

Case Report

Papillary glioneural tumor presenting with multiple ischemic strokes: an aggressive presentation of a “benign” entity

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ABSTRACT

Papillary glioneural tumors are infrequent neoplasms of the central nervous system, classically presenting with an indolent clinical course, rarely being related to an aggressive presentation, and not being associated with ischemic or another type of paraneoplastic phenomena. We describe the first case of this type of presentation with a literature review of the current knowledge of this entity. A 16-year-old female presented with a hemorrhagic intra-axial lesion, confirmed to be a papillary glioneural tumor in the histopathological analysis, being associated with multiple ischemic cerebral and posterior fossa strokes without another discernable cause than the presence of a paraneoplastic syndrome, not previously reported with this type of neoplasms. A literature review is presented detailing the current knowledge about this entity and emphasizing the need for greater knowledge about its natural history, immunobiology and treatment alternatives, opening a new window for the study of this pathology and establishing the need for a strict follow-up of patients who have this kind of tumors in order to learn more about their evolution. The papillary glioneural tumor, a rare entity having generally with a benign course, can have different presentations. Greater knowledge is needed to understand this behavior in order to optimize patient's outcomes.

Keywords: Papillary glioneural tumor, Ischemic infarct, Paraneoplastic syndrome

INTRODUCTION

Papillary glioneural tumor are infrequent neoplasms of the central nervous system.^{1,2} Generally, these tumors present an indolent clinical course.³ There are no reports in the literature that associate these lesions with ischemic phenomena that may suggest a paraneoplastic syndrome; however, we report the case of an atypical presentation in relation to multiple intracranial ischemic lesions.

CASE REPORT

A 16 years old female patient presented with two months of headache, asthenia, emesis and vertigo, symptoms that were markedly exacerbated on the day of the consultation. She had no relevant pathological history. The neurological examination documented limitation for

abduction of the left eye, right homonymous hemianopia and left peripheral facial palsy associated with flaccid dysarthria. The patient was right-handed. Initially, a brain MRI study was requested (Figure 1) showing a predominantly subacute early hematoma in the medial and superior aspect of the left occipital lobe with a heterogeneous image inside which presented a central enhancement as well as multiple early subacute acute ischemic infarcts in both cerebral hemispheres and in the right cerebellar hemisphere. Surgical intervention was performed through a neuronavigation-guide craniotomy, performing an en bloc resection. Postoperatively, the patient was monitored in the intensive care unit without presenting an additional neurological deficit. Autoimmunity studies were carried out ruling out systemic diseases, as well as primary vasculitis of the central nervous system, with additional studies that ruled out metabolic disease, and coagulopathy workup that had

negative findings. Cardiac studies had no abnormal findings, considering the ischemic phenomena in relation to the underlying tumor pathology.

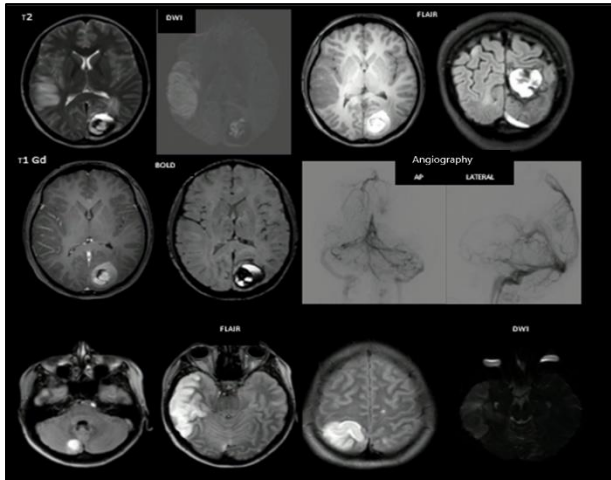


Figure 1: MRI and conventional angiography showing an early subacute hematoma in the medial and superior aspect of the left occipital lobe with a heterogeneous image in its interior as well as multiple acute ischemic infarcts - early subacute in. Angiographic study with low tumor perfusion.

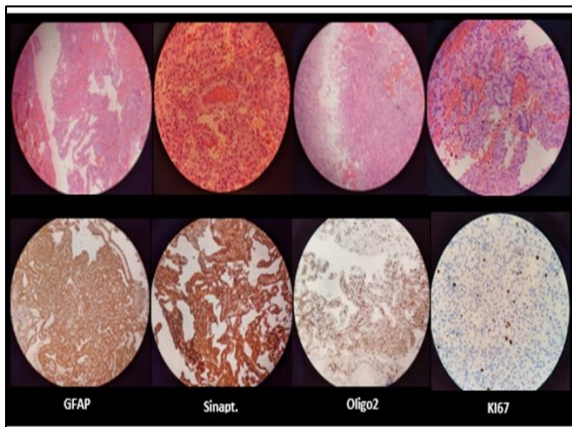


Figure 2: 20× HE staining showing a lesion with pseudo papillary formation delineated by a single layer of cuboidal cells with a scant cytoplasm and nucleus without atypia within a cell stroma. Immunohistochemical staining showing a mixed glioneuronal lineage and a low rate of cell proliferation.

The patient was discharged home after this. The pathology study (Figure 2), in the hematoxylin-eosin sections at low magnification, showed a well-defined tumor lesion with a benign appearance, with minimal microvascular proliferation, without necrosis or cellular atypia. Glial differentiation was evidenced, as well as areas of pseudo papillary formation delineated by a single layer of cuboidal cells with scant cytoplasm and a nucleus without atypia, which surround blood vessels with hyalinized walls. Regarding cell morphology, cells

with a neural appearance that formed perivascular rosettes with vascular hyalinization were evidenced. Likewise, hemosiderin deposits were identified. Immunohistochemistry showed the glial component oriented around the hyalinized blood vessels, highlighted with PAGF and OLIGO2, while the neuronal component that was distributed in the papillary area, presented neurocytic and ganglionic morphology, with marked positivity in NeuN and light with synaptophysin. The cell proliferation index (KI67) was low, being less than 2%.

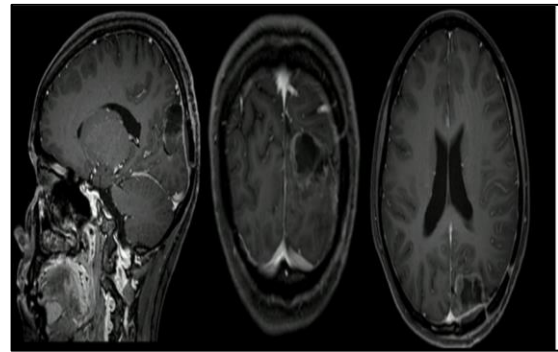


Figure 3: Postoperative brain magnetic resonance imaging showing complete resection of the lesion.

A follow-up imaging study was performed at 3 months, which ruled out residual disease (Figure 3) or recurrence, having recovery from the previously described deficit and persisting only with a known visual field compromise.

DISCUSSION

The papillary glioneuronal tumor typically presents and indolent behavior and slow growth, being predominantly supratentorial, generally adjacent to the lateral ventricular system and in relation to the temporal lobe, being reported in patients from the first to the eighth decade of life (4 to 75 years), and corresponding to less than 0.02% of intracranial neoplasms.² The first report of this pathology dates from 1998, however, it was not described as a particular entity until 2007.^{1,3}

The clinical presentation of these lesions is variable; however, the majority of patients are asymptomatic or present a scarce neurological compromise, generally having a benign clinical course.^{4,5} Bleeding associated with this type of tumor is not frequent. Carangelo et al only found two cases with hemorrhage in a series of 67 of this type of tumors, finding possibly related to the thin wall of the blood vessels in the solid region and their hyalinization in the papillary region.^{1,2}

Imaging studies characterize it as a circumscribed lesion, with a cortico-subcortical extension, or deeper in relation to the ventricular system, with cystic and solid components. Its solid components are Iso-Hypo intense in T1 and Iso-Hyper intense in T2, classically presenting a patchy or ring enhancement after gadolinium

administration. They may additionally present calcifications or have a hemorrhagic component, as well as be associated with edema or mass effect if the lesions are large.⁷

According to the WHO 2016 central nervous system tumor classification, this tumor is located in the section of mixed neuronal and glioneural tumors. It is characterized by a prominent pseudo papillary architecture, a single or pseudo-stratified layer of flattened or cuboidal glial cells with round nuclei and scant cytoplasm, located around hyalinized blood vessels together with intervening collections of neurocytes and medium-sized ganglion cells with accompanying neuropil.¹² In its histology, a fundus that can be fibrillary or micro cystic is described. Neurocytes frequently resemble oligodendrocytes. Towards the periphery of the tumor, scattered tumor cells intermingle with glyotic areas that may present Rosenthal fibers, eosinophilic granular bodies, hemosiderin, and micro calcifications.^{13,14} It is necessary to clarify that these glial elements lack atypia and mitotic activity, likewise, microvascular proliferation and necrosis is minimal, characteristics that give this tumor benignity.

Immunohistochemical studies show positivity for fibrillar glial acid protein (GFAP) and S100 in cells surrounding the pseudo papillae, as well as immunoreactivity for synaptophysin, neurofilaments, and OLIG2 in neuronal elements that are located in the interpapillary areas.^{14,15} Tumor cells are negative for epithelial membrane antigen (EMA) and cytokeratins. The cell proliferation index measured with KI67 is generally low.¹²

Molecularly, the fusion in the SLC4A1-PRCKCA gene has been found to be highly specific for this entity. Mutations in the BRAF V600E gene have also been described.^{2,8}

The treatment of these injuries is essentially surgical associating this therapy modality with even injury-free progression and very good overall survival.^{1,2,9} In a meta-analysis it is reported that the 1.5-year progression-free survival is 86% with an overall survival in the same period of 98%.¹⁰

It has not been clarified in the reports that exist on this pathology if the clinical presentation is established as a risk factor for its greater aggressiveness, however, we are facing the first case of this entity that is associated with a paraneoplastic phenomenon of multiple multi topographic intracranial ischemic events that do not correlate with any other alteration other than the presence of this tumor entity. The paraneoplastic syndrome in the context of an oncological pathology at the level of the nervous system can have extensive involvement (brain, spinal cord, cranial nerves, retina, peripheral nerve and neuromuscular junction), being these alterations generally associated with tumor lesions with an expression of proteins with neuroendocrine potential, immunoglobulin production, or associated with organs with immune

regulatory potential, characteristics that have not been described as present in papillary glioneural tumors and that open a spectrum of study about these apparently indolent tumors.^{5,11}

CONCLUSION

The papillary glioneural tumor, a rare entity and generally with a benign course, can show extremes of presentation, as discussed in this article. The need for greater knowledge about its natural history, immunobiology and treatment alternatives, opens a new window for the study of this pathology and establishes the need for a strict follow-up of patients who have this entity in order to learn more about its evolution. The first reported case associated with a presentation for neoplastic disease was described, which leads to question the “indolent” characteristic of this lesion and opens the question of a potential multi-systemic compromise associated with it.

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