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Overt nickel and cobalt hypersensitivity after pipeline embolization device placement: A case report

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Abstract:

Nickel and cobalt are frequently found in metallic alloys used in the manufacture of aneurysm clips and endovascular prostheses, such as the pipeline embolization device (PED). Nickel hypersensitivity can affect up to 15% of the population, however, it is very rarely overt in patients who undergo endovascular stent placement. Here, we present the case of a 35-year-old woman who developed allergic symptoms after PED placement and was later confirmed to be allergic to both nickel and cobalt by patch testing. Fortunately, she responded well to pharmacologic treatment, rendering surgical intervention unnecessary. To the best of our knowledge, this is the first report of symptomatic nickel hypersensitivity, and the second report of symptomatic cobalt allergy caused by the PED. Despite its low prevalence, we believe that surgeons should actively inquire patients in the postoperative period about allergic symptoms, to facilitate early diagnosis and treatment.

Keywords:

Cobalt, endovascular aneurysm repair, hypersensitivity, nickel, pipeline embolization device

Introduction

Nickel is a component frequently found in metallic alloys used in the manufacture of aneurysm clips and endovascular prostheses (stents, flow diverters, and coils).[1] In addition, it is also the metallic element most commonly associated with hypersensitivity reactions, affecting up to 15% of the general population.[2] Cobalt, another component sometimes associated with allergic reactions, is also ubiquitous in the manufacture of these materials.[1] Therefore, it is clear that allergy to these metals can represent a problematic situation for neurosurgeons and patients with cerebral aneurysms. Here, we report a case of nickel and cobalt allergy in a patient who underwent embolization with coils and placement of a pipeline embolization device (PED) for the treatment of the two internal carotid artery (ICA) aneurysms, the first association between PED and hypersensitivity reactions.

Case Report

A 35-year-old woman underwent a computed tomography angiography of the skull which demonstrated the presence of two cerebral aneurysms. Angiography confirmed the presence of three unruptured ICA aneurysms, one in the ophthalmic segment, measuring 7 mm, one in the carotid cavum, measuring 3 mm, and another in the cavernous segment, measuring 3 mm. The ophthalmic segment aneurysm was successfully embolized with balloon-assisted platinum coils remodeling technique. The other two aneurysms, on the other hand, due to their location and size/characteristics, were not immediately treated.

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The patient underwent control angiographies in the following years, which demonstrated complete obliteration of the treated aneurysm, and stability of the other lesions. However, in a new control exam performed 3 years after treatment, we observed an increase in the size of the cavum aneurysm. In addition, the patient reported exhaustion to the care needed to monitor her condition, especially in regarding the need for angiographies, a procedure she considered extremely uncomfortable and distressing. After discussion with the team and the patient, we decided to treat both the carotid cave and cavernous aneurysms simultaneously, and the PED was considered the best option. The intervention was successful, and the patient was discharged the next day without neurological deficits. A control angiography performed 12 months later demonstrated complete exclusion of the cavernous aneurysm; however, there was still a small residual blood flow in the carotid cave aneurysm. There were no signs of in-stent stenosis or intimal hyperplasia [Figure 1].

The patient lost neurosurgical follow-up for 4 years when she returned to the neurosurgery service with the diagnosis of hypersensitivity to nickel and cobalt (both present in the composition of PED), confirmed by patch tests performed in a dermatology service (cobalt chloride +/+++, nickel sulfate +++/+++) 2 months before the new neurosurgical consultation. During previous consultations with the neurosurgical team, the patient did not report any symptoms that could lead us to think of an allergic reaction to the materials used in her treatment. However, during the follow-up consultation, after establishing the diagnosis of hypersensitivity, the patient reported the onset of allergic symptoms a few days after implantation of the flow diverter.

She reported the onset of crises of generalized pruritus, mild intensity, as the first symptom. Over time, pruritus intensity increased, and the patient began symptomatic self-treatment with antihistamines and, sometimes, oral corticosteroids, which controlled her symptoms. She also began to notice the occurrence of lip edema in association with the pruritus crises, but as this symptom also resolved with the use of oral antiallergy medication, she did not seek medical evaluation. Furthermore, the patient revealed that about 18 months after PED implantation she sought medical attention due to respiratory symptoms and was diagnosed with late-onset asthma, which proved refractory to standard bronchodilator therapy and associated with chronic sinusitis. All of these symptoms, which lasted throughout the entire period, are highly suggestive of a hypersensitivity reaction, but the diagnosis was not made until about 4 years after PED implantation, partially because of delayed recognition by practitioners and partially because of the patient's poor adherence to medical instruction and follow-up. Fortunately, the patient responded well to the treatment with continuous oral antihistamines initiated by the dermatology team after the etiological diagnosis of the atopic symptoms.

The need for reintervention, to remove the allergenic implants, was discussed between the dermatology and neurosurgery team, being ruled out due to the good control of the symptoms with pharmacological treatment and the high surgical morbidity. The patient remains under follow-up by both teams to this day. Informed consent forms were acquired before the beginning of the article's production.

Discussion

Despite its high prevalence in the general population (10%–15%), nickel allergy is rarely overt in patients who undergo treatment using materials composed of nickel in the context of vascular diseases, whether endovascular prostheses or clips.[1,2] A systematic review conducted by Tsang *et al*.[1] in 2018 found only

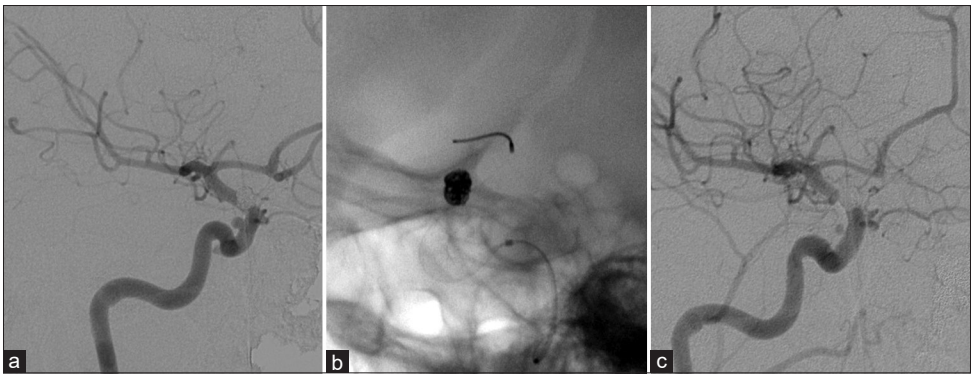

Figure 1: (a) Angiography, lateral view of the right internal carotid artery, showing the presence of three aneurysms, one embolized ophthalmic segment aneurysm overlaying the internal carotid artery and two untreated aneurysms, one in the carotid cavum and the other in the cavernous segment, both measuring approximately 3 mm. (b) Work incidence showing the deployment of the pipeline embolization device (PED). (c) Lateral view of the control angiography, performed 12 months after PED implantation, showing the complete exclusion of the cavernous aneurysm, however, there was still a small residual blood flow in the carotid cave aneurysm. There were no signs of in-stent stenosis or intimal hyperplasia the embolized ophthalmic segment aneurysm is overlaying the internal carotid artery

10 cases of overt nickel hypersensitivity after treatment of brain aneurysms in the literature, even with its broad search criteria. The presentation was dermatological in two and neurological in eight, including cases of cerebritis and cerebral edema, and the latency between treatment and onset of symptoms ranged from 10 days to 12 months. Our case constitutes the first respiratory presentation in this population, but it should be noted that this symptomatology has already been described with nickel implants used in other locations.

The main component of PED is the nickel-alloy 35NLT, which is comprised 33%–37% nickel. Despite its high nickel concentration, this device has never been involved in hypersensitivity cases in the past. Furthermore, interestingly, Tonetti *et al*.[3] reported the use of the PED in two patients previously diagnosed with nickel allergy, confirmed by preoperative patch testing, and these did not present any symptoms or intrastent stenosis in 36 months of follow-up. Our patient was not so lucky and presented allergic symptoms within a few days, albeit mild. In regard to cobalt hypersensitivity, Fujii *et al*.[4] reported the only case of in-stent stenosis probably caused by cobalt allergic reaction (confirmed by patch testing) with the use of PED, making ours the second reported case of symptomatic cobalt allergy caused by PED.

The management of these patients begins with the confirmation of hypersensitivity, performed with patch testing for the desired metals. The use of a reagent isolated directly from a similar endovascular device may be of value in establishing a definitive diagnosis of allergic reactions secondary to an implant, but in developing countries, like ours, such use of endovascular devices is too costly and not performed.[1] Treatment can be pharmacological or involve surgical removal of the allergenic material – the decision on surgical intervention is made along with the patient, according to the severity of the condition and degree of response to pharmacological therapy. Pharmacological therapy in these cases follows the same principles of any other hypersensitivity reaction, with antihistamines and corticosteroids being the most commonly used drugs, at standard doses. If pharmacological therapy fails, removal of endovascular devices associated with arterial reconstruction can be performed; however, due to its high morbidity, this method should be used as a last option in severe refractory cases. Clip removal is less morbid but is still reserved for refractory cases.[1,5,6]

Preoperative screening for metal allergy can be performed, but the difference between prevalence in the general population and the number of treated patients who become symptomatic should be kept in mind. A positive patch test will often deprive a patient, who would not develop any hypersensitivity symptoms, of the treatment of choice for their condition, as demonstrated by Tonetti *et al*.[3] The research published by Vanent *et al*.[7] in 2022 also supports this point of view. They analyzed the nickel release from seven intracranial stents, including the PED, embedded in plasma-like media, and concluded that there was no nickel release from the stents in 30 days. This result suggests that allergic symptoms to the nickel content of the tested stents are unlikely or even impossible, but we must keep in mind that patients with severe allergies need very small amounts of metal to present symptoms, and we cannot overlook the importance of the direct interaction between the vessel wall and the endovascular device, which may affect nickel release. Furthermore, we cannot overlook neither the clear cause–effect relationship between device implantation and symptoms onset nor the clear benefit of hypersensitivity treatment, with cases of complete clinical improvement after device removal.[5] Therefore, studies on serum nickel concentration after stent implantation are necessary to confirm the findings of Vanent *et al*.[7] Nevertheless, although rarely significant in neurosurgical practice, we should be aware of the possibility of a hypersensitivity reaction, especially in the postoperative period, where early pharmacological and/or surgical interventions can prevent the evolution of the allergic condition to severe conditions such as difficult-to-control asthma, cerebral edema, and in-stent stenosis.

Conclusion

To our knowledge, this is the first report of symptomatic nickel hypersensitivity, and the second report of symptomatic cobalt allergy caused by the PED. This rare complication can happen with the implantation of any kind of endovascular device and can entail dramatic consequences, but it is easily diagnosable, making early recognition and treatment a must. Despite its low prevalence, we believe that surgeons should actively inquire patients in the postoperative period about allergic symptoms, to facilitate early treatment. Preoperative patch testing must be used with caution, as the gap between populational hypersensitivity prevalence and overt hypersensitivity after treatment is enormous, and a positive patch test will deprive patients of the most effective treatment of their condition way more often than prevent hypersensitivity cases, most of which can be treated pharmacologically.

Author contributions

Dr. Martio: Concepts, design, definition of intellectual content, literature search, data acquisition, data analysis, manuscript preparation, manuscript editing, manuscript review; Dr. Kieling: Concepts, design, definition of intellectual content, literature search, data acquisition,

manuscript preparation, manuscript review; Dr. Manzato: Concepts, design, definition of intellectual content, manuscript preparation, manuscript review; Dr. Vanzin: Concepts, literature search, data acquisition, manuscript preparation, manuscript editing, manuscript review.

Ethics approval

The study was conducted in accordance with the declaration of Helsinki.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Data availability statement

All data generated and/or analyzed during this study are included in this published article [and its supplementary information files].

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Nil.

Conflicts of interest

There are no conflicts of interest.

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