Surgical clipping is an effective treatment option in the complete obliteration of intracerebral aneurysms. Prior to the introduction of clips made of titanium alloy, aneurysm clips used in clinical practice were most commonly made of stainless steel. Phynox, or Elgiloy, an alloy composed of 39%–41% cobalt, 19%–21% chromium, 14%–16% nickel, and other minor elements, is commonly used for this purpose (for example, Aesculap Yasargil Phynox, Sugita Elgiloy).

The Phynox aneurysm clip is a safe and effective option in the treatment of intracranial aneurysms, with well-studied histological, mechanical, and biochemical properties. However, there is theoretical concern regarding the likelihood of allergic reactions to metallic clip components, most notably to nickel. This is a worthwhile consideration given that 15% of the general population demonstrates hypersensitivity to nickel in the form of contact dermatitis.

We report the second case of a patient with a Type IV (cell-mediated) hypersensitivity reaction to a Phynox aneurysm clip. This is the first time cerebral edema has been described in relation to Phynox hypersensitivity, and the first time an acute chronic hypersensitivity reaction due to a Phynox aneurysm clip has been reported. Additionally, we review the literature describing hypersensitivity reactions to nickel-containing implants.

Case Report

History and Examination. This 60-year-old right-handed woman initially presented in August 2009 with an incidental finding of a right middle cerebral artery (MCA) aneurysm diagnosed during an investigation for migraines. Her medical history includes epilepsy, hypothyroidism, and lumbar canal stenosis. She regularly takes phenytoin and thyroxine and is a lifelong nonsmoker. She
has a known nickel allergy causing cutaneous bullae on contact. The aneurysm was not thought to be the cause of her headaches. Preoperative diagnostic cerebral angiography demonstrated a trifurcation of the right MCA, with a bilobed aneurysm measuring 5.7 × 6.0 mm, arising from each junction of the right MCA, and precluding endovascular intervention. The patient underwent surgical clipping of the aneurysm in which two Aesculap Yasargil Phynox aneurysm clips (FE740 K) were routinely applied. Operative closure was performed in a routine fashion. A postoperative cerebral angiogram revealed successful clipping with no residual aneurysms. Her postoperative course was uneventful. She was discharged on the 8th postoperative day in a clinically well condition and without complications.

On routine postoperative cerebral MRI 2 months after discharge, marked T2 hyperintensity had developed in the right frontal and temporal lobes surrounding the aneurysm clip, producing mild mass effect (Fig. 1A and B). There was no restricted diffusion on diffusion-weighted imaging. Given that the patient was headache free and asymptomatic, a conservative approach was adopted. Follow-up cerebral MRI performed 21 months later revealed significant resolution of the T2 hyperintensity (Fig. 1C and D).

The patient eventually re-presented in June 2013 with new-onset headaches of increasing intensity. She had no neurological deficits and was seizure free on regular phenytoin. Cerebral MRI revealed recurrent, extensive cerebral edema in the form of T2 hyperintensity in the right frontal and temporal lobes causing subfalcine herniation (Fig. 1E and F). A small ring-enhancing lesion was noted in the inferior frontal gyrus adjacent to the aneurysm clips. A cerebral angiogram again showed no residual aneurysm and no evidence of venous sinus thrombosis. As the patient was symptomatic with radiological evidence of mass effect, a decision was made to perform an exploratory stereotactic craniotomy. The aim was, firstly, to obtain a tissue diagnosis and, secondly, to potentially exchange the Phynox aneurysm clips with titanium-based clips.

Operation. Access was gained through the initial incision, and the bone flap was lifted. On opening the dura mater, the aneurysm clips were relatively superficial and readily visible. On inspection, the cerebral parenchyma was grossly edematous with multiple hard lumps adjacent to the clips. The lumps were incised, whereupon a soft center was encountered. The region around the clips was further dissected, but significant scarring precluded the possibility of titanium clip exchange. Multiple specimens of the lumps and brain parenchyma were sent for histopathological and microbiological analysis.

![Fig. 1](image_url) Axial T2-weighted MR images demonstrating the evolution of relapsing-remitting cerebral edema. **A and B:** Vasogenic cerebral edema appeared 2 months after aneurysm clipping. **C and D:** Significant resolution of the cerebral edema occurred 21 months post-aneurysm clipping. **E and F:** Marked increase in cerebral edema with associated midline shift at re-presentation prior to exploratory craniotomy. **G and H:** Four months after exploratory craniotomy, a significant decrease in cerebral edema and resolution of mass effect were apparent.
Histopathological Findings. Gram staining of the intraoperative samples revealed polymorphs only, with no organisms grown on prolonged cultures. Histopathological examination demonstrated gliosis with focal areas of necrosis (Fig. 2). Immunohistochemical studies demonstrated a prominent histiocytic infiltrate (Fig. 3) and lymphocytes in the form of CD4 (Fig. 4 left) and CD8 (Fig. 4 right) T cells. There was no suggestion of bacterial, fungal, mycobacterial, or viral organisms. Similarly, there was no evidence of neoplasm. In some samples, there were intracytoplasmic bacilli-like structures positive for PAS and PAS-D (PAS diastase). The anatomical pathologist found the above findings of an acute-on-chronic inflammatory response with a concomitant histiocytic infiltrate consistent with a cell-mediated hypersensitivity reaction.

Postoperative Course. There were no postoperative complications, and the patient had an uneventful recovery. Her headaches improved postoperatively. A systematic multidisciplinary approach was undertaken to resolve the diagnostic uncertainty surrounding her presentation. An abscess was ruled out with down-trending inflammatory markers and negative cultures from intraoperative samples. Further, the relapsing-remitting pattern of vasogenic cerebral edema since clip application in 2009 was inconsistent with cerebral abscess. Given the unknown significance of the intracytoplasmic bacilli-like structures positive for PAS and PAS-D, a gastroscopic small-bowel biopsy was performed and Whipple’s disease was excluded by negative testing of Tropheryma whippelii DNA polymerase chain reaction. A primary or secondary neoplastic process was similarly thought unlikely, as it was not supported by histopathological analysis. Given the histopathological diagnosis of a cell-mediated hypersensitivity process, the exclusion of key differentials, and the patient’s history of severe nickel contact dermatitis, a final diagnosis of cell-mediated (Type IV) hypersensitivity reaction to the Phynox aneurysm clip was determined as the etiological factor for the patient’s symptomatology and radiological and intraoperative findings. The patient was started on oral prednisolone. She remained symptom free 4 months postcraniotomy, and follow-up cerebral MRI demonstrated significant resolution of cerebral edema (Fig. IG and H).

Discussion

This case is unique in that it is the first instance of vasogenic cerebral edema due to an aneurysm clip described in the literature. It is worth noting that while the extent of edema was significant enough to produce mass effect, the patient remained well and asymptomatic for a period of 4 years prior to exploratory craniotomy. From serial cerebral MRI, we observed the relapsing-remitting nature of the vasogenic edema and thus the intermittent nature of the hypersensitivity reaction. We postulate that this reaction is the result of sporadic leeching of nickel from the Phynox clip producing an acute-on-chronic cell-mediated hypersensitivity response.7

Two related cases were found after a thorough review of the published literature. Ross et al.8 described a case of Type IV hypersensitivity to a Phynox aneurysm clip used to treat a ruptured aneurysm where the patient developed generalized intense pruritus and a papular rash 1 month after operation. Removal of the Phynox clip resulted in complete resolution of the patient’s symptoms, and a Type IV hypersensitivity reaction was confirmed on histopathological examination of intraoperative specimens. No cerebral edema was noted in this case. In 2012, Ulaş et al.9 documented a case of vasogenic edema after stent-assisted coiling of an MCA aneurysm. In this case two nitinol (55% nickel, 45% titanium) stents were deployed. Two months postprocedure the patient presented with headaches and multiple patchy cortical and subcortical hyperintensities on T2-weighted MRI in the ipsilateral frontal, parietal, and temporal lobes. No diffusion deficit appeared on diffusion-weighted MRI. The vasogenic edema spontaneously resolved with the resolution of the patient’s headaches. These two cases show that intraxial clips and stents sited within the subarachnoid or intravas-
cular space can cause foreign body reactions in the form of Type IV allergic reactions. These reactions likely result in a spectrum of symptoms, ranging from local effects in the form of cerebral inflammation causing headaches to distant effects presenting as the pruritus and urticaria seen in contact dermatitis. Reviewing the literature at large, we noted that the most prominent concerns regarding nickel allergy appeared in the cardiac literature. Multiple case series have documented the development of migraines after percutaneous closure of atrial septal defects and patent foramen ovale using an Amplatzer device made of nitinol. It is postulated that there is an association between nickel allergy, prothrombosis, and the subsequent development of migrainous headaches. This theory is supported by the fact that the administration of clopidogrel led to the resolution of migraines in a significant proportion of these patients. However, it should be noted that there has been no radiological evidence of ischemic cerebral infarction in these cardiac patients. While these papers lend support to the possibility of a nickel allergy with implantable medical devices, their relation to nickel-containing aneurysm clips may be limited. Firstly, nitinol cardiovascular devices have a chemical profile different from that of nickel-containing aneurysm clips (that is, Phynox) postdeployment and may incite an inflammatory response different from that occurring with nickel-containing aneurysm clips. Secondly, there is no current evidence in the neurosurgical literature that hypersensitivity reactions to nickel-containing aneurysm clips (or stents) cause ischemic cerebral infarcts.

Nickel was the presumptive offending element in this case given the known allergenic properties of the metal and the patient’s known sensitivity to nickel. However, since patch testing to other components of Phynox (that is, chromium, cobalt) was not undertaken in the patient, it is possible that a hypersensitivity reaction to chromium or cobalt had occurred in this case. Indeed, both cobalt and chromium have been proven to cause cell-mediated hypersensitivity reactions in vitro.

Conclusions
In summary, the neurosurgical community should be aware that allergic reactions to nickel-containing aneurysm clips can occur. Fortunately, patients with clipped aneurysms are routinely followed up with cerebral MRI, and the development of cerebral edema will be readily picked up even if the patient remains asymptomatic. Given the advent and use of titanium-based clips, the already low risk of nickel allergy in aneurysm clipping can be nullified.

Disclosure
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Tan, Han. Analysis and interpretation of data: Tan, Tee. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Tan.

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Accepted June 3, 2014.

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