

# Intermixed arteriovenous malformation and hemangioblastoma: case report and literature review

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We report the third presentation of an intermixed arteriovenous malformation and hemangioblastoma. The rare occurrence of the diagnostic histologic features of both a neoplasm and vascular malformation in a single lesion is more common in gliomas, as angioglioma, and is termed an 'intermixed' lesion. We review the literature concerning the developmental biology of each lesion, and potential interplay in the formation of an intermixed vascular neoplasm and vascular malformation. The roles of cellular origin, genetic susceptibility, favourable microenvironment, altered local gene expression and key regulatory pathways are reviewed. Our review supports angiography and genetic profiling in intermixed lesions to inform management strategies. Consideration should be given to multimodality therapeutic interventions as required, including microsurgical resection, stereotactic radiosurgery and further research to exploit emerging molecular targets.

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Arteriovenous malformation (AVM) and capillary hemangioblastoma (HB) are distinct lesions, constituting vascular malformations and vascular neoplasms of the CNS, respectively [1].

As AVM and HB are distinct lesions with respect to classification, developmental biology and management, their copresentation – spatially, temporally or as intermixed lesions – is a rare occurrence. We report the third presentation of an 'intermixed' AVM and HB.

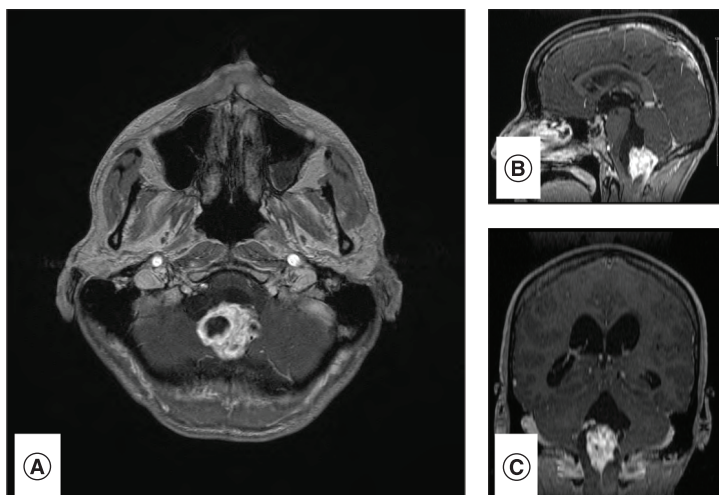
'Intermixed/intermingled/coexistent' is the pathological finding of diagnostic pathological features of two lesions present within the same lesion. For example, in glioma, the term angioglioma is used to describe such intermixed lesions [2,3]. Only two such intermixed AVM-HB lesions have been previously described [4,5]. The paucity of this occurrence raises questions about the (co)development, of such lesions.

In addition, we review the literature regarding such lesions in isolation and mechanisms of co-existence in the context of emerging developmental biology. Finally, we explore management options if such a rare lesion is suspected.

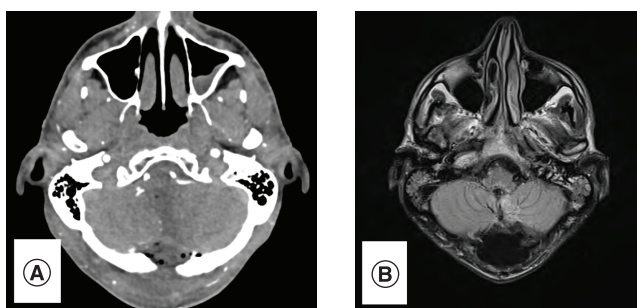
## Case report

### History

A 46-year-old man presented with a 2-month history of worsening headache, vomiting, weight loss and tinnitus. On examination, the patient had a broad-based ataxic gait, profound lateral nystagmus, past-pointing on the right and oropharyngeal dysphagia. Past medical and family histories were noncontributory. Neuroimaging (Figure 1) revealed a large 3.5 × 2.8 cm mixed cystic and solid posterior fossa lesion with moderate obstructive hydrocephalus, suggestive of a HB. Computed tomography thorax abdomen and pelvis and spinal MRI were unremarkable. The patient underwent a posterior fossa craniectomy and total resection of a craniocervical junction lesion (Figure 2).



**Figure 1. Radiology pre-resection.** MRI demonstrates obstructive enhancing mixed solid-cystic lesion in axial (A), sagittal (B) and coronal (C) planes.



**Figure 2. Radiology post-resection.** Total resection of lesion on postoperative computed tomography angiogram (A) and MRI brain (B).

Intraoperatively, this was a highly vascular lesion, extending from the vermis to involve the posterior spinal cord, which hemorrhaged at high pressure resulting in 1500 ml estimated blood loss.

### Pathological findings

Microscopy found the lesion to be composed of thick- and thin-walled dilated blood vessels which were partly separated from each other by gliotic neuropil in which there was 'neovascularization'. Within the gliotic neuropil there were numerous Rosenthal fibers. Amorphous nonrefractile eosinophilic material was located within some of the vascular channels. Arteries, veins and arterIALIZED veins were all present. Evidence of prior perilesional hemorrhage in the form of hemosiderin granules was noted. Fragments of 'surgical' were included. In isolation the appearances were those of an AVM (Figure 3 & Figure 4).

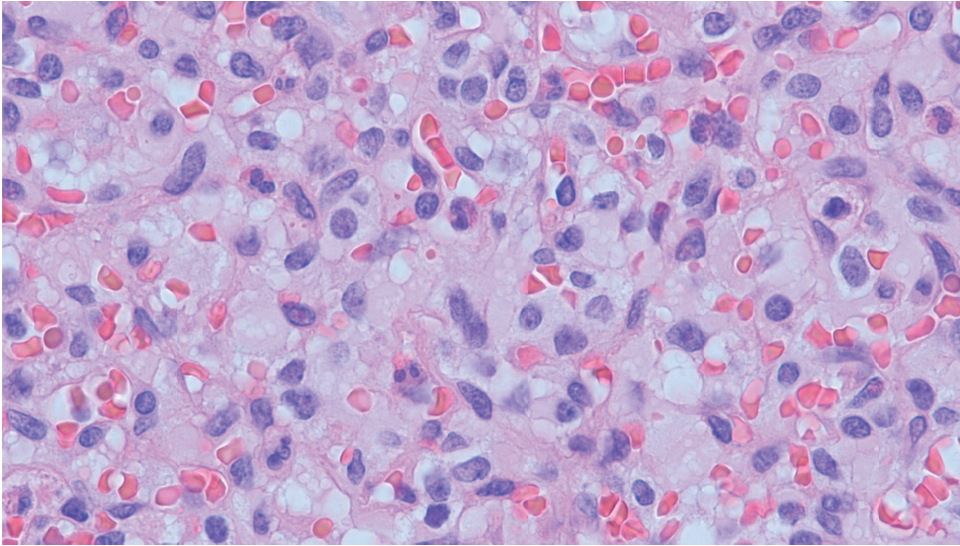
Additionally, however, the degree of 'neovascularization' in the form of proliferating capillary vessels was intense and was accompanied by large vacuolated lipid filled cells. Mitoses were not present. Necrosis was not present. Taken in isolation, these appearances were those of a capillary HB. However, the overall appearances were of a capillary HB, WHO grade I with an AVM, together with evidence of prior perilesional hemorrhage.

### Discussion

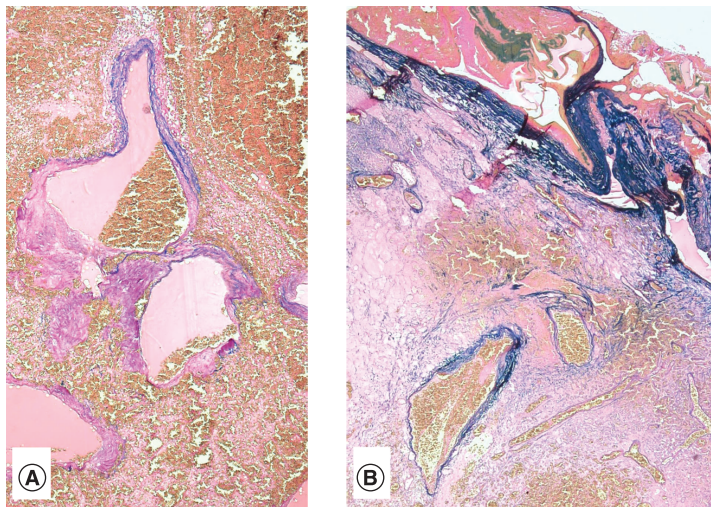
#### Intermixed lesions

We report the third presentation (Table 1) of an intermixed AVM and HB, in other words, the finding of diagnostic pathological features of two classified lesions present within the same lesion [4,5].

AVM and HB may be considered distinct lesions with regard to morphology, classification and physiology. AVMs are high-flow vascular malformations, involving aberrant arteriovenous shunting between dysplastic arteries and veins, with the characteristic absence of an intervening capillary bed [6]. There is no intervening neural parenchyma in the nidus [7,8]. In contrast, HB are well-circumscribed WHO grade I vascular neoplasms, which may be solid or solid with a peritumoral cystic component, and histologically comprise numerous capillary channels separated by neoplastic stromal cells [1,9,10].



**Figure 3. Haemangioblastoma.** Representative image of hemangioblastoma characterized by vacuolated stromal cells separated by capillary vessels filled with red blood cells.



**Figure 4. Arteriovenous malformation.** (A) Large thin-walled vessels located in center of tumor and (B) extending up on to meningeal surface of brain.

Notably, in response to the case of Raynor and Kingman [5], Stehbens [8] suggests that the AVM described may be the hypervascularization of an HB, rather than intermixed lesions. This observation is noted by Medvedev *et al.*, and refuted as an explanation for their intermixed lesions. Medvedev *et al.* reference the ‘interspersed and distinct nature of the thick-walled blood vessels, without evidence of neoplastic involvement’ as most supportive of two distinct pathological processes [4].

### Developmental biology

It is suggested that intermixed AVM and HB features may be attributable to a common cellular origin [4]. AVMs are agreed to originate from mesoderm-derived angioblasts during the formation of the vascular plexuses between week 3–8 of embryogenesis [5,11]. However, there is controversy as to the tumor initiating cell of HB. Most authors favor the mesoderm-derived, embryologically arrested hemangioblast [6,12–14]. These cells may remain arrested, with subsequent reactivation of the hematopoietic or endothelial differentiation potential under various environmental stimuli, thus forming HB [13,15]. This is supported by analysis of protein expression shared by hemangioblast progenitors and stromal cells (the neoplastic cell in mature HB) [15–17]. It is the neoplastic stromal cells which further differentiate into the ‘vasoformative elements’ (endothelial cells and pericytes) [10]. Controversy exists however, with Ma *et al.* favoring the HB tumor-initiating cell to originate from neoplastic transformation

Table 1. Intermixed arteriovenous malformation and hemangioblastoma, reported cases and characteristics.

Study (year)	Age (years), sex	Type of tumor/malformation	Location of lesion	Vascular anatomy	Size	Presentation	Management	Outcome	Ref.
Raynor & Kingman (1965)	19, M	HB/AVM	Cerebellar – vermian	Large midline vascular lesion, suggestive of AVM	5.5 × 4 × 3 cm	Hemorrhage of lesion (confirmed on lumbar puncture)	Initial posterior fossa exploration without resection owing to lesion complexity; subsequent resection for interval growth on angiography	Mortality, day 12 post-operatively	[5]
Medvedev <i>et al.</i> (1991)	38, M	HB/AVM	Cerebellar – mesobasal aspect of left cerebellar hemisphere	Left AICA and PICA feeder vessels rapidly shunting to the tentorial sinuses	4 × 4 × 4 cm	Symptomatic hydrocephalus and cerebellar signs	CSF diversion (ventricular catheter); posterior fossa exploration and total excision	Survival	[4]
Healy <i>et al.</i> (2020)	46, M	HB/AVM	Cerebellar and spinal – vermian and including posterior cervical cord	No angiographic phase pre-operatively	3.5 × 2.8 cm	Symptomatic hydrocephalus and cerebellar signs	Posterior fossa exploration and total resection	Survival, some lower cranial nerve dysfunction	Current article

AICA: Anterior inferior cerebellar artery; AVM: Arteriovenous malformation; CSF: Cerebrospinal fluid; HB: Hemangioblastoma; PICA: Posterior inferior cerebellar artery.

of neuroectodermal-derived neural stem cells/progenitors (via SSEA-1 expression analysis) with multiprogenitor ability suggested, dependent on a HB niche microenvironment [18]. In the context of a disputed cell of origin for HB, it is not possible to definitively attribute the pathological findings within an intermixed lesion to a shared cellular origin.

Second, the interplay of genetics and environment must be considered in an intermixed lesion. It is possible that one initiating lesion may constitute the appropriate microenvironment to provoke the development of the second pathology. This may be in the context of genetic susceptibility, or in the maturation of a pre-existing structural vascular lesion. There is precedence in the multiple cases reports of glial neoplasms in close association with AVMs. This refutes classical thinking, which suggested AVM and HB to be formed at different time points – approximately preweek 8 (i.e., congenital) for AVM and after week 12 for HB [5].

It is now accepted that both genetic and environmental roles contribute to the development of clinically significant AVMs and HB. In HB, this is supported by arrest-reactivation theories of hemangioblast development, as above [13,15]. In AVM, emerging research finds a large subpopulation of AVMs to be an acquired pathology. Morales-Valero supports this by the rarity of neonatal AVM diagnoses despite high-resolution imaging, in addition to multiple case reports of *de novo* AVMs, despite previously negative neuroaxis imaging [24].

Under the Morales-Valero model, the 'acquired' AVM formation is the result of genetic susceptibility – in other words, appropriate single nucleotide polymorphisms (SNiPs) – in the context of appropriate microenvironmental triggers or 'second hits' – such as cerebral infarction, inflammation, trauma or in association with neoplasia [2,19,20]. For example, the genetic 'first hit' of gap-junction protein Connexin40 deficiency-forming transient arteriovenous shunts, which may develop into clinically significant AVMs in the appropriate microenvironmental 'second hit' [21,22]. This is in keeping with Ramey *et al.*'s hierarchical model, whereby following embryogenic vasculogenesis, a structural vascular dysgenesis is believed to form aberrant arteriovenous shunts without intervening capillary networks. Ramey *et al.* propose such arteriovenous fistulae constitute 'AVM precursors', which mature via an environmental 'second hit' into a clinically significant AVM [19,23,24]. A physico-epigenetic component is suggested by Thomas *et al.*, whereby altered local hemodynamics affect cellular metabolism, triggering epigenetic factors that modulate AVM-associated genes to direct aberrant vessel phenotypes [25]. Thus, one lesion may constitute a favorable microenvironment for the development of a second lesion, in the context of genetic susceptibility.

Third, in both HB and AVM, there is a significant genetic component to development, which overlaps between lesions. This overlap, such as must be appreciated in an intermixed lesion, continues to be elucidated as the individual processes of neovascularization in HB and AVM continues to be researched, including the differential role of component cell types, and their variable activation of angiogenic pathways [26,27].

HB tumorigenesis strongly associates with von Hippel–Lindau (VHL)-silencing, in all familial HB and >78% sporadic HB [16,28–30]. However, familial and sporadic may be distinguished by markers of glial, neuroepithelial and neuronal differentiation [17]. VHL tumor suppressor gene inactivation results in less pVHL-mediated degradation of hypoxia-inducible factor 1 alpha (HIF-1 $\alpha$ ). The normoxic VHL cell therefore behaves as if in a hypoxic state, with accumulating HIF-1 $\alpha$  associating with HIF-1 $\beta$  to exert transcriptional roles on target genes to produce multiple synergistic angiogenic and growth factors [28,31,32]. These include primarily VEGF/VEGFR2, but also: Notch/Dll4, EphB4/EphrinB2 and SDF1 $\alpha$ /CXCR4 pathways [33]. HB neovascularization results from VHL-silencing associated mechanisms which include the classically appreciated VEGF-mediated angiogenesis in addition to VEGF-independent angiogenesis and vasculogenesis [12,26,34,35]. VEGF-independent mechanisms of angiogenesis also exist, increasingly discovered following disappointing clinical trials focused on VEGF-mediated angiogenesis [36,37]. Endothelial VHL-silencing associated Twist1 accumulation is a VEGF-independent mechanism of common angiogenesis that is only recently reported [26,37].

There is some overlap between HB and the key regulatory pathways associated with sporadic AVM development, including: VEGF, Notch/Dll4, Eph/Ephrin ligand-receptor, TGF- $\beta$ , hedgehog pathways and others [38]. Inherited AVM syndromes, such as hereditary hemorrhagic telangiectasia (HHT), associate with the TGF- $\beta$  superfamily members such as ALK1/Avcr1, ENG/Endoglin or Smad4 mutations [39]. SMAD4 induces both endothelial cell proliferation and hypertrophy, in addition to exhibiting altered mural cell coverage and distorted artery-vein gene expression, including decreased VEGFR2 expression. This SMAD4 murine model thus links the TGF- $\beta$  superfamily and VEGF signaling pathways – one example of the overlap and potential synergism between HB and AVM [40].

Finally, in terms of location, all reported cases of intermixed AVM-HB lesions were cerebellar. Classically, HBs favor the cerebellum (76%), while AVMs exhibit an anatomic predilection for cerebral hemispheres [16]. Lindau and Bailey originally suggested the predilection of HB for the cerebellum occurs due to the coincident development of the cerebellum and vascular mesenchyme on the posterior medullary velum in the third month. This vascular primordium is situated at the cerebello-pontine angle, and becomes a rich capillary network, which comes to form the choroid plexus of the fourth ventricle [5].

### Management considerations

AVMs are dynamic lesions, exhibiting vascular remodeling, progressive growth and aberrant hemodynamics – frequently progressing from low-flow juvenile lesions to medium-to-high flow, high pressure lesions over time [5,7]. These features contribute to the pathologic characteristics of presentation, including mass effect, mural instability and hemorrhagic propensity [7,23].

Posterior fossa AVMs exhibit a more aggressive natural history than supratentorial AVMs, with annual rupture rates as high as 11.6%, supporting more aggressive treatment [41,42]. While the modified Spetzler-Martin AVM grading system and three-tiered management system informs treatment, posterior fossa location must be considered in intermixed lesions, if pre-operative angiographic imaging is suggestive and individualized treatment favored.

In HB, the need for treatment is dependent on both symptoms and location. It is clear from case series in VHL disease patients that both size and rate of growth correlate with symptoms. While almost all tumors exhibited measurable growth, many tumors never produce symptoms and do not require treatment [43]. Neurological symptoms and morbidity frequently result from peritumoral cysts. Cyst development was associated with germline partial deletion of the VHL gene [9]. In VHL disease with multiple lesions, radiological progression alone is deemed not an indication for treatment [43].

Genetic profiling may be insightful, in that genetic differences differentiating syndromic versus sporadic AVM significantly determine clinical presentation. In HHT, AVMs are typically smaller, multiple, of lower Spetzler-Martin grades, less frequently temporal and may exhibit a lower hemorrhagic risk than sporadic lesions [44–48]. Tissue from intermixed lesions could be considered for genetic profiling to elucidate a causative genetic basis.

If intermixed lesions are suspected, from vascularity or nidus, pre-operative digital subtraction angiography and discussion at neurovascular multidisciplinary meeting may be indicated. Consideration must be given to classical features of AVM classification and resectability and clinical symptoms.

### Therapeutic strategies

In AVM, treatment strategies are multiple and include: (micro)surgical resection, stereotactic radiosurgery (SRS), endovascular embolization and combined multimodality management. Analyses report very good outcomes for all

modalities; however, high-quality comparative data to individualize treatment is limited [49–59]. Medical management alone may constitute appropriate and effective treatment as per the ARUBA trial, noting, however, that long-term follow-up may favor other treatment modalities – resection, SRS, etc. [60–63].

HB may be approached by resection, SRS or surveillance only. However, independent predictors of overall survival include surgical management, younger age and Caucasian race, while radiation therapy outcomes were not validated (possibly owing to short follow-up and HB growth patterns) in a SEER-based analysis [64]. A 2018 paper supports gross total resection as the gold standard, and suggests SRS has comparable outcomes to subtotal resection only [65].

In mixed lesions, individualized treatment including multidisciplinary team discussion is favored.

In terms of emerging molecular targets in AVM, radiosurgery is seen to both induce thrombotic occlusion of nidus vessels in addition to inhibiting Notch1 and Notch4 signaling in endothelial cells [66]. Both increased and decreased Notch activity induce AVM formation in sporadic AVM and syndromic-type Alk1 knockout models, respectively [21,67,68]. Of note, Notch normalization induces structural regression of arteriovenous shunts, and may be normalized as part of the response to radiation in SRS treatment [69].

Genetic profiling of lesions is important, to replicate successes such as endoglin and ALK1 now offering promising therapeutic targets in HHT AVMs. These genes induce disease states by haploinsufficiency, which may be amenable to therapeutic approaches to enhance protein expression/function [39,70]. For example, the administration of an exogenous endoglin isoform, soluble endoglin, in murine models partly restores normal protein expression patterns of endothelial cells, decreasing AVM size and incidence. However, the soluble endoglin effect appears to depend on endogenous expression of endoglin [71]. Bazedoxifene, a selective estrogen receptor modulator, has been demonstrated *in vivo* to compensate for ENG and ALK1 haploinsufficiency, increasing ENG and ALK1 mRNA levels and reducing HHT lesion-associated hemorrhage [72].

For HB, the clinical translation of anti-angiogenic therapeutics has been disappointing [73]. In HB, this is attributed, at least in part, to the lack of knowledge in terms of the cytological origin, evolutionary processes and neovascularization in this lesion [37]. A 2009 Dartmouth trial (NCT01015300) of anti-VEGF bevacizumab (Avastin) in VHL disease-associated unresectable/recurrent HB was terminated in 2012 due to low accrual, while a case report of favorable outcome exists [74]. EGFR expression suggests tyrosine kinase activity may represent the signal transduction initiator [13,36]. In terms of tyrosine kinase inhibitors, a single trial and multiple case reports exist in the use of multityrosine kinase inhibitor pazopanib for VHL disease associated HB, with moderate success [75–78]. Other multityrosine kinase inhibitor trials for HB were disappointing, with the dovitinib trial discontinued owing to toxicity, while erlotinib and sunitinib were found to be of limited benefit [79–82]. Emerging research into HB neovascularization mechanisms – such as Twist1 signaling, described above – may provide additional anti-angiogenic therapeutic targets [26].

In the context of the above, intermixed lesions are of limited precedence, and must therefore be approached on an individualized basis. Multimodality interventions, or combinations thereof, may be of value in such complex lesions. The emerging role of molecular therapeutics is promising.

## Conclusion

In summary, we contribute a case of intermixed AVM and HB, and review the literature concerning the developmental biology of each lesion, and potential interplay in the formation of an intermixed vascular neoplasm and vascular malformation. The roles of cellular origin, genetic susceptibility, favourable microenvironment, altered local gene expression and key regulatory pathways are reviewed. Significant potential for overlap and synergism is appreciated, and continues to be elucidated as the individual processes of neovascularization in HB and AVM continues to be researched, including the differential role of component cell types, and their variable activation of angiogenic pathways.

Clinically, our review supports pre- and post-operative angiography in suspected highly vascular lesions to inform management strategies. Consideration should be given to intermixed lesions as a differential diagnosis. Genetic profiling should be considered in atypical cases, in that genetic differences differentiating syndromic versus sporadic arteriovenous malformations and hemangioblastomas may significantly determine lesion anatomopathology and clinical presentation, which may inform management. Multidisciplinary discussion should inform individualised treatment, that appreciates management considerations of both neoplastic lesions and vascular malformations. Consideration should be given to multimodality therapeutic interventions as required, including surgery, stereotactic radiosurgery, endovascular embolisation and further research to exploit emerging molecular targets.

### Executive summary

- Angiographic imaging should be considered pre- and post-operatively in suspected highly vascular lesions, with consideration given to intermixed lesions as a differential.
- Genetic profiling should be considered, in that genetic differences differentiating syndromic versus sporadic arteriovenous malformations and hemangioblastomas may significantly determine lesion anatomopathology and clinical presentation, which may inform management.
- Individualized treatment, informed by multidisciplinary discussion, should be considered that appreciates management considerations of both neoplastic lesions and vascular malformations.
- Management strategies should consider multimodality treatment, including combinations of microsurgical resection, stereotactic radiosurgery, endovascular embolization and/or further research to exploit emerging molecular therapeutics.
- Surveillance alone, as a management practice in isolated hemangioblastomas, may not apply in the presence of an intermixed vascular malformation, and particularly should appreciate the higher rate of rupture of infratentorial arteriovenous malformations.
- Consideration of consented submission of specimens to appropriate biobanks or research bodies may be considered as per local policy.

### Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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### Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient for the inclusion of their medical and treatment history within this case report.

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