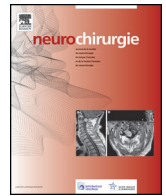




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Original article

Growth of giant intracranial aneurysms: An aneurysmal wall disorder?

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ABSTRACT

The enlargement of giant intracranial aneurysms (IA) can be observed in 30 % of cases resulting in a neurological deficit and epilepsy due to its mass effect. This growth process could be due to a morphological disorder of the IA wall. The authors report on 2 cases of giant IA growth responsible for intracranial hypertension. The treatment of these giant IA required a microsurgical excision combined with a series of cerebral revascularization procedures. The role of *vasa vasorum* on the inflammatory granuloma outside the vessel, which induced the enlargement, is discussed. These cases illustrate the abluminal vasculopathy as the main involvement of this unfavourable natural history.

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1. Introduction

The giant intracranial aneurysm (IA), representing 2–4 % of all aneurysms [1–5], are unstable dynamic entities responsible for a morbidity and mortality rate of approximately 65 % at 2 years [6–10]. In addition to the aneurysm fissuration which occurs in 40 to 60 % of patients at 5 years [9,10], the aneurysm enlargement has been observed in 30 % of patients over a period of 16 days–5 years resulting in neurological deficit and epilepsy due to its mass effect [11–13]. This growth event probably occurs in a particular subgroup of giant IA which are the partially thrombosed aneurysms. These aneurysms are differentiated from those that are completely perfused and more prone to fissuration [14]. This process of growth could be due to a morphological disorder of the IA wall [15]. The aim of our study was to report 2 cases of giant IA, which illustrated the process of growth from the wall sac and discuss the pathology involved reported in the literature.

2. Case report

2.1. Case #1

2.1.1. Initial management

A 20-year-old male patient was admitted in emergency for drug-resistant headaches. The patient presented with intensive headaches, nausea, and a memory disorder reported by his mother. At examination, we observed a bilateral papillary edema on the fundus without any decrease in visual acuity, a mini mental scale (MMS) of 23/30 and no sensitive or motor deficit. His previous medical history was characterized in 2009 by the diagnosis on MRI of a fusiform dilatation on the horizontal (M1) segment of the right middle cerebral artery (MCA) combined to smoking as a vascular risk factor. The neurovascular team proposed an annual radiological follow-up of this arterial fusiform dilatation of 7 mm and an end to smoking addiction due to the benefit-risk balance of treatment. The patient was lost to follow-up in 2012 (Fig. 1).

At the admission, the CT scan with no contrast agent revealed a 30 mm nodular lesion occupying all the temporal fossa, opening the right sylvian fissure and responsible for an hydrocephalus with mass effect on the third ventricle. The brain magnetic resonance imaging (MRI) suggested the diagnosis of serpentine giant aneurysm on MCA due to a large partial thrombosis (Fig. 2). The cerebral angiography confirmed a serpentine channel on the superior aspect of the aneurysm located on the right side of the MCA. The occlusion test balloon of the right internal carotid artery (ICA)

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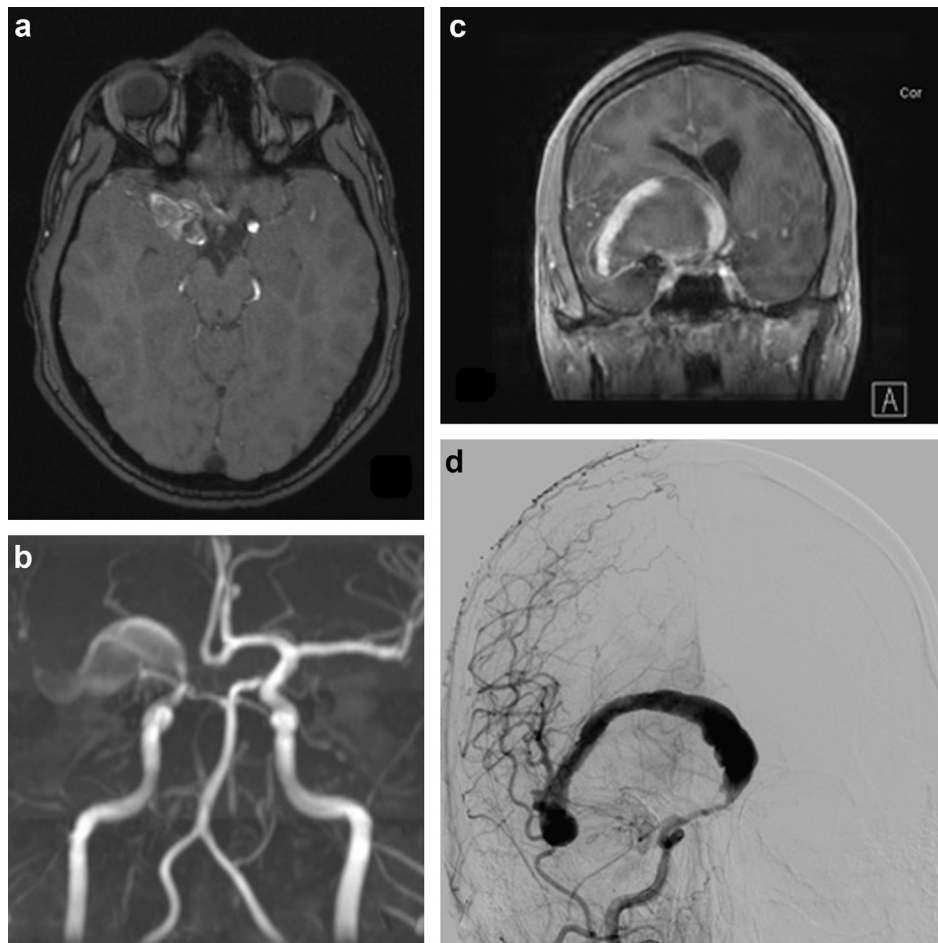


Fig. 1. a: axial time of flight (TOF) image shows the tumoral and circulating part of the aneurysm, measuring $30 \times 21 \times 17$ mm, justifying the conservative treatment; b: frontal rebuilding views of TOF revealed the circulating part of the dysplasia concerning the M1 segment of the right MCA. Segment M2 is free from the dysplasia; c: three years later, coronal gadolinium enhancement T1-weighted MRI showed bulky thrombosed part, and permeable channel at the upper part of the aneurysm are found, like in the Digital Subtraction Angiography (DSA); d: it was measured to $61 \times 30 \times 39$ mm. The important midline shift showed on this MRI, because of the volumetric growing (+370 %), make chosen quick surgical management.

was negative due to the absence of perfusion on the distal territory of the MCA via the anterior communicating artery.

Prior to the optimal management of this complex aneurysm, the papillary edema required a ventriculo-peritoneal shunt (VPS) implantation in emergency. A visual deterioration, due to the persisting mass effect, was observed despite the complete resolution of a papillary edema: binocular diplopia related to third cranial nerve paralysis and visual acuity of the left eye which decreased to 2/10.

After discussion with several neurovascular teams, we proposed a procedure of cerebral revascularization permitting a resolution of mass effect by removal of the giant aneurysm.

2.1.2. Operative report

Under general anesthesia, installation of an extracorporeal circulation (ECC) system was performed. The arc shape cutaneous incision for a fronto-pterional access was carried-out in front of the superficial temporal artery (STA), previously identified by Doppler ultrasound. Then ECC was started under hypo-coagulation. The proximal part of the fusiform aneurysm was disconnected from the supraclinoid portion of the ICA and clipped. After performing an end-to-side anastomosis between the STA and the M2 segment of the MCA, the intra-aneurysmal thrombosis was removed in order to resolve the mass effect. Intraoperative video and indocyanine angiography confirmed bypass patency. The histopathological report confirmed inflammatory reaction in the aneurysmal wall

with large atherosclerosis and thrombosis. Moreover, neoangiogenesis and intra-mural bleeding occurred.

2.1.3. Outcome

The immediate postoperative CT angiography confirmed the good permeability of the STA-MCA bypass. A ventricular dilation required drainage by external ventricular derivation (EVD). The patient awoke with an incomplete left hemiplegia, which gradually improved. One month after the surgery, the patient presented with a left hemiparesis (4/5), and a left hand deficit thin movement and diplopia. At 6 months, the patient was able to walk, with disability to run. We also found a paresis of left upper limb and left central facial paralysis grade I, with no diplopia. The MMS was evaluated at 28/30.

Postoperative MRI, revealed a right hemispherical hypoperfusion: right side cerebral blood flow was estimated at 19.83 ml/sec for the left side at 49.2 ml/sec and cerebral blood volume of 2.4 ml on the right for 3.4 ml on the left. At 6th months, the MRI showed no cortical ischemia. The STA-MCA anastomosis diameter was measured at 1.8 mm.

2.2. Case #2

2.2.1. Initial management

A 57-year-old male patient consulted for fortuitous diagnosis of giant aneurysm located at the major bifurcation of the right MCA

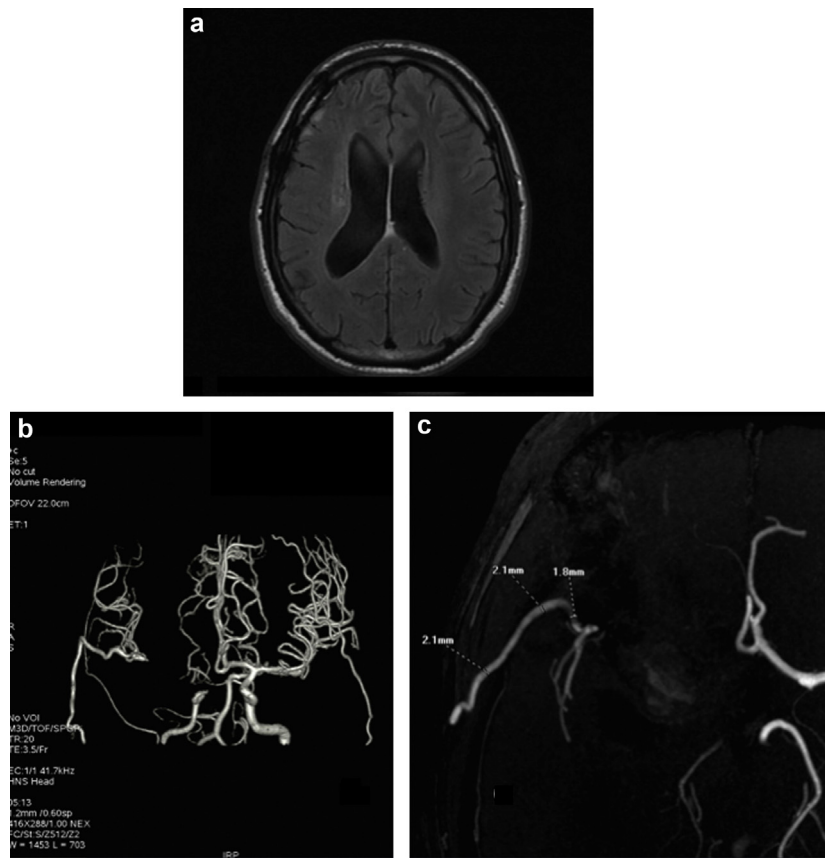


Fig. 2. a: T2-weighted FLAIR MR image postoperative revealed no cerebral ischemia in the right MCA territory; b: 3D reconstruction from TOF sequence showed perfectly the right cerebral vascularization by the external carotid artery; c: the STA-MCA anastomosis diameter was measured to 1,8 mm in proximal and 2,1 mm in distal.

revealed by MRI (Fig. 3a). His previous medical history was characterized by chronic limb arteriopathy and a vascular risk factor of arterial hypertension, dyslipidemia and smoking. The cerebral angiography confirmed the partial thrombosis of a giant aneurysm (Fig. 3b), only the upper part of the aneurysm circulated. After prescription of antiplatelet agent, the National College of Vascular Neurosurgeons proposed surgical treatment using a cerebral revascularization procedure.

Two months later, the patient was admitted in emergency for sudden and severe headaches. The clinical examination revealed a memory disorder, executive and linguistic difficulties (MMS = 19/30). The MRI showed a major (130 %) size × aneurysm diameter increase due to a dissecting hematoma in the sac wall (Fig. 4) responsible for a large mass effect. The CT angiography confirmed the size increase due to a dissecting hematoma in the sac wall from the thrombosis part of the aneurysmal sac, the bifurcation remained circulating.

The rapid neurological deterioration due to the intracranial hypertension required an early neurosurgical solution.

2.2.2. Surgery report

Under general anesthesia, an arc shape incision was performed for a fronto-pterional access, in front of the STA, individualized by Doppler ultrasound. After a craniotomy, the mass effect resulted in a primary reduction of the giant aneurysm from the non-circulating part of the aneurysm. This reduction permitted the dissection of the MCA bifurcation, but the endocranial atherosclerosis required to sacrifice the major MCA bifurcation. At first, an end-to-end anastomosis was performed between M1 and temporal artery (M2) and an end-to-side between the frontal artery (M2) and M1. Intraoperative video indocyanine angiography confirmed bypass patency and

the complete removal of the aneurysmal sac was performed. The histopathological report confirmed the inflammatory reaction in aneurysmal wall with inflammatory granuloma and intrasaccular thrombosis. Moreover, neoangiogenesis with intra-mural bleeding was present.

2.2.3. Outcome

The immediate postoperative CT angiography confirmed the good permeability of the MCA-MCA bypass. In the postoperative period, the patient awoke with an incomplete left hemiplegia, associated with a left hemianopsia, and left hemispatial neglect. Two weeks after the surgery, the left hemiparesis had disappeared, but hemianopsia and hemispatial neglect persisted in association with a temporo-spatial disorientation. At discharge, the patient was able to walk, and presented a MMS evaluated at 17/30.

At 6 months, the MRI showed ischemia in the territory of the temporal branch of the right MCA, and the MMS was evaluated at 26/30.

3. Discussion

In our 2 cases, the intracranial hypertension due to this growing giant IA was the major argument to propose these complex strategies, of microsurgical resection combined with various bypass techniques, with recovery of functional autonomy at 6 months. Our cases illustrated by serial neuroimaging the instability of giant aneurysms, which may even occur after some weeks as in our case #2. In the absence of the histopathological investigation of both reported aneurysmal cases, it is not possible to argument one mechanism but only serves to illustrate growth and stimulate reader's curiosity.

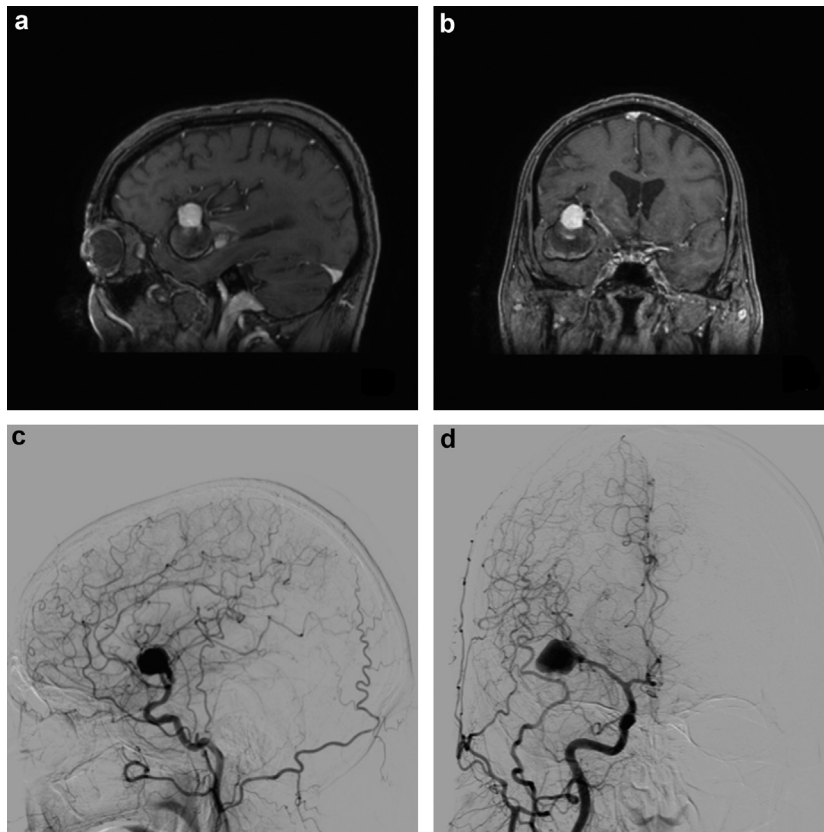


Fig. 3. T1-weighted MRI with gadolinium enhancement in sagittal (a) and coronal (b) views showed a giant aneurysm partially thrombosed, measuring approximately 37×34 mm with a circulating part of 15×16 mm. At its posterior portion, was showed a high signal intensity on T1-weighted who traduced a sub-acute hemorrhagic event due to neovascularization of the aneurysm's wall. DSA (c, d) confirmed this aneurysm of the right middle cerebral artery, measuring 16×18 mm with a neck measured to 5 mm.

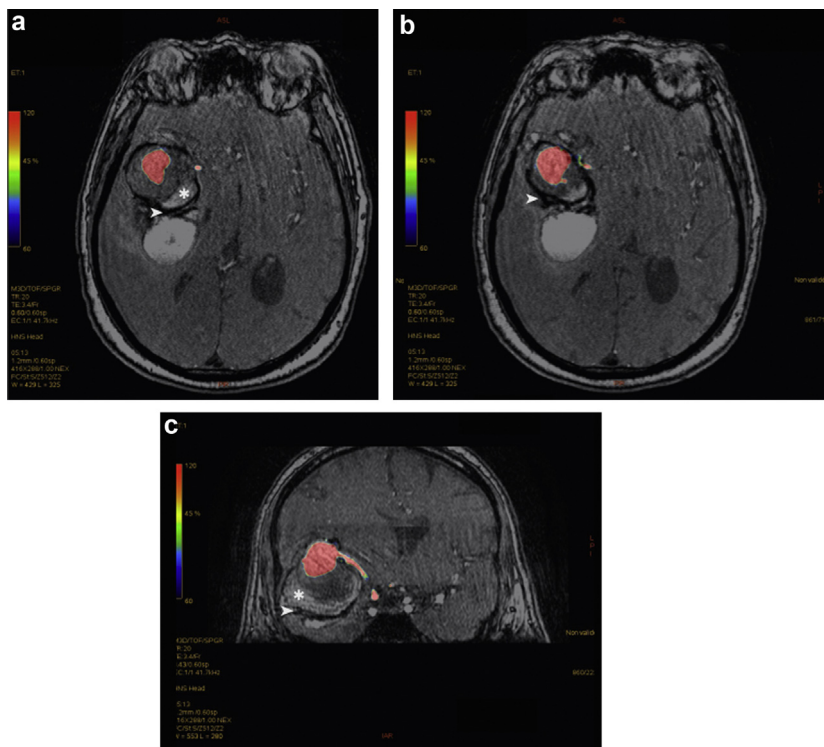


Fig. 4. Fusion between, the two month later images, T1-weighted MRI and CT angiography. The colored part corresponded to the circulating portion of this aneurysm. On axial reconstruction (a, b), the arrow showed the wall's aneurysm. The recent bleeding was inside this wall at the peripheral part, corresponding to the T1 high signal intensity (*). Coronal view (c) showed the important mass effect on the midline, due to the growing, with a deviation of 11 mm towards the left.

The growth of giant IA, classically considered as a pseudo-tumor, could be the result of the interplay between luminal and abluminal factors applied on the IA wall [14,15]. Based on our literature analysis, we were able to better understand the parameters which determined this malicious natural history.

3.1. Luminal vasculopathy: shear stress thrombus formation hypothesis

The growing IA process is a complex association of mechanisms depending on hemodynamic conditions. The most representative hemodynamic parameter is the wall shear stress (WSS), defined as the frictional force exerted by the blood flowing tangentially on the vessel lumen [16–18]. WSS is a mechanical trigger transducing to the vessel wall into biological signals (mediators of remodeling) reported by Chalouhi et al. [19] as endothelial dysfunction related to hemodynamic stress. It is determined by its vulnerability, the initial outpouching, the IA growth and its geometric outcome [16,20,21].

Taking into account the intraoperative observation of unruptured IA, the giant IA may be considered as a type II phenotype [22,23]. These types of aneurysms are characterized by their large size with an irregular surface on which yellowish plaques of atherosclerosis obstruct the intra-aneurysmal blood flow. The histologic analysis of this type II phenotype IA confirmed a low rate of thin-walled regions with high rate of thick walls with atherosclerotic changes and inflammatory cells [24–26]. Moreover, recent studies using image-based computational fluid dynamics (CFD) have shown the confusing role of low or high WSS involved in the development of IA. Interestingly, Meng et al. hypothesized that the WSS-low-driven could be responsible for type II IA [21,27].

This inflammatory-cell-mediated pathway could be considered as a repair or remodeling process of the IA wall determining the histological characteristics of unruptured IA (such as inflammatory infiltration, smooth muscle cell migration to intima and thrombus organization [26]). This atherosclerotic process inside the IA wall subsequently determined the formation of luminal thrombus related to the exposition of thrombogenic material from atherosclerotic plaque to the blood stream [28–30]. This intramural thrombus, initially atherosclerotic, might become growing by combination of inflammatory process to recurrent bleeding secondary to neoangiogenesis in type II IA wall.

The growing geometry of giant aneurysm was due to abluminal process determining thrombus expansion mediated by inflammatory processes. The 5-lipoxygenase (5-LO) pathway of arachidonic acid metabolism, leading to the biosynthesis of the potent lipid inflammatory mediators leukotrienes, would involve in the neoangiogenesis process. Moreover, the Krüppel-like zing-finger transcription factor 5 (KLF5) was highly expressed in large and giant unruptured aneurysms [31].

3.2. Abluminal vasculopathy: intramural dissection hypothesis

Some authors have reported their detailed observations of this IA growth process. Kaneko et al. [13], describing a serial neuroimaging of a distal anterior cerebral artery IA becoming giant in an 82-year-old patient, focused their observation on a lobulus growth appearing as high intensity on T1- and low intensity on T2-weighted images at its periphery. This small lesion was considered to indicate a new hemorrhage 2 months after the diagnosis of aneurysm growth. Katayama et al. [32], reported a case of completely thrombosed IA becoming giant despite the absence of patent arterial lumen. Its onion-skin appearance on MRI was interpreted as various stages of hemoglobin degradation [33,34]. The layers of fresh thrombus are diagnosed within the periphery of giant aneurysm. In contrast, older thrombus could be detected in the central parts [33,35,36]. In our case #2, the growing process was

located on the periphery (temporal pole of IA) away from the circulating blood flow component.

This “onion-skin” organization of the intramural thrombus argues in favor of the hypothesis of intramural recurrent hemorrhage rather than intraluminal accumulation of thrombotic material. The apposition of new layers of thrombus in periphery of the giant IA could involve the neoangiogenesis developed within the aneurysmal wall. As proposed by Lasjaunias et al. [37], the growth of a giant IA must be understood as an abluminal process from the outside of the lesion. Curiously, our 2 cases differed morphologically: serpentine IA in contrast to the nodular could be determined by the initial location and shape of the atherosclerotic thrombus. The IA neck size combined to the blood flow axis of the parent vessel could be the determining factors. For example, a sessile IA could determine an extensive intramural thrombus by the shear flow, resulting in the constitution of serpentine giant IA.

Moreover, the intramural recurrent hemorrhage could be related to dissection process driven by the shear stress on the edge of the aneurysm neck or at the vessel dissection point. Nevertheless, this place of least resistance may be far from the far from the origin of bleed.

3.3. Vasa vasorum involving

This intramural recurrent hemorrhage of growing IA could be related to the pathological wall involving the *vasa vasorum* [14,15]. The *vasa vasorum* constitutes an arterial network of 20–30 μm within the adventitial layers supplying nutriment and oxygen to the media and adventitia [38]. In contrast to the extracranial arteries, the intracranial *vasa vasorum* does not exist at the birth. However, in some autopsy series of adults, specimens were observed at the proximal portion of the ICA and vertebral artery just in contact with the dural penetration [39–42]. There is evidence that the *vasa vasorum* develops in response to a pathological process such as atherosclerosis [43] or large aneurysm [39,44–47]. Different mechanisms require the involvement of *vasa vasorum* in the growth of giant aneurysm. The repeat bleeding from *vasa vasorum* deposits outer layers of intramural hematoma [37]. The inflammatory process on the aneurysmal wall was induced by *vasa vasorum* and release of vascular growth factors [48]. This process could be involved into some associated perianeurysmal edema related to the loss of brain blood barrier in contact to the *vasa vasorum* [49].

Moreover, this inflammation induces a vicious circle of wall neoangiogenesis from the *vasa vasorum* like within the neomembrane of the chronic subdural hematoma. The complete or partial occlusion of *vasa vasorum* may create some points of weakness in the vessel wall [50]. This process was responsible for necrosis or intramural fissuration. CT scan and the MRI could be able to identify the density increasing of neoangiogenesis into the wall of this growing aneurysm. From report of 3 cases of giant aneurysm analyzed by CT scan, Byrd et al. [51] speculated that the adventitial inhomogeneous enhancement represented wall neoangiogenesis. Iihara et al. [47], reporting an anatomo-clinic case of thrombosed giant vertebral aneurysm, revealed during the intraoperative observation a plethora of *vasa vasorum* from the dura mater appearing as a hyperintense rim on Gd-enhanced T₁-weighted images. Nakatomi et al. [46], from 8 cases of serpentine aneurysms with anatomo-imaging analysis, showed the correlation of the contrast-enhancement of the inside of the aneurysmal wall on MRI and the intimal neoangiogenesis on histological examination. In our case #1, we observed a rim enhancement on the aneurysmal wall on the preoperative MRI. The identification of focal aneurysm wall enhancement on MRI could be considered as the sign of *vasa vasorum* formation. The sequences on 3-T MR Imaging to explore these intracranial vessel walls would be a two-dimensional

T₁-weighted fluid-attenuated inversion recovery (FLAIR), a high-resolution three-dimensional isotropic turbo spin-echo acquisition (VISTA) and a Gd-enhancement T₁-weighted [38].

3.4. Clinical implications

In contrast to the general assumption, the inflammatory process is crucial for the development of this giant aneurysm. Recent study underlined the interest of anti-inflammatory agents in this indication [52,53]. Moreover, the modifications of hemodynamic shear stress by flow diversion could be an interesting way to develop in order to stop the inflammatory process. The use of a pipeline embolization device could determine the protection against the inflammatory vasculopathy [54,55].

4. Conclusion

The growing of giant aneurysm is related to an inflammatory granuloma involving the development of *vasa vasorum* network. This process may occur in some weeks, responsible for intracranial hypertension, requiring the proposition of complex management. In giant IA, the combination of luminal and abluminal vasculopathy is the probable substratum of its growth.

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Disclosure of interest

The authors declare that they have no competing interest.

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