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Perianeurysmal parenchymal cysts – Case series and literature review

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1. Introduction

Intracranial cysts are associated with a number of intracranial pathologies, including some vascular lesions including arteriovenous malformations (AVM) and cavernomas. Perianeurysmal parenchymal cysts (PPC) are however a very rare clinical entity that have only been reported in a handful of case reports. As a consequence, little is known about the mechanisms that give rise to their development and natural history. Nonetheless, a number of hypotheses have been proposed, with PPCs observed to arise both prior to and following aneurysm obliteration with either open or endovascular techniques. We report our institutional experience of 3 such cases together with an updated literature review.

2. Material and methods

Three cases with PPCs were available for review at our institution from 2010 to 2021. A retrospective chart review was then performed to analyze the clinical and radiological data for these cases. These cases were then grouped in order to present common themes. In order to further analyze this topic a systematic literature search was performed utilizing two separate databases Pubmed/MEDLINE and Google Scholar. All the available case reports/series were reviewed and the data summarised in Table 1.

3. Results

3.1. Case 1

A 61-year-old woman was found to have an incidental 20 mm left terminal internal carotid artery (ICA) aneurysm (Fig. 1a). The aneurysm was treated with endovascular coiling achieving satisfactory occlusion but a residual neck remnant. Routine 6-month follow-up cranial MRI, demonstrated a small amount of surrounding oedema around the coiled aneurysm (Fig. 1b and c). Repeat MRI one year later revealed an increasing amount of perianeurysmal oedema as well as further aneurysmal growth (Fig. 1d and e). She underwent stent-assisted coil embolisation, with standard dual antiplatelet therapy in addition to a short course of dexamethasone.

Subsequent cranial MRIs (Fig. 1f–k), 21–119 months post-initial embolisation demonstrate the development of progressive oedema and progressive enlargement of cystic spaces, the largest measuring 3.5 cm and stabilising at 100 months without evidence of additional growth so far.

The latest MRA revealed an aneurysmal remnant measuring 15 mm. She did not develop any neurological deficits. She remains under follow-up.

3.2. Case 2

A 68-year-old man was referred with an incidental 21 mm left terminal ICA aneurysm, that was treated with endovascular coiling

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Abbreviations

AComm	Anterior communicating artery
AVM	Arteriovenous Malformation
BA	Basilar Artery
CT	Computed Tomography
FLAIR	Fluid-attenuated inversion recovery
MCA	Middle cerebral artery
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
PCA	Posterior cerebral artery
PPC	Perianeurysmal Parenchymal Cyst
SAH	Subarachnoid Haemorrhage
TICA	Terminal internal carotid artery
VRS	Virchow Robin Spaces

(Fig. 2a). One day post coiling a cranial CT demonstrated some oedema superior to the coiled aneurysm (Fig. 2b and c). Follow-up cranial MRI at 1 month revealed persistent reactive oedema around the coiled aneurysm (Fig. 2d and e) which did not seem to respond to a trial of dexamethasone and nonsteroidal anti-inflammatory agents (NSAIDs). The aneurysm had a small neck remnant on repeat imaging at 6 months follow-up. With the progression of oedema, a small cystic lesion with a diameter of 10.5 mm developed adjacent to the aneurysm and enlarged 12–33 months after embolisation (Fig. 2f–k) achieving a diameter of 3.3 cm. This was treated conservatively. 18 months post-coiling, MRA showed a partial recanalization of the aneurysm neck, the morphology of which on cerebral angiography was not considered appropriate for additional coiling after multidisciplinary review. He remains headache free but developed a progressive visual field deficit.

3.3. Case 3

A 75-year-old lady was referred with a large partly-thrombosed left middle cerebral artery bifurcation aneurysm, measuring 21 mm (Fig. 3a and b), identified on imaging to investigate an episode of collapse and speech disturbance. The patient originally declined intervention. Four months later, she presented with a subarachnoid haemorrhage. The aneurysm was treated satisfactorily with coil embolisation but with a small residual neck and some flow reduction noted in the inferior M2 division. Follow-up imaging revealed an enlargement of the aneurysmal remnant which was treated with additional endovascular coiling again leaving a broad neck remnant given the local neck morphology incorporating the two M2 branches. These follow-up MRI scans also revealed a significant amount of perianeurysmal oedema around the treated aneurysm, with the MR angiogram revealing a 14 mm associated cyst (Fig. 3c,d,e). The cyst expanded, measuring up to 44 mm and 50 mm at 4 and 6 months later respectively, once again in association with considerable surrounding oedema (Fig. 3f–k). This was associated with worsening speech difficulty. After MDT discussion, she underwent an image-guided endoscopic fenestration of the left temporal cyst to the left lateral ventricle. Xanthochromic viscous cyst fluid was encountered – cytospins revealed modest numbers of red blood cells and scattered lymphocytes, monocytes and macrophages, without a significant acute inflammatory infiltrate or atypical cells. The cyst wall histology returned fragments of gliotic tissue, with no epithelial cyst lining of note and no neoplastic cells. Her speech impairment appeared to improve over the subsequent weeks, but she represented 2 months later with further worsening of her dysphasia and radiological persistence of the cyst with ongoing mass effect. A cysto-peritoneal valveless conduit was inserted but this failed to decompress the cyst or improve the patient's neurology, presumably due to the viscous nature of the cyst fluid. She had further intervention 3 months later with the insertion of an access device and serial aspirations that resulted in symptomatic improvement and radiological volume reduction (Fig. 3 l,m). The aneurysm continued to show slow progressive enlargement but the patient was not keen on reintervention. Apart from epilepsy developed after the SAH, she remained stable from a neurological perspective and passed away in 2020 of unrelated causes.

4. Discussion

Parenchymal cysts associated with other vascular lesions have been previously reported. These include those associated with cavernomas and less often with AVMs. Perianeurysmal parenchymal cysts (PPC) are a rarer clinical entity which has only been previously described in very few case reports and case series. Together with our case series, there are only 20 cases presented in the literature to date (Table 1).

4.1. Presentation and cyst characteristics

The average patient age of presentation with PPC in the reported literature, including our cases, is 63 years (range 35–80 years). There appears to be a fairly equal distribution between the genders.

At the time of identification, the majority of reported cases of PPC are associated with unruptured aneurysms. Only 1 PPCs was identified following aneurysmal SAH (Benvenuti et al., 2006). One case presented with weakness and speech disturbance 30 years after a SAH (Hirota et al., 1999) and another 17 months following SAH (Marcoux et al., 2002). Pedro and Sih describe a pontomesencephalic cyst that was thought to represent a haemangioblastoma, without evidence of an aneurysm on pre-operative MRA but with subsequent intra-operative identification of a P2 aneurysm (Pedro and Sih, 2020). One of our cases had a SAH, and the cyst developed in a delayed fashion after coil embolisation. These cysts present either incidentally pre- or post-treatment of the adjacent aneurysm with chronic headaches or as a consequence of mass effect secondary to the cyst.

The vast majority are associated with large aneurysms with radiological (Benvenuti et al., 2006; Hirota et al., 1999; Jayakumar et al., 2019; Sato et al., 2000; Takai et al., 2001; Martinez Galdamez et al., 2011) or histological (Pedro and Sih, 2020) evidence of thrombosis or arose after coil-induced thrombosis (Marcoux et al., 2002; Friedman et al., 2003; König et al., 2011; Barber et al., 2014; Norris et al., 2015). Of the 15 reported cases that include aneurysmal dimensions at presentation, including ours, the average aneurysm diameter is 1.9 cm (Range 0.9–4 cm). All 3 of our reported cases presented after endovascular coil embolisation. 14 of the 20 reported PPCs, including our own, were associated with aneurysms arising in the anterior circulation (Hirota et al., 1999; Marcoux et al., 2002; Jayakumar et al., 2019; Sato et al., 2000; Martinez Galdamez et al., 2011; Friedman et al., 2003; König et al., 2011; Norris et al., 2015; Kulwin et al., 2015). Posterior circulation aneurysms were reported in the remaining 6 cases (Benvenuti et al., 2006; Pedro and Sih, 2020; Sato et al., 2000; Takai et al., 2001; Barber et al., 2014).

The cysts tend to be centred primarily in the region of the basal ganglia, temporal lobe and pontomesencephalic region. Of the 12 cases reporting cyst dimensions, the average diameter of those reported was 3.4 cm (range 1.5–5.5 cm).

The ones that have been surgically explored were found to have xanthochromic fluid (Benvenuti et al., 2006; Hirota et al., 1999; Marcoux et al., 2002; Pedro and Sih, 2020; Jayakumar et al., 2019; Friedman et al., 2003). Cyst biopsies were generally reported as showing areas of reactive gliosis (Benvenuti et al., 2006; Sato et al., 2000; Friedman et al., 2003; Kulwin et al., 2015), with varying reports of associated neovascularisation (Takai et al., 2001) and inflammatory cells (König et al., 2011). The presence of xanthochromic fluid with a gliotic cyst wall is similar to our experience.

4.2. Mechanism of cyst development

Although numerous mechanisms have been proposed in an attempt to

Table 1
A summary of the literature on Perianeurysmal Parenchymal Cysts.

Author	Age (years)	Sex	Clinical Presentation	Aneurysm			Cyst			Outcome	
				Location	Size (cm)[a]	Thrombus	Size (cm)[a]	Characteristics	Location	Aneurysm	Cyst
Hirota et al. (Hirota et al., 1999)	71	M	Weakness Speech disturbance History of SAH	MCA	"giant"	Yes	N/A	Xanthochromic fluid	B.G./Temporal	Clipping	Open fenestration
Sato et al. (Sato et al., 2000)	51	M	Seizures	PCA	2.0	Yes	3.5	Gliosis	B.G.	Endovascular	Biopsy
Sato et al. (Sato et al., 2000)	62	M	Incidental	TICA	1.5	No	1.5	N/A	B.G.	Endovascular	–
Sato et al. (Sato et al., 2000)	35	F	Headache	PCA	1.9	No	2.5	N/A	M.B.	Clipping	–
Sato et al. (Sato et al., 2000)	46	M	Headache	ACA	0.9	No	2.0	N/A	Frontal	Clipping	–
Sato et al. (Sato et al., 2000)	57	M	Unknown	ACA	4.0	Yes	3.4	N/A	Frontal	Died of aneurysmal rupture	–
Takai et al. (Takai et al., 2001)	64	F	Alexia Anomic aphasia	PCA	2.5	Yes	5.5	Gliosis Neo-vascularisation	B.G.	Endovascular	Endoscopic fenestration
Marcoux et al. (Marcoux et al., 2002)	62	F	Post-endovascular coiling History of SAH	AComm	N/A	N/A	2.5	Xanthochromic fluid	Interhemispheric	Endovascular	Open fenestration
Friedman et al. (Friedman et al., 2003)	70	F	Post-endovascular coiling Dysarthria Dysphaghia Weakness	BA	1.5	N/A	N/A	Xanthochromic fluid Gliosis High protein	Ponto-mesencephalic	Endovascular	Open fenestration – valveless cysto-peritoneal shunt - recurrence
Benvenuti et al. (Benvenuti et al., 2006)	54	M	SAH	MCA	"large"	N/A	N/A	Xathochromic fluid	Temporal	Clipping	Open fenestration
Martinez et al. (Martinez Galdamez et al., 2011)	74	M	Headache	MCA	2.0	Yes	N/A	N/A	Temporal	Endovascular x2	Spontaneous resolution
Konig et al. (König et al., 2011)	60	F	Post-endovascular coiling	TICA	1.7	N/A	5.0	Gliosis Macrophages	B.G./Frontal	Endovascular x2	Open fenestration - Endoscopic fenestration - Open lesionectomy with coil mass removal
Barber et al. (Barber et al., 2014)	72	F	Post-endovascular coiling Visual complaints Headache	BA	1.6	N/A	N/A	N/A	Ponto-mesencephalic	Endovascular	–
Norris et al. (Norris et al., 2015)	80	F	Post-endovascular coiling	TICA	1.3	N/A	N/A	N/A	B.G.	Endovascular x2	–
Kulwin et al. (Kulwin et al., 2015)	74	F	Headache Gait disturbance	MCA	N/A	N/A	N/A	Gliosis "Greenish" fluid	B.G.	Surgical trapping	Open fenestration
Jayakumar et al. (Jayakumar et al., 2019)	64	M	Altered behaviour Gait disturbance	TICA	N/A	Yes	N/A	Xanthochromic fluid	B.G.	Clipping	Endoscopic fenestration + VAD - > Open fenestration
Pedro et al. (Pedro and Sih, 2020)	50	F	Weakness Numbness	PCA	1.2	Yes	2.9	Xanthochromic fluid	Pontomesencephalic	Clipping	Open fenestration
Zammit et al.	61	F	Incidental	TICA	2	No	3.6	N/A	B.G.	Endovascular x2	–
Zammit et al.	68	M	Incidental	TICA	2.1	No	3.3	N/A	B.G.	Endovascular	–
Zammit et al.	75	F	Collapse	MCA	2.1	Yes	5.0	Xanthochromic fluid/ Proteinaceous	B.G.	Endovascular x2	Endoscopic fenestration - Cysto-peritoneal shunt - Access device insertion

VAD – ventricular access device, MB - Midbrain, B.G. – Basal ganglia, N/A – not available.
[a] Average diameter.

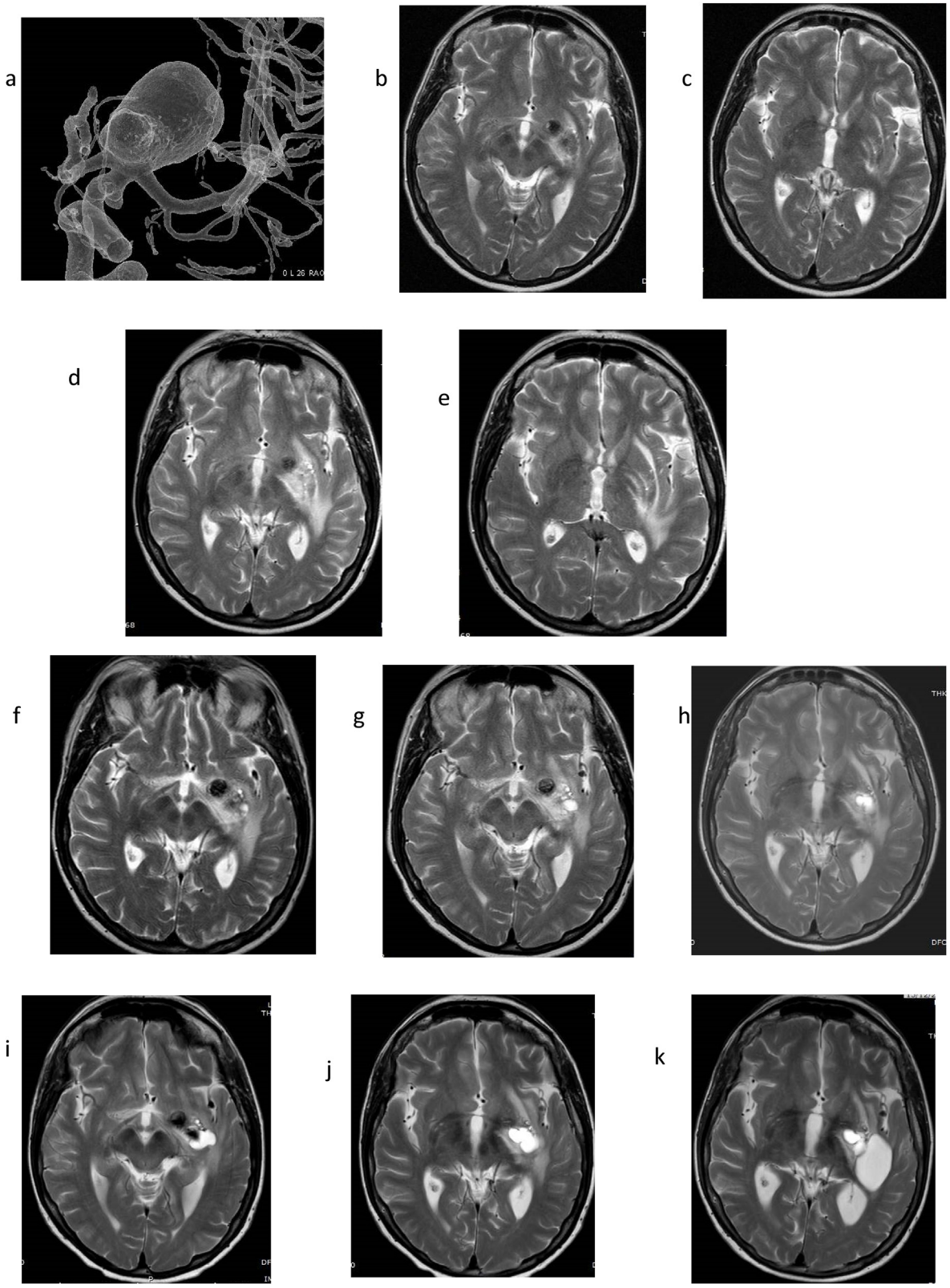

Fig. 1. Frontal projection left frontal internal carotid artery 3D DSA demonstrates a giant terminal internal carotid artery aneurysm (a). T2W axial MR images 6 months (b,c), 18 months (d,e), 21 months (f), 27 months (g), 36 months (h), 51 months (i,j) and 119 months (k) after embolisation demonstrate development of progressive oedema and progressive enlargement of cystic spaces.

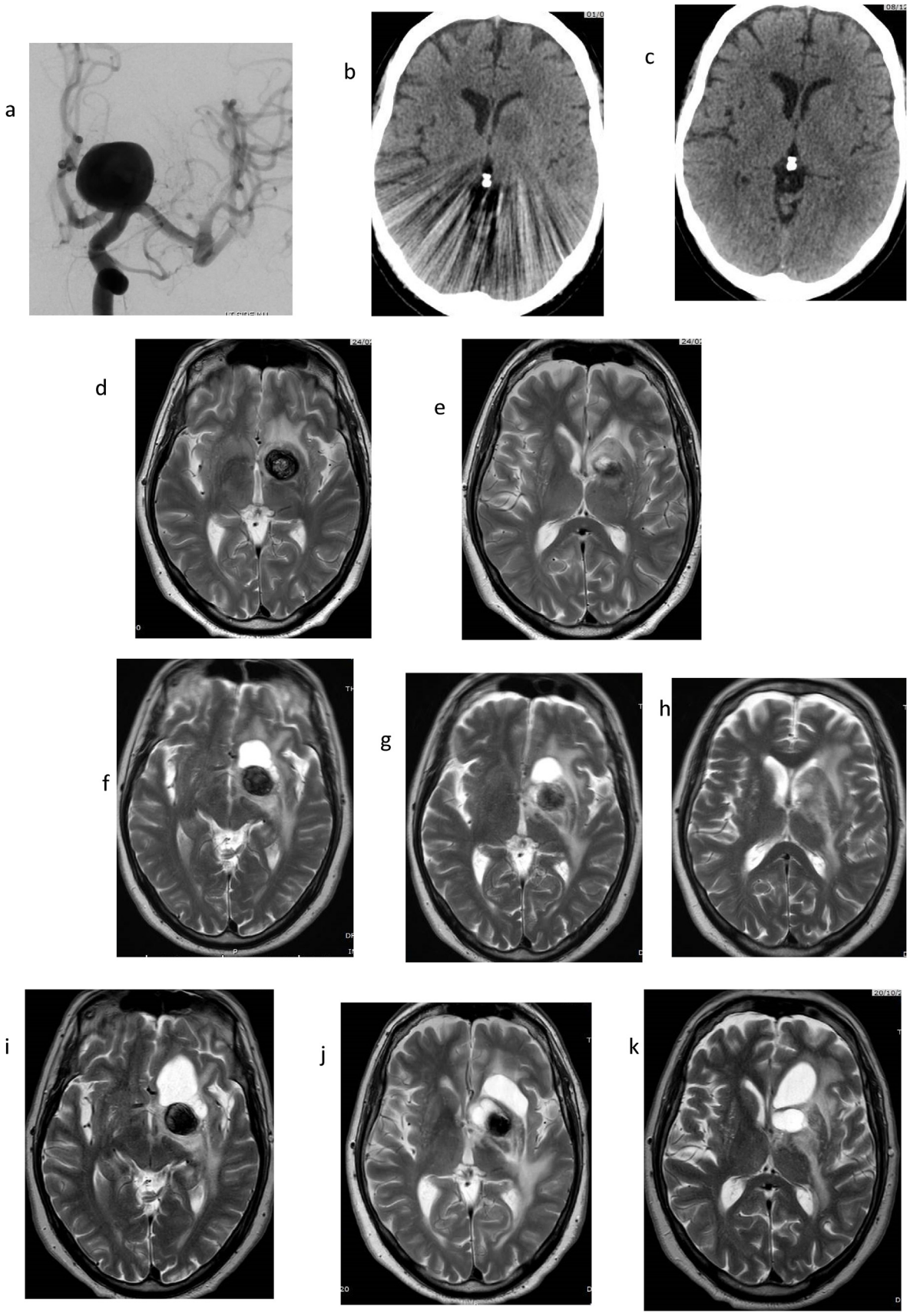

Fig. 2. Frontal projection of a left internal carotid angiogram (a) demonstrates a large terminal internal carotid artery aneurysm. Axial unenhanced cranial CT scans (b,c), the day after embolisation, show a small amount of oedema in the left basal ganglia.
T2W axial MR images one month (d,e), 12 months (f,g,h) and 33 months after embolisation (i,j,k) show progressive oedema, development and enlargement of the perinaneurysmal cysts.

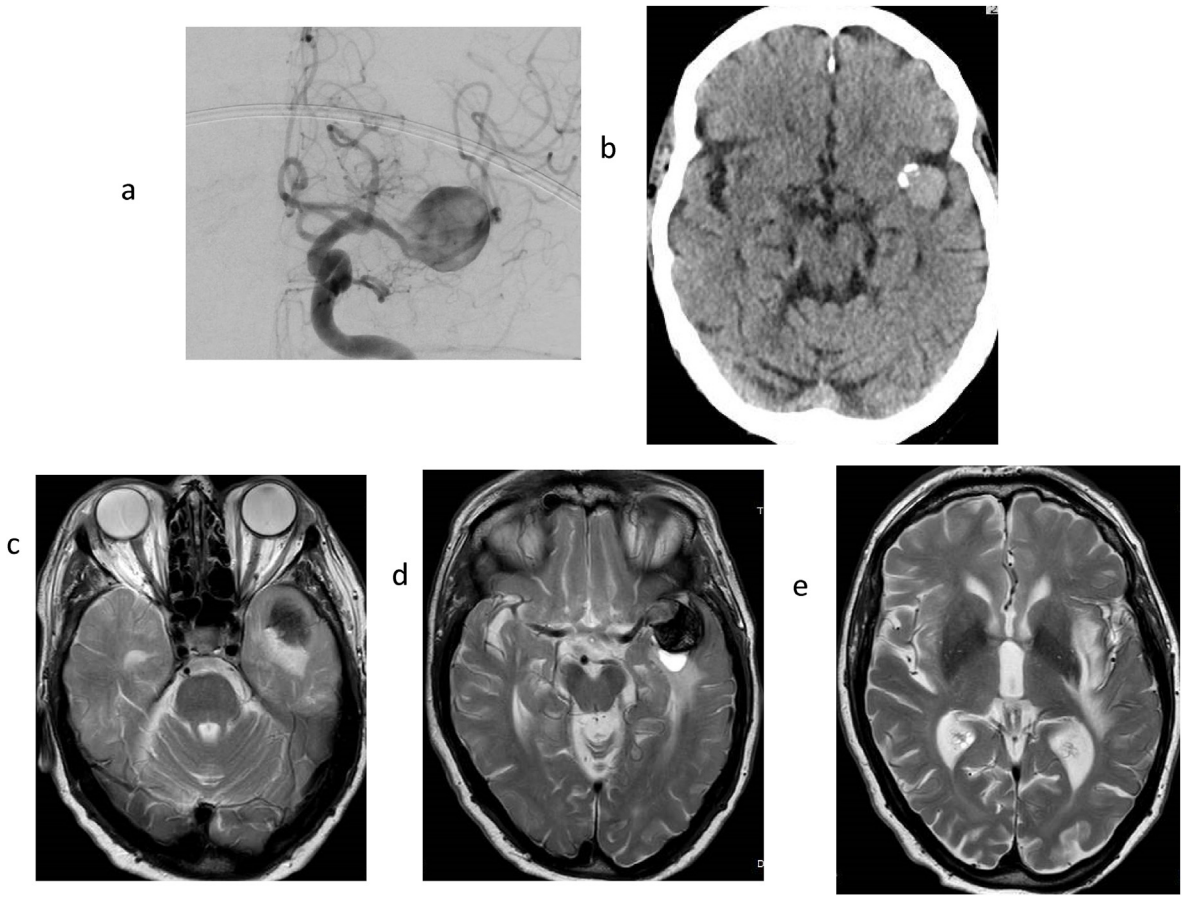

Fig. 3. Frontal projection left internal carotid angiogram demonstrating the giant bifurcation left middle cerebral artery aneurysm (a), axial unenhanced cranial CT scan pre-embolisation demonstrating the aneurysm without associated oedema or cyst formation (b), and T2W axial MR images 6 months post embolisation (c,d,e), demonstrating the development of oedema in the left temporal lobe, deep to the insula and in the posterior limb of the left internal capsule and optic radiations. Axial T2W MR images at 14 months post embolisation (f,g,h), show some increase in oedema and enlargement of the cyst, 21 (i,j) and 27 (k) months post embolisation and 33 (l,m) months post embolisation, demonstrate further significant cyst enlargement with increasing oedema (i,j,k) and decrease in both oedema and cyst volume post shunt insertion (l,m). There has also been progressive ventricular enlargement, the result of a communicating hydrocephalus.

explain the formation of these cysts, the cause remains uncertain.

Extrapolating from the observations made above, it is likely that frank SAH plays a limited role in the development of a PPC. However, asymptomatic or subclinical microhemorrhages could be linked to the development of cystic changes, as previously observed in cavernomas (Bellotti et al., 1985; Gangemi et al., 1989; Hatashita et al., 1991; Itakura et al., 1989; Savoiardo and Passerini, 1978; Steiger et al., 1987; Yagi et al., 2005; Huang et al., 2011) and AVMs (Hatashita et al., 1991; Itakura et al., 1989; Sakamoto et al., 1997; Takifuji et al., 1989; Yamaguchi et al., 1993). In the remaining cases, other possible mechanisms put forward include direct exudate from the aneurysm itself, pulsations of the aneurysm resulting in a cyst, blood-brain barrier breakdown or the effect of abnormal angiogenic growth factors, such as vascular endothelial growth factor (Hirota et al., 1999; Sato et al., 2000). Some of these putative factors are similarly implicated in the pathogenesis of cysts in a variety of other pathologies, including tumours (Lohle et al., 1992) and other vascular lesions (Harrigan, 2003; Skirgaudas et al., 1996; Weindel et al., 1994). Friedman also suggested that ischemic encephalomalacia adjacent to the aneurysm, occurring during thrombosis maturation, serves as a focus of least resistance for exudate to accumulate (Friedman et al., 2003).

In our series, all patients developed PPCs after a period of preceding perianeurysmal oedema. Based on this observation from our series and other cases reported in the literature we have also developed our hypotheses of other possible driving forces behind the origin of PPCs.

a) Dilated Perivascular Virchow-Robin Spaces

Perivascular Virchow-Robin spaces are pial-lined interstitial-fluid-filled spaces that surround the walls of arteries, arterioles, veins and venules as they course from the subarachnoid space through the brain parenchyma. Whereas small Virchow-Robin spaces appear in all age groups, larger Virchow-Robin cysts (VRC) can sometimes develop (Wani et al., 2011). The fluid residing in these spaces arises from bulk flow diffusion of parenchymal interstitial fluid. This process is thought to have a significant role as a drainage pathway for metabolites arising within the brain parenchyma. However, the direction of flow, as well as the anatomical structures involved and the driving forces are as yet unclear (Kwee and Kwee, 2007; Bakker et al., 2016).

VRC predominantly arise in the region of the basal ganglia and pontomesencephalic junctions (Kwee and Kwee, 2007), similar to the previously highlighted distribution of PPCs. Histological evidence from PPCs in our series and others previously published in the literature described a thin gliotic wall with no pial layer. The absence of a pial layer has also been previously described in large VRCs (Salzman et al., 2005). It is, therefore, possible that PPCs represent a form of VRC. The combination of increased interstitial fluid in the surrounding parenchyma as a consequence of oedema, possible impairment of perivascular space drainage pathways, coupled with a possible increase in oncotic pressure within these spaces from the accumulation of protein consistent with the observed xanthochromic discolouration of PPC fluid, could drive the creation of a cystic cavity in these spaces.

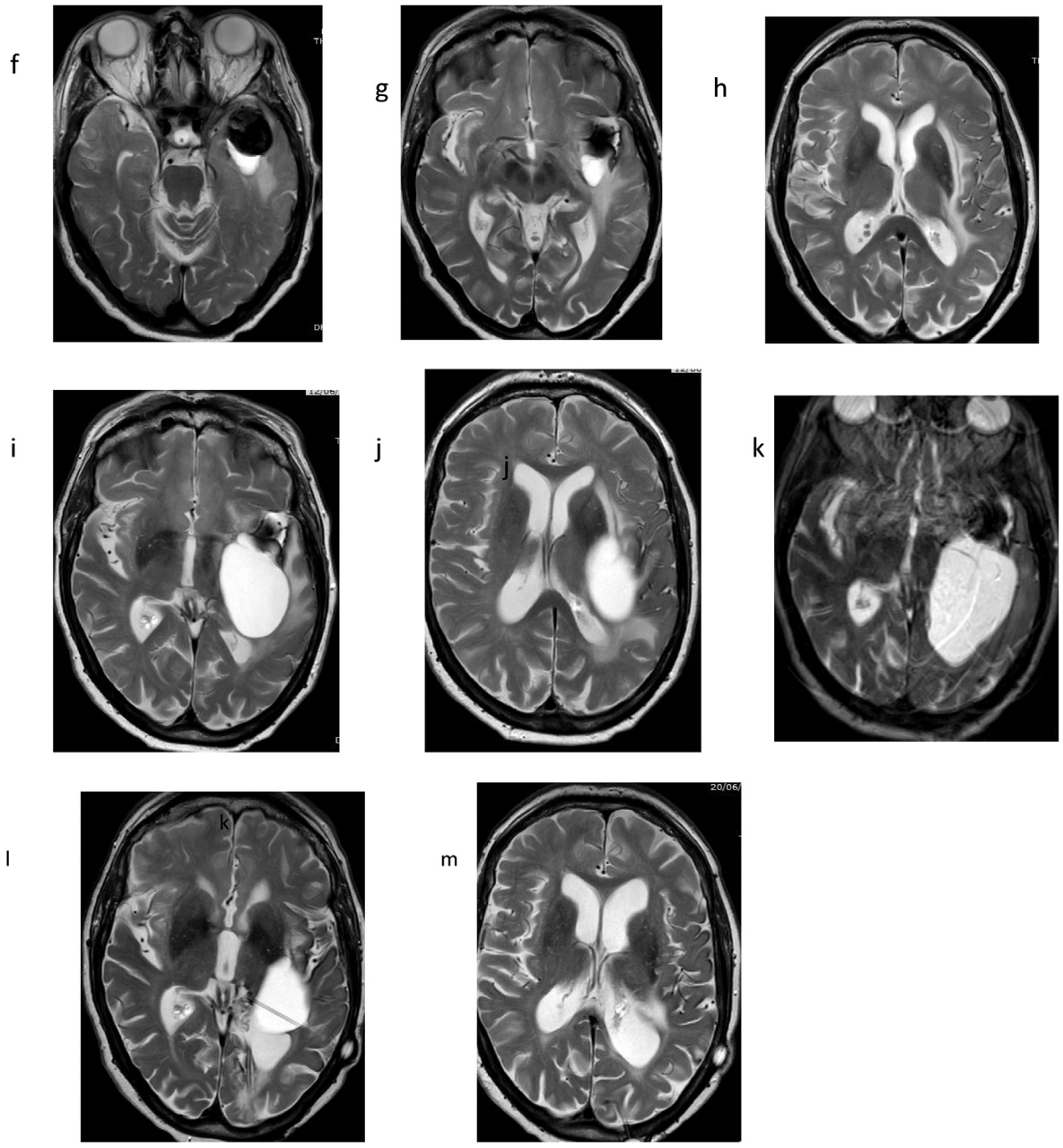

Fig. 3. (*continued*).

Similar to PPC, progressive dilatation of isolated VRC has also been observed. Some of the theories previously put forward to explain VRC growth could also apply to PPC progression, including obstruction of drainage routes of interstitial fluid (Homeyer et al., 1996; Mascalchi et al., 1999; Pollock et al., 1997), increase in the permeability of the associated vessel in the VRS (Poirier et al., 1983; Benhaïem-Sigaux et al., 1987) and gradual leaking of the interstitial fluid from the intracellular compartment to the pial space around the metarteriole through alteration of blood-brain barrier (Adachi et al., 1998).

Furthermore, increased MRI T2 and FLAIR signal, similar to the precursor radiological 'oedematous' changes noted in the perianeurysmal regions, is also noted around giant VRC (Salzman et al., 2005).

b) Inflammatory Process

It has been previously suggested that inflammation plays a role in aneurysmal development, enlargement and thrombosis (Krings et al., 2007; Dengler et al., 2015), with thrombosis and inflammation known to be interlinked through numerous factors (Sexton and Smyth, 2014). Of note, therefore, is the fact that the majority of the aneurysms associated with PPC either have evidence of thrombosis at presentation or arise in patients who have been treated endovascularly with subsequent coil-mediated thrombosis.

There is a clear link to endovascular management of aneurysms, with 12 of the 20 reported PPCs developing in patients treated with endovascular coiling. Reports of inflammatory reactions to coiling of ruptured and unruptured aneurysms have been published in the literature – the most pronounced being the ones associated with modified coated coils (Fanning et al., 2008; Bavinzski et al., 1999; Onofrj et al., 2021; Molyneux et al., 1995; Stracke et al., 2007). These coils were introduced to improve occlusion rates and reduce recanalization by introducing coating with an expandable matrix. Fanning et al. observed the development of de novo perianeurysmal oedema in 8.9% of unruptured aneurysms treated with coated coils (HydroCoil)(Fanning

et al., 2008). Aseptic meningitis with the development of delayed hydrocephalus was also reported in 18% of this series of coiled unruptured aneurysms. Both are suggestive of inflammatory responses that extend beyond the vessel wall into the adjacent brain parenchyma and CSF respectively. The mechanism by which this inflammatory response occurs is still unclear, however, it was noted even in embolized small aneurysms and it is therefore not a function of the extent of thrombosis alone.

Thrombosis and coiling may therefore play important roles in initiating inflammatory cascades manifesting as perianeurysmal oedema observed to precede PCC. This could potentially drive neoangiogenesis and increased vessel permeability, with subsequent microhaemorrhages or proteinaceous exudate, in turn, coalescing into cystic collections.

4.3. Natural history and management

The natural history of these PPC is unpredictable. There is a tendency for most reported cysts to enlarge and become symptomatic. Most cases required some form of surgical treatment of the cyst for mass effect or relief of hydrocephalus. This came in the form of open or endoscopic fenestration, cysto-peritoneal shunting, ETV and surgical excision of the coil mass, with some cases requiring combined approaches. Of the latter, Friedman inserted a valveless cystoperitoneal shunt following an open fenestration – this improved the patient's symptoms even though there was further evidence of cyst growth on the 3-month post-operative imaging (Friedman et al., 2003). Konig reported no recurrence of the cyst at 5-month follow-up after an open removal of a recurrent cyst together with clip reconstruction and lesionectomy of the coil mass (König et al., 2011).

In our case series, 1 received treatment because of rapid enlargement and symptomatic mass effect. The patient underwent an endoscopic fenestration, cysto-peritoneal shunt and a subsequent access device insertion with regular aspirations. We believe that the viscous nature of the cystic fluid encountered in this patient impeded effective continuous drainage via shunting. The final insertion of the access device afforded therapeutic relief, with improvement in the patient's dysphasia. Despite the similar pattern of radiological evolution of the cyst to our other 2 reported cases, it is possible that the increased blood products from the SAH could have contributed to the rapid growth of the cyst. Nonsteroidal anti-inflammatories and steroids do not seem to influence the formation and evolution of cysts.

Delayed surgical clipping was not pursued in our historical case series. In retrospect and after reviewing the available literature this could have represented a more viable management strategy in the setting of symptomatic perianeurysmal cysts, especially in association with enlargement of aneurysm remnant. Repeat endovascular management attempts in patients with PPC might also presumably be associated with multiple inflammatory insults leading to progressive PPC enlargement.

A few reports of conservatively managed PPCs exist. Sato reported no intervention in 4 of his 5 cases with no reported follow-up for the conservatively managed group (Sato et al., 2000). Martinez's case is unique in that the PPC present pre-embolisation enlarged significantly after the first coiling procedure but resolved spontaneously after an intra-procedural rupture of second coiling to treat an aneurysmal recurrence caused an intracystic haemorrhage (Martinez Galdamez et al., 2011). Norris reported ongoing cyst growth over 15 months, with associated worsening of their patient's movement disorder successfully managed with increasing doses of levodopa (Norris et al., 2015). Barber managed hydrocephalus associated with outflow obstruction secondary to the PPC with an ETV, with no report available on PPC growth after that (Barber et al., 2014).

Our first 2 conservatively-managed cases have been followed up with yearly MRI/MRA, with a duration of follow-up so far of 9 and 4 years since cyst formation and general follow-up from aneurysm diagnosis of 9 and 6 years, respectively. So far, these conservatively managed cysts have either stabilized or enlarged at a slow rate.

5. Conclusions

PPC continue to present a puzzling clinical entity and several hypotheses have been presented to explain their occurrence. They have been reported to occur both before and following aneurysm obliteration, either by microsurgical clipping or endovascular coiling, although are commoner in the latter group. The cases described are generally larger, partially-thrombosed aneurysms, in older patients. The cysts tend to enlarge over time if not treated and can recur following treatment. As the number of cases reported accumulates, it will also improve our understanding of the pathophysiology and natural history of these cysts. Our case series further contributes to the expanding body of information about this rare condition. To our knowledge, this is the only series highlighting progressive perianeurysmal oedema and cyst formation.

CRediT author statement

Adrian Zammit: Analysis & Interpretation, Writing – Original, Review & Editing. Andrei Tudose: Data curation, Writing- Original draft preparation. Nicklaus Khan: Writing – Review & Editing. Shelley Renowden: Writing – Review & Editing, Resources. Mario Teo: Conceptualization, Project administration & Supervision, Writing – Review and Editing.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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