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RESEARCH ARTICLE

HEPATIC HYDROTHORAX ASSOCIATED WITH HEPATOCELLULAR CARCINOMA: A CONTROVERSIAL PRESENTATION

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ABSTRACT

Hepatic hydrothorax is defined as a unilateral and mainly right-sided pleural effusion, showing a transudative pattern, non-justified by any secondary causes. Rarely, it may occur independently from and concomitantly with a hepatocellular carcinoma (HCC) with or without pulmonary metastasis, keeping its transudative features. In this article, we address the case of a 64-year-old-woman with liver cirrhosis due hepatitis C virus (genotype 2) with a large, transudative and recurring right-sided pleural effusion characterized as hepatic hydrothorax since 2013, period in which evaluation exams for hepatic cancer were negative. However, two years after the beginning of the hepatic hydrothorax, the existence of hepatocellular carcinoma was evidenced, even though the patient shows lung metastases which were found in the necropsy, and also because she made use of diuretics, in all analyzed pleural fluids – in different moments – the pleural effusion patterns remained transudative, reinforcing that the pleural effusion was due to the portal hypertension and not because of the neoplastic process. This case showed that, even though hepatic hydrothorax and hepatocarcinoma are not frequently seen together, they do not exclude each other and they need to be recognized as different disease entities which need different approaches for a better patient management.

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INTRODUCTION

Hepatic hydrothorax (HH) was described for the first time in 1958 by Morrow[1] and since then it has been defined as significant pleural effusion (> 500 ml) exclusively related to portal hypertension in patients with hepatic cirrhosis (Morrow*et al*., 1958; Al-Zoubi *et al*., 2016).Its diagnosis may be remembered when an advanced and decompensated chronic liver disease patient presents unilateral pleural effusion, most often right-sided, associated with the presence or absence of clinically detectable ascites, although the latter is a rarer condition (Al-Zoubi *et al*., 2016). The thoracocentesis reinforces its suspicion if the Light's criteria determine the fluid is transudative (Singh *et al*., 2013).Hepatic hydrothorax should not be justified by other causes of pleural effusion such as cardiac, pulmonary, pleural or neoplastic causes, although in rare cases, it may occurindependently from and concomitantly with a hepatocellular carcinoma (HCC) with or without pulmonary metastasis, keeping its transudative features.

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Therefore, the aim of this study was to present a clinical case of a patient with advanced hepatic cirrhosis due to hepatitis C virus (HCV) associated with hepatocellular carcinoma (HCC) and hepatic hydrothorax.

Case Report

A64-years-old-woman, originally from Manacapuru/AM, who had been developing shortness of breath associated with moderate to large right-sided pleural effusion (Figure 1), who needed repeated thoracocentesis in 2013, 2015 and 2016. The patient had hepatic cirrhosis due to HCV, genotype 2, since 2005 (undetectable viral load in July 5th, 2016 after treatment with Sofosbuvir and Ribavirin for 12 weeks), she has also had superficial chronic gastritis for 12 years and SAH (Systemic Arterial Hypertension) for more than 10 years. She has a previous history of varicose veins esophageal elastic ligature in 2013 and 2015. She has had a perineoplasty, appendectomy, and oophorectomy for more than 30 years.Her last hospitalization, in July/2016, was as a result of severe dyspnea due to large right-sided pleural effusion, with no alterations of lung parenchyma and in need of a thoracocentesis, presenting clinical improvement after the procedure was done.

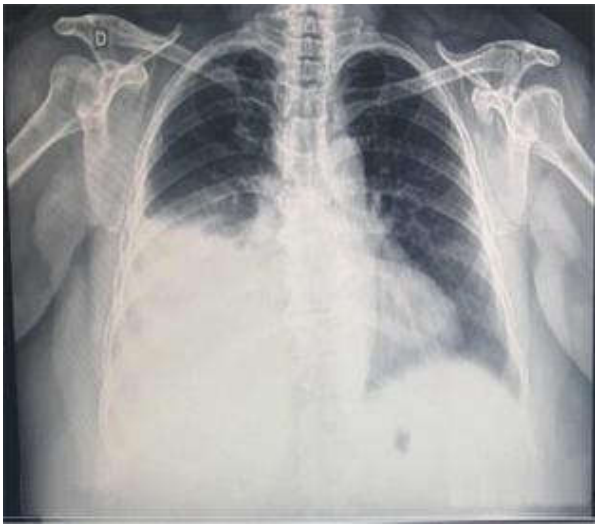

Figure 1. Chest x-ray showing a large right hydrothorax in October 2013, before hepatocellular cancer

On her admission in August/2016 for a diagnostic evaluation, her chest radiography showed again evidence of moderate pleural effusion associated with right lower lobe collapse, with no alteration of lung parenchyma, swollen lymph nodes, or any other alterations (Figure 2).

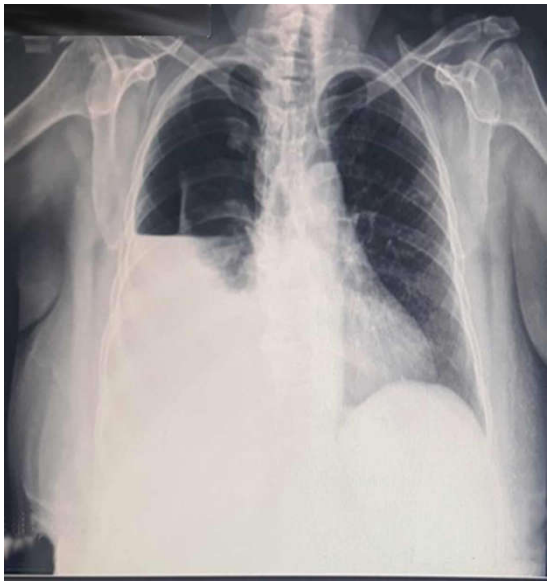

Figure 2. Chest x-ray demonstrating a right hydrothorax in August 2016

Similar alterations were found in previous CT scans in 2013 and 2014. Echocardiogram (ECHO) and electrocardiogram (ECG) also showed no alterations.The patient was regularly accompanied in an outpatient chronic liver disease clinic, being submitted to complete abdominal ultrasounds and tumor marker tests - alpha-fetoprotein (AFP), cancer antigen (CA) 19-9 and carcinoembryonic antigen (CEA) every 6 months. In 2015, an abdominal ultrasound showed signs of chronic liver disease, without abnormalities. Tumor marker tests which were also performed around the same time also showed no signs of alterations. In 2016, an abdominal ultrasound presented a liver nodule, which could be seen in an abdominal and pelvis MRI scan as a sparse and heterogeneous nodule formation, located in the V and VI segments of the right lobe of the liver, measuring 5 and 6,5 cm diameter respectively, showing predominantly peripheral heterogeneous gadolinium enhancement; it also showed gallbladder polypoid budding lesions that would extend from the infundibular region, reaching that body region, also associating itself with surrounding hematic content measuring about 6,6 x 4,0 cm, neoplastic process considered. However, hepatic and canalicular enzymes, tumor and liver function markers showed no alterations.

All the pleural fluid analysis, including the samples from 2013, 2015 and 2016 showed transudative fluid, with no evidence of neoplastic cells, negative bacilloscopy, fungal and microbateria culture tests resulted negative and with no abnormalities. A pleural biopsy performed in August/2016 showed unsatisfactory sample.The patient died on August 30th, 2016 due to acute respiratory failure and when, during necropsy, the histological examinations (Figure 3) and immunohistochemistry analysis (Figure 4) were carried out, hepatic cirrhosis associated with hepatocellular carcinoma (HCC) was evident, although with no signs of metastasis or other alterations. Therefore, due to the fact that the pleural effusion started before the beginning of thehepatocellular carcinoma, the final diagnosis was confirmed as hepatic hydrothorax even though there was a hepatocellular carcinoma.

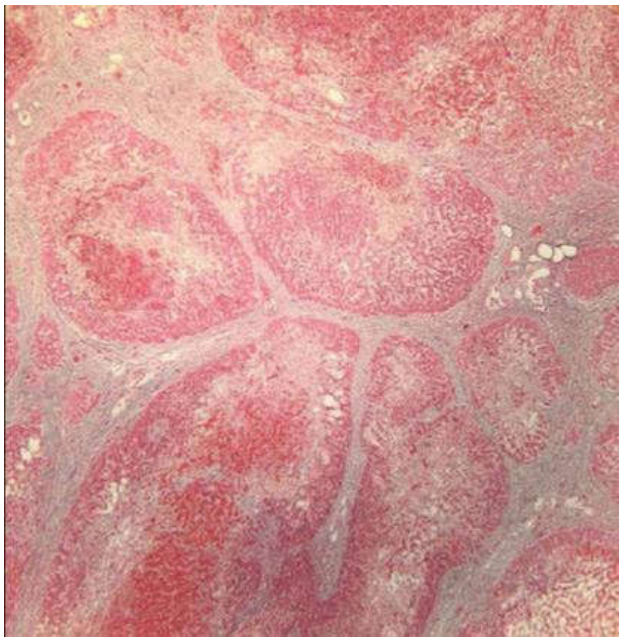

Figure 3. Histological examination of the liver of a 64-year-old woman with hepatocellular carcinoma

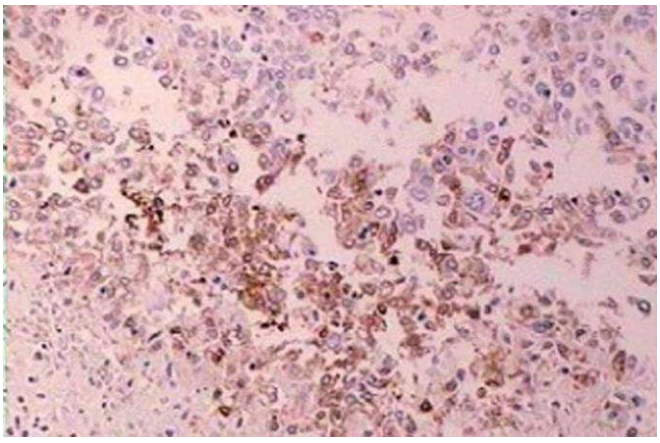

Figure 4. Human hepatocellular carcinoma stained with anti-arginase-1 antibody anti-Arginase-1 antibody (SP156)

DISCUSSION

The study presents the case of a patient with hepatic cirrhosis due to HCV who also developed hepatic hydrothorax, which corresponds to 2-3% of the pleural effusions, and usually happens in patients with portal hypertension with no other associated cardiac, pulmonary or pleural disease that would justify its origin. In our clinical case, even though the patient shows lung metastases which were found in the necropsy, and also because she made use of diuretics, in all analyzed pleural fluids – in different moments – the pleural effusion patterns remained transudative, the neoplastic cells culture and research were both negative, reinforcing that the pleural effusion was due to the portal hypertension and not because of the neoplastic process (Al-Zoubi *et al*., 2016; Singh *et al*., 2013). Eighty per cent of the patients with HCV progress to chronic hepatitis, and 20% of those develop hepatic cirrhosis, favoring the development of the hepatocellular carcinoma, which mainly occurs through indirect ways: chronic inflammation, hyperplasia, transcriptional deregulation, aneuploidy and progression to neoplasia (Andrade *et al*., 2009). Hepatic cirrhosis is also the primary factor to the development of portal hypertension, which happens due to the increase in the blood pressure within the venous portal system (Andrade *et al*., 2009; Balogh *et al*., 2016). The portal hypertension and the consequent splanchnic vasodilation have an important role in the formation of both the ascite and the hepatic hydrothorax.Some mechanisms have been proposed to the formation of the HH such as hypoalbuminemia leading to the decrease of the colloid osmotic pressure (Kim *et al*., 2016), deviation of the thoracic duct lymph and peritoneal fluid to the pleural space through embryonicdefects on the diaphragm most often to the right due to its anatomical proximity to the liver (Al-Zoubi *et al*., 2016; Singh *et al*., 2013). Such defects could also stem from the pleural-peritoneal air bubbles rupture resulting from the cough's high intra-abdominal pressure, tensions or ascites (John *et al*., 2009). These defects' microscopic examinations reveal discontinuity on the collagen fiber structure of the diaphragm's sinewy part. The negative intrathoracic pressure acts like a one-way valves system of ascitic fluid into the pleural cavity (Al-Zoubi, 2016; Singh *et al*., 2013; Kim *et al*., 2016; John *et al*., 2009). In patients who do not develop ascites, the HH formation mechanism is similar. In those patients, almost all the ascitic fluid quickly crosses the diaphragm to the pleural cavity. Ascites develop in these patients when the formation of the ascitic fluid exceeds the lymph absorption and the transfer to the pleural space (Singh *et al*., 2013). In the presented clinical case, the patient did not show any clinically observed ascite and the hydrothorax was larger on the right side, agreeing with the findings in other articles.

The initial evaluation of the hydrothorax pleural effusion is done through the analysis of the pleural fluid which is determined transudative according to the Light's criteria and through the serum-pleural fluid albumin gradient greater than (>) 1.2. Cellularity also shows under 250 cells, with a 100% MMN predominance, dismissing the possibility of an associated pleural empyema. Such characteristics were present on all the pleural fluid analyses in our clinical case.

The patient presented a symptomatic refractory hydrothorax needing repeated thoracentesis to relieve the dyspnea, which is a very common symptom due to the lower complacency of the pleural cavity in relation to the peritoneal cavity, 1-2 liters pleural effusions are capable of bringing intense breathing discomfort. The dyspnea was the first no ascite hepatic cirrhosis' symptom in this patient, a fact which was also reported inother studies (Kim *et al*., 2016; John *et al*., 2016). The thoracentesis complication rates such as pneumothorax and hemothorax is low (Al-Zoubi *et al*., 2016), although it increases according to the number of times the procedure is repeated (Singh, 2013). In this clinical case, the patient progressed to pneumothorax after numerous thoracentesis were performed, then needing a thoracic drainage. However, this procedure should not be performed frequently for it leads to unstoppable loss of fluids and increase in mortality, as was our patient's case, who eventually showed respiratory complications after the thoracic drainage – sepsis, septic shock and death. The aim of the hydrothorax treatment is to relieve the symptoms and prevent pulmonary complications through sodium restriction, diuretics and relief thoracentesis (Singh, 2013; Kim *et al*., 2016; John *et al*., 2016), procedures which were adopted in this patient's management. However, the hydrothorax was refractory to the adopted measures. In cases like this, other procedures are commonly adopted such as pleurodesis with continuous positive airway pressure, video thoracoscopy defect repair, TIPS and liver transplant, when possible (Al-Zoubi, 2016; Kim *et al*., 2016; John *et al*., 2009). Nevertheless, due to the unfavorable outcome of this patient, such therapies could not be adopted. Therefore, this case report means to alert the medical community that repeated pleural effusions in patients with cirrhosis can be caused by portal hypertension, even in patients with hepatocellular carcinoma, and that its early treatment may be a distinguishing factor for a better outcome in this clinical context (Kim *et al*., 2016; John *et al*., 2009).

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