythrocyte sedimentation rate (ESR)	2 (2%)	2 (11%)	2 (33%)	0 (0%)	0.03*	0.0001*
↑ C-reactive protein (CRP)	2 (2%)	3 (17%)	2 (33%)	1 (8%)	0.002*	0.0001*
↑ p-ANCA	1 (1%)	1 (6%)	1 (17%)	0 (0%)	0.12	0.003*
↑ c-ANCA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A	

Plus-minus values are means ± SD; **Abbreviations:** DIC, disseminated intravascular coagulation; HPE, hydrophilic polymer emboli; ICU, intensive care unit; PEA, pulseless electrical activity; SIRS, Systemic inflammatory response syndrome

^c Indicates patients with documented abnormality (not all patients were tested)

^d Indicates number of patients, and percent

^b Defined by fevers, chills, malaise, and sweats or weight loss

^d P values are based upon comparison of patients with no HPE

* Indicates P<0.05