CASE REPORT

Bulbar dysfunction and aspiration pneumonia due to a brainstem haemangioblastoma: an unusual complication of von Hippel-Lindau disease

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SUMMARY

A 44-year-old woman with a history of von Hippel-Lindau (VHL) disease, a rare inherited neoplasia syndrome, presented acutely to hospital with a productive cough, symptoms of respiratory tract infection and odynophagia (painful swallowing). A chest X-ray confirmed right-sided pneumonia. Investigation of the persistent odynophagia using barium swallow revealed aspiration of the contrast into the lungs and suggested a neurological cause for her chest infection. Clinical assessment and speech and language therapy confirmed a pseudobulbar palsy. Subsequent neuroimaging identified a cystic haemangioblastoma, located at the cervicomedullary junction of the brainstem, as the cause of the pseudobulbar palsy. Urgent neurosurgical excision produced symptomatic relief and with continuing medical therapy, and clinical resolution of her pneumonia. In patients with VHL disease and other inherited cancer syndromes, a high index of suspicion should be maintained for new tumours presenting with common medical symptoms and signs.

BACKGROUND

von Hippel-Lindau (VHL) disease is a rare autosomal dominant syndrome predisposing to neoplasia caused by mutations in the *VHL* gene.¹ It is characterised by highly vascular retinal and central nervous system (CNS) haemangioblastomas, as well as clear cell renal cell carcinoma, pheochromocytoma, paraganglioma, pancreatic neuroendocrine tumours, endolymphatic sac tumours and renal and pancreatic cysts. The CNS haemangioblastomas occur in the cerebellum, brain stem or spinal cord and typically present with cerebellar signs, raised intracranial pressure or focal neurological signs due to cystic expansion. Brain stem lesions account for only about 10–15% of CNS haemangioblastomas and typically present with a range of overlapping neurological symptoms and signs including headache, swallowing difficulties, hiccough, gait abnormalities, altered speech, ataxia and sensory disturbance.²

Individuals with VHL disease are typically reviewed annually in specialist multidisciplinary clinics and offered age-related screening for the major features of the disease. This involves physical and retinal examination, abdominal imaging and biochemical testing of plasma-free metanephrines.³ CNS imaging may be offered if symptoms develop or routinely every few years according to local practice. However, some patients will present

acutely to general medical services with symptoms caused by the rapid growth of tumours, especially CNS haemangioblastomas which can undergo rapid cystic expansion.

CASE PRESENTATION

The patient, a 44-year-old woman, had a 20-year history of VHL disease. Predictive genetic testing while asymptomatic due to a family history of VHL disease in her father was positive at the age of 22 years. She therefore started annual surveillance for VHL disease-associated complications (see [table 1](#)). Prior to this presentation she had other VHL disease-associated complications included a cerebellar haemangioblastoma which required neurosurgical excision and ventriculoperitoneal (VP) shunting following the development of acute hydrocephalus, a renal cell carcinoma and a pancreatic neuroendocrine tumour treated with total pancreatectomy and splenectomy. She was treated with insulin, pancreatic enzyme supplements and post-splenectomy prophylaxis with penicillin V.

Six months after a full recovery from the total pancreatectomy, she presented acutely to her local hospital with fever, coryzal symptoms, a cough productive of purulent sputum and a short history of odynophagia. A chest X-ray revealed right-sided lower lobe consolidation and blood gas analysis showed she was in type 1 respiratory failure. After 2 weeks of treatment with intravenous antibiotics her pneumonia had not resolved. She continued to produce mucopurulent sputum and her inflammatory markers remained elevated. In addition, her insulin-dependent diabetes mellitus was difficult to control and nasogastric feeding was established due to difficulties with swallowing and progressive weight loss. An upper gastrointestinal endoscopy to investigate the cause of the swallowing difficulties and odynophagia was reported as normal. However, a barium swallow test revealed prompt aspiration of the contrast into the lungs after swallowing. A CT scan of the head and neck ordered to investigate the cause of the bulbar dysfunction revealed the VP shunt, evidence of previous cerebellar surgery and a cervicomedullary cystic mass at the level of the foramen magnum. She was therefore transferred to a regional neurosurgical centre for further assessment.

After transfer, the patient reported a productive cough, difficulty in swallowing and general upper airway 'discomfort' but no breathlessness. Examination revealed her voice to be raspy and her

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Table 1 A typical surveillance protocol for von Hippel-Lindau disease³

0–4 years	Annual ophthalmoscopy or retinal imaging, to screen for retinal haemangioblastoma
From age ~16 years	Annual neurological questionnaire and examination—with neuraxial MRI every 1–3 years (dependent on the presence of signs and symptoms), to screen for CNS haemangioblastoma
From 16 years	Annual abdominal ultrasound scan alternating with or MRI, to screen for renal and pancreatic tumours
From age 8 years	Annual blood pressure monitoring and 24 hour urine catecholamine metabolite studies (or plasma normetanephrine levels from 8 years-old if high-risk), to screen for pheochromocytoma

CNS, central nervous system.

speech was mildly dysarthric. Her gag reflex was absent and neurological examination revealed hyper-reflexia and non-sustained clonus of the upper limbs, which was not present in the lower limbs. Breath sounds were diffusely bronchial with coarse basal crepitations on the right.

Speech and language therapy demonstrated ‘hypernasal speech, reduced soft palate elevation, leftward tongue deviation and audible pharyngeal in coordination with reduced hyolaryngeal excursion on swallowing’, which was consistent with bulbar dysfunction due to a pseudobulbar palsy.

INVESTIGATIONS

Further investigations were carried out after transfer. A plain radiograph of her chest (figure 1) was consistent with bibasal consolidation and blood gas analysis was now consistent with compensated type II respiratory failure. Sputum samples from the referring hospital confirmed infection with *Pseudomonas aeruginosa* and she was treated with intravenous piperacillin and tazobactam. This was later converted to meropenem.

CT scan of the chest and abdomen, the latter which was due as part of her annual VHL disease surveillance and postpancreatectomy follow-up, confirmed the bibasal consolidation and previous intra-abdominal surgery but there were no new VHL disease-associated lesions.

After the review of previous neuroimaging (figure 2 is a representative example showing postsurgical damage from 8 years prior), she was sent for repeat gadolinium-enhanced MRI of her head (figure 3). This showed a small enhancing nodule associated with a cystic lesion expanding the medulla and extending

Figure 1 Chest radiograph showing right lower lobe consolidation, with nasogastric tube also visible. Features and location are consistent with aspiration pneumonia.

down to the upper cervical cord, typical of a haemangioblastoma. The nodule was visible in routine follow-up MRI from at least 8 years prior to the current admission but was not associated with focal neurological symptoms or cystic expansion when last visualised 6 years previously (figure 4). In addition, a new tiny enhancing nodule was identified at the T1 spinal level.

DIFFERENTIAL DIAGNOSIS

The initial presentation was compatible with a community-acquired upper-to-lower respiratory tract infection in an individual with a history of VHL disease and a previous splenectomy. Her odynophagia was considered most likely to be due to a combination of pharyngitis or occult candida infection and mucosal ulcers.

However, the clinical course was prolonged and the odynophagia persisted in combination with difficulty swallowing. Following the demonstration of aspiration, a diagnosis of bulbar dysfunction was made. In the context of VHL disease it was most likely a pseudobulbar palsy due to a disease-associated lesion of the brainstem. Other causes of a pseudobulbar palsy include cerebrovascular events, demyelinating disease and motor neuron disease.

Additional CNS imaging was obtained with more detailed assessment of bulbar function. The finding of a cervicomedullary haemangioblastoma associated with cystic expansion, confirmed a diagnosis of VHL disease-associated pseudobulbar palsy.

TREATMENT

Despite her significant comorbidity which included slowly-resolving pneumonia, poor glycaemic control and poor nutritional status (low serum albumin at 24 g/L), early neurosurgical excision of the cervicomedullary nodule and associated cyst was deemed urgent due to its significant brainstem extension and high risk for further brain stem compression. During surgical excision, the hypoglossal nerve was found attenuated by the nodule but was successfully dissected out and preserved. Histology confirmed a 7 mm haemangioblastoma. The patient made a good recovery up to discharge, with resolution of her respiratory failure and bulbar function.

OUTCOME AND FOLLOW-UP

The patient continues to attend the VHL disease surveillance clinic annually. Since this admission, an asymptomatic cerebellar haemangioblastoma and several simple renal cysts have been discovered. The spinal nodule at T1 remains asymptomatic.

DISCUSSION

This case report describes a patient with a common medical diagnosis, pneumonia, and a known rare disease, VHL disease. Investigation revealed that the persistent pneumonia was due to a pseudobulbar palsy caused by a cystic cervicomedullary haemangioblastoma. Key to making this diagnosis was the failure of the pneumonia to resolve with standard therapy and the identification of the underlying VHL disease-associated complication. Owing to its rarity, with an approximate incidence of 1 in 36 000,¹ VHL disease remains an elusive clinical entity to many doctors and is typically managed in specialist centres. Its manifestations are protean due to the nature of the disease, with focal lesions occurring in many organ systems at all ages. Commoner complications are related to the expansion of cystic CNS haemangioblastomas, especially in the cerebellum, but also include rarer syndromes such as hypertension and autonomic hyperactivity due to pheochromocytoma, endocrine

Figure 2 MRI from 8 years prior to presentation showing postsurgical damage to the right cerebellar hemisphere on T2-weighted axial view (left) a tiny enhancing nodule at the left medulla oblongata on gadolinium-enhanced T1-weighted coronal view (right).

hypersecretion syndromes due to pancreatic neuroectodermal tumours and hearing loss due to endolymphatic sac tumours. Rare complications of a rare disease may therefore present as apparently common medical diagnoses. An important learning point is that in the context of a known diagnosis of VHL disease, prompt consideration should be given to the likelihood of a disease-associated complication and advice sought from a specialist centre.

There are two similar cases reported in the medical literature, in both cases the patient died. The first report describes a patient with VHL disease who died of aspiration pneumonia secondary to swallowing problems.⁴ The postmortem showed a

dorsolateral cervicomedullary haemangioblastoma with an associated syrinx that had spread up into the medulla and down to the thoracic spinal cord. The similarity to this case suggests that rapid surgical excision of brainstem haemangioblastomas, even with the risk of significant perioperative morbidity, confers a favourable survival outcome in patients at risk of continued aspiration. The other case differs in that the haemangioblastoma was a sporadic, large cystic cerebellar lesion presenting with cerebellar signs as well as aspiration pneumonia.⁵ This patient died as a result of extensive postoperative haemorrhage. Therefore, the case described here is the first report of a successfully treated VHL disease-associated brainstem haemangioblastoma that presented with aspiration pneumonia.

Morbidity and mortality in VHL disease is now increasingly due to the complications of CNS haemangioblastomas since the introduction of effective surveillance protocols,^{3 6 7} a typical example of which is outlined in table 1. Most developed countries now register and enrol patients with VHL disease into registries and surveillance programmes, which has resulted in improved life expectancy from 43 to 59 years.⁸ Importantly, prospective studies show that VHL disease-associated haemangioblastomas have a propensity to grow in a saltatory or exponential manner⁹ and that larger medullary haemangioblastomas are associated with more postoperative complications.¹⁰ Many UK centres managing patients with VHL disease will only perform cranial and neuraxial imaging as part of neurosurgical follow-up or if new neurological symptoms are reported. Regular 2 yearly MRI screening may also be offered but repeat imaging is required if new symptoms develop irrespective of the fact that previous imaging may have been unremarkable. In a series of 44 patients with VHL disease with brainstem haemangioblastomas, a third presented with swallowing difficulties.² This case report emphasises that the development of respiratory infection or difficulty swallowing in VHL disease should prompt a rapid assessment of bulbar function and evidence of aspiration. Imaging of the CNS should be considered in all cases where a previous asymptomatic lesion was present or where signs of pseudobulbar dysfunction are present. Close liaison with the patient's primary VHL clinician is essential.

The recognition of the occurrence and frequency of pseudobulbar dysfunction in VHL disease should prompt enquiry about specific symptoms during routine and acute assessment. In this case it may have identified the enlarging medullary syrinx earlier and avoided inappropriate investigations, which

Figure 3 MRI during presentation; T2-weighted axial view (left) and gadolinium-enhanced T1-weighted axial view (right) both showing an enhancing nodule at the cervicomedullary junction associated with a large fluid-filled cavity in the medulla oblongata and upper cervical cord, consistent with cystic haemangioblastoma. A tiny enhancing nodule is also visible at the level of the T1 spinal vertebra.

Figure 4 MRI showing peripheral location of the cervicomedullary enhancing nodule, and development of significant size and cystic expansion over time; gadolinium-enhanced T1-weighted axial views from 6 years prior (left) and during presentation (right).

may have resulted in a shorter clinical course. Patients with VHL disease may benefit from carrying personalised medical histories and information about VHL disease when presenting to medical practitioners who are unfamiliar with this condition.

In summary, a high index of suspicion for new VHL disease-associated complications is required in all patients presenting with new symptoms, even those mimicking common diseases

such as community-acquired pneumonia. This is likely to be important for focused investigation and management, as well as long-term outcomes.

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Learning points

- ▶ von Hippel-Lindau (VHL) disease is a rare autosomal dominant inherited neoplasia syndrome characterised by central nervous system (CNS) and retinal haemangioblastomas. Mutations in the *VHL* gene are found in over 95% of cases meeting diagnostic criteria.
- ▶ VHL disease is typically managed in specialist centres with annual screening for the recognised complications. However, patients are still most likely to present to their general practitioners (GPs) and local hospitals with common but unrelated symptoms.
- ▶ This case report highlights the fact that VHL disease-associated CNS tumours may present with apparently unrelated symptoms and complications mimicking common diseases such as a community-acquired pneumonia.
- ▶ Patients with VHL presenting with new symptomatology to mainstream clinical specialties provides an opportunity to rapidly investigate and treat otherwise life-threatening complications between screening intervals. Close liaison with screening centres is essential.

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