Case report

Hepatocellular carcinoma complicating cystic fibrosis related liver disease

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Abstract

Early diagnosis and treatment of the respiratory and gastrointestinal complications of cystic fibrosis (CF) have led to improved survival with many patients living beyond the fourth decade. Along with this increased life expectancy is the risk of further disease associated with the chronic manifestations of their condition. We report a patient with documented CF related liver disease for which he was under routine surveillance that presented with histologically proven hepatocellular carcinoma (HCC). It is important that physicians are aware of this association as increased vigilance may lead to earlier diagnosis and perhaps, a better outcome.

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1. Introduction

Improved understanding of cystic fibrosis (CF) and advances in treatment have led to increased patient life expectancy over the past two decades. Cystic fibrosis is the most common life-limiting autosomal recessive disease among people of European descent and is no longer an illness only affecting childhood. Current average life expectancy is over 30 years and it is anticipated that, with improvements in nutrition and disease modification, life expectancy will extend to more than 40 years [1]. This improvement in longevity is due to advances in management of disease complications and new therapies, which are altering the natural history of the disease. Unfortunately, improved survival has been associated with new manifestations of chronic disease; the odds ratio is 20:1 for developing a gastrointestinal malignancy in cystic fibrosis patients between the ages of 20 and 29 years of age [2]. Two case reports in the literature, one of which was in our institution, have previously highlighted the association between cystic fibrosis related liver disease and hepatocellular carcinoma (HCC) [3,4]. We present a further case occurring in a patient with previously documented cirrhosis.

2. Case

A 34-year-old man, diagnosed with cystic fibrosis at 4 years of age, was under routine surveillance for documented severe cirrhosis and portal hypertension, which had required gastrooesophageal variceal, banding 15 years previously. His clinical course and biochemical markers had remained stable over the previous 5 years; bilirubin 21(1–21 µmol/L), alkaline phosphatase 218 U/L (35–129 U/L), gamma glutamyl transferase 155 U/L (5–36 U/L), alanine aminotransferase 43(4–50 U/L), albumin 23(30–90 g/L). His international normalised ratio (INR) was 1.29, erythrocyte sedimentation rate (ESR) 22(0–25) and C-reactive protein was 14(0–4). Haematological laboratory investigations revealed a thrombocytopenia with platelets of 36 (150–400×10⁹), which was secondary to his splenomegaly. All other laboratory investigations were normal. Respiratory function had also remained stable over the previous years;
FEV 0.92(33%), FVC 2.54(23%), O₂ saturation was 92% on room air with infrequent hospital admissions for infective exacerbations. A routine 6 monthly liver ultrasound revealed two new hypo echoic lesions in segment 4 of a small nodular liver which had a diffusely heterogeneous echo texture. He was also noted to have portal vein thrombosis. Contrast enhanced liver ultrasound and triphasic computed tomography (64 slice MDCT, Siemens Erlanger, Germany) revealed a more extensive mass lesion that measured 7 cm, with early arterial phase contrast hyper-enhancement followed by contrast washout in the later phases. Since there was a high suspicion of hepatocellular carcinoma, a double contrast MRI liver was performed showing typical appearances of hepatocellular carcinoma: arterial phase contrast hyper-enhancement (Fig. 1) and lack of uptake of super

Fig. 1. a) Post gadolinium enhanced T1weighted images through the liver show a hypervascular area on the arterial phase image. b) Axial MRI image following administration of the paramagnetic contrast agent SPIO shows a focal area of decreased uptake in a large central area in the liver. The liver has a macronodular cirrhotic pattern with focal confluent fibrosis. Note the presence of splenomegaly with multiple siderotic nodules.

Fig. 2. H&E, 200×. A higher power image showing tumour cells, arranged in trabeculae of three or more cells in thickness, with bile production.
paramagnetic iron oxide (SPIO) negative contrast agent. (Fig. 1b). The imaging also confirmed that this was a single lesion. Ultrasound guided core biopsy was then performed which confirmed the diagnosis of hepatocellular carcinoma (Fig. 2). In consultation with the hepatobiliary surgical unit, it was decided that the size of the tumour and presence of severe liver disease precluded any form of surgical resection. He was commenced on the tyrosine kinase inhibitor Sorafenib. Interestingly his alpha-fetoprotein levels were within normal parameters 3.7(0–5.8), however CA19-9 was elevated at 162.3 (0–37). He remains well at follow-up, 21 months after the diagnosis of HCC with a follow-up CT showing a marginal increase in tumour size however no evidence of metastatic disease.

3. Discussion

The clinical manifestations of liver disease in cystic fibrosis (CF) may occur at any age. However, the likelihood of liver disease in an individual patient increases with age until adolescence [5]. Up to 40% of patients with CF develop liver disease but only 1–2% progress to end-stage liver disease [6–8].

Although the presence of macro nodular cirrhosis makes the diagnosis of HCC by ultrasound difficult, ultrasound remains the first line investigation as recommended by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) [6–8]. The performance of ultrasound (US) as a screening tool varies widely depending on the experience of the examiner and the technology used. Recent studies generally indicate a 60% sensitivity and specificity greater than 90% with a positive predictive value of 70% for diagnosis HCC on ultrasound [9].

It is becoming clear that all patients with CF-related liver disease should have bi-annual liver US in specialist centres where comparison with previous images is mandatory to assess for any interval change. Ultrasound is easy to perform, is cost effective and provides a rapid assessment of the liver but it is subjective and depends on the experience of the user. The hepatic sonographic appearances include patchy or diffuse hyper-echogenicity reflecting fatty infiltration, coarse or irregular parenchyma changes, nodularity and thickened hypo-echoic periportal tissues representing periportal fibrosis [9,10]. These changes are thought to be due to thickened inspissated bile secretions causing biliary obstruction and cirrhosis. Biliary duct and gallbladder dilatation and appearances of portal hypertension (including portal venous flow and calibre abnormalities), splenomegaly and varices are common extra hepatic manifestations. Several scoring systems have been recommended, however no consensus agreement has been reached on the optimum grading and scoring systems have been found in at least one report to have wide intra-observer variability [10]. Recent EASL and AASLD guidelines also include contrast-enhanced US in primary investigation of cirrhotic livers and several reports attest to the ability of contrast-enhanced US to diagnose HCC with an accuracy that approaches that of optimized multidetector computed tomography (MDCT) or dynamic magnetic resonance (MRI) [11]. Double contrast MRI is becoming the most common second line examination of choice in patients with cirrhosis as it is reliable and reproducible with a high negative predictive value [12,13] with the advantage of no ionising radiation and a large field of view which can assess the entire liver in arterial phases of enhancement, a limitation of conventional and contrast-enhanced US. Most centres recommend that biannual blood alpha-fetoprotein (AFP) levels should also be obtained at the time of US assessment; although they were within normal limits in our patient they may indicate early HCC even in the absence of the typical imaging appearances.

In our patient the HCC lesion was advanced at diagnosis precluding curative treatment and suggesting that this tumour had an aggressive growth pattern as the patient had been routinely followed with bi-annual ultrasound. As more patients with cystic fibrosis survive into adulthood, we recommend increased awareness and vigilance of this increasingly prevalent complication with early referral for further imaging.

References