



## Pseudocavernoma—a new diagnosis?

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Hubert Luschka was the first to describe a cerebral “Cavernöse Blutgeschwulst” (cavernous malformation) in 1854 [17]. In 1928, Cushing and Barlow classified cavernous malformations as a solid subtype of hemangioblastomas [5]. Today, the terms cavernoma, cavernous hemangioma, cavernous angioma, and cavernous malformation are used interchangeably and appear equally frequent in the literature. The terms cavernoma, cavernous angioma, and cavernous hemangioma suggest that it is a neoplastic lesion, which is inaccurate as cavernous malformations are true vascular malformations. The term cavernous hemangioma is also confusing as cavernous hemangiomas in the cavernous sinus or in the orbit; both are slow-growing neoplastic diseases unrelated to vascular malformations. We will therefore in the following use the term cavernous malformation (CM) in spite the fact that some lesions develop in adult ages [7].

CMs were difficult to diagnose in the pre-MRI era. They are invisible on angiogram and thus the term AOVM (angiographically occult arteriovenous malformation) was sometimes used. However, the venous angioma sometimes seen in association with a CM was visible on angiogram, and thus believed to be the source of the hemorrhage seen, even though in reality it was the CM that had hemorrhaged. Thus, venous angiomas were sometimes treated, also with radiosurgery, a management that was soon aborted [16].

The introduction of MR imaging increased the number of diagnosed CMs as a CM that has hemorrhaged has a typical

appearance on MR images (MRI). An unruptured CM cannot, however, be seen. Consequently, a CM diagnosed in a patient with an earlier normal MRI does not necessarily represent a de novo CM. It may be a CM that was present but invisible on an earlier scan that now can be seen due to an earlier hemorrhage with sequel signals depicted on MRI.

Ciricillo et al. suggested in 1994 that CMs (they used the term cryptic vascular malformations) may be induced by radiation [4]. Since, numerous reports have been published confirming the development of CMs after radiation. The diagnosis is always based on MRI, sometimes with histopathology as verification. A pubmed search using the terms “radiation” and “cavernoma” resulted in 54 publications reporting a total of 274 cases of radiation-induced CMs. Ten of them reported a total of 21 patients with CMs induced by radiosurgery (as defined by Leksell), implying that this is a rare phenomenon [3, 6, 10, 18, 19, 21–23, 25, 26].

We recently published an article about long-term follow-up in patients with unruptured AVMs treated with Gamma Knife surgery [11]. A total of 670 patients were followed for more than 5 years, and CMs at the site of the AVM were found in ten of them, suggesting that this may be a more frequent finding than earlier assumed. One of the reviewers of the manuscript suggested that what we described as CMs actually represented radiation-induced damages. This is in line with our rare observation of a “chronic hematoma” at the site of AVMs treated with radiosurgery many years earlier. Furthermore, others have suggested that radiation-induced damages can mimic CMs [3, 12], and we thus changed our manuscript accordingly.

The above as well as the articles in the present issue of *Acta Neurochirurgica* highlight the need for further analysis and investigation of this phenomenon [20, 24]. Is it possible that radiation may result in damages in the tissue causing a response with an end result mimicking a CM? If so, the term radiation induced CMs is a misnomer, at least in some cases. We believe that this is the case and we therefore suggest the term pseudocavernoma to describe radiation-induced changes mimicking a CM, and the reasons are given below.

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There are histopathological findings supporting the term pseudocavernoma as significant histopathological differences exist between pseudocavernomas and CM. Kleinschmidt-DeMasters et al. analyzed 13 cases with radiation-induced CMs [12]. The histopathological features were cavernoma-like in five cases while the other eight were histopathologically different and pseudocavernoma-like with an organizing coagulum-like appearance that exhibited features of fibrinous deposits containing aggregates of vasculature with ill-defined walls and borders [12]. Cha et al. compared seven CMs that developed following radiosurgery to ten de novo CMs. They found significant histopathological differences between the two groups. They described radiation induced CMs (pseudocavernomas) as consisting of “irregular, partly compressed capillary-sized vascular channels, with capillary proliferation-like area in the center of the lesion, whereas de novo CM were composed of thick well-formed vessels”. The vascular walls of the pseudocavernomas lacked  $\alpha$ -SMA expression, and collagen content in the vessels differed between the two. Furthermore, ectatic vessel walls of pseudocavernomas were thin and less hyalinized as compared to the thick, hyalinized walls of de novo CMs. Finally, with CD68 staining, pseudocavernomas showed infiltration of foamy macrophages into vessel walls whereas only scattered macrophages, located in old hemorrhage and outside vessel walls, were found in de novo CM. The fact that all seven cases studied by Cha et al. were pseudocavernomas while this was the case in 8/13 cases studied by Kleinschmidt-DeMasters et al. may be ascribed to the fact that all cases in the Cha study had been treated with radiosurgery while the cases studied by Kleinschmidt-DeMasters were treated either with radiosurgery or with radiotherapy.

Pozzati et al. also observed that the histology was different in pseudocavernomas as compared to CMs. They found that “in patients with de novo lesions after irradiation, the structure of malformations was mainly composed of back-to-back caverns with minimal collagenous support and was devoid of typical long-standing changes (calcifications, hyalinosis, organized trombi)” [22]. Finally, Gastelum et al. observed that radiation-induced CM show a spectrum of histology features [9]. Thus, based on the observations referred to above, the term pseudocavernoma seems justified from a histopathological point of view.

Imaging characteristics of pseudocavernomas sometimes deviate from that of CMs. Cha et al. compared eight pseudocavernomas to ten de novo CMs unrelated to radiation [3]. They found that all pseudocavernomas showed enhancement, which is not the case for CMs. In addition, cystic and solid components were seen on T2-weighted images with perilesional edema. Six of the eight had uniloculated cysts, while de novo CMs usually had multiloculated cysts. Half of the pseudocavernomas had no popcorn-like appearance and half “showed an incomplete popcorn-like appearance accompanied by only occasional partial hemosiderin rims”. In

contrast, all de novo CMs “exhibited a classic popcorn-like appearance with a complete hemosiderin rim on T2-weighted sequence and mild or absence of perilesional edema”.

Of note, the images illustrating the article of Nussbaum et al. are not suggestive of a CM [20]. In addition, in our experience, pseudocavernomas share more radiological features with encapsulated chronic hematomas (which has been reported as a late complication following AVM radiosurgery [13]) than with CM. These observations support the hypothesis that pseudocavernomas represent radiation induced damages unrelated to CM.

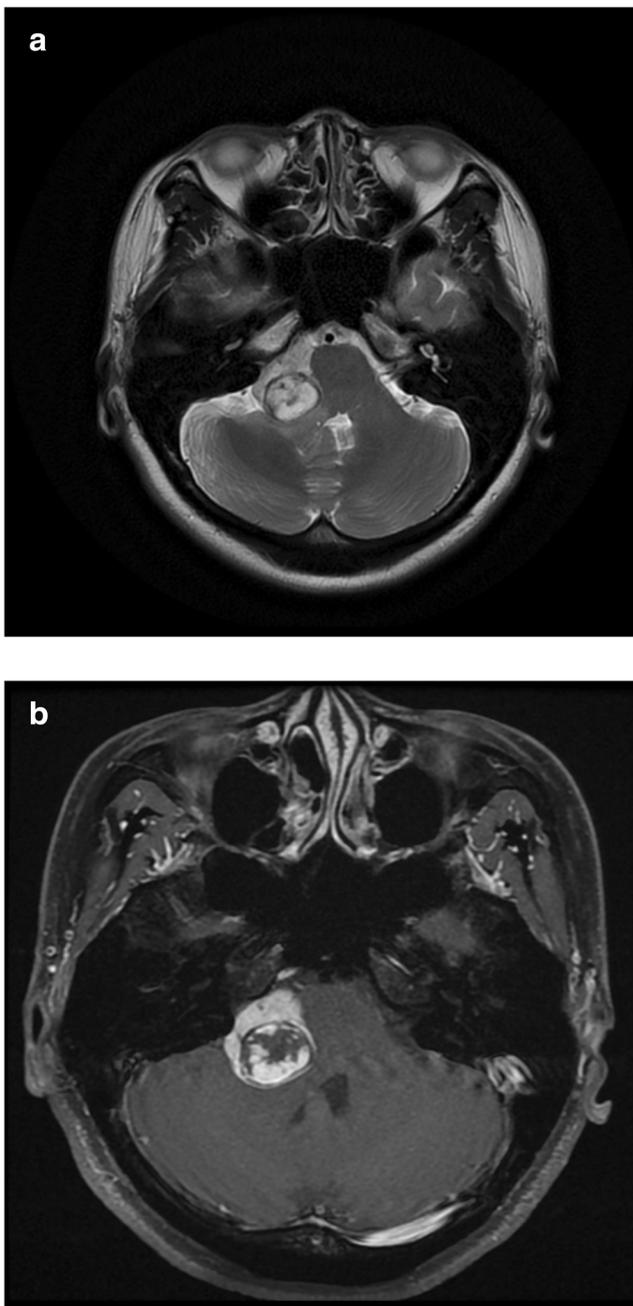
Another observation supporting the existence of pseudocavernomas is that a radiation-induced CM disappeared following administration of bevacizumab [1], just as radiation-induced complications sometimes do [15]. Thus, the radiation-induced cavernoma reported here is likely to represent a pseudocavernoma.

Clinically, Cutsford-Gregory et al. found that asymptomatic pseudocavernomas had a higher incidence of hemorrhages as compared to asymptomatic CMs [6]. di Giannatale et al. suggested that pseudocavernomas may have a lower incidence of seizures as compared to CM [8]. Larson et al. suggested that the risk for hemorrhage is higher in pseudocavernomas as compared to CM [14]. Thus, there may be clinical differences between pseudocavernomas and CMs, although the data supporting this is sparse at present.

Based on the arguments above, it can be concluded that pseudocavernomas exist and should be considered to be a differential diagnosis to radiation-induced CMs in the future. This does not mean that all radiation-induced CMs are pseudocavernomas. It is reasonable to assume that some radiation-induced CMs actually are earlier non-hemorrhaged CMs that now have hemorrhaged, some are true radiation-induced CMs and some are pseudocavernomas.

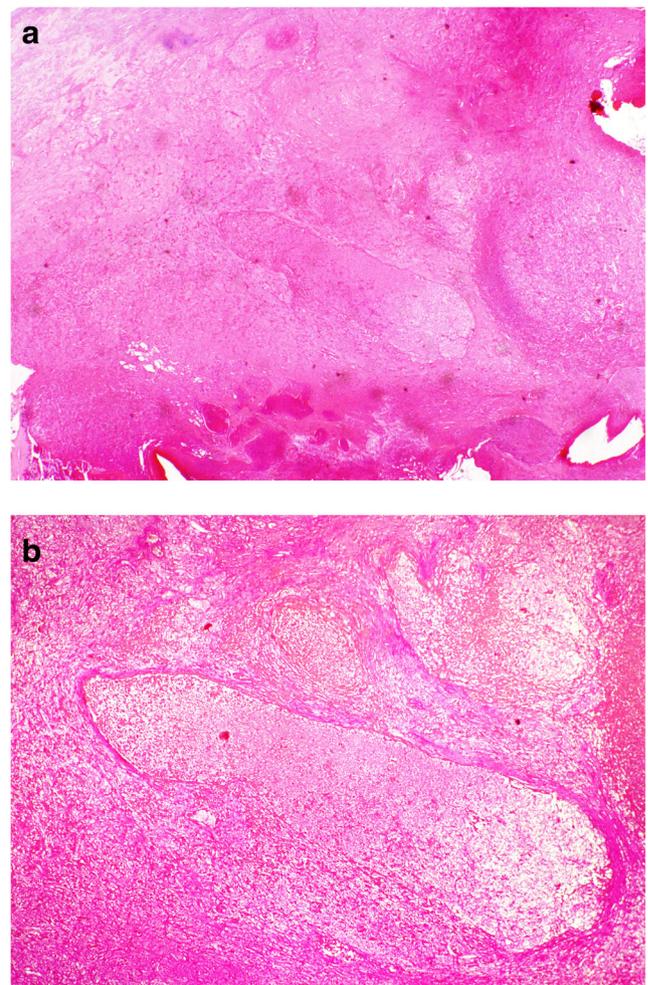
So what is our own experience? One of our patients developed an intratumoral lesion in a vestibular schwannoma 4.5 years after radiosurgery (Fig. 1). The radiation dose given to this area was around 20 Gy. The lesion increased in size and became symptomatic, and was thus removed 5.5 years after radiosurgery. The radiological differential diagnoses were neoplasm and CM.

The histopathological examination showed no evidence of neoplastic process but amorphous coagulum and fibrinous material with occasional, poorly recognizable, ectatic vascular spaces (possibly representing a re-canalization process) (Figs. 2 and 3). These vascular spaces lack elastic tissue fibers and smooth muscle within their walls, as demonstrated by the elastic tissue Verhoeff’s Van Gieson (EVG) histochemical stain and desmin immunohistochemistry, respectively. With these histopathological features, the lesion is likely the result of radiation-induced damages as well as the repair process it has triggered. Thus, a neoplasm as well as a CM could be excluded.



**Fig. 1** **a** AX T2 PROP image and **b** Contrast-enhanced AX T1 FS image of a vestibular schwannoma 5.5 years after GKS

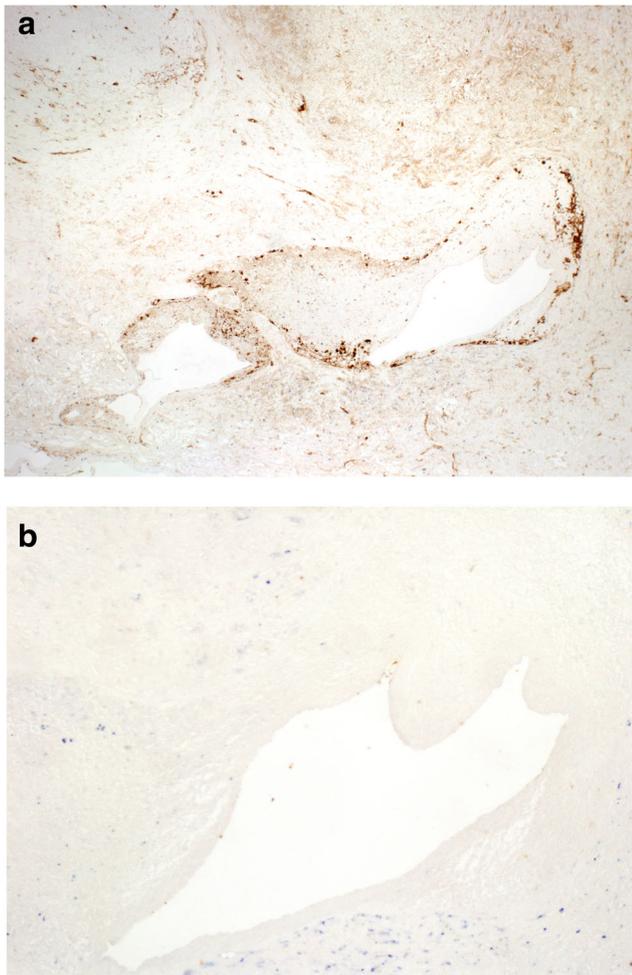
Another patient developed a CM-like lesion 8 years after radiotherapy for a tonsillar cancer. The tumor radiation dose was 70 Gy in 35 fractions. The lesion was removed due to a hemorrhage impairing the CSF circulation. The histopathological examination showed abundant amorphous coagulum and fibrinous material in the background. There was a relatively well-defined vascular malformation in a small area composed of back-to-back, dilated, thin-walled vascular caverns. Thus, the lesion was compatible with a CM.



**Fig. 2** Histopathological images from the lesion in the vestibular schwannoma. **a** Hematoxylin and eosin (HE) stain, 20× magnification and **b** elastic tissue Verhoeff's Van Gieson (EVG) stain, 40× magnification. There is mainly amorphous coagulum and fibrinous material, with occasional, poorly recognizable, ectatic vascular spaces. These vascular spaces lack elastic tissue fibers within their walls, as demonstrated by the elastic tissue Verhoeff's Van Gieson (EVG) histochemical stain

One may hypothesize that pseudocavernomas may develop after the high and sometimes necrotic radiation dose delivered in radiosurgery while CM-like lesions may develop after the low non-necrotic doses delivered in radiotherapy. This is compatible with what is reported in the literature. Baumgartner et al. reported three patients with CM-like lesions that developed after radiotherapy, and in all patients the diagnosis CM was radiologically and histopathologically confirmed [2]. In contrast, Cha et al. reported seven patients with CM-like lesions that developed after radiosurgery, and all were histopathologically incompatible with CMs and thus representing pseudocavernomas [3].

In conclusion, our own cases as well as our literature review support that at least some of the radiation induced CMs, especially those which develop following radiosurgery, have



**Fig. 3** Immunohistochemistry (IHC) images from the lesion in the vestibular schwannoma. **a** CD31 antibody and **b** Desmin antibody, both 40× magnification. CD31 IHC highlights the presence of attenuated endothelial cells lining the ectatic vascular spaces. Desmin IHC confirms the absence of smooth muscle in the walls of the vascular spaces

little in common with CMs and thus the term pseudocavernoma is appropriate in these cases. More knowledge is needed about the natural course of pseudocavernomas in order to manage them appropriately. Cave radiosurgery for these lesions as they may be an expression of radiation-induced damage and repair, which could be worsened if additional radiation is given.

## References

- Aguilera D, Tomita T, Goldman S, Fangusaro J (2010) Incidental resolution of a radiation-induced cavernous hemangioma of the brain following the use of bevacizumab in a child with recurrent medulloblastoma. *Pediatr Neurosurg* 46:303–307
- Baumgartner JE, Ater JL, Ha CS, Kuttesch JF, Leeds NE, Fuller GN, Wilson RJ (2003) Pathologically proven cavernous angiomas of the brain following radiation therapy for pediatric brain tumors. *Pediatr Neurosurg* 39:201–207
- Cha YJ, Nahm JH, Ko JE, Shin HJ, Chang JH, Cho NH, Kim SH (2015) Pathological evaluation of radiation-induced vascular lesions of the brain: distinct from de novo cavernous hemangioma. *Yonsei Med J* 56:1714–1720
- Ciricillo SF, Cogen PH, Edwards MS (1994) Pediatric cryptic vascular malformations: presentation, diagnosis and treatment. *Pediatr Neurosurg* 20:137–147
- Cushing H, Bailey P (1928) Tumors arising from the blood-vessels of the brain. Charles C. Thomas, Springfield
- Cutsforth-Gregory JK, Lanzino G, Link MJ, Brown RJ Jr, Flemming KD (2015) Characterization of radiation-induced cavernous malformations and comparison with a nonradiation cavernous malformation cohort. *J Neurosurg* 122:1214–1222
- Detwiler PW, Porter RW, Zabramski JM, Spetzler RF (1997) De novo formation of a central nervous system cavernous malformation: implications for predicting risk of hemorrhage. Case report and review of the literature. *J Neurosurg* 87:629–632
- Di Giannatale A, Morana G, Rossi A, Cama A, Bertoluzzo L, Barra S, Nozza P, Milanaccio C, Consales A, Garrè ML (2014) Natural history of cavernous malformations in children with brain tumors treated with radiotherapy and chemotherapy. *J Neuro-Oncol* 117:311–320
- Gastelum E, Sear K, Hills N, Roddy E, Randazzo D, Chettout N, Hess C, Cotter J, Haas-Kogan DA, Fullerton H, Mueller S (2015) Rates and characteristics of radiographically detected intracerebral cavernous malformations after cranial radiation therapy in pediatric cancer patients. *J Child Neurol* 30:842–849
- Iwai Y, Yamanaka K, Yoshimura M (2007) Intracerebral cavernous malformation induced by radiosurgery. Case report. *Neurol Med Chir (Tokyo)* 47:171–173
- Karlsson B, Jokura H, Yang H-C, Yamamoto M, Kawagishi J, Guo W-Y, Beute G, Pan D, Aiyama H, Chung W-Y, Söderman M, Yeo T (2018) The NASSAU (New ASSESSment of cerebral Arteriovenous Malformationa yet Unruptured) analysis: are the results from the ARUBA trial also applicable to unruptured arteriovenous malformations deemed suitable for Gamma Knife surgery? *Neurosurgery*. <https://doi.org/10.1093/neuros/nyy391>
- Kleinschmidt-DeMasters BK, Lillehei KO (2016) Radiation-induced cerebral vascular “malformations” at biopsy. *J Neuropathol Exp Neurol* 75:1081–1092
- Kurita H, Sasaki T, Kawamoto S, Taniguchi M, Kitanaka C, Nakaguchi H, Kirino T (1996) Chronic encapsulated expanding hematoma in association with gamma knife stereotactic radiosurgery for a cerebral arteriovenous malformation. Case report. *J Neurosurg* 84:874–878
- Larson JJ, Ball WS, Bove KE, Crone KR, Tew JJ Jr (1998) Formation of intracerebral cavernous malformations after radiation treatment for central nervous system neoplasia in children. *J Neurosurg* 88:51–56
- Levin VA, Bidaut L, Hou P, Kumar AJ, Wefel JS, Bekele BN, Grewal J, Prabhu S, Loghin M, Gilbert MR, Jackson EF (2011) Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys* 79:1487–1495
- Lindquist C, Guo WY, Karlsson B, Steiner L (1993) Radiosurgery for venous angiomas. *J Neurosurg* 78:531–536
- Luschka H (1854) Cavernöse Blutgeschwulst des Gehirnes. *Virchows Arch* 6:458–470
- Motegi H, Kuroda S, Ishii N, Aoyama H, Terae S, Shirato H, Iwasaki Y (2008) De novo formation of cavernoma after radiosurgery for adult cerebral arteriovenous malformation—case report. *Neurol Med Chir (Tokyo)* 48:397–400
- Murakami K, Jokura H, Kawagishi J, Watanabe M, Tominaga T (2011) Development of intratumoral cyst or extratumoral arachnoid cyst in intracranial schwannomas following gamma knife radiosurgery. *Acta Neurochir* 153:1201–1209

20. Nussbaum LA, Kallmes K, Bellairs E, McDonald W, Nussbaum ES (2018) De novo cavernous malformations arising in the wall of vestibular schwannoma following stereotactic radiosurgery: case report and review of the literature. *Acta Neurochir*. <https://doi.org/10.1007/s00701-018-3734-2>
21. Park YS, Kim SH, Chang JH, Chang JW, Park YG (2011) Radiosurgery for radiosurgery-induced cavernous malformation. *World Neurosurg* 75:94–98
22. Pozzati E, Acciarri N, Tognetti F, Marliani F, Giangaspero F (1996) Growth, subsequent bleeding, and de novo appearance of cerebral cavernous angiomas. *Neurosurgery* 38:662–669
23. Sasagawa Y, Akai T, Itou S, Iizuka H (2009) Gamma knife radiosurgery-induced cavernous hemangioma: case report. *Neurosurgery* 64:E1006–E1007
24. Seiger K, Pendharkar A, Samghabadi P, Chang S, Cho N, Choi CVH, Wang C, Soltys SG (2018) Cavernous malformations are rare sequelae of stereotactic radiosurgery for brain metastases. *Acta Neurochir*. <https://doi.org/10.1007/s00701-018-3701-y>
25. Wang X, Hui XH, Liu JP, Mao Q (2012) Radiation-induced cavernous malformation at the site of arteriovenous malformation following gamma knife radiosurgery: case report. *Clin Neurol Neurosurg* 114:1289–1289
26. Yeon JY, Suh YL, Kim JH, Lee JI (2010) Development of de novo cavernous hemangioma after radiosurgery for cavernous hemangioma. *J Korean Neurosurg Soc* 48:532–533