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Hepatocellular Carcinoma in Chad: A Retrospective Study of 219 Cases

Ali Mahamat Moussa[1*], Pascal Pineau[2], Mayanna Habkreo[1], Gumbo Nedjim[1], Tahir Mahamat Saleh[3], Adoum Abderrazak Fouda[4], Mahamat Ali Hachim[1], Adawaye Chatté[4], Bessimbaye Nadlaou[5], Moussa Kalli[6], Choua Ouchemi[6]

[1]Service de Médecine Interne et Gastroentérologie, Centre Hospitalier Universitaire La Référence Nationale, N'Djamena, Tchad
[2]Unité "Organisation Nucléaire et Oncogenèse", Institut National de la Santé et de la Recherche Médicale U993, Paris, France
[3]Service de Médecine Interne, Centre Hospitalier Universitaire La Renaissance, N'Djamena, Tchad
[4]Programme de Lutte contre le VIH et SIDA, Hépatites et Infectins Sexuellement Transmissibles, Ministère de la Santé Publique, N'Djamena, Tchad
[5]Service du Laboratoire, Centre Hospitalier Universitaire La Reference Nationale, N'Djamena, Tchad
[6]Service de Chirurgie Générale, Centre Hospitalier Universitaire La Reference Nationale, N'Djamena, Tchad
Email: *alimahamatmoussa@hotmail.com

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Abstract

Background: Although hepatocellular carcinoma was historically considered an important scourge in Middle Africa, there is no publication describing this disease in Chad. **Methods:** We conducted a retrospective analysis of 219 patients with hepatocellular carcinoma (HCC) attending care at the University Reference Hospital of Ndjamena between 2007 and 2016. **Results:** This series of HCC was characterized by a male predominance (M:F = 2.4) with a mean tumor onset at the end of the fifth decade of life (49.9 ± 14.7 years). Tumors appear on a cirrhotic liver in 70% of cases and were already multifocal at diagnosis in two thirds of the patients. Alpha-fetoprotein was above the physiological threshold (10 ng/mL) in 73.4% of cases measured and above the so-called diagnostic level (400 ng/mL) in 53.4% of patients. The principal risk factor was chronic infection with hepatitis B virus, detected in 52.6% of cases. Patients seropositive for hepatitis C virus were infrequent (8.6%) and heavy alcohol intake was even less prevalent (5.9%). Remarkably, a very large subset of patients did not present any infectious or lifestyle risk factor (43.4%). Mean AFP values or fibrosis assessment scores are usually lower in these patients than in HBV-infected ones. **Conclusions:** The etiological spectrum of HCC is far from being fully established in Chad. Further epidemiological research is warranted to identify risk factors involved in a large proportion of cases. Exposure to aflatoxin B1 and dysmetabolic conditions affecting the liver have to be investigated as priority.

Keywords

Chad, Middle Africa, Hepatocellular Carcinoma, Hepatitis Viruses,

Alcohol, Idiopathic

1. Introduction

Hepatocellular carcinoma (HCC) still represents a considerable burden of diseases and death in sub Saharan Africa (SSA) due to the high prevalence of the main etiological agents for this tumor type in the general populations of those regions [1] [2]. Populations of SSA are still massively infected with viruses responsible for chronic hepatitis such as hepatitis B (HBV), C (HCV) or Delta viruses (HDV) [3]. Besides these largely documented infectious risk factors, more insidious agents such as the consumption of alcoholic beverages with a poorly defined chemical composition, or the common use of aflatoxin B1-contaminated foodstuffs represent additional causal factors considered as significantly responsible of HCC incidence in SSA [4] [5] [6]. All regions of SSA are not considered to be affected to the same extent by HCC. It is generally admitted that HCC epidemiology is particularly worrying in West Africa (in the Gambia and Guinea more specifically), whereas the situation is better in East Africa. Middle Africa occupies in this context an intermediate position [7] [8]. Chad is a large (1.2 million km^2) and landlocked country of 15 million habitants located at the Northern end of Middle Africa. In the country, liver diseases are considered the first cause for hospitalization. The number of liver cancer cases observed each year is around 400 with an incidence of 2.6/1.0 E+05 habitants [8]. National estimates are, however, frequently considered as substantially lowered due to diagnostic bias by epidemiologists of the subcontinent [9]. Some of the main risk factors of HCC are actually widespread in the Chadian populations. It is mostly the case for persistent infection with HBV [10] [11]. The role played by other risk factors such as aflatoxin B1 is barely assessed while the importance of hepatitis C or that of alcohol abuse is still poorly documented or controversial [12] [13] [14]. The toll taken by liver cirrhosis on Chadian populations remains hitherto unknown.

To date, no descriptive study of HCC presentation in Chad is available. In the present work, we present a retrospective series of 219 cases of HCC diagnosed at the general hospital of N'Djamena between 2007 and 2016 to better understand what are the prevailing etiologies of HCC and the form commonly taken by the disease at diagnosis.

2. Patients and Methods

Patients and diagnosis of hepatocellular carcinoma

A series of 219 records from patients with HCC attending healthcare in the Department of Internal Medicine and Gastroenterology of the University Reference Hospital of N'Djamena (CHU-RN) between April 2007 and August 2016 was recovered from archives. The diagnosis of HCC was obtained according to

the presence of single or multiple hepatic nodular lesions in ultrasonography with, whether or not associated or not with AgHbs, anti-HCV serology, AFP levels above 400 ng/ml. Our data collection tool was a data sheet containing all the variables considered for the study (demography, clinical features, hematological parameters, tumors features, risk factors such as HBV and HCV status, alcohol intake, clinical symptoms and mortality). Patients, and notably subjects with liver cirrhosis (n = 268), without any clearly apparent liver nodule at ultrasound were excluded from the analysis. Ultrasound was performed either with a LOGIQ 400 cc (General Electric Healthcare, Waukesha, WI, USA) or a MINDRAY 40C (Mindray Biomedical electronics, Shenzhen, PR China) apparatus. This research received the approval of the Ethics committee of the Ndjamena School of Medicine). No informed consent was obtained due to the retrospective design of our project.

Serological tests

Viral serologies targeting HBV surface antigen (HBsAg) and immunoglobulins directed against HCV (anti-HCV) were performed in a VIDAS® apparatus (bioMérieux, Craponne, France). Clinical biochemistry parameters including alpha-foetoprotein were also determined on a VIDAS automat.

Statistical analyses

Statistical analyses were performed using a Prism 8.0.2 statistical package (GraphPad, USA). Numerical variables were summarized by their median, mean, and range according to their types of distribution (normal or not). For comparisons of two groups, a Student's t-test, or by Mann-Whitney test was used depending on the distribution of numerical variables (normal distribution or not). ANOVA was used when three groups or more were compared. Categorical variables were summarized as frequencies compared using Fisher's exact test. All tests were univariate and two-sided. Level of significance was set at $p < 0.05$.

3. Results

Demographical of the 219 patients are summarized in Table 1. In brief, a large majority of them (80%) was dwelling in N'Djamena and their mean age was located in the late fifth decade of lifespan (49.9 ± 14.7 years, median = 50 years, inter-quartile range: 39 - 60) A mild male predominance (M:F = 2.4) was noticed. Tumors developed mostly on a cirrhotic liver tissue (70.4%) and presented as multiple nodules at diagnosis in 65.9% of cases (see Table 2).

Infectious risk factors were towered by chronic infection with hepatitis B virus (HBV) as surface antigen of this virus was detected in 52.6% of cases (n = 71/135). Among the subset tested for the presence of immunoglobulin directed against hepatitis C virus (anti-HCV, n = 104), only 8.6% were positive. A co-infection (B+C) was found in 4(3.8%) patients (see Table 1). From the subset of 98 patients for whom both serologies of hepatitis B and C viruses were available, 43 were negative for both (43.8%). Concerning the toxic risk factors of HCC, the notion of excessive alcohol consumption was infrequently retrieved (5.9%).

Table 1. Demographical and risk factors in patients with HCC.

Demography and Risk factors	Values
Demography	
Age (years)	49.9 ± 14.7
Sex-ratio (M/F)	2.4
Risk factors	%
HBsAg (+)	52.6
Anti HCV (+)	9.3
Co-infection HBV + HCV	3.8
Non HBV non HCV	43.8
Heavy alcohol intake	5.9

Table 2. Characteristics of tumors and clinical features of patients with HCC.

Tumors features	%
Multiple nodule (n = 138)	65.9
Liver cirrhosis	70.4
Abdominal pain	65.7
Clinical symptoms and mortality	**%**
Feeling abdominal mass	51.1
Hepatomegaly	42.6
Deterioration of general condition	47.8
Ascites	33.8
Severity of ascites	
I	13.4
II	59.7
III	26.8
Jaundice	23.4
Death during hospitalization	39.5

Tobacco consumption, metabolic antecedents (obesity, type 2 diabetes, metabolic syndrome) or history of exposure to mycotoxins were unknown.

Motifs of consultations were primarily abdominal pain (65.7%) and feeling of an abdominal mass (51.1%). Patients were reporting a fatigue in 35.6% of cases. Clinical examination revealed hepatomegaly in 42.6% and presence of ascites in 33.4% of cases. Jaundice was present in a minority of patients (23.4%). The death of the patients occurred during hospitalization in 39.5% of cases. Laboratory tests reported that alpha-fetoprotein (AFP) was above the physiological threshold (10 ng/mL) in 73.4% of cases and above the so-called diagnostic level for HCC (400 ng/mL) in 53.4% of patients.

We tried thereafter to gain insights into disease presentation and evolution by exploring biochemical and hematological parameters (Table 2) following stratification of the patients according to the main demographical and etiological features.

Male sex was characterized by a significantly higher prevalence of multinodular tumors at presentation (75.5% vs 48.7%, OR = 3.20, 95%CI: 1.4 - 7.5, p = 0.0047). Jaundice was slightly more frequent as well in men (26.0% *vs.* 9.5%, p = 0.0092). The pathophysiological bases of these differences are unknown. Surprisingly, age was not a strong determinant of disease presentation. The lower median for age was only characterized by more severe prothrombin time (PT) values (47.1% ± 21.1% *vs* 79.8% ± 18.0%, p = 0.0038).

The status of non-tumorous liver tissue was an important feature apparently conditioned by disease etiology and conditioning in itself some aspects of disease presentation. Development of HCC on a cirrhotic liver was characterized with a lesser prevalence of multiple tumor nodules (58.5% vs 87.5%, OR = 0.2101, 95% CI = 0.05 - 0.60, p = 0.0012). Regarding etiological factors, these patients were less often developing a cryptogenic (nonB, nonC, non-alcoholic) HCC (23.4% *vs* 53.3%, OR = 0.23, 95%CI = 0.08 - 0.61, p = 0.0011) while HBsAg tend to be more frequent in cirrhotics albeit without reaching the level of significance (57.7% *vs* 37.8%, p = 0.058, ns). As expected, liver enzymes, platelets, and fibrosis assessment scores were all deteriorated in the subset of patients with liver cirrhosis when compare with others (not shown).

The multiple or single nodular form taken by the tumor had, of course, both clinical and biological consequences for patients. HCC presenting as multinodular at diagnostic, already mentioned above as more frequent in male patients and in case of not cirrhotic livers were associated with several clinical and hematological signs. In case of multinodular tumors, patients were more often mentioning a sensation of mass in the abdominal cavity (57.6% *vs* 34.7%, OR = 2.53, 95%CI = 1.1 - 5.7, p = 0.0184). Accordingly, examination by the clinicians revealed more often a hepatomegaly (52.3% *vs* 19.4%, OR = 4.4, 95% CI = 1.6 - 13.9, p = 0.0014). Multiple tumor nodules were characterized by considerable alterations of the blood cell count with an increase of neutrophils and a decrease of monocytes and lymphocytes that results as expected in an increased mean value of neutrophils-to-lymphocytes ratio (NLR, 5.0 ± 3.7 *vs* 3.3 ± 2.4, p = 0.0143) considered as a sign of poor prognosis. Patients who died during the hospitalization that followed the diagnosis of HCC, tended to be older (52.5 ± 14.4 *vs* 46.5 ± 14.0, p = 0.0648) and to be more often affected from nauseas or vomiting (20.8% *vs* 2.8%, p = 0.0360, OR = 8.6, 95% CI = 0.9 - 434.2) than patients who died outside hospital at distance from inaugural diagnosis. They were presenting as well higher levels of blood leukocytes than other patients (13.7 ± 9.6 G/L *vs* 9.4 ± 7.6 G/L, p = 0.0191).

Finally, the presence or absence of the different risk factors in a given patient was changing clinical presentation to various extents. Plausibly, due to the small number of anti-HCV (+) and alcoholic patients, it was difficult to associate these

etiologies with specific features. As expected, anti-HCV (+) patients were thirteen years older than anti-HCV (−) subjects (59.7 ± 20.4 *vs* 46.8 ± 14.3 years, $p = 0.016$), reflecting either time of contamination in patient's lifespan or a more indolent tumor process. Patients with records of alcohol abuse tend to be more often men than women (92.3% *vs* 66.9%, $p = 0.0672$, ns). By contrast, HBsAg (+) and nonB, nonC patients were divergent for a variety of features. Mean AFP values were much increased in case of HBV infection and significantly lower in nonBnonC cases (292 ± 161 ng/mL *vs* 143 ± 172 ng/mL, $p = 0.0070$). Likewise, aminotransferases (ALT, AST), platelets, non-invasive fibrosis assessment scores (APRI) a short-term survival assessment score, were all worsen in case of infection with HBV when compared with nonB, nonC subjects (see **Table 3**).

4. Discussion

HCC is a multistep and often multifactorial tumor, its clinical presentation is important as it provides important clues to get a better appraisal about infectious agent transmission routes, lifelong toxic exposure and nutritional status of the concerned population [15] [16] [17] [18]. Concerning age of onset, it is similar in Chad to that observed in Ivory Coast but higher than the mean age measured in a multicentric study performed in seven countries south of the Sahara [19] [20] [21]. This relatively late age of onset with regards to SSA standards could not be attributed locally to HCV infection (only 8.5% of cases) generally associated with a significantly later tumor onset [22] [23]. It suggests that risk factors

Table 3. Hematological parameters in the series of patients with HCC.

Biological Features Clinical biochemistry	Values	
	Mean ± SD	Median
AST (IU/mL)	177 ± 251	48.5
ALT(IU/mL)	78 ± 121	30.0
Gamma GT (IU/mL)	373 ± 1072	71.0
Creatinine (mg/L)	16.9 ± 18.2	9.8
Urea (g/L)	1.4 ± 5.1	0.3
Total bilirubin (mg/L)	90.89 ± 365	14.4
Albumin (g/L)	46.1 ± 92.2	23.0
Prothrombin time (%)	60.9 ± 25.6	49.0
Platelets (G/L)	288 ± 156	165.0
AFP (ng/mL)	260 ± 203	400
API	3.8 ±	4.0
Fibro Alpha	4.3 ± 2.6	5.0
FIB-4	7.7 ± 24.3	2.5
APRI	3.5 ± 10.0	0.91

present in Chad do not dramatically cooperate to accelerate liver tumor development.

The male-to-female sex ratio observed in Chad (M:F = 2.4) was similar to that measured in a large multicentric study in SSA (2.2) or more recently in Ivory Coast (2.6) or Mozambique (2.3) [2] [19] [23]. It seems to be in keeping with values currently observed on the sub-continent where male predominance appears as less pronounced than in the past. As in most countries of the world, alcohol abuse was more often observed in Chadian men than women [19] [24] but according to patient self-reporting, its importance remains marginal in Chad (5.9%). This temperance is most probably due to the influence of Islam, the religion of the majority of Chadian citizens. Another difference between sexes, was the most frequent multifocality of HCC on Chadian men than in women (78.5% *vs* 48.7%, $p = 0.0047$). The patho-physiological bases of this observation are unknown. It has been suggested, however, that multinodular HCC was more frequent in patients presenting multiple tumor risk factors [25]. More recently, an animal model observed more multinodular HCC in males than in females [26].

In Chad, the distribution of risk factors of HCC presents some peculiarities that bring it close to Sudan, its Eastern neighbor. The prevalence of HBsAg in patients with HCC (52.2%) is in keeping with the rate reported by Yang and coworkers in a multicentric study (50%) or in single center description made in Ghana or South West Nigeria [2] [27] [28]. This rate is, however, much lower than in immediately neighboring countries such as Cameroon (68%), Niger (71%) or North Eastern Nigeria (Maiduguri, 86%) and similar or slightly higher than in Sudan (49%) or Central African Republic (41%) [22] [29] [30] [31] [32]. The low seroprevalence rate of anti-HCV in Chadian patients with HCC (8.6%) was also similar to that observed in Sudan (11%) but somewhat lower than in North Eastern Nigeria (18%) [32] [33]. It was dramatically lower, though, than the rates observed in Cameroun (26%), another neighbor country [22]. Overall, concerning infectious risk factors of HCC, the current situation in Chad looks very much like that described almost two decades ago in Sudan by Omer and coworkers [32]. The proportion of NonBnonC HCC cases (43%) in Chad is again similar to that observed previously in Sudan (47%) and confirmed recently [32] [34]. It is therefore much higher than the corresponding rates observed in the West as in Ivory Coast (21%), in the South as in Cameroon (15%) or in the large multinational survey of Yang *et al.* (22%) [2] [19] [22]. A similar proportion of nonBnonC cases (36%) has been found recently in Mozambique, a country notoriously known for the heavy exposure of populations to aflatoxin B1 [23] [35]. Hence, it has been suggested that a particularly large proportion (26% - 60%) of HCC cases could be attributed to aflatoxin B1 exposure in SSA and particularly in Sudan [36] [37]. It seems plausible, thus, that in countries from SSA where nonBnonC proportion of HCC cases is larger than usual, populations are in fact submitted to particularly intense exposure to aflatoxins. Our data suggest that it could be the case as well in Chad. Further studies combining mycological,

chemical and molecular analyses are now warranted in Chad to confirm this hypothesis. Obesity and its consequences for liver tissues might be another hitherto neglected in Chad. It is considered however that, in SSA, obesity is already a matter of worries only in the austral part of the continent and it is underweight conditions affecting children that are notoriously prevalent in Middle Africa [38] [39]. In Chad, obesity has been estimated to be 6.8% and 2.6% in men and women [40]. Although we cannot confirm that none of the patients included in the present study met the criteria of obesity, we assume that their number should be relatively low and cannot summarize the nonBnonC cases.

Our study suffers from various weaknesses. Serological methods used to investigate the patients were restricted to the minimum due to lack of resources. Notably, we have no notion of hepatitis Delta virus prevalence in this series. No nucleic acid testing that would have undoubtedly reduced the proportion of nonBnonC cases was employed to detect potential occult B infections. Furthermore, clinical and biological data were often not available for all patients of the series. We tried to compensate these shortcomings by the large number of HCC records retrieved on a long period of time (2007-2016). More importantly, we provide in the present paper the first landscape of HCC in a country that was before us a *terra incognita* for the medical literature about that disease. Despite or because of these imperfections, we hope that our data will stimulate clinical and translational research about HCC in Chad with the aim to primarily clarifying its etiological spectrum.

In conclusion, HCC epidemiology is characterized in Chad by a mild male predominance and an age of onset rather late with regards to the standards of SSA. Its presentation adopts the traits usually observed on the sub-continent with, notably, a high rate of multifocality (66%) at diagnosis and a substantial proportion of cases developed on cirrhotic livers (70%). Despite the widespread occurrence of HBV infection in Chadian HCC cases (52%), the second subset of patient by importance is represented by nonBnonC cases, a situation already observed in the neighboring Sudan. Further studies aiming at measuring the rate of occult B infections, determining the genotypes involved in liver tumorigenesis as well as the role played by aflatoxin B1 or dysmetabolic liver diseases are now eagerly expected to allow implementation of efficient prevention and surveillance.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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