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Liver pathology in HIV-positive subjects undergoing liver transplantation

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BACKGROUND

- Liver transplantation (LT) represents the best therapeutic option for end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC). Although LT in HIV+ showed similar survival rates compared to HIV- recipients, HCV recurrence and HCC severity seem more harmful.
- The classification of HCC has changed over time, so the comparison of tumor pathologic features is not easy.
- The most used pattern classification includes:
  - HCC
    - Trabecular
      - Trabecular, clear cells variant
      - Trabecular, giant cells variant
    - Pelioid
    - Pseudoglandular/acinar
    - Sarcomatoid
    - Solid
    - Scirrhous
    - Fibrolamellar
    - Steatohepatitic
  - Lymphoepithelioma-like carcinoma
  - Combined HCC/Cholangiocarcinoma.
- Aims of this study is to compare pathologic features of livers explanted from patients who underwent LT.

Table 1. Baseline clinical features of Study population.

		HIV+ (n=31)	HIV- (n=268)	p
Male sex, %		83.9	83.2	.9255
Age (ys), median (IQR)		53 (50-56)	58 (53-63)	**<.0001**
BMI, median (IQR)		23 (21-25)	25 (23-28)	**.0012**
Viral co-infection, %	HBV	16.1	23.9	**.0176**
	HCV-Ab+/ HCV-RNA+	38.7	54.1	
	HCV-Ab+/ HCV-RNA-	45.2	22.0	
HCV Genotype, %	1A	42.3	14.2	**.0036**
	1B	19.2	43.1	
	2	--	6.9	
	3	23.1	27.9	
	4	15.4	7.8	
Alcohol use, %	No	41.9	74.3	**<.0001**
	Moderate	41.9	7.8	
	Abuse	16.2	17.9	
Diabetes, %		12.9	30.6	**.0394**
ECOG Status, %	0	29.0	27.6	**.0306**
	1	25.8	33.6	
	2	9.7	19.8	
	3	22.6	16.4	
	4	12.9	2.6	
CD4+ count (cell/mmc), median (IQR)		368 (220-518)	--	
CD4/CD8 Ratio, median (IQR)		0.69 (0.64-0.92)	--	
TDF/TAF-based regimen, %		51.6	--	
INSTI-based regimen, %		64.5	--	

Despite a more favorable distribution of traditional risk factors for Hepatocellular Carcinoma (HCC), HIV+ subjects showed macroscopic and pathologic features in explanted livers comparable to HIV-. Histotype distribution is different among groups: diverse gene signature mutations leading to distinctive pathways of HCC development could be hypothesized.

METHODS

- This monocentric, retrospective analysis included all Caucasian subjects with HCV/HBV infection who underwent LT for ESLD or HCC from 2012 to 2019.
- Demographic and clinical features as well as macroscopic and histopathologic characteristics of explanted livers were collected. Patients were stratified according to HIV serostatus.
- Descriptive statistics and non-parametric tests (Chi-square, Fisher's exact and Mann-Whitney U, as appropriate) were used.

RESULTS

- 299 individuals, mainly men (83.3%), with a median age of 57 years (IQR 52-63) were included; HCC was the indication for LT in 66.6% of cases. Thirty-one subjects (10.4%) were HIV+: all had undetectable viral load and a good immunologic status.
- Table 1 shows baseline demographic and clinical features: HIV+ subjects were younger, more commonly HCV+ in Sustained Virologic Response and infected by HCV genotype 1a. Traditional risk factors for HCC (older age, viremic HCV, diabetes) are more favorable in HIV+.
- Table 2 shows features of explanted livers: HIV+ were comparable to HIV- individuals in terms of number and size of lesions, grading stage, capsular structure, portal vein thrombosis and vascular invasion.
  - Of note, above 30% of cases in both groups did not satisfy the so-called Milan criteria for LT eligibility.
- Histotype distribution resulted different, for a higher presence of pseudoglandular pattern and cholangiocarcinoma in HIV- subjects, who showed also higher margin invasion.
- HIV+ showed a worse rate of HCC relapse, especially with an extra-hepatic involvement.

Table 2. Pathologic features of explanted livers.

		HIV+ (n=31)	HIV- (n=268)	p
Reason for LT, %	ESLD	38.7	31.0	.4972
	HCC	58.1	67.5	
	Fulminant hepatitis	3.2	1.5	
Liver weight (g) in ESLD, median (IQR)	BMI≤25	1380 (1020-1420)	1000 (870-1330)	*.0629*
	BMI>25	1470 (1340-1660)	1220 (1025-1375)	*.0588*
Liver volume (cm^3) in ESLD, median (IQR)	BMI≤25	2385 (2096-3025)	2130 (1732-3186)	.5961
	BMI>25	2178 (1713-2849)	2584 (1974-3069)	.5755
Number of pre-LT Tx, mean (DS)		2.3 (1.2)	1.8 (0.9)	**.0044**
BCLC Stage, %	A	83.3	54.7	.1061
	B	16.7	22.1	
	C	--	22.7	
	D	--	0.5	
Presence of HCC in explanted liver, %	No HCC	38.7	27.6	.2355
	HCC cured	12.9	11.2	
	HCC Milan-in	12.9	29.9	
	HCC Milan-out	35.5	31.3	
Unexpected HCC in explanted liver, %		3.2	4.9	.6851
Single HCC lesion, %		38.9	37.1	.8815
Number of HCC in explanted liver, median (IQR)		3 (1-7)	2 (1-4)	.1471
Cumulative HCC diameter (cm), median (IQR)		4.6 (0.7-6.1)	2.9 (1-4.7)	.2420
HCC Grading, %	G1	21.1	13.4	.5875
	G2	47.4	51.0	
	G3	10.5	20.1	
	Missing	21.1	15.5	
Histotype distribution, %	Trabecular	52.6	38.7	**.0384**
	Trabecular, clear cells variant	5.3	12.9	
	Pseudoglandular	--	3.6	
	Trabecular/pseudo-glandular (mixed)	--	22.2	
	Cholangiocarcinoma	--	7.2	
	Missing	42.1	15.5	
Capsular structure, %	Capsulated	10.5	9.5	
	Pseudocapsulated	31.6	30.7	.9837
	Missing	57.9	59.8	
Infiltrative margins, %		15.8	42.7	**.0225**
Portal thrombosis, %		19.4	13.8	.4045
Vascular invasion, %		42.1	27.3	.1736
Overall Mortality, %		16.1	19.0	.6951
HCC relapse, %		26.3	8.8	**.0164**
Extra-hepatic HCC relapse, %		16.1	4.9	**.0124**

CONCLUSIONS

- Despite a different distribution of risk factors for HCC, several pathologic features were similar in the two groups.
- Histopathologic patterns are different among groups: although no histologic type has been included in prognostic staging systems because of poor reproducibility, it is recognized that each HCC feature is associated with different gene signature mutations, thus possible different mechanisms in tumor development in the two populations could be alleged.