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Case report

Giant intracranial aneurysm following radiation therapy: literature review with a novel case discussion

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Summary. *Background:* The aim of this paper is to report the results of our review of the literature of published cases of intracranial aneurysms appearing after radiotherapy, and to present our case to add it to the current literature, in order to discuss the role of inflammation. *Methods:* We searched the PubMed database using combinations of the following MeSH terms: intracranial aneurysm, radiosurgery, radiotherapy, inflammatory changes in aneurysmal walls from 1967 to 2019. *Results:* 51 studies, for a total cohort of 60 patients, are described. The median latency between the radiation treatment and the diagnosis was 9,83 years, ranging from a minimum of 0,33 to a maximum of 33. The modality of rays' administration was variable, and the dosage ranged from a minimum of 12 grays to a maximum of 177,2 grays. The anterior circulation appeared to be more frequently involved, and the most compromised vessel was the internal carotid artery. Radiation-induced vascular diseases have already been described in literature as well as RT-induced cellular and structural changes such as necrosis, macrophage or mononuclear cell infiltration, and several data support the role of inflammation in the development and remodelling of intracranial aneurysms, that, on one hand, favours them and, on the other, is necessary to their healing after endovascular treatment. *Conclusions:* Our team suggested a new insight in the management of these vascular lesions, which corresponds to a lower threshold when deciding whether or not to treat, and a longer and stricter follow-up.

Keywords: aneurysm, Giant, radiation therapy, radiosurgery, intracranial aneurysm, changes in aneurysmal walls

Introduction / Background

During the past years, the use of radiation for both diagnostic and therapeutic purposes has largely increased. Moreover, thanks to advances in multidisciplinary treatment, life expectancy of cancer patients is also increasing. This allows the observation of long-term complications/consequences of patients that underwent radiotherapy (RT).

Radiation-induced vascular diseases have already been described in literature, with a focus primarily on occlusive stroke and atherosclerosis (1,2), but various articles have also reported the formation of intracranial aneurysms. Even if it is hard to state whether or not there is a direct correlation between the exposure to ionizing radiation and the formation of intracranial aneurysms, and no clear pathognomonic findings have been described up to date, different authors report similar findings from a histopathological point of view when analysing vessels and aneurysmal walls. These findings include well known RT-induced cellular and structural changes such as necrosis, macrophage or mononuclear cell infiltration, intimal fibrosis, and intraluminal thrombotic material (3,4,5). In fact, there are several data supporting a role of inflammation in the development, remodelling, and rupture of intracranial aneurysms (IA), which add a further layer of complexity in IA pathogenesis (6,7). In this paper we report the results of our review of the literature of published cases of IA appearing after RT, and we present our case to add it to the current literature.

Methods

We reviewed the literature for published articles reporting IA documented via neuroimaging in patients that underwent RT. We searched the PubMed database using combinations of the following MeSH (Medical Subject Headings) terms: "intracranial aneurysm", "radiosurgery", "radiotherapy", "brain aneurysm and inflammation", "vessel wall imaging in IA", "inflammatory changes in aneurysmal walls", "ankylosing spondylarthritis brain aneurysm". We also conducted a research with Google Scholar with the same MeSH terms. We considered only full papers and excluded abstracts. We did not exclude papers based on publication language.

Results

We chose to include 51 studies, for a total cohort of 59 patients plus an additional one described here. Age, sex, type of lesion requiring radiation therapy, vessel from which the aneurysm arose, latency between first radiation and diagnosis of aneurysm, presentation, dosage and modality of radiation treatment were registered. Mean age at diagnosis was 44,86 years (Min: 5; Max: 83), comprehending 38 females and 22 males. The most common lesion was nasopharyngeal carcinoma, accounting for up to 13 cases, followed by 8 medulloblastomas, 6 gliomas (5 LGG and 1 HGG), 6 vestibular schwannomas, 4 optic gliomas, 4 adenomas, 4 arteriovenous malformations, 3 craniopharyngiomas, 3 meningiomas, 2 metastases, 2 Ewing sarcomas, one germinoma, one chordoma, one chondrosarcoma, one retinoblastoma, and one lymphoma. Generally, the involvement of the anterior circulation appeared to be more frequent: the vessel from which the aneurysms arose was mostly the internal carotid artery (ICA), accounting for 25 cases, followed by the middle cerebral artery (MCA) and the anterior cerebral artery (ACA), each affected in 7 cases, and the anterior communicating artery (ACoA), implicated in 5 cases. Instead, the aneurysm arose from the anterior inferior cerebellar artery in 7 cases, from the posterior cerebral artery (PCA) in 6 cases, from the basilar artery in 3 cases, from the posterior inferior cerebellar artery (PICA) in 2 cases, and from the superior cerebellar artery (SCA) in only one case. In 39 of the cases the diagnosis was made following the rupture of the aneurysm. The median latency between the radiation treatment and the diagnosis was 9,83 years, ranging from a minimum of 0,33 to a maximum of 33 years. The modality of rays' administration consisted in involved-field radiation therapy (IFRT) in 29 cases, whole-brain radiation therapy in 12 cases, gamma-knife in 11 cases, stereotactic radiotherapy in 4 cases, and brachytherapy in one case. The dosage ranged from a minimum of 12 grays to a maximum of 177,2 grays. (Tab. 1)

Case Presentation

In this paper we present the case of a 69-year-old female who referred to our Institution in April 2017 because of diplopia, left eye ptosis, and anisocoria with the left pupil wider than the right one. Neurological examination showed no other symptoms. On admission, the patient underwent brain Computed Tomography (CT) scan, Magnetic Resonance Imaging (MRI) with and without contrast, and MR Angiography (MRA), showing the presence of an aneurysm (27 x 20 mm) of the supraclinoid segment of the left carotid artery (Fig1b). The multidisciplinary decision-making process brought us to recommend endovascular treatment (ET).

The patient's medical history was characterized by ankylosing spondylarthritis treated with methotrexate and adalimumab, both reduced few months prior to hospitalization. In 2005, the patient underwent surgery for the treatment of gastric cancer, followed by chemotherapy with a negative follow-up. The patient

Table 1. Showing the results. HGG: high grade glioma; LGG: low grade glioma; NF: nasopharyngeal; MET: metastasis; OG: optic glioma; VS: vestibular schwannoma; RB: retinoblastoma; AVM: arteriovenous malformation.

ARTICLE	AGE	SEX	LESION	VESSEL	LATENCY	RUPTURE	GRAY	TYPE
Aichholzer et al., 2001	11	M	LGG	ACoA	11	YES	54	IFRT
Akai et al., 2015	65	M	AVM	MCA	15	NO	40	GKS
Akamatsu et al., 2009	83	F	VS	AICA	8	YES	12	GKS
Aoki et al., 2002	20	F	OG	ICA	19	YES	90	IFRT
Benson and Sung, 1989	21	M	MEDULLO	PCA	10	YES	47,2	WBRT
Benson and Sung, 1989	31	F	MEDULLO	PCA	17	YES	45	WBRT
Benson and Sung, 1989	14	M	MEDULLO	PCA	9	YES	50	WBRT
Casey et al., 1993	65	F	LGG	MCA	3,5	YES	60	IFRT
Casey et al., 1993	44	M	AVM	MCA	21	YES	40	WBRT
Chen et al., 2004	55	M	NF CARCINO	ICA	0,33	YES	81,8	IFRT
Cheng et al., 2001	59	M	NF CARCINO	ICA	7	YES	120	IFRT
Cheng et al., 2008	57	M	NF CARCINO	ICA	3	YES	128,4	IFRT
Cheng et al., 2008	37	M	NF CARCINO	ICA	2	YES	120	IFRT
Dho et al., 2017	27	M	AVM	MCA	10	YES	36,5	GKS
Endo et al., 2011	62	M	ADENOMA	ICA	17	YES	90,2	GKS
Fujita et al., 2014	29	M	ERWING	ICA	4	YES	162	SRS
Fujita et al., 2014	61	M	MENINGIOMA	ICA	11	YES	59,6	SRS
Gabriel et al., 2004	60	F	ADENOMA	ICA	29	NO	--	BRACHY
Gomori et al., 1987	47	M	NF CARCINO	BASI-LAR	3	YES	--	IFRT
Gonzales-Portillo and Valdivia, 2006	12	M	RB	ACA + ICA	12	YES	103	IFRT
Gulati et al., 2014	30	M	NF CARCINO	ACA	8	YES	60	IFRT
Holodny et al., 1996	62	F	MET	BASILI	7	YES	31,8	WBRT
Huang et al., 2001	19	F	AVM	ACA	9	NO	37,5	SRS
Hughes et al., 2015	57	F	VS	AICA	10	NO	39	GKS
Huh et al., 2012	77	F	CHONDRO	ACoA	8	YES	59,4	IFRT
Jensen and Wagner, 1997	9	M	MEDULLO	ACA	0,8	YES	48	WBRT
John et al., 1993	55	M	NF CARCINO	ICA	5	YES	66	IFRT
Kamide et al., 2016	17	M	MEDULLO	PICA	8	NO	55,8	WBRT
Kellner et al., 2015	68	F	MENINGIOMA	SCA	10	NO	16	GKS
Lam et al., 2001	47	M	NF CARCINO	ICA	8	YES	116	IFRT
Lam et al., 2001	55	M	NF CARCINO	ICA	7	YES	66	IFRT
Lam et al., 2001	65	M	NF CARCINO	ICA	12	YES	111	IFRT
Lau and Chow, 2005	53	M	NF CARCINO	ICA	12	NO	60	IFRT
Liu et al., 2009	5	M	CRANIOFAR	ICA	2	NO	58,8	IFRT
Louis et al., 2003	61	M	LYMPHOMA	ICA	27	NO	43,5	IFRT
Mak et al., 2000	72	F	NF CARCINO	ICA	6	YES	--	IFRT

ARTICLE	AGE	SEX	LESION	VESSEL	LATENCY	RUPTURE	GRAY	TYPE
Maruyama et al., 20004	15	M	OG	ACA	14,6	YES	110	IFRT
Matsumoto et al., 2014	39	M	GERMINOMA	ICA	31	NO	60	--
Moriyama et al., 19924	51	F	ADENOMA	MCA + PCA	1	YES	50	IFRT
Murakami et al., 2002	30	M	CRANIOFAR	PCA + BASIL	19	NO	50	IFRT
Nanney et al., 2014	38	M	MEDULLO	PICA	33	NO	79,66	WBRT
Nishi et al., 1987	57	M	ADENOMA	ICA	9	NO	50	IFRT
Parag et al., 2016	40	F	LGG	MCA	3	NO	60	IFRT
Park et al., 2009	74	M	VS	AICA	5	YES	18	GKS
Pereira et al., 2002	19	F	CRANIOFAR	ICA	5	NO	54	IFRT
Sciubba et al., 2006	24	M	MEDULLO	MCA	15	NO	55,8	WBRT
Scodary et al., 1990	59	M	LGG	ACA	12	YES	65	WBRT
Sunderland et al., 2014	60	F	VS	AICA	10	YES	25	GKS
Takao et al., 2006	69	F	VS	AICA	6	YES	18	GKS
Tamura et al., 2013	29	M	ERWING	ICA	4	YES	177,2	IFRT
Twitchell et al., 2018	37	M	LGG	ACoA	12	NO	--	WBRT
Twitchell et al., 2018	38	F	CHORDOMA	PCA		YES	--	--
Vogel et al., 2011	16	F	OG	ICA	1	YES	54	GKS
Woodin and Phatouros, 2018	53	M	NF CARCINO	ACoA	2	NO	66	IFRT
Wu et al., 2014	68	F	MET	ICA	3	NO	60	IFRT
Wu et al., 2016	17	M	MEDULLO	AICA	12	YES	132,5	WBRT
Yamaguchi et al., 2009	73	F	VS	AICA	6	YES	50	SRS
Yoon et al., 2011	57	M	HGG	ACA	0,8	YES	59,4	IFRT
Yucesoy et al., 2004	48	F	OG	ACoA	6	NO	--	--
Present study	69	F	MENINGIOMA	ICA	18	NO	60	GKS

also underwent surgery in 1999 for an incomplete removal of a left tentorial meningioma; further treatment of the lesion was achieved with gamma-knife at the isodose of 55%. Neuroimaging follow-up showed, up to 2009, the optimum outcome regarding the residual meningioma and the absence of any vascular malformation (Fig1a).

Endovascular Treatment (ET)

Due to the absence of headache and of bleeding signs in the pre-procedural neuroimaging, we decided to treat the patient endovascularly with Flow-Diverter and coils. Administration of antiplatelet drugs (ASA 300 mg/die and Plavix 75 mg/die) was started five days before the procedure.

Under general anaesthesia, in triaxial technique (Vista Brite Tip 8F 95cm J&J and Neuron 6F 105cm Penumbra), the M2 segment was reached with a microcatheter Headway 27 (Microvention) and Traxcess microwire 0.014 (Microvention). Due to the difficulty of reducing the microcatheter loop, we changed it with a Scepter XC 4x11 balloon (Microvention). Inflating the balloon, we were able to straighten the system. Then, after deflating the Scepter, we removed it and changed it with a microcatheter Headway 27. Thus,

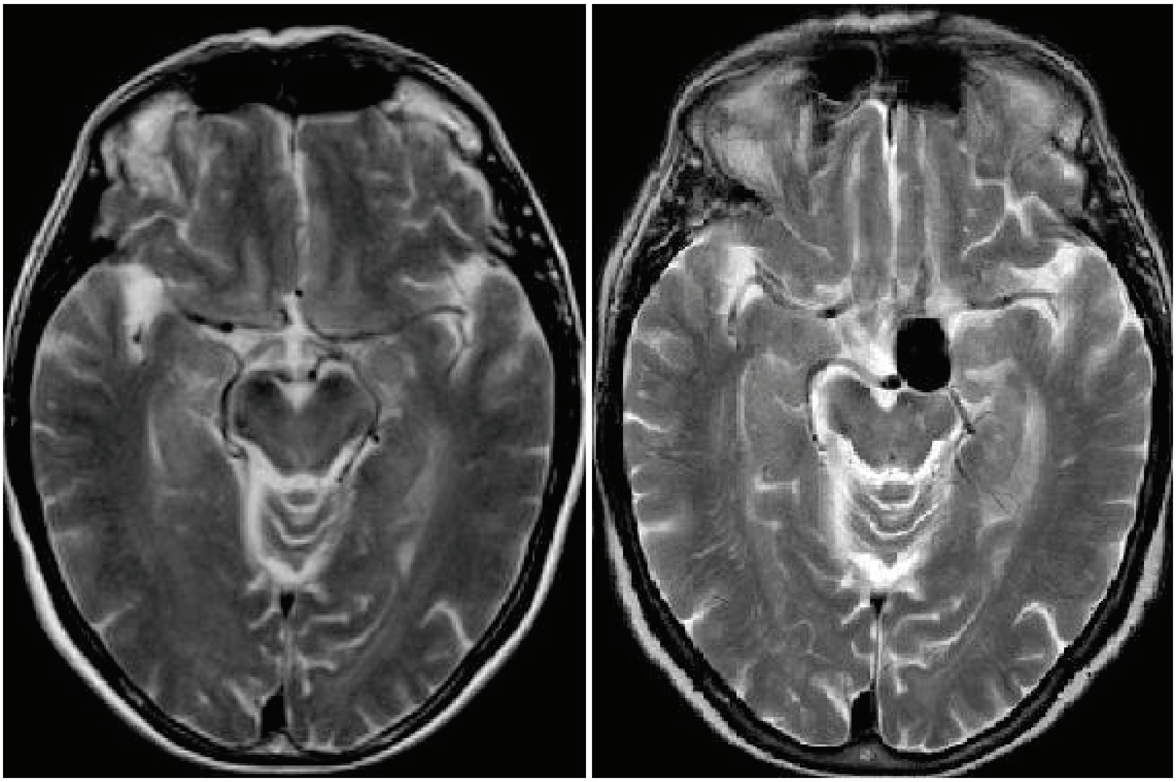

Figure 1. a) T2-weighted image in 2009. No presence of Aneurysm in the left carotid artery; b) T2-weighted image in 2017. Giant Aneurysm in the left carotid artery

the microcatheter Headway Duo (Microvention) with Traxcess 0.014 microwire (Microvention) was placed inside the aneurysm. A Fred stent 5x26 was deployed at the supraclinoid and intracavernous segments of ICA. Finally, in "jailing technique" we put coils into the aneurysmal dilatation (Fig2).

Post-procedural observation showed no further new neurological deficits.

Two days after treatment, the patient suffered from a lipothymic episode with head trauma. A brain CT scan revealed a left sylvian subarachnoid haemorrhage (SAE) (Fig3). No sign of recent haemorrhage was detected in the perimesencephalic space, whereas emergency angiography showed the stability of the treated aneurysm. The sylvian space bleeding was interpreted as a possible periprocedural complication due to a very distal vessel perforation or as a post-traumatic haemorrhage, and not as a rupture of the aneurysm. Therefore, given the good neurological state, the follow-up was observational, and a brain CT scan obtained 10 days later showed complete resolution of the haemorrhage.

Five months after the successful endovascular treatment, the patient referred again to our Institution and was subsequently hospitalized. Brain MRI and MRA showed once again stability of the treated aneurysm, with signs of thrombosis in the aneurysmal sac, aneurysmal wall enhancement (AWE), enlarged ventricles, and signs of transependymal oedema. Because of the concurrent presence of symptoms related to hydrocephalus, such as gait impairment, together with the previously known ptosis and anisocoria, a ventriculo-peritoneal shunt with adjustable valve was placed (VPS) (Polaris - Sophisa set at 150 mmH_2O).

Radiological and clinical 3-year follow-up showed smaller ventricles, absence of transependymal oedema, and regression of the neurological deficits: isocoria, normal eyelid movements, and no gait impairment. At

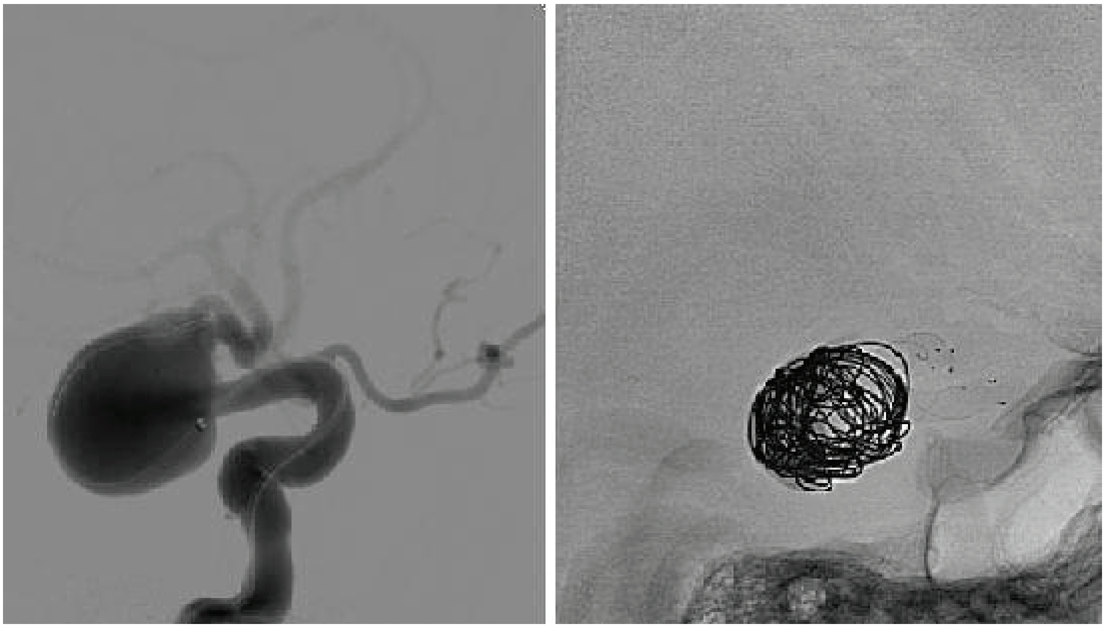

Figure 2. a) DSA lateral view. Working projection shows the loop of the microwire inside the Aneurysm; b) DSA lateral view shows the deployment of the Fred stent and the coils inside the Aneurysm

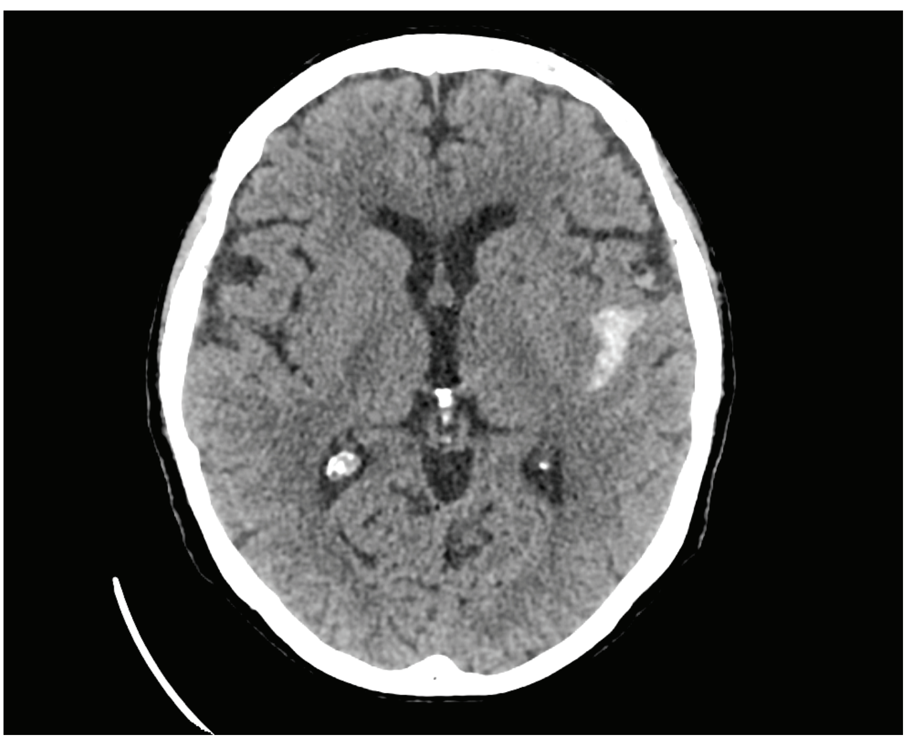

Figure 3. CT scan revealing left sylvian SAE

angiographic follow up, the treated aneurysm resulted completely excluded, the indirect sign of inflammation, AWE, was also reduced, and the aneurysmal sac was completely filled with coils and thrombotic material (Fig4a and 4b).

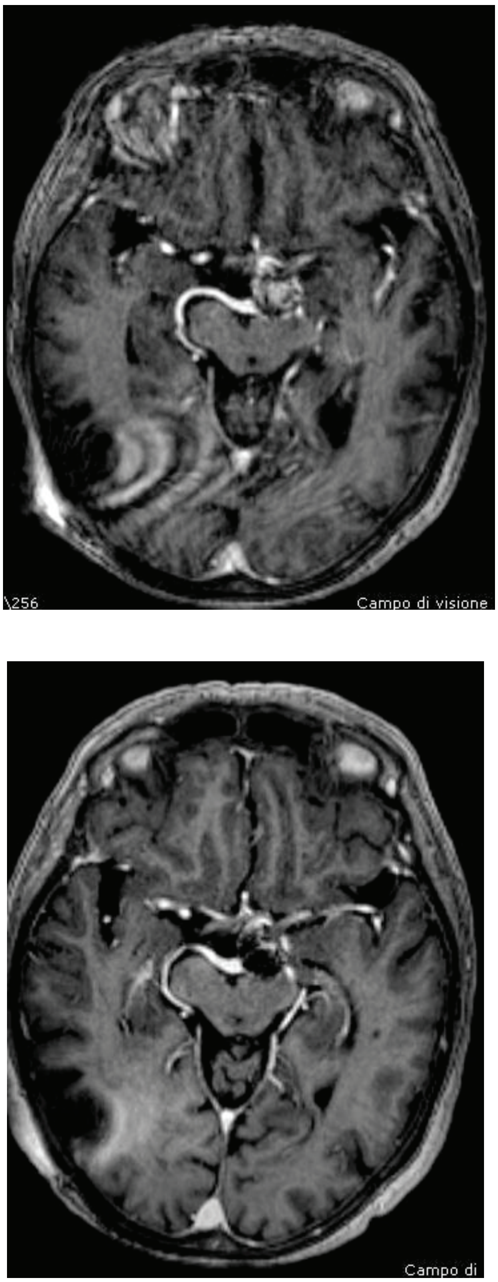

Figure 4. a) T1-weighted image in 2017. The enhancement inside the Aneurysm is the sign of inflammation; b) T1-weighted image in 2020. Strong reduction of the enhancement inside the Aneurysm and strong improvement of neurological symptoms

Discussion

Vernooij et al. report an incidence of steno-occlusive changes after RT of 1.8% (9), while Omura et al. report an incidence as high as 19% (10). The first case of IA following RT was reported in 1967, and since then few case reports and very short case series have been described. Adib et al. underline how the problem of radiation-induced aneurysms could be at the same time underreported, because of the cease of the novelty, and overreported, because of the unique type of presentation. Therefore, the real incidence of aneurysms emerging after RT is yet to be established, but a recent nationwide study conducted over a 10-year follow-up found that RT was a significant risk factor for IA development (11).

Cerebral aneurysms that arise in previously irradiated fields appear to be more susceptible to rupture; this consideration must be taken into account in the decision-making process when facing an incidental aneurysm. Although there is no clear causal connection between RT and the formation of IAs, some authors hypothesize that the integrity of the parent artery wall is degraded by radiation, making it more vulnerable to shear stress (5). In addition, histopathological examinations showed changes in the cellular composition of irradiated vessels. Lubimova and Hopewell demonstrated reduction in endothelial cells within 24 hours of radiation in a rat brain irradiated with 25Gy (7). Another study showed how large cultures of endothelial cells exposed to radiation were more likely to adhere to neutrophils and platelet cells (8). Endothelial dysfunction is related to IA formation in experimental models, and partial or total de-endothelialisation is associated with human IA rupture (12). Chronic inflammation has become understood as an important phenomenon in IA wall pathobiology (13), with a role in probable biological processes leading to IA formation, growth and rupture.

Inflammation is a proapoptotic state, but chronic inflammation seems to have multiple functions in IA wall, favouring both IA wall degeneration and reparative mechanisms.

Radiation may also induce an inflammatory cascade, including the release of cytokines and growth factors necessary for tissue healing (14).

The inflammation of the aneurysmal sac, which is considered a sign of instability, is common in aneurysms that arise following radiotherapy. It appears in fact that common denominators in the histopathological analysis of these aneurysms are the presence of active macrophages, neovascularization and decreased elastin (3,4,5).

Several studies have suggested that aneurysmal wall enhancement (AWE) on MRI may help in identifying unruptured intracranial aneurysms with a higher risk of rupture, since aneurysms exhibiting AWE have been shown to be significantly more prone to be unstable than those which do not display it (15,16,17). Recent systematic review and meta-analysis have demonstrated that aneurysms which demonstrate AWE are significantly more likely to be unstable than those which do not exhibit wall enhancement (18).

In our case, even if a histopathological examination was not achievable due to the chosen treatment, the indirect sign of the aneurysmal wall inflammation, which is represented by the AWE (17), was present at the MRI study right after treatment, and was significantly reduced after treatment during the 3-year follow-up.

It should however be mentioned that ET could have local or global intracranial effects. Early AWE was previously reported to likely represent the normal healing process of early acute inflammatory reactions (19). AWE is a phenomenon that in most cases remains stable over years (20,21), and several studies conclude that it should be considered an expected post treatment finding (19,20,22).

It is interesting to notice that, in our case, symptoms appeared only few months after the patient's immunosuppressant therapy for the treatment of spondylarthritis was reduced. The MRI acquired after the ET but before the placement of VPS showed effects of chronic inflammation: the aneurysmal sac was filled with thrombotic material and enhanced after administration of gadolinium; the symptomatic hydrocephalus with enlarged ventricle and the transependymal oedema were also registered as effects of chronic inflammation (19).This case is peculiar because the patient presented a chronic systemic proinflammatory state on top of which the radiating therapy added its effects locally, resulting in a giant aneurysm and in the further development of hydrocephalus. In support of our thesis, the clinical and radiological findings were recorded only few months after the patient's immunomodulating therapy was reduced, and they were found to be significantly reduced after ET when corticosteroid therapy was reintroduced (20). The inflammatory process happening inside the treated aneurysm, induced by the presence of the flow-diverter, permits the healing of the aneurysm; therefore, systemic immunosuppressive therapy could potentially interfere with and favour the healing process. On the other hand, when a chronic inflammatory state is present, and an RT-induced aneurysm is detected, corticosteroid drugs could find a use in the follow-up of these patients. We are well aware that a single case does not allow to obtain an ultimate truth, but it is enough to raise doubts and ask questions.

Conclusion

Different theories have incorporated a combined explanation for IA formation, that includes haemodynamic stress, endothelial dysfunction, and inflammation (15,23,24), which all contribute to the production of the pro-inflammatory phenotype. Intracranial aneurysms that arise from previously irradiated fields are an uncommon long-term complication when compared to other vascular issues such as stenosis or atherosclerosis. These aneurysms are particularly fragile and tend to have a higher risk of rupture, and therefore a more dramatic type of presentation. Thus, it is of primary importance to warrant special attention to RT-induced aneurysms when diagnosed. Our team suggested a new insight in the management of IAs, which corresponds to a lower threshold for treatment indication of these incidental unruptured aneurysms, and a longer and stricter follow-up, moreover given the high level of wall instability associated with the already described inflammation state a peri-procedural steroid administration would be advisable. The decision of the optimal treatment, either surgical or endovascular, should be done case by case.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards

of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Written informed consent to the interventions, CT and the MR exams was obtained from all subjects in this study.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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