

Letter to the Editor

Unexpected mediastinal mass in a liver transplanted patient

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To the Editor:

The risk of *de novo* cancer increases by 2 to 7-fold after liver transplantation [1]. The most common *de novo* cancers are both solid (non-melanoma skin cancers, colorectal carcinoma, genito-urinary and head-neck cancer) [2,3] as well as hematologic malignancies, in particular the so-called post-transplant lymphoproliferative disorder [4]. Immunosuppressive regimen could be the most important cause for increased cancer risk, since currently used drugs lead to a chronic impairment of immune-surveillance against cancer, thus promoting proliferation and survival of malignant cellular clones [5]. Recurrence of hepatocellular carcinoma (HCC) in patients transplanted for HCC within Milan criteria is another aspect of the oncologic scenario related to post-transplant period. Indeed, about 10% of liver recipients experience HCC recurrence, and this event is associated to male gender, size of HCC, vascular invasion and viral hepatitis [6]. We report a case who developed a mediastinal solid malignancy 7 years after liver transplantation.

A 72-year-old male patient was admitted to our unit for irritating cough in October 2017. He underwent liver transplantation in 2010 for hepatitis B (HBV) and hepatitis C (HCV) viral cirrhosis, complicated with a single HCC nodule < 3 cm, previously treated with radiofrequency ablation. Later, he underwent periodical liver ultrasound scans (all normal) without further thorax computed tomography imaging because he was asymptomatic. In 2015 he failed a 24-week antiviral therapy against HCV based on sofosbuvir and ribavirin (genotype 1b). HBV replication was suppressed by entecavir and the immunosuppressive regimen was based on tacrolimus. He suffered, moreover, from obesity and diabetes treated with insulin.

A plain X-ray film of the thorax revealed an enlargement of mediastinum profile; therefore, a computed tomography of thorax and abdomen was performed and showed in the inferior and posterior mediastinum a solid inhomogeneous lesion of 9 cm in diameter which was very close to esophagus, aorta, diaphragm and left pulmonary vein. The liver and other abdominal organs were normal. For a better diagnostic definition, the patient underwent endoscopy ultrasound (EUS) through the esophagus, which con-

firmed the presence of a large hypoechoic mass with uncertain limits in the inferior mediastinum. During the procedure a fine-needle aspiration cytology (FNAC) was performed. Surprisingly, the examination of hematoxylin-eosin stain showed polygonal cells resembling hepatocytes with well-defined cytoplasmic border, large nuclei with prominent nucleoli, eosinophilic granular cytoplasm and trabecular pattern of cells (Fig. 1A and B). This picture was highly suggestive of HCC. Therefore, immunohistochemistry for CK8-18 and Hep Par-1, which are markers of hepatocellular epithelial neoplasm, was carried out and the diagnosis of HCC was confirmed (Fig. 1C and D). Since there were no imaging signs of active HCC in the liver graft, an accurate analysis of the slides from liver that was explanted in 2010 in the course of transplantation was performed. This histological retrospective analysis demonstrated HCC foci with endovascular invasion (Fig. 2).

The mediastinum lesion was judged inoperable by surgeons and the patient was addressed to an oncologic hospital, where a course of sorafenib was started and successively withdrawn for the onset of severe fatigue and mucositis. At the moment, the patient is on palliative care in another oncologic center.

Intra-thoracic localization of HCC metastasis is quite frequent in advanced cancer stage, since they represent the 12% of all extra-hepatic HCC metastasis [7]. The most common ones are metastases to lung and mediastinum lymph nodes, as described in some case reports [8,9]. Three routes of diffusion have been described: (i) from left lobe of the liver to parasternal or subcarinal lymph nodes through anterior phrenic lymph nodes, (ii) to parasternal or paratracheal lymph nodes through the hepatic falciform ligament and (iii) from right lobe to paratracheal lymph nodes through the right triangular ligament. In our case, it is likely that the large mediastinal mass was a lymph node that had been totally invaded and enlarged by metastatic tissue, therefore the EUS-FNA found only HCC fragments.

As we have already highlighted, HCC recurrence after liver transplantation is quite common, but distant mediastinal metastases have been rarely described. Alraiyes et al. [10] reported a liver recipient due to HCC who developed subsequently a mediastinal metastasis. This diagnosis was achieved through transbronchial EUS-FNAC and, similarly to our experience, Hep Par-1 staining was positive. Even histological analysis of explanted liver displayed vascular invasion such as in our patient. Similarly, Shinya et al. [11] reported a HCC metastasis in the fibro-adipose tissue of mediastinum

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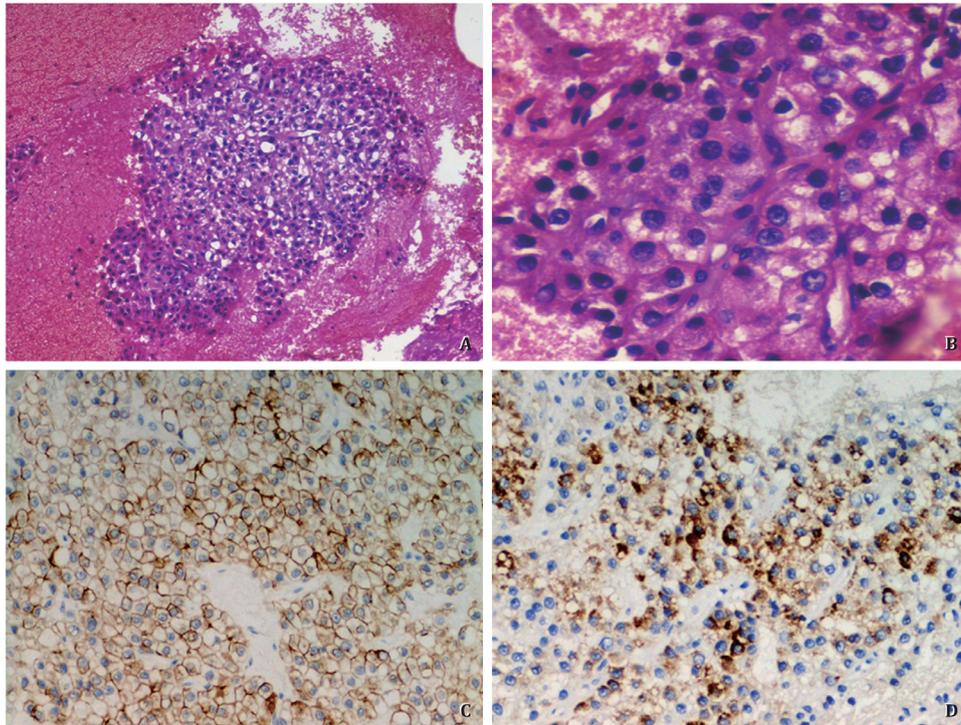


Fig. 1. Inferior mediastinal lesion: microscopic features of fine-needle aspiration cytology (FNAC). **A:** At low magnification ($\times 40$), classical hepatocellular carcinoma with acinar/solid architectural pattern; **B:** at high magnification ($\times 400$), there are typical polygonal cells resembling hepatocytes with moderate amounts of granular cytoplasm and round nuclei with evident nucleoli and occasional pseudo-inclusions (cell block preparation; hematoxylin-eosin stain). **C** and **D:** The neoplastic cells are positive for CK8-18 (C) and positive for Hep Par-1 (D) (FNAC; cell block preparation; immunoperoxidase stain) (medium magnification, $\times 100$).

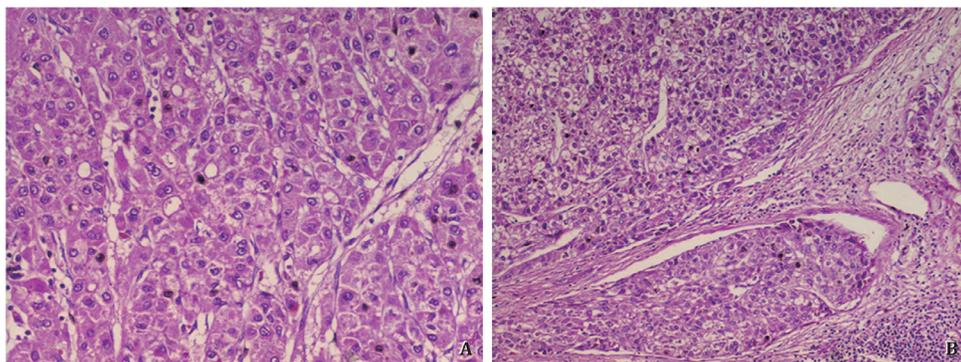


Fig. 2. Microscopic features of the explanted liver at transplantation (hematoxylin-eosin stain). **A:** At high magnification ($\times 200$), the image shows a moderately differentiated hepatocellular carcinoma; **B:** at low magnification ($\times 40$), a hepatocellular carcinoma area associated with vascular invasion.

two years after liver transplantation. In this case the resection of the metastatic tissue was possible. These reports demonstrated that HCC spreading to the mediastinum is rare but possible. Nevertheless, we believe that the period from transplantation time to metastasis onset (7 years) is an exceptional finding. Additionally, our case deserves a further food for thought: it is possible that the metastasis originated from the liver before transplantation, invaded the vessels (Fig. 2) and then hid himself for 7 years in a mediastinal site.

Despite surgery by thoracoscopy has been proposed as a curative treatment [8,10], when HCC is unresectable, radiotherapy [8] or systemic treatment could be advised. In particular, sorafenib, a multi-kinase inhibitor, has demonstrated to reduce the size of lung metastasis [12]. However, its toxicity led to drug withdrawal in our patient, therefore we were not able to evaluate the cancer response to sorafenib.

In conclusion, we believe that our experience could give some important lessons. The risk of cancer development in patients

under immune suppression should never be underestimated, even a long-time after transplantation. The recurrence of HCC should be always kept in mind and, at transplantation time, tumor vascular invasion in HCC arising from viral cirrhosis should be accurately taken into account.

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Contributors

LG, MA and CNM collected data about the patient. PA performed endoscopic ultrasound. IG performed pathological diagnosis. LG, IG and PA wrote the paper. All authors read and approved the final version of the manuscript. PA is the guarantor.

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Ethical approval

The patient gave informed consent for endoscopy procedures and to publish the paper in anonymous form.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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