A convoluted path to the diagnosis of hepatocellular carcinoma in a resource-limited setting

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Abstract

Worldwide, chronic hepatitis B virus infection remains the main aetiology of hepatocellular carcinoma, while human immunodeficiency virus may hasten the evolution of hepatocellular carcinoma in those co-infected with hepatitis B virus/human immunodeficiency virus. We describe a 29-year-old female with unmonitored hepatitis B virus infection for over 5 years, human immunodeficiency virus disease on a tenofovir-based antiretroviral regimen for 11 months, who presented with a 2-week history of epistaxis and abnormal vaginal bleeding, associated with unintentional weight loss of 4 months duration. After extensive investigation, a definitive diagnosis of hepatocellular carcinoma was established based on histopathological assessment in the presence of a positive hepatitis B envelope antigen, mildly raised alpha feto-protein, and a non-cirrhotic liver. Periodic surveillance for hepatocellular carcinoma in patients with chronic hepatitis B virus infection is important, particularly in those with evidence of actively replicating hepatitis B virus for early detection and implementation of curative therapies to reduce mortality and morbidity.

Keywords

Hepatocellular carcinoma, hepatitis B virus/human immunodeficiency virus co-infection, antiretroviral therapy, monitoring of hepatitis B infection, alpha feto-protein

Introduction

Hepatocellular carcinoma (HCC) is a primary liver tumour which occurs predominantly in patients with underlying liver disease and cirrhosis.[1] However, in about 30% of patients with HCC, there exists no evidence of cirrhosis. In chronic hepatitis B viral (HBV) infection, HCC arises secondary to the direct oncogenic effect of HBV on hepatocytes, regardless of underlying fibrosis.[1,2] Hepatitis B virus infection remains the major aetiology of HCC globally.[2] Worldwide, HCC ranks as the second most common cause of cancer-related mortality.[3] The HBV vaccination reduces the incidence of HBV infection and HCC. However, globally over 250 million unvaccinated persons (mostly in Asia and Sub-Saharan Africa (SSA)) had HBV infection in 2015.[2] Human immunodeficiency virus (HIV) infection is thought to hasten the evolution of HBV-related HCC, hence resulting in an earlier age of presentation, often with advanced disease in persons with HBV/HIV co-infection compared to HIV negative persons.[3,4] A case–control study conducted within a Swiss HIV cohort reported an association between a low cluster of differentiation (CD4) cell count and an increased risk of developing HCC among HIV/HBV co-infected patients.[3,5]

The diagnosis of HCC can often be established based on non-invasive investigations; however, in a minority of persons, the diagnosis can prove to be challenging.[1,6] Most patients with chronic HBV infection are inadequately managed to prevent further transmission of infection and/or poorly monitored for early detection of HCC.[2,6] Currently, the incidence of HCC is underestimated in many countries,

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Table 1. Laboratory results of this patient.

Full blood count and iron studies			Liver function			Hepatitis screen	
WCC (×10⁹/L)	12.2	4.0–10.0	TP (g/L)	55	60–78	HBsAg	Pos
HB (g/dL)	4.8	12.0–15.0	ALB (g/L)	22	35–52	HBsAb	Neg
MCV (fL)	92.4	83.0–98	T.BIL (µmol/L)	5	5–21	HBc IgM	Neg
MCH (pg)	30.5	27.0–32.0	ALT (U/L)	128	7–35	HBcAb	Pos
Platelets (×10⁹/L)	357	11.6–14.0	AST (U/L)	842	13–35	HBeAg	Pos
Iron (µmol/L)	8.5	9.0–30.4	ALP (U/L)	293	42–98	HBV-DNA	Rej
Transferrin (g/L)	2.31	2.5–3.80	GGT (U/L)	237	0–35	Hep C	Neg
Saturation (%)	15	15–50	INR	1.79	0.8–1.2		
			AFP (µg/L)	22.9	0–10		

WCC: White cell count; HB: haemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; e-GFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; INR: international normalised ratio; TP: total protein; ALB: albumin; T.BIL: total bilirubin; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; HBsAg: hepatitis B surface antigen; HBsAb: hepatitis B surface antibody; HBc IgM: hepatitis B core IgM; HBcAb: hepatitis B core total Ab; HBeAg: hepatitis B e-Antigen; Hep C: hepatitis C; HBV-DNA: hepatitis B viral DNA; AFP: alpha-fetoprotein; Pos: positive; Neg: negative; Rej: rejected, due to insufficient blood sample.

particularly in low- and middle-income countries (LMICs), which is attributed to limited access to care coupled with poor reporting of health data.[6] In 2012, at least 120,722 cases of HCC were estimated to have been missed, which led to a significant underestimation of the incidence of HCC in 78 countries, of which 34 (44%) were countries from Africa, including Africa South Africa.[6]

We present a case of a young female with HBV infection who was not subsequently monitored accordingly to detect chronic HBV replication who now presented with hepatitis B-related HCC. This case also serves as a reminder to clinicians to maintain a high index of suspicion for HCC in high-risk patients irrespective of age and details some of the diagnostic challenges associated with HCC.

Case presentation

A 29-year-old mother of two children was diagnosed with HIV infection at the 8-week mark of her last pregnancy and started on a tenofovir/lamivudine/efavirenz combination antiretroviral therapy with good HIV disease control (CD4 count of 844 cells/m³ and a suppressed HIV viral load).

She presented to the department of Gynaecology 4 months post-partum with a 2-week history of metrorrhagia and intermittent epistaxis that had worsened in the preceding 4 days prior to presentation. She was treated symptomatically by transfusion of two units of blood and one unit of frozen dried plasma and vitamin K in view of elevated international normalised ratio (INR) level. Gynaecological pathology was excluded, and the Department of Internal Medicine was consulted to take over patient management since she had a deranged liver function test. She also reported significant weight loss (27 kg) over a period of 4 months with no other associated symptoms. The patient had used traditional medicine in the form of scarification but reported no history of herbal ingestion. She had no previous surgery with no family history of malignancies. Obstetric history revealed that both

her pregnancies were delivered by normal vaginal delivery, with her first and second pregnancies at age 14 years and 29 years, respectively. Her last delivery was complicated by a post-partum haemorrhage requiring red cell blood transfusion with no complications thereafter. She was employed as a general worker at a pharmacy with no history of smoking but reported occasional recreational use of alcohol.

Significant findings on clinical examination revealed generalised muscle wasting, a tattoo on her right upper arm with stria on the torso and arms. She was pale, anicteric with subcentimeter epitrochlear and axillary lymphadenopathy. She had no skin bruising nor any stigmata of chronic liver disease or liver cirrhosis. Abdominal examination revealed scarification marks in the epigastric region and hepatomegaly (liver span of 18 cm) with no other palpable masses.

Blood investigations revealed severe normocytic normochromic anaemia, deranged liver function (mixed pattern), and elevated INR. Hepatitis studies revealed a picture of chronic active hepatitis B infection in view of the positive hepatitis B surface antigen (HBsAg) and hepatitis B envelope antigen (HBeAg). HBV viral load was rejected due to an insufficient blood sample submitted to the laboratory. Alpha-fetoprotein (AFP) was marginally elevated at 22.9 µg/L (0–10 µg/L) (Table 1). A search on the National Health Laboratory Services (NHLS) Labtrack® system revealed that blood tests done 5 years before her presentation had shown a positive HBsAg and an alanine transaminase (ALT) of 75 U/L (42–98). Importantly, the patient was not aware of this diagnosis, and neither was there any further monitoring instituted.

Abdominal ultrasonography at this presentation demonstrated an enlarged liver measuring 17.28 cm with multiple heterogeneous ill-defined lesions on the left lobe, the largest measuring 8.12 cm × 5.24 cm. No portal hypertension, free fluid, or other lesions were identified (Figure 1). Contrast-enhanced computed tomography (CT) of the abdomen revealed gross hepatomegaly with multiple intrahepatic

lesions, and on the arterial phase, there is intense enhancement of the lesion supplied by the left hepatic artery. The lesion is relatively isodence on the delayed phase and the venous phase. Considerations included a multifocal HCC or primary hepatic lymphoma (Figure 2(a) and (b)). Lung parenchymal nodules were also noted, which were thought to be metastatic in origin. As imaging was not definitively diagnostic in this case, an ultrasound-guided liver biopsy was performed with subsequent light microscopy and immunohistochemical stains of the liver tissue. Histology confirmed hepatocellular carcinoma (Figure 3(a)–(c)). In addition, the hepatitis B core antigen immunoperoxidase stain was positive in the adjacent liver tissue, which was consistent with active hepatitis B virus infection (Figure 3(d)–(f)).

During hospitalisation, the patient was further transfused two units of red blood cells to optimise the low haemoglobin. During counselling, it was noted that the patient was not aware of the history of HBV infection as alluded above. She was then advised to get her children and her sexual partner

tested for HBV infection. She was referred to the Department of Oncology for further management, where she was assessed as having advanced stage (c) HCC with lung metastasis according to the Barcelona Clinic Liver Cancer (BCLC) algorithm.[2] Her treatment plan included receiving six cycles of Doxorubicin® since this is the drug available in the public hospital in South Africa. Unfortunately, the patient demised at home 2 months later following her diagnosis before initiation of chemotherapy.

Discussion

Symptoms and signs of HCC are non-specific, hence the need for increased clinical vigilance in high-risk patients (those with HBV infection, HIV infection, and HIV/HBV co-infection). The clinician must take cognisance that these high-risk patients might develop HCC at a much younger age than what is traditionally known.[1]

Blood tests for HBsAg have high sensitivity and specificity for screening and diagnosing HBV infection and have been adopted globally for use in the general population.[2,7] However, negative results of this test should be interpreted with caution in patients living with HIV (PLWHIV), as the sensitivity of HBsAg may be lower in this subpopulation.[8] HCC surveillance in patients of Asian descent with HBV infection is recommended to be introduced at the age of 40 years for males and 50 years for females, while in patients of African descent, surveillance is recommended to begin at the time of diagnosis of HBV infection as HCC tends to develop at a younger age as compared to other carriers.[9] Global HCC screening guidelines recommend ultrasonography bi-annually as the imaging modality of choice for HCC surveillance.[1,6]

Although the use of AFP for HCC screening has been controversial because of its low sensitivity for diagnosing early-stage disease and low specificities in patients with active liver inflammation of any cause or liver cell regeneration,[1,6] the World Gastroenterology Organization still recommends that it should be used especially in SSA and Asia and other

Figure 1. Transverse ultrasound image of the liver demonstrating heterogeneous lesions as indicated by the arrows.
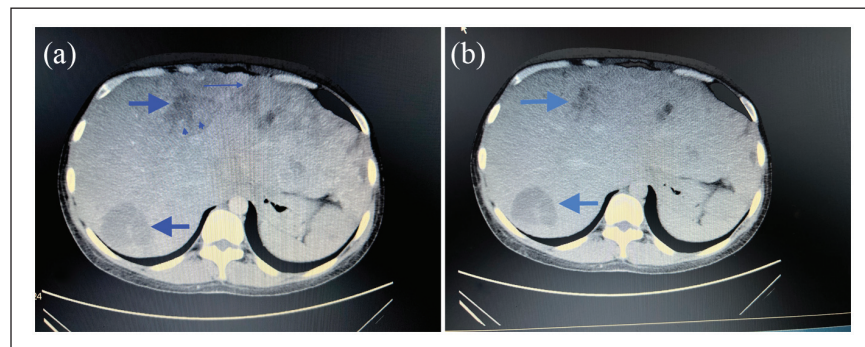

Figure 2. ((a) Arterial phase and (b) venous phase): enhanced computed tomography of the abdomen. Selected images of the abdomen demonstrating multifocal parenchymal (thick arrows), subcapsular (thin arrows) lesions and necrosis (arrow head) enhance during the late arterial phase (image (a)) and hypoattenuating in the portal venous phase (image (b)). These are in keeping with a multifocal HCC.
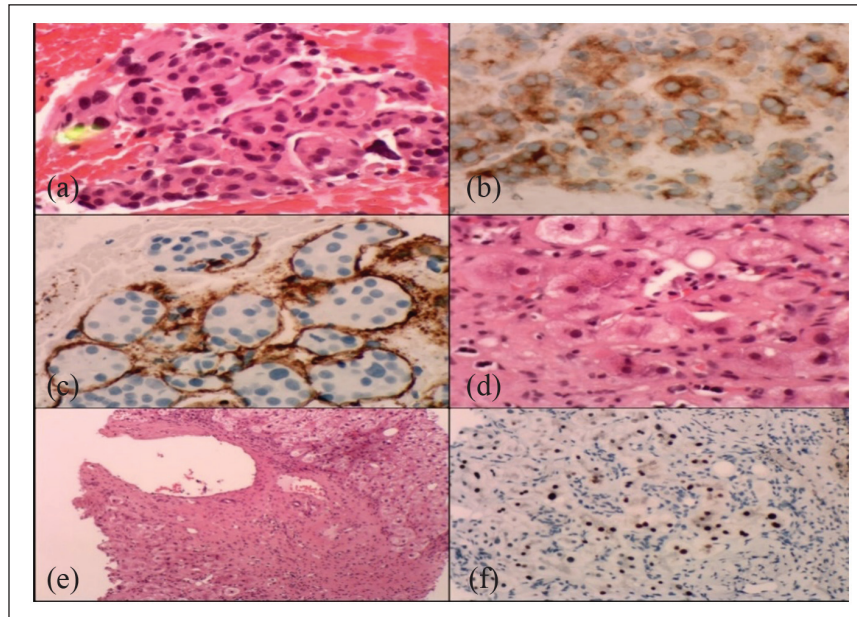
Figure 3. (a)–(f): liver biopsy demonstrating hepatocellular carcinoma and hepatitis B virus infection. (a) Haematoxylin and eosin section show trabeculae and nests of hepatocytes invested by endothelial cells (400×). The neoplastic cells are positive for Glypican-3 (b), and capillarization of sinusoids is confirmed by CD34 (c) (400/). (d): H&E section shows resident liver tissue with hepatocytes displaying eosinophilic cytoplasm and nuclear twinning (400×). (e): H&E section shows portal tract expanded by fibrous tissue and scattered inflammatory cells (200×). (f): Immunoperoxidase stain hepatitis B core antigen nuclear staining (200×).

geographical areas where many patients usually present with advanced-stage disease.[6] It is paramount for clinicians to follow the recommended surveillance guidelines as alluded to above in order to achieve a reduction in HCC-related morbidity and mortality. In the Global HCC BRIDGE study, countries with established and effective national HCC surveillance programmes had a substantially better median overall survival in patients with HCC.[6]

The most commonly used biomarker for diagnosing HCC is serum AFP concentration, and its role in the diagnosis of HCC is evolving as the accuracy of imaging improves.[1] Importantly, not all HCC tumours secrete AFP and serum level concentrations can be within normal ranges in up to 40% of cases. Two studies that included over 1800 patients with chronic liver disease and used an AFP cut-off level of 100–200 µg/mL found that they have a sensitivity of about 60% and specificity approximating 80% for detection of HCC. They demonstrated that higher levels are more specific but less sensitive, and therefore, it has been accepted that serum levels >400 µg/mL in a high-risk patient are diagnostic of HCC.[1,10] A systemic review and meta-analysis study by Zhang et al.[11] concluded that serum AFP levels showed good accuracy in HCC diagnosis, and the threshold of AFP with 400 ng/mL was better than that of 200 ng/mL in terms of sensitivity and specificity no matter whether AFP is used alone or combined with ultrasound. Given the inherent problems with sensitivity and specificity, serum AFP has been removed from some of the guidelines as a diagnostic test for HCC, for example, the organ procurement and

transplant network/united network for organ sharing (OPTN/UNOS).[1] The relationship between tumour growth and the rise in serum AFP was evaluated in a report that included 22 Japanese patients with cirrhosis and HCC lesions smaller than 3 cm and who were followed for up to 37 months without treatment.[12] Serum AFP level tends to be raised when the tumour mass has attained a diameter of greater than 3 cm; especially, a sudden acceleration in the rate of increase of AFP level often coincided with a significant change in the ultrasound appearance of the tumour. The serum AFP levels progressively rose between 1000 and 10,000 ng/mL as the tumours increased in size past 5 cm in diameter.[12] These findings allude to the variability in serum AFP levels in patients with HCC and highlight the need for increased vigilance for patients with HBV infection with and without HIV infection, irrespective of age.

Protein induced by vitamin K absence-II (PIVKA-II) is a potential screening biomarker for HCC with a sensitivity of 60% sensitivity, 88% specificity, and when combined with AFP has been shown to improve the diagnostic accuracy and has a better sensitivity of 70% and specificity of 94% as compared to the individual biomarkers.[13] Unfortunately, the PIVKA-II test is not available in the public healthcare sector in South Africa and in most LMIC.

According to the American Association for the Study of Liver Disease (AASLD) guidelines, the diagnosis of HCC can often be made on imaging alone without the need for biopsy.[1,2,10] Contrast-enhanced CT and/or magnetic resonance imaging (MRI) are good diagnostic tools. For lesions

larger than 2 cm, HCC may be confirmed by hypervascularisation during the arterial phase and washout during the venous phase.[1,10] However, MRI is not readily available in most facilities in LMICs. In the case illustrated, we were presented with inconclusive results of the images, hence the need for liver biopsy with subsequent histopathological evaluation. Liver biopsy with histopathological evaluation of liver tissue specimen remains the diagnostic standard for HCC, although it has its limitations as the yield for smaller lesions is decreased, and complications associated with the procedure must be considered.[1,10]

The only proven potentially curative therapy for HCC remains surgical, either hepatic resection or liver transplantation.[14] Therefore, it is imperative that the diagnosis of this life-threatening condition be made early.

Conclusion

This case highlights the importance of long-term clinical and biochemical follow-up of patients with HBsAg positivity for early diagnosis of HCC. It also serves to remind clinicians to have a high index of clinical suspicion for the diagnosis of HCC in high-risk patients, even in the presence of a normal AFP level and/or non-cirrhotic liver. Furthermore, this case underscores the importance of communicating the diagnosis and follow-up plans with the patient to reduce the disease burden associated with communicable diseases such as HBV infection and its complications.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval to report this case was obtained from medical manager of King Edward VIII Hospital and Department of Health Research Unit.

Informed consent

Written informed consent was provided by the patient legal guardian for their anonymised information to be published in this article.

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