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Summary

Hepatocellular carcinoma (HCC) is one of the most predominant tumor types worldwide, being particularly prevalent in sub-Saharan Africa and East Asia. However, HCC is inexplicably underreported in South America, despite unsettling clinical epidemiological trends of the disease on this continent. Here, we review the current knowledge on HCC presentation in Peru. We emphasize the well documented occurrence of an early-age nosological form of the disease in Andean descent populations. We further discuss the reasons for such clinical presentation, as well as the implications for liver cancer screening, management, and prevention.

Keywords

Liver cancer; Cancer risk factor; Hepatitis B virus (HBV); Indigenous people; Low- and middle-income countries; Global health transition

Abbreviations

AFP, alpha-fetoprotein; CELAC, Community of Latin American and Caribbean States; HBV, Hepatitis B virus; HBsAg, HBV surface antigen; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; INEN, National Cancer Institute of Peru

Introduction

Hepatocellular carcinoma (HCC), the main form of primary liver cancer, is the seventh most common malignancy in incidence and the third leading cause of tumor-related death in the world [1]. Global clinical epidemiology of HCC reported hitherto chiefly delineates a prominent patient profile corresponding grossly to males over 45 years old with chronic liver diseases [2]. The incidence rate of HCC has doubled worldwide during the last two decades, with nearly 85% of the recorded cases and highest rates of disability-adjusted life-years occurring in low- and middle-income countries [3–5]. The largest burdens of HCC are borne in sub-Saharan Africa and East Asia, where the highly endemic chronic infection with hepatitis B virus (HBV) and dietary exposure to mutagenic aflatoxins potentialize one another [6,7]. In contrast, the incidence of HCC observed in more economically developed countries is associated most of all with hepatitis C virus (HCV) infection and heavy alcohol intake that are often associated with comorbid conditions, such as non-alcoholic fatty liver disease, diabetes mellitus, hereditary hemochromatosis or even α-1 antitrypsin deficiency [6,8–10]. These risk factors trigger overtime liver cirrhosis that progresses in a significant proportion of cases in a hepato-carcinogenic process.

Reviews of the global burden of liver cancer have repetitively overlooked the epidemiology of the disease in South America creating a gap between the existing situation in the field and the overall clinical epidemiology of HCC described in the relevant literature [2,11]. Yet, while the incidence rate of primary liver cancer in South America is considered low to intermediate, the

epidemiological trends and the clinical presentation of HCC on this continent are displaying striking and worrying features as a whole. For example, South America is part of the Community of Latin American and Caribbean States (CELAC), which is the world region with the greatest incidence rise for liver cancer monitored during the last decade [12]. Furthermore, some physicians have reported on the continent, since the seventies, the dual occurrence of an early-onset form of HCC in younger individuals concomitantly with a more conventional older patient population.

Clinical epidemiological peculiarities and historical background

In the first instance, Donayre and colleagues reported in a cohort of 60 Peruvian HCC patients between 1969 and 1997 a mean age of 45 years old, with as many individuals in their third decade as people in their seventh decade [13]. The gender ratio (Male:Female) was balanced at 1.3, which appears to be another peculiarity of the clinical epidemiology of HCC in South America compared with elsewhere where the disease afflicts significantly many more men than women [14]. Forty-five percent of the patients were seropositive for the HBV surface antigen (HBsAg). Unfortunately, no formal diagnosis of cirrhosis was provided in this study. However, the authors consistently described an extensive hepatomegaly due to the explosive development of HCC in a short timescale as the predominant feature of clinical presentation.

Second, our group of medical practitioners and researchers described the clinical and demographic features of 232 consecutive patients who underwent

liver resection for HCC between 1990 and 2006 at the National Cancer Institute of Peru (INEN) [15]. In this cohort, the data were consistent with the observations made previously by Donayre and colleagues: the gender ratio was 1.5 and the mean and median ages were relatively young with 41.4 and 36 years old, respectively. Forty-four percent of the patients were HBsAg seropositive [HBsAg(+)], and individuals presented with an extended hepatomegaly due to the development of sizeable HCC of 15 cm-diameter on average. Surprisingly, only 16.3% of the patients had cirrhosis, and the serum level of alpha-fetoprotein (AFP) was exceedingly high with a mean value over 100,000 ng/mL.

Building on these studies, and in order to provide further insight into this intriguing clinical epidemiological situation, we assembled the largest cohort to date in South America; 1,541 Peruvian patients who were consecutively diagnosed with HCC at INEN between 1997 and 2010 [16]. A comprehensive analysis of the demographics substantiated that both mean and median ages observed were misleading and resulted, in fact, from a genuine bimodal Gaussian age-based distribution with a first peak at age 25 and a second peak at age 64, each mode integrating 50% of the overall patient population (Bimodality Index: 1.95; Moment of Mixture: 44.8 years old; Skewness Coefficients: +0.4 and -0.6, respectively).

This age-based dispersion delineated two distinct subpopulations of HCC patients with specific clinical features in terms of, *inter alia*, gender balance, tumor size, distant metastasis and recurrence [16]. For example, 71% of the

111 younger patient individuals were HBsAg(+) compared with 22.5% in the older
112 patient population. As mentioned above, two remarkable hallmarks of HCC
113 clinical presentation in Peru were the significant sizing of an intrahepatic
114 tumor and the overall low frequency of associated cirrhosis in only 10% of the
115 cases examined, this ratio barely reaching 5% in the younger patient
116 population. Noticeably, AFP serum concentration was dramatically heightened
117 in the younger patient group compared with the older one, culminating with c.
118 380,000 ng/mL on average. Taken together, these findings support the idea
119 that a singular biological process is driving liver tumorigenesis in a fraction of
120 HCC patients in South America; and the clinical context described herein is
121 uniquely concerning enough to be an important research topic.
122
123 Afterward, investigators originating from a broad consortium of regional
124 countries have recently conducted a multicenter study in six South American
125 countries including Argentina, Brazil, Colombia, Ecuador, Peru, and Uruguay.
126 In two different articles analyzing the dataset collected from 1,336 patients
127 with HCC between 2005 and 2015, they corroborated at an upper regional
128 level the peculiarities of the disease originally observed in the Peruvian HCC
129 patient population; unfortunately, though, they did not refer to the works
130 previously published on this specific issue [17,18]. In their studies, the authors
131 highlighted the large proportion of HCC diagnosed below age 50 in South
132 America, notably in Peru, and correlated here again the occurrence of early
133 age HCC with a high prevalence of HBV and mild pervasiveness of
134 associated cirrhosis. In a subsequent scientific correspondence, Debes
135 suggested environmental toxins as a foe on early-age HCC in South America,

pointing out the putative role of dietary aflatoxin exposure as already described in Africa [19,20].

Mutation spectrum

For our part, we undertook in a second phase a molecular analysis of nine HCC-related gene mutation hotspots (*i.e.*, *ARID2*, *AXIN1*, *BRAF*, *CTNNB1*, *NFE2L2*, *H/K/N-RAS*, and *TP53*) in 80 Peruvian HCC patients in furtherance to deepen our understanding of HCC in South America [21]. We demonstrated therein that Peruvian HCC featured a peculiar pattern of somatic mutations. The number of genetic alterations observed within these mutational hotspots was relatively low (0 to 3 per tumor) and the intensity of the mutagenic process rather mild with only two mutation hotspots (*i.e.*, *CTNNB1* and *TP53*) reaching 22% of mutants in both early- and late-onset forms of HCC. The preeminent class of HCC-associated genetic defects was epitomized by short deletions affecting notably the Wnt pathway. To the best of our knowledge, this mutation spectrum is not only unprecedented for HCC but also unique among solid tumors in which indels are usually monitored as a marginal subset of genetic alterations, confirming further the distinctive positioning of HCC in South America [22].

Risk factors

In the same study mentioned above from 2014, we addressed the commentary made *a posteriori* first by Chan and colleagues in 2017 and then by Debes in 2018 on the putative brunt of dietary aflatoxin intoxication in early-age onset of HCC afflicting the patients in South America [17,20].

Among the 80 Peruvian patients analyzed, we found only one carrier of the aflatoxin B1-induced R249S *TP53* gene mutation, who was, for the record, an older individual [21,23]. Together with the evaluation of the dietary aflatoxin risk factor, we also considered the possibility of a traditional misapplication of medicinal plants that could contribute to the development of early-age onset of HCC. Indeed, such self-medication disuse that enhances the risk of cancer has been highlighted for *Aristolochia* plants in Chinese traditional medicine [24]. We thus performed a cross-sectional study among 88 Peruvian patients with liver cancer to document their herbal medicine practices [25]. Most of the plant species cited in the survey were of common use in Peru, not being reported hitherto to have carcinogenic potential. Moreover, we discarded, in another preliminary report, the possibility in Peruvian HCC patients of chronic infection with the liver fluke *Fasciola hepatica*, which is found to be endemic in the Andean highlands and has previously been associated with liver parenchymal insults [26,27].

Histology

Taking into account that a significant fraction of HCC patients from South America do not present with full-fledged cirrhosis, we then decided to comprehensively specify, from a histological point of view, the pathological features of both tumor and non-tumor liver parenchymata of 50 HCC patients from Peru [28]. Interestingly, younger HCC patients presented with virtually no fibrolamellar carcinomas, which is a histotype occurring almost exclusively in non-cirrhotic liver and allegedly earlier than age 40 [29]. In addition, a large share of the liver tumors was steato-hepatitic HCC, a relatively rare variant

that is ordinarily associated with non-alcoholic fatty liver diseases and HCV-related cirrhosis [30]. Above all, our survey emphasized the relatively healthy status of the liver in Peruvian HCC patients. Tumors were arising mostly in liver parenchyma with low to mild degrees of fibrosis; this figure is at odds with the current view on the topic, as HCC in non-cirrhotic, non-fibrotic livers is claimed to represent a small minority of the cases [31]. Similarly, the levels of fatty liver and steatohepatitis (8%), as well as siderosis, were relatively low; this latter observation refuting one of the hypotheses formulated by Ponzetto and colleagues to explain the occurrence of early-age HCC among patients in South America [19]. In addition, the micro-steatotic pattern observed in case of infection with the genotype III of hepatitis Delta virus was conspicuously absent from the series. However, a significant proportion of younger HCC patients presented with a high density of clear cell foci of cellular alteration within the non-tumor liver parenchyma [28]. From a morpho-histological perspective, these hepatic foci are reminiscent of liver lesions observed in rodent models that have been subjected to genotoxic chemicals [32]. The exact burden of these clear cell foci and their potential role in liver carcinogenesis has to be ascertained in HCC patients from South America. Therefore, together with prevalent HBV infection, it is likely that the intercession of hitherto poorly documented environmental, metabolic, or infectious cofactors, such as alternative mycotoxins to aflatoxin B1, diabetes mellitus, or even co-infection with *Helicobacter* spp., which is highly endemic in the region [8,19,20,33].

Role of hepatitis B virus

As HBV is still suspected to be the prominent etiological agent and its prevalence monitored serologically associates with younger HCC patients in South America, we performed an in-depth molecular study of HBV infection in 65 HCC patients from Peru [34]. A narrow majority of individuals (51%) were monitored HBsAg(+) and, thus, considered as genuinely infected at the onset of the disease. Using an ultra-sensitive assay, HBV DNA was, however, detected at a very low viral DNA burden in more than 80% of cases, disclosing hence a substantial rate of occult HBV infections in HCC patients [28,34,35]. A phylogenetic analysis of the viral sequences clustered every isolate within the sub-genotype F1b, which is a clade encountered historically in indigenous people of the Americas, notably in Alaska where the occurrence of early-age HCC has been described as well [36–38]. Intriguingly, HBV DNA sequence variations suggest an age-dependent restriction process, as viral genomes in younger patients displayed significantly higher frequency of mutations at di-pyrimidine sites (*i.e.*, TpT and CpC), which was until that time an unprecedented feature in the HBV genome [34]. These findings sharply contrast with the prevailing paradigm that relates higher HBV DNA loads with early-age HCC development [39]. We made assumptions that, in Native communities of the Americas, HBV-associated hepato-carcinogenesis might depart substantially from that broadly observed in other populations [34].

Clinical management

Altogether, the clinical and biological singularities of HCC and associated comorbidities observed in South America have some implications for the management strategies for screening, detection, diagnosis, and prognosis of

HCC patients from the region, as well as the vigilance of the population at risk. For instance, protocols used to screen for HBV infection, notably occult ones, as well as to detect early HCC development in subjects at risk should be tailored to the local situation. Furthermore, Trevisani and colleagues asserted that non-cirrhotic, non-fibrotic HCC clinically represents a distinctive nosological form of HCC with good amenability to liver resection even in cases of major hepatectomy [31]. This observation was confirmed by our review of the 253 Peruvian HCC patients who consecutively underwent a curative hepatectomy at INEN between 1991 and 2011 [40]. In our hands, the survival outcomes of liver resection observed were in good standing with those recorded with liver transplantation in cirrhotic patients with an early-stage tumor, despite the fact that the greatest part of the interventions performed were major hepatectomies due to the size and topography of the tumors exsected. This should be of great concern to the health policy-makers and group of experts aiming to build a regional consensus for HCC prognosis stratification and treatment guidelines and provide state-of-the-art prescriptions for local physicians and scientists, such as the Latin American Association for the Study of the Liver (LAASL) [41].

Concluding remark

Finally, another uncertainty concerns the magnitude of the phenomenon frequently observed in Peru; as to whether it is restricted to the Peruvian Andean communities or also occurs in other human populations, perhaps to a lesser degree. The observations made by Debes and colleagues confirm our original findings at an upper South American continental level [17,18].

Nevertheless, the occurrence of early-age forms of HCC in Alaskan Native people, 10,000 km distant from the indigenous communities of Peru but infected with the very same HBV clade, leads to speculation about the eventuality of a widespread, particular hepato-carcinogenic process shared among all populations with Americas' indigenous ancestry component [16,34,37,42].

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