A Case Report on Hepatocellular Carcinoma with Inferior Vena Cava and Right Atrium Tumor Thrombus in a Patient with COVID-19 Infection*

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Abstract

Background

Hepatocellular carcinoma (HCC) is the fourth most common cancer in the Philippines and is the second leading cause of cancer-related death due to advanced stage at diagnosis in many patients. Advanced HCC commonly has macrovascular invasion such as portal and hepatic veins however, cases that describe tumor extension into the inferior vena cava (IVC) and right atrium (RA) are rare.

Case Summary

We present a case of a 50-year old female with liver cirrhosis from Chronic Hepatitis B infection who presented with shortness of breath. She was diagnosed with HCC based on dynamic enhancement pattern on CT scan with IV contrast and highly elevated alpha-fetoprotein. CT imaging demonstrated hepatic vein invasion with large tumor thrombus extending to the inferior vena cava and right atrium. Patient also had a mild COVID infection. We treated her with modulated radiotherapy targeting the tumor thrombus along with lenvatinib, tenofovir, and apixaban. The COVID infection did not significantly affect the patient's over-all clinical status.

Conclusion

Vascular invasion of HCC into the IVC and RA portends poor prognosis. While there is no consensus on the intervention on these patients, our case may suggest the use of radiotherapy and oral anticoagulation along with lenvatinib to prolong survival and preserve quality of life.

INTRODUCTION

Hepatocellular Carcinoma (HCC) is one of the leading causes of cancer and cancer-related deaths worldwide. In the year 2020 in the Philippines, HCC was the fourth most common site of new cancer diagnosis but ranked second in terms of cancer-related death in the country [(1)]. This is partly due in fact because there is a high prevalence of hepatitis B (approximately 17%) in the Philippines [(2)]. Hepatocellular carcinoma is often diagnosed late and may invade major hepatic vessels, the most common of which will be the portal vein (3)(4). However, tumor extension into the inferior vena cava (IVC) and right atrium (RA) may also occur but are relatively rare with an incidence rate of 4% or less (3,4). Once HCC has spread to hepatic vasculature especially the IVC and RA, prognosis tends to be poor and in some studies, median survival is less than two months as patients may succumb to pulmonary embolism, heart failure or sudden cardiac death (4)(5). Once patients present with IVC and RA thrombus, treatment options will be limited and commonly they will be managed with best supportive care [(4)]. However, recent studies have shown that transarterial embolization, external-beam radiation therapy, systemic chemotherapy, surgery or combination therapy may show promise in prolonging survival and increasing time to tumor progression [(4,6,7)].

Our case describes a patient with IVC and RA thrombus from HCC secondary to chronic hepatitis B who was also infected with COVID-19.

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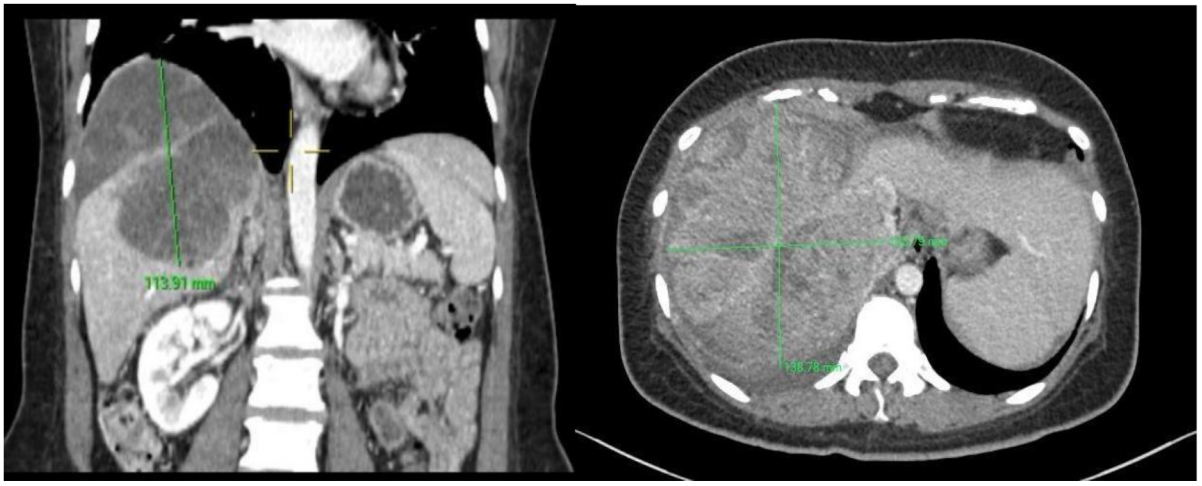
CASE REPORT

Presentation

We describe the case of a 50 year-old female who presented with a two-month history of bloatedness and progressive exertional dyspnea without abdominal pain or jaundice. She has not had significant weight loss, tea-colored urine, acholic stools, or edema. She was initially worked up in another institution where ultrasound incidentally showed right hepatic lobe mass. Follow-up CT scan of the abdomen with IV contrast in our hospital showed cirrhotic liver with nodular margins with a large heterogeneously enhancing mass (arterial enhancement and venous washout) predominantly involving segments 8, 7 and 6 approximately 138 x 123 x 130 mm with features of tumoral hemorrhage (Figure 1). Tumor thrombus was also present in the suprahepatic inferior vena cava and right atrium. The right and middle hepatic veins were not clearly delineated and the portal veins were patent. Tumoral extension was noted in both external iliac veins. There was some minimal pelvic fluid and note of few prominent lymph nodes in the porta hepatis and perigastric region. Spleen was normal in size and the rest of the abdominal organs were unremarkable. There was minimal ascites on initial CT scan of the abdomen.

Figure 1. Quadruple-phase contrast CT scan of the abdomen showing the liver mass

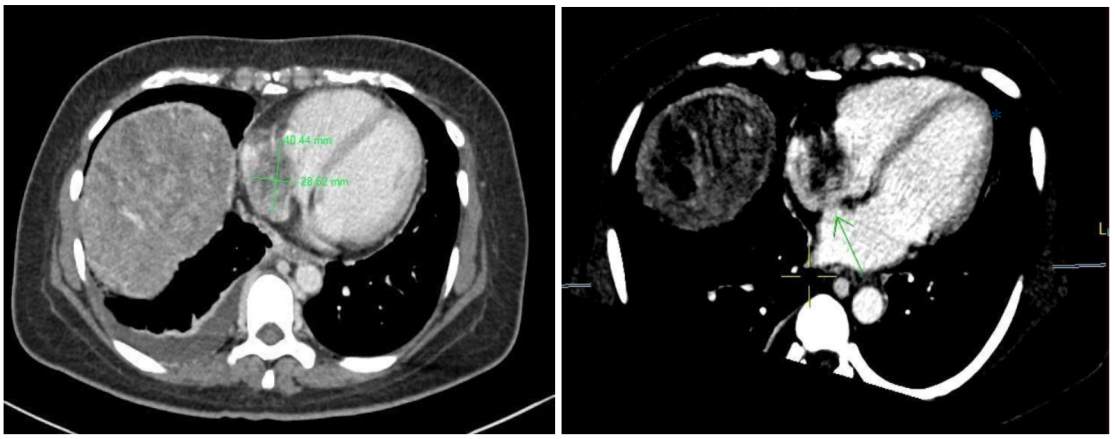


Patient's Alpha-feto protein was 82, 965 ng/mL and CEA and CA 19-9 were both normal. She was positive for Chronic HBV (reactive HbsAg and Anti-HBS) with a viral load of 26,392, 277 IU/mL.

Initial ALT was 60 U/L (normal range: 5-55) AST was 312.8 U/L (normal range: 5-34). Total Bilirubin was 1.2 mg/dL (normal 0.2-1.2), Direct 0.71 mg/dL (normal 0-0.5), and Indirect bilirubin was 0.5 mg/dL (normal 0.2-0.7). Albumin was 2.69 g/dL (normal 3.5-5) and INR ranged from 1.2 to 1.4. Sodium was 128 meq/L and Creatinine was 0.76 mg/dL. Hemoglobin 11.6mg/dL, Hematocrit 35.5 WBC 4.4 platelet 130 x 10^9/L. Child-Pugh Turcotte score on admission was B8 with MELD score of 9.

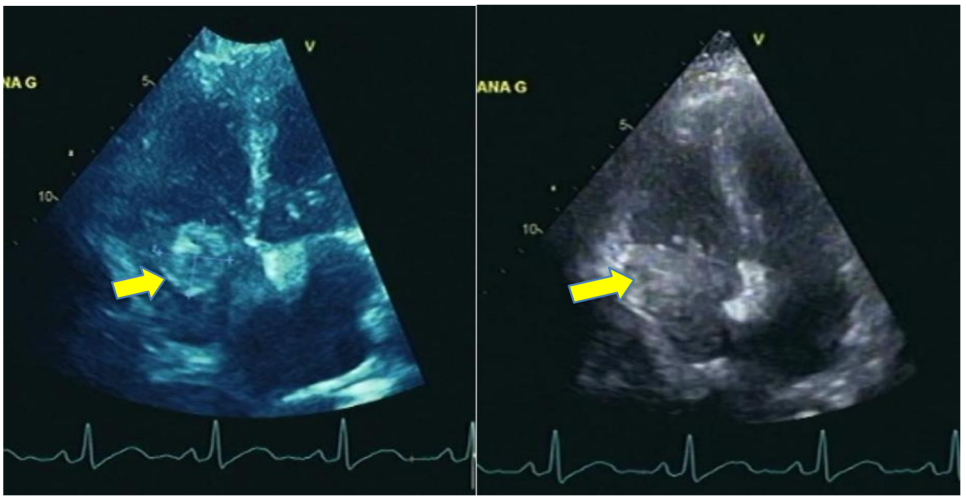
CT scan of the chest with IV contrast showed an irregular filling defect in the right atrium and inferior vena cava which appeared contiguous with the hepatic mass, likely representing tumor thrombus (Figure 2). Filling defects were noted in the left lower lobar pulmonary artery, medial segmental artery and distal lobar artery of the right middle lobe and segmental artery of the superior segment of the right lower lobe, which could represent pulmonary embolism. There were ground-glass densities in both lobes, possibly infectious pneumonia and non-calcified pulmonary nodules in both upper and left lower lobes (largest 6x6mm), thought to be pulmonary metastases. There was also note of minimal pleural effusion in the right. Heart was normal in size without pericardial effusion.

Figure 2. Contrast CT of Chest showing the thrombus in the right atrium and IVC (green arrow).



Transthoracic echocardiography revealed a 4.2 x 2.6cm echogenic density occupying almost the whole right atrium. Right atrium and ventricle size as well as pulmonary artery and left atriums and ventricular dimensions were normal. Pulmonary artery pressure and ejection fraction were normal as well.

Figure 3. Transthoracic echocardiogram showing the right atrium thrombus (yellow arrow)



COVID RT-PCR done on initial consult was positive for SARS COV-2. However, the patient was only mildy symptomatic with cough but no desaturations. Her AST and ALT were transiently elevated 2-3x upper limit of normal and inflammatory markers such as CRP, LDH and Ferritin were elevated as well. CT scan of the chest revealed some ground glass opacities but this resolved on follow-up imaging done 3 months later. Patient was given vitamin C and zinc supplementation and was quarantined for 14 days without any any deterioration in clinical status. Repeat PCR done after 14 days was negative.

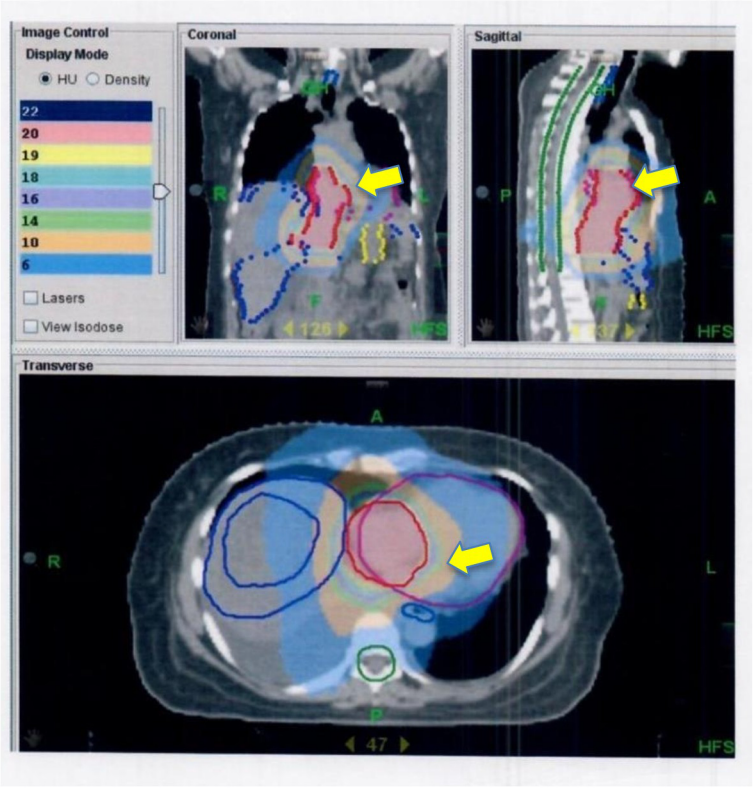
The patient however, developed right-sided pleural effusion during her final days of admission. Pleural fluid tested positive for atypical cells (likely malignant pleural effusion), and was negative for bacteria or tuberculosis culture and GeneXpert. A chest pigtail was then placed for drainage of malignant fluid.

Management

A multidisciplinary discussion with a team composed of medical oncology, radiation oncology, interventional oncology, cardiovascular and pulmonary medicine was convened. Systemic

chemotherapy was contemplated but the risk of bleeding in light of the patient's cirrhosis was deemed too risky. The patient was thus given TomoHelical Intensity modulated Radiotherapy with 5 fractions of 400 cGy (total 2000 cGy), targeting the venous thrombus in the right atrium.

Figure 4. Radiation dose distribution into tumor thrombus in the inferior vena cava and right atrium (highlighted by red areas)

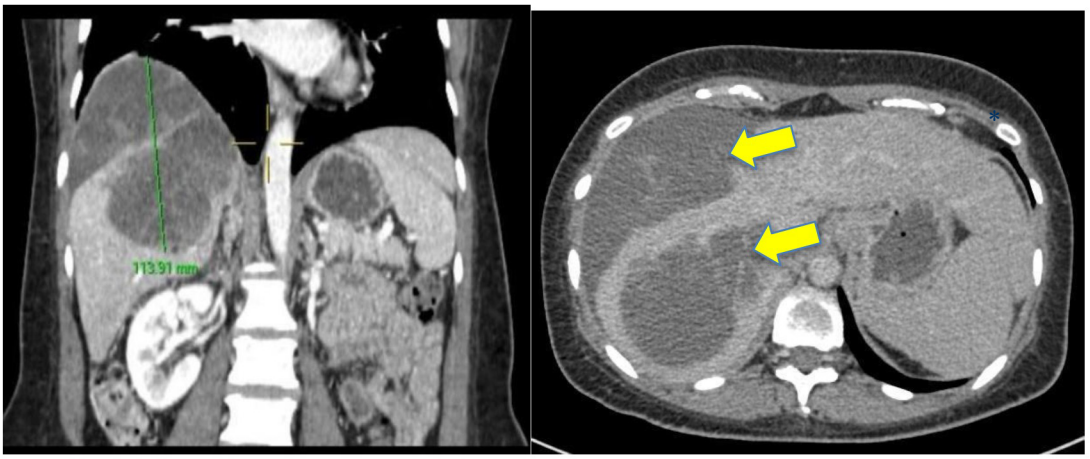


Along with this, Lenvatinib was given at a dose of 8mg/day. Tenofovir 300mg/day was given for her Chronic hepatitis B. During admission, she was also put on lycyrrhizic acid (Minopahgen-C) drip and ursodeoxycholic acid at 1000mg/day. To help stabilize the thrombus, patient was given subcutaneous injections of enoxaparin and later, oral apixaban on discharge. Carvedilol and Ivabradine were also given. Treatment for HCC was not withheld despite the patint's COVID infection.

Follow-up

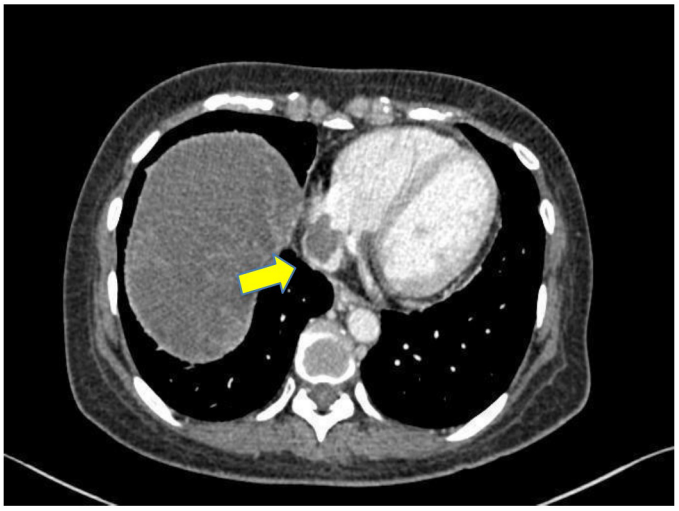
On follow-up 7 weeks after radiation therapy, patient's liver function was relatively stable. She no longer felt short breath, was able to ambulate and had better over-all well-being with an ECOG performance status of 1-2 from 3. Repeat IV contrast CT of the upper abdomen (Figure 5) showed decrease in the size of the mass occupying hepatic segments 7/8 and 6 slightly measuring 136 x 113 x 114 mm (APxWxCC) (previously 138 x 123 x 130 mm). There was note of some cystic degeneration. Extension to the suprahepatic inferior vena cava and right atrium were still noted along with non-enhancement of the left and middle hepatic veins. The portal veins remained patent. Spleen was normal in size and there was minimal ascites. Intra-abdominal lymph nodes remained to be subcentimeter in size as well.

Figure 5. Follow-up upper abdominal CT scan with IV contrast showing the size of the liver tumor after 7 weeks of lenvatinib.



Patient's Chest CT scan with IV contrast done three months after RT showed stable thrombus size in the right atrium and inferior vena cava (Figure 6). However, there were filling defects noted in the right superior segmental artery and pars basalis with extension to the proximal portion of the superior lingular artery, worrisome for pulmonary embolism. Clinically however, patient remained well and able to ambulate. Oral apixaban was continued without any incidents of bleeding episodes.

Figure 6. Chest CT scan IV contrast after 3 months with stable size tumor thrombus in IVC, RA (yellow arrow)



DISCUSSION

Hepatocellular carcinoma with tumor invasion into the inferior vena cava and right atrium are said to occur with a prevalence of 0.6% to 4 [8]. In literature, it was found that having significantly elevated AFP >1,000 ng/mL and tumor size >5cm both independently predict tumor vascular invasion in HCC[9]. These two factors were present in our patient.

Studies have shown that treatment for IVC/RA thrombus may be approached through several methods, ranging from surgical, locoregional, systemic chemotherapy or a combination of the above. A study by Chun et. al showed that only active treatment beyond best supportive care may provide prolonged survival for patients [4].

For this particular case with a Child Pugh score of B9 and Barcelona Clinic Liver Cancer (BCLC) stage C, we used a combination of targeted external beam palliative radiotherapy and oral lenvatinib. Response was favorable as there was slight decrease in size of the liver-dominant mass, stable tumor thrombus in the IVC and RA, preserved liver function and most of all, good performance status more than three months after diagnosis and initiation of treatment. Our patient's clinical course is consistent with some studies which show that radiotherapy can prolong survival in in patients with IVC and RA tumor invasion. A study done by Li et. al revealed that time to tumor progression was

significantly longer among patients who were given external beam radiotherapy (EBRT) compared to those who had surgery [6]. However, this same study also showed that there was no significant difference in over-all survival between the EBRT group and surgery group [6]. Meanwhile a small retrospective cohort study done by Lou et. al. on patients with either IVC thrombus or IVC and RA thrombus showed a high efficacy among patients who were given hypofractionated radiotherapy with nearly all patients having either partial or complete response and stable disease [5].

Lenvatinib, a multi-kinase inhibitor which is an antagonist to endothelial growth factor, has been approved for first-line treatment of advanced HCC since 2018 (9). It has been shown to be more significant in producing longer progression-free survival and non-inferior to sorafenib in over-all survival [10].

Finally, COVID 19 infection can present with a wide spectrum from asymptomatic to severe disease. Patients with pre-existing liver conditions, especially hepatocellular carcinoma, are known to be at higher risk for both acquiring infection and progression to severe disease [11]. Hepatic injury may occur in patients with COVID-19 through either of the following mechanisms: direct cytopathic effect on hepatocytes, immune-mediated inflammation, and/or hypoxia from pneumonia [11]. Fortunately, our patient presented with minimal symptoms for the duration of her infection and liver enzymes were only transiently elevated.

CONCLUSION

Our case demonstrates that for advanced HCC with extensive vascular invasion and tumor thrombus to the IVC and RA, offering a combination of treatment modalities may offer patients the best chance for longer over-all survival, even if management is palliative. In the era of COVID-19, HCC patients must be continually followed up and treatment tailored to their needs. Overall, the value of a multidisciplinary approach to management cannot be overemphasized in order to achieve the most appropriate plan for patients.

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