PTCH1 mutant small cell glioblastoma in a patient with Gorlin syndrome: A case report

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Abstract. Gorlin syndrome or nevoid basal cell carcinoma syndrome is a rare genetic disease characterized by predisposition to congenital defects, basal cell carcinomas and medulloblastoma. The syndrome results from a heritable mutation in *PATCHED1* (*PTCH1*), causing constitutive activation of the Hedgehog pathway. The present study described a patient with Gorlin syndrome who presented early in life with characteristic basal cell carcinomas and later developed a small cell glioblastoma (GBM), World Health Organization grade IV, associated with a Patched 1 (*PTCH1*) *N97fs*43* mutation. Comprehensive genomic profiling of GBM tissues also revealed multiple co-occurring alterations including cyclin-dependent kinase 4 (*CDK4*) amplification, receptor tyrosine-protein kinase 3 (*ERBB3*) amplification, a fibroblast growth factor receptor 1 and transforming acidic coiled-coil containing protein 1 (*FGFR1-TACC1*) fusion, zinc finger protein (*GLI1*) amplification, E3 ubiquitin-protein ligase (*MDM2*) amplification and spectrin α chain, erythrocytic 1 (*SPTA1*) *T1151fs*24*. After the biopsy, imaging revealed extensive leptomeningeal enhancement intracranially and around the cervical spinal cord due to leptomeningeal disease. The patient underwent craniospinal radiation followed by 6 months of adjuvant temozolomide (150 mg/m^2) with good response. She was then treated with vismodegib for 11 months, first combined with temozolomide and then with bevacizumab, until disease progression was noted on MRI, with no significant toxicities associated with the combination therapy. She received additional therapies but ultimately succumbed to the disease four months later. The current study presents the first documentation in the literature of a primary (non-radiation induced) glioblastoma secondary to Gorlin syndrome. Based on this clinical experience, vismodegib should be considered in combination with standard-of-care therapies for patients with known Gorlin syndrome-associated glioblastomas and sonic hedgehog pathway mutations.

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Introduction

Nevoid basal cell carcinoma syndrome (NBCCS), often referred to as Gorlin syndrome (Online Mendelian Inheritance in Man [OMIM] #109400), is a cancer predisposition syndrome caused by mutations in the *PTCH1* gene with an autosomal dominant inheritance pattern (1). It was first identified as a distinct syndrome in 1960 by the dentist Dr. Robert J Gorlin, who described a case series of similar patients. In his publication he noted two young patients presenting with numerous nevoid basal cell carcinomas, epithelial-lined cysts of the jaw (odontogenic keratocysts), and the radiographic findings of bifid ribs (1). In 1984, Drs. Mortimer and Geaney reported a correlation between the development of medulloblastoma and NBCCS (2). The prevalence estimates of Gorlin syndrome range from 1 in 31,000 in the US (3) to 1 in 256,000 (4) in Italy, with a male-female ratio of 1:1 (5). The mainstay of treatment in Gorlin syndrome is chemotherapy, with avoidance of radiation as a first line therapy due to high genetic predisposition to radiation induced tumorigenesis (6).

The hallmark feature for this syndrome is the development of multiple basal cell skin carcinomas (BCCs) that most frequently arise on the face, back, and neck as early as two years of age but more commonly in the adolescent and young adult years (7). Incidence of BCCs among patients with Gorlin syndrome varies by ethnicity, ranging from 40% among black patients to 90% among white patients, and are rarely fatal (5).

Treatment with radiation therapy must be avoided, as this can result in tumors in the radiation field even years later (6). Importantly ~5% of individuals with Gorlin syndrome develop medulloblastoma, while the prevalence is less than 2% in patients with Gorlin syndrome and the *PTCH1* mutation (8,9). The development of medulloblastoma can be the first presentation of Gorlin syndrome as these tumors arise at a mean age of two years (10). These tumors are typically fatal, but survivors of medulloblastoma that have been treated with radiation therapy have a high risk of developing large numbers (>1000) of basal cell carcinomas in radiated areas (11). A wide spectrum of other tumors have been reported in patients with Gorlin syndrome, but the relative risk for these patients developing cancer compared to the normal populations is unclear.

Here we report a patient with Gorlin syndrome who presented early in life with characteristic basal cell carcinomas and at age 28 developed a primary (non-radiation induced) small cell glioblastoma associated with a *PTCH1 (N97fs*43)* mutation. Our report represents the first documentation in the literature of a primary glioblastoma developing secondary to Gorlin syndrome.

Case report

This retrospective case study was reviewed by the Wake Forest School of Medicine Institutional Review Board and determined to not meet the federal definition of research involving human subject research as outlined in the federal regulations 45 CFR 46. The patient first presented to an outside institution for evaluation of possible basal cell nevus syndrome at the age of 11. Three weeks prior, she was diagnosed with odontoid cysts of the jaw and noted to have palmar pits, calcification of the falx cerebri and bifid ribs. A complete skin evaluation was significant for multiple benign-appearing, hyperpigmented macules and papules consistent with benign nevi. Examination of the hands confirmed multiple, punctate, keratotic erythematous pits, while multiple yellowish nodules along the gingiva were noted in the oral mucosa that were consistent with odontoid cysts. A biopsy of an atypical posterior auricular area suspicious for atypical basal cells was performed to confirm a diagnosis of basal cell carcinoma. The patient was followed with routine visits and new skin lesions evaluated accordingly. At the age of 23, an incidental right posterior parahippocampal/thalamic lesion was discovered during routine sinus imaging and the lesion was monitored with serial imaging.

At the age of 28, the patient presented with headaches, nausea, and vomiting. Head CT demonstrated enlargement of the previously documented parahippocampal/thalamic lesion as well as obstructive hydrocephalus due to effacement of the cerebral aqueduct by the tumor (Fig. 1A). Neurosurgical intervention was pursued and a ventriculo-peritoneal shunt was placed in addition to a biopsy of the tumor.

Histopathology procedures were as follows: the tumor was fixed in 10% neutral buffered formalin overnight. The formalin-fixed tissue was processed, embedded in paraffin, and cut at 5 micrometers in thickness. Tissue sections were stained with hematoxylin-and-eosin. For immunohistochemical staining, 5 micrometer sections of formalin-fixed, paraffin-embedded (FFPE) tissue were placed on positive charged slides and allowed to dry. Following removal of paraffin, endogenous peroxidase activity was quenched with hydrogen peroxide in methanol, after which the sections were hydrated with water. The tissue sections were then stained for GFAP (clone GA5, dilution 1:100, Leica Biosystems), synaptophysin (clone 27G12, prediluted by the manufacturer, Leica Biosystems), and Ki-67 (clone SP6, prediluted by the manufacturer, Cell Marque). Histopathologic examination of resected tissues revealed a densely cellular glioma composed of small, poorly differentiated tumor cells associated with frequent mitoses, pseudo-palisading necrosis and microvascular proliferation. Tumor cells were diffusely positive for GFAP and the Ki-67 proliferation index was 20-30% (Fig. 2A-F). Additionally, the tumor expressed synaptophysin, a neuronal marker, which has been previously reported in a subset of gliomas (12) Overall, the findings were most consistent with glioblastoma (GBM), WHO Grade IV, small cell variant based on the Fourth Edition of the World Health Organization (WHO) Classification of Central Nervous System Tumors.

Comprehensive genomic profiling of GBM tissues was performed in a CAP-accredited/CLIA-certified laboratory (Foundation Medicine). DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) tissue and subjected to hybrid-capture-based next-generation sequencing covering 236 cancer-related genes and the intronic regions of 28 genes commonly involved with rearrangement mutations (FoundationOne® assay). Sequence data were analyzed for clinically relevant classes of genomic alterations, including base pair substitutions, insertions/deletions, copy number alterations, rearrangements/fusions (13).

The analysis revealed a *PTCH1 (N97fs*43)* variant as well as multiple co-occurring alterations including *CDK4* amplification, *ERBB3* amplification, *FGFR1-TACC1* fusion, *GLI1* amplification, *MDM2* amplification and *SPTA1 (T1151fs*24)* (Table I). There was no evidence of alterations in *IDH1/2*, *TP53*, *PDGFRA*, or *EGFR*. The constellation of genomic findings is consistent with that reported in *FGFR-TACC* fusion positive GBMs which lack alterations involving *IDH1/2* and *EGFR* but often show *MDM2* and *CDK4* amplification (14).

After the biopsy, imaging showed extensive leptomeningeal enhancement intracranially and around the cervical spinal cord (Fig. 1B) due to leptomeningeal disease. The patient underwent craniospinal radiation followed by six months of adjuvant temozolomide (150 mg/m^2) with good response (Fig. 1C). Note that concurrent treatment with temozolomide was held because of poor tolerance (namely intractable nausea, vomiting, fatigue) by the patient due to radiation therapy. In June 2015, she was started on combination temozolomide and vismodegib (150 mg po daily), a smoothened receptor (SMO) antagonist which leads to inhibition of the hedgehog signaling pathway. She remained on combination therapy until late March 2016 at which point temozolomide was discontinued and replaced with bevacizumab due to imaging-confirmed progression of her disease (Fig. 1D). Combination bevacizumab and vismodegib was continued until May 2016. In total, she was treated with vismodegib for 11 months with no significant toxicities associated with the combination therapy approach. Despite these interventions, the patient continued to have leptomeningeal progression noted on MRI and was treated sequentially with lapatinib and bevacizumab, followed

Table I. Summary of genomic alterations detected in the patient's tumor.

Genomic alterations	Gene	Coding sequence effect	Protein effect	Alteration	Copy number	*FGFR1* breakpoint	*TACC1* breakpoint
Short variants	*PTCH1*	283_284insA	N97fs*43				
	SPTA1	3449_3450insA	T1151fs*24				
Copy number alterations	*ERBB3*			Amplification	12		
	GLI1			Amplification	22		
	CDK4			Amplification	25		
	MDM2			Amplification	44		
Rearrangement	*FGFR1-TACC1*					Exon 18	Intron 6

PTCH1, PATCHED1; *SPTA1*, spectrin α chain, erythrocytic 1; *ERBB3*, receptor tyrosine-protein kinase ERBB3; *GLI1*, zinc finger protein GLI1; *MDM2*, E3 ubiquitin-protein ligase MDM2; *FGFR1-TACC1*, fibroblast growth factor receptor 1 and transforming acidic coiled-coil containing protein 1 fusion.

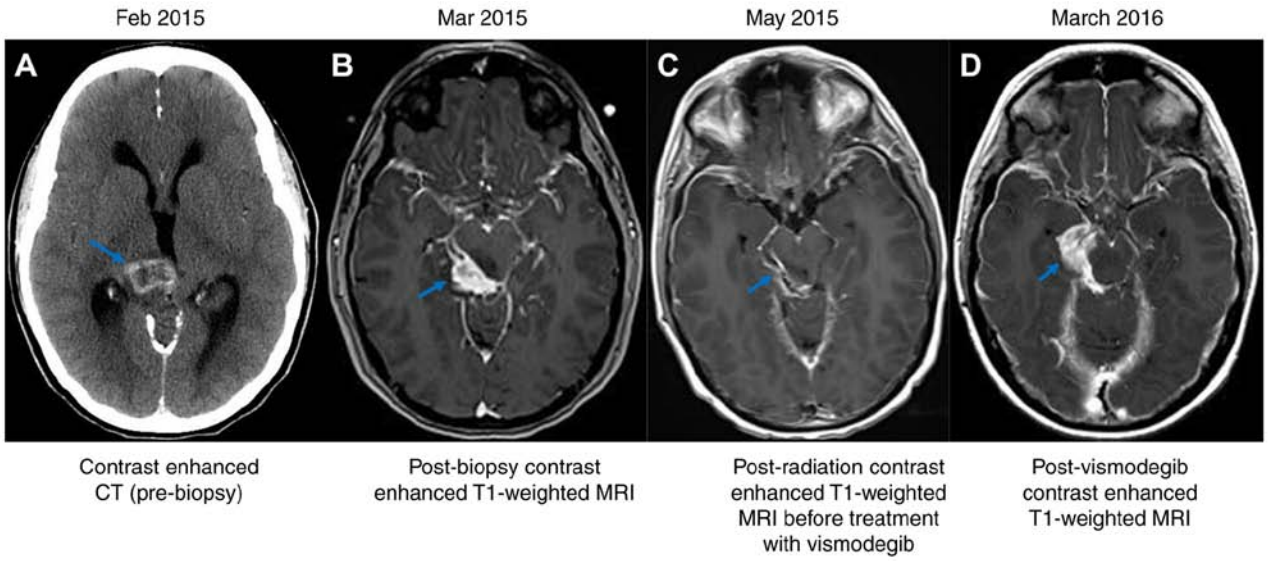

Figure 1. Longitudinal neuroradiological findings. (A) Heterogeneously enhancing mass centered in the medial aspect of the right thalamus (blue arrow) extends inferiorly into the midbrain with mass effect on the tectum resulting in hydrocephalus. Age-advanced dural calcifications also noted which is common in Gorlin syndrome. (B) The mass extends into the right ambient cistern (blue arrow). There is diffuse leptomeningeal enhancement throughout the basal cisterns and along the inferior frontal lobes due to extensive seeding of tumor throughout the subarachnoid space (white arrows). (C) Decreased size of the mass within the right ambient cistern after radiation (blue arrow). There is residual enhancement along the leptomeninges (white arrows). (D) Progression of diffuse leptomeningeal enhancement (white arrows), worst within the right ambient cistern (blue arrow).

by pembrolizamb and bevacizumab, for the remaining four months until she ultimately succumbed to the disease.

Discussion

This study highlights a patient with lifelong sequelae related to a cancer predisposition syndrome and the rare development of a small cell variant glioblastoma. Gorlin syndrome is an autosomal dominant disease caused by inherited mutations in *PTCH1* located on chromosome 9q22.32. PTCH1 is an inhibitor of the smoothened (SMO) protein, which regulates downstream Hedgehog (Hh) pathway activation (15). The Hedgehog pathway is fundamental in embryonic development, with roles in establishing anterior-posterior body axis, cell differentiation, and cell proliferation. Aberrant activation of the Hh pathway was first identified in Gorlin syndrome (16), as it is the primary driver of BCC development (17) and contributes to one-third of medulloblastoma (18), the main clinical manifestations of Gorlin syndrome. Other cancers with Hh pathway activation include pancreas, breast, colon, ovary, and small-cell lung cancer, accounting for one-third of all malignant tumors (15).

Among the three vertebrate Hh genes, sonic hedgehog (Shh), desert hedgehog, and Indian hedgehog, the Shh signaling pathway has been analyzed extensively due to strong Shh activity and expression early in development in the neural tube, and at postnatal stages in the maintenance, proliferation, differentiation, and migration of adult neural stem cells (19). The Ptch gene is induced by Shh, and the accumulation of Ptch blocks the Shh signal (20). Decreases in Gli2 transcription downregulates Shh signal transduction (21). *PTCH1* is altered in ~4% of GBM patients (22), though robust correlation

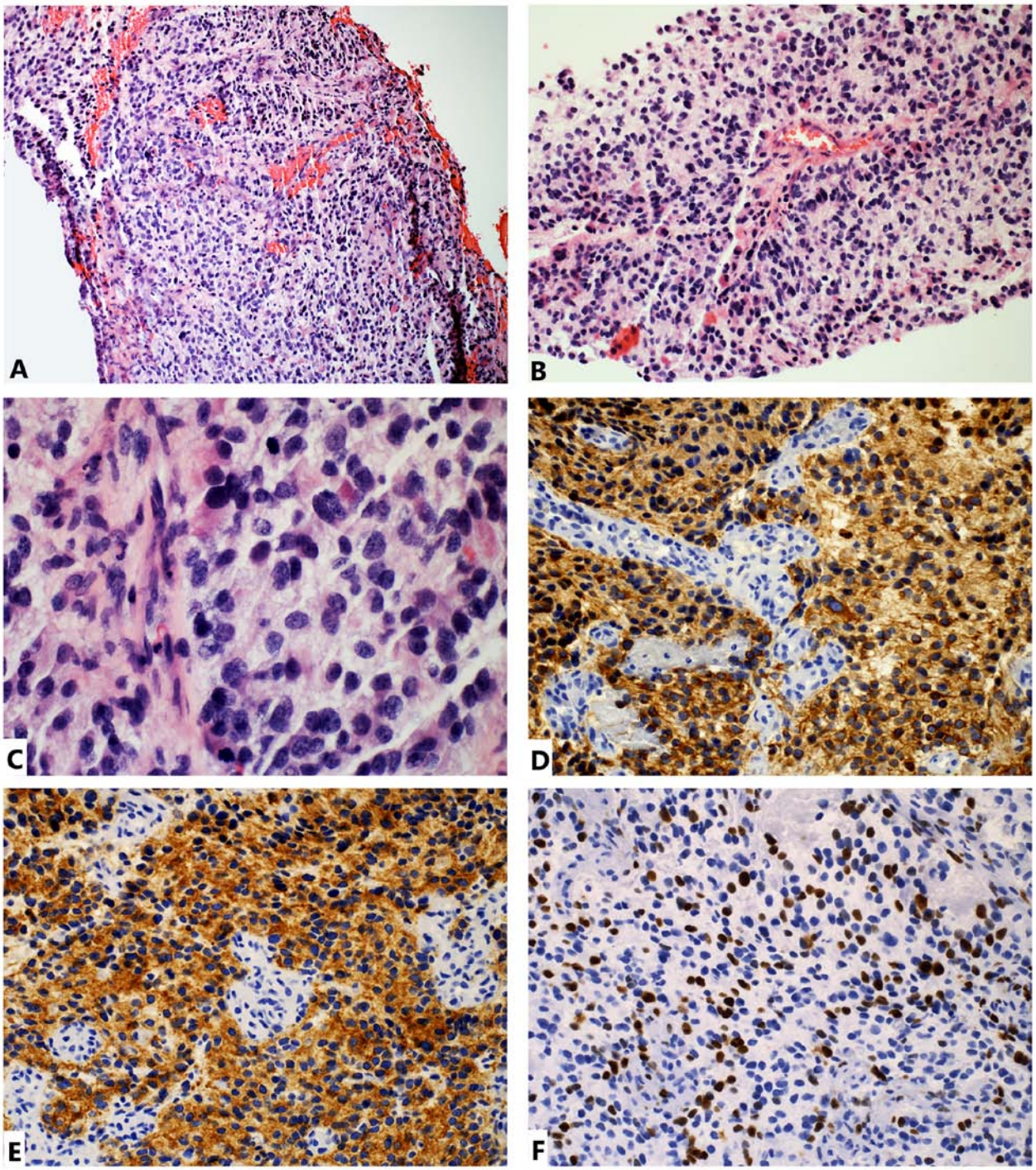

Figure 2. Histopathological and immunohistochemical characterization of tumor. (A) Tumor is a densely cellular malignant glioma with vascular endothelial proliferation (H&E; magnification, x100) and (B) necrosis (H&E; magnification, x100). (C) Tumor cells have small, dark nuclei and scant cytoplasm (H&E; magnification, x200). Immunohistochemical studies revealed strong expression of (D) GFAP (magnification, x200) and (E) synaptophysin (magnification, x200) characterized by diffuse brown staining. (F) Ki-67 labeling index is upwards of 20-30% (magnification, x200). H&E, hematoxylin and eosin; GFAP, glial fibrillary acidic protein.

between PTCH1 and GLI1 mRNA expression has been documented as an indication of the canonical Shh pathway activity in GBM (23). Alterations in components of the SHH pathway are rarely observed in adult or pediatric glioblastoma (22). Based on data from The Cancer Genome Atlas (TCGA, cbioportal.com), of the 281 glioblastomas with copy number and mutation analysis, only two samples harbored loss-of-function driver mutations in *PTCH1* or *SUFU* and only 1% of all cases harbored mutations in upstream components of the SHH pathway (*PTCH1*, *SMO* and *SUFU*) (24). Genomic alterations in the downstream transcriptional activator *GLI1* were more prevalent with 9% of cases harboring amplifications that encompassed this gene. While SHH pathway activation has been demonstrated in GBM through increased GLI1 expression, the role this signaling cascade has in gliomagenesis remains unclear.

Evaluating the efficacy of using Hh pathway inhibitors in brain tumors with evidence of pathway activation remains an

active area of investigation. As with most therapies used for brain tumors, penetration of the blood-brain barrier remains a fundamental limitation; however preclinical mouse model studies have demonstrated robust reductions in tumor growth and improvement in overall survival with Shh pathway inhibitors. For example, PF-5274857, a SMO antagonist, crossed the blood brain barrier and reduced GLI1 activity and prolonged survival in a medulloblastoma mouse model (25). Additionally, a 2013 study demonstrated utility for combined PI3K and Shh pathway inhibition, using the SMO antagonist NVP-LDE225, as a novel therapeutic approach in GBM using patient xenograft mouse models (26).

In 2012, vismodegib became the first Hh pathway inhibitor to gain U.S. Food and Drug Administration (FDA) approval as it demonstrated the ability to penetrate the blood-brain barrier and produce rapid, although transient, reductions in tumor growth for patients with medulloblastoma (27). Phase II clinical trials for adult and pediatric patients with recurrent medulloblastoma demonstrated that vismodegib had activity against tumors which harbor Shh pathway mutations, which resulted in prolonged progression-free survival; however no responses were observed for patients with non-Shh-medulloblastoma (28). Together, these studies highlight the potential of Shh pathway inhibitors for specific patient populations.

Given the rarity of *PTCH1* mutations in patients with glioblastoma, evaluating the role of Hh pathway inhibitors in this patient population would be very challenging in a randomized clinical trial. Nonetheless, given the germline status of these alterations, they represent an attractive target for treatment. In NCT00980343, a randomized phase 0/I trial with 40 patients undergoing resection for recurrent GBM, they evaluated the efficacy of vismodegib treatment on progression-free survival. In an abstract, the authors concluded that the drug was well tolerated however treatment did not improve progression free survival in recurrent GBM (29).

In conclusion, our patient tolerated the combination of vismodegib and temozolomide and later the combination of vismodegib and bevacizumab without adverse events. While we did not observe profound anti-tumor response following the introduction of vismodegib, the combination therapy approach may have contributed to her disease stability over time. Based on our clinical experience, our recommendation is that vismodegib should be considered in combination with standard-of-care therapies for patients with known Gorlin syndrome-associated glioblastomas and Shh pathway mutations.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JTD, RTM, CML, NB, SHR, BBM, AC, ATD, MC, ST and GJL made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; were involved in drafting the manuscript or revising it critically for important intellectual content; and read and approved the final manuscript to be published. Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content; and JTD, RTM, CML, NB, SHR, BBM, AC, ATD, MC, ST and GJL agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GJL and SHR confirm the authenticity of the raw data.

Ethics approval and consent to participate

This retrospective case study was reviewed by the Wake Forest School of Medicine Institutional Review Board and determined to not meet the federal definition of research involving human subject research as outlined in the federal regulations 45 CFR 46.

Patient consent for publication

Not applicable.

Competing interests

Nicholas Britt and Shakti H. Ramkissoon declare employment at Foundation Medicine. The remaining co-authors have no conflicts of interest to declare.

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