Sorafenib induced hepatic encephalopathy

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Abstract

A 60 year old male, known case of Hepatitis C related cirrhosis was diagnosed with exophytic Hepatocellular carcinoma (size 2.1 x 2.2 cm), Barcelona Clinic Liver Cancer Stage A, on routine surveillance. He refused liver Transplant and underwent laparoscopic segmental resection. Thereafter patient was started on Tablet Sorafenib 400mg twice daily to prevent recurrence of Hepatocellular carcinoma. On 18st post-operative day, patient presented with Hepatic encephalopathy. Routine investigations and MRI Brain were normal; Venous ammonia was high. Sorafenib was discontinued, and neurological symptoms resolved within 24 hours. The ammonia level decreased from 112 to 30 µmol/L. Hepatic encephalopathy recurred 14 days after Sorafenib reintroduction at a dose of 400 mg / day. It resolved within 24 hours of withdrawal of Sorafenib. Sorafenib induced recurrent acute overt Hepatic encephalopathy with biochemical corroboration is reported here. (Acta gastroenterol. belg., **2017**, 80, **537-538**).

Keywords : Sorafenib, Hepatic Encephalopathy, Hepatocellular carcinoma.

Case report

A 60 year old male patient, known case of HCV related cirrhosis, underwent routine abdominal ultrasound for surveillance of Hepatocellular Carcinoma (HCC). Ultrasound revealed cirrhosis with an exophytic hypoechoic lesion (2.1 x 2.2 cm) in Segment VI of liver. Further, triphasic Contrast Enhanced CT of the abdomen was carried out, which revealed cirrhosis with a 2.2 x 2.2 cm exophytic lesion in segment VI of liver, showing arterial enhancement and venous washout suggestive of HCC (Fig. 1). His biochemical investigation were as follows-Serum Bilirubin : 1.0, Direct Bilirubin: 0.6, Albumin: 3.0, INR: 1.43. There was no evidence of ascites on CT of abdomen and patient did not have hepatic encephalopathy. Upper gastrointestinal endoscopy revealed mild portal hypertensive gastropathy with no varices. The Child Turcotte Pugh (CTP) class was A, and the Barcelona Clinic Liver Cancer Stage was A.

As the tumour was a single nodule <3 cm with no varices (normal Portal pressure and normal bilirubin) a laparoscopic resection of the hepatocellular carcinoma was done. Postoperatively, Patient was started on tablet Sorafenib 400mg (Cipla Ltd., Mumbai, India) twice daily to prevent recurrence of HCC. After 18 days of surgery, patient presented to the hospital with drowsiness

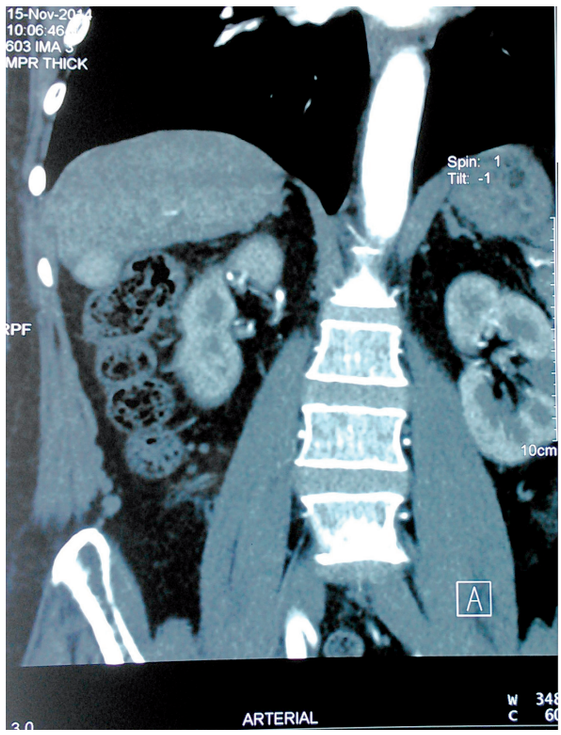

Fig. 1. — Triphasic Contrast Enhanced CT abdomen : Shows cirrhosis exophtic Segment VI HCC 2.2 x 2.2 cm.

and aggressive behaviour. There was no history of fever, gastro-intestinal bleed, constipation or abdominal distension. Patient was not taking diuretics or sedatives. His vital signs were normal. Central Nervous System examination revealed disorientation for time and asterixis. Other systemic examination was normal. He had a normal blood count, serum creatinine, electrolytes and calcium. The liver function tests revealed: Total Bilirubin : 1.0 mg/dl, Direct Bilirubin: 0.6 mg/dl, Total Proteins : 7.1 Gm/dl, Albumin: 3.0 gm/dl, SGOT : 43 U/L, SGPT : 40 U/L. Blood and urine cultures were sterile. Serum

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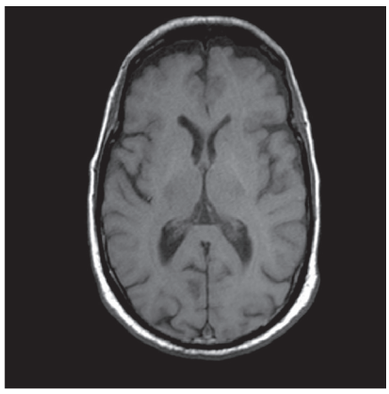

Fig. 2. — MRI Brain : showed symmetrical T1 hyperintensity in the globus – pallidus, but no metastasis.

ammonia level was 112 µmol/L [checked by Blood Ammonia Meter PocketChem BA PA-4140 (ARKRAY Healthcare Pvt. Ltd.)]. MRI Brain was done which showed symmetrical T1 *hyperintensity in the globus pallidus,* without metastases. (Fig. 2). Repeat Chest X-ray showed no pneumonia, Ultrasound abdomen showed no ascites. Diagnosis of drug (Sorafenib) induced acute overt Grade 2 Hepatic Encephalopathy was suspected. Sorafenib was discontinued, and patient was managed with standard medical therapy including lactulose (Per oral/ Enema). Within 24 hours, neurological symptoms resolved. Ammonia level decreased to 30µmol/L. Sorafenib was restarted 2 weeks later at a dose of 400 mg/ day. Patient had a recurrent episode of overt hepatic encephalopathy the following day. It resolved within 24 hours of withdrawal of Sorafenib. Thus, the diagnosis of Sorafenib induced overt hepatic encephalopathy was confirmed.

Discussion

Sorafenib is a multikinase inhibitor of Raf-1, B-Raf, vascular endothelial growth factor (VEGFR2), platelet-derived growth factor (PDGFR), c-Kit receptors (1). Here, we report a case of Sorafenib induced recurrent hepatic encephalopathy with biochemical corroboration. In the present case, rapid improvement of Hepatic Encephalopathy and decline of ammonia level after Sorafenib withdrawal strengthens the role of Sorafenib in precipitating Hepatic Encephalopathy. Recurrence of Hepatic Encephalopathy after restarting Sorafenib confirms the diagnosis.

Hootegen AV *et al*., reported a patient with hepatocellular carcinoma with lung metastases who developed high fever and a severe hepatitis that rapidly evolved into liver coma and death, two weeks after the initiation of Sorafenib (2).

Marks *et al.* (3) reported the development of confusion and asterixis occurring 20 days after Sorafenib initiation for hepatocellular carcinoma, which resolved within 24 hours of withdrawal of the drug. Ammonia levels were not reported.

In the SHARP trial (4), overall incidence of serious adverse events was similar in the Sorafenib and the placebo groups. None of patient experienced Hepatic Encephalopathy in the Sorafenib and Placebo group.

The EASL and AASLD 2015 guidelines are silent on the use of Sorafenib, as post HCC resection, adjuvant therapy to prevent recurrence.

Sorafenib significantly reduced mortality and prolonged overall survival of HCC patients after curative resection, probably by inhibiting tumor growth after tumor recurrence (5). Sorafenib can be used as an adjuvant therapy for hepatocellular carcinoma to prevent early reoccurrence after hepatic resection (6).

Sorafenib should be added to the list of drugs that may lead to the drug-induced hypersensitivity syndrome and possibly also to the DRESS syndrome. The oxidative metabolism of Sorafenib occurs primarily in the liver and is mediated by the cytochrome P450 (CYP)3A4. Eight Sorafenib metabolites have been identified with pyridine N-oxide being the main circulating metabolite in plasma. It could be hypothesized that an underlying cytochrome P450 dysfunction and the presence of biologically reactive drug metabolites might lead to this Sorafenib-induced severe liver dysfunction (2).

Hence, we conclude that suggest that the possibility of drug induced acute hepatic encephalopathy should be kept in any case presenting with encephalopathy after introduction of Sorafenib for the treatment of HCC.

References

1. WILHELM S., CARTER C., LYNCH M., LOWINGER T., DUMAS J., SMITH R.A., *et al*. Discovery and development of sorafenib : a multikinase inhibitor for treating cancer. *Nat. Rev. Drug Discov*., 2006, **5** : 835-44.
2. HOOTEGEM A.V., VERSLYPE C., STEENBERGEN W.V. Sorafenib-Induced Liver Failure : A Case Report and Review of the Literature. *Case Reports in Hepatology*, Volume 2011, Article ID 941395, 4 pages doi : 10.1155/2011/941395.
3. MARKS A.B., GERARD R., FOURNIER P., COUPE P., GAUTIER S. Sorafenib-induced hepatic encephalopathy. *Ann. Pharmacother*., 2009, **43** : 2121.
4. JOSEP M., LLOVET M.D., RICCI S., HILGARD P., GANE E., BLANC J.F., *et al.* SHARP Investigators Study Group. Sorafenib in Advanced Hepatocellular Carcinoma. *N. Engl. J. Med*., 2008, **359** : 378-390.
5. ZHANG W., ZHAO G., WEI K., ZHANG Q., MA W., SONG T., *et al*. Adjuvant sorafenib reduced mortality and prolonged overall survival and post-recurrence survival in hepatocellular carcinoma patients after curative resection : A single-center experience. *BioScience Trends*, 2014, **8** (6) : 333-38.
6. WANG S.N., CHUANG S.C., LEE K.T. Efficacy of sorafenib as adjuvant therapy to prevent early recurrence of hepatocellular carcinoma after curative surgery: A pilot study. See comment in PubMed Commons below. *Hepatol. Res*., 2014 May, **44** (5) : 523-31. doi : 10.1111/hepr.12159.