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Imbalance and Gait Disturbance from Tyrosine Kinase Inhibition in Hepatocellular Cancer

Rebecca A. Miksad,

Division of Oncology, Beth Israel Deaconess Medical Center, Shapiro 9, Boston, MA 02215, USA

Kuan-Chi Lai,

Division of Oncology, Beth Israel Deaconess Medical Center, Shapiro 9, Boston, MA 02215, USA

Marion C. Stein,

Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Megan E. Healy,

Division of Oncology, Beth Israel Deaconess Medical Center, Shapiro 9, Boston, MA 02215, USA

Rafael Rojas,

Department of Radiology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Katherine M. Krajewski, and

Department of Radiology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Andrew X. Zhu

Division of Oncology, Massachusetts General Hospital, Boston, MA, USA

Rebecca A. Miksad: rmiksad@bidmc.harvard.edu

A 69-year-old male with chronic autoimmune hepatitis and hepatocellular cancer presented with progressive imbalance and gait disturbance 2 weeks after initiating treatment with the receptor tyrosine kinase inhibitor agent sunitinib malate (SU11248, Sutent; Pfizer Pharmaceuticals Group, New York, NY) in an Institutional Review Board approved Phase II clinical trial [1]. Approved for the treatment of metastatic renal cell cancer and gastrointestinal stromal tumors, sunitinib inhibits vascular endothelial growth factor receptors (VEGFR-1 and 2), platelet-derived growth factor receptors α and β , c-Kit, and FLT-3 [2–4].

Our patient was originally diagnosed with hepatocellular carcinoma (HCC) in April 2007 when he presented with 3 months of fatigue, right upper quadrant pain, pruritus, and a 10 lb weight loss. His past medical history was significant for well-controlled cardiovascular disease and diabetes, and two episodes of vertigo 10 years previously. The patient did not have hepatitis B or C, and he did not have a history of smoking, alcohol use, or intravenous drug use. Computed tomography (CT) revealed an 11.6-cm solitary liver lesion with arterial enhancement, his alpha-fetoprotein (AFP) was 466 ng/mL, and biopsy confirmed HCC. He underwent a left hepatic lobectomy, and pathology confirmed an 11 cm well-differentiated HCC with large vessel invasion but negative margins and two negative lymph nodes. Postoperatively, the patient's AFP normalized to 1.3 ng/mL.

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Three months after resection, the patient's AFP rose to 27.1 ng/mL and CT showed multiple lesions in the right lobe of the liver ranging from 1.1 to 5.6 cm in size, and encompassing less than 50% of the liver. Although there was no portal vein thrombosis or metastatic disease, a 2.5×5.3 cm right phrenic lymph node was noted. His laboratory parameters were significant only for alanine transaminase (ALT) of 43 IU/L (normal, 0 to 40 IU/L), aspartate transaminase (AST) of 70 IU/L (normal, 0 to 40 IU/L), and albumin of 3 g/dL (normal, 3.4–4.8 g/dL). Bilirubin and prothrombin time were within normal limits. At the time of recurrence, he had no neurologic or other symptoms, his Eastern Cooperative Oncology Group performance status was zero and there were no significant findings on physical exam, including no encephalopathy and no ascites. The patient consented to participate in an open label Phase II clinical trial of sunitinib malate (37.5 mg by mouth daily for 4 weeks every 6 weeks) for HCC, and he initiated treatment after meeting all eligibility criteria.

The patient first complained of mild gait imbalance on day 15 of sunitinib therapy, although he had no other symptoms and his physical and laboratory exams were unchanged. Over the next 7 days, the patient noted worsening balance and gait disturbance such that he bumped into walls while walking, could not walk unassisted, had two witnessed falls, and was unable to dress himself while standing. His wife noted that he would lean to either side while seated. Over this 7-day time course, the patient also noted new nausea, diarrhea, headaches, and yellow skin discoloration, consistent with known sunitinib side effects. Although the nausea, diarrhea, and headache were largely controlled with standard outpatient treatment, sunitinib was discontinued on day 17, the patient was admitted to the hospital on day 22 because for progressive imbalance and gait disturbance.

On admission, the patient presented in a wheelchair and complained that he felt as though he was “on a moving train.” He was emphatic that his gait was impaired by imbalance and he specifically denied vertigo, lightheadedness, tinnitus, and focal weakness. Physical exam, including vital signs, was unremarkable except for neurologic findings. When walking, the patient was frequently unstable to either side, although his base was only mildly widened. In particular, he could not negotiate two steps of tandem gait before veering to either side or falling. He could not stand alone on either foot, and he manifested a positive Romberg. In addition, he exhibited moderate truncal instability to either side when seated. Pertinent negative neurologic findings were: no alterations in mental status, no hearing loss over baseline, no diplopia, no pathologic nystagmus, no dysarthria, and no appendicular ataxia (e.g., normal finger-nose-finger and heel-to-shin testing). Power and reflexes were normal. Although he had mild loss of pin prick and vibratory sensation in the feet consistent with mild diabetic peripheral neuropathy, his proprioception was intact. He had minor, chronic tremulousness, but no asterixis.

Magnetic resonance imaging (MRI) of the brain was negative for metastatic disease, reversible posterior leukoencephalopathy (RPLS), leptomeningeal disease, and infection (Fig. 1). In addition, there were no cerebellar or vascular abnormalities and no evidence of infarction or hemorrhage. A nonspecific 11 mm focus of increased signal of the dura located over the right post-central gyrus was noted on fluid-attenuated inversion recovery images (FLAIR), although these findings were not seen 6 days later on follow-up contrast-enhanced CT (Fig. 2). Laboratory evaluation was notable for an absolute granulocyte count=920/uL, ALT=66 IU/L, AST=60 IU/L, total bilirubin=2.1 mg/dL, and sodium=128 mmol/L. Electro-nystagmogram and other otovestibular testing were not pursued because it was unlikely these tests would distinguish between bilateral peripheral vestibulopathy and central vestibulopathy.

Three days after hospitalization, the patient's imbalance and gait disturbance improved and he was able to walk unassisted. In addition, all of the patient's non-neurologic symptoms

and laboratory abnormalities completely resolved in this time period. However, he had residual gait and balance symptoms for an additional 2 months. The patient was not rechallenged with sunitinib, and he was removed from the clinical trial.

The patient's neurologic presentation was most consistent with an isolated or pure bilateral peripheral vestibulopathy. In addition, there was no evidence of cerebral, cerebellar, brain stem, psychiatric, systemic, or middle ear causes of imbalance and gait disturbance. The onset and time course of his neurologic symptoms correlated with sunitinib exposure and closely followed the onset and time course of known sunitinib side effects. Therefore, a toxic peripheral vestibulopathy from sunitinib exposure was diagnosed as the cause of this patient's imbalance and gait disturbance.

To our knowledge, this is the first report of imbalance and gait disturbance secondary to sunitinib. Sunitinib is generally well tolerated, and the most common neurologic side effects are dizziness, headache, and insomnia [5]. In a metastatic renal cell cancer trial, dizziness was reported in 7% of patients receiving sunitinib compared with 12% of patients receiving interferon alpha, with grades 3 and 4 dizziness occurring in less than 1% of patients [5, 6]. It is possible that some patients who reported dizziness may have been manifesting incipient symptoms of a toxic peripheral vestibulopathy.

RPLS has been reported as a rare and potentially fatal neurologic complication of sunitinib [7, 8]. RPLS has also been reported secondary to immunosuppressive drugs, cytotoxic agents, bevacizumab, and sorafenib, a tyrosine kinase inhibitor agent approved for the treatment of advanced hepatocellular cancer [9–11]. The potential etiology of RPLS is unclear, but may be caused by the antiangiogenic and pro-hypertension effects of sunitinib. RPLS is identified by symmetrical and reversible characteristic findings on MRI and CT in the setting of headache, seizure, impaired vision and acute hypertension [10]. Our patient did not fit this clinical picture.

Reversible cognitive disorders have been described in three elderly patients treated with sunitinib for metastatic renal cell cancer, all of which resolved after discontinuation of sunitinib [12]. The authors of these case reports hypothesized that sunitinib may decrease cerebral blood flow through VEGFR-2-mediated vasoconstriction in the setting of preexisting cerebral vascular disease. It is possible that our patient's underlying diabetic neuropathy and/or vascular disease contributed to the development of his neurologic symptoms.

Animal studies suggest that sunitinib and its metabolites readily cross the blood-brain barrier, with concentrations in the brain reaching 30–40% of plasma concentrations [13]. However, case reports of sunitinib for renal cell cancer metastatic to the brain describe variable responses, suggesting that clinically significant concentrations may not always be achieved [14–18]. The association of increased intracerebral hemorrhage in patients with renal cell cancer brain metastases may be related sunitinib's VEGF inhibition in the cerebral vasculature [19]. VEGF appears to increase the permeability of the blood-brain barrier and promote angiogenesis in the ischemic brain [20].

The small focus of increased signal consistent with edema on FLAIR images (white arrow) on our patient's MRI is superficial and appears to be bisected by a blood vessel (black arrow) (Fig. 1). Because this finding is not near cerebellar or vestibular structures, we do not believe that it is directly related to our patient's balance and gait symptoms. However, this area of edema may be indirect evidence of vascular permeability as a potential etiology for sunitinib's effect on the dura and central nervous system.

Patients with HCC often have underlying liver cirrhosis which places them at risk for hepatic encephalopathy. Therefore, elucidation of sunitinib's effects on the brain may be particularly important for patients with HCC and cirrhosis in order to help distinguish between sunitinib side effects and hepatic encephalopathy, metastatic disease or other primary central nervous system processes. With the increasing use of receptor tyrosine kinase inhibitors and antiangiogenic agents for the treatment of gastrointestinal cancer, awareness of toxic peripheral vestibulopathy as a potential side effect is important when evaluating neurologic symptoms. Additional research into neurologic side effects of receptor tyrosine kinase inhibitor and antiangiogenic agents is warranted.

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Fig. 1. Magnetic resonance imaging (MRI) of the brain was negative for metastatic disease, reversible posterior leukoencephalopathy, leptomeningeal disease, and infection. The small focus of increased signal consistent with edema on FLAIR images (*white arrow*) on our patient's MRI is superficial and appears to be bisected by a blood vessel (*black arrow*)

Fig. 2.
Follow-up contrast enhanced CT of the brain