COLD SPRING HARBOR
Molecular Case Studies

RESEARCH REPORT

PIK3CA mutation in a case of *CTNNB1*-mutant sinonasal glomangiopericytoma

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Abstract Glomangiopericytomas are rare, primary sinonasal tumors. The existing literature is mostly limited to reports describing the clinicopathologic characteristics of these tumors. Comprehensive genetic characterization of glomangiopericytomas remains lacking. Whole-exome sequencing of a case of glomangiopericytoma was performed under an institutional review board–approved protocol. A 69-yr-old female underwent surgical resection of a glomangiopericytoma. Whole-exome sequencing revealed somatic mutations in *CTNNB1* and *PIK3CA*, the former previously associated with this pathology but the latter not described. Concurrent dysregulation of Wnt/β-catenin and PI3K/AKT/mTOR signaling, secondary to mutations in these two oncogenes, may be amenable to targeted treatment with existing clinically approved drugs. Genomic characterization of glomangiopericytomas remains lacking. This study reports novel coexistence of *PIK3CA* and *CTNNB1* mutations in a case of glomangiopericytoma that may offer insight into the pathogenesis and potential for targeted medical therapies of this rare tumor.

[Supplemental material is available for this article.]

INTRODUCTION

Glomangiopericytomas, also known as sinonasal hemangiopericytomas, are rare mesenchymal neoplasms with a myoid phenotype, exhibiting positivity for smooth muscle actin (SMA), which distinguishes them from other soft tissue tumors (Park et al. 2017). They are rare tumors, comprising <0.5% of all sinonasal tumors and considered to have low malignant potential (Stelow and Bishop 2017), but local recurrence and metastasis may occur in a subset of patients, despite complete surgical excision (Kazi et al. 2021). Most of the existing literature on glomangiopericytomas has been limited to single reports or case series, describing clinicopathologic characteristics. Comprehensive genetic study of glomangiopericytomas remains lacking, which may improve criteria for diagnosis and guide adjuvant treatment of surgically refractory tumors.

RESULTS

Case Description

A 69-yr-old female with no relevant past medical history, recent trauma, or carcinogenic exposures presented with recurrent epistaxis over the past year, increasing in frequency over the past several months. She underwent nasal endoscopy, which revealed a right nasal mass. Computed tomography (CT) demonstrated a hypodense, partially cystic mass in the

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Ontology term: thick skull base

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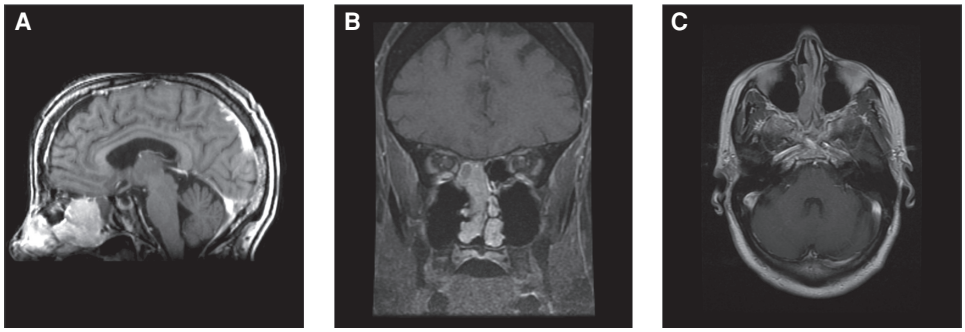

Figure 1. Representative (*A*) sagittal, (*B*) coronal, and (*C*) axial slices of a T1-weighted magnetic resonance imaging (MRI) after gadolinium contrast demonstrate a 3.3 × 1.2-cm enhancing soft tissue mass within the right nasal cavity, protruding into the ipsilateral sphenoid sinus without definite intracranial extension.

right nasal cavity causing obstruction and opacification of the right posterior ethmoid air cells and sphenoid sinus, as well as bony remodeling of the ipsilateral cribriform plate and lateral lamella. Magnetic resonance imaging (MRI) demonstrated a 3.3 × 1.2-cm enhancing soft tissue mass, protruding into the ipsilateral sphenoid sinus without definite intracranial extension (Fig. 1). Subsequently, an endoscopic biopsy of the lesion revealed a diagnosis of sinonasal glomangiopericytoma, and after discussion at a multidisciplinary head and neck tumor board, local complete excision was recommended.

The patient subsequently underwent endoscopic endonasal resection of her tumor via a right total sphenoethmoidectomy, frontal sinusotomy, and maxillary antrostomy. Intra-operatively, the tumor was noted to attach medially on the superior posterior septum without extension through the septum and pushed the middle turbinate and superior turbinate laterally. There was no epidural involvement to suggest intracranial extension. Gross total resection was achieved with negative pathologic margins. The patient's postoperative course was uneventful, and further follow-up imaging is pending.

Pathologic review of the resected specimen revealed a tumor composed of bland spindle cells, arranged in sheets and ill-defined fascicles (Fig. 2A,B). There were tumor cells swirling around blood vessels showing perivascular hyalinization and focally formed a palisading pattern alternating with acellular hyalinized stroma. Focal mitoses was present (Ki-67 index 5%–8%) but without necrosis, atypical mitoses, or nuclear pleomorphism. Immunohistochemistry demonstrated diffusely positive staining for nuclear β-catenin and SMA (Fig. 2C,D). Stains for S100 and STAT6 were negative.

Genomic Analysis

Whole-exome sequencing (WES) revealed 19 somatic single-nucleotide variant (SNV)/indels with a variant allele frequency (VAF) > 10% in the tumor tissue. This translated into a relatively low tumor mutational burden (TMB) of 0.6 mut/Mb. We also analyzed the mutation signature for the missense mutations and identified 22% were C:G > T:A, 5.6% were C:G > A:T, 5.6% were T:A > A:T, 39% were T:A > C:G, and 28% were T:A > G:C alterations. This small number of missense mutations precluded assessment of a specific cancer-associated mutational signature (Alexandrov et al. 2013).

We prioritized the 19 somatic variants by the number of cases reported with the exact same mutation in the COSMIC database (Tate et al. 2019) and also with predicted pathogenicity, based on the ClinVar algorithm (Landrum et al. 2018). Based on these prioritizations, we identified two missense alterations, *CTNNB1* (rs121913407, c.T133C: p.S45P) and *PIK3CA* (rs121913279, c.A3140G: p.H1047R) (Table 1). Both somatic variants have been

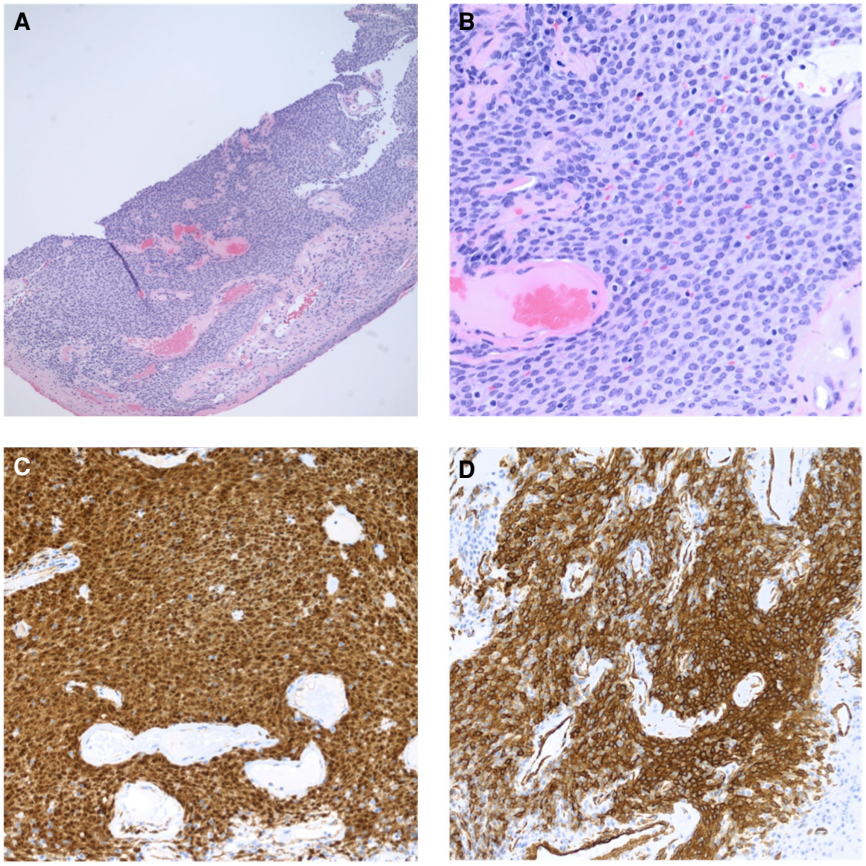

Figure 2. Histopathology. (*A*) A submucosal solid proliferating tumor with hyalinized vasculature is noted at low magnification (10×). (*B*) At higher power (40×), the tumor is comprised of monotonous ovoid to spindled cells. (*C*) The tumor cells are diffusely positive for β-catenin (nuclear) and (*D*) smooth muscle actin (SMA).

reported extensively in the COSMIC database (COSM5663 for *CTNNB1*, COSM775 for *PIK3CA*) and predicted to be highly pathogenic based on the SIFT (Vaser et al. 2016) and MutationTaster (Schwarz et al. 2014) algorithms. WES analysis did not identify any copy number or loss of heterozygosity events.

DISCUSSION

Glomangiopericytomas are a rare sinonasal tumor, now recognized as a subset of hemangiopericytoma arising from pericytes within the sinonasal region. Clinically, their diagnosis can be challenging to differentiate them from more common sinonasal tumors with malignant

Table 1. Genetic findings of index patient

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect	dbSNP ID	Genotype/variant allele frequency
CTNNB1	3	c.T133C	p.S45P	Missense	Substitution	rs121913407	NA/42.6%
PIK3CA	3	c.A3140G	p.H1047R	Missense	Substitution	rs121913279	NA/43.6%

potential, such as various carcinomas and esthesioneuroblastoma, among others (Llorente et al. 2014). However, advances in molecular characterization of sinonasal tumors have aided in the ability to accurately differentiate these pathologies, such as the presence of NAB2–STAT6 translocations in solitary fibrous tumors (Robinson et al. 2013) but otherwise absent in hemangiopericytomas (Agaimy et al. 2014). *CTNNB1* mutations were subsequently shown to characterize glomangiopericytomas with positive immunohistochemical staining for β-catenin as a valid diagnostic marker (Haller et al. 2015; Lasota et al. 2015). In particular, the *CTNNB1* p.S45F mutation, affecting the same protein sequence as in our patient, has demonstrated strong immunohistochemical nuclear localization as a means of pathway activation (Koike et al. 2019). However, further comprehensive genomic study of glomangiopericytoma remains lacking to guide diagnostic criteria and development of targeted therapies.

CTNNB1 mutations were originally associated with the pathogenesis of glomangiopericytomas by Haller et al. (2015). The authors performed WES in six patient samples and demonstrated recurrent hotspot *CTNNB1* mutations in all cases, although notably lacking the *NAB2–STAT6* fusion, characteristic of solitary fibrous tumors. Subsequently, several reports confirmed the prevalence of *CTNNB1* mutations in glomangiopericytoma and their association with positive staining for β-catenin on immunohistochemistry (Lasota et al. 2015; Anzai et al. 2018; Kono et al. 2019; Obeidin et al. 2019). As such, β-catenin staining is now routinely used to clinically diagnose glomangiopericytomas and differentiate them from other soft tissue tumors of the sinonasal tract. The *CTNNB1* variant (p.S45P) detected in our patient was also observed in one of the patients from the Haller et al. study and likewise has been reported as a pathogenic mutation in many systemic cancers according to the COSMIC database (Tate et al. 2019). Although there are no specific therapies targeting *CTNNB1* directly, inhibition of tankyrase, a downstream regulator of Wnt/β-catenin signaling, has demonstrated promising results in preclinical studies of β-catenin-driven colorectal cancers (Prossomariti et al. 2020). However, despite the prevalence of *CTNNB1* mutations across the human cancer landscape, targeted therapies remain lacking, highlighting a need for further molecular characterization of glomangiopericytomas.

Our study notably revealed a *PIK3CA* mutation, a known oncogene in many solid human cancers (Samuels et al. 2004) but not previously reported in glomangiopericytoma. PI3Ks comprise a large group of kinases that regulate multiple downstream signaling pathways, affecting cellular proliferation, adhesion and motility, as well as survival. Activating mutations in the catalytic subunit p110α of PI3K (PIK3CA) leads to increased signaling through the canonical, oncogenic PI3K/Akt/mTOR pathway (Shayesteh et al. 1999). To our knowledge, this is the first report of a pathogenic *PIK3CA* mutation in glomangiopericytoma. Notably, there are several PI3K inhibitors in various stages of clinical development for advanced solid tumors, including alpelisib, buparlisib, copanlisib, and pictilisib (Vitale et al. 2021). Currently, alpelisib is clinically approved to treat patients with advanced *PIK3CA*-mutated breast cancer (André et al. 2021), whereas copanlisib is approved to treat relapsed lymphoma (Dreyling et al. 2017). Additionally, there are numerous clinically approved therapies targeting mTOR, a downstream effector of the PI3K/AKT pathway, most notably rapamycin and everolimus (Faivre et al. 2006). As such, there are existing clinically approved targeted therapies for PI3K/Akt/mTOR pathway dysregulated tumors, highlighting the need for further genomic characterization of glomangiopericytomas to determine whether targeting this pathway is a valid therapeutic strategy.

There are preclinical data to suggest that the Wnt/β-catenin and PI3K/AKT/mTOR pathways work synergistically in promoting tumorigenesis (Solzak et al. 2017; Prossomariti et al. 2020). Interestingly, *PIK3CA* mutations may induce a senescent, stem cell–like state in HER2-overexpressing breast tumors, which may together contribute to tumorigenesis (Chakrabarty et al. 2019). Potential for a similar synergistic relationship between *PIK3CA* and *CTNNB1* mutations may exist and contribute to our understanding of glomangiopericytoma formation.

Clinicopathologically, the presence of the *PIK3CA* mutation in our patient's tumor did not differentiate it significantly from other *CTNNB1*-mutated glomangiopericytomas in regard to measures, such as tumor size and Ki-67 index (Haller et al. 2015; Kono et al. 2019). As such, preclinical study of coexisting *PIK3CA*- and *CTNNB1*-mutated cancer models are needed to predict relevance for disease prognosis and management. Clinically, the combination of dysregulated Wnt/β-catenin and PI3K/AKT/mTOR pathways has been best described in a subset of colorectal cancers (Prossomariti et al. 2020). Wnt/β-catenin pathway dysregulated tumors may exhibit treatment resistance to targeted inhibition of the PI3K/AKT/mTOR pathway (Vitale et al. 2021). However, targeting both PIK3CA and mTOR simultaneously may be an effective therapeutic strategy in colorectal cancers driven by both PI3K and β-catenin signaling, characterized by *PIK3CA* and *APC* mutations (Foley et al. 2017). Although the prevalence of dysregulated PI3K/AKT/mTOR signaling remains unclear in *CTNNB1*-mutated glomangiopericytomas, these aforementioned data suggest promising therapeutic potential in tumors, driven by overactivation of both oncogenic pathways.

This is the first report of the somatic genomic profile of glomangiopericytoma through WES, which revealed coexistence of *CTNNB1* and *PIK3CA* mutations, presenting with a low tumor burden of 0.6 mut/Mb, similar to the burden reported in hemangiopericytomas (Robinson et al. 2013). Although *CTNNB1* mutations have been associated with this pathology, *PIK3CA* mutations have not been reported until now. Notably, there appears to be a cross talk between the PI3K/Akt/mTOR and Wnt/β-catenin signaling and therapeutic potential for dual inhibition of both pathways with existing clinically approved drugs. Further reports of comprehensive genetic analysis of glomangiopericytomas are needed to elucidate the prevalence of dysregulated PIK3CA activity in *CTNNB1*-mutated tumors.

METHODS

This study was conducted under an institutional review board–approved protocol at Yale University. The patient's blood and tumor tissue were collected after obtaining written informed consent. Histopathology, including immunohistochemical studies, was evaluated by a board-certified oncologic surgical pathologist.

WES and analysis was performed in accordance with our previously described methods at the Yale Cancer for Genome Analysis (YCGA) (Fomchenko et al. 2019). Briefly, genomic DNA from the tumor and blood were isolated and exome captured with IDT xGen Exome Research Panel v1 (Integrated DNA Technologies) and then sequenced on the Illumina NovaSeq6000 WES platform with 2 × 100 base pair reads. Downstream analysis of raw reads, including alignment, duplicate marking, realignment, and base quality recalibration was performed according to "GATK Best Practice" recommendations (v.4.1.9, Grch37). Somatic SNVs, indels, and copy-number variations (CNVs) were identified as previously described (Fomchenko et al. 2019). Mean coverage of 139.4× was achieved for blood and 240× for tumor tissue (Supplemental Table 1).

Competing Interest Statement

The authors have declared no competing interest.

Referees

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ADDITIONAL INFORMATION

Data Deposition and Access

All variants discussed in this manuscript have been submitted to the European Genome-phenome Archive (EGA: https://ega-archive.org/) under the accession ID EGAS00001005653.

Ethics Statement

This study was conducted under an institutional review board–approved protocol at Yale University. The patient's blood and tumor tissue were collected after obtaining written informed consent.

Author Contributions

All authors were involved in the clinical care of the patient and drafting of the manuscript. C.S.H., E.Z.E.-O., and S.B.O. reviewed and conducted analysis of data from genomic sequencing.

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