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CEREBELLAR HEMANGIOBLASTOMA AND ACUTE LYMPHOBLASTIC LEUKEMIA: A CHANCE OR GENETICALLY DETERMINED ASSOCIATION?

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ABSTRACT

Introduction: Hemangioblastomas are benign neoplasms with well-defined histopathological characteristics, which arise from the disordered growth of stromal and vascular cells. Despite some controversy, they are described by the WHO as being of meningeal origin. They represent 1.5-3% of CNS tumors and can occur sporadically or in association with von Hippel Lindau disease. Hemangioblasts are precursor cells that can give rise to hematopoietic and endothelial cells. Objective: To report a rare association of an isolated cerebellar hemangioblastoma with acute lymphoblastic leukemia (ALL) and review of the literature. Patients and Methods: A 16-year-old patient with cerebellar expansive process underwent tumor resection with a histopathological diagnosis of hemangioblastoma. Some aspects of the literature are discussed. Results: Although some articles correlate hematological diseases with tumors of vascular origin, to the best of our knowledge, no cases of ALL and hemangioblastoma have been found so far. Conclusions: Hemangioblastomas are rare CNS tumors and the association with ALL has been described for the first time. Although speculative, the association between the two neoplasms can be justified by the origin of the same precursor cell – hemangioblasts.

Keywords: Cerebellar Hemangioblastoma. Acute lymphoid leukemia. Genetic Association. Genetic predisposition.

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INTRODUCTION

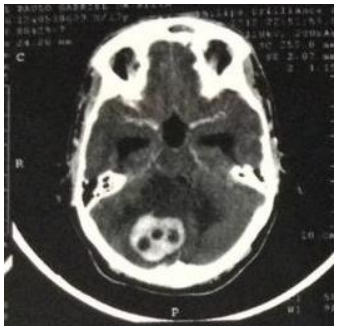
Hemangioblastomas are benign, highly vascularized tumors composed of neoplastic and vascular stromal cells. They are embryologically derived from hemangioblasts, multipotent embryogenic cells that are precursors of hematopoietic and endothelial cells. Association with acute lymphoblastic leukemia is extremely rare. We describe a case of this rare association, discussing the fact that they share the same precursor cell in its genesis.

CLINICAL CASE

A 16-year-old male patient with a history of headache, vomiting and visual blurring of insidious onset, which led him to seek the emergency room of the hospital. He underwent a CT scan of the head that showed acute hydrocephalus and a cerebellar hemispheric expansive process on the left. In view of the acute nature of the disease, he underwent emergency peritoneal ventricle shunt and resection of the lesion on the following day. The patient evolved uneventfully in the postoperative period, with symptoms showing significant improvement in the postoperative period, and was discharged from the hospital 7 days after hospital admission. He was investigated for VHL disease with abdominal CT, neuraxial MRI, and ophthalmologic examinations, ruling out retinal hemangioblastoma.

A 2-year-old report of ALL at a time of age was noteworthy in his previous pathological history, being followed up at a referral hospital for the treatment of hematological diseases from 1997 to 1999, where he received anthracycline at a dose of 240mg/m2 and prophylactic cranial radiotherapy in 1998 at a dose of 12Gy. The treatment was uneventful, with no remission of the disease, and he was discharged by hematology in August 2010.

Figure 1. CT scan of the head showing a hyperdense lesion in the posterior fossa, with significant associated hydrocephalus



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DISCUSSION

Hemangioblastomas are benign, highly vascularized tumors composed of neoplastic and vascular stromal cells. Embryologically, they originate from hemangioblasts, multipotent embryogenic cells that are precursors of hematopoietic and endothelial cells. The association with acute lymphoid leukemia is uncommon. (1)

They represent 1.5 to 3.0% of all CNS tumors, affecting the age group of 40-50 years, and may be sporadic or associated with Von Hippel-Lindau disease (VHL). When associated with Von Hippel Lindau's disease, the most affected age group is 20-30 years. (1, 2)

In the sporadic form, they present in the cerebellum (83-95%), spinal cord (3.2-13%) and brainstem (2.1%). In adults, 7-10% grow in the posterior fossa. (1, 3)

The diagnosis is suggested by MRI, with isointense T1-weighted and hyperintense T2-weighted images, which demonstrate nodular contrast uptake, usually with a cerebellar cystic area, or homogeneous uptake on the surface of intraraqueal lesions. They are sometimes associated with syringomyelia and spinal cord edema. Angiography can help in surgical planning by highlighting the feeding vessels of hemangioblastoma. These images are not pathognomonic and may have as a differential diagnosis astrocytoma, ganglioglioma, and metastases. (1)

The treatment consists of microsurgery, with or without preoperative embolization of the nourishing arteries, aiming at reducing tumor vascularization. Patients with small, asymptomatic lesions are followed up with periodic neurological and imaging examinations, and surgery is indicated only for symptomatic patients.

Surgical treatment determines definitive therapy for sporadic, isolated hemangioblastomas, usually cerebellar. In VHL disease, surgical treatment is less defined due to the presence of other concomitant diseases. Although there is no randomized trial comparing radiation therapy and surgery, deep or multiple lesions can be treated with both therapeutic options.

Genetically, VHL disease is associated with a mutation in the VHL tumor suppressor gene, located on chromosome 3p25. In hemangioblastomas, both sporadic and associated with VHL disease, there is loss of alleles and mutations of the VHL tumor suppressor gene in stromal cells. (3)

Acute lymphoblastic leukemia (ALL) is a malignant neoplasm of the hematopoietic system with alterations in the growth and proliferation of lymphoid cells in the bone marrow,

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accumulating undifferentiated cells. It is the most frequent malignant neoplasm (70%) in children under 15 years of age, with a peak incidence of 2 to 5 years. Its treatment involves radiotherapy and/or chemotherapy of the CNS, according to the presence or absence of neoplastic cells in the cerebrospinal fluid. (4)

In the study by Park et al., hemagioblasts demonstrated coexpression of mesodermal markers, FLK-1 (vascular and endothelial growth factor) and leukemic stem cell in patients with Hemangioblastoma associated with Von Hippel-Lindau Disease (VHD). Neoplastic cells also express hematopoietic stem cell antigens, where among the receptors were: CD 133, CD34, c-Kit, Scl and erythropoietin; and in specific microenvironments the hemangioblasts replicated and differentiated into erythrocytes, granulocytes and endothelial progenitors. (5)

In addition, morphological analyses show the formation of blood islands in these tumors, indicating extramedullary hematopoiesis, suggesting a relationship between hemangioblastoma and tumors of hematopoietic origin. (5)

The cytologic origin of CNS hemangioblastomas is uncertain, but there is usually a subpopulation of specific embryogen-stage cells with antigen 1 expression, which have been defined as tumor initiator cells (TICS). TICS are universal neural cells with characteristics of stem cells, present in both sporadic and familial hemangioblastomas. (2)

In these tumors, there are positive SSEA1 (embryogenic stage-specific antigen 1) subpopulations with the ability to differentiate into stromal and vascular cells. In the presence of specific hemangioblastoma niches, it is suspected that the SSEA1-positive cells may be the TICS of hemangioblastomas. (2)

In the study by Price and Johnson, the intracranial involvement of patients with ALL was evaluated, and of 126 brains examined at autopsy, 70 had arachnoid leukemia, as well as gliosis, necrosis, hemorrhage, and non-hemorrhagic encephalopathy. These authors confirmed the involvement of the Central Nervous System, with 60-70% of the patients presenting intracranial leukemia at the time of death. (6)

Leukemia is a systemic disease and its extension in the CNS occurs gradually, reaching the cerebrospinal fluid and later gray and white matter, respectively. In this work, two hypotheses were raised to justify leukemia in the CNS: Migration of leukemia cells through the venous endothelium or malignant transformation of pre-existing undifferentiated germ elements, with hematopoietic potential in the venous walls of these cells. (6)

Revista ARACÊ
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Although there was no correlation with hemangioblastomas or with other intracranial tumors, the second hypothesis could suggest a correlation between leukemia and tumors with hematopoietic potentials, such as hemangioblastomas. It is noteworthy that both the patients in the study and the patients in our institution underwent chemotherapy prior to the detection of intracranial injury.

In addition, to our knowledge, there is no case in the literature describing the association between ALL and hamangioblastoma, which reinforces the extremely unusual nature of this association. However, further genetic studies should be carried out in order to seek this association. The possibility of the appearance of these lesions in a patient with ALL can be seen not as a coincidence, but as an association, justifying the need for long-term follow-up and the need for periodic CNS imaging.

CONCLUSION

Hemangioblastomas are rare CNS tumors and the association with ALL was described for the first time, and both tumors have precursors of hematopoietic cells. Genetic studies should be developed in order to determine the relationship between both diseases, since this association justifies the performance of periodic brain imaging tests in patients diagnosed with ALL in the long-term clinical follow-up.

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