

## Radiation-Induced Cerebral Micro bleeds

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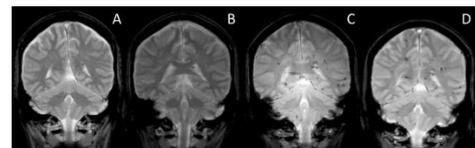
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### Case Review

A 29 year-old Thai female presented with a right-sided headache for 3 days prior to hospital admission. The patient complained of severe pain and upon examination, pain was found to be localized only on the right parietal area. Initially diagnosed as a migraine headache, the pain gradually improved with simple analgesics. She had neither history of head trauma, hypertension, diabetes, psychiatric problems, nor family history of Alzheimer's disease. Seven years earlier at the age of 22 years, the patient presented with progressive headaches with nausea and vomiting followed by generalized tonic clonic seizures. The neurological examination at that time showed bilateral papilledema. Initial computed tomography (CT) scan (Figure 1) of the brain revealed a pineal region tumor with obstructive hydrocephalus. However, magnetic resonance imaging (MRI) of the brain was not performed at the initial diagnosis. Right occipital transtentorial craniectomy with near total tumor removal and ventriculo peritoneal shunt placement were performed. The pathological finding of the tumor was reported to be pineal parenchymal tumor grade III/IV based on the currently proposed system or pineal parenchymal tumor of intermediate differentiation (gr III or IV) according to WHO classification[1,2]. She received 30 Fractions of whole brain irradiation with 6 cycles of chemotherapy (cyclophosphamide and vincristine). The radiation dose ranged from 42 to 90 cGy per dose of each radiation site (total dose 36 Gy of whole brain irradiation with booster at tumor base up to 54 Gy). She received her first MRI 5 months after the last dose of radiation which showed only a few cerebral micro bleeds (CMBs) in the subcortical white matter of the left cerebral hemisphere. Magnetic resonance angiography (MRA) of the brain was normal and there was no evidence of cerebral infarction. Serial MRI of the brain was performed at 5 years after the cranial radiation and showed a markedly increase in number of CMBs (Figure 2)



**Figure 1:**Initial contrast enhanced CT brain showing round shape homogeneous hyperdensity mass at pineal region with obstructive hydrocephalus



**Figure 2:** T2-weighted Gradient-recalled echo (GRE) during seven-year follow up demonstrated increasing number of blooming of low signal on T2 WI suggesting cerebral micro bleeds. (A) MRI 5 months after whole brain irradiation (B) MRI 1 year after whole brain irradiation (C) MRI 5 years after whole brain irradiation (D) MRI 7 years after whole brain irradiation

At the last presentation, both her general physical and neurological examinations were normal. MRI of the brain demonstrated sub-acute brain infarction at the head and body of the right caudate nucleus and globus pallidus. There was also a small focal sub-acute hemorrhage at deep white matter of the right parietal lobe. An interval increase in number of micro hemorrhages in subcortical and deep white matters of the cerebral and cerebellar hemispheres and brain stem were noted. MRA of the brain revealed a mild irregular luminal narrowing at distal M1 segment of the right MCA.

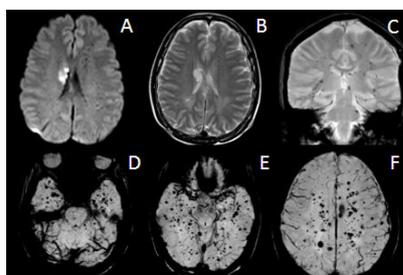
### Discussion

Here we report a patient with an increasing number of CMBs after receiving large doses of cranial radiation and chemotherapy for treatment of pineal parenchymal tumor. Serial MRIs were performed and demonstrated an increasing number of CMBs overtime. Since the patient is a young adult without any other obvious causes of CMBs, we strongly believe that the CMBs were a direct result of cranial radiation.

Radiation therapy is a highly effective treatment for pineal tumors but it may lead to several complications such as focal brain necrosis, diffuse white matter injury, brain atrophy, mineralizing microangiopathy, telangiectasias, optic neuropathy, and large artery vasculopathy [3]. Complications of cranial radiation can be classified into three categories based on the timing after exposure to the radiation; acute complication, early delayed complication, and late complication [3]. Vascular injury including large and small vasculopathy related to radiation usually occurs as a delayed complication [4]. A previous report of cranial irradiation in pediatric patients with brain tumor showed that the risk of stroke was 100-fold higher than general pediatric population due to delayed vasculopathy [5]. Furthermore, cranial radiation doses greater than 30 Gy also increased the risk of stroke [6]. In our case, an increasing number of CMBs occurred during the 7 year period after the patient's initial radiation treatment. There was also evidence of brain infarction in the caudate and globuspallidus which may represent small vascular injury.

Radiation-induced telangiectasias or radiation-induced micro bleeds is one common complication that affects microcirculation. It was previously described as cryptic vascular malformation [7]. Pathology of radiation induced cerebral micro bleeds consist of deposition of perivascular hemosiderin or hemorrhage adjacent to the capillary sized telangiectasia [7].

CMBs is a term describing small areas of signal void with associated blooming visible on T2\*-weighted MRI or other sequences that are sensitive to susceptibility effect. The CMBs are normally not visible on CT, FLAIR, T1-weighted or T2-weighted sequences. The size of CMBs is generally 2-5 mm in diameter but can be as large as 10 mm. The CMBs are well defined, round or oval-shaped hemorrhagic lesions which can appear as homogeneous hypointense lesions on T2\*-weighted gradient-recalled echo (T2\* GRE) and susceptibility-weighted (SWI) MRI sequences [8-10]. The best imaging technique to detect CMBs at present is the SWI which is more sensitive than T2\*GRE as shown in Figure 3. It is necessary to distinguish between CMB mimics such as calcium and iron deposition, cross-section of pial blood vessels, and partial volume artifact from bones which are paramagnetic substances. These CMB mimics can also be seen as hyposignal intensity lesions by T2\*GRE and SWI [8]. The incidence of radiation-induced telangiectasia or CMBs detected by T2-weighted MR images is approximately 20% among children who underwent cranial irradiation [11]. However, actual incidence may be higher if better sensitivity imaging is used [12]. Although CMBs has been reported in several neurological and metabolic conditions, a large number of CMBs of more than 10 are generally related to hypertension [13], cerebral amyloid angiopathy [14], Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) [15], and diffuse axonal injury [16]. In a series of radiation-induced microbleeds, only 1 patient (2.94%) had numerous CMBs [12].

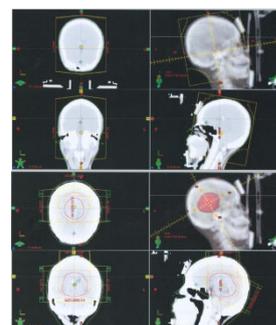


**Figure 3:** The present MRI of the brain 7 years after whole brain irradiation. (A) Diffusion weighted image (DWI) demonstrates restricted diffusion at the head and body of right caudate nucleus and globus pallidus. (B) T2 weighted image (T2WI) demonstrates spots of low signal intensity areas in the subcortical and deep white matter of both hemispheres. (C) GRE T2\*WI demonstrates blooming dark signal spots in the subcortical and deep white matter areas of bilateral hemispheres. (D,E,F) Susceptibility weighted image (SWI) shows numerous spots of micro hemorrhage in subcortical and deep white matters of the bilateral cerebral hemisphere.

According to a previous report, the latency between radiation exposure and the occurrence of CMBs ranged between 5 months to 22 years [7]. Another case series using a high sensitivity MRI technique for detection of CMBs showed that the CMBs could be detected as early as 3 months after radiation [12]. In our case, the first MRI was

performed at 5 months after radiation and found a small number of CMBs in the subcortical region.

Location of radiation-induced micro bleeds is different from CMBs caused by hypertensive vasculopathy, cerebral amyloid angiopathy, and diffuse axonal injury. Cerebral micro bleeds resulting from hypertensive vasculopathy are typically located in basal ganglia, thalamus, brainstem, and cerebellum whereas lobar distribution especially, in the posterior cortical region, is typical for cerebral amyloid angiopathy [8]. Diffuse axonal injury after trauma can also cause cerebral micro bleeds and most of the micro bleeds are located in frontal and temporal lobes. The location of radiation-induced micro bleeds usually depends on the site of irradiation. In patients who had local brain radiation therapy, CMBs are generally limited only to the radiation field [11]. However, among patients who underwent whole brain radiation therapy CMBs frequently appeared in the temporal lobe [11]. In this present case where the patient underwent whole brain radiation, CMBs were scattered in bilateral subcortical and deep white matter of cerebral hemispheres as well as in bilateral temporal lobes. Moreover, there are more CMBs in the path of the beam (focal boost) than in other, less irradiated, parts of the brain. The external beam radiation treatment plan for whole brain radiation and focal boost are presented in Figure 4.



**Figure 4:** External beam radiation treatment (EBRT) plans for pineal parenchymal tumor in the present case. (A) EBRT plans for whole brain irradiation. (B) EBRT plans for focal boost. Total dose 36 Gy of whole brain irradiation and booster at tumor base up to 54 Gy.

In addition to the location of CMBs, the onset of CMBs, underlying diseases, other clinical presentations, neuroimaging, and brain pathology can also aid in a more effective differential diagnosis. Cerebral amyloid angiopathy most commonly presents in elderly populations or in those with family history of Alzheimer's disease. Therefore, MRI findings with lobar hemorrhage without definite cause may also be more useful in diagnosis. Although one large study in post mortem with malignant neoplasm showed an increasing prevalence of vascular amyloid (pathological proven amyloid  $\beta$  protein ( $A\beta$ ) deposit) affected by aging and brain radiation, there was no  $A\beta$  protein deposit in post mortem under 40 years. However, in CADASIL, most patients usually present with dementia, psychiatric disturbance, migraine with aura, and recurrent stroke. MRI findings normally show subcortical white matter lesions, anterior part of the temporal lobe lesions or lacunar infarction, which differs from the patient in this case.

A previous report suggested that the number of CMBs is significantly related to the dose of radiation. In one study, radiation-

induced micro bleeds were detected at radiation doses greater than 25 Gy [12] where CMBs occurred in 4 out of 11 patients with whole brain radiation. However, the dosage of whole brain radiation in this series was 24-30 Gy which was much less than the dose given to our patient. The wide spread and large number of CMBs in our patient confirms previous findings that CMBs occurrence is dose and region dependent.

Complications of radiation therapy usually depend on the total dose, patient age, underlying disease, and concomitant therapy. In our case, in addition to radiation treatment, the patient also received chemotherapy with cyclophosphamide and vincristine. However, previous studies did not demonstrate the association between CMBs and chemotherapy [11,12]. Thus, it is unlikely that the large number of CMBs in our case is related to chemotherapy.

In this reported case, the clinical course and serial neuroimaging highly indicated that numerous CMBs were caused by exposure to high doses of cranial irradiation. Therefore, we did not perform any genetic testing for hereditary forms of cerebral amyloid angiopathy and NOTCH3 gene for CADASIL which are the causes of CMBs in young patients. Lack of CMBs histopathology pose as limitations that need further clarification in future study.

In conclusion, radiation induced-micro bleeds are a result of microvascular injury from radiation. We report a case of radiation-induced micro bleeds with serial MRI studies. Large doses of radiation over the whole brain area results in increasing numbers of CMBs over time.

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