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Complicated HCC - A Case of IVC Thrombosis

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Abstract Hepatocellular cancer (HCC) is known to be among one of the commonest primary liver tumors globally with rising incidence and it is often implicated as a frequent cause of cancer-related death. It usually carries a poor prognosis because it is not often diagnosed early until the advanced stages of the disease with distant metastatic spread, vascular invasion, and thrombus formation. The pathophysiologic evolution of HCC is complicated involving prolonged inflammatory damage with sequelae of hepatocyte necrosis, regeneration, and fibrosis. Involvement of the vasculature portends a dismal outcome (less than 6 month survival) although inferior vena cava (IVC) tumor thrombus occur far less commonly than portal and hepatic veins. This can present a significant challenge in patient management despite advances in diagnostic and therapeutic modalities, due to late clinical presentation and lack of consensus regarding treatment. We report a 71-year old man who presented with syncope with incidental finding of large hepatocellular cancer with IVC thrombosis. Following extensive workup, the patient was ineligible for surgical intervention and was referred for chemoembolization with possible immunotherapy. This case highlights vigilance for occult malignant processes in patients that may present atypically.

Keywords: *hepatocellular carcinoma, inferior vena cava thrombus, syncope, hepatitis, trans-arterial chemoembolization*

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1. Introduction

Liver cancer was ranked sixth most popular cancer and fourth in terms of cancer-related mortality worldwide in 2018 [1]. More importantly, HCC contributes the largest share of primary liver cancers [1]. A 2018 report also recognised it as one of the commonest causes of cancer-related deaths in the United States (US), second in East Asia and sub-Saharan Africa, and ranked among the top ten in western countries [2]. The disease is more common in males compared to females (2.4 to 1), however, its incidence is higher with advanced age peaking between ages 65 to 70 [2]. Risk factors for HCC include cirrhosis which can be sequelae of various conditions ranging from chronic HBV or HCV, alcohol abuse, aflatoxin exposure, metabolic syndrome, and hemochromatosis [2]. However, alpha-1 antitrypsin deficiency, autoimmune hepatitis, Wilson's disease, and cholestatic liver disorders are less commonly implicated. In the US, non-alcoholic steatohepatitis (NASH) associated with obesity and diabetes is now an emerging cause for HCC [3]. IVC thrombosis is a rare outcome of HCC and it portends poor prognosis with survival reduced by more than 60% [4]. It can however be found in cancers involving the kidneys and adrenal cortex [5]. Tumor thrombus majorly involves the portal vein (35% cases) and hepatic vein (2% cases) with consequent development of portal hypertension in the former [5]. Hepatic vein tumor thrombus (Budd Chiari syndrome) can progress to involve the right atrium causing pulmonary embolism [6].

Therefore, our case highlights the atypical presentation of a patient with hepatocellular carcinoma with inferior vena cava thrombus presenting with syncope, without the expected symptoms of venous congestion or even pulmonary embolism.

2. Case Presentation

A 71-year old man was brought into the emergency department on account of dizziness and light-headedness which occurred at home. He lost consciousness briefly but was held up by his son to prevent him from collapsing to the ground, before fully regaining his consciousness. The son also reported that he had poor appetite, generalized weakness and weight loss, over the preceding couple of months. However he denied any other symptoms. He has medical history significant for diabetes, hypertension, hyperlipidemia, and dementia. He had a long smoking history of over 50 pack years but drank alcohol socially on weekends. There was no history of intravenous drug use and his family history was non-contributory. He previously had colonoscopy a year prior to presentation, which showed benign findings of hyperplastic rectal

polyps and diverticulosis. In the field, Emergency Medical Services (EMS) documented hypotension to systolic 80s while blood glucose was normal at 82 mg/dl. Initial physical findings were notable for cachectic appearance with weight of 60.6kg and Basic Metabolic Index (BMI) of 20.3kg/m^2. His temperature was 36.2 degrees Celsius, heart rate was bradycardic at 54 beats/minute, respiratory rate and blood pressure was normal at 16 breaths/minute and 118/69 mmHg respectively. Abdomen was not distended or tender and the liver was enlarged to about 6cm below costal margin. There was no pedal edema or varicosities in the lower extremities. His premorbid Eastern Cooperative Oncology Group (ECOG) performance status was 2 (two) at best (ambulatory and capable of all self-care but unable to carry out any work activity; up to about >50% of waking hours).

Workup revealed anion gap metabolic acidosis with lactate (6.3mmol/l), bicarbonate (21mmol/l), transaminitis with conjugated hyperbilirubinemia - Aspartate Transaminase (160U/L, normal 0-35U/L), Alanine Transaminase (116U/L, normal 0-35U/L), Alkaline Phosphatase (525U/L, normal 36-92U/L), direct (2.9mg/dl, normal <0.3mg/dl) and total bilirubin (4.0mg/dl, normal 0.3-1.2mg/dl), hypoalbuminemia (3.80g/dl, normal 3.5-5.5g/dl), mildly elevated coagulation factors - Prothrombin Time (13.3secs) and International Normalized Ratio (1.21). Complete blood count was however normal while electrocardiogram was negative for any arrhythmias.

Computed Tomography (CT) scan of abdomen and pelvis revealed a large heterogeneous attenuating intrahepatic mass measuring 10.2 x 14.7 x 10.8cm with areas of internal necrosis and peripheral rim enhancement. A mass effect was noted in the IVC demonstrating a filling defect from the level of the right renal vein to the bifurcation of iliac arteries, highly suggestive of an IVC thrombus. In addition, a chronic L2 vertebral compression fracture was also seen (Figure 1).

Triphasic CT scan with liver protocol confirmed the diagnosis of hepatocellular carcinoma with 14.8 x 11.1cm hepatic mass located at anterior right lobe and left medial segment which was heterogeneously hyper-enhancing with areas of necrosis on arterial phase images as well as washout on portal venous and delayed phases, which revealed enhancing pseudo-capsule. An exerting mass effect was also noted in the portal and hepatic veins (Figure 2). Chest and brain CT scans were also requested and ruled out metastatic spread but diffuse bone demineralization of axial and appendicular skeleton was however noted. No pulmonary emboli was noted on imaging while echocardiogram was grossly unremarkable. Alpha-Fetoprotein (AFP) was markedly elevated (131573ng/ml, normal <10ng/ml) however Carcinoembryonic Antigen, CA-19-9 and Prostate Specific Antigen were normal. The Hepatitis B and C panel was negative while multiple myeloma workup was requested. He was classified as Child Class B based on a Child-Pugh score of 7.

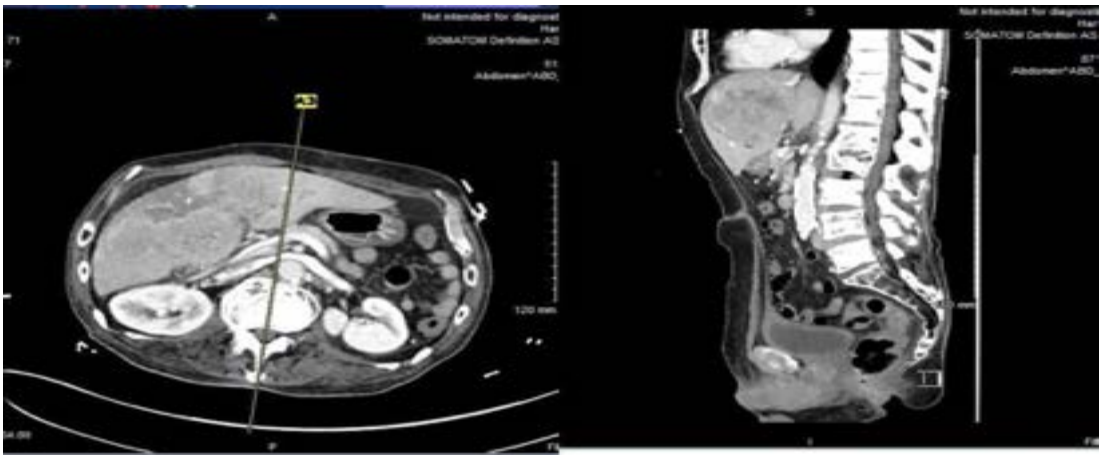

Figure 1. CT scan of abdomen and pelvis showing a large heterogeneous intrahepatic mass

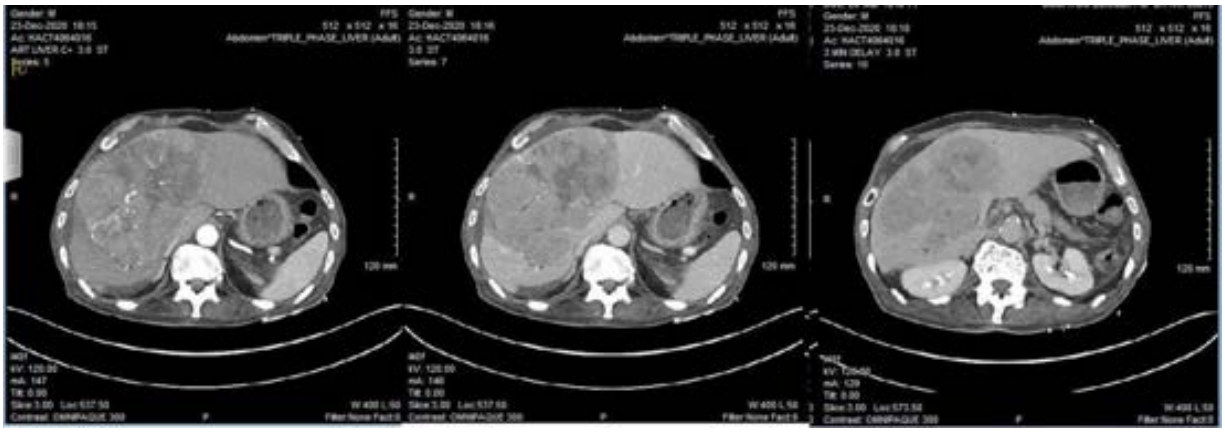

Figure 2. Triple CT scan of abdomen and pelvis showing hepatic mass with heterogeneous hyper-enhancement and areas of necrosis on arterial phase as well as early washout on portal venous and delayed phases

The case was discussed extensively at the interdisciplinary tumor board conference with consensus that the patient was not a candidate for transplant or surgical resection due to advanced age, huge tumor size, large tumor thrombus, high Child-Pugh score and poor ECOG performance status. Patient was started on therapeutic enoxaparin subcutaneous injections 60 mg/0.6 mL every 12 hours. The patient was medically optimized before he was planned for expeditious transfer to a sister institution for trans-arterial chemoembolization (TACE) with possible immunotherapy. Alternative options for hospice care were also discussed in view of the poor prognosis of his condition.

3. Discussion

HCC is a very aggressive tumor with a great affinity for vascular invasion. This leads to tumor thrombus (TT) formation in major vessels such as the portal and hepatic veins. The pathophysiology of syncope in our case could be explained by IVC compression leading to consequent reduced venous return and cardiac output. Based on the location of the thrombus in relation to the heart, TT can be divided into three types, which is helpful when a decision is to be made to treat surgically [7]. Type I (or inferior hepatic) involves the IVC but is limited to below the diaphragm, Type II (or superior hepatic) extends above the diaphragm without right atrium (RA) involvement while Type III (or intracardiac) extends and involves the RA [7]. The median survival for HCC patients with Type III TT who undergo resection is less than 3 years, which emphasizes the need for adjuvant chemotherapy as there is a high chance of postoperative recurrence [7]. Type III TT is associated with an increased risk of myocardial infarction, pulmonary embolism, and systemic metastases, with two cases of resultant acute Budd-Chiari syndrome, already described [8]. Although our patient was diagnosed with a triphasic CT scan, other modalities such as color doppler ultrasound, angiography, magnetic resonance imaging, and positron emission tomography imaging can be utilized. Generally, angiography is regarded as the gold standard for diagnosis, color doppler ultrasound has been found to be as effective as a triphasic CT scan [9]. Hepatectomy with tumor removal and thrombus extraction could be advocated for selected patients, studies have shown that survival is not improved with attendant risk of distant metastases and recurrence [9,10,11]. In situations where there is tumor extension into RA, the need for a major open surgery with cardiopulmonary bypass is required [12].

The Barcelona Clinic Liver Cancer (BCLC) staging system is commonly used for evaluating and planning therapeutic modalities for different HCC stages, as it considers the tumor burden, vascular involvement, portal hypertension, hepatic dysfunction, and current performance status of the patient [11,13]. In contrast, the Hong Kong Liver Cancer (HKLC) staging system is employed for Asian patients because of the disparity in causative agents of HCC between them and Europeans [13]. At the early stages of HCC (BCLC stage 0/A), ablation, hepatectomy or transplantation are potential therapeutic options while for intermediate stages (stage B), palliative locoregional therapies (TACE) remain the most preferred, although median survival is less than 5 months [11,13]. On the other hand, most patients present at advanced stages on first contact (stage C) when beneficial treatment cannot be employed. In patients with stage B, systemic therapy can be started if there is TACE toxicity, poor response, or disease progression despite TACE characterized by vascular or extrahepatic spread (stage C) [13]. Sorafenib has been the first therapy for advanced HCC due to its angiogenic and antimitotic effects, however, newer second line agents (regorafenib, nivolumab and pembrolizumab) have been approved and a tyrosine kinase inhibitor, lenvatinib, is also available as an alternative first line agent [14,15].

In our case, the patient was deemed ineligible for surgical intervention due to advanced age, high tumor burden, and poor premorbid ECOG performance status, with a referral for TACE sessions at a tertiary hospital. In certain situations, TACE can be used to label tumor margins which can be subsequently followed up with percutaneous radio-ablative techniques to remove the thrombus and associated tumor masses. Pulmonary embolism from dislodged thrombus appears to be a potential problem, although it still remains largely unreported [5].

4. Conclusion

Patients with HCC and liver cirrhosis who present in advanced disease stages or with large tumor thrombus have limited therapeutic options and poor outcomes. This case further sheds more light on the possibility of an atypical presentation of HCC with IVC tumor thrombus. It also emphasizes the need to broaden differentials when evaluating a patient with syncope, as deranged laboratory values could be a pointer to a sinister diagnosis, as our case elucidated. More extensive clinical research and newer therapies should be encouraged to improve outcomes in advanced HCC cases. Patient education on modifiable risk factors such as alcohol cessation, weight loss in tandem with early treatment of hepatitis among high-risk patients would result in early intervention and favorable patient outcomes. A multidisciplinary approach is of the utmost importance to set up an optimal treatment plan, with strong consideration of current morbid status and potential complications, with respect to the patient's desired quality of life.

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