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Co-Occurrence of Pineal-Region and Pituitary-Stalk Hemangioblastomas in a Patient Presenting with Von Hippel-Lindau Disease – A Case Report

Ocorrência simultânea de hemangioblastomas na região pineal e na haste hipofisária em paciente com doença de Von Hippel-Lindau – Relato de Caso

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Abstract

Introduction Hemangioblastomas of the pineal region or pituitary stalk are extremely rare. Only two cases of hemangioblastomas involving the pineal region have been reported, and four involving the pituitary stalk. The purpose of the present manuscript is to describe an unusual case of supposed hemangioblastoma found concomitantly in the pineal region and pituitary stalk of a patient diagnosed with Von Hippel-Lindau (VHL) disease.

Case Report A 35-year-old female patient with a previous diagnosis of VHL complaining of occipital headaches and balance disturbances for three weeks, who previously had a cerebellar hemangioblastoma resected. The visual characteristics of the tumor suggested a friable vascular lesion with a reddish-brown surface, and an incisional biopsy was performed. The tumor consisted of a dense vascular network surrounded by fibrous stroma abundant in reticulin and composed by both fusiform and dispersed xanthomatous cells; the immunohistochemistry was immunopositive for neuron-specific enolase and immunonegative for epithelial membranous antigen. The patient

Keywords
- tumor
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has been monitored closely for 2 years, and the supratentorial masses have not presented any volume alteration.

Conclusion This rare association must be taken into account in patients with VHL disease, or at least be suspected in patients who present a thickening of the pituitary stalk and a pineal-region mass. We believe a biopsy of our asymptomatic patient could have been dangerous due to inherent complications like intraoperative bleeding. We recommend close observation of asymptomatic lesions with MRIs every six months or until the lesions become symptomatic. If the pineal-region tumor does become symptomatic, gross resection via a transcallosal approach would be ideal.

Resumo

Introdução Hemangioblastomas da região pineal ou da haste hipofisária são raros. Apenas 2 casos foram reportados para a pineal e 4, para a haste hipofisária. O objetivo deste artigo é relatar um caso incomum de supostos hemangioblastomas encontrados concomitantemente na pineal e na haste hipofisária em paciente com Doença de Von Hippel-Lindau (VHL).

Relato de Caso Mulher de 35 anos, com diagnóstico de VHL e histórico de ressecção de hemangioblastoma cerebelar, apresentou cefaleia occipital e queixas relacionadas ao equilíbrio por 3 semanas. As características visuais do tumor sugeriam lesão vascular friável com superfície vermelho-amarronzada, sendo realizada biópsia incisional. O tumor consistia de rede vascular densa rodeada de estroma fibrótico abundante em reticulina e composto de células xantomatosas. Imunohistoquímica positive para enolase específica de neurônios (NSE) e negative para antígeno membranoso epitelial (EMA). Paciente monitorada por 2 anos, sem alteração nas massas.

Conclusão Essa associação rara deve ser suspeitada em pacientes com VHL, na presença de espessamento da haste hipofisária e massa pineal. Acreditamos que uma biópsia, para a paciente assintomática, seria perigosa devido a complicações inerentes como hemorragia intra-operatória. Recomendamos observação de lesões assintomáticas com RM a cada 6 meses ou até que as lesões se tornem sintomáticas. Caso o tumor da região pineal se torne sintomático, ressecção macroscópica por via transcalosa seria ideal.

Palavras-chave
- tumor
- Von Hippel-Lindau
- hemangioblastoma

Introduction

Hemangioblastomas are hypervascular tumors that correspond to approximately 2% of all primary central nervous system (CNS) neoplasms. According to the World Health Organization (Grade I), this pathological entity is composed of benign, non-metastasizing tumors, and is found mainly in the cerebellum and spinal cord. Although their origin is unknown, hemangioblastomas may occur sporadically or in association with Von Hippel-Lindau (VHL) disease in 20% to 38% of the cases.[1–14]

Hemangioblastomas that affect the pineal region or the pituitary stalk are extremely rare. To the best of our knowledge, there have only been two case reports of hemangioblastomas involving the pineal region, while hemangioblastomas on the pituitary stalk have been reported in four cases. Besides, there is only a single report of VHL patients with hemangioblastoma in the pineal region in concurrence with pituitary hemangioblastoma.[12–14]

Thus, the purpose of the present manuscript was to describe an unusual case of supposed hemangioblastoma found concomitantly in the pineal region and pituitary stalk of a patient diagnosed with hemangioblastosis. Given its unusual location, one must classify this lesion under a distinct diagnosis of VHL disease in patients with masses in the pineal region and pituitary stalk.

Case Report

A 35-year-old female patient with a previous diagnosis of VHL was referred to a neurology reference service. She had been complaining of occipital headaches and balance disturbances for three weeks. The patient reported that she had undergone a posterior fossa surgical intervention in order to resect a cerebellar hemangioblastoma during the previous year in another institution. She reported a close relative also diagnosed with VHL, although the patient herself had no known abdominal tumors or retinal hemangiomas.

A physical examination detected a segmental loss of pain and temperature with intact proprioception in the upper limbs, as well as mild tetraparesis with hyperreflexia, clonus,

and a bilateral Babinski sign. The lower cranial nerves were intact. The pupils presented no sign of pseudo-Argyll Robertson. Both the direct and consensual pupilar reflexes were preserved. A complete ophthalmological examination with fundoscopy presented no abnormalities.

The results of a magnetic resonance imaging scan performed in the emergency room indicated T1-weighted brightly enhancing masses in the pineal region and the pituitary stalk— with the absence of hydrocephalus. Moreover, there was also a large and brightly enhancing mass in the posterior fossa, syringomyelia, small lesions in the caudal portion of the cerebellum, and a cluster of hemangioblastomas in the area postrema of the medulla. There were no clinical or laboratory endocrinological alterations suggesting a functional pituitary tumor. Complete blood and cerebrospinal fluid investigations did not yield any results indicating a distinct diagnosis of other pineal-region tumors. The supratentorial lesions were closely monitored since the patient had no symptoms related to them. The posterior-fossa lesion was resected via a suboccipital approach, and the syringomyelic cavity was drained, resulting in a significant improvement of the symptoms.

During the transoperative approach, the visual characteristics of the tumor suggested a friable vascular lesion with a reddish-brown surface. An incisional biopsy was performed, followed by an uneventful wound closure.

Sections for a microscopic examination were taken at thicknesses of 3 µm, and they were stained with hematoxylin and eosin (H&E). The tumor mass consisted of a dense vascular network surrounded by fibrous stroma abundant in reticulin and composed by both fusiform and dispersed xanthomatous cells (►**Figure 1**). An immunohistochemistry analysis was performed, and the tumor was immunopositive for neuron-specific enolase (NSE) and immunonegative for epithelial membranous antigen (EMA). Based on both the microscopic and immunohistochemical analyses, the diagnosis of hemangioblastoma was established.

After the diagnosis, the patient has been monitored closely for 2 years, and the supratentorial masses have not presented any volume alteration (►**Figure 2**).

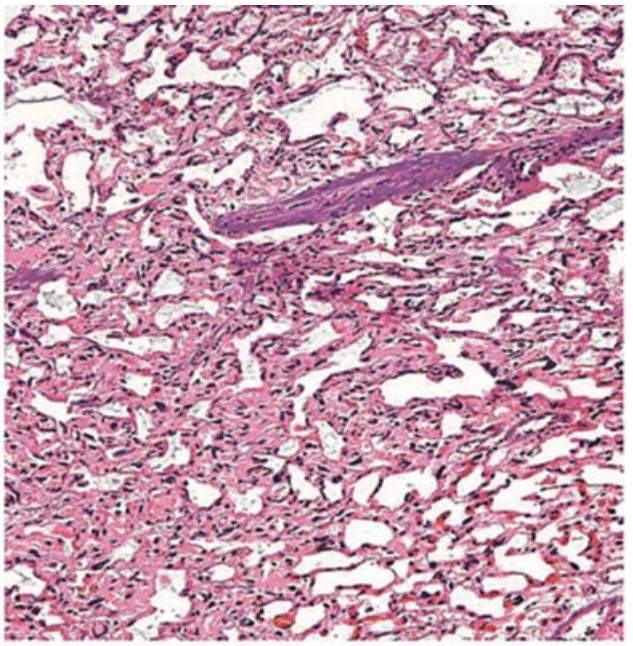

Fig. 1 Histological features of the hemangioblastoma demonstrating an intensive vascular network surrounded by fibrous connective tissue.

Discussion

Nearly 25% of hemangioblastomas are associated with VHL disease.[2,13] The tumor grows slowly and is frequently associated with cerebellar cysts or a syrinx in the brain stem or spinal cord. Von Hippel-Lindau disease is an autosomal-dominant neoplasia syndrome caused by a germline mutation or deletion of the VHL tumor suppressor gene that lies in the short arm of chromosome 3 (p25.3). This disease has a prevalence of approximately 1 in 39,000 persons. The clinical criteria for VHL disease are those established by Melmon and Rosen.[8] According to these criteria, for a patient to be diagnosed with VHL disease, they need at least two central nervous system (CNS) or retinal hemangioblastomas (present case), or one hemangioblastoma associated with renal carcinoma, pheochromocytoma, pancreatic cyst, or papillary cystadenoma of the epididymis.

In the absence of family history, the presence of a single hemangioblastoma or another manifestation of VHL disease can confirm the diagnosis. A sample of peripheric blood is enough to confirm the presence of the VHL gene mutation. The overall risk of finding VHL germline mutations ranges from 4% to 14% in patients with a single CNS hemangioblastoma without other clinical criteria for VHL disease. Patients with VHL disease affected with CNS hemangioblastomas typically develop symptoms early in life (average age of manifestation: approximately 33 years).[12,15]

Whereas sporadic hemangioblastomas are nearly always solitary, cerebellar hemangioblastomas in patients with VHL disease are often multiple and associated with additional retinal, brainstem, spinal cord, or lumbosacral nerve root hemangioblastomas.[7,11,16] The presence of a synchronous pituitary lesion neither supports nor discredits the potential diagnosis of hemangioblastoma in the case presented, given the several alternatives of differential diagnoses. This co-occurrence of a pineal region hemangioblastoma with a pituitary hemangioblastoma in patients with VHL is very rare. As reported by the sole study[17] reporting such a case, very similar histopathological analyses between both lesions were found, as well as the concomitant radiological enhancement after an injection of gadolinium.

Tumors in the pineal region correspond to around 1% of CNS neoplasms. A wide variety of tumors can affect this region, the most common being germ-cell tumors, gliomas, and pineal-cell tumors.[5] Despite being powerful diagnostic tools, the MRI and computed tomography (CT) are both low in sensitivity and specificity when it comes to the differential diagnosis of pineal-region masses. The diagnostic accuracy increases with the measurement of serum or cerebrospinal fluid alpha fetoprotein (AFP), human chorionic gonadotrophin (HCG), and

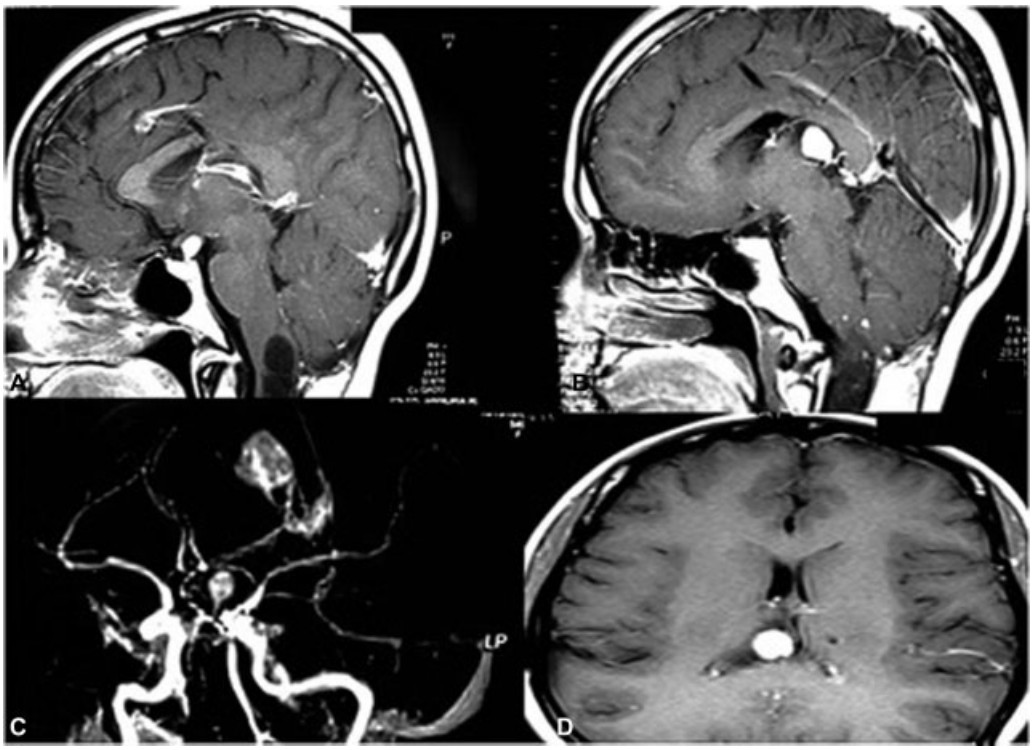

Fig. 2. (**A**) Sagittal T1 gadolinium-enhanced MRI showing a brightly enhancing mass in the pituitary stalk. (**B**) Sagittal T1 gadolinium-enhanced MRI showing a brightly enhancing mass in the pineal region and a cluster of hemangioblastomas in the area postrema of the medulla. (**C**) Magnetic resonance angiography demonstrating a vascular tumor in the suprasellar region and pineal region. (**D**) Axial gadolinium-enhanced MRI showing a brightly enhancing mass in the pineal region.

carcinoembryonic antigen (CEA). If the HCG is positive, one must consider either choriocarcinoma, mixed germ-cell tumor with choriocarcinomatous elements, or a mixed germ-cell tumor with syncytiotrophoblastic giant cells. A positive AFP may point to endodermal sinus tumor or mixed germ-cell tumors with endodermal sinus tumor. Germinoma, embryonal carcinoma, mature teratoma, immature teratoma, mixed germ-cell tumors, pineocytoma, and pineoblastoma should be taken into account when the HCG and AFP are negative.[5]

The pituitary stalk region can harbor tumors (pituitary-stalk tumors, PSTs) or other infiltrative processes, such as histiocytosis, sarcoidosis, infections or autoimmune diseases.[3,18,19] Central diabetes insipidus with isolated PST can result from various lesions. In one study,[16] a precise etiology was recognizable at the first manifestation of symptoms in 4 out of 26 patients (15% of the cases): these 4 patients had Langerhans histiocytosis. Germinoma should be suspected in all patients with Diabetes Insipidus (DI) and PST, even when neurological and ophthalmological symptoms are absent. From anatomical findings, the primary site of germinomas in the hypothalamic-neurohypophyseal axis seems to range from the posterior lobe of the pituitary gland to the stalk.[20] A PST with an identical aspect has also been reported in adult patients with idiopathic DI who do not present with germinoma, Langerhans histiocytosis, sarcoidosis, or infectious granuloma.[6] There have been four cases of pituitary stalk hemangioblastoma,[17] with only one being surgically treatable.[11]

Conclusion

This rare association must be taken into account in patients with VHL disease, or at least be suspected in patients who present a thickening of the pituitary stalk and a pineal-region mass. We believe a biopsy of our asymptomatic patient could have been dangerous due to inherent complications like intraoperative bleeding. We recommend close observation of these asymptomatic lesions with a series of MRIs every six months or until one of the lesions becomes symptomatic. If the pineal-region tumor does become symptomatic, we believe that a gross resection via a transcallosal approach would be ideal.

Conflict of Interests

The authors have no conflict of interests to declare.

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