Seeding of hepatocellular carcinoma into the stomach wall following endoscopic ultrasound and fine-needle aspiration biopsy

M. Kasi1,†, Samin Rashid2,†, S.A.J. Wallace3, Vijayendran Sujendran2, Bill Griffiths2, Andrew Butler2, Paul Gibbs2, Loveena Sreedharan2, A.M. Zaitoun3, S. Venkatachalapathy1, M.W. James1 and G.P. Aithal1

1Nottingham Digestive Diseases Centre (NDDC) and NIHR Nottingham Biomedical Research Centre (BRC), Nottingham University and Nottingham University Hospitals NHS Trust, Nottingham, UK, 2Liver Unit, Addenbrooke’s Hospital, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK, and 3Division of Histopathology, Nottingham University Hospitals NHS Trust, Nottingham, UK

*Correspondence address. Nottingham University Hospitals NHS Trust, Digestive Disease and Thoracis, Derby Road, Nottingham NG7 2UH, UK. E-mail: madhavi.kasi@yahoo.com

Abstract

Delayed gastrointestinal metastasis is a rare complication of hepatocellular carcinoma (HCC). We present the case of a patient who presented with melaena and microcytic anaemia 6 years after receiving an orthotopic liver transplant for hepatitis B-induced HCC. Oesophagogastroduodenoscopy revealed a fungating gastric mass at the lesser curve and histology from biopsies confirmed metastatic recurrence of HCC in the stomach. The route of metastasis is likely due to iatrogenic seeding of tumour cells during pre-transplant endoscopic ultrasound (EUS) and fine needle aspiration (FNA) biopsy. Subsequent positron emission tomography and magnetic resonance imaging failed to reveal further metastatic disease and the patient was managed with a total gastrectomy. This is the first reported description in the literature of needle-track metastasis in the stomach due to liver EUS–FNA for HCC.

CASE REVIEW

Gastric metastasis from hepatocellular carcinoma (HCC) is a rare complication, the incidence varies from 0.08 to 2% [1–3]. A biopsy is considered in patients with HCC when there are diagnostic challenges as risk of tumour seeding is reported to be 2.7% [4]. Endoscopic ultrasound (EUS) guided trans-gastric biopsy of the lesion has been used where accessible to establish diagnosis. Tumour seeding through this has not yet been reported.

A 43-year-old male of oriental origin, with background chronic hepatitis B infection related cirrhosis developed HCC detected during routine surveillance tests (Raised AFP-69 and on Ultrasound). He had undetectable viral load with lamivudine monotherapy. Magnetic resonance imaging (MRI) showed a 3.3×3 cm² lesion in the caudate lobe of liver but not entirely consistent with HCC. Hence, he had a EUS guided trans-fundal fine needle aspiration (FNA) of the lesion which confirmed HCC.

© The Author(s) 2018. Published by Oxford University Press. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Staging MRI and CT scans confirmed the disease as T2N0M0. As he was within the Milan criteria, he was listed for orthotopic liver transplantation and received bridging trans-arterial chemo-embolization (TACE). Orthotopic liver transplantation from a non-heart beating donor was carried out ~5 months after diagnosis. The explant histological analysis showed that the HCC was poorly differentiated with a final histology of T2N0M0 with no nodular or micro-vascular metastatic invasion.

His immune-suppression during the immediate post-transplant period was azathioprine, prednisolone and sirolimus (trough levels of 5–6). The choice of sirolimus over a calcineurin inhibitor was made at that time due to the risk of metastasis given the worrying features of the explant histology. He received adefovir, lamivudine and hepatitis B immunoglobulin for chronic hepatitis B prophylaxis. Post-transplant follow up included 6-monthly contrast-enhanced CT imaging, routine blood tests and alpha-fetoprotein levels for surveillance of HCC recurrence. After 3 years of CT surveillance, the lack of any findings and the general excellent clinical condition of the patient the decision was made to stop CT surveillance.

Seven years in to post-transplant follow up, he was investigated for iron deficiency anaemia, with a gastroscopy and colonoscopy. Gastroscopy (Fig. 1) performed at local Hospital showed a 25 mm ulcerated mass in the lesser curvature of the stomach, just below the cardia. Biopsies obtained from the mass lesion were consistent with HCC. Further gastroscopies are performed (Fig. 2) at 6 weeks following the index gastroscopy showed a polypoid growth in the fundus with healed ulceration over this. Further gastroscopy (Fig. 3) in transplant centre as a perioperative investigation showed large ulcerated mass in the fundus.

HISTOLOGY

The biopsy (Fig. 4) showed gastric type mucosa and squamous lined mucosa consistent with the gastro-oesophageal junction sample site. There were tumour fragments with extensive areas of necrosis. Large polygonal tumour cells were seen and arranged in trabeculae with frequent mitoses.

Immunohistochemistry was performed to characterize these cells. The tumour cells stained positive for CAM 5.2, Inhibin, Hepatocyte Paraffin 1 (focal) with a high Ki67 proliferative index (>50%). The tumour cells did not stain for CK7, Calretinin, Synaptophysin, Chromogranin, S100, CD117 and DOG1.

He underwent staging for his recurrence by positron emission tomography (PET) (PET image shown in Fig. 5) and MRI (MRI image shown in Fig. 6) which has confirmed the diseases localized to stomach.

Based on these features and the clinical and radiological findings the patient was diagnosed with metastatic HCC that was localized to stomach and underwent total gastrectomy.

The patient had an uncomplicated total gastrectomy and no other residual disease was found intra-operatively. Histology of the resected specimen showed variable areas of moderate-to-poorly differentiated HCC. Overall, 15 retrieved local lymph

Figure 1: Index gastroscopy showing large ulcer in lesser curvature.

Figure 2: Repeat gastroscopy in 6 weeks—showing ulcer healing.

Figure 3: Endoscopic images of the recurrence of HCC in the gastric fundus projecting into the cardia.

Figure 4: Biopsy showing variable areas of moderate-to-poorly differentiated HCC.
nodes showed no evidence of tumour metastasis. The patient made an uneventful recovery from surgery and was discharged on Day 10. However, follow up imaging at 2 months showed multiple liver lesions, including a cluster of lesions in the caudate lobe (where his native liver tumour was). Three further small lesions in segments I, II and VI. This was confirmed as biopsy proven metastatic HCC of his graft. Unfortunately the only options now are palliative.

DISCUSSION

The likely mechanism of dissemination of this patient’s HCC was by needle-track seeding from EUS–FNA that was performed for initially diagnosis of primary HCC after 7 years of initial diagnosis. HCC most often metastasizes to lungs, bone, abdominal lymph nodes, adrenal glands, peritoneum or brain. In a study of 403 patients with HCC not a single case metastasized to the stomach making it unlikely that a mechanism other than seeding led to metastasis in this patient [5]. Moreover, the pre-transplantation FNA and the gastric recurrence were both located at the lesser curvature of the stomach and the explant specimen did not reveal direct extension of the primary HCC lesion to the lesser curvature of the stomach. Hypothesizing that needle-track seedling as most likely mode of spread. Levy et al. has provided some basic science support for the idea of needle track implantation. They demonstrated the presence of malignant cells within gastrointestinal tract luminal fluid following EUS–FNA in 3 out of 26 patients with pancreatic cancers. Importantly, malignant cells were not found prior to EUS–FNA in these patients or in those following EUS–FNA for non-malignant indications [6].

To our knowledge this is the first case of needle-track implantation of HCC into the stomach wall following EUS–FNA sampling of the liver. One argument in favour of using EUS–
FNA as opposed to percutaneous liver FNA is the purported greater risk of needle-track metastasis with percutaneous approaches [7]. A systematic review of 1340 patients evaluated the risk of needle track seeding following percutaneous FNA of HCC as 2.7% overall or 0.9% per year [4]. As experience with liver EUS-FNA increases, studies with longer follow up periods are needed to establish the risk of needle track seeding for EUS-FNA.

Our patient has been established on Sirolimus, (mTOR—mammalian target-of-rapamycin inhibitor) which has shown to have a protective effect from de novo cancers and HCC recurrence [8]. However, Sirolimus is not shown to improve long-term recurrence free survival beyond 5 years [9]. He underwent loco-regional therapies for his native HCC prior to transplantation which are proven to control tumour burden. His HBV DNA remains undetectable throughout the post-transplant period implying that there is no reactivation of hepatitis B. Despite of this he has developed delayed metastasis. As the lesion correlates well with the biopsy site, the recurrence might be secondary to tumour seeding.

There are no central guidelines suggesting any HCC surveillance post-transplant; however, these patients are followed up closely with 6 monthly contrast CT scans for a maximum 5 years depending on the local practice. In this particular case metastasis was identified outside the follow up period.

Treatment algorithm for recurrence of HCC has been proposed in 2013 by Geneva group that summarizes for extrahepatic metastasis mTOR inhibitors should be considered along with reduction of their immunosuppression. Resection should be considered for isolated metastasis and for cancers which are not resectable Sorafenib remains the choice of treatment [10]. In our case as his ECOG performance state is zero and we have identified isolated metastasis resection is considered as the initial option of management.

CONCLUSION

There is a possibility of needle-tract metastasis of HCC following liver EUS-FNA and delayed presentation of gastric metastasis. This report also highlights the need for meticulous surveillance using serial tumour markers and regular haematology and biochemistry bloods post-liver transplantation for HCC.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Chen L-T, Chen CY, Jan CM, Wang WM, Lan TS, Hsieh MY, et al. Gastrointestinal tract involvement in hepatocellular carcinoma: clinical, radiological and endoscopic studies. Endoscopy 1990;22:118–23. doi:10.1055/s-2007-1012815.
2. Lin CP, Cheng JS, Lai KH, Lo GH, Hsu PI, Chan HH, et al. Gastrointestinal metastasis in hepatocellular carcinoma: radiological and endoscopic studies of 11 cases. J Gastroenterol Hepatol 2000;15:536–41. doi:10.1046/j.1440-1746.2000.02152.x.
3. Hu ML, Tai WC, Chiu SK, Chiu YC, Wu KL, Chou YP, et al. Gastric metastasis of hepatocellular carcinoma via a possible existing retrograde hematogenous pathway. J Gastroenterol Hepatol 2010;25:408–12. doi:10.1111/j.1440-3545.2010.06150.x.
4. Silva MA, Hegab B, Hyde C, Guo B, Buckels JAC, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. Gut 2008;57:1592–6. doi:10.1136/gut.2008.149062.
5. Katyal S, Oliver JH, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahaepatic metastates of hepatocellular carcinoma. Radiology 2000;216:698–703. doi:10.1148/radiology.216.3.r00se24698.
6. Levy MJ, Gleeson FC, Campion MB, Caudill JL, Clain JE, Halling K, et al. Prospective cytological assessment of gastrointestinal luminal fluid acquired during EUS: a potential source of false-positive FNA and needle tract seeding. Am J Gastroenterol 2010;105:1311–8. doi:10.1038/ajg.2010.80.
7. Parekh PJ, Majithia R, Diehl DL, Baron TH. Endoscopic ultrasound-guided liver biopsy. Endoscopic Ultrasound 2015;4:85–91. doi:10.4103/2303-9027.156711.
8. Toso C, Merani S, Bigam DL, Shapiro AMJ, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. Hepatology 2010;51:1237–43. doi:10.1002/hep.23437.
9. Geissler EK, Schnitzbauer AA, Zülke C, Lamby PE, Proneth A, Duvoux C, et al. Sirolimus use in liver transplant recipients with hepatocellular carcinoma: a randomized, multicenter, open-label phase 3 trial. Transplantation 2016;100:116–25. doi:10.1097/TP.0000000000000965.
10. Toso C, Mentha G, Majno P. Integrating sorafenib into an algorithm for the management of post-transplant hepatocellular carcinoma recurrence. J Hepatol 2013;59:3–5. doi:10.1016/j.jhep.2013.03.029.