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Original article

## A rare condition: Spontaneous subarachnoid haemorrhage due to spinal hemangioblastoma: Report of 2 cases and review of the literature

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### Abstract

#### **Introduction**

Subarachnoid haemorrhage (SAH), secondary to spinal hemangioblastoma (HBL), is extremely rare, with only a few case reports to date. We report the experience of our reference centre for spinal tumours and Von Hippel-Lindau (VHL) disease in patients with spinal HBL presenting with SAH. We further performed a systematic review of the literature.

#### **Methods**

We report two cases. A systematic search was performed using the PubMed, Embase and Cochrane databases, with no limit for publication date. Inclusion criteria were: patients with HBL presenting with SAH, with or without VHL. The systematic review retrieved only 10 studies, including 16 patients.

#### **Results**

In our centre, the first case concerned radicular HBL at D12 level, presenting with spinal and brain SAH. The patient underwent uneventful microsurgical *en bloc* resection. Postoperative course was normal. The second case concerned HBL with SAH at the cervico-medullary junction, with rapidly fatal course. The systematic review revealed female predominance, at a median age of 40 years, with HBL predominantly located at cervical level, common preoperative symptoms being headache and signs of meningeal irritation.

### ***Conclusions***

In conclusion, spinal HBL is an extremely rare cause of SAH. The systematic review found putative risk factors: female gender, age 40–50 years, cervical location, and median size 2 cm. Diagnosis can be difficult when presentation mimics intracerebral SAH. We advocate early surgical removal. The risk of rapidly fatal course, in case of major haemorrhage, needs to be borne in mind.

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**Keywords:** Hemangioblastomas; Subarachnoid haemorrhage; Spinal; Von Hippel-Lindau

## **1 Introduction**

Hemangioblastomas (HBL) are highly vascularised lesions of the central nervous system (CNS), most frequently within the cerebellum and spinal cord [1-3]. They account for approximately 2-3% of primary spinal cord tumours [4]. They are considered benign (World Health Organisation grade I) [5]. However, they can lead to significant morbidity and mortality through their mass effect, with specific clinical manifestation depending on the anatomical location [6]. In most cases, HBL is sporadic (70 to 80% [7]), although 20-30% of cases are related to a dominantly inherited genetic familial cancer syndrome known as von Hippel-Lindau (VHL) [6,8]. Thirteen per cent of HBLs occur in the spinal canal [9].

Spinal diseases are an extremely rare cause of spontaneous subarachnoid haemorrhage (SAH), accounting for less than 1% of all non-traumatic cases [10]. Haemorrhage secondary to spinal HBL is extremely rare, with currently only a few reports.

The present report describes our experience as a reference centre for spinal tumours and VHL disease, regarding HBL presenting with SAH. We detail clinical course, surgical management (if such was the case) and postoperative assessment. We further performed a systematic review of the literature for publications describing patients with HBL presenting with SAH, with or without surgical exploration, together with clinical and radiological outcomes. The purpose was to investigate potential factors that could help distinguish this rare clinical entity.

## **2 Methods**

### **2.1 Patient population and selection**

This was a retrospective, single-centre observational study. All patients had been diagnosed and treated in our reference centre for spinal neoplasms, vascular disorders and VHL disease (CHU de Bicêtre, France), over a period of 30 years. The local review board of the Bicêtre University Hospital was notified.

Inclusion criteria were: patients harbouring an HBL at the level of the spine and craniocervical junction who presented with SAH confirmed by anatomopathological diagnosis (of the same or another lesion in the context of VHL). Exclusion criteria were: refusal or inability to understand and sign the informed consent form.

After cross matching between the surgeons' (CT, FB) and the pathologist's patients list (CA), 2 cases were included for analysis.

### **2.2 Systematic review of the literature**

#### ***2.2.1 Literature search***

We performed a systematic search using the PubMed, Embase and Cochrane databases, with no limit for dates. The PubMed database was searched using the following word combinations in the "title" or "title/abstract" item: ("hemangioblastoma" AND "haemorrhage" AND "bleeding"), ("hemangioblastoma" AND "bleed" AND "subarachnoid") etc. We also used the Google Scholar and Google search engines to expand our list of studies, including Abstracts; for final analysis, only peer-reviewed papers were included.

#### ***2.2.2 Study selection***

Inclusion criteria were patients:

- with HBL;
- who presented with SAH;
- notwithstanding their VHL status.

Exclusion criteria were: non-English-language studies and articles reporting other type of haemorrhage (i.e., intrasial).

Titles and Abstracts were screened by two different people (CT, FP). Potentially relevant articles were selected for full-text screening evaluation, independently performed by 3 investigators (CT, NA, FP). Discrepancies were resolved by the corresponding and senior authors (CT, FP).

### 2.2.3 Data extraction

Ten studies were finally selected, including 16 patients (Table 1). The study flowchart is shown in Supplementary Fig. S1. Study characteristics, publication year, sample size, pre- and postoperative symptoms, and lesion location and size were extracted.

**Table 1** Systematic review of the literature.

alt-text: Table 1

Publication	Number of patients	Age	Sex	Location	Syrinx (yes/no)	Preoperative symptom	Preoperative sign	Preoperative status	Confirmation of SAH	Size (cm)	Postoperative status
Djindjan (1978) <sup>1</sup>	1	30	M	Upper lumbar	No	Acute low back pain	Acute low back pain	Coma	Intraoperative	2	-
Kormos (1980) <sup>2</sup>	1	31	F	C1	Yes	Paresthesias left side	Meningeal irritation	Normal	LP	2	Normal
Hille (1986) <sup>3</sup>	1 (recurrent)	37	M	C2	No	Left upper limb paresthesias	Meningeal irritation	Normal	LP	4	Normal
Neumann (1989) <sup>4</sup>	2.1. 2.2. 2.3.	27 53 71	F F F	C1-C2 T10-T11 C2-C4	No No No	Headaches Weakness Brachialgia	Meningeal irritation Motor weakness Sensory and motor deficit	Normal Motor deficit Sensory and motor deficit	LP LP CT	2 1 4	- - -
Cerejo (1990) <sup>5</sup>	1	36	F	C1	No	Headaches, confusion	Meningeal irritation	Normal	CT	1.5	Normal
Yu (1994) <sup>6</sup>	2.1. 2.2. (VHL)	31 28	F M	T6-T7 T7-T8	No No	Neck pain Lower back electric shock like	Acute lower limb weakness Lower limb paresthesias	Acute paraplegia Paraplegia	LP Intraoperative/MR	5 -	Paraplegia Paraplegia
Cervoni (1995) <sup>7</sup>	1	20	F	C3	No	None	None	Normal	CT	2	Normal
Minami (1998) <sup>8</sup>	1	48	M	C0	No	Severe headache	None	Slight hypoesthesia	CT	1.5	Normal
Irie (1998) <sup>9</sup>	1	41	M	C5-C6	No	Nuchal pain	Nuchal rigidity	Normal	CT	1	Normal
Berlis (2003) <sup>10</sup>	1 (VHL)	47	F	C0-C1	No	Severe headache	Right paresis	Right paresis	CT	1	-
Gläsker (2005) <sup>11</sup>	4.1. 4.2. (VHL) 4.3. 4.4.	27 47 53 71	F F F F	C1-C2 C4-C5 T10-T11 C2-C4	No No No No	Asymptomatic Asymptomatic Motor weakness Brachialgia	None None Motor weakness Brachialgia	Normal Normal Motor deficit Sensorimotor deficit	CT CT CT CT	3 4.5 1.5 4	- - - -
Nishimura (2012) <sup>12</sup>	1 (VHL)	56	M	L2-L3	No	Lumbar pain Neck pain Headache	-	Transient paraparesis	CT (brain SAH)	3	Normal
Current series (2019)	1 (VHL) 2 (VHL)	64 61	M F	T12	No No	Headache, Motor weakness	Paraparesis, urinary retention	Transient paraparesis and urinary retention	CT, MRI CT	1.7 1.5	Normal Dead (no

## 3 Results

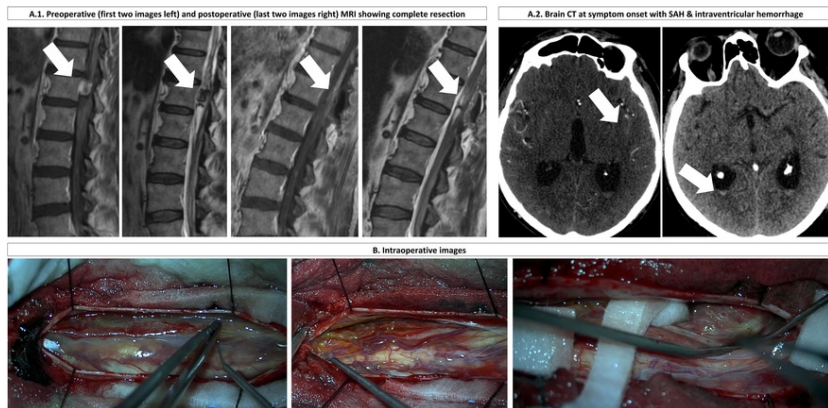
### 3.1 Case series

#### 3.1.1 Illustrative case 1

A 64 year-old male was diagnosed with VHL syndrome at the age of 46 years, with pancreatic neuroendocrine tumours and renal tumours. He underwent surgery for cerebellar HBL at another institution 18 years previously and resection of a left cerebellar HBL one year before presentation. Multiple spinal HBLs were already diagnosed, at levels C3, C4-5, T4, T12 and L1-L2.

One year after the second posterior fossa surgery, he presented with acute headache, urinary retention and mild progressively reversible paraparesis. Spinal MRI revealed SAH at T12-L1: i.e., the location of a known HBL (Fig. 1A1). Recent MRI scans (18 days and 11 months beforehand) further documented the SAH. Spinal digital subtraction angiography (DSA) revealed the anterior spinal artery at the left T11 level. He underwent a brain CT scan, showing SAH at the sylvian fissure and intraventricular haemorrhage (Fig. 1A2). Brain DSA revealed no arteriovenous malformation (AVM) and no vasospasm. MRI confirmed the presence of the known lesion (Fig. 1B).

#### Illustrative case 1



**Fig. 1** Illustrative case 1: A1. Spinal MRI at different time-points before surgery, with subsequent haemorrhage at symptom onset. A2. Brain CT at symptom onset with SAH and intraventricular haemorrhage. B. Preoperative MRI (18 days after symptom onset) including, from left to right, sagittal and axial T2 sequences and sagittal and axial gadolinium-injected sequences. C. Intraoperative images. D. Preoperative images (first two on the left) and postoperative images (last two on the right).

In standard D12-L1 laminectomy, dural exposure revealed arachnoid webs spanning both segments around the lesion, together with SAH (Fig. 1C). After arachnoid dissection, no other HBL than the one located along the D12 rootlets was noted. Following dissection of the posterior rootlet attached to the HBL, the artery and veins were coagulated and monobloc resection was performed. Postoperative course was uneventful, and MRI confirmed complete microsurgical resection (Fig. 1D).

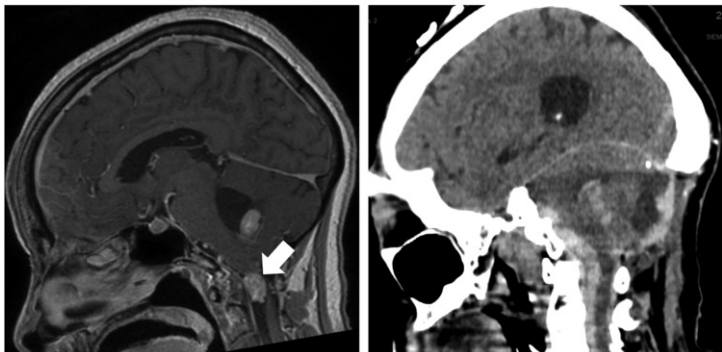
#### 3.1.2 Illustrative case 2

A 61 year-old female was diagnosed with VHL syndrome at the age of 23. She had surgical history of pheochromocytoma, and also a pancreatic neuroendocrine tumour and pancreatic and renal cyst. She presented with multiple central nervous system HBLs, including a growing cerebellar HBL for which she had refused surgery, and an HBL at the medulla oblongata (Fig. 2A).

Illustrative case 2

A. Before SAH

B. At the moment of SAH



**Fig. 2** Illustrative case 2: A. Before SAH, and B. after SAH.

She initially presented with obstructive hydrocephalus, for which she underwent ventriculocisternostomy, and went on to undergo microsurgical resection of the cerebellar HBL. External ventricular drainage was performed postoperatively due to posterior fossa edema and acute hydrocephalus.

She further presented acute spontaneous SAH due to the HBL of the medulla oblongata (Fig. 2B), 17 days after the posterior fossa surgery, clinically manifesting with tetraplegia, respiratory failure and swallowing disorder, revealed during her stay in our intensive care unit.

She died several days later after a multidisciplinary decision to stop further treatment.

### 3.2 Systematic review

The systematic review retrieved 10 case series, including 16 patients. A vast majority were females (female to male sex ratio: 10/6; Table 1). Three had VHL syndrome.

Median age was 39 years (mean 42.9, range 27-71).

The most common symptoms were headache and signs of meningeal irritation.

CT usually confirmed the SAH, the vast majority of which were cervical (9 out of 16). Syrinx was rarely present. Median size was 2 cm (mean 2.6, range 1-5).

When detailed postoperative status was reported, it was normal in most cases, even in patients with major preoperative symptoms. However, as in our series, severe complications sometimes occurred, including death.

## 4 Discussion

The present study detailed the course of two patients harbouring HBL, exceptionally associated with SAH. One concerned radicular HBL at D12, and the second was located at the cervico-medullary junction, with rapidly fatal course. The systematic review revealed female predominance (unlike in Von Hippel-Lindau in general, where the ratio is 1/1), a median age of 39 years, with cervical location, and common preoperative symptoms being headache and signs of meningeal irritation.

Owing to their vascular histology, the risk of haemorrhage, whether spontaneous, intraoperative or postoperative, is well known in HBL. However, the most common symptoms of spinal HBL are related to progressive spinal cord compression [4]. The most common symptom of SAH is sudden headache, while the most common sign is meningeal irritation. For HBL presenting with SAH, spinal cord or root deficits are sometimes observed. When haemorrhage arises in the cervical region, bleeding may extend intracranially, and clinical differential diagnosis versus intracranial SAH may be difficult [11]. Symptom severity usually depends on severity of bleeding. Absence of pre-SAHA neurological symptoms and signs makes diagnosis of HBL difficult. To date, only one case of brain SAH in a patient harbouring lumbar HBL was reported [12], and was surprisingly similar to the present case n° 1.

Arteriovenous malformation is the most frequent etiology of spinal SAH, followed by spinal cord tumour (mostly ependymoma), then neurinoma, paraganglioma and dissemination of malignant spinal tumour [13]. Hemangioblastoma is an extremely rare case of spinal SAH. In a recent study, the risk of spontaneous haemorrhage per person per year in spinal HBL was 0.0024 [14], while the risk of SAH was even lower (0.06%) [15]. The lesion size

associated with spontaneous haemorrhage is much greater. Moreover, it is important preoperatively to differentiate HBL from other types of tumour, as treatment strategies differ.

Before the advent of MRI, HBL was diagnosed on digital subtraction angiography (DSA) [16]. MRI is now the gold standard for HBL diagnosis [17]. The classical aspect is a well-circumscribed mass, often associated with a cyst. An associated syrinx was reported in more than 60% of intramedullary lesions [9], but seems rarely associated with HBL presenting with SAH. The SAH might be further explained by the superficial location of medullary HBLs, whereas cerebellar HBLs tend to bleed intraparenchymally [14].

Tumour size is considered by some authors to be implicated in spontaneous and/or postoperative bleeding [14]. In our systematic review, the median size was 2 cm. This might be explained by the high blood flow through these lesions. Some authors postulated pathophysiological mechanisms similar to those in AVM, and that partial transmission of arterial pressure to the venous side, together with the high flow, ultimately causes structural changes that lead to vascular vulnerability [14].

Nowadays, complete removal with low morbidity is possible with microsurgery [18]. Early bipolar coagulation of the nutrient artery of spinal cord HBL is the essential surgical step that facilitates resection and reduces surgical risk.

The present study had several limitations: Firstly, its retrospective nature and small number of cases; and secondly, in the systematic review, some cases may be missing, in spite of our attention, particularly if published as short and undetailed cases within much larger series.

## 5 Conclusion

In conclusion, spinal HBL is an extremely rare cause of SAH, usually sporadic, and rarely occurring in a context of VHL. The systematic review including 16 cases revealed a majority of female patients, in their forties, with cervical lesions with a median size of 2 cm. Haemorrhagic spinal HBL might lead to diagnostic difficulties when presentation mimics intracerebral SAH. We advocate early surgical removal. The possibility of rapidly fatal course in case of major haemorrhage should be borne in mind.

## Ethical statement

The authors confirm that they have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## Ethical approval

This study was approved by the review board of the Assistance publique–Hôpitaux de Paris. Written informed consent was obtained.

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## Disclosure of interest

Dr Tuleasca is a scientific advisor for Elekta Instruments, AB, Sweden. The present research project did not benefit from other sources of funding with the one exception of the university hospital. The other authors declare that they have no competing interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.neuchi.2020.05.008>.

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## Online supplement Supplementary data

[Multimedia Component 1](#)

### Queries and Answers

**Query:** The author names have been tagged as given names and surnames (surnames are highlighted in teal color). Please confirm if they have been identified correctly.

**Answer:** correct

**Query:** Correctly acknowledging the primary funders and grant IDs of your research is important to ensure compliance with funder policies. We could not find any acknowledgement of funding sources in your text. Is this correct?

**Answer:** Acknowledgments: Constantin Tuleasca gratefully acknowledges the University of Lausanne (Unil), Faculty of Biology and Medicine (FBM) for the receipt of a grant "Jeune Chercheur en Recherche Clinique"

**Query:** Please cite footnotes “\_1-12\_”.



**Answer:**

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