Cavernous malformation etiology

Radiation-induced cavernous haemangiomas (RICHs) are a known late complication of radiation exposure, especially in young children.

Cavernous malformation induction following stereotactic radiosurgery (SRS) is largely unreported.

Seiger et al. from the Department of Radiation Oncology, Department of Neurosurgery, Department of Pathology Stanford University, Harvard Medical School, Boston, Department of Radiation Oncology, Santa Clara Valley Medical Center, San Jose, describe two cases of cavernous malformation formation years following SRS for brain metastases. A 20-year-old woman with breast cancer brain metastases received treatment with whole brain radiotherapy (WBRT), then salvage SRS 1.4 years later for progression of a previously treated metastasis. This lesion treated with SRS had hemorrhagic enlargement 3.0 years after SRS. Resection revealed a cavernous malformation. A 25-year-old woman had SRS for a brain metastasis from papillary thyroid carcinoma. Resection of a progressive, hemorrhagic lesion within the SRS field 2 years later revealed both recurrent carcinoma as well as cavernous malformation. As patients with brain metastases live longer following SRS, this cases highlight that the differential diagnosis of an enlarging enhancing lesion within a previous SRS field includes not only cerebral necrosis and tumor progression but also cavernous malformation induction [1].

Genetics

Occurring in familial autosomal dominantly inherited or isolated forms. Once CCM are diagnosed by magnetic resonance imaging, the indication for genetic testing requires either a positive family history of cavernous lesions or clinical symptoms such as chronic headaches, epilepsy, neurological deficits, and hemorrhagic stroke or the occurrence of multiple lesions in an isolated case. Following these inclusion criteria, the mutation detection rates in a consecutive series of 105 probands were 87% for familial and 57% for isolated cases. Thirty-one novel mutations were identified with a slight shift towards proportionally more CCM3 mutations carriers than previously published (CCM1: 60%, CCM2: 18%, CCM3: 22%). In-frame deletions and exonic missense variants requiring functional analyses to establish their pathogenicity were rare: An in-frame deletion within the C-terminal FERM domain of CCM1 resulted in decreased protein expression and impaired binding to the transmembrane protein heart of glass (HEG1). Notably, 20% of index cases carrying a CCM mutation were below age 10 and 33% below age 18 when referred for genetic testing. Since fulminant disease courses during the first years of life were observed in CCM1 and CCM3 mutation carriers, predictive testing of minor siblings became an issue [2].

1)
Seiger K, Pendharkar AV, Samghabadi P, Chang SD, Cho N, Choi CYH, Wang C, Gephart MH, Soltys SG. Cavernous malformations are rare sequelae of stereotactic radiosurgery for brain metastases. Acta Neurochir (Wien). 2018 Oct 17. doi: 10.1007/s00701-018-3701-y. [Epub ahead of print] PubMed PMID: 30328524.

2)
Spiegler S, Najm J, Liu J, Gkalympoudis S, Schröder W, Borck G, Brockmann K, Elbracht M, Fauth C, Ferbert A, Freudenberg L, Grasshoff U, Hellenbroich Y, Henn W, Hoffjan S, Hüning I, Korenke GC, Kroisel PM, Kunstmann E, Mair M, Munk-Schulenburg S, Nikoubashman O, Pauli S, Rudnik-Schöneborn S, Sudholt I, Sure U, Tinschert S, Wiednig M, Zoll B, Ginsberg MH, Felbor U. High mutation detection rates in cerebral cavernous malformation upon stringent inclusion criteria: one-third of probands are

minors. Mol Genet Genomic Med. 2014 Mar;2(2):176-85. doi: 10.1002/mgg3.60. Epub 2014 Jan 14. PubMed PMID: 24689081.

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