PTCH1-GLI1 Fusion–Positive Ovarian Tumor: Report of a Unique Case With Response to Tyrosine Kinase Inhibitor Pazopanib

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ABSTRACT

Recurrent *GLI1* gene fusions have been recently described in a subset of soft tissue tumors showing a distinct monotonous epithelioid morphology with a rich capillary network and frequent S100 protein expression. Three different fusion partners—*ACTB*, *MALAT1*, and *PTCH1*—have been reported with the *PTCH1-GLI1* fusion from 2 patients only, both with head and neck tumors. Herein, we report for the first time a *PTCH1-GLI1* fusion in a primary ovarian tumor from a female patient aged 54 years who presented with a 21-cm right ovarian mass and mesenteric metastasis. The tumor was diagnosed as “favor malignant melanoma” based on histologic examination and extensive immunohistochemistry studies. The patient received 4 cycles of pembrolizumab and 2 cycles of trabectedin but developed multiple metastases. A next-generation sequencing-based assay detected a *PTCH1-GLI1* fusion, which led to a revised pathologic diagnosis and a change of the patient’s management. The patient was switched to the tyrosine kinase inhibitor (TKI) pazopanib to target the sonic hedgehog pathway. Her disease was stable 49 months post TKI therapy. Our case report is the first to show that a tumor with *GLI1* oncogenic activation was sensitive to a TKI. The morphologic and immunohistochemistry similarities of our patient’s tumor to other recently described tumors harboring *GLI1* fusions suggest that these tumors may all belong to the same entity of *GLI1* fusion–positive neoplasms and may be treated similarly.

J Natl Compr Canc Netw 2021;19(9):998–1004
doi: 10.6004/jnccn.2021.7058

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Case Report

A female patient aged 54 years presented with abdominal distension and tenderness, lack of appetite, early satiety, constipation, and urinary frequency. Her serum CA-125 level was 220 U/mL. A CT examination revealed a 21-cm solid and cystic pelvic mass suspected to be of right ovarian origin. Peritoneal carcinomatosis and ascites were also present (Figure 1A, B). The right ovarian mass and attached fallopian tube were received for intraoperative consultation. On gross examination, the mass had a smooth outer surface with multicystic cut surfaces and focal areas of hemorrhage. The cysts were filled with clear watery to viscous fluid. A preliminary diagnosis of possible granulosa cell tumor (GCT) was made based on the morphology. Clinically the patient had no evidence of hyperestrogenism.

The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, lymph node dissection, staging biopsies, and omentectomy and achieved optimal cytoreduction. Laparotomy revealed a large right ovarian mass and normal-appearing left ovary and bilateral fallopian tubes.

Histologic Findings

Histologic examination of the permanent sections showed that the tumor had monotonous epithelioid cells with eosinophilic to clear cytoplasm, arranged in nests, cords, and tubules. There were cystic spaces filled with eosinophilic content, resembling the macrofollicular growth pattern of adult-type GCT and formation of Call-Exner–like bodies. The tumor nests were separated by a rich capillary network and loose edematous stroma in some areas. The mitotic count was up to 39/10 high power fields (HPFs). Areas of tumor necrosis were noted (Figure 2A–C). Extensive metastatic disease was identified in the colonic mesentery, but all pelvic and aortic lymph nodes (30 total) were negative for tumor.

Given the ovarian origin and epithelioid morphology, an initial immunohistochemistry (IHC) workup was performed to rule in/out primary ovarian epithelial, sex-cord stromal, specifically adult-type GCTs, germ cell tumors, and neuroendocrine tumors, or common metastatic

Figure 1. CT with intravenous contrast from patient's initial presentation. **(A)** Preoperative coronal CT images show a large, lobulated, septated cystic and solid mass filling the pelvis and involving both adnexa (circle). **(B)** Preoperative axial CT images of the upper abdomen show peritoneal carcinomatosis (arrow). **(C)** Coronal CT images show recurrence of disease with multiple hepatic metastases (arrows) and bilateral retroperitoneal and pelvic tumor implants (circles) post 3 cycles of pembrolizumab. Incidental small hepatic cyst (arrowhead). **(D)** Coronal CT images show decreased size of multiple necrotic bilateral retroperitoneal and pelvic tumor implants (circles) and necrotic hepatic metastases (arrows) 2 months post pazopanib therapy.

diseases such as malignant melanoma and carcinomas of breast, lung, gastrointestinal, and urinary tract origin. The tumor cells showed patchy but strong positivity for S100 protein and focal positivity for Melan-A and epithelial membrane antigen (EMA) (Figure 2D–F). BRG1 expression was intact, and p53 showed a wild-type staining pattern. All other IHC markers were negative. The tumor was diagnosed as a “malignant neoplasm favor malignant melanoma.” However, the patient had no history of melanoma or current melanoma elsewhere in the body.

Molecular Findings and Response to Targeted Therapy

Based on the immunoreactivity for some of the melanocytic markers, a custom-designed next-generation

sequencing (NGS) panel for malignant melanoma was performed. No mutations were identified.

The patient was started on pembrolizumab. At the beginning of the fourth cycle, PET and CT scans showed disease progression with hepatic and pelvic metastasis and retroperitoneal adenopathy (Figure 1C). At this time (3 months post diagnosis), an RNA-based NGS panel detected a *PTCH1-GLI1* fusion that involved fusion of exon 1 of *PTCH1* with exon 6/7 (alternative splicing) of *GLI1*. The presence of this fusion transcript was confirmed by Sanger sequencing (Figure 3). Two weeks later, information on this patient was sent to the NCI for consultation, and the diagnosis was *GLI1* fusion-positive sarcoma. At the same time, the patient underwent exploratory laparoscopy and tumor debulking due to disease progression. She was then started on trabectedin chemotherapy. After 2 cycles, her follow-up

Figure 2. Morphologic features and immunohistochemistry findings of the ovarian tumor: (A) nested growth pattern with large cystic spaces and malformed blood vessels (H&E, original magnification x2), (B) area with extensive necrosis (H&E, original magnification x2), (C) epithelioid cells with eosinophilic cytoplasm and mitosis (H&E, original magnification x40), (D) strong S100 protein immunoreactivity (original magnification x2), (E) focal weak Melan-A expression (original magnification x2), and (F) focal positivity for epithelial membrane antigen (original magnification x2). Abbreviation: H&E, hematoxylin-eosin.

CT scan showed continued disease progression in the liver and pelvis. Given the lack of response to immunotherapy and chemotherapy, the patient was switched to 800 mg/d of pazopanib, a multitarget tyrosine kinase inhibitor (TKI). A CT scan 2 months post pazopanib therapy showed significant response with necrotic liver lesions and resolved peritoneal nodules (Figure 1D). During pazopanib treatment, the patient developed severe headache and nausea. The dosage was reduced to 400 mg/d and later maintained at 600 mg/d. Fourteen months post pazopanib therapy, a CT scan showed no evidence of disease. The patient then self-discontinued pazopanib and experienced recurrence in the liver, mesentery, and retroperitoneal lymph nodes. She was restarted on 600 mg/d pazopanib and showed recontinguation of response to therapy. Her most recent CT scan

(January 2021), which was performed 49 months post initial histologic diagnosis and 41 months post pazopanib therapy, showed stable disease.

The tumor was later tested by an expanded NGS panel that had 214 genes and could detect copy number variations (CNVs). No pathogenic variants or CNVs were detected.

Background

GLI1 encodes a transcription factor in the sonic hedgehog (SHH) signaling pathway. The binding of SHH to its receptor patched (PTCH) leads to accumulation of smoothened (SMO), which in turn, results in the activation of *GLI* and the SHH signaling pathway.¹ The SHH pathway regulates key events during embryonic development, organogenesis, tissue repair, and

Figure 3. PTCH1-GLI1 gene fusion identified in the tumor. Integrative genome viewer of fusion detected by the Archer FusionPlex Sarcoma Kit (top). Breakpoints (indicated by the vertical line) were in exon 1 of the PTCH1 gene and exon 6/7 of the GLI1 gene (middle). Electrogram of Sanger sequencing confirmation of the PTCH1-GLI1 fusion products (bottom).

the maintenance of stem cells.² It has also been shown to be involved in the tumorigenesis of breast, prostate, and small cell lung cancers and may serve as a potential therapeutic target.^{1,3–6}

Activation of the SHH signaling pathway in tumors by gene fusions involving *GLI1* was first described by Dahlén et al⁷ in 5 spindle-cell neoplasms with perivascular arrangement, consistent actin expression, and pericytic features by electron microscopy. The fusion partner was *ACTB*, and the described neoplasms were diagnosed as pericytomas with t(7;12) translocation.

Subsequently, Antonescu et al⁸ reported a series of 6 soft tissue malignant epithelioid neoplasms with genomic rearrangements involving the *GLI1* gene. These *GLI1* fusion-positive tumors predominantly occurred in the soft tissue, with rare tumors and a single tumor reported in the bone, stomach, and ovary.^{9–11}

Histologically, the neoplastic cells in the study by Antonescu et al⁸ grew in nests and solid sheets, with cystic spaces and a rich capillary network, and in a myxoid background. Among the 6 reported neoplasms, 4 showed strong and diffuse expression of the S100 protein and no consistent positivity for other markers by IHC; 3 patients who had follow-up information developed lymph node metastases.⁸

Only 2 patients with *PTCH1-GLI1* fusion have been reported. The first, a female patient aged 32 years, had a submandibular mass.⁸ The tumor was S100 positive, had a mitotic index of 6 per 10 HPFs, and tumor necrosis. The patient later developed local recurrence and distant metastases to the lymph nodes and lung. The second, a male patient aged 38 years, had a tongue mass.¹² The tumor also expressed the S100 protein but had a low mitotic count (1/10 HPFs), with no tumor necrosis or recurrence/metastasis.

Herein, we report another patient with a positive *PTCH1-GLI1* fusion: a female patient aged 54 years with an ovarian mass identified by an NGS-based assay. Our case report is the first to show that a tumor with *GLI1* oncogenic fusion was sensitive to a TKI.

IHC and Molecular Studies

IHC studies were performed in our clinical laboratory using standard protocols. Total nucleic acid isolated from formalin-fixed, paraffin-embedded tissue was used for NGS libraries preparation. Two custom-designed DNA-based NGS assays were used for the detection of mutations. The first was a 25-gene panel for the detection of recurrent variants in malignant melanomas. It covered the complete coding sequence of *BAP1* and the hotspot regions of the remaining 24 genes. Twenty nanograms of DNA were used to generate the library, and sequencing was performed on the Ion S5 XL System (Thermo Fisher Scientific Inc.). Data were analyzed using Ion Torrent Suite Software 5.10 (Thermo Fisher Scientific Inc.) and the laboratory-developed Variant Impact Analysis pipeline. The second assay was a 214-gene panel covering the full coding sequence of 94 genes and the hotspot regions of 120 genes, and it could detect CNV in 49 genes. Forty nanograms of DNA were used to generate the library, and sequencing was performed on the NextSeq (Illumina, Inc.). Data were analyzed using the Burrows Wheeler Aligner and PISCES Variant Caller version 2.1 (Illumina, Inc.).

The Archer FusionPlex Sarcoma Kit (Invitae) was used for the detection of gene fusions as described previously.¹³ The presence of the *PTCH1-GLI1* fusion was confirmed by Sanger sequencing.

Discussion

The hedgehog signaling pathway is one of the major pathways in embryonic development. Increasing evidence has also established its role in human carcinogenesis.^{1,7–10} Both *PTCH1* and *GLI1* encode for protein components of this pathway. *PTCH1* is considered a tumor suppressor, and *GLI1* is regulated by *TP53*. Neoplasms associated with SHH deregulation can be caused by ligand-independent, mutation-driven mechanisms such as in Gorlin syndrome which is caused by germline *PTCH1* mutations, and sporadic cancers such as basal cell carcinoma and medulloblastoma.^{10,14} Other mechanisms include ligand-dependent autocrine and paracrine activation in solid tumors such as carcinomas of the pancreas, upper gastrointestinal tract, breast, prostate, ovary, and lung.^{3–6,14,15} Activation of the SHH signaling pathway by gene fusions involving *GLI1* likely represents a third mechanism of SHH pathway activation. *GLI1* has 12 domains. Its DNA-binding zinc finger domains are encoded by exons 7 to 10, and the transactivation domain is encoded by exon 12. Similar to other *GLI1* fusions reported in the literature,⁸ the breakpoint of *GLI1* in our patient's tumor was located upstream of exon 6/7, so the key domain of *GLI1* was retained in the fusion gene and the fusion transcript product was most likely functional.

The *GLI1* fusion-positive neoplasms reported in the literature had a predilection for the soft tissue, especially the head and neck region. Grossly, the tumors usually had a solid growth pattern with cystic cut surfaces. Histologically, the cells tended to grow in nests, cords, and tubules; typically were monotonous epithelioid cells with eosinophilic and clear cytoplasm; and had a perivascular pattern resembling pericytic or myoepithelial tumors. The presence of dilated and malformed blood vessels was a common feature. Extensive immunophenotyping has been performed on most of the *GLI1* fusion-positive neoplasms reported in the literature. S100 protein expression was seen in two-thirds of tumors, and the expression of cytokeratin and immunomarkers of other lineages were rarely observed.^{1,7–10} In addition to tumors in the soft tissue, tumors of gastric origin have been reported.¹⁶ These *GLI1* fusion-positive tumors usually had an indolent progression but with metastatic potential, and metastasis usually involved the lymph nodes.⁷

In normal tissue, *GLI1* expression is restricted to the fallopian tubes, myometrium, and testis. Interestingly, only 1 *GLI1* fusion-positive tumor (*ACTB-GLI1*)

was reported in these organs, which was an ovarian tumor from a female patient aged 11 years.¹⁷ Her tumor had a low mitotic count and benign behavior. Our patient had the second *GLI1* fusion-positive tumor of gynecologic origin. Unlike the younger patient, our patient had widespread metastatic disease at presentation. Her tumor had a high mitotic count and extensive necrosis characteristic of a high-grade sarcoma.

GLI1 amplification has been described as a possible fourth mechanism of SHH pathway activation.¹⁸ The same group of authors⁸ who reported *GLI1* fusion-positive neoplasms encountered a subset of *GLI1* fusion-negative soft tissue tumors that had similar epithelioid cells but with focal spindle-cell morphology, a higher mitotic rate, necrosis, and an inconsistent IHC profile.¹⁸ Combined NGS testing and fluorescence in situ hybridization revealed that these tumors had *GLI1* amplification with frequent coamplification of *MDM2* and *CDK4*. Similar findings were reported by another group.¹⁹ *GLI1* amplification could not be measured using our NGS panel, but CNVs in *MDM2*, *CDK4*, and 47 genes were assessed and found to be normal. No amplification or pathogenic variants were identified in our patient's tumor, supporting the above findings that amplification and fusion may represent 2 mechanisms of SHH pathway activation. The lack of pathogenic variants and CNV in our patient's tumor also suggested that the *GLI1* fusion product was the oncogenic driver of the sarcoma.

The *GLI* family of transcription factors includes *GLI1*, *GLI2*, and *GLI3*. A recent study in ovarian sclerosing stromal tumors identified recurrent *FHL2-GLI2* fusion in up to 65% of tumors (n=26).²⁰ In vitro studies showed that the fusion transcript was likely the oncogenic driver. More important, targeted inhibition of the SHH pathway resulted in the reversal of these oncogenic properties.²⁰

Hedgehog pathway inhibitors are currently being studied as potential cancer therapies. Cyclopamine and its derivatives, which bind and inhibit SMO, were shown to possibly counteract the results of an altered *PTCH1* gene and GLI antagonist GANT61, a small-molecule inhibitor, may be able to reduce the unchecked *GLI1* and *GLI2* transcriptional activity that accompanies alterations in *GLI1*.²¹ The FDA approval of larotrectinib as a pan-cancer drug for *NTRK* fusion-positive adult and pediatric solid tumors led us to expect that these seemingly unrelated *GLI1* fusion-positive tumors might also be treated using therapies targeting the SHH pathway.

Pazopanib is an oral multitarget angiogenesis inhibitor that has been approved by the FDA for the treatment of patients with advanced soft tissue tumors

Figure 4. Proposed mechanism of pazopanib action on *GLI1*-fusion-positive tumor. *PTCH1-GLI1* fusion led to overexpression of *GLI1* (double red arrows) and translocation of *GLI1* into the nucleus, resulting in activation of the SHH pathway to promote cell proliferation and angiogenesis. *GLI1* may activate the PI3K and MAPK pathways through an autocrine loop by promoting *PDGFR* β phosphorylation and upregulation of *VEGFR* (green dotted arrows), ultimately leading to tumorigenesis. The antitumor effect of pazopanib in *GLI1* fusion-positive tumor is likely through inhibiting the *GLI1*-mediated activation of the PI3K and MAPK pathways (red lines with bar). The SHH pathway is normally inhibited by *PTCH1* through inhibition of smoothened. *PTCH1-GLI1* releases the inhibition, leading to activation of the SHH pathway. GANT61 inhibits the SHH pathway through direct inhibition of overexpressed *GLI1*.

Abbreviations: ???, unknown genes; GANT61, GLI antagonist; KIT, KIT protooncogene, receptor tyrosine kinase; PDGFR, platelet-derived growth factor receptor; SHH, sonic hedgehog; SMO, smoothened; VEGFR, vascular endothelial growth factor receptor.

and clear cell renal cell carcinoma.²² It is a second-generation TKI that blocks tumor growth and angiogenesis through the inhibition of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3; platelet-derived growth factor receptor (PDGFR) α and PDGFR β ; and KIT, among others, subsequently leading to the inhibition of phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways.²³ To elucidate the mechanism underlying the antitumor activity of pazopanib, Suehara et al¹⁹ performed integrative and functional analyses on patients with advanced sarcomas and complete response to pazopanib. They identified 12q13-14 amplification in 2 patients: 1 had coexisting *PDGFRA* amplification and long-term stable disease, and the other had coexisting *CDK4* amplification and complete response with no aberration in any known targets of pazopanib. The 12q13-14 region does not contain the known pazopanib-target genes but does include *GLI1*. Quantitative PCR showed an overexpression of *GLI1* mRNA in both patients and *GLI1*-transfected 3T3 cells showed transforming potential, increased PDGFR β expression, and phosphorylation.¹⁹ In vivo study showed that pazopanib could inhibit cell proliferation and PDGFR β phosphorylation in *GLI1*-overexpressed cells.¹⁹ These exciting discoveries paved the way to our understanding of the inhibitory effect of pazopanib on the SHH pathway.

The discovery of a truncated *GLI1* (*tGLI1*) and its effect on VEGFR-2 expression may also shed some light on the mechanism of pazopanib action. *tGLI1* is an alternatively transcribed *GLI1* that lacks exons 3 and 4 and is expressed exclusively in tumor cells.^{24,25} *tGLI1* was shown to upregulate VEGFR-1 and VEGFR-2 expression, leading to a distinct autocrine loop that promoted angiogenesis and cell growth.²⁵ The fusion transcript in our patient's tumor lacked exons 1–5 of the *GLI1* gene. It is possible that the fusion product functions as a *tGLI1*, resulting in VEGFR upregulation.

In our patient, the *GLI1* fusion product may have acted similarly. *PTCH1-GLI1* fusion led to overexpression of *GLI1* and translocation of *GLI1* into the nucleus, resulting in the activation of the SHH pathway. *GLI1* may activate the PI3K and MAPK pathways through an autocrine loop by promoting PDGFR β phosphorylation and upregulation of VEGFR, ultimately leading to tumorigenesis. The antitumor effect of pazopanib could result from the inhibition of the MAPK and PI3K pathways through direct targeting of the receptor tyrosine kinases PDGFR β and VEGFR (Figure 4). No SHH inhibitor was used in this patient, suggesting that although *GLI1* is a component of the SHH pathway, the oncogenic activity of the *GLI1* fusion transcript was mainly through activation of the MAPK and PIK pathways. The rich capillary network in *GLI1* fusion-positive

tumors also supports the upregulation of angiogenesis in this type of tumor.

Conclusions

The dramatic response of our patient's advanced disease to pazopanib provided evidence for the first time that the *GLI1* fusion transcript product was the underlying oncogenic mechanism for tumorigenesis and could serve as a target for therapy. The histologic and immunophenotypic similarities among the *GLI1* fusion-positive and *GLI1* amplification-positive tumors suggest that they might be treated similarly using an FDA-approved multitarget TKI such as pazopanib. Additional studies such as gene expression profiling, proteomics, and functional studies may help identify

other components involved in *GLI1* fusion-mediated oncogenesis and facilitate the development of targeted therapies.

Acknowledgments

The authors acknowledge Markku Miettinen, MD, PhD, Laboratory of Pathology, NCI/NIH, for providing expert consultation.

Submitted November 24, 2020; final revision received April 9, 2021; accepted for publication May 3, 2021.

Disclosures: The authors have disclosed that they have not received any financial considerations from any person or organization to support the preparation, analysis, results, or discussion of this article.

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