

# Bilateral lateral ventricular subependymoma with extensive multiplicity presenting with hemorrhage

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## Abstract

This 48-year-old-man who had undergone right thyroid lobectomy for undifferentiated thyroid carcinoma nine years earlier developed generalized seizures. His cerebrospinal fluid was xanthochromic with elevation of total protein. Computed tomography (CT) showed mixed-density bilateral ventricular masses. Magnetic resonance imaging (MRI) revealed multiple nodules in both lateral ventricles; they were heterogeneously enhanced by gadolinium. Diffuse hyperintensity in the right medial temporal lobe and bilateral subependymal area was noted on fluid-attenuated inversion recovery images. Susceptibility-weighted imaging showed low intensity in the masses and cerebellar sulci suggesting hemorrhage and hemosiderin deposition. The preoperative diagnosis was disseminated malignant tumor with recurring hemorrhage. Histological examination of biopsy specimens showed clusters of cells with small uniform nuclei embedded in a dense fibrillary matrix of glial cells and microcystic degeneration. Pseudo-rosettes indicating ependymoma were absent. Microhemorrhages and hemosiderin deposits were noted. Immunohistochemically, the background fibrillary matrix and neoplastic cells were positive for glial fibrillary acidic protein. Mutated isocitrate dehydrogenase-1 was negative. The MIB-1 index was 1.5%. The tumor was pathologically diagnosed as subependymoma containing microhemorrhages and hemosiderin deposits. The extensive multiplicity and hemorrhage encountered in this case have rarely been reported in patients with subependymoma.

## Keywords

Subependymoma, multiplicity, hemorrhage

## Introduction

Subependymoma, a noninvasive, intraventricular, slow-growing neoplasm was first described by Scheinker in 1945.<sup>1</sup> It accounts for less than 1% of all intracranial neoplasms; its World Health Organization (WHO) classification is grade 1.<sup>2</sup> It is seen most commonly in the fourth- and lateral ventricles and rarely in the third ventricle and spinal cord.<sup>3</sup> Most of these tumors are asymptomatic and detected incidentally at autopsy. We report a rare hemorrhagic intraventricular subependymoma with extensive multiplicity.

## Case report

The patient is a 48-year-old man who had undergone right partial thyroidectomy for undifferentiated thyroid carcinoma nine years earlier. He received thyroid-stimulating hormone suppression therapy with thyroxine for six years and had been followed up regularly. At the time of admission to our hospital his mental status was

altered after a general seizure. His cerebrospinal fluid was xanthochromic; total protein was increased to 157.1 mg/dl.

Computed tomography (CT) showed masses in both anterior horns of the lateral ventricles with mixed hyper- and iso-density and a low-density mass in the right medial temporal region (Figure 1). Magnetic resonance imaging (MRI) revealed multiple round

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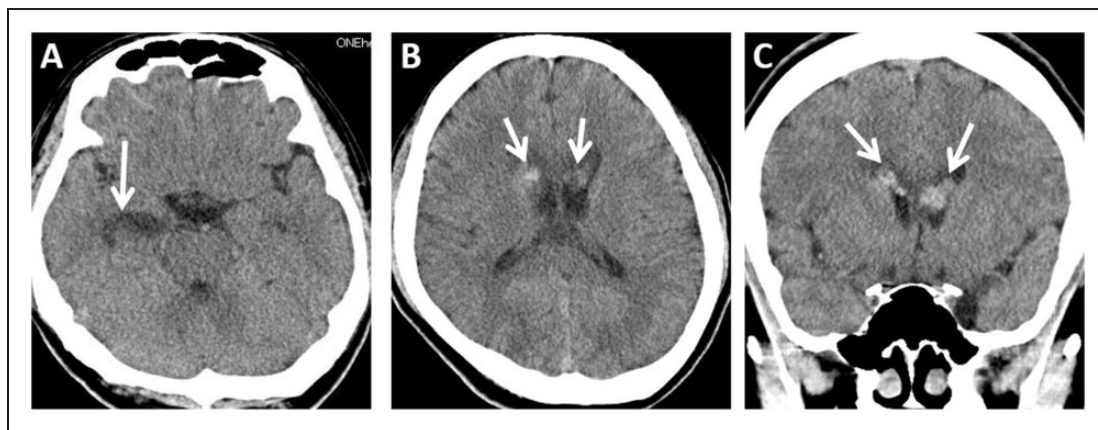
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**Figure 1.** Computed tomographic (CT) scan.

- (a) Axial CT scan at the level of the hippocampus showed a low-density mass at the head of the hippocampus (arrow).  
 (b) Axial CT scan at the level of the lateral ventricle showed basically high-density masses in the bilateral anterior horns (arrows).  
 (c) Coronal CT scan also revealed high-density masses in the bilateral anterior horns (arrows).

nodule-like lesions in both lateral ventricles (Figure 2(a)). The masses were basically hyperintense on T2-weighted images but contained low-intensity areas (Figure 2(b)). Susceptibility-weighted images showed very low intensity in the ventricular masses and cerebellar sulci (Figure 2(c) and (d)). Fluid-attenuated inversion recovery (FLAIR) imaging revealed hyperintense masses in the lateral ventricles, third ventricular floor, and in the inferior horn of the right lateral ventricle extending into the amygdala. Small nodules were also seen on the ependym and septum pellucidum (Figure 2(e) and (f)). The masses were heterogeneously gadolinium enhanced (Figure 2(g) and (h)). These imaging findings suggested intraventricular metastasis from thyroid carcinoma and other malignancies such as glioblastoma and primary central nervous system lymphoma (PCNSL) and hemorrhage in the masses; pial hemosiderosis was suggestive of recurrent hemorrhage from the tumors.

Endoscopic biopsy was performed via a left frontal burr hole. Whitish lobulated masses were observed in the lateral ventricular wall (Figure 3(a)). Some masses were dark, suggesting chronic-phase of hemorrhage (Figure 3(b)). Through the foramen Monroi, a well-demarcated mass was observed in the pre-mammillary area (Figure 3(c)). These masses were biopsied using a flexible punch.

On pathological examination, clusters of neoplastic cells with small uniform nuclei were seen to be embedded in a dense fibrillary matrix of glial cells. Microhemorrhages and hemosiderin deposits were noted (Figure 4(a)). Microcystic degeneration was also seen (Figure 4(b)). No perivascular pseudo-rosettes suggesting ependymoma were observed. Berlin blue staining showed scattered iron deposits against the fibrillary background (Figure 4(c)). Immunostaining for glial fibrillary acidic protein (GFAP) showed strong positivity of the whole tissue except the vascular structures (Figure 4(d)). CD-34-positive microvessels were abundant in some restricted areas (Figure 4(e)).

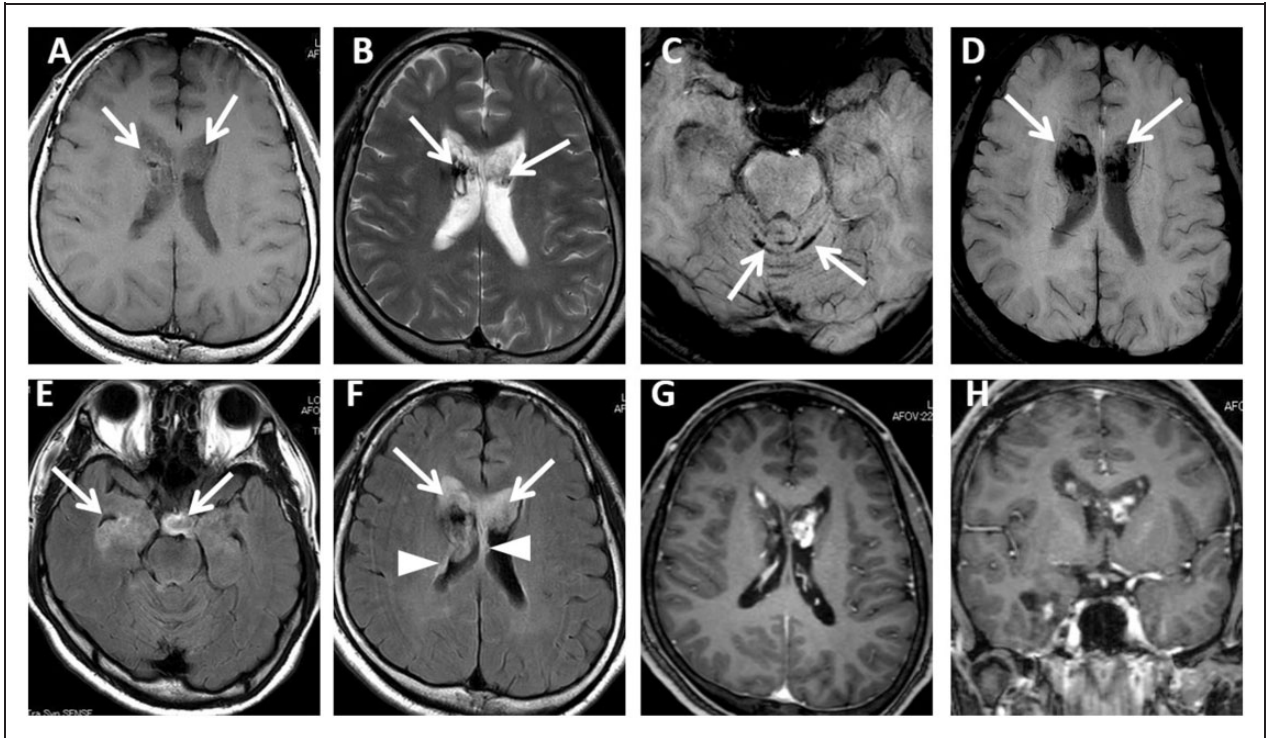
Oligo2 was ubiquitously expressed in the neoplastic cells (Figure 4(f)). There was little dot-like epithelial membrane antigen (EMA) expression, characteristics of ependymoma, in the cytoplasm (Figure 4(g)). The MIB-1 labeling index was as low as 1.5% (Figure 4(h)). The pathologic diagnosis was subependymoma (WHO grade 1). No mutated isocitrate dehydrogenase 1 (IDH1) protein was present.

A follow-up MRI study performed six months after surgery showed no residual tumor growth and the patient has been seizure free for the last eight post-operative months.

## Discussion

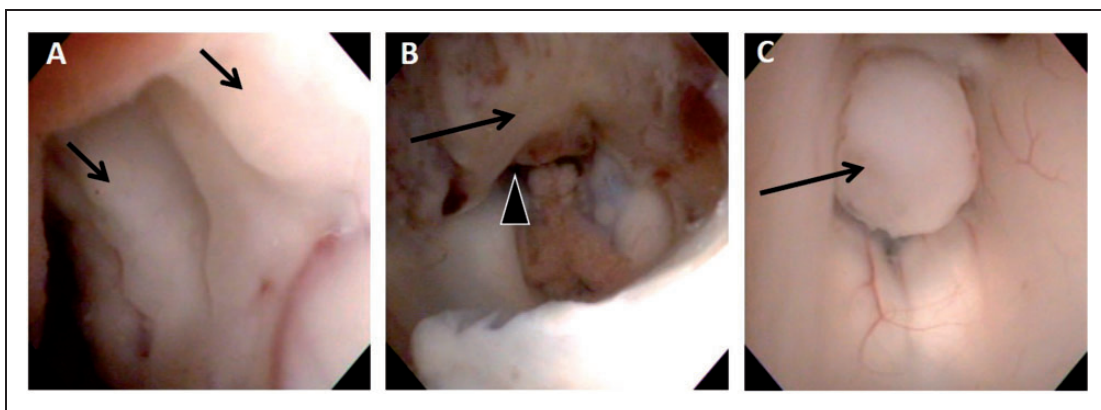
Subependymoma is defined as a slow-growing, exophytic, intraventricular glial neoplasm; it is seen most commonly in middle-aged and elderly men.<sup>4</sup> Most of these tumors arise as solitary lesions, but large subependymomas may extend to both lateral ventricles. Multiple subependymomas are extremely rare. All six patients reported to date presented with double tumors (Table 1); in three they were located in the bilateral lateral ventricles,<sup>5-7</sup> in two they were found in the lateral and third ventricle,<sup>8</sup> and in one patient they arose in the lateral ventricle and cerebellopontine (CP) angle.<sup>9</sup> Our patient harbored at least four major masses at different sites, i.e. the bilateral anterior horns, the third ventricle, and the inferior horn of the right lateral ventricle. Tumorlets on the ependym and septum pellucidum were also noted. This extensive multiplicity suggests a cerebral developmental disorder as the background pathogenesis of these tumors, which has been suggested in familial cases including identical twins.<sup>10</sup>

Common neuroimaging characteristics of this intraventricular tumor are well demarcated, lobulated, hypo- to iso-intense on T1-weighted image and no enhancement on contrast MRI.<sup>4</sup> Intramural cyst and calcification are frequently reported, but the paraventricular extension, high vascularity, and intramural



**Figure 2.** Magnetic resonance imaging (MRI) findings.

- (a) Axial T1-weighted image (WI) showing low- to high-heterogeneous intensity masses in the bilateral anterior horns (arrows).  
 (b) Axial T2-WI revealed intraventricular high intensity masses that included low-intensity areas (arrows).  
 (c) Axial susceptibility-weighted images (SWIs) at the level of the cerebellar culmen revealed very low intensity indicating hemosiderin deposits in the cerebellar sulci (arrows).  
 (d) Axial SWIs at the level of the lateral ventricles showed very low intensity in the masses in the anterior horns suggesting intratumoral bleeding (arrows).  
 (e) Fluid-attenuated inversion recovery (FLAIR) images at the level of the hippocampus showed a hyperintense area in the right medial temporal structure and a mass at the third ventricle (arrows).  
 (f) FLAIR images at the level of the lateral ventricle revealed hyperintense masses in the anterior horns (arrows) and tumorlets on the ependym and septum pellucidum (arrowheads).  
 (g), (h) Gadolinium-enhanced axial (g) and coronal (h) scans showed heterogeneous enhancement of the masses.



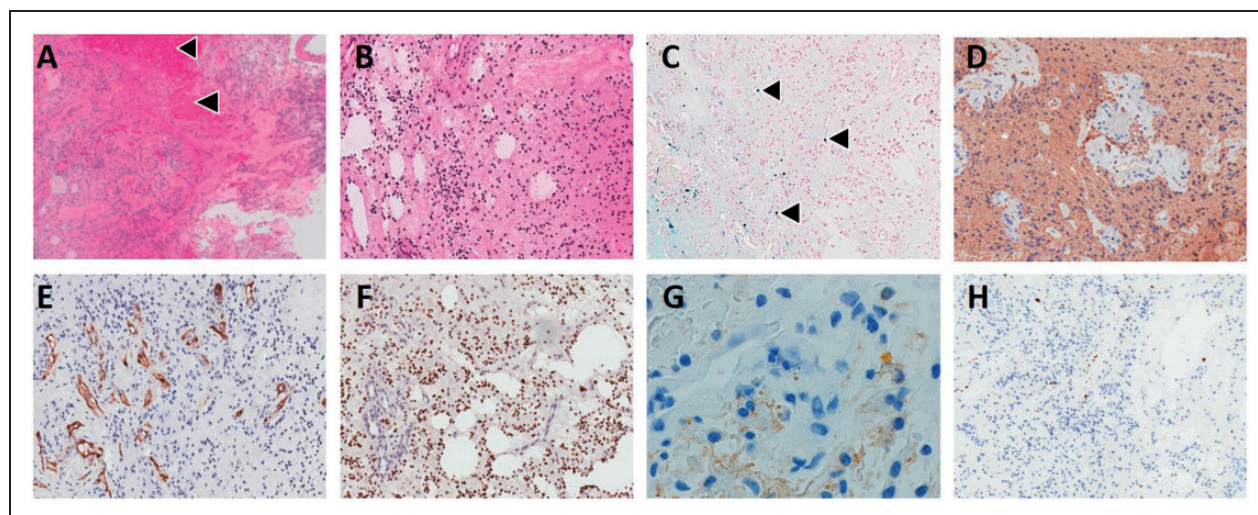
**Figure 3.** Intraoperative findings during endoscopic biopsy through a left frontal burr hole.

- (a) Multiple protuberant lesions on the septum pellucidum (arrows).  
 (b) A mass (arrow) with brownish discoloration in front of the foramen Monroi (arrowhead).  
 (c) Mass in the third ventricular floor (arrow).

hemorrhage seen in our case are very rare findings.<sup>4</sup> Preoperative MRI suggested intratumoral clots and hemosiderin deposits on the cerebellar sulci, indicative of recurrent bleeding from the tumor. This was

histologically confirmed by the observation of hemosiderin deposits and microhemorrhages. We suspect that the rich microvasculature in some limited areas accounted for the microhemorrhages. To date,





**Figure 4.** Histopathology of excised tumor tissue.

- (a) Hematoxylin-eosin (HE) staining at low magnification ( $\times 50$ ) showed clusters of cells with small uniform nuclei embedded in a dense fibrillary matrix intermingled with micro-hemorrhages (arrow heads).  
 (b) HE staining at higher magnification ( $\times 100$ ) revealed microcystic degeneration in the dense fibrillary background.  
 (c) Berlin blue staining revealed dots of hemosiderin deposits (arrowheads) ( $\times 100$ ).  
 (d) Glial fibrillary acidic protein (GFAP) was diffusely positive in neoplastic cells and the fibrillary matrix ( $\times 100$ ).  
 (e) CD34-positive microvessels were abundant in restricted areas of the tumor tissue ( $\times 100$ ).  
 (f) Olig2 was diffusely positive in neoplastic cell nuclei ( $\times 100$ ).  
 (g) Dot-like expression was rarely positive in some limited areas ( $\times 200$ ).  
 (h) The MIB index was 1.5% ( $\times 100$ ).

**Table 1.** Cases of multiple subependymoma reported in the literature.

No.	First author/Year	Age/Gender	Clinical presentation	Location	Resection
1	Rath/2005 <sup>5</sup>	20/M	Not mentioned	LVB	Partial
2	Kandenwein/2011 <sup>9</sup>	48/M	Headache, cranial nerve palsies, ataxia	Right ventricle and right CPA	Total
3	Hou/2012 <sup>8</sup>	44/F	Headache	Left and third ventricle	Total
4	Hou/2012 <sup>8</sup>	33/F	Headache	Right and third ventricle	Total
5	Kumar/2012 <sup>7</sup>	20/M	Raised ICP	LVB	Total
6	Miguel/2015 <sup>6</sup>	69/F	Headache, focal neurological deficits	LVB	Partial
7	Present case	48/M	Seizure/altered consciousness	LVB, third ventricle, SP	Partial

ICP: intracranial pressure; LVB: lateral ventricle (bilateral); SP: septum pellucidum; CPA: cerebellopontine angle; M: male; F: female.

16 patients with hemorrhagic subependymomas have been reported.<sup>6,11,12</sup> The clinical presentation of hemorrhagic subependymomas differs; subarachnoid hemorrhage, an acute, suddenly increased mass effect, and obstructive hydrocephalus have been documented.<sup>6</sup> Our patient did not present with massive hematoma in the ventricles, cerebellar parenchyme, or subarachnoid space and he suffered no acute symptoms suggestive of intracranial bleeding before his first generalized seizure. Consequently, we posit that the microbleeds were insidious. His generalized seizure, the initial clinical presentation, may have been a direct consequence of bleeding although we cannot rule out parenchymal changes in the medial temporal lobe as a cause of seizure.

The sole other multiple subependymoma presenting with hemorrhage was reported in a 69-year-old woman who suffered progressive headache, ataxia, and

right-sided weakness.<sup>6</sup> MRI showed bilateral ventricular tumors; the tumor on the right side bled but no factors leading to bleeding from the basically avascular tumor were suggested.

The differential diagnosis of multiple intraventricular masses in older patients should include metastatic brain tumor, malignant glioma, and malignant lymphoma. Associated hemorrhage is occasionally observed in these tumors. The suggested malignant nature of the tumors in this case by neuroimaging studies and the impossibility of radical tumor removal due to an extensive multiplicity urged us to perform transventricular endoscopic biopsy; which led to the definite diagnosis.

In conclusion, ours is the second reported patient with multiple subependymoma with recurrent insidious bleeding detected on neuroimaging and pathologic studies. Although MRI scans performed six months after

surgery showed no significant changes, because of the risk of subsequent massive bleeding we are following this patient closely and continue to monitor his blood pressure.

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#### Conflict of interest

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