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Case Report

Hepatocellular Carcinoma: Massive Tumor Pulmonary Emboli causing Sudden Death

Anwar Ul Haque
Department of Pathology, Pakistan Institute of Medical Sciences, Islamabad

A 65-year-old man had a long history of treatment for his progressively deteriorating rheumatoid arthritis. He was admitted to with complaints of shortness of breath and pain in the chest. He was found dead in the early morning in his hospital bed. The autopsy revealed an unexpected hepatocellular carcinoma (HCC) in his liver with venous extension to the right heart and massive tumor emboli in almost all branches of pulmonary arteries. Although emboli are frequent in hepatocellular carcinoma, massive pulmonary tumor emboli is rare; ours is the fourth reported case! The treating physicians must be aware of this complication as new modalities are being developed to remove the tumor emboli which can prevent sudden death. .
Keywords: Hepatocellular carcinoma, pulmonary tumor emboli, sudden death

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies all over the world. [1] It is more frequent in high hepatitis prevalence areas. [2] Both hepatitis C and B, have relatively higher rates of cirrhosis and HCC. [3] HCC has many other etiological factors including alcohol consumption which cause persistent damage to the liver cells. Of course genetics play important role in all these cases [4]. We here report a case of a 65 year old veteran American-Mexican man who was heavy alcohol consumer and suffered from long standing rheumatoid arthritis involving almost all of his joints along with severe rheumatoid lung disease. At his current admission he suddenly died. The autopsy revealed an unexpected HCC with massive bilateral pulmonary emboli.

Report of a Case

History & Physical Findings

A 65 year old man was hospitalized with respiratory difficulty and arthritis. In the past he has also worked as bartender. He had progressively increasing restriction of movements at various joints with severe pain and swellings due to his long standing rheumatoid arthritis. The elbow, wrist, metacarpophalangeal, proximal interphalangeal, knee,

Anwar Ul Haque
Department of Pathology, Pakistan Institute of Medical Sciences, Islamabad

ankle, metatarsopharayngeal, proximal interphalnageal and intervertebral joints were all involved. For last several months he had to be confined to the wheel chair. He had also developed severe rheumatoid lung disease with associated signs and symptoms. He also suffered from hemochromatosis and diabetes mellitus. He had negative viral serology for hepatitis. On third hospital day he was found dead in his bed by a nurse. Pertinent laboratory findings included Rheumatoid factor of 1: 160 titre, ESR of 40 mm/first hour, Low serum albumin (48%) . A WBC count of 14,700, a low T4 for which he was on synthoid 0.1 mg daily. The patient had been treated with intramuscular gold which were stopped a few months back and he was given pencillamine as chelating agent.

The salient autopsy findings in this obese well built man with deformed joints and peri-articular

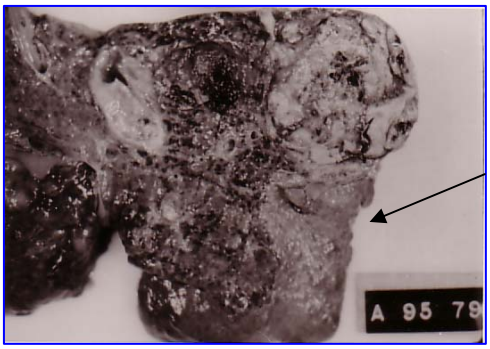


Fig. 1 The hepatocellular carcinoma in the upper right hand corner, posterior aspect of liver

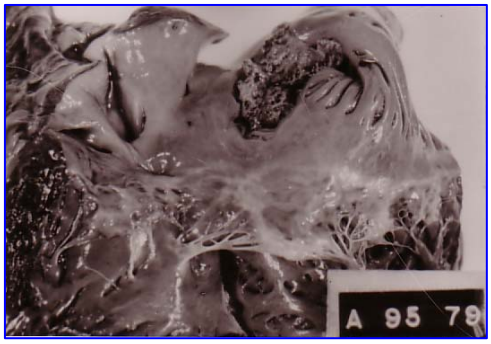


Fig. 2. The tumor embolus in the right atrium

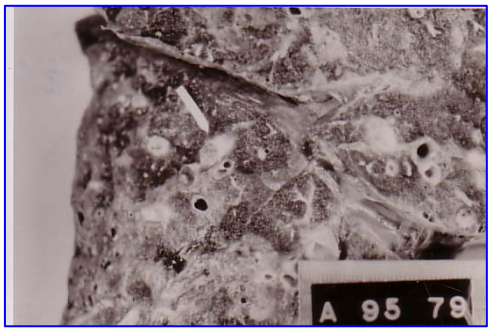


Fig. 3. Pulmonary artery branches occluded by the tumor emboli of hepatocellular carcinoma

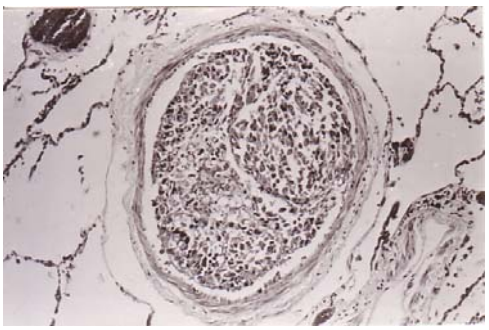


Fig. 4. Tumor embolus in the pulmonary artery

(H&E X 400)

Fig. 5. Rheumatoid honeycomb lung (H &E X 40)

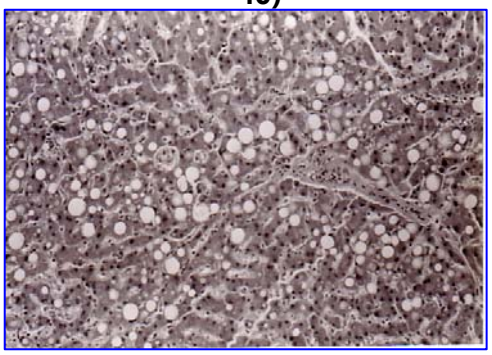


Fig. 6. Non neoplastic hepatocytes with fatty change due to alcoholism (H&Ex400)

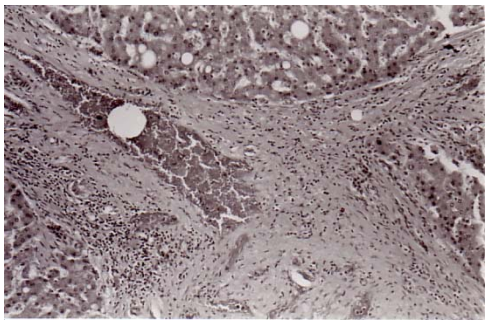
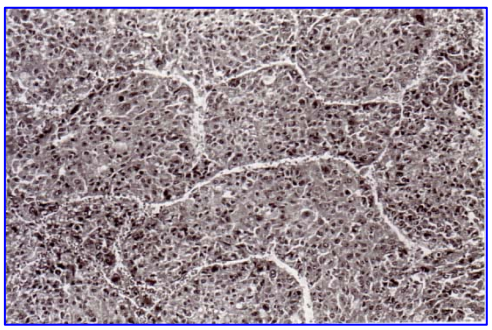


Fig. 7. Macronodular cirrhosis. Note the tumor spread in the vessels (Masson Trichrome X 100)



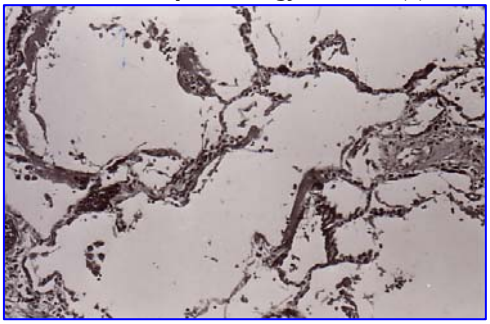


Fig. 8. Hepatocellular carcinoma, moderately differentiated. The tumor cells are forming sheets. The neoplastic hepatocyes show moderate aniso and poikionucleosis. (H&E X 100)

swellings revealed a hitherto unrecognized 5 x 5 x 2.5 cm HCC on the posterior aspect of right lobe of the cirrhotic liver (Figure 1). There were prominent tumor emboli in the superior vena cava and right heart (Figure 2) and bilateral massive pulmonary emboli occluding all the pulmonary arterial branches (Figures 3 & 4).

The lung otherwise had marked destruction of interalveolar septa resulting in honey combed rheumatoid lungs. (Figure 5). The non-tumorous areas of liver revealed marked fatty change (Figure 6). There was pronounced mixed micro & macro-nodular cirrhosis (Figure 7). The tumor was made of trabecullae and sheets of neoplastic hepatocytes containing moderately dysplastic and hyperchromatic nuclei. Frequent vascular invasion was present (Figure 8)

Discussion

HCC is one of the leading causes of death from malignancies. It's the only cancer which is increasing in incidence in USA. It typically occurs in the background of cirrhosis which could be due to any cause. [1-4] In the present case the most likely causes were heavy alcohol consumption and hemochromatosis. The mortality of HCC is related to malignancy itself and metabolic and hemodynamic derangements of cirrhosis. A mild association with diabetes mellitus is also claimed. [5] Viral etiology is well established. [6] Clinical guidelines are well described. [7]

The HCC are very vascular tumors as angiogenesis play significant role in its genesis and progression. These can bleed easily and lead to sudden intraperitoneal hemorrhages. Surgery plays important role in cure of early HCC. For conventional HCC resection, chemotherapy, and local ablative techniques have all been proposed as treatments. The current standard, and the only curative approach, however, is surgical resection: Patients with resected HCC have a 5-year survival rate of 37%–56%.. Factors that are associated with a negative prognosis following [resection] include multiple lesions, lesions that are larger than 5 cm, vascular invasion, α-fetoprotein greater than 2000 µg/ml, and positive resection margins [8]

There are some variants of HCC which are not associated with cirrhosis e.g. fibrolamellar type seen in younger age group and carry better prognosis. They lack many features of common HCC and appear to be a different disease. [9]

Massive pulmonary embolism in cancer patients can be due to detached thrombi of the tumor. Pulmonary tumor embolism is often undiagnosed ante mortem. Only a handful cases have been reported in undiagnosed HCC causing sudden and fatal bilateral pulmonary thrombi. [10-12]. Slow, long standing small emboli may cause subacute cor pulmonale. [13]

Intra-arterial embolization to control growth and spread of HCC is used with variable successes and side effects. Lipiodol is frequently used as therapeutic chemo-embolization agents. However, it may result in pulmonary embolism, which is a potentially fatal complication. In children, Lipiodol should be used with extreme care. Consideration should be given to replacing it with other materials; including albumin or collagen [14] Radiofrequency is increasingly used to manage liver tumors. This at times itself can lead to hemobilia developed, followed by respiratory distress and collapse. The diagnosis of bile pulmonary embolism was established on the basis of high biliary acid concentrations in pulmonary fluid aspiration and plasma. Radiofrequency thermo ablation provides local control of advanced liver tumors with low recurrence and morbidity. However, this interventional procedure risks damage to liver parenchyma involving vascular and biliary structures, which may lead to biliary-venous fistula and possible bile emboli. [15]

HCC thrives on newly formed blood vessels which in turn are formed due to hypoxia. Measurement of Vascular Endothelial Growth Factors (VEGF) in the serum had been found useful in assessing tumor aggression. Several antiangiogenic factors had been found useful in controlling tumor angiogenesis and ts spread. These include BB-94 (Batimastat), TNP 470 and Carboxylamide trizole (CAT) etc. [16]

HCC while remaining undetected can invade and spread through bile duct and give the picture of obstructive jaundice with dark urine and clay colored

stools. [17]

In our case the tumor emboli travelled through hepatic veins, inferior vena cava, the right heart, pulmonary trunk to all branches of both pulmonary arteries blocking almost all of them and explaining . sudden death in our case.

The tumor emboli are now well recognized complication of HCC. These are closely monitored. Various procedures are adopted to remove emboli from inferior vena cava and heart. There are however complications associated with these e.g. these may lead to progression of the emboli and may cause hyper-perfusion and marked pulmonary edema. [18]

Our patient was routinely seen. His HCC was missed perhaps due to macro-nodular cirrhotic nodules and its location on the posterior aspect of the right lobe of the liver. As he had severe rheumatoid lung disease previous episodes if any of less substantial tumor emboli might have been missed as the symptoms and signs might have been referred to the rheumatoid lung disease.

In conclusion we suspect that minor degree of emboli may be rather more frequent and warrant watchful eye and close follow ups. Anticoagaulative measures may not be that useful since tumor itself is very vascular and can easily bleed. On the contrary the factors inhibiting vascular neogenesis as pointed out above may be more important. ISuppression of vascular neogenesis and haemorrhages may help in preventing progress of the disease.

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