# Recurrent Ascites in a Patient With Low-grade Astrocytoma and Ventriculo-Peritoneal Shunt Treated With the Multikinase Inhibitor Sorafenib

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**Summary:** This report describes a 6-year-old boy with disseminated low-grade astrocytoma and ventriculo-peritoneal shunt, who developed recurrent ascites while receiving sorafenib on a clinical trial. Laboratory analysis of the peritoneal fluid showed no elevation of protein content and no evidence of underlying infection or tumor dissemination. This report highlights ascites as a previously unrecognized adverse reaction to sorafenib in a patient with a ventriculo-peritoneal shunt. We conclude that such patients should be closely monitored for this complication when treated with sorafenib.

**Key Words:** pediatric low-grade astrocytoma, ascites, sorafenib, toxicity

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Sorafenib is a small molecule multikinase inhibitor targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, c-kit, and rapidly accelerated fibrosarcoma kinase, with strong anti-angiogenic properties. It was granted approval by the US Food and Drug Administration in 2005 and 2007 for use in advanced renal cell and unresectable hepatocellular carcinoma, respectively.[1,2] Sorafenib shares a number of common side effects with similar multikinase inhibitors, such as sunitinib and pazopanib, including diarrhea, rash, and hypertension.

We describe the case of a young pediatric patient treated with sorafenib for progressive low-grade astrocytoma on a clinical trial who developed recurrent ascites within the first 2 months of treatment.

## CASE REPORT

A 6-year-old boy with a progressive and disseminated low-grade astrocytoma was enrolled on our phase II clinical trial with sorafenib for children and young adults with recurrent or progressive low-grade astrocytomas (ClinicalTrials.gov identifier NCT01338857).

His past medical history was notable for chronic gastrointestinal symptoms, including frequent constipation and intermittent emesis, without a known malabsorption syndrome or other gastrointestinal pathology.

He was initially diagnosed at 2 years of age with a history of torticollis and right head tilt since birth, and an approximately 6- to 12-month history of ataxia. The brain and spine magnetic resonance imaging (MRI) disclosed a large posterior fossa mass with spinal dissemination, for which he underwent partial resection. The pathology was consistent with a low-grade astrocytoma with piloid features. Molecular genetic testing of the tumor showed wild-type BRAF and absence of a KIAA-BRAF tandem duplication. A KIAA-BRAF tandem duplication at chromosome 7q34 is present in the majority of pilocytic astrocytomas and produces a fusion gene between KIAA1549 and the kinase domain of BRAF, resulting in the constitutive activation of BRAF and the downstream effector MEK/ERK signaling pathway.[3]

One month after the initial surgery, the patient required placement of a ventriculo-peritoneal (VP) shunt to relieve progressing hydrocephalus. He was subsequently treated with carboplatin and vincristine for approximately 1 year. At 5 years of age, he suffered from tumor progression both in the brain and spine, as well as an enlarging, trapped fourth ventricle. After surgical decompression of the trapped fourth ventricle, a stent was placed from the fenestrated fourth ventricle to the cervical subarachnoid space. The stenting was not effective, however, and a catheter was placed into the dilated fourth ventricle and connected to the pre-existing VP shunt to drain the cavity. After recovery, he received chemotherapy with thioguanine, procarbazine, CCNU, and vincristine, but came off treatment after 4 cycles due to progressive disease. He subsequently enrolled on our phase II clinical trial with sorafenib for progressive low-grade glioma.

Sorafenib was administered at 200 mg/m$^2$/dose orally twice daily. The patient was monitored weekly with clinical examinations and screening laboratories during the first 4-week cycle of the protocol therapy. He experienced expected minor toxicity on treatment with loose stools, hypokalemia, hypophosphatemia, facial rash, stomatitis, dry skin, alopecia, and pancytopenia (all grade 1). His baseline intermittent emesis remained unchanged.

At the completion of his fourth week on sorafenib, abdominal distension was evident on physical examination. His abdomen was distended, but remained soft and nontender with hyperactive bowel sounds, without any evidence of peripheral edema. The complete blood count and comprehensive metabolic panel including hepatorenal function (total protein, albumin, creatinine) were normal. A 1.5 kg weight gain was noted since starting sorafenib. Abdominal x-ray revealed few prominent loops of air-filled small bowel in the right mid-abdomen without bowel obstruction. Abdominal ultrasound disclosed a moderate to large amount of complex abdominal ascites without any other abnormalities, including a well-visualized VP-shunt catheter without pseudocyst formation (Fig. 1). Paracentesis yielded 1.8 L of fluid with protein of 1 g/dL, white blood cell count of 23/mm$^3$, glucose of 94 mg/dL, albumin of 0.7 g/dL, and negative bacterial and fungal cultures. Cytology was negative

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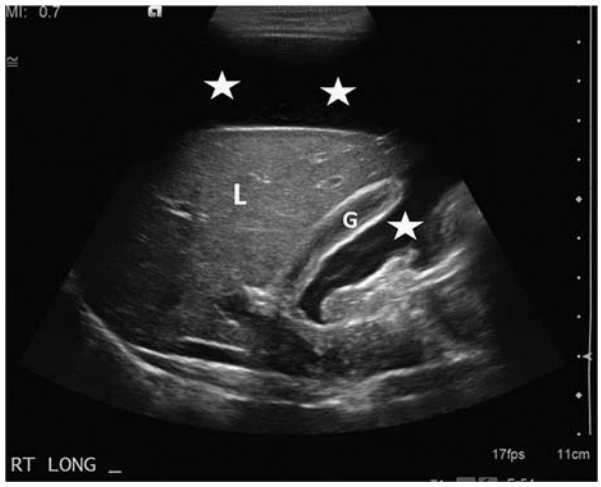


**FIGURE 1.** Abdominal sonogram obtained after 4 weeks on sorafenib. Longitudinal view of the liver (L) and gallbladder (G), demonstrating a large amount of ascites within the abdomen (stars).

for tumor cells. A follow-up abdominal ultrasound 1 week later did not demonstrate any fluid reaccumulation and sorafenib was resumed at the initial dose.

Subsequently, his abdominal girth again increased, from 51 cm at the umbilicus before restarting study drug to 54.5 cm 2 weeks later. The patient remained asymptomatic and afebrile, with no laboratory evidence of abnormal hepatorenal function. A repeat abdominal ultrasound confirmed reaccumulation of a large amount of intraperitoneal fluid and sorafenib was again stopped. A follow-up spine MRI showed a significant amount of reaccumulated peritoneal fluid and the brain MRI disclosed progressive growth of predominantly nonenhancing tumor (Fig. 2). The patient came off study due to progressive disease and sorafenib was discontinued permanently, resulting in spontaneous resolution of abdominal distension over the next few weeks. Treatment was subsequently switched to bevacizumab and irinotecan, and the patient remains on this regimen without further reaccumulation of ascites, with a total follow-up period of >19 months since discontinuing sorafenib.

## DISCUSSION

Ascites arising as a complication from a VP shunt has been recognized for many decades since its first report in 1967 by Ames,[4] and observed in patients with or without an underlying neoplasm.[5–11] The timing of ascites onset after shunt placement varies greatly and has been reported from the first postoperative day to several years after shunt placement.[7] Overall, it remains a rare complication with diverse and possibly multifactorial causes. Two well-recognized causes, infection, and tumor seeding, need to be carefully investigated and

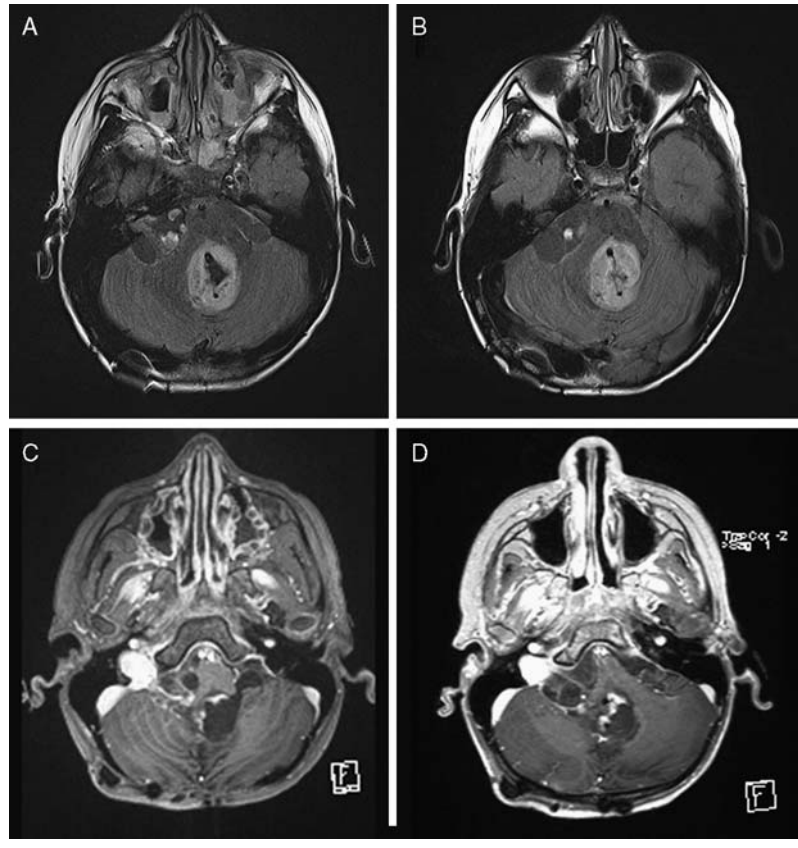


**FIGURE 2.** Neuroimaging of the patient's primary pilocytic astrocytoma at baseline and after 8 weeks on sorafenib. Magnetic resonance imaging axial views of (A) fluid-attenuated inversion recovery (FLAIR) and (C) T1-weighted postcontrast selected images obtained before initiating treatment showing the disseminated enhancing tumor in the fourth ventricle and within the dorsal midbrain, associated with an encysted fluid collection in the right cerebellopontine angle into the right internal auditory canal. Similar (B) FLAIR and (D) T1-weighted postcontrast axial planes after 2 cycles of treatment with sorafenib showing interval increase in the size of the area of abnormal FLAIR hyperintensity with further effacement of the fourth ventricle and thickening of the nodular contrast enhancement, consistent with tumor progression.

appropriately treated. The differential diagnoses include cerebrospinal fluid (CSF) malabsorption due to abdominal pathology caused by previous abdominal surgery or multiple shunt revisions.[7] Infection with subsequent peritonitis is the most commonly reported culprit, whereas sterile ascites is rare. Other reported etiologies in patients with sterile ascites have included immune reactions to the shunt and elevated CSF protein levels, either from an abnormal blood-brain barrier in the tumor blood vessels or from protein production by the tumor itself, both leading to impaired fluid absorption capacity of the peritoneal cavity.[6] In our patient, tumor seeding and infection were ruled out by peritoneal fluid sampling. The protein level in the paracentesis fluid was within the normal range, arguing against an elevated protein level in the CSF as a causative factor.

VEGF expression by some tumors has been postulated to elicit peritoneal hyperpermeability and fluid leakage, which has been suggested to contribute to the development of ascites in the presence of a CNS tumor-related VP shunt.[6,12] In the absence of a VP shunt, ascites among other fluid retention complications has also been observed in adults treated for recurrent or refractory epithelial ovarian cancer or primary peritoneal cancer with the abl (including bcr-abl fusion protein), c-kit, and platelet-derived growth factor receptor modulator imatinib.[13,14] Posadas et al[14] found a 25% rate of developing ascites in their patients, including exacerbation of preexisting ascites and new onset ascites. Progressive disease is typically thought to represent the cause of de novo ascites in ovarian cancer patients. Indeed, Posadas and colleagues identified tumor cells in 3 out of 4 patients' peritoneal fluid. The observed prompt reversibility upon withholding drug therapy in these patients made the authors conclude that imatinib treatment can cause and/or exacerbate ascites, especially malignant ascites. In their experience, ascites and pleural effusions developed between 2 and 6 months of drug therapy. Of note, general fluid retention and edema are well-recognized toxicities observed specifically with imatinib. However, ascites has also been reported in patients treated with similar multitargeted tyrosine kinase inhibitors, that is, with sunitinib in the setting of advanced gastric cancer or mixed advanced solid malignancies[15,16] and with pazopanib in recurrent ovarian cancer.[17] In contrast with these observations, therapeutic targeting of VEGF had previously been proposed to be beneficial for the treatment of malignant ascites.[18,19]

The use of sorafenib in our pediatric patient led to multiply recurrent, reversible ascites without evidence of peritoneal tumor seeding. To our knowledge, this is the first patient report of abdominal ascites occurring in a patient with a nonabdominal tumor treated with sorafenib. Although the precise mechanism is unclear, the use of other multikinase inhibitors similar to sorafenib might also put patients at risk of developing this complication. A literature review of Pubmed and Embase, however, did not disclose previous reports of ascites occurring in brain tumor patients treated with sorafenib or cediranib, a vascular endothelial growth factor receptor inhibitor. We conclude that patients receiving sorafenib or similar agents, especially with VP shunts or other intra-abdominal susceptibility or pathology, should be closely monitored for this complication. It remains to be seen if this toxicity is unique to sorafenib or may also occur with next-generation BRAF inhibitors, which are currently being investigated for the treatment of astrocytomas in children and adults.

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