Mediastinal mass diagnosed by endobronchial ultrasound as recurrent hepatocellular carcinoma in a post-liver transplantation patient

Abdul Hamid Alraiyes¹, Pichapong Tunsupon², Fayez Kheir³ and Daniel A Salerno⁴

Abstract
Objective: We presented a rare case of recurrent hepatocellular carcinoma after liver transplant manifested as an isolated mediastinal mass.

Methods: A 62-year-old man was referred for evaluation of atypical chest pain and abnormal finding of a computed tomography of the chest. He had history of chronic hepatitis C liver cirrhosis and hepatocellular carcinoma underwent orthotopic liver transplant as a curative treatment three years earlier.

Results: The computed tomography of the chest demonstrated paratracheal mediastinal lymphadenopathy. He subsequently underwent endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA). The right paratracheal lymph node station 4R was sampled. Rapid on-site cytology evaluation demonstrated recurrent metastatic hepatocellular carcinoma.

Conclusion: Pulmonologist should be cognizant of diagnostic utility of EBUS-TBNA in this clinical setting as more transplant patients on immunosuppressive medications with enlarged mediastinal lymphadenopathy of unknown origin will be referred for further evaluation.

Keywords
Endobronchial ultrasound, recurrent hepatocellular carcinoma, liver transplantation

Date received: 16 January 2016; accepted: 24 March 2016

Case report
A 62-year-old man referred to our facility for the management of abnormal computed tomography of the chest identified during investigation for atypical chest pain. His past medical history was significant for chronic hepatitis C complicated by liver cirrhosis and hepatocellular carcinoma (HCC). He underwent chemoembolization and radiofrequency ablation of the liver as bridging therapies prior to uneventful orthotopic liver transplantation (OLT), a curative treatment for HCC. The explanted liver was cirrhotic and contained two 4.5 cm extensively necrotic lesions consistent with poorly differentiated HCC on pathological examination. There was an extensive intravascular invasion, and tumor was presented within an intracaval thrombus, which was removed during surgery. After the OLT, he was maintained on immunosuppressive therapy with tacrolimus and prednisone. Unfortunately, he was diagnosed with prostate cancer a few months later and underwent prostatectomy as curative treatment. At this time, his immunosuppressant was changed from tacrolimus

¹Roswell Park Cancer Institute, Buffalo, NY, USA
²School of Medicine and Biomedical Sciences, University at Buffalo—State University of New York (SUNY), Buffalo, NY, USA
³Health Sciences Center, Tulane University, New Orleans, LA, USA
⁴Temple University, Philadelphia, PA, USA

Corresponding Author:
Abdul Hamid Alraiyes, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, USA.
Email: abdul.alraiyes@roswellpark.org
to sirolimus, which had shown to delay HCC recurrence when compared to regimens that use tacrolimus in retrospective study.

Physical examination of his chest revealed normal breath sounds. Cardiovascular examination was unremarkable for abnormal heart sounds or murmurs. The rest of his physical examination was normal. Cardiac workup was negative for myocardial injury. Computed tomography of his chest images is shown in Figure 1. The patient subsequently underwent endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) of right paratracheal lymph node station 4R (Figure 2).

Pathological examination revealed highly cellular and clusters of large, loosely cohesive sheets of tumor with thin-walled traversing blood vessels. The tumor cells had a moderate amount of granular cytoplasm containing occasional hyaline globules. Nuclei were round to oval in shape and moderately pleomorphic, with prominent nucleoli and scattered intranuclear pseudoinclusions. Bile pigment was not identified. Numerous nuclei stripped of cytoplasm were present in the background of the smears (Figure 3). The specimen did not contain appreciable lymphoid tissue, but small aggregates of macrophages with anthracotic pigment were present; these macrophages indicate that the tumor was located within a mediastinal lymph node (Figure 4). Immunohistochemical stains were positive for hepatocyte paraffin 1 (HepPar1) (Figure 5) and alpha-fetoprotein (AFP), and stains for cytokeratin (CK)-7, CK-20, thyroid transcription factor-1 (TTF-1), and monoclonal carcinoembryonic antigen (CEA) were all negative.

**Figure 1.** (a) A transverse cut in CT scan of the chest showing enlarged right paratracheal lymph node (white arrow) and (b) a coronal cut in CAT scan of the chest showing enlarged right paratracheal lymph node (white arrow) and enlarged right hilar lymph node (black arrow).

**Figure 2.** Endobronchial ultrasound view of the right paratracheal lymph node with transbronchial needle aspiration.
Final diagnosis
Recurrent metastatic HCC in mediastinum.

Discussion
We described a case of a 62-year-old male with two enlarged mediastinal masses demonstrated on computed tomography of the chest during investigation for atypical chest pain. The differential diagnosis of mediastinal masses in elderly with history of HCC included different types of malignancies, such as recurrent HCC, metastatic lung cancer, post transplant lymphoproliferative disorder (PTLD), teratoma, seminoma, and neuroendocrine tumors, until proven otherwise.

The incidence of HCC is increasing worldwide as several risk factors for liver cirrhosis are on the rise globally. Liver transplant is the treatment of choice for patients with early-stage HCC if there are no contraindications. Despite careful selection, 15%–20% of those patients will eventually develop recurrent HCC. The most common sites for recurrence of HCC after OLT in a retrospective cohort of 28 recurrent HCC were liver (n = 7), lung (n = 7), bone (n = 5), adrenal gland (n = 2), peritoneum (n = 2), lymph node (n = 2), skin (n = 2), and cerebral (n = 1). Metastasis of HCC occurs through direct invasion, hematogenous, or lymphatic dissemination. Distal lymph node metastasis in HCC occurs in 12% with the mediastinal lymph nodes reported as the most common site. The most common organ of distant metastasis of HCC after OLT is lung. Although OLT is a curative treatment for patients with HCC, computed tomography of the chest has a fair sensitivity of 65% to detect HCC during pretransplant evaluation. This may result in failure to detect early hematogenous dissemination or inadequate disease staging.

The presence of two enlarged mediastinal lymphadenopathy with unknown primary in our case warranted a tissue sample to establish a definite diagnosis. EBUS is a non-invasive procedure that could visualize airways, mediastinal structures, and the lung parenchyma. A diagnostic accuracy of EBUS-TBNA for mediastinal lymph node was 92% sensitivity and 100% specificity. Mediastinal lymph node, in particular, right paratracheal lymph node (4R) as well as station 1–3, 7, and 6–12 is approachable by EBUS. Mediastinoscopy
is an alternative option to obtain larger tissue sample to establish a definite diagnosis particularly in cases that are highly suspicious for lymphoma, however, this procedure is more invasive and requires general anesthesia. Shinya et al. reported a rare case of metachronous metastases of HCC to superior mediastinum and brain years after OLT. The lesion in the superior mediastinum was surgically resected and pathological examination confirmed diagnosis of metastatic HCC. Our patient was not a surgical candidate due to several reasons. First, mediastinal lesions were located adjacent to the trachea and carina. Second, the size of the tumor was too large to be surgically removed via video-assisted thoracoscopic surgery (VATS). Third, the involvement of two mediastinal lymph nodes precluded him from surgical resection. Thus, less invasive diagnostic procedure of choice for mediastinal lymphadenopathy in this case is EBUS-TBNA. In certain cases with multiple mediastinal lesions, fluorine-18-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) could identify the “hottest” mediastinal lymph node of choice to be biopsied. However, the result of fluorodeoxyglucose–positron emission tomography (FDG-PET) in our case would not preclude the procedure to obtain a tissue diagnosis.

Pathological examination revealed cohesive sheets of cells with abundant granular cytoplasm, which were consistent with malignant cells. The tumor cells were cytologically similar to the patient’s primary HCC. Several non-specific features of HCC were presented in this case such as traversing vessels, the background of naked nuclei, intranuclear pseudo-inclusions, and granular cytoplasm with hyaline globules. Immunohistochemistry profile was consistent with HCC. The presence of vascular invasion on explanted liver indicated that occult metastasis potentially occurred before OLT and not detected during pretransplant evaluation. HepPar1 was an antibody to liver mitochondrial enzyme and had the highest sensitivity >90% to confirm diagnosis of HCC, but not specific as it stained positive in adenocarcinoma cell types. The sensitivity of HepPar1 was approximately 50% in poorly differentiated HCC as reported in this case.9,10 Our patient also had CK7/CK20 immunophenotype, which was found in HCC approximately 75% and was rarely seen in adenocarcinomas.11 To our knowledge, this is the first case report of mediastinal HCC metastasis after OLT diagnosed by non-invasive EBUS-TBNA.

Opportunistic infections after OLT was the leading cause of death during the first 3 years after transplantation while on potent immunosuppressants.12 However, the presence of mediastinal lymphadenopathy without constitutional symptoms and lung parenchymal involvement was very unusual. The incidence of PTLD after OLT was between 2% and 8.4%.13 Clinical presentation of PTLD ranged from benign infectious mononucleosis-like illness to non-Hodgkin’s lymphoma with nodal and extra-nodal site involvement.12 PTLD usually presented radiologically with multiple pulmonary nodules, enlarged mediastinal and hilar lymph nodes. In our case, findings on pathological examination excluded PTLD.

Tacrolimus-based immunosuppression was the most common regimen after OLT. The higher level of immunosuppression was associated with higher recurrence rates of HCC.14 Inhibitors of the mammalian target of rapamycin (mTOR) like sirolimus had shown in retrospective studies to delay tumor recurrence when compared to tacrolimus-based regimen.15,16 A prospective randomized trail comparing sirolimus-containing versus mTOR inhibitor–free immunosuppression in OLT patients for HCC to estimate recurrence-free survival 5 years after OLT was completed pending final results (NCT00355862). In general, intrahepatic HCC recurrence after OLT was more common than extrahepatic recurrence. Options for intrahepatic HCC recurrence were surgical resection, radiofrequency ablation, transarterial embolization or radioembolization, and systemic treatment depended on the location, size, and number of tumor recurrence.2 Unfortunately, the data for systemic treatment of extrahepatic HCC is sparse.

After the diagnosis of recurrent HCC, our patient underwent palliative thoracic radiation and sorafenib chemotherapy. He tolerated the treatment well and his AFP level trended down. Sorafenib was a multi-tyrosine kinase and angiogenesis inhibitor that has been approved for use in advanced primary HCC, which showed to prolong median survival and the time to radiologic progression to almost 3 months in patients treated with sorafenib compared to those given placebo.17 In addition, a retrospective cohort study favored the combination of sorafenib and mTOR inhibitor as immunosuppressant in recurrent HCC after OLT that are not candidates for surgery or loco-regional treatment.18

Conclusion
This case illustrates a rare but important presentation of recurrent metastatic HCC as an isolated mediastinal mass. Pulmonary physicians should be cognizant of high diagnostic utility of EBUS-TBNA in this entity as more transplant patients on immunosuppression with enlarged hilar and mediastinal lymphadenopathy of unknown origin will be referred for further management.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval
Our institution does not require ethical approval for reporting individual cases or case series.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.
Informed consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

References

1. Llovet JM, Fuster J and Bruix J. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl 2004; 10(2 Suppl. 1): S115–S120.
2. Welker MW, Bechstein WO, Zeuzem S, et al. Recurrent hepatocellular carcinoma after liver transplantation—an emerging clinical challenge. Transpl Int 2013; 26(2): 109–118.
3. Escartin A, Sapisochin G, Bilbao I, et al. Recurrence of hepatocellular carcinoma after liver transplantation. Transplant Proc 2007; 39(7): 2308–2310.
4. Katyal S, Oliver JH 3rd, Peterson MS, et al. Extrahepatic metastases of hepatocellular carcinoma. Radiology 2000; 216(3): 698–703.
5. Bates MJ, Farkas E, Taylor D, et al. Pulmonary resection of metastatic hepatocellular carcinoma after liver transplantation. Ann Thorac Surg 2008; 85(2): 412–415.
6. Marsh JW, Dvorchik I, Subotin M, et al. The prediction of risk of recurrence and time to recurrence of hepatocellular carcinoma after orthotopic liver transplantation: a pilot study. Hepatology 1997; 26(2): 444–450.
7. Chandra S, Nehra M, Agarwal D, et al. Diagnostic accuracy of endobronchial ultrasound-guided transbronchial needle biopsy in mediastinal lymphadenopathy: a systematic review and meta-analysis. Respir Care 2012; 57(3): 384–391.
8. Shinya S, Noritomi T, Yamauchi Y, et al. Two rare metachronous metastases of hepatocellular carcinoma after liver transplantation. Int Surg 2013; 98(4): 432–436.
9. Fan Z, van de Rijn M, Montgomery K, et al. Hep par 1 antibody stain for the differential diagnosis of hepatocellular carcinoma: 676 tumors tested using tissue microarrays and conventional tissue sections. Mod Pathol 2003; 16(2): 137–144.
10. Kakar S, Muir T, Murphy LM, et al. Immunoreactivity of Hep Par 1 in hepatic and extrahepatic tumors and its correlation with albumin in situ hybridization in hepatocellular carcinoma. Am J Clin Pathol 2003; 119(3): 361–366.
11. Gyure KA and Morrison AL. Cytokeratin 7 and 20 expression in choroid plexus tumors: utility in differentiating these neoplasms from metastatic carcinomas. Mod Pathol 2000; 13(6): 638–643.
12. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007; 357(25): 2601–2614.
13. Dhillion MS, Rai JK, Gunson BK, et al. Post-transplant lymphoproliferative disease in liver transplantation. Br J Radiol 2007; 80(953): 337–346.
14. Vivarelli M, Cucchetti A, La Barba G, et al. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. Ann Surg 2008; 248(5): 857–862.
15. Toso C, Meeberg GA, Bigam DL, et al. De novo sirolimus-based immunosuppression after liver transplantation for hepatocellular carcinoma: long-term outcomes and side effects. Transplantation 2007; 83(9): 1162–1168.
16. Zhou J, Wang Z, Wu ZQ, et al. Sirolimus-based immunosuppression therapy in liver transplantation for patients with hepatocellular carcinoma exceeding the Milan criteria. Transplant Proc 2008; 40(10): 3548–3553.
17. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359(4): 378–390.
18. Gomez-Martin C, Bustamante J, Castroagudin JF, et al. Efficacy and safety of sorafenib in combination with mammalian target of rapamycin inhibitors for recurrent hepatocellular carcinoma after liver transplantation. Liver Transpl 2012; 18(1): 45–52.