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Histopathological assessment of fatal ipsilateral intraparenchymal hemorrhages after the treatment of supraclinoid aneurysms with the Pipeline Embolization Device

Report of 3 cases

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Object. Delayed ipsilateral intraparenchymal hemorrhage has been observed following aneurysm treatment with the Pipeline Embolization Device (PED). The relationship of this phenomenon to the device and/or procedure remains unclear. The authors present the results of histopathological analyses of the brain sections from 3 patients in whom fatal ipsilateral intracerebral hemorrhages developed several days after uneventful PED treatment of supraclinoid aneurysms.

Methods. Microscopic analyses revealed foreign material occluding small vessels within the hemorrhagic area in all patients. Further analyses of the embolic materials using Fourier transform infrared (FTIR) spectroscopy was conducted on specimens from 2 of the 3 patients. Although microscopically identical, the quantity of material recovered from the third patient was insufficient for FTIR spectroscopy.

Results. FTIR spectroscopy showed that the foreign material was polyvinylpyrrolidone (PVP), a substance that is commonly used in the coatings of interventional devices.

Conclusions. These findings are suggestive of a potential association between intraprocedural foreign body emboli and post-PED treatment–delayed ipsilateral intraparenchymal hemorrhage.
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Key Words • **Pipeline Embolization Device** • **aneurysm** • **hemorrhage** • **vascular disorders**

The Pipeline Embolization Device (PED) (ev3-Covidien) is an effective tool in the treatment of complex intracranial aneurysms of the anterior circulation and is generally associated with a low complication rate.[4,5] A recently noted phenomenon is delayed ipsilateral intraparenchymal hemorrhage (IPH) observed in patients days to weeks after the uneventful treatment of their aneurysms.[7] Although the incidence of IPH appears low, sporadic, and unpredictable, the pathophysiology of this adverse event has been difficult to elucidate. The present report details histopathological findings derived from 3 separate cases of delayed ipsilateral IPH that resulted in death. All 3 deaths occurred after uneventful treatment with the PED. Occlusive foreign embolic material identified as polyvinylpyrrolidone (PVP), which is a material used in the coating of interventional tools, was found in the vasculature of the hemorrhagic regions in all 3 patients and on the PEDs in 2 of the patients. This report is the first to describe the histopathological findings of autopsy specimens obtained from patients with delayed IPH following uneventful treatment with the PED.

Abbreviations used in this paper: COCOA = Complete Occlusion of Coilable Aneurysms; FTIR = Fourier transform infrared; IPH = intraparenchymal hemorrhage; PED = Pipeline Embolization Device; PITA = Pipeline for the Intracranial Treatment of Aneurysms; PUFS = Pipeline for the Treatment of Uncoilable and Failed Aneurysms; PVP = polyvinylpyrrolidone.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

Case Reports

Case 1

During an evaluation for sinusitis, a 73-year-old man with a history of chronic leukocytic leukemia was found to have an incidental left paraophthalmic artery aneurysm (Fig. 1). The patient's cardiovascular history included hyperlipidemia treated with atorvastatin, but he was a nonsmoker with no history of hypertension. After a discussion of options, the patient expressed his wishes to have the aneurysm treated by endovascular means. A single PED was successfully deployed, reconstructing the left internal carotid artery. The patient was discharged to home neurologically intact the morning after the procedure. Three days later, he experienced a syncopal episode and died of a large left IPH. At autopsy, the brain was removed for neuropathological examination and the left internal carotid artery, encased in the sphenoid and petrous portion of the temporal bone, was removed, placed in formalin, and sent for histological analysis (CVPath Institute, Inc., Gaithersburg, MD).

Case 2

A 63-year-old woman, with a family history of subarachnoid hemorrhage and clipping of bilateral intracranial aneurysms, was known to have a small, approximately 5-mm, medially directed, unruptured left paraophthalmic segment aneurysm (Fig. 2A). After a discussion of the treatment options, the patient elected to have the aneurysm treated with the PED. The left internal carotid artery was successfully reconstructed with a single PED. The patient was discharged to home the following day and remained neurologically intact during the immediate postoperative period and the ensuing 5 days. On postoperative Day 6, she experienced precipitous neurological decline, and CT scanning demonstrated a large ipsilateral IPH that proved ultimately fatal (Fig. 2B). At autopsy, the brain was removed for neuropathological examination, and the left internal carotid artery was explanted en bloc with the left-side portion of the skull base, placed in formalin, and sent for histological analysis (CVPath Institute, Inc.).

Case 3

A 66-year-old woman, a smoker with mild chronic obstructive pulmonary disease and well-controlled hypertension, was found to have an incidental 13-mm left paraophthalmic artery aneurysm. The aneurysm was partially thrombosed and heavily calcified (Fig. 3A and B). Her treatment was initially uncomplicated and consisted of placement of two PEDs (Fig. 3C and D). She was seen by her primary care physician 5 days after the PED procedure, and her blood pressure was recorded as 128/82 mm Hg. Approximately 2 weeks posttreatment, she died of a large ipsilateral IPH centered in the left frontal lobe. At autopsy, the brain was removed for neuropathological evaluation. The petrous portion of the temporal bone encasing the left internal carotid artery was placed in formalin and sent for histological analysis (CVPath Institute, Inc.).

Operative Techniques

All patients were treated with 325 mg aspirin and 75 mg clopidogrel at least 72 hours prior to placement of the PED. All treatments were performed under general anesthesia and with intraoperative monitoring (somatosensory evoked potentials and electroencephalography) in a biplanar fluoroscopic angiography suite. Femoral access was achieved with an 8-F, 65-cm Super Arrow-Flex sheath (Arrow) through which a 6-F, 90-cm Flexor Shuttle Select Guiding Sheath (Cook Medical) was placed (Cases 1 and 3) or directly with a Cook 6-F Shuttle Guiding Sheath alone. In Case 1, the Cook introducer was advanced into the target carotid artery coaxially with a 6-F Neuron guide catheter over an Anplatz exchange wire. In Cases 2 and 3 the Guiding Sheaths were advanced into the carotid arteries over a Cook 5-F Slip-Cath (Vitek or JB-1) using a

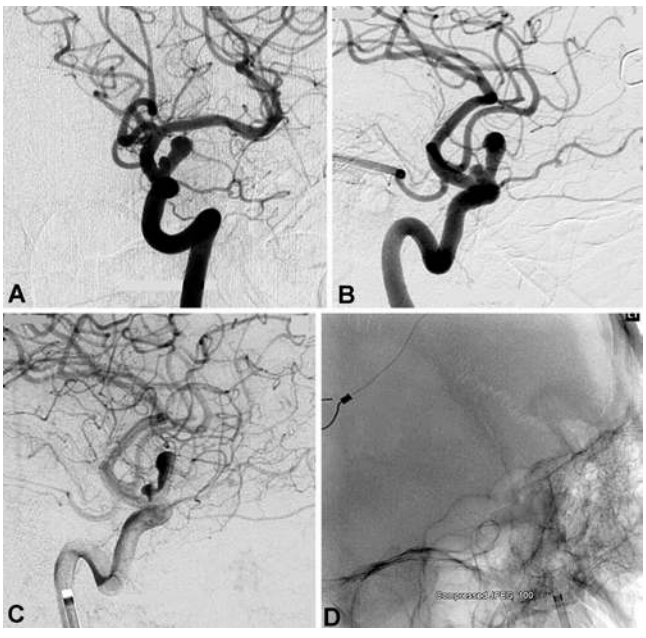

Fig. 1. Case 1. **A and B:** Cerebral angiograms demonstrating working angles for PED reconstruction of a left paraophthalmic artery aneurysm. **C:** Post–PED placement angiogram revealing the stagnation of contrast within the aneurysm. **D:** Subtracted lateral view outlined the course of the PED stent.

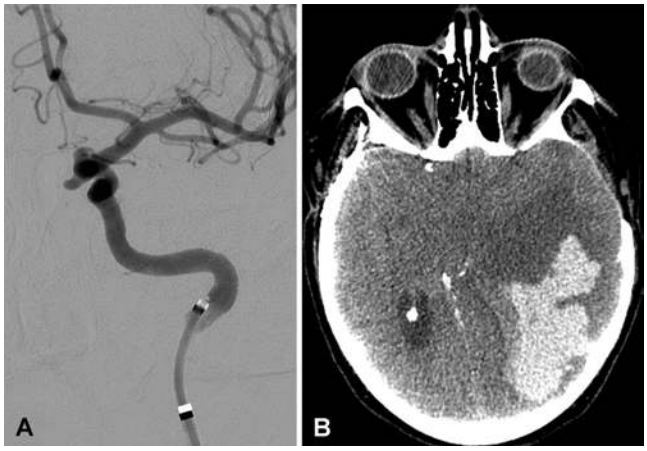

Fig. 2. Case 2. Pre–PED placement angiogram **(A)** showing left paraophthalmic segment aneurysm, and CT image **(B)** obtained after intracranial hemorrhage.

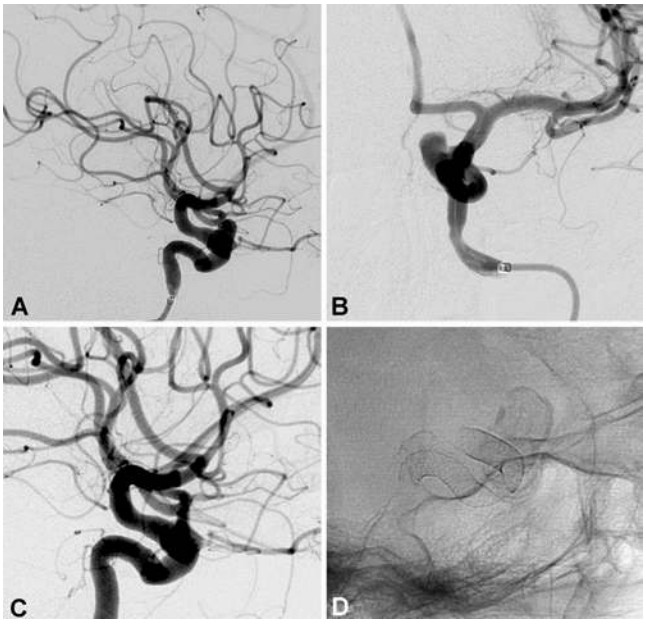

Fig. 3. Case 3. Angiograms obtained before **(A and B)** and after **(C)** PED placement for the endovascular treatment of a calcified partly thrombosed left paraophthalmic artery aneurysm. Unsubstracted lateral angiogram **(D)** shows the outline of the PED stent.

standard 0.035-in Benston or a Glidewire. In Cases 1 and 3, a 6-F, 105-cm Neuron guide catheter was maneuvered into the distal petrous segment of the intracranial carotid artery. In the patient in Case 2, a 6.3-F 105-cm DAC 070 distal access catheter (Concentric Medical) was used for intracranial access.

At this point, conventional and 3D cerebral angiography studies were acquired.

Intravenous heparin was administered to achieve an activated clotting time of between 250 and 300 seconds. A Marksman or Renegade HI-FLO microcatheter was introduced and manipulated under high-magnification fluoroscopic roadmap imaging beyond the aneurysm into the ipsilateral M_1 segment. In Case 1, a 5-mm × 20-cm PED was used. The patients in Cases 2 and 3 were both treated with two PEDs placed in a telescoping fashion. In Case 2, both devices were 4 × 20–mm PEDs; and in Case 3, 3.75 × 20–mm and 4 × 20–mm devices were used. In Cases 2 and 3, the PED did not fully expand, and balloon angioplasty was employed to optimally appose the stent against the parent vessel wall. Devices common to all 3 procedures were the 0.35-in Glidewire (Terumo), the 0.014-in Synchro microguidewire (Stryker), and the Cook Shuttle Guiding Sheath.

Results

Three patients (1 man and 2 women) whose mean age was 66 years underwent elective treatment for paraclinoid region aneurysms of varying sizes (mean size 10.2 mm, range 5–13.3 mm) with the PED. All 3 patients emerged from general anesthesia at their neurological baseline, and all were discharged to home the following day. Death from a delayed ipsilateral IPH occurred in all patients between 3 and 14 days after the procedure (mean 7.7 days).

In all patients, postmortem examination revealed a large IPH ipsilateral to the implanted PED. In all 3 cases, the target aneurysms were intact, and there was no evidence of rupture or aneurysm hemorrhage (Figs. 4 and 5). The hemorrhages were anatomically remote from the implanted devices and treated aneurysms.

In all 3 cases, histopathological evaluation of the brain parenchyma demonstrated coiled filamentous, basophilic staining, nonpolarizable, nonbiological material occluding the lumen of vessels where the material was present (Figs. 6–8). The vessels were typically about 100 μm in diameter at the level of the occlusions. The material was distributed only within vessels in the region of the observed hemorrhage. Vessels in the unaffected regions of the brain were spared. The embolic inclusions seen in Case 2 were more extensive than those in the other cases. Free inclusions not associated with vessels were also noted within areas of extensive hemorrhage (Fig. 8E). Inflammation associated with the foreign inclusion was absent or minimal, with no indication of foreign body granulomas.

Notably, many postcapillary venules showed attenuation of the tunica media with extravasated erythrocytes (Fig. 6B and 8A–D). These findings suggest that a rise in venule pressure as a result of foreign body embolic occlusion may have been responsible for the increased microvascular permeability and resultant hemorrhagic infarction.

In Cases 1 and 2 (Fig. 9), a large amount of the same material was also found on the cavernous portion of the PED stent. There was no evidence of large anoxic territories in the peri-regional brain tissue.

The foreign embolic material found in the patients in Cases 1 and 2 was analyzed using Fourier transform infrared (FTIR) spectroscopy. This analysis was performed by McCrone Associates, Inc., of Westmont, IL. The amount of material in Case 3 was insufficient for FTIR spectroscopy. The material was identified as polyvinylpyrrolidone (PVP; also known as povidone), a hydrophilic material used in the coating on a variety of commonly used interventional devices but not used on the PED itself.

Discussion

Delayed ipsilateral IPH after endovascular reconstruction of cerebral aneurysms with the PED represents a significant potential limitation of this device. This limitation is particularly true given that PED reconstruction is usually performed electively for unruptured aneurysms and because a significant proportion of the aneurysms within the labeled indication for use are extradural, involving the cavernous and petrous segments of the internal carotid artery. Establishing the relationship of IPH to the device and/or the procedure, defining its incidence, and understanding its mechanism have been, and remain, challenging.

The most important finding of the present case series is the presence of occlusive, intraarterial, foreign body emboli identified within the region of the IPHs in each of 3 cases in which histopathological evaluation of brain specimens obtained at autopsy was performed. In 2 of the 3 patients, the same foreign embolic materials were found on the PED stents covering the treated aneurysms. As noted above, PVP is a commonly used coating, and

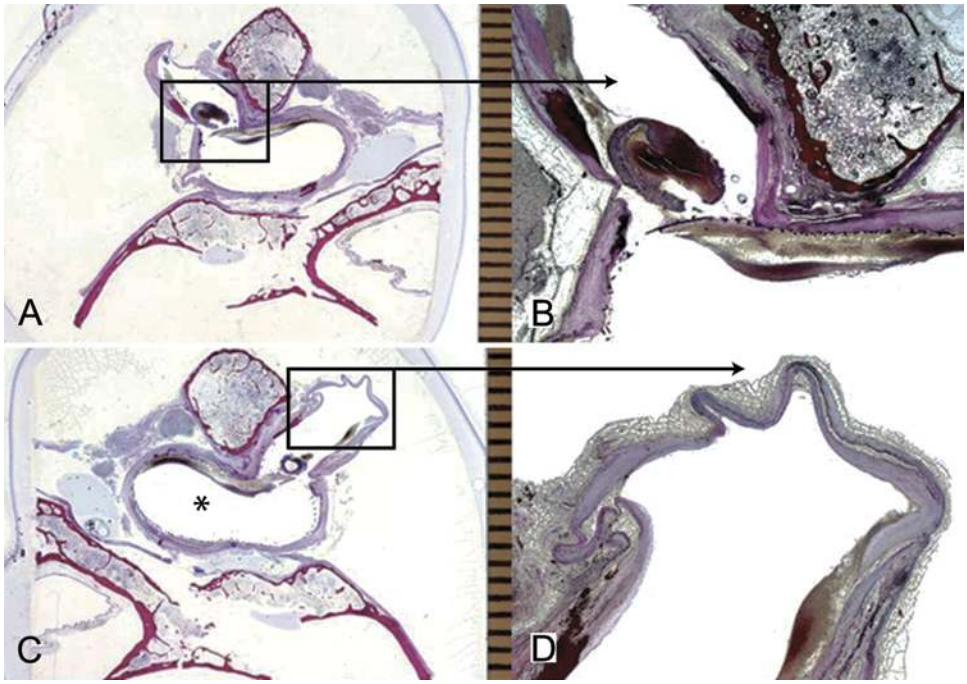

Fig. 4. Case 1. Histological sections of the internal carotid artery *(asterisk)* showing the stent struts to be well apposed to the vessel wall with minimal peri-strut fibrin thrombus deposition. Complete coverage of the neck of the aneurysm by the PED stent can be visualized **(A and B)**. Low-power **(C)** and high-power **(D)** magnification photomicrographs demonstrating the intact dome of the aneurysm. All sections: plastic embedded using EXAKT Micro-Grinding system, polished and stained with Toluidine Blue O/basic fuchsin. Magnifications not available.

further analysis using FTIR spectroscopy confirmed the embolic materials to be identical to the coating of the Cook Shuttle Guiding Sheaths, as collected in the demonstration videos linked to this report (Videos 1 and 2). These data potentially provide some insight into the etiology of this complication.

Video 1. Video montage of 3 separate instances of SlipCaths being withdrawn from Cook Flexor Shuttle Select Guiding

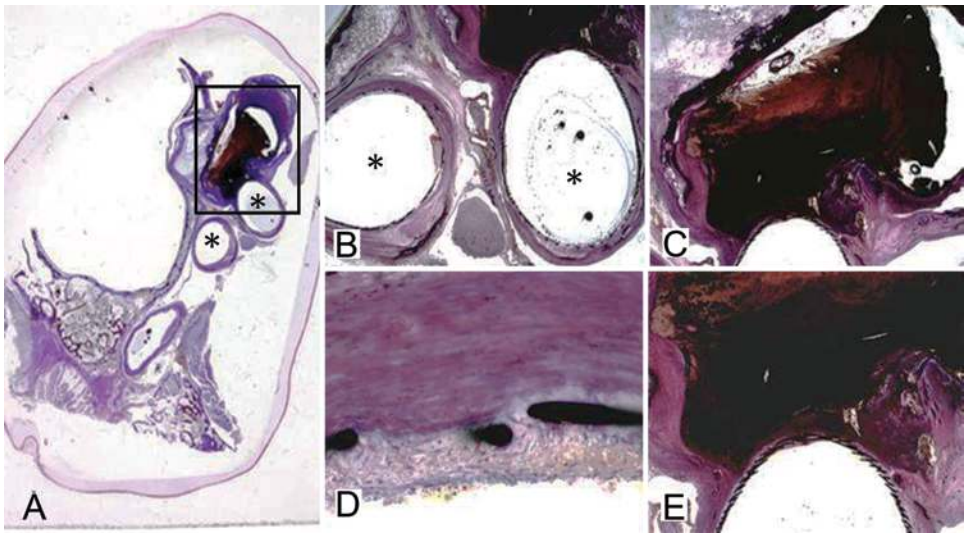

Fig. 5. Case 3. Histological sections of the internal carotid artery *(asterisks)* demonstrating the stent to be well apposed to the vessel wall. **A–C:** The PED stent completely covers the orifice of the aneurysm with organized thrombus on the outer surface of the stent. Area in *box* shown in A contains sectioned parent carotid artery with PED covering the aneurysm neck and, beyond that, the intact aneurysm dome. Higher magnification views of this enclosed area are shown in C, D, and E. **C and E:** Photomicrographs showing that the dome of the aneurysm consisted of organized mural thrombus with calcification, while the center predominantly contained unorganized thrombus. **D:** A thin neointima with minimal inflammatory reaction, including lymphocytes, histiocytes, eosinophils, and rare giant cells, as well as focally adherent platelets on the luminal surface. All sections: plastic embedded using EXAKT Micro-Grinding system, polished and stained with Toluidine Blue O/basic fuchsin. Magnifications not available.

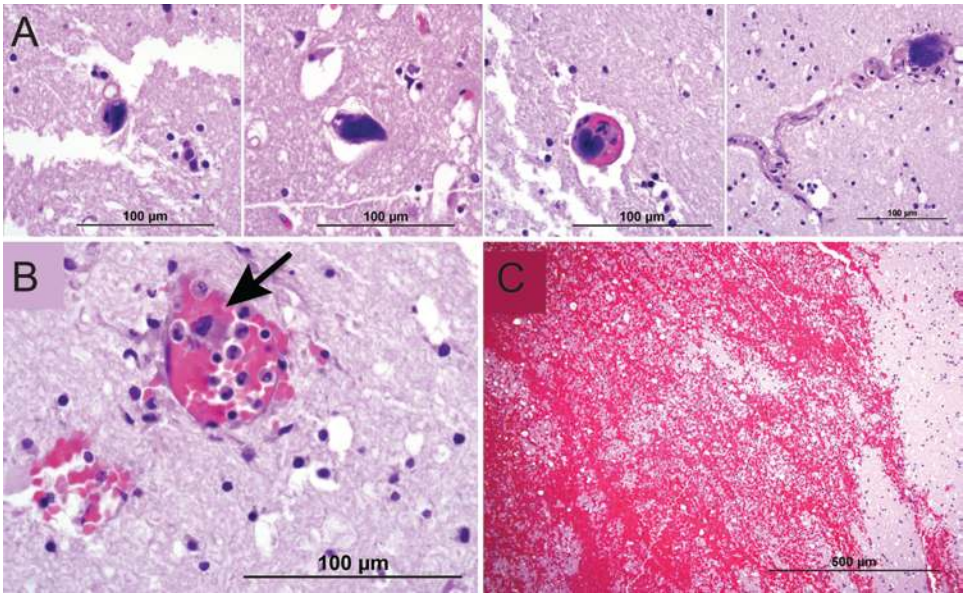

Fig. 6. Case 1. **A:** Histological sections showing multiple foci of embolic vascular inclusions. **B:** Intracerebral vessel (venule) exhibiting attenuation of the medial wall *(arrow)* with extravasated erythrocytes. **C:** Hemorrhagic infarction. H & E.

Sheaths, resulting in residue of foreign material at the tip of the Shuttle Select introducers. Copyright Barrow Neurological Institute. Published with permission. Click here to view with Media Player. Click here to view with Quicktime.

Video 2. Withdrawal of Slip-Cath from the Cook Flexor Shuttle Select Guiding Sheath, leaving residue of foreign material in the rotating hemostatic valve. Copyright Barrow Neurological Institute. Published with permission. Click here to view with Media Player. Click here to view with Quicktime.

Incidence of Delayed Ipsilateral IPH After PED Reconstruction

The existing data indicate that delayed IPH after PED reconstruction of the carotid artery seems to be relatively uncommon. In the Pipeline for the Treatment of Uncoilable and Failed Aneurysms (PUFS) Trial, 5 delayed IPHs (4.6%) were reported during the treatment of 108 cases.[4] All hemorrhages were ipsilateral to the reconstructed artery. One was thought to have resulted from trauma sustained during a fall. One additional PUFS trial patient was reported to have had unexplained sudden death that was presumed to be cardiac in etiology but was never confirmed to be nonneurological by imaging or autopsy. In the Pipeline for the Intracranial Treatment of Aneurysms (PITA) study, no delayed ipsilateral IPHs were observed during the treatment of 29 anterior circulation aneurysms.[17] In the Complete Occlusion of Coilable Aneurysms (COCOA) study, 8 patients were randomized to treatment with the Pipeline device and 1 experienced a fatal delayed ipsilateral IPH.[12] While additional cases of delayed ipsilateral hemorrhage have also been reported in the literature[7,21] and presented at scientific meetings, these individual reports have been sporadic and not useful for establishing the incidence of this complication. Thus, with consideration given to the PUFS, COCOA, and PITA data, 6 cases of delayed ipsilateral IPH observed in a population of 145 patients with Pipeline-treated anterior circulation aneurysms yields an incidence of 4.1%, with a 95% confidence interval (with continuity correction) ranging between approximately 1.7% and 9.2%. This rate is consistent with the 3% IPH rate reported in the meta-analysis of Brinjikji et al.[5] By contrast, in our prospectively analyzed experience with over 120 patients treated consecutively at Barrow Neurological Institute since FDA approval of the device, no delayed ipsilateral IPHs have been observed.

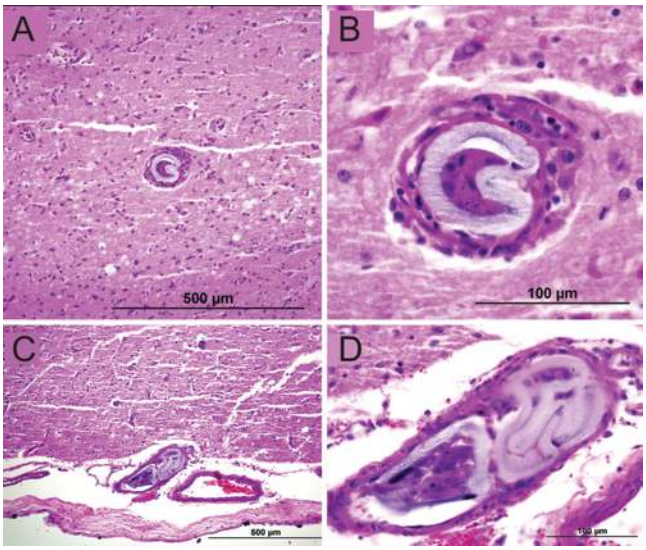

Fig. 7. Case 2. Low-power **(A)** and high-power **(B)** photomicrographs of an intraarteriolar vascular inclusion. Low-power **(C)** and high-power **(D)** photomicrographs demonstrating obstructive vascular inclusions also found in vessels within the leptomeningeal circulation. H & E.

Putative Mechanisms of Delayed Ipsilateral IPH

Putting aside for a moment the observation of intravascular foreign body material in the present series of patients, several common characteristics among the cases provide

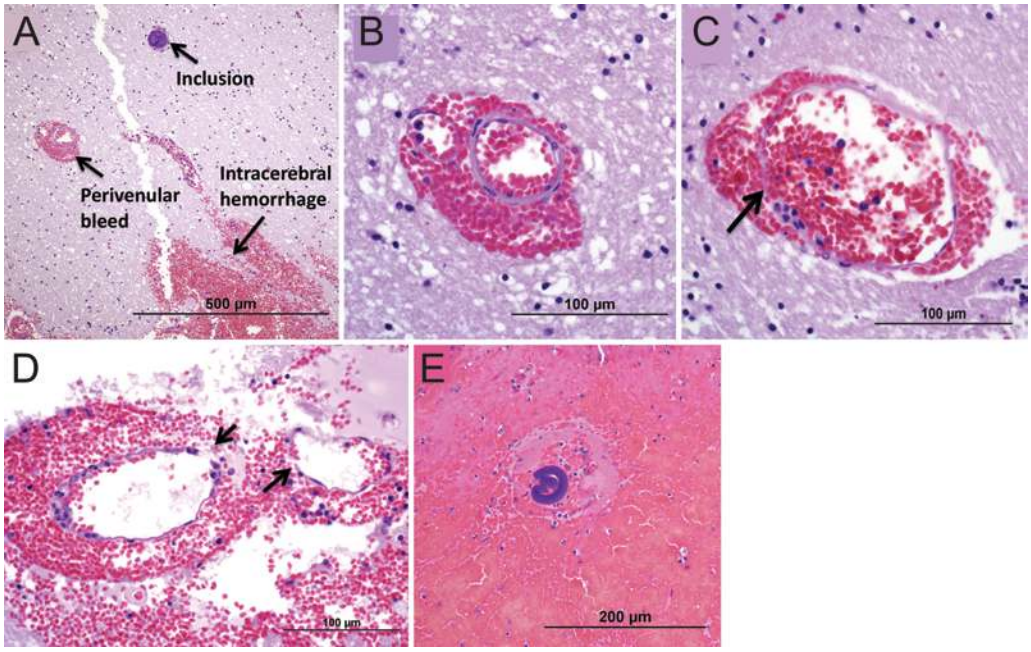

Fig. 8. Case 2. Photomicrographs showing a foreign body inclusion near a region of intracerebral hemorrhage. **A–D:** Small venules exhibiting perivenular bleeding with extravasated erythrocytes and intracerebral hemorrhage. The *arrows* in panels C and D show attenuation of the venule wall. **E:** Free foreign body inclusion within an area of intracerebral hemorrhage. H & E.

insight into potential mechanisms for delayed IPH. It is difficult to attribute the observed bleeds to hemorrhagic conversion of bland periprocedural infarcts. The lack of any major focal neurological deficits preceding the ictal clinical presentation and the absence of large territories of acute stroke on pathological examination of the brain tissue suggests that the observed delayed IPHs are not likely to be attributable to hemorrhagic conversion of large procedural or postprocedural strokes. The incidence of small, nonclinically evident, diffusion-positive periprocedural infarcts following endovascular procedures has been reported in 20%–70% of patients after endovascular aneurysm treatment.[1,2,6,18,20] Even in patients receiving postprocedural dual antiplatelet therapy, it is highly unusual for these lesions to spontaneously evolve into clinically evident IPHs. In a series of 284 patients treated with the Neuroform stent, only 3 spontaneous delayed IPHs were observed, and only 1 of these was ipsilateral to the stented artery.[10] A delayed presentation of technical/procedural complications, such as distal microwire perforation, is also an inadequate explanation for these observations, given the considerable delays between the procedure and the hemorrhagic ictus.

Dual antiplatelet medications alone are a risk factor for spontaneous IPH, but the rates of cerebral hemorrhage associated with these agents are substantially lower than those observed after PED reconstruction. For example, in the MATCH trial, stroke patients treated with both aspirin and clopidogrel had a 1.1% rate of intracranial hemorrhage over the 18-month study period.[8] The rates observed in the available prospective series (PUFS, COCOA, and PITA) are approximately 4 times as high, and all occurred within an observation period of only 2 weeks. In addition, if the observed hemorrhages were a sequela of antiplatelet therapy alone, it would be extremely improbable for all events to occur in a distribution ipsilateral to the reconstructed vessel.

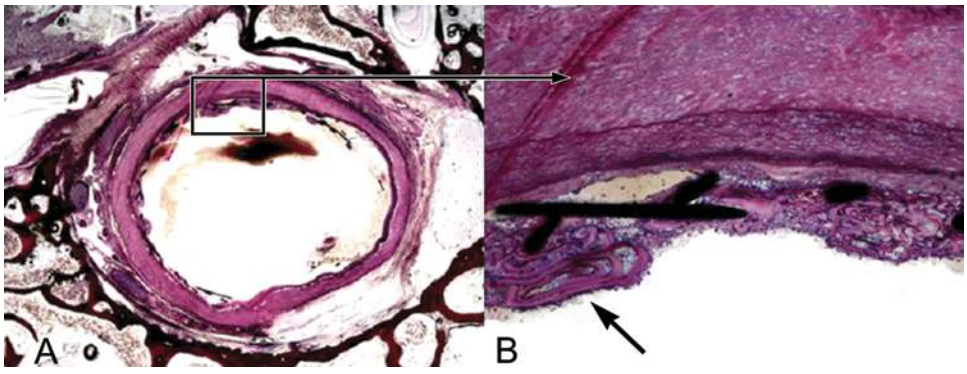

Fig. 9. Case 2. Low-power **(A)** and high-power **(B)** photomicrographs of the cavernous segment of the PED showing hydrogel *(black arrow)* on the luminal surface of the PED. All sections: plastic embedded using EXAKT Micro-Grinding system, polished and stained with Toluidine Blue O/basic fuchsin. Magnifications not available.

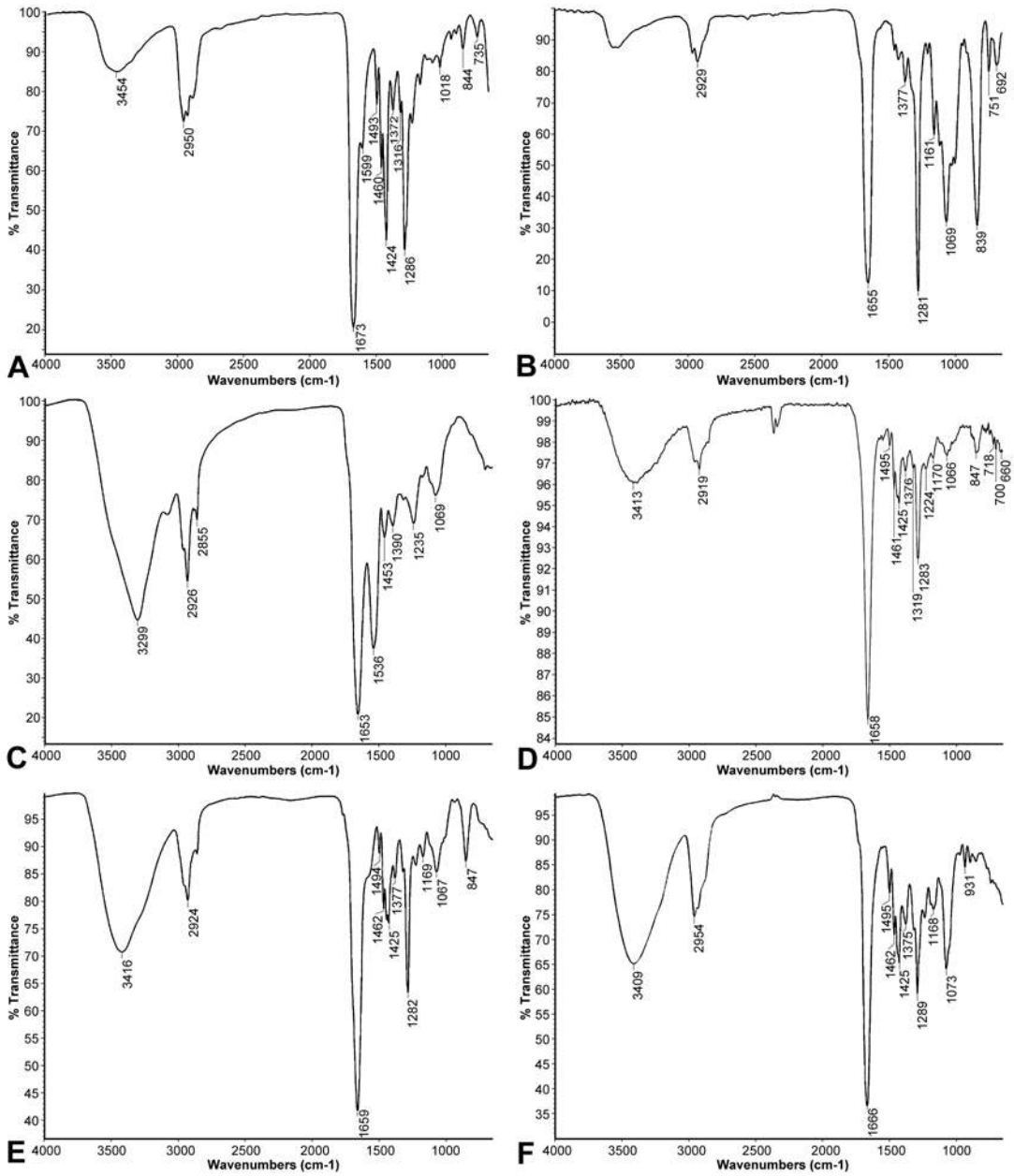

Fig. 10. Absorption band spectra from FTIR spectroscopy of PVP **(A)**, collodion **(B)**, normal tissue **(C)**, inclusion materials from Cases 1 **(D)** and 2 **(E)**, and debris from Shuttle/Slip-Cath system **(F)**. Specifically, the absorption bands within the 1500–1400-cm^{-1} band, specific for PVP, are identical to those in Cases 1 and 2 and to the debris from the Shuttle/Slip-Cath system. The corresponding PVP bands are not visualized on FTIR spectroscopic analysis of collodion or of normal tissue.

It has been speculated that flow diverters may alter the arterial pulse pressure wave (the Windkessel effect) and thereby in some manner predispose patients to downstream hemorrhages, but no data to support this speculation have been published.

Potential Sources of the Foreign Embolic Materials

The discovery that foreign embolic materials were found in the vasculature of the hemorrhagic regions distal to the PEDs in all 3 of our patients raises significant concerns, and potentially imposes limitations on neuroendovascular interventions. Histological analysis of the emboli revealed a nonpolarizable, tortuous, coiled material that stained strongly with basic fuchsin. The appearance of these emboli strongly suggests the shedding of the hydrophilic coatings that are ubiquitous among the catheters, guidewires, and coils. A comparison of the procedures performed among the 3 patients from two different institutions (Barrow Neurological Institute and Oregon Health & Science University) identified 3 common items that were used: the 6-F Cook Shuttle, the 0.035-in Glidewire, and the 0.014-in Synchro microwire.

Using FTIR spectroscopy, the foreign emboli within the hemorrhagic regions of the patients were identified as PVP, a material commonly used in the outer coating of many interventional devices. Shavings of the coatings

shed during benchtop manipulation of the Cook Shuttle/Slip-Cath combination were collected. The fragments were confirmed by FTIR to be of the same material—that is, PVP. Whether there is a cause-and-effect relationship in the development of delayed ipsilateral IPHs and PVP is difficult to determine since data pertaining to the biological effects of PVP on cerebral vasculature are very limited.

Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectroscopy represents an extremely useful tool for identifying unknown organic compounds. The distinctive collection of absorption bands provides a "fingerprint" of the compound and confirms the identity of a pure compound or detects the presence of specific impurities. Fourier transform infrared spectroscopy is a third-generation infrared spectroscopy tool and provides several prominent advantages over earlier-generation FTIR as follows: 1) improved signal-to-noise ratio, 2) extremely high resolution and accuracy, 3) wide scan ranges, and 4) reduced interference from stray light.

For control samples, collodion (nitrocellulose in transfer medium), normal tissue on the slides, and the Cook Shuttle/Slip-Cath debris (collected as demonstrated in Videos 1 and 2) were prepared and compared with the isolated foreign inclusions identified on the pathology slides of specimens collected in Cases 1 and 2. The pathological tissues with the inclusions were dissolved with bleach, leaving the inclusions for definitive FTIR analysis.

Absorption band spectra were obtained from PVP, collodion, normal tissue, and the inclusions in the pathological samples from Cases 1 and 2, as well as from the debris collected from the Shuttle/Slip-Cath system (Fig. 10A–F). The absorption bands confirmed that the debris (Fig. 10F) obtained from the Shuttle/Slip-Cath system was PVP (Fig. 10A). The absorption band spectra of collodion (Fig. 10B) and PVP (Fig. 10A) have some similarity (bands near 1680–1650 cm^{-1} and 1290–1280 cm^{-1}), but the remaining bands in the spectra are sufficiently different to detect the presence of PVP in the 1500- to 1400-cm^{-1} region. Compared with the PVP absorption bands, analyses of the inclusions in the samples from Cases 1 (Fig. 10D) and 2 (Fig. 10E) after the tissues were dissolved conclusively identified these emboli to be PVP.

Biological Effects of Foreign Hydrophilic Emboli on the Vasculature

In the interventional cardiology literature, the findings of hydrophilic embolic material and reactions in the periarterial spaces from the Cook introducer sheath have been well described. It is generally accepted that shedding can occur during the twisting and sliding of the sheath as it is inserted into the radial artery. Furthermore, many series have reported the delayed appearance of granulomas in the perivascular soft tissues surrounding the radial artery, with some patients requiring excisions of the vessel and the granulomas. In the 37 reported cases of radial artery lesions, the time frame for granuloma presentation was between 3 days and 3 months. Interestingly, most occurred within 2 weeks after the procedures. Ceasing to use this hydrophilic-coated sheath has resulted in the disappearance of this complication.[9,13,22,23]

There have been previous reports of catheter coating resulting in emboli in the cerebral and other vascular territories,[3,16] but few studies have reported on the biological effects of PVP and its derivatives on the cerebral vasculature. Polyvinylpyrrolidone is generally considered safe and has been approved by the FDA. It is commonly used in other products including plasma expanders, resins in hair sprays, and as a binder in pharmaceutical tablets.

Autopsies of the pulmonary vasculature of drug users who intravenously injected aqueous suspensions of tablets intended for oral consumption have demonstrated pulmonary injuries due to crospovidone, an insoluble polymer of PVP.[11] Crospovidone causes angiothrombosis, foreign body granulomatosis, and granulomatosis angiitis leading to vascular injuries.

In the current series, the disintegration of vessel walls resulting from foreign body reactions to the hydrophilic emboli may explain the cause of these patients' ipsilateral intracerebral hemorrhages, although no such granulomatous changes were identified. The risk of IPH is certainly increased with the weakening and disruption of the surrounding vasculature. This situation would account for the observed delayed presentation as the integrity of the vessel walls became weakened and ultimately led to vessel rupture and IPH. The fact that these patients often have other comorbidities (for example, age, vasculopathy, and hypertension) should be taken into consideration. The vasculature in these patients is often diseased and more readily susceptible to further damage. Since no clinical ictuses were observed preceding the sudden fatal events and no large vascular infarcts were identified in the autopsy examinations, the current findings support our proposed pathomechanism. Combined with dual antiplatelet therapy, the severity of the hemorrhages was magnified in these patients and unfortunately resulted in death.

Arguments Against the Emboli as the Sole Cause of the Hemorrhages

In previous documentations of similar intravascular embolic material in patients undergoing other neurointerventional procedures, associated hemorrhages have been rarely observed. Barnwell et al. reported 4 patients in whom, at autopsy, foreign bodies were found in small arteries after neurointerventional procedures, and they noted only 1 patient who suffered thalamic hemorrhages.[3] The other 3 patients presented with infarctions. Mehta et al. reported remote intravascular hydrophilic emboli found in a patient after embolization of a giant intracerebral aneurysm.[15] Widespread infarcts were noted on autopsy. Other case series including peripheral interventional procedures reported ischemic events within the respective organs, and hemorrhagic events at autopsy were rarely encountered.[16] However, dual antiplatelet therapy was not part of the treatment regimen and may account for the differences in the presentations.

Challenges to the Recognition of Delayed Ipsilateral IPH as a Complication of PED Reconstruction

The relationship of the delayed IPH to the device and

procedure is not straightforward. With the incidence of delayed IPH approximately at 4%, it is statistically possible for a given operator to have performed more than 25 cases without seeing a single delayed IPH. The hemorrhages are anatomically remote from the aneurysm and not attributable to aneurysm rupture or device erosion through, or perforation of, the parent artery. The patients are on dual antiplatelet medications after the procedure—agents that predispose patients to intracranial hemorrhage. These patients are often older and have other significant comorbidities that could place them at risk for spontaneous IPH (for example, poorly controlled hypertension and vasculopathy). Given the uncommon, unpredictable, delayed, and sporadic incidence of the hemorrhages, it may not be intuitively obvious to the operator that these events are related to the procedure. For this reason, it is likely that, within the context of commercialization and widespread use of the device, these hemorrhages are underreported. It is similarly possible, if not likely, that a higher index of suspicion and lower threshold for when to perform pathological evaluation would lead to more frequent identification of foreign embolic material as a possible contributing factor in the appearance of delayed IPHs.

Implications of the Current Findings

The finding of cerebral PVP emboli is a cause for serious concern. The association of these emboli with hemorrhages does not prove causality, but it is equally plausible that some of the ischemic events that occur after neurointerventional procedures, whether clinically silent or apparent, are the consequence of unrecognized PVP embolizations that fortunately do not go on to cause hemorrhage. Failure to identify PVP as a source of ischemia would not be surprising, because even at autopsy the findings are sufficiently subtle such that, in our Case 3, the foreign material was not noted at the time of the initial pathological examination. Case 2 was examined specifically looking for emboli because of the prior findings in Case 1, and after confirmation of the findings in Case 2, the autopsy material preserved from Case 3 was reexamined, leading to discovery of the previously overlooked embolic material.

In attempting to understand the phenomenon of post–PED treatment IPHs, we, like many others, have speculated that the use of dual antiplatelet medications must play a central role. A puzzling aspect with this line of thought is that these same dual antiplatelet medications are routinely used with stent-assisted aneurysm coiling, but delayed ipsilateral IPHs have not been linked to stent-assisted coiling. Similarly, PVP is widely used as a coating on catheters and guidewires, so it is probable that some of this material is released into the cerebral circulation in both stent-assisted coiling cases and in PED cases. It may be that a combination of factors, such as dual antiplatelet therapy plus a threshold volume of embolic material, is required to cause an IPH.

Regarding the cases reported here, while it is possible that the identified emboli arose from more than one source, there were 3 devices common to the 3 procedures: the 0.035-in Glidewire, the Synchro 0.014-in microguidewire, and the Cook Shuttle Guiding Sheath. Intuitively, and based on clinical observations, the Shuttle Guiding Sheath seems a more probable source for significant volumes of PVP emboli. On benchtop evaluations, macroscopic amounts of PVP can be observed to be released from the Shuttle device with minimal manipulation, and foreign material can also be demonstrated to be shed from the Slip-Cath when it is withdrawn from the Shuttle Guiding Sheath (Video 1). It could be that advancing and deploying the PED generates greater frictional forces than occur with other neurointerventional procedures because of the PED's stiffness, but the cases reported here were not those that posed greater than typical challenges in this regard. Although dual antiplatelet medications, Glidewires, and Synchro microguidewires are frequently used for stent-supported intracranial aneurysm coiling, the Cook Shuttle generally is not.

Conversely, this very useful Shuttle Guiding Sheath/Slip-Cath combination is the "workhorse" access device in carotid artery stenting, another cerebrovascular intervention in which, like treatment with flow diverters, dual antiplatelet therapy is standard. McDonald et al. examined the National Inpatient Sample (NIS) database and found that intracranial hemorrhages were much more common in patients after carotid artery stenting than after carotid endarterectomy. In symptomatic patients, intracranial hemorrhages occurred in 4.4% of patients after carotid artery stenting versus 0.8% of patients after carotid endarterectomy.[14] This rate of intracranial hemorrhages is, however, higher than that noted in the CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) where only 3 (0.5%) of 594 major strokes occurring within 30 days of stent placement were reported in asymptomatic patients. It was not specified as to whether these major strokes were ischemic or hemorrhagic.[19]

Conclusions

Delayed ipsilateral IPHs after uneventful PED placements for the treatment of intracranial aneurysms are few and sporadic. The etiology of these hemorrhages remains difficult to elucidate with certainty. The discovery of hydrophilic foreign body emboli in the cerebral vasculature surrounding these hemorrhages is highly concerning and demands further research to understand the association with PED procedures. While careful back-flushing of catheters may reduce the risk of PVP emboli, it is clear that back-flushing alone is insufficient. A better understanding of the risks associated with particular endovascular devices and with combinations of devices is required so that appropriate solutions may be engineered to minimize the risk.

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Disclosure

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