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Review

Role of intraoperative indocyanine green video-angiography to identify small, posterior fossa arteriovenous malformations mimicking cavernous angiomas. Technical report and review of the literature on common features of these cerebral vascular malformations

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ABSTRACT

Objective: To illustrate the usefulness of intraoperative indocyanine green videoangiography (ICG-VA) to identify the nidus and feeders of a small cerebellar AVM resembling a cavernous hemangioma. To review the unique features regarding the overlay between these two vascular malformations and to highlight the importance to identify with ICG-VA, and treat accordingly, the arterial and venous vessels of the AVM.
Methods: A 36-year old man presented with bilateral cerebellar hemorrhage. MRI was equivocal in showing an underlying vascular malformation but angiography demonstrated a small, Spetzler–Martin grade I AVM. Surgical resection of the AVM with the aid of intraoperative ICG-VA was performed. After hematoma evacuation, pre-resection ICG-VA did not reveal tortuous arterial and venous vessels in keeping with a typical AVM but rather an unusual blackberry-like image resembling a cavernous hemangioma, with tiny surrounding vessels. Such intraoperative appearance, which could also be the consequence of a "leakage" of fluorescent dye from the nidal pathological vessels, with absent blood-brain barrier, into the surrounding parenchymal pathological capillary network, is important to be recognized as an unusual AVM appearance.
Results: Post-resection ICG-VA confirmed the AVM removal, as also shown by postoperative and 3-month follow-up DSAs.
Conclusions: Despite technical limitations associated with ICG-VA in post-hemorrhage AVMs, this case together with the intraoperative video, demonstrates the useful role of ICG-VA in identifying small AVMs with peculiar features.

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1. Introduction

Posterior fossa AVMs are rare congenital vascular lesions accounting for 5–20% of all cerebral AVMs [1,2]. Among the former, those involving the cerebellum are more frequent, representing about 60–75% [3,4], and usually present with hemorrhage [1,3,5,6]. Bleeding AVMs are the main cause of hemorrhagic stroke in young healthy patients [1,3,4,7–9], raising concerns regarding their diagnosis and treatment. Current opinions on the management of AVMs suggest a multimodal approach, based on a combination of different types of therapy, including non-surgical ones [2,10,11]. In the contemporary "endovascular era" [11], surgery still plays a crucial role in selected cases [6], also considering the lowest recurrence rate if compared with non-surgical options [1,12]. Intraoperative angiography [13–16] and microscope-integrated indocyanine green video-angiography (ICG-VA) [17] are helpful tools in the surgical management of cerebral vascular malformations. Initially tested to help in intracranial aneurysms surgery [18–27] and to assess cerebral blood flow [28–31], ICG-VA has gained popularity also for its application in brain and spinal AVMs and arterio-venous fistulas [32–37]. Recently, positive experiences with ICG-VA during brain tumor surgery [38–40], resection of cerebral or spinal cord cavernous angiomas [41,42] and carotid endoarterectomy [43] have also been reported. The goal of this paper is to describe, and demonstrate with an intraoperative video the usefulness of ICG-VA during the resection of a small cerebellar AVM showing peculiar morphological features resembling those of a cavernous hemangioma, and to review the literature on the unique features regarding the overlay between these two vascular malformations.

2. Materials and methods

2.1. History and examination

An otherwise healthy 36-year old man, with no evidence of allergy to contrast media, presented with three days history of recurrent episodes of vomiting, nausea and confusion, following an initial "unusual headache". He was conscious but complained of progressively worsening visual and language impairment. Routine blood tests were normal. Neurological examination revealed left-sided dysmetria, dysarthria and diplopia on lateral gaze. Computed tomography (CT) scan showed a left cerebellar hemorrhage extending to the contralateral hemisphere (Fig. 1), with mild compression of the fourth ventricle. Magnetic Resonance Imaging (MRI) confirmed such findings, but uncertain signs of underlying vascular malformation were demonstrated (Fig. 2A). Angiography revealed a cerebellar left-sided AVM, with a small nidus sited in the lateral and superior area of the ipsilateral hemisphere, supplied by feeders originating from an hyperplastic postero-inferior cerebellar artery (PICA) and the superior cerebellar artery (SCA). The main nidus venous drainage was provided by a vein empting into the left transverse sinus (Figs. 3A and 4A). The AVM was graded 1 according to the Spetzler–Martin (S–M) classification.

2.2. Operation

A posterior fossa craniotomy was performed, with patient in prone position. After opening the dura, a large inferior hemispheric vein joining the inferior vermian vein and draining into the left tentorial sinus was visualized on the left hemisphere's cortex. A Carl Zeiss OPMI Pentero (Oberkochen, Germany) microscope with INFRARED 800 module was used. An intravenous bolus of 0.25 mg/kg of ICG was then administered and video-angiography was performed to study the cortical blood flow. This confirmed the large inferior hemispheric vein on the left side as well as a large inferior vermian vein. An obvious cortical hemorrhagic alteration was disclosed above that vein, suggesting the best entry point to access the hematoma. This was drained only from the left side, and the mass effect was reduced. At this time, we identified and coagulated small-caliber and abnormal arterial and venous vessels on the cavity's hemorrhagic walls (Video). Another intravenous bolus of ICG was then administered and video-angiography was recorded in order to localize the AVM. This appeared like a blackberry, with multiple spots gaining fluorescence and becoming bright (Video). The understanding of the AVM's anatomy and of the surrounding structures guided the first Author to identify the vascular malformation under both ICG fluorescence and microscopic white light, and allowed its safe and total resection using standard microsurgical technique. A control ICG-VA was repeated and the "blackberry-like" AVM was no longer visualized but only patchy hemorrhagic spots in the surrounding parenchyma became fluorescent, requiring careful hemosthasis (Video). Histological examination confirmed the diagnosis of AVM (Fig. 5).

2.3. Postoperative course

The patient sustained an uneventful recovery and his neurological deficits gradually improved over the first week after surgery. A postoperative MRI and angiography, respectively, confirmed the large clot removal and the small AVM resection (Figs. 2B, 3B, and 4B). A 3 months follow-up angiogram confirmed the AVM resection (Figs. 3C and 4C).

Fig. 1. Preoperative, axial CT image shows a large left-sided cerebellar hematoma extending across the midline into the contralateral hemisphere and compressing the fourth ventricle.

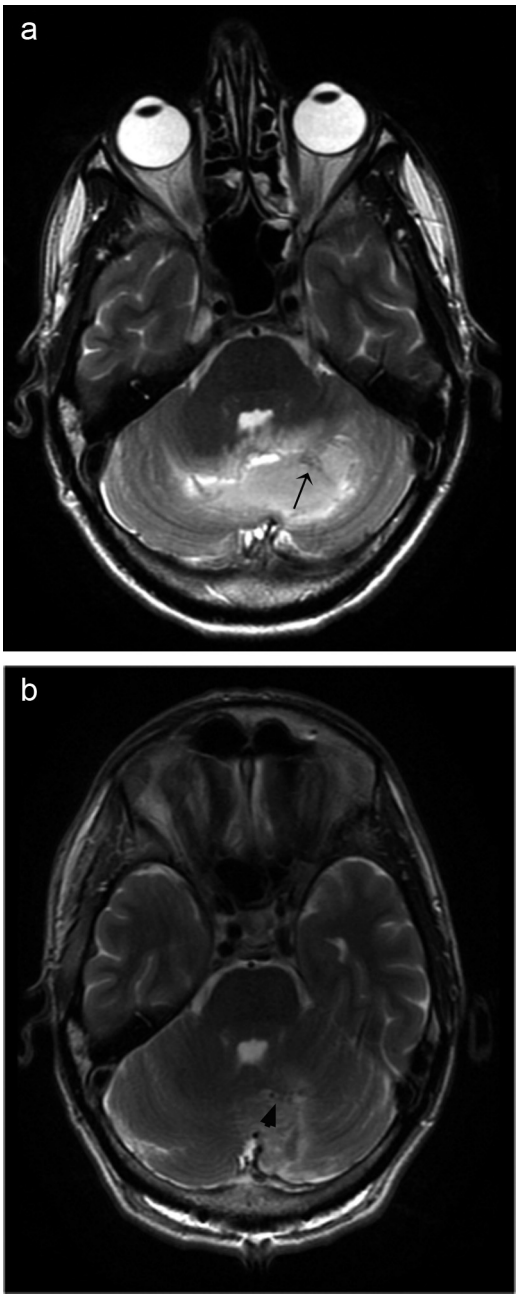

Fig. 2. (A) Preoperative, axial, T2-weighted MRI demonstrates the cerebellar hematoma slightly hyperintense. Some small flow voids suggesting an abnormal vascularization are clearly depicted along the anterosuperior margin of the hematoma (arrow). (B) Postoperative axial, T2-weighted MRI shows the hematoma removal and few irregular residual vessels in the cavity (arrowhead).

2.4. Review of the literature

A systematic review of the existing literature concerning the application of ICG-VA to the surgical treatment of the brain AVM has been performed, specifically searching for studies reporting similarities and common features shared by AVMs and cavernous angiomas. The PubMed website has been queried using "indocyanine green and arteriovenous malformation", "ICG videoangiography and arteriovenous malformations" and "ICG videoangiography and cavernous angiomas" as keywords. The search was restricted to publications in English language and revealed 16 papers on this topic. The relevant findings of these papers will be discussed below.

3. Discussion

Although multimodal step-by-step treatment seems to be the best compromise in the management of posterior fossa AVMs [1,2,11], surgery still remains the only viable option in cases of failure of non-surgical treatments [6] or ruptured AVMs associated with intraparenchymal hemorrhage, like in the patient here reported. In these posterior fossa cases, identification of small AVMs in the context of a large hematoma can be difficult [34], despite preoperative digital subtraction angiography (DSA) information. Intraoperative DSA and microvascular Doppler sonography (MDS) have been used for several years in order to properly find and resect the AVMs while preserving the normal vasculature [13,22]. Despite the clear advantage of intraoperative DSA, its reliability in small vessels visualization has been questioned [29,34].

Brain AVMs may present similar MRI appearances to cavernomas. Cavernomas are vascular malformations typically defined as "angiographically occult vascular malformation" or "slow-flow vascular malformations". However, a variegate spectrum of histopathological features related to different enhancement characteristics after MRI contrast administration has been demonstrated as a consequence of different patterns of vascular supply to cavernomas [44]. Conversely, AVMs may be featured by a moderate enhancement after MRI contrast administration, especially in cases of small AVMs with partially trombosed vessels. This suggests that cavernomas and AVMs might have a similar MRI appearance in certain cases, despite they are separate pathological entities.

Several authors investigated the differences and correlations between cavernous hemangioma and arterio-venous malformations. After initial reports highlighting the clinical and neuroradiological patterns featured by these two vascular developmental anomalies [45], further studies focused on the histological aspects making cavernomas distinguishable from AVMs. Cavernous malformations are histologically characterized by the presence of immature vessel walls, causing brittle hemorrhagic tendency and epileptogenesis, whereas arteriovenous malformations are typically featured by the lack of capillary beds and manifest apoplectic bleeding under high-flow conditions. These differences have been demonstrated as related to cellular, molecular, and genetic factors, although a common substrate in the genesis of cavernomas and AVMs may be found in the alterations of vasculogenesis resulting in different dysmorphic vessel phenotypes [46]. Variable degrees of alteration involving different phases in the process of vascular assembly may explain the different spectrum of clinical and histological manifestation.

Distinct patterns of expression of molecular markers of differentiation and maturity of vascular smooth muscle cells distinguish AVMs form cavernomas, with different expression of muscle cells proteins [47,48].

Moreover, the existence of the so-called "mixed" vascular malformations of the brain [49], exhibiting a common phenotype of AVMs, cavernomas and venous anomalies, reinforces the hypotheses of a common origin of brain vascular malformations. The variegate spectrum of histopathological features of brain vascular malformation influences the behavior of such lesions after MRI contrast administration. Different degrees of enhancement have been demonstrated for cavernous malformations as a consequence of different patterns of vascular supply [44]. Conversely, AVMs are commonly featured by a moderate enhancement after MR contrast administration, especially in cases of small AVMs with partially trombosed vessels. This suggests that cavernomas and AVMs might have a similar MRI appearance in certain cases [44].

Ultrastructural analysis of AVMs and cavernomas using electron microscope, individuated further differences between these two pathologies: tight junctions between endothelial cells are present

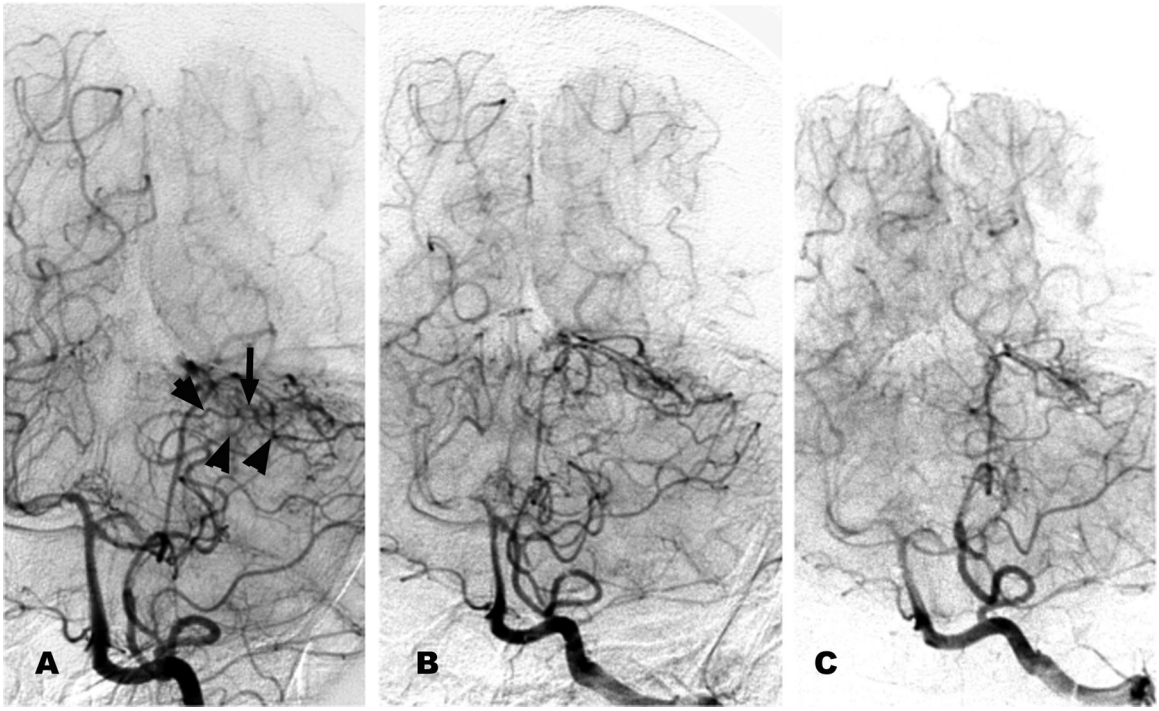

Fig. 3. Antero-posterior views of vertebrobasilar angiography: (A) preoperative study shows a small AVM nidus (arrow) with multiple, small arterial feeders (arrowheads) and early emptying venous vessels. Early postoperative (B) and 3-month follow-up angiograms (C) demonstrate the resection of AVM nidus; arterial feeders are no longer visible.

in AVMs, whereas substantial gaps in intercellular space have been demonstrated in cavernomas [50].

Following the successful experience in ophthalmology [51], ICG-VA was also introduced in neurosurgeon's armamentarium in 2003 [29]. Since Raabes et al.'s experience [29], ICG video-angiography has been used during cerebrovascular surgeries [18–27,36] and, more recently, in the management of spinal vascular malformations [35,37,41,52] and brain tumors [38–40].

ICG-VA application in AVMs surgery was considered particularly useful to distinguish AVM-related vessels from normal ones [34] and to detect ruptured AVMs within a cerebral hematoma [34].

Hänggi et al. [32] and Taddei et al. [53], respectively, demonstrated the role of intraoperative ICG-VA in ruling out the presence of post-resection small residual AVMs or in providing intraoperative additional information to change surgical strategy according to blood flow characteristics.

Our literature review revealed interesting studies addressing the utility of ICG-VA in highlighting specific hemodynamic features of AVMs as opposed to cavernous angiomas [36]. Based on the encouraging data already available in patients with AVM [54], Faber et al. [55], Jhawar et al. [56] and Kato et al. [57], independently, focused on the possibility to enhance traditional ICG-VA

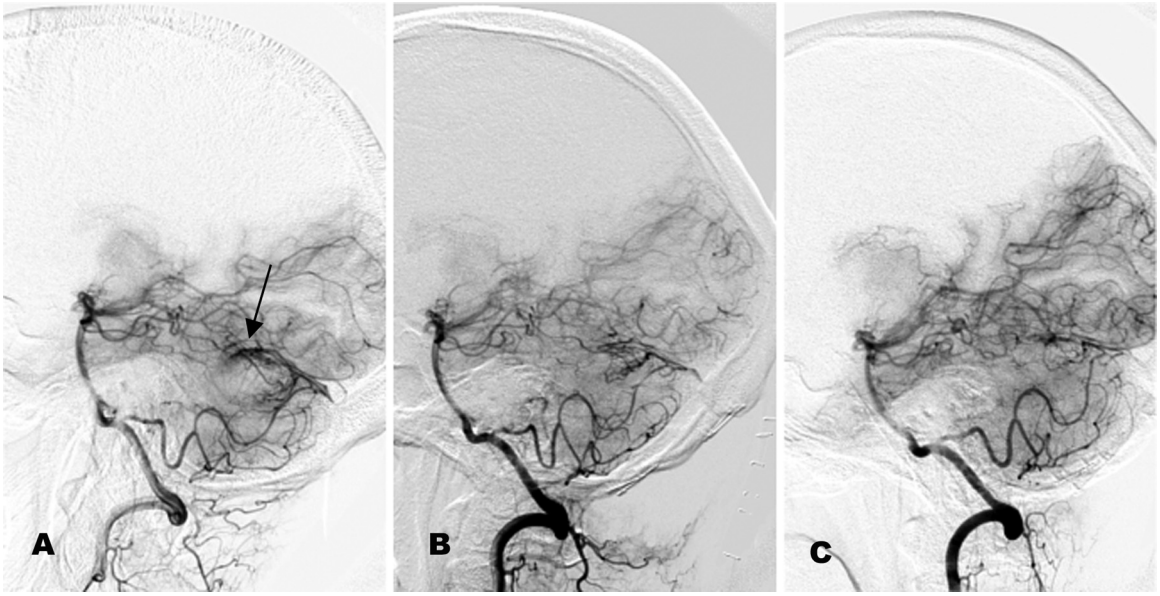

Fig. 4. Lateral views of vertebrobasilar angiography: (A) preoperative study shows small peripheral arteries with low-flow around the superior margin of the hematoma (arrow). A more regular vascularization is seen on early postoperative (B) and 3-month follow-up angiograms (C) and the peripheral vessels are less clearly visible.

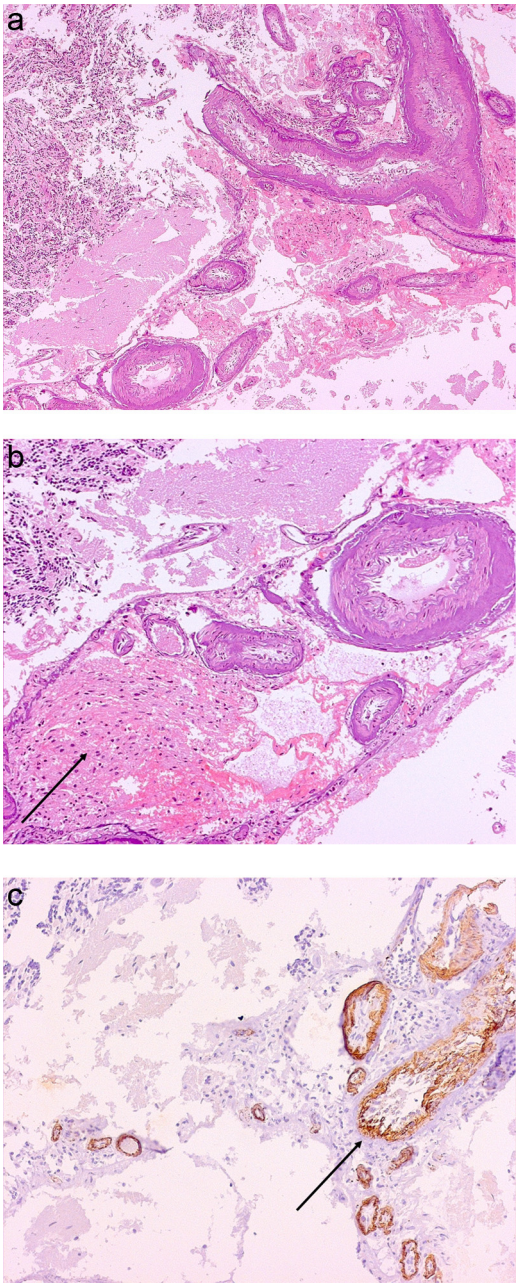

Fig. 5. (A) The arteriovenous malformation is composed of vessels that vary greatly in type [arteries and veins] and in caliber [H&E 50×]. (B) Note the intervening parenchyma typical of arteriovenous malformations (arrow) [H&E 100×]. (C) Immunostaining for actin highlights the irregular layers of myocytes in abnormal arteries (arrow) [IHC 100×].

with a color encoded analysis (FLOW 800) to better visualize intraoperatively non-ruptured or deep-seated brain AVMs. Also, Kamp et al. [58] measured the different flow times (mean rise time, mean time to peak, mean transit time) associated with ICG-VA in different brain pathologies.

Recently, Ng et al. [36] further developed previous studies [59] and reported their experience with quantitative and qualitative flow analysis in AVM patients treated with ICG-VA. They used a second microscope-integrated module, which enabled them to obtain two intraoperative maps: one showing the maximum fluorescence intensity attained at each region of interest within the AVM and a second one, displaying the direction and temporal sequence of blood flow in the AVM. However, this interesting adjunct requires additional technical preparation: the surgical field must be dry, cottonoids should be removed from the surgical field, and the latter has to be zoomed and focused in order to have the nidus in the direct line of vision [36]. Our literature review did not reveal significant differences in ICG-VA pattern in ruptured and un-ruptured AVM. However, several authors highlighted the importance of flow analysis in visualization of un-ruptured AVMs as well as the role of ICG-VA in the identification of AVM after the evacuation of a hematoma, as in the present case [36,56,57].

Of course, all these specific flow studies performed with the aid of ICG-VA in AVM cases have never been described in cases of CAs, most likely due to the known typical structural and hemodynamic differences between these two vascular malformations.

In the present case we could not observe before surgery obvious signs of an AVM on MRI, despite some images raised concerns regarding a possible vascular malformation (Fig. 2A); conversely, angiography showed an abnormal vascular pattern, which was in keeping with a small vascular malformation (Figs. 3A and 4A).

We did evacuate the hematoma and careful exploration of the cavity's anterior wall revealed some small pathological vessels, which were coagulated (video); no clear nidus was initially identified and only a dubious area, which looked like a residual small clot tightly adhering to one of the cavity's wall, was seen. At that stage we decided to inject the ICG and obtain a video-angiography. Arterial phase did not show classical injection of afferent arteries, as commonly seen. During the capillary phase, a blackberry-like structure, composed of multiple fluorescing spots, started becoming bright and gained a full fluorescence in the venous phase (video). Interestingly, although such features resembled a cavernous angioma, as in the only cerebellar case studied with ICG-VA and recently reported [42], it was rather in keeping with a small AVM. Indeed, surgical findings, in particular the multiple arterial feeders which we had to coagulate and section circumferentially (video), and histological examination confirmed that we dealt with an AVM and ruled out a possible diagnosis of cavernous angioma (Fig. 5). Small arterial feeders, were not clearly visible during first ICG-VA, probably because they were covered by the blackberry-like lesion. The peculiar behavior of the lesion after dye infusion may be due to the fact that the small afferent vessels did not supply a high blood flow to the lesion. This made the small AVM nidus resembling a cavernoma. Indeed, a slow and low perfusion within CCM has been demonstrated using ICG-VA, by Murakami et al. [42]. The similar appearance of cavernous malformation and AVM using ICG-VA, may be correlated to the previously described behavior of cavernomas and AVM after MRI contrast administration [44]. However, several concerns about the real usefulness of ICG-VA in cavernoma surgery have been raised, and its use is still debated.

The present case confirms the above described advantages of ICG-VA in showing a small blackberry-like AVM (video) and, combining fluorescence with microscopic view, in guiding us to approach it microsurgically. Moreover, before proceeding with dissection we could playback the recorded video-angiography images on both the microscope and theater monitors, focusing on arterial and venous phases, and this allowed a real-time analysis and understanding of the AVM's features. Interestingly, AVM's arterial feeders were not distinctly identified nor were draining venous vessels, but while performing our resection the AVM bled again, so confirming that the ICG-VA information was correct and we were dealing with the vascular malformation. After having completed the resection and before securing the final hemostasis, we performed a check ICG-VA and no residual AVM was shown. It is known that pathological vessels of arteriovenous malformations may lack a blood-brain barrier [60] and that in the perinidal parenchyma a pathologically capillary network can be connected to the AVM [61,62]. The pathogenesis of this phenomenon has been well described by Tu et al. [60]. The ultrastructural analysis of perinidal capillaries

surrounding AVMs demonstrated the absence of basement membranes and astrocytic foot processes of blood-brain barrier, with large gaps at endothelial intercellular junctions. These may permit the extravasation of some red blood cell without major hemorrhage. Similarly, we submit that in the present case the peculiar appearance we obtained after ICG infusion, resembling a blackberry, may also be the consequence of a "leakage" of fluorescent dye from the nidal pathological vessels into a surrounding capillary network.

This is the second cerebellar AVM resected with the aid of intraoperative pre-, intra- and post-resection ICG-VA, respectively. The cerebellar case included in Ng et al's series cannot be considered in the present analysis as those authors did not perform ICG-VA before and during AVM resection but only afterwards to confirm its removal [36]. As such we lack the intraoperative, pre-resection information provided by indocyanine green. Nonetheless, the only other case reported by Killory et al. [34] substantially differs from ours, being a Spetzler–Martin grade 4 AVM and, hence, showing the typical tortuous arterial and venous vessels.

The intraoperative video, the first one so far shown in the literature, may be useful to neurosurgeons to realize, and hence recognize during surgery, how a small cerebellar AVM in the context of a previous deep hemorrhage can present, despite unusual and peculiar appearance. The relevance of our report relies upon the fact that failing to recognize that a surgeon is dealing with a proper AVM, and not with a cavernous angioma, may cause second bleedings if the vascular malformation's afferent and efferent vessels are not carefully considered and dealt with. In conclusion, we submit that ICG-VA is a safe, accurate and reliable tool, which can be helpful during intraoperative diagnosis and resection of small and "atypical" AVMs.

Conflict of interest statement

The Authors declare that they have no conflicts of Interest to disclose; no funding has been or will be received from any grant-giving organization in conjunction with the generation of this manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clineuro.2015.07.016

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