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CASE REPORT - BRAIN TUMORS

Disseminated central nervous system hemangioblastoma in a patient with no clinical or genetic evidence of von Hippel-Lindau disease—a case report and literature review

Simer J. Bains[1] · Pitt F. Niehusmann[2] · Torstein R. Meling[3] · Cathrine Saxhaug[4] · Mark Züchner[3] · Petter Brandal[5,6,7]

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Abstract

Background Hemangioblastomas (HB) are benign tumors of the central nervous system (CNS) that can appear sporadic or as part of von Hippel-Lindau (VHL) disease. It is often curable with surgical resection, but upon relapse, the disease exhibits a treatment-refractory course.

Case report A patient treated for sporadic cerebellar HB relapsed 12 years post-surgery. She developed disseminated disease throughout the CNS, including leptomeningeal manifestations. Repeat surgery and craniospinal radiation therapy were unsuccessful.

Conclusion This case is in line with previous publications on disseminated non-VHL HB. Available treatment options are inefficient, emphasizing the need for improved understanding of HB biology to identify therapeutic targets.

Keywords Central nervous system · Disseminated disease · Hemangioblastoma · Leptomeningeal carcinomatosis · Metastatic disease · von Hippel-Lindau disease

Introduction

Hemangioblastoma (HB) is a rare and exceedingly vascular tumor of the central nervous system (CNS), which is often located in the cerebellum, brain stem, or spinal cord [3, 4]. It is generally considered a benign, slow-growing, non-metastasizing neoplasm [6] that causes symptoms through compression of adjacent structures or tumor-associated hemorrhage.

Sporadic HB lesions are usually solitary and account for 70% of cases, whereas in 30% of patients, they are manifestations of von Hippel-Lindau (VHL) disease and are often multifocal. Other common features of the autosomal dominant disorder VHL include retinal hemangioblastoma, clear cell renal cell carcinoma, renal and pancreatic cysts, and pheochromocytoma [5]. Manifestations of VHL disease develop if the *VHL* tumor suppressor gene on chromosome band 3p25 is subject to inactivation [14]. Some sporadic cases of HB have been found to have gain-of function mutations in hypoxia-inducible factor-1 and hypoxia-inducible factor-2 (HIF1 and HIF2), which is regulated by VHL [27], and others have reported the presence of VHL promotor hypermethylation [28], somatic mutations in coding sequences of the VHL gene [18], and other VHL-inactivating events [26].

This article is part of the Topical Collection on *Brain Tumors*

✉ Simer J. Bains
simer.bains@ncmm.uio.no

[1] Department of Oncology, Akershus University Hospital, Lørenskog, Norway

[2] Department of Neuropathology, Oslo University Hospital, Oslo, Norway

[3] Department of Neurosurgery, Oslo University Hospital, Oslo, Norway

[4] Department of Radiology, Oslo University Hospital, Oslo, Norway

[5] Department of Oncology, Oslo University Hospital, Oslo, Norway

[6] Section for Cancer Cytogenetics, Institute for Cancer Genetics and Informatics, Oslo University Hospital, Oslo, Norway

[7] Centre for Cancer Biomedicine, Faculty of Medicine, University of Oslo, Oslo, Norway

Disseminated HB in patients without VHL disease is exceedingly rare, with only 18 published cases (Table 1) [1, 2, 5, 9, 11, 12, 15, 17, 21–23, 29, 30]. In this report, we present a patient with disseminated HB including leptomeningeal spreading, without genetic findings or other clinical manifestations of VHL disease. The first ever karyotype in such a clinical situation is also reported.

Case history

A 34-year-old female presented with 1-year history of occipital headaches and neck pain as well as periods with unsteady gait and blurred vision. On examination, she had unsteady gait, but no focal neurological deficits. A cranial computed tomography (CT) performed in January 2003 showed a large cystic tumor located in the right cerebellar hemisphere and an obstructive hydrocephalus. Magnetic resonance imaging (MRI) was consistent with a HB (Fig. 1). She underwent surgery at another neurosurgical department. A near total gross total resection (GTR) was obtained and histology confirmed the diagnosis of HB. The patient was screened for VHL disease with no genetic evidence using exome sequencing, nor any clinical or familial evidence of such, and she was defined as a sporadic case. A post-operative MRI showed a small remnant in the cerebellopontine angle and a repeat MRI scan 3 months after surgery showed no growth of the remnant. For reasons unknown to us, the patient had no further MRI scans.

She remained free of symptoms for 10 years, but from December 2014 onwards, the patient developed headaches, neck pain, difficulties walking, blurred vision, dysphagia, and hoarseness. An MRI was performed in March 2015, demonstrating a large tumor recurrence with lesions in the right

Table 1 Published non-VHL hemangioblastoma cases with disseminated CNS disease

Authors and year	Age (years), sex	Original site	Genetic VHL	Clinical VHL	Primary surgery	Secondary surgery	Adjuvant therapy	Interval to dissemination	Survival after disseminated disease
Mohan et al. 1976	28, M	Cerebellum	N/A	No	R0	N/A	Deep X-rays	8 years	1 year
	39, M	Cerebellum	N/A	No	R0	N/A	Radiotherapy	14 years	4 weeks
Tohyama et al. 1990	51, M	Cerebellum	N/A	No	R0	Yes	None	14 months	14 months
Hande et al. 1996	4, F	Cerebellum	N/A	No	None	N/A	Radiotherapy	12 months	N/A
Raghavan et al. 2000	53, M	Cervical spine	No	No	R0	Yes	N/A	5 years	N/A
Weil et al. 2002	43, F	Cerebellum	No	No	R0	No	Interferon-2a + minocycline	7 years	2 months
	47, F	Cerebellum	No	No	R0	Yes	Radiotherapy	6 years	1 year
	34, M	Cerebellum	No	No	R0	Yes	Radiotherapy	7 months	1 year
	41, M	Cerebellum	No	No	R0	Yes	Radiotherapy	8 years	3 months
Kato et al. 2005	50, F	Cerebellum	N/A	N/A	R0	Yes	Radiotherapy	22 years	N/A
Lightfoot et al. 2006	71, F	CMJ	No	No	R0	Yes	N/A	N/A	N/A
Ramachan et al. 2008	75, M	Spinal cord	No	No	R0	No	N/A	N/A	N/A
Kim et al. 2009	41, M	Cerebellum	No	No	R0	Yes	Radiotherapy	10 years	1 year
Chung et al. 2014	59, M	Cerebellum	No	No	R0	Yes	Cyberknife	5 years	Alive[b]
Akimoto et al. 2014	45, F	Cerebellum	No	No	R0	Yes	SRT and radiotherapy	38 months	2 years
	57, F	Cerebellum	No[a]	No	R0	No	Radiotherapy	53 months	2 years
Seystahl et al. 2014	70, M	Cerebellum	No	No	R0	No	Bevacizumab	6 years	N/A
Amelot et al. 2015	42, M	Cerebellum	No	No	R0	Yes	N/A	30 years	N/A

CMJ, cervicomedullary junction; *HB*, hemangioblastoma; *N/A*, not available; *M*, male; *F*, female; *VHL*, von Hippel-Lindau disease; *SRT*, stereotactic radiotherapy; *R0*, radical resection

[a] No germline mutation in VHL gene, but allelic loss of VHL gene was observed

[b] Alive 5 years after relapse, at the time of publication

cerebellar hemisphere and in the brain stem (Fig. 1). She was reoperated to obtain a GTR, but a small piece of tumor was left attached to the caudal cranial nerves and the posterior, inferior cerebellar artery (PICA). Neuropathological analysis revealed a highly vascular tumor with histomorphological and immunohistochemical characteristics of a HB (WHO grade I). Large parts of the tumor showed abundant thin-walled vessels and a dense net of reticulin fibers (Fig. 2). Also, circumscribed areas with cohesive nests of epithelioid stromal cells were present (not shown). Due to the prevalence of tumor tissue with dense capillary network, the tumor was classified as a reticular HB variant.

Following surgery, the patient was fully ambulant and transferred to rehabilitation. However, her symptoms continued to progress with vomiting, back pain, and unsteady gait. Two months post-toperatively, a craniospinal MRI demonstrated growth of the residual lesions in the posterior fossa, as well as diffuse intraspinal, extramedullary spinal tumor masses causing a spinal cord compression at the Th10–Th11 level (Fig. 3). Adjuvant treatment with RT was suggested, but the patient declined the offer.

Two months later, a new MRI revealed rapid tumor growth with neoplastic lesions affecting the vermis cerebelli, medulla oblongata, and the spinal canal at several cervical and thoracic levels (Figs. 1 and 3). In August 2015, a laminectomy of Th10/Th11 was performed to remove the most threatening lesion. The histopathological diagnosis was again that of a HB WHO grade I. In contrast to the previous cerebellar lesion, this time, the neuropathological analysis only revealed areas with reticular differentiation without substantial cellular clusters (Fig. 2). A repeat resection of the posterior fossa lesions was considered not beneficial as GTR could not be accomplished without causing a complete jugular foramen syndrome post-operatively. Due to disseminated leptomeningeal manifestations, adjuvant RT was offered and the patient now accepted this strategy. Fractionated RT with 1.8 Gy × 20 to the CNS-axis, with two boost volumes receiving 1.8 Gy × 6 (thoracic lesions) and 1.8 Gy × 10 (posterior fossa), was given between late September and early November 2015.

In spite of RT, the patient's functional level deteriorated gradually, with difficulties walking and back pain. A new craniospinal MRI performed in January 2016 (Figs. 1 and 3)

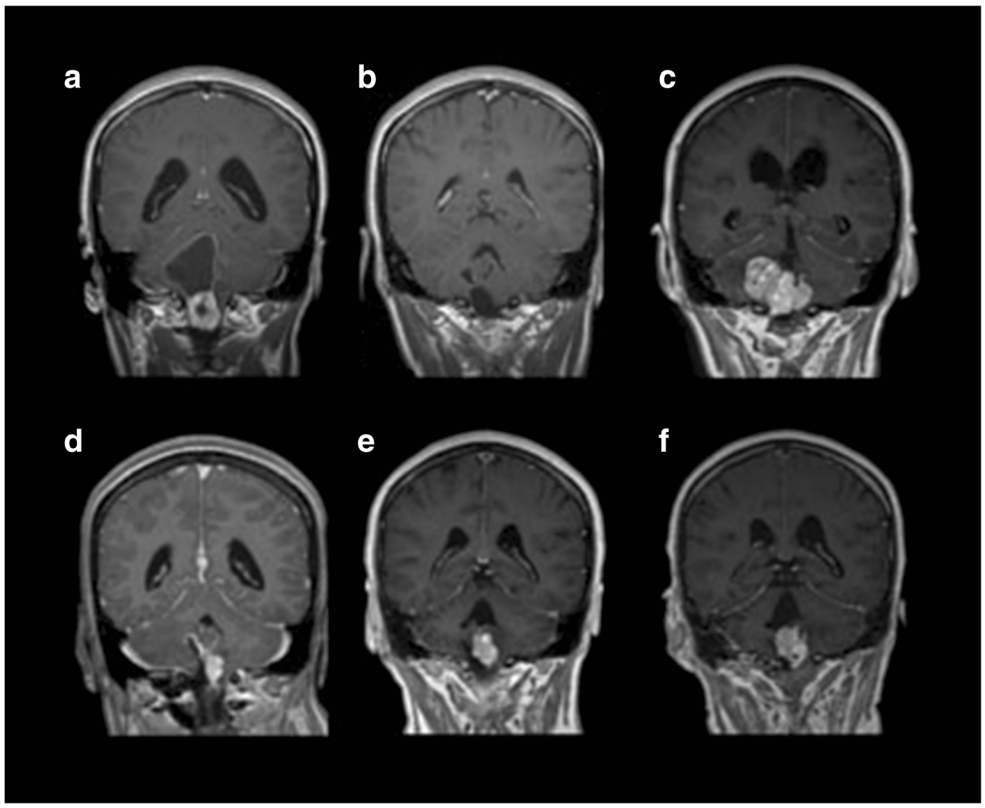

Fig. 1 Coronal T1 weighted post-gadolinium magnetic resonance images of the brain. The first scan from February 2003 (**A**) showed a mixed cystic and solid tumor in the posterior fossa, followed by the post-operative image which showed some residual tumor (**B**). The next MRI was performed 12 years later in March 2015 and showed a tumor relapse with lesions in the cerebellum and the brain stem (**C**). The patient then underwent surgical resection of the tumor in the right cerebellar hemisphere (**D**). Unfortunately, the MRI from July 2015 (**E**) showed growth of the posterior fossa HB lesions, as well as diffuse growth of hemangioblastoma in the spinal canal resulting in spinal stenosis in level Th10–Th11. Following this, the patient underwent surgery for removal of the lesion causing spinal stenosis and thereafter radiation therapy against the entire CNS-axis, but the last image (**F**) from January 2016 nonetheless showed further growth of the posterior fossa lesions

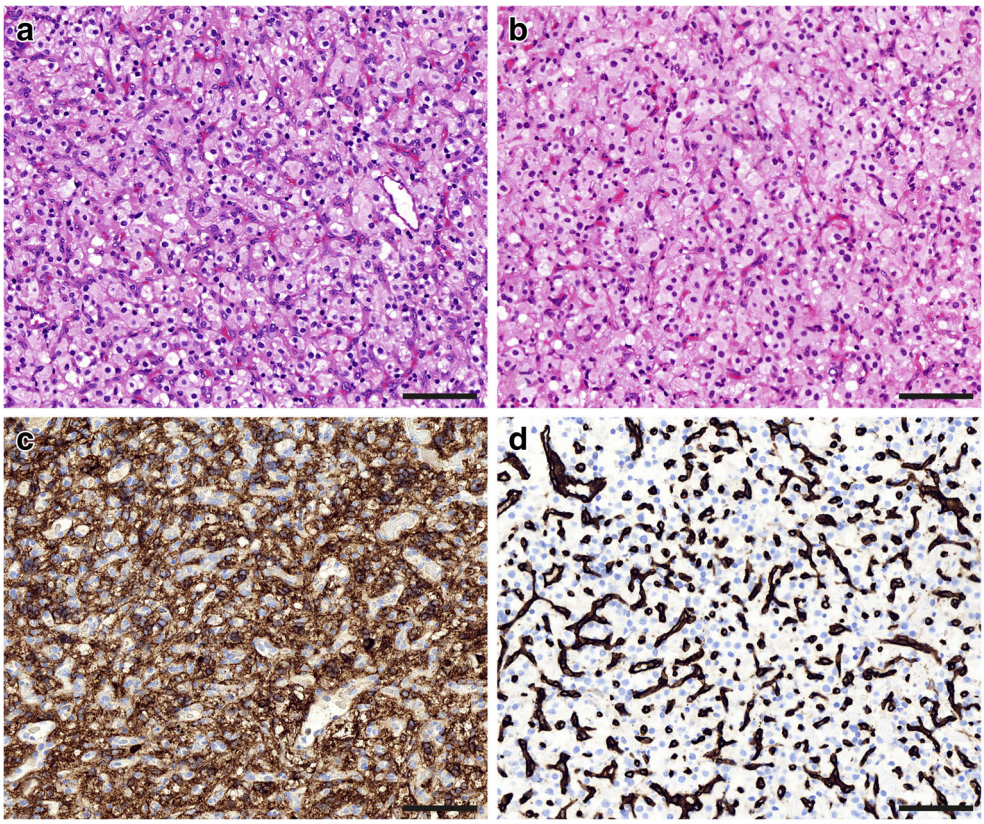

Fig. 2 H&E-stained sections from the cerebellar tumor resection in March 2015 (**A**), as well as the spinal tumor resection in August 2015 (**B**). Material from both resections revealed mesenchymal tumor tissue with two main components: prominent stromal cells characterized by a large cytoplasmic compartment with considerable vacuolization, and a vascular component. The stromal cells showed a strong expression of inhibin (**C**), whereas the vascular tumor component had a strong CD34 expression (**D**). Based on the strong prevalence of areas with dense reticulin network, the tumor was classified as reticular variant of a hemangioblastoma. Scale bars, 100 μm

showed significant progression of the posterior fossa and spinal neoplastic lesions. Repeat surgery was judged to be futile and she was offered best supportive care. The patient passed away in April 2016, a mere 13 months after the radiologically confirmed relapse.

Tumor material from the second surgical procedure in March 2015 was processed for cytogenetic analysis using standard methods as described by Mandahl et al. [16]. The chromosomes of the dividing cells were G-banded, and a karyotype was established in accordance with ISCN 2009 [25].

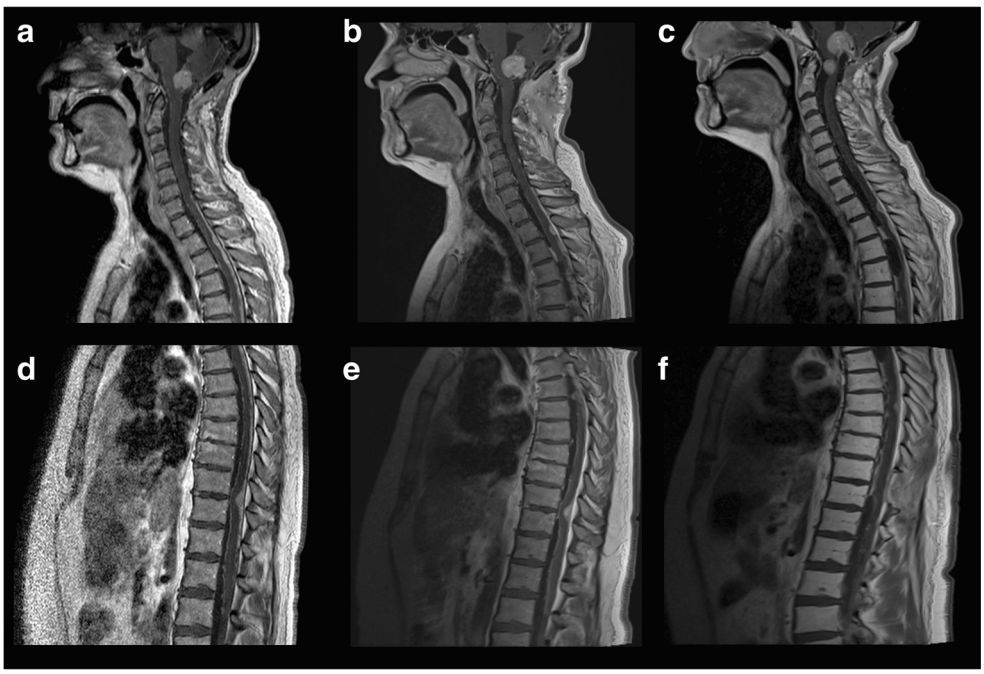

Fig. 3 Sagittal T1-weighted post-gadolinium magnetic resonance images of the back. Images (**A**) and (**D**) were taken in May 2015. They showed growth of posterior fossa disease 2 months after surgical resection, as well as disseminated disease in the spinal compartment. In July 2015 (**B** and **E**), there were increased size of tumor lesions affecting the vermis cerebelli and medulla oblongata. Images (**C**) and (**F**) from January 2016 showed a further progression of HB lesions, despite treatment efforts with radiation therapy

The karyotype was hypertriploid and contained several numerical aberrations, but no structural abnormalities: 72~76,XXX,+2,−3,+5,-6,+7,+11,+12,+13,-14,+15,+19,+20,+21[cp9]/46,XX [1] (Fig. 4).

Discussion

Sporadic HB in the absence of VHL disease is a rare neoplasm that is usually curable with surgery, whereas recurrent or multifocal disease that is surgically inaccessible is often treated with radiation therapy (RT). Another potential therapeutic approach is with systemic, anti-angiogenic treatment targeting VEGF and basic fibroblast growth factor (bFGF), although both the use and success of such strategies have been limited [23].

Patients with sporadic HB tend to develop neoplasms at a later age than those who have VHL disease, with an average age of 35 years at presentation [12]. In this case report, we present a patient that underwent a surgical procedure for a solitary cerebellar HB lesion at 34 years of age, leaving only a small tumor remnant. The patient remained disease-free for 12 years before the tumor showed regrowth, upon which the previously benign lesion had acquired a malignant, treatment-resistant biology including the presence of disseminated intraspinal leptomeningeal disease manifestations. The latter is exceedingly rare in HB patients without VHL disease with only 18 published cases in the literature (Table 1). The average interval from primary disease presentation to diagnosis of disseminated disease in these published cases was 8.2 years (range 7 months to 30 years), in accordance with the patient presented here. The overall survival in published cases with disseminated non-VHL HB ranges from weeks to 5 years, with only two patients surviving beyond 2 years. This is in line with our patient who survived only 13 months after her radiologically confirmed leptomeningeal disease spread, and about 6–7 months following RT.

In total, our patient underwent three tumor resections and was also treated with RT of the CNS axis. Despite this fairly aggressive treatment approach, her neoplastic disease progressed rapidly. In previous reports, all but one non-VHL HB case with leptomeningeal disease spread was subject to complete primary tumor removal at the time of primary diagnosis [9]. Upon diagnosis of disseminated disease, 11 of 18 patients underwent surgical resection of recurrent lesion(s); four did not have surgery, [1, 2, 5, 11, 12, 15, 21, 29, 30]; for two patients, there is no information regarding surgery [17], and one patient neither had primary nor secondary surgery [9]. In none of the reported cases where surgery was part of the treatment of newly diagnosed disseminated HB disease was a GTR (R0) of all lesions achieved [11, 12, 15, 21, 30]. Eleven patients received RT [1, 5, 9, 12, 17, 30], amongst

Fig. 4 A karyogram from one metaphase. Cytogenetic analysis revealed a hypertriploid karyotype with several numerical aberrations, but no structural abnormalities: 72~76,XXX,+2,−3,+5,−6,+7,+11,+12,+13,−14,+15,+19,+20,+21[cp9]/46,XX [1]

whom six patients received fractionated RT at doses ranging from 30 to 45 Gy targeting the posterior fossa, the whole brain, or other parts of the CNS axis. Two patients also received single-session RT of 20 Gy and unknown dose [1, 30], respectively, against relapsed lesions. Another two patients were treated with Cyberknife with total doses of 5.4 Gy and 17 Gy, respectively [1, 5]. For the latter two patients, reported fraction doses were 1.8 and 3.4 Gy, although 1.8 Gy × 3 seems like a low dose for controlling tumor growth. For three patients [17], the RT doses and target volumes are unknown. Despite adjuvant irradiation, all patients recurred, suggesting that HB with leptomeningeal dissemination is a radio-resistant neoplasm. However, it should also be noted that some of the RT doses applied might be considered suboptimal, which may, in part, explain their apparent lack of efficacy in controlling further tumor growth. In one case report, one patient received adjuvant vascular-endothelial growth factor (VEGF) inhibition in the form of bevacizumab [23], whereas another patient received a combination of interferon-2a and minocycline, which decreases bFGF production and inhibits endothelial cell proliferation [31]. However, also these strategies proved unsuccessful, leading to the conclusion that irradiation and currently available systemic therapy seem to be inadequate for achieving disease control in patients with disseminated HB [8, 19, 20].

The karyotype from the second tumor resective surgery is the first reported from a CNS HB. No structural aberrations were found, but numerous numerical ones with a hypertriploid karyotype. Although the finding is interesting, the practical implication is limited as of now. Further genetic investigations, preferably at a higher resolution level, of more cases of sporadic HB, might shed more light on the pathogenetic processes underlying disease development. Although our patients had no signs of familial VHL disease, as per exome sequencing, there is an increasing evidence that support the importance of the VHL-signaling pathway in sporadic HB tumorigenesis [13, 18, 26–28]. On the other hand, the study by Gijtenbeek et al. suggests that the underlying disease mechanisms differ between sporadic and familial HB cases [7].

However, regardless of whether the VHL pathway is responsible for disease development or not, the clinical manifestation of sporadic HB is usually different from the more aggressive disease course of familial HB, suggesting that more knowledge is needed to dissect the relevant pathogenic mechanisms in play, to direct future therapeutic approaches.

Although the risk of tumor recurrence in sporadic HB is considered low, rare cases with disseminated recurrent disease occur. An article from 1989 reported that relapse of HB might be seen in up to 25% of HB cases in a population of both sporadic and VHL-related cases [24]. The tumors from our patient were classified as a reticular subtype, which usually displays a more indolent disease course with reported recurrence rates of only 8%, as compared to the more aggressive cellular subtype with reported recurrence rates of 25% [10].These data suggest that a regular follow-up also of some sporadic cases of HB may be warranted, regardless of the histopathological subtype. More importantly, identification of distinctive molecular biological and possibly also clinical features that recognize patients at risk of relapse is still needed, as is availability of more effective treatment measures.

Compliance with ethical standards

The patient has consented to the writing and submission of the case report. The interpretation and reporting of this case is the sole responsibility of the authors. The case report has been written in accordance with COPE guidelines and comply with the CARE statement. There are no conflicts of interests for any of the contributing authors. No portion of this case report has been presented or published previously.

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