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Case Report

Hepatocellular carcinoma in an adult with Alagille syndrome: case report and literature review ☆,☆☆

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ABSTRACT

Alagille syndrome (AS) is an autosomal dominant multisystem disorder which can lead to hepatopathy and the development of focal hepatic lesions. The majority of the hepatic lesions are benign, including regenerative nodules, focal hyperplasia, and adenoma. Hepatocellular carcinoma (HCC) is extremely rare in AS, with very few cases reported in the literature. A 38-year-old man complaining of acute right upper quadrant pain with long-standing diagnosis of Alagille syndrome. On imaging, the patient had a large hepatic mass in the right lobe, with arterial hyperenhancement, washout appearance, and areas of internal hemorrhage. The patient underwent a right hepatectomy and histopathology demonstrated HCC. The patient passed away 3 months after the surgery due to infectious complications. HCC is a rare complication of AS, although rare, it should be considered. This case also emphasizes the need of HCC screening in patients with AS in order to allow an early diagnosis and treatment, which can improve patients' outcome.

Abbreviations: AFP, alpha-fetoprotein; AS, Alagille syndrome; HCC, hepatocellular carcinoma.

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☆☆ Patient consent statement: We have not attached the patient consent inform because there are no images or personal information that might identify our patient in this case report. We have only attached non-identifiable images such as magnetic resonance images, tomography images and pathology slides. None of the images contains any identifying marks and are not accompanied by text that might identify the individual concerned.

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Introduction

Alagille syndrome (AS) is an autosomal dominant multisystem disorder which varies from mild to severe clinical presentation [1]. The diagnosis of AS relies on bile duct paucity in association to at least 3 of the following 5 main criteria: (1) chronic cholestasis; (2) typical facial phenotype, including prominent forehead, deep-set eyes, bulbous tip of nose, pointed chin, and prominent ears; (3) congenital heart disease, being peripheral pulmonary artery stenosis the most frequent one, followed by pulmonary atresia, atrial and ventricular septal defect and tetralogy of Fallot; (4) bone abnormalities, specially "butterfly" vertebrae and occasionally hemivertebrae and spina occulta; and (5) eye abnormalities, frequently posterior embryotoxon [2].

Chronic cholestasis is present in the vast majority of the patients and generally is diagnosed in the first 3 months of life due to jaundice and conjugated hyperbilirubinemia. Liver biopsy typically demonstrates paucity of intrahepatic bile ducts. Eventually, liver damage can cause cirrhosis and liver failure, being an indication of liver transplantation. The hepatic imaging features of AS include signs of cholestasis and chronic cholangitis, such as bile ducts strictures, dilations and biliary distortion, heterogeneity of liver parenchyma, and hypertrophy of the central areas of the liver (particularly segment 4), which can lead to pseudotumoral appearance. Furthermore, focal hepatic lesions may also be detected and the

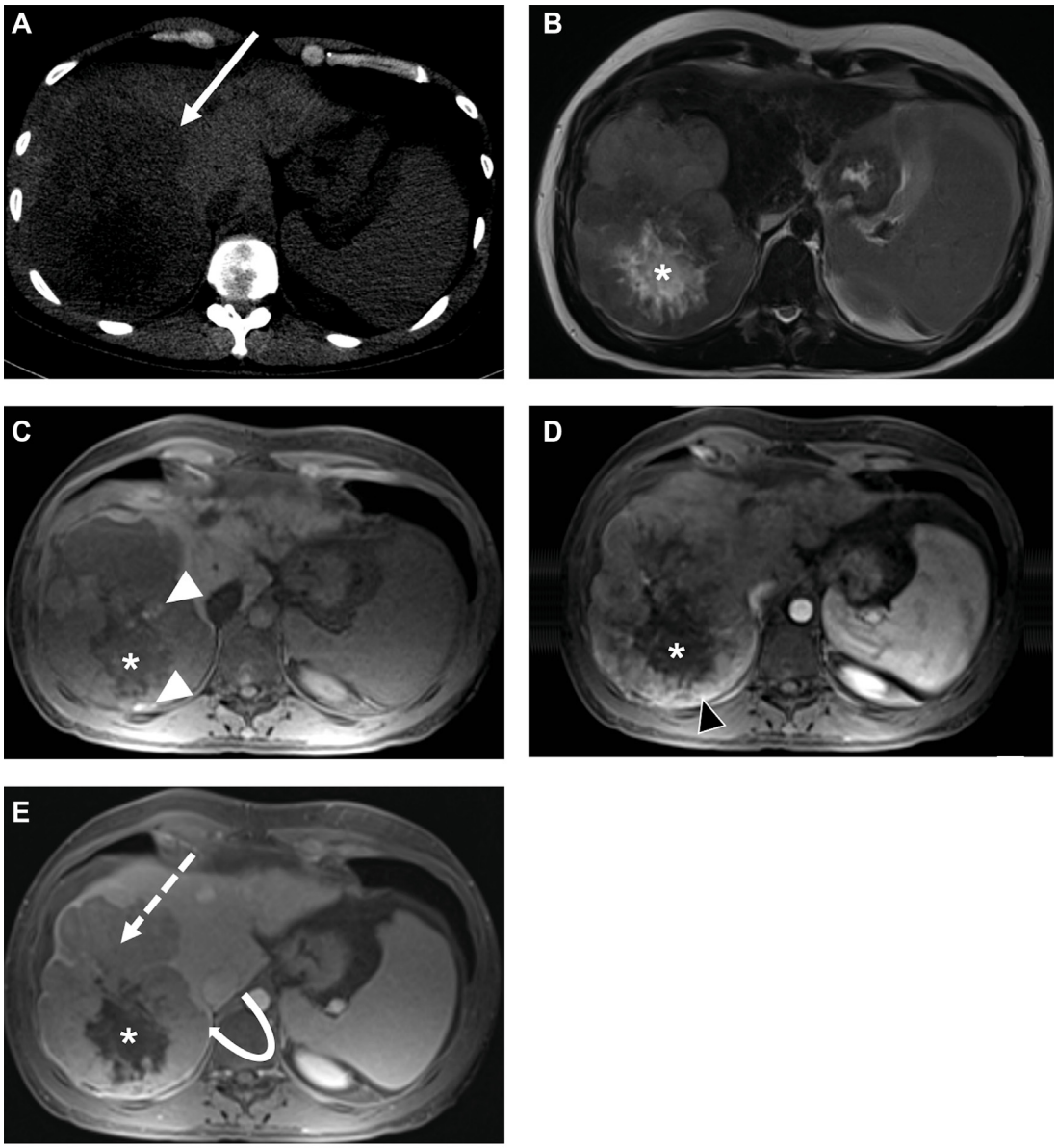

Fig. 1 – (A) Noncontrast computed tomography showed signs of chronic liver disease, splenomegaly, and a 14-cm hypoattenuating mass in the right hepatic lobe (arrow). (B-E) Magnetic resonance imaging demonstrated the heterogeneous mass with central necrosis (asterisks), moderate high signal intensity (SI) on T2-weighted image (WI) (B), low SI on T1WI with areas of high SI suggestive of internal hemorrhage (C, white arrowheads), areas of arterial hyperenhancement (D, black arrowheads), washout appearance (dashed arrows) and capsule (curved arrow) on delayed phase (E).

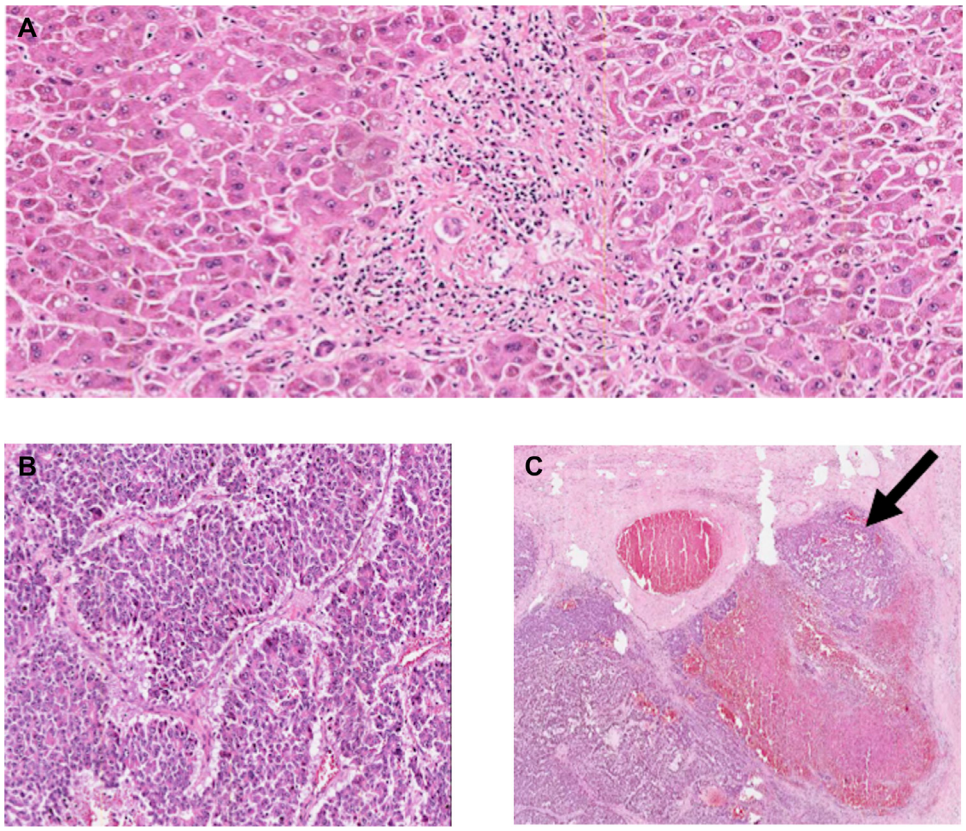

Fig. 2 – (A) On histopathologic analysis, the liver parenchyma showed portal tract fibrosis, ductopenia, and moderate lymphoid infiltrate. Only small and irregular ducts are observed (hematoxylin and eosin, 200×). (B) The analysis of the hepatic nodule demonstrates a predominantly solid architecture with areas of pseudoacinar structures. The cells show enlarged nuclei and conspicuous nucleoli (hematoxylin and eosin, 100×). (C) Venous invasion was also detected (arrow).

majority of them are benign, including regenerative nodules, focal hyperplasia, and adenoma. Hepatocellular carcinoma (HCC) is extremely rare in AS, with very few cases reported in the literature [1,3–6].

The aim of this study is to describe a case of an adult with AS and HCC and to review the literature.

Case presentation

A 38-year-old man complaining of acute right upper quadrant pain was admitted in the emergency department of our institution. He had a long-standing diagnosis of AS; however, he lost to follow-up 8 years before. Physical examination was normal, except for mild discomfort in right upper abdomen. Laboratory studies demonstrated marked elevation of gama-glutamyl transferase (1456 U/L, normal range: 12-73 U/dL), mild elevation of the transaminases (70 U/dL, normal range: under 41 U/dL), and alkaline phosphatase (233 U/L, normal range: 40-129), and elevation of alpha-fetoprotein (AFP) (187 U/mL, normal range: under 7 U/dL).

An abdominal computed tomography without contrast was requested to evaluate his symptoms and demonstrated signs of chronic liver disease, splenomegaly, and a 14 cm hypoattenuating mass in the right hepatic lobe (Fig. 1A). Magnetic resonance imaging showed a 14-cm heterogeneous hepatic mass, with arterial hyperenhancement, washout appearance, capsule, and central necrosis (Fig. 1B-E). T1-weighted images sequence also demonstrated areas of high signal intensity suspicious of internal hemorrhage. HCC was considered in the differential diagnosis.

The patient underwent right hepatectomy. Histopathology evidenced hepatocellular carcinoma. On histopathologic analysis, the liver parenchyma showed portal tract fibrosis, ductopenia, and moderate lymphoid infiltrate. The analysis of the hepatic nodule demonstrated a predominantly solid architecture with focal areas of pseudoacinar structures with enlarged nuclei and conspicuous nucleoli. Venous invasion was also detected (Fig. 2A-C).

Unfortunately, the patient passed away 3 months after the surgery due to infectious complications.

Discussion

HCC is extremely rare in AS, and to the best of our knowledge, up to now there are less than 10 cases reported in the literature. It can occur even in children without cirrhosis, probably due to inflammation and vascular changes that coexist with

the biliary damage. Even patients in screening programs may develop an advanced HCC with metastasis or complications at the time of the diagnosis.

We have reviewed the literature and summarized the main studies that reported cases of HCC in patients with AS [1,3–6]. The average age of patients at the time of diagnosis of HCC was 9 years (range 1-48) and the diagnosis of AS was predominantly between 3 and 4 months of life; however, 1 patient was diagnosed with AS and HCC at the same time with 48 years old [4]. The majority of patients was male [1,4,5] (6/7, 86%), but in one case the gender was not described [6]. Cirrhosis was present in the vast majority of the patients (7/8, 88%) and AFP was elevated in all patients, ranging from 2.800 to 264.200 ng/dL. Our patient was 38-year-old, thus older than the majority of the previous cases. He was also cirrhotic and had elevation of AFP, but it was lower than in the other studies.

Regarding the imaging features of HCC in the previous studies, the majority of the patients had a solitary lesion (7/8, 88%) with a mean diameter of 6.5 cm. One patient had multiple hepatic nodules [5] varying from 0.7 cm to 6.1 cm. The most common imaging features were arterial hyperenhancement on CT and MRI; however, the imaging characteristics of the nodules were not described in a standardized way among the studies. Of note, 1 patient had internal areas of hemorrhage on CT [5] and 1 patient had tumoral portal vein thrombosis [1]. Metastatic disease was present in few cases [1,3,5] (3/8, 38%). The imaging findings observed in our patient were in line with previous study and, as observed by Kim et al., there were areas of high signal intensity on T1-weighted images which suggested hemorrhage.

With regards to treatment and outcomes, the most common management was palliative treatment [1,3,5] (4/8, 50%) due to advanced disease. Three out of 8 patients (38%) underwent liver transplantation [4-6] and only 1 patient (13%) underwent hepatectomy [1], which was the treatment option of our patient. Similarly to our patient, the one described by Bhadri et al. also died due to infection 3 months after hepatectomy. Among the patients who underwent liver transplantation, 1 lost follow-up [5,6] and the other 2 were alive after 20 and 24 months [4,5]. Among the 4 patients who were managed with palliation, 1 lost follow-up [5] and the other died after 2-6 weeks [1,3,5] of the diagnosis of HCC.

This case report emphasizes the importance of considering HCC in patients with AS. This case also stresses the need of HCC screening in patients with AS in order to allow an early diagnosis and treatment, which can improve patients' outcome.

Author contribution

KS: Data curation; Formal analysis; Methodology; Roles/Writing—original draft.

CMFR: Data curation; Methodology; Writing—review & editing.

MCG: Data curation; Methodology; Writing—review & editing.

ARMS: Data curation; Methodology; Writing—review & editing.

GP: Data curation; Methodology; Writing—review & editing.

NH: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Supervision; Roles/Writing—original draft; Writing—review & editing.

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