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INTERVENTIONAL NEURORADIOLOGY

Non-ischemic cerebral enhancing lesions secondary to endovascular aneurysm therapy: nickel allergy or foreign body reaction? Case series and review of the literature

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Abstract
Introduction Delayed onset of non-ischemic cerebral enhancing (NICE) lesions is a rare complication of intracranial aneurysms' endovascular therapy (EVT). The purpose of this study is to report this rare complication and its potential pathophysiology in a single-center case series and review the relevant literature.
Methods After retrospective review of all patients managed by EVT at our institution from January 1, 2012 to December 31, 2014, 2 out of 374 patients (0.5 %) with such a complication were identified. Skin patch testing was performed with all endovascular devices used in the two patients and with the European baseline series, including nickel. All previously published cases in the English literature were reviewed based on exhaustive PubMed and Embase research.
Results Patient no. 1 developed NICE lesions 1 month after balloon-assisted coiling of a ruptured anterior communicating artery aneurysm. Patient no. 2 developed NICE lesions 12 months (the longest delay reported to date for such a complication) after the treatment of a right carotid-ophthalmic aneurysm by loose coiling and flow diversion. Patient no. 2 demonstrated nickel skin reactivity, but none of the two patients presented allergic reaction to the devices used during interventions.
Conclusions Based on our observations and review of the literature, we hypothesize that delayed non-ischemic cerebral enhancing lesions after EVT are more likely related to foreign body emboli rather than nickel allergy. The two presented cases demonstrate the potential for recurrence and prolonged fluctuation of NICE lesions, warranting long-term follow-up for all patients presenting this complication.

FDM, NS, and FC contributed equally to this study.

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Keywords Aneurysm · Endovascular therapy · Brain-enhancing lesions · Nickel allergy · Embolism

Abbreviations

ACA	Anterior cerebral artery
ACom	Anterior communicating artery
CT	Computed tomography
DAC	Distal access catheter
DCI	Delayed cerebral ischemia
DIPH	Delayed ipsilateral parenchymal hemorrhage
DSA	Digital subtraction angiography
DWI	Diffusion-weighted imaging
EVT	Endovascular therapy
ICA	Internal carotid artery
JAK2	Janus kinase 2

FDS	Flow diverter stent
FLAIR	Fluid-attenuated inversion recovery
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
NICE	Non-ischemic cerebral enhancing
PCA	Posterior cerebral artery
PCom	Posterior communicating artery
PVP	Polyvinylpyrrolidone
SAH	Subarachnoid hemorrhage

Introduction

Intracranial aneurysm rupture results in potentially devastating subarachnoid hemorrhage (SAH). Endovascular therapy (EVT) has gained wide acceptance as a safe and effective technique to prevent aneurysm rupture and rebleeding [1]. The two most common serious complications of EVT are thromboembolic ischemia and intraoperative rupture [2]. A rarely reported complication after EVT is delayed non-ischemic cerebral enhancing (NICE) lesions [3–8]. These lesions have most often been attributed to foreign body emboli and subsequent granulomatous reaction [3, 4, 6, 7]. More recent reports point to the possible implication of cerebral hypersensitivity and nickel allergy [5, 8]. Given the widespread use of nickel in neurointerventional devices, we sought to explore the possible role of nickel allergy in delayed cerebral enhancing lesions after intracranial aneurysm EVT.

Methods

Study population

A retrospective review of patients with intracranial arterial aneurysms managed by EVT at the Pitié-Salpêtrière Hospital, Paris, from January 1, 2012 to December 31, 2014, was undertaken. During this 3-year period, 374 consecutive patients were treated by endovascular means. Among them, two patients (0.5 %) developed NICE lesions after intracranial aneurysm EVT.

Skin patch tests

In order to test the possible role of nickel allergy in the NICE lesions after intracranial aneurysm EVT in these two patients, skin patch testing was performed with the European baseline series [9] which is a recommended set of allergens, including nickel, issued by the European Society of Contact Dermatitis to which all patients suspected of contact dermatitis should be tested. Hypersensitivity reaction to nickel was tested as well as reaction to all endovascular devices used during EVT. Testing was performed by cutting a fragment of each endovascular device and patching it to the back of the patient. Skin reactions were evaluated at 48 and 96 h. For patient 1, the following endovascular devices were tested: six French Envoy sheath (Codman Neurovascular, Raynham, MA), Radiofocus 0.035″ hydrophilic guidewire (Terumo, Tokyo, Japan), Echelon 10 microcatheter (eV3, Irvine, CA), Traxcess 0.014″ micro guidewire (Microvention, Tustin, CA), Radiofocus 0.012″ GT micro guidewire (Terumo), Transform balloon (Stryker Neurovascular, Fremont, CA), Target coil (Stryker Neurovascular), and a Hydrosoft hydrocoil (Microvention). For patient 2, the following endovascular devices were tested: a Radiofocus 0.035″ hydrophilic guidewire (Terumo), Vasco microcatheter (Balt, Montmorency, France), PX400 microcatheter (Penumbra, Alameda, CA), Traxcess 0.014″ micro guidewire (Microvention), Penumbra 400 coil (Penumbra), and Silk flow diverter stent (Balt). A potential limitation of this method is that the coating of the inner lumen of catheters is not exposed during the skin patch tests.

Literature review

All previously published cases in the English literature were reviewed based on exhaustive PubMed and Embase research. The following data were recorded: age, gender, EVT technique, time to onset or lesion detection, clinical findings, magnetic resonance imaging (MRI) findings, allergology testing, pathology findings, treatment, clinical evolution, and radiological evolution. The authors of one of the reports [3] kindly provided additional information upon request regarding patients' ages, gender, and time to onset.

Summary of cases

Case no. 1

History

A 45-year-old male patient with medical history of penicillin allergy presented with a ruptured 4-mm anterior communicating artery (ACom) aneurysm. Within 24 h, EVT was performed by means of a six French right transfemoral approach, left internal carotid artery (ICA) catheterization, and balloon-assisted aneurysm coiling (Fig. 1). The procedure was uneventful.

Postoperative course

On day 28, the patient presented with progressive onset of right-sided hypoesthesia and headache. A CT scan on day 32

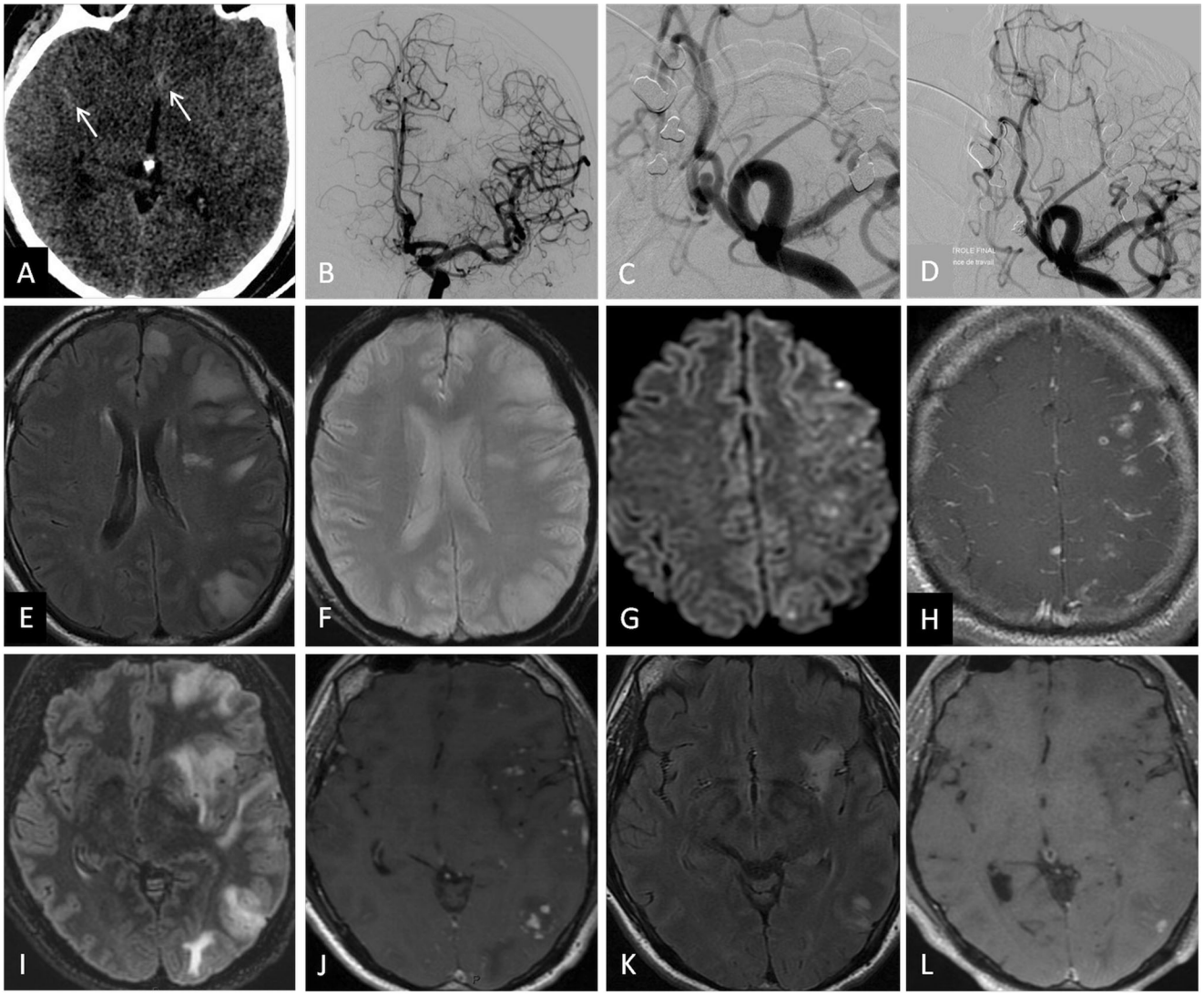

Fig. 1 Case 1 imaging features. Computed tomography (CT) brain scan demonstrating subarachnoid hemorrhage (*white arrows*, **a**). Anteroposterior projection digital subtraction angiography (DSA) of the left internal carotid artery (ICA) showing patency of the anterior communicating artery (ACom, **b**). DSA in the working projection demonstrating a ruptured ACom aneurysm before (**c**) and after endovascular aneurysm coiling (**d**). On day 35 postendovascular therapy (EVT), brain magnetic resonance imaging (MRI) T2 fluid-attenuated inversion recovery (FLAIR) (**e**), T2* (**f**), diffusion-weighted imaging (DWI) (g), and contrast-enhanced T1 (**h**) sequences showed multiple leptomeningeal, cortical and subcortical micronodular, and annular enhancing lesions and peri-lesion edema with vascular distribution in the territories of the right anterior cerebral artery (ACA), left ACA, and left middle cerebral artery (MCA). MRI on day 45 post-EVT (**i**, **j**) showing significantly increased edema causing a 12-mm midline shift. MRI 10 weeks after EVT (**k**, **l**) with slight residual enhancing lesions and edema

showed multifocal left frontal and parietal hypodensities. MRI (3T) showed multiple leptomeningeal, cortical and subcortical micronodular and annular enhancing lesions, and T2 hyperintense peri-lesion edema with vascular distribution in the territories of the right anterior cerebral artery (ACA), left ACA, and left middle cerebral artery (MCA), suggestive of NICE lesions. Only a subset of the NICE lesions appeared hyperintense on the diffusion-weighted imaging (DWI) sequence with lowered apparent diffusion coefficient. None of the NICE lesions appeared hypointense on the T2* sequence. Serum and cerebrospinal fluid analyses were all negative for infection. The edema significantly increased and symptoms worsened within the next 10 days with onset of speech disturbance, right arm weakness, and seizure. Corticosteroid treatment was started (1 g/day of intravenous methylprednisolone for 7 days), followed by rapid regression of the NICE lesions and the peripheral edema and the resolution of the symptoms. Five months after EVT, the patient was asymptomatic and the follow-up MRI showed only slight residual NICE lesions and edema. Ten months after EVT, the patient presented with recurrent hypoesthesia. MRI demonstrated increased NICE lesions and perilesional edema. Corticosteroid treatment was

started (1 g/day of intravenous methylprednisolone for 5 days) and the patient recovered.

Skin patch testing

Skin patch testing with nickel and all the endovascular devices similar to those used during the original procedure was found to be unreactive.

Case no. 2

History

A 54-year-old female patient underwent EVT of an incidentally discovered right carotid-ophthalmic aneurysm. EVT was performed by means of a right transfemoral approach, right ICA catheterization, loose coiling, and deploying a flow diverter stent (FDS) in the right ICA covering the aneurysms' neck (Fig. 2). The procedure was uneventful.

Postoperative course

The first follow-up MRI performed at 6 months demonstrated no signal abnormalities. Twelve months after the procedure, a second follow-up MRI was performed while the patient was asymptomatic, demonstrating multiple regions of right hemisphere subcortical edema. The occurrence of seizure at 17 months of EVT prompted a new MRI with contrast material injection that showed extension of the T2 hyperintense lesions and leptomeningeal and cortical micronodular and annular enhancements with vascular distribution in the territories of the right MCA and possibly right posterior cerebral artery (PCA), suggestive of NICE lesions. Minor magnetic susceptibility was observed for a subset of lesions. None of the NICE lesions appeared hyperintense on DWI. The biological workup was negative and a stereotactic biopsy was performed. Corticosteroids were started (10 mg/day of prednisone). Follow-up MRI showed fluctuation of the NICE lesions and the edema. At 40-month follow-up, the patient was asymptomatic. Corticosteroids are to be discontinued.

Pathological findings

A stereotactic cerebral biopsy was performed 21 months after EVT. Pathological examination found a non-specific lymphocytic inflammatory infiltration, reactive astrocytes, and a minimal eosinophilic leukocytoclastic vasculitis, without any foreign body emboli or giant cell reaction (Fig. 3). There was no sign of glioma, lymphoma, demyelination, or infectious disease. Gram, Ziehl-Neelsen, PAS, and Grocott stains; Epstein-Barr virus in situ hybridization; and JC virus immunolabeling were negative.

Skin patch testing

Skin patch testing with endovascular devices similar to those used during the original procedure was found to be unreactive. In particular, skin patch testing with a silk FDS (Balt) was unreactive. Nickel, cobalt, and copper induced skin reactivity.

Discussion

Delayed NICE lesion is a seldom reported complication after EVT of intracranial arterial aneurysms [3–8]. It is characterized by delayed onset of punctate, nodular or annular foci of leptomeningeal, cortical, and subcortical enhancements and vasogenic T2 hyperintense peri-lesion edema with a vascular distribution in the territory of the endovascular access of EVT. In our two cases, the territories involved were fed by the ICA where the guiding catheter was placed for the embolization procedure. Distribution variation of the involved territories was due to circle of Willis individual variations (patent ACom in patient no. 1, fetal PCA with patent posterior communicating artery [PCom] in patient no. 2). To our knowledge, a total of 17 cases have been previously reported in the literature (Table 1). Age and gender were unavailable for five patients [6]. For the 14 remaining patients (including the two cases reported herein), mean age at diagnosis was 53 years (range 32 to 71 years). Twelve out of 14 patients were females and 2 were males. In the overall population of 19 patients, a total of 20 aneurysms were treated in 21 EVT procedures, including 4 coilings, 5 balloon-assisted coilings, 4 stent-assisted coilings (including one case of retreatment), and 8 treatments with FDS. We report 2 cases out of 374 patients treated during a 3-year period (0.5 %). Shapiro et al. report 5 cases out of nearly 720 patients treated at 6 different institutions during a 2-year period (0.6 %) [6]. Incidence may be higher because asymptomatic patients usually do not undergo MRI and may be missed. Indeed, 4 out of 19 patients previously reported were asymptomatic [3]. Symptoms were largely non-specific and included seizure, headache, motor deficit, involuntary movements, spasm, visual disturbance, central facial nerve palsy, and speech disturbance. Mean delay to symptoms' onset or discovery of asymptomatic lesions was 12 weeks (range 2 weeks to 12 months).

As demonstrated by the two cases reported here, NICE lesions can fluctuate under corticosteroid therapy and may recur. In the first case, symptoms recurred 10 months after EVT. The second patient has the longest delay to onset of symptoms and presented fluctuating lesions under corticosteroid therapy 40 months after EVT. Corticosteroids have been administered in 7 of the 17 previously reported cases with inconstant clinical improvement [3, 5, 6]. In one case, NICE lesions and symptoms recurred after corticosteroid taper [6].

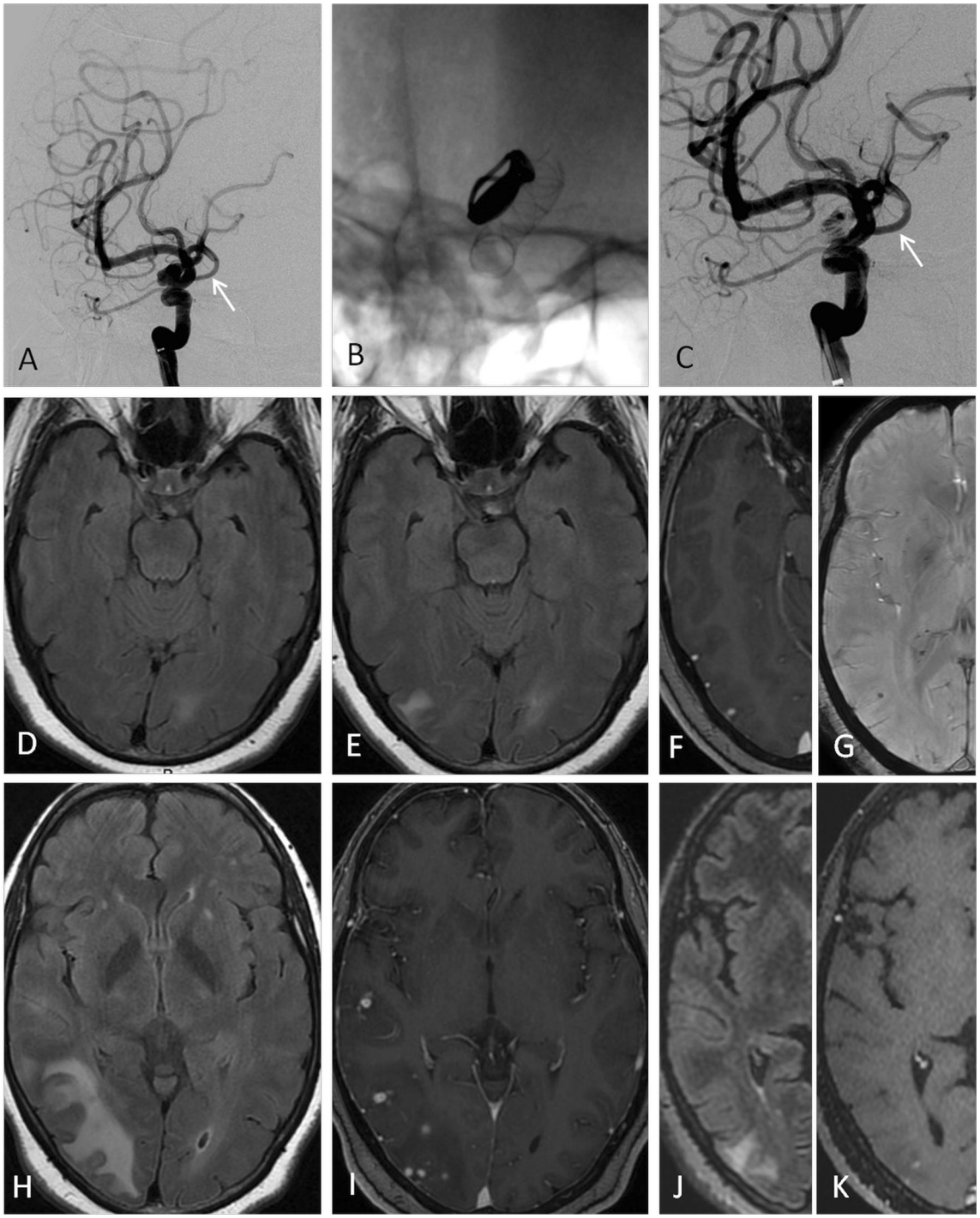

Fig. 2 Case 2 imaging features. Right ICA DSA in the working projection demonstrating a right carotid-ophthalmic aneurysm before and immediately after EVT with a patent right posterior communicating artery (PCom; *white arrow*, **a**–**c**). Normal MRI T2 FLAIR sequence 6 months after EVT (**d**). MRI T2 FLAIR (**e**), contrast-enhanced T1 (**f**), and susceptibility-weighted imaging (SWI)(**g**) sequences 17 months post-EVT showing enhancing lesions, edema, and magnetic susceptibility with vascular distribution in the territories of the right MCA and possibly right posterior cerebral artery (PCA). MRI 20 months after EVT (**h**, **i**) demonstrating significantly more enhancing lesions and edema. Thirty-four-month follow-up MRI (**j**, **k**) showed significant regression of the enhancing lesions and edema

NICE lesions and symptoms have been reported to resolve spontaneously or under corticosteroid administration, improve partially, fluctuate, or aggravate with time. Long-term follow-up is warranted for all patients presenting with NICE lesions after EVT, given the still unclear natural history of this complication.

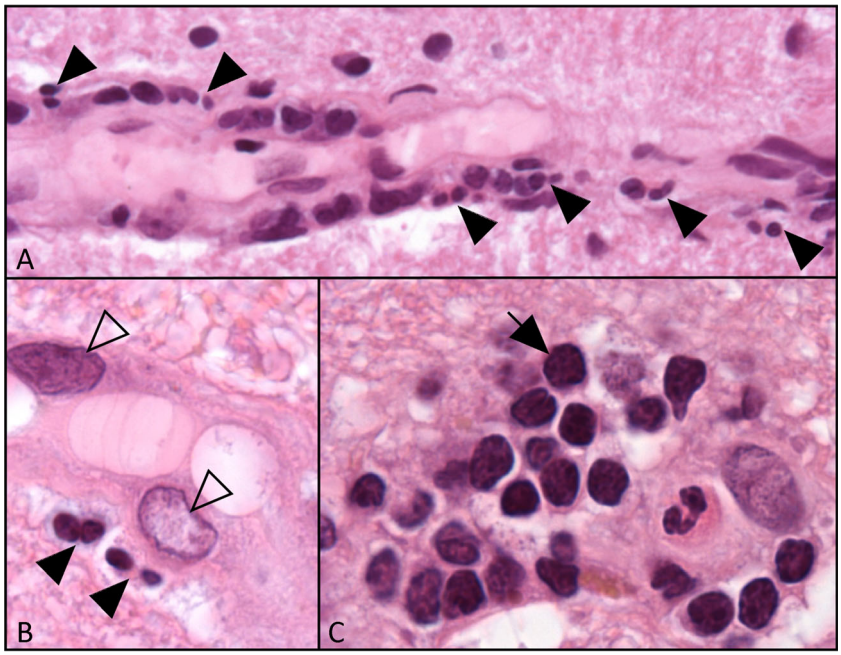

Fig. 3 Case 2 pathological findings. **a** HE ×400. **b**, **c** HE×1000. Few polymorphonuclear leukocytes with predominant eosinophils (*solid arrowheads* in **a**, **b**) were present around capillaries with turgescent endothelial cells (*open arrowhead* in **b**); some of the polymorphonuclear leukocytes presented a fragmentation of their nuclei. Frequent eosinophil margination in capillaries (*arrow* in **c**) and scarce perivascular lymphocytic inflammatory infiltrate were observed (*solid arrow* in **b**)

Allergic reactions to endoprosthesis are uncommon and reported in association with orthopedic, dental, endovascular, and other implanted devices [10]. Nickel hypersensitivity reactions have been reported after percutaneous patent foramen ovale occlusion and endovascular abdominal aortic aneurysm repair [11–14]. Nickel is increasingly used in devices for intracranial endovascular procedures [15]. In two previously reported cases of delayed NICE lesions after aneurysm EVT, the complication was attributed to nickel allergy [5, 8]. In the second case reported in this article, the patient also presented a positive patch test reaction to nickel. However, several arguments contradict the hypothesis of an imputability of the nickel allergy with these intracranial enhancing lesions. First, nickel sulfate is the most frequently identified allergen in population-based patch test studies (16.7 % of the population) [16], raising the possibility that the observed association in the reported cases was fortuitous. Second, we report a second case where patch testing was negative for nickel. In our two cases, none of the endovascular devices tested for cutaneous hypersensitivity were positive, including the nitinol (55 % nickel, 45 % titanium) FDS in case no. 2. The reported delays between EVT procedures and the reactions were quite long in our experience, up to 12 months in patient no. 2, the longest delay reported to date, which is quite uncommon even for delayed hypersensitivity reactions. Finally, most reactions were not restricted to the site of the aneurysm but instead affected large vascular territories downstream of the endovascular access used for EVT.

Inadvertent foreign body embolization may complicate diagnostic and therapeutic cerebral angiographies [17]. Embolization of hydrophilic coating from endovascular devices has been reported [18]. Such emboli have been implicated in cerebral ischemia [19, 20] and ipsilateral intraparenchymal hemorrhages after the treatment of supraclinoid ICA aneurysms with FDSs [21]. Cardiologists acknowledge that hydrophilic transradial sheaths can be responsible for sterile abscess at the radial puncture site [4, 22–28]. Pathological examination of these lesions demonstrates prominent foreign-body granulomatous reaction in response to dislodged hydrophilic coating [4]. Such foreign-body granulomatous reaction to hydrophilic coating has also been reported in the myocardium [29–31], kidneys [31], and lungs [32] after cardiac and peripheral endovascular procedures. Fealey et al. and Shapiro et al. have reported three cases of delayed NICE lesions after EVT with pathological examination of the lesions [4, 6]. Biopsy revealed granulomas, granulomatous angiitis, and microabscesses encasing foreign material. The foreign material identified was composed of non-refractile filamentous blue-gray material identical to what was previously reported in radial artery cases. Shapiro et al. identified the foreign material as being identical in stain appearance to a polyvinylpyrrolidone (PVP) catheter coating. Hu et al. previously used mass spectroscopy to identify PVP in fatal ipsilateral intraparenchymal hemorrhages after EVT of supraclinoid aneurysms with FDSs [21]. No such foreign material was identified in our case. This however does not exclude the possibility that the delayed NICE lesions in case no. 2 are indeed foreign body reactions to hydrophilic coating emboli. The stereotactic biopsy may have missed sites of embolic material. The eosinophilic leukocytoclastic vasculitis observed could correspond to hypersensitivity angiitis related to embolic foreign material. We also cannot exclude that pathology was negative for hydrophilic catheter coating because of the delay between EVT procedure and biopsy (21 months).

Table 1 Reported cases of non-ischemic cerebral enhancing lesions after endovascular aneurysm therapy

Reference	Age, sex (M/F)	Aneurysm location	EVT device	Time from procedure to lesion detection	Treatment	Clinical evolution	Radiological evolution	Pathology findings	Nickel allergy testing
Fealey et al. 2008 [4]	58, F	Right ICA	Coiling	9 months	Antibiotics	Not reported	Variation in size	Necrotizing granulomatous inflammation with polymer filaments	NA
Skolarus et al. 2010 [7]	46, F	Basilar artery	Balloon-assisted coiling	1 month	None	Aggravation at 10 weeks, near complete resolution at 9 months	Resolution	NA	NA
	56, F	Basilar artery	Coiling and additional stent-assisted coiling 8 months later	1 month after stent-assisted coiling	None	Resolution at 1 month of symptom's onset	Complete resolution at 4 months	NA	NA
Ulus et al. 2012 [12]	41, F	Left MCA	Stent-assisted coiling	1 month	None	Regression at 7 weeks	Complete resolution at 6 months	NA	NA
Cruz et al. 2014 [3]	Seven patients, six female and one male; median age 54 (32–71)	Six anterior circulation aneurysms, one posterior circulation aneurysm	Coiling ($n=2$), balloon-assisted coiling ($n=2$), stent-assisted coiling ($n=1$), FDS ($n=2$)	Median time 63 days (range 43–118 days)	None ($n=3$), antibiotics ($n=2$), antibiotics and corticosteroids ($n=1$), antiepileptic drugs ($n=1$)	Resolution ($n=1$), not reported ($n=2$), remained asymptomatic ($n=4$)	Resolution ($n=1$), reduction ($n=3$), stable ($n=1$), increase ($n=2$), median f/u 21.5 months	NA	NA
Lobotesis et al. 2015 [5]	60, F	Right ICA	Balloon-assisted coiling	19 days	Corticosteroids, antiepileptic drugs	Improvement	Regression over 16 months	NA	Nickel allergy, unreactive to balloon
Shapiro et al. 2015 [6]	Not reported	Six anterior circulation aneurysms in five patients	Coiling and FDS ($n=5$), stent-assisted coiling ($n=1$)	Median 8 weeks (range 2 to 12 weeks)	Corticosteroids in all cases, antibiotics ($n=1$)	Resolution ($n=1$), stable ($n=1$), recurrence after steroid taper ($n=1$), not reported ($n=2$)	Partial regression ($n=4$), recurrence after steroid taper ($n=1$)	Granulomatous reaction to foreign bodies ($n=2$), NA ($n=3$)	NA
Present study	45, M	ACom	Balloon-assisted coiling	1 month	Antibiotics, antiepileptic drugs, corticosteroids	Rapid resolution after corticosteroid treatment, recurrence at 10 months	Incomplete resolution, recurrence at 10 months	NA	Negative
	54, F	Right ICA	Coiling and FDS	12 months	Anti-TB antibiotics, corticosteroids	Resolution	Persistent fluctuation at 40 months	Lymphocytic inflammatory infiltration	Nickel allergy, unreactive to EVT devices

ACA anterior cerebral artery, *ACom* anterior communicant artery, *ICA* internal carotid artery, *INR* interventional neuroradiology, *FDS* flow diverter stent, *f/u* follow-up, *MCA* middle cerebral artery, *NA* not available, *PICA* posterior inferior cerebellar artery, *TB* tuberculosis

Cruz et al. reported two cases of coexisting painless aseptic secretion and swelling at the arterial puncture site out of seven patients [3]. Shapiro et al. reported a case of bilateral lesions following two separate procedures performed in a 4-week interval [6]. Both these observations raise the interesting possibility that patients experiencing PVP embolization develop clinicopathologic manifestations based on individual susceptibility. Four out of the five patients reported by Shapiro et al. [6] had previously presented allergy. Both our patients presented with an allergic background (penicillin allergy in patient no. 1 and nickel, cobalt, and copper allergy in patient no. 2).

The procedures were uneventful in both cases we report. Thus, if the mechanism of the delayed NICE lesions is indeed a foreign body reaction, the hydrophilic coating emboli cannot be attributed to unusual or aggressive endovascular device manipulation. To limit hydrophilic coating dislodgement, some authors have recommended avoiding potentially tight-fitting catheter combination [6]. Benchside experimentation is needed to determine the extent of hydrophilic coating embolization for different devices. We cannot determine if delayed NICE lesions are a rare reaction to common hydrophilic coating embolization or, conversely, the manifestation of a rare embolic complication.

Delayed ipsilateral parenchymal hemorrhage (DIPH) remote from aneurysms is a dreaded complication of FDSs [33, 34]. Several mechanisms have been advanced to explain this complication, including flow alterations related to stent placement and hemorrhagic transformation of ischemic lesions, but these explanations remain controversial [34, 35]. As mentioned earlier, Hu et al. have identified PVP in fatal DIPHs after EVT of supraclinoid aneurysms with FDSs [21]. It is unclear if DIPH and NICE lesions are two manifestations of the same phenomenon. Indeed, to our knowledge, there is no report of both complications occurring in the same patient. Moreover, DIPH is restricted to FDS EVT while NICE lesions have been reported for various EVT techniques.

Conclusions

Based on the vascular distribution of the lesions and on the negativity of all skin tests for the devices used during both procedures, we hypothesize that the delayed NICE lesions after EVT that we report herein are more likely granulomatous lesions secondary to foreign body emboli rather than nickel allergy. Given that pathological examination of the lesions in one of the two cases did not demonstrate embolic material, we cannot however exclude that another yet to be found mechanism is implicated.

Compliance with ethical standards We declare that our institution does not require ethics committee approval or patient consent for retrospective analyses of patients' records and imaging data. We declare that the two patients gave informed consent for skin patch tests.

Conflict of interest We declare that we have no conflict of interest. All tested endovascular devices were provided by the manufacturers free of charge.

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