

Original Article

Hepatic carcinoma with indolent T-lymphoblastic proliferation (iT-LBP)

Mei Kong¹, Zhaoming Wang¹, Xiaodong Teng¹, Liming Xu¹, Jiming Liu^{1,2}, Chaozhe Jiang¹, Lisong Teng³

¹Department of Pathology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China; ²Department of Pathology and Molecular Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Canada L8S 4K1; ³Department of Oncology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China

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Abstract: Although indolent T-lymphoblastic proliferation (iT-LBP) in the extrathymic location have been shown to be a distinct clinicopathologic entity, carcinoma composed iT-LBP are rare. We retrospectively analyzed the clinicopathological features of 7 hepatic carcinoma cases with iT-LBP. There were 5 male and 2 female patients, aged from 37-54 (mean 47) years. All patients had a clinical history of chronic hepatitis B viral infection with high serum AFP level. Microscopically, these carcinomas were characterized by admixed with increased amounts of fibrous and small lymphocytes composed of regressive germinal centers. Immunohistochemically, in lymphoid tissues, some TdT⁺ cells were highlighted in the CD3⁺ area. These lymphoblasts localized predominantly between the cords of the carcinoma and interfollicular regions, diffused or only focal presented more than 50 TdT⁺ lymphoblasts/HPF. No EBV infection cells and T-cell antigen clonal rearrangement was detected. 3/4 cirrhotic patients developed HCC recurrence, while the 4-y survival rate was 100% in non-cirrhosis patients. It-LBP is a rare unusual proliferation and easily be misdiagnosed in HC patients. It does not seem to be associated with a specific HCC type. If HC companied with numerous small lymphocytes infiltration and showed high Ki67 index, a primary HC with iT-LBP should be considered in the lists of diagnosis.

Keywords: Hepatic carcinoma, indolent T-lymphoblastic proliferation, immature T lymphocyte

Introduction

Although indolent T-lymphoblastic proliferation (iT-LBP) in the extrathymic location have been shown to be a distinct clinicopathologic entity [1], the exact lineage of the T-lymphoblasts in this rare disorder remains uncertain, and its differential diagnosis from lymphoblastic lymphoma and other primary lymphoid processes sometimes can be difficult, particularly on needle biopsies with only tiny materials.

iT-LBP is often associated with other pathologic conditions, all patients have lymphoproliferative disorder or with a discrete tumor mass [2-12]. Although the features of involved carcinoma have been described in 3 papers: 5 cases with hepatocellular carcinoma (HCC) [7, 11, 12] and another with acinic carcinoma [7], there has been no detailed study of hepatic car-

cinoma with this disorder. Accordingly, we reviewed the clinicopathological features of 7 hepatic carcinoma cases in attempt to clarify their clinical presentation and evolution.

A retrospective search of the hospital pathology electronic database was conducted from January 1, 2009 to December 31, 2015 on patients having surgical resection for liver cancer with co-existing lymphocytes and TdT⁺ lymphoblast. Hepatic carcinoma histology was studied in detail.

The presence of more than 50 TdT⁺ lymphoblasts/high power field (HPF) was used for case selection [7]. 6 HCC and 1 combined hepatocellular and cholangiocarcinoma (cHC-CC) cases met criteria. Tumor staging was determined by the seventh edition of American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging system. The main clinical fea-

Table 1. Clinical and pathological characteristic of the hepatic carcinoma with iT-LBP

Patients	1	2	3	4	5	6	7
Age/sex	45/M	52/M	51/F	49/M	44/M	37/F	54/M
HBV Status	+	+	+	+	+	+	+
Serum AFP (ng/ml)	286	4.7	2224.5	2308.5	319.9	477.3	2753.2
Tumor Location	LL	RL	RL	RL	RL	Caudate	Caudate
Tumors number	1	1	1	2	>3	1	1
Maximal diameter	3	1.5	1.5	3.5	3	2.5	2
Histopathology	HCC	HCC	HCC	HCC	HCC	HCC	cHC-CC
Architectural	Trabecular	Trabecular	Trabecular	Trabecular	Trabecular	Trabecular Pseudoglandular	Stem-cell features
Fatty Change	Yes	Yes	Yes	Yes	Yes	No	Focal
L/T (%)	30	10	25	15	20	25	40
LF	Yes	No	Yes	Yes	Yes	Yes	Yes
GC	Small	/	Small	Small	Small	Big, Atrophy	Big, Atrophy
Stroma fibrosis	Yes	Yes	Yes	Yes	Yes	Yes	Yes
AFP stain	+	Focal+	+	+	+	+	+
Distribution of TdT ⁺ cells	Diffuse	Focal	Diffuse	Diffuse	Focal	Focal	Diffuse
Number of TdT ⁺ cells/HPF	>300	Focal, >50	>300	>300	>50	>50	>300
Cirrhosis	No	Yes	No	Yes	Yes	Yes	No
Grading	MD	MD	MD	MD	MD	MD	/
Stage	I	I	I	II	II	I	I
Treatment	O	O+TACE+OLT	O	2O+TACE	2O+TACE	O	TACE+O
Outcome	NED (8 y)	Recurrere (4.5 y) NED (1 M)	NED (4.5 year)	Recurrence (8 M), DOD (10 M)	Recurrence (2 M) NED (10 M)	NED (2 y)	NED (4 y)

M: male; F: female; HCC: hepatocellular carcinoma; cHC-CC: combined hepatocellular-cholangiocarcinoma; L/T (%): lymphocytes volume/Total tumor volume; LF: lymphoid follicle; GC: germinal center; MD: moderately differential HCC; O: operation. NED: No evidence of disease. DOD: died of recurrent tumor.

tures of 7 patients included in this study were briefly reviewed.

Materials and methods

The original slides and formalin fixed paraffin blocks (FFPB) were available for the study. Sections of 4-µm thickness from FFPB were used for routine Hematoxylin and eosin (HE) and immunohistochemical (IHC) stains. The following antibodies were used in the study, which included Hepar I (DAKO, 1:200), AFP (LabVision, 1:1000), CD3 (DAKO, 1:200), CD4 (Leica, 1:50), CD5 (LabVision, 1:80), CD8 (LabVision, 1:300), CD1a (Changdao, 1:60), CD20 (Leica, 1:500), CD23 (LabVision, 1:50), CD34 (LabVision, 1:200), Ki67 (LabVision, 1:200), Cytokeratin 19 (LabVision, 1:200), Cytokeratin 7 (LabVision, 1:200), MPO (Genetech, 1:500), and TdT (Genetech, 1:60). The antigen retrieval was performed by the induction cooker in citrate buffer. EBV-encoded RNA was detected by in situ hybridization.

T-cell receptor gene rearrangement study

PCR was performed to analyze T-cell clonality by T-cell receptor (TCR) β and γ gene rearrangement. DNA was extracted from 8 paraffin sec-

tions at 8 µm by phenol: chloroform. Three separate tests were performed, one with primers of Vγ1f, Vγ10, Jp1/2 and Jγ1/2, the second with primers of Vγ9, Vγ11, Jp1/2 and Jg1/2, and the third with primers of D2 and J2 [13]. Jurkat cells were used as positive controls.

Results

Clinical findings

All patients received surgical resection for primary HCC. 4 patients received transcatheter arterial chemoembolization (TACE) before or after the operation. The clinical findings are summarized in **Table 1**. There were 5 male and 2 female (M:F ratio 5:2). The patients were 37-54 (mean 47) years of age. All patients were clinically asymptomatic and had a chronic hepatitis and related to virus B. Hepatic lesions were identified incidentally during the routine follow-up using abdominal ultrasound. 6/7 had an elevated serum AFP level of >280 ng/L and 1 patient had an increased AFP level for three years prior to the identification of a hepatic mass. Complete blood counts (CBC) were all normal and no patient had splenomegaly or retroperitoneal lymphadenopathy on abdominal ultrasound or CT examination. According to the

HC with iT-LBP

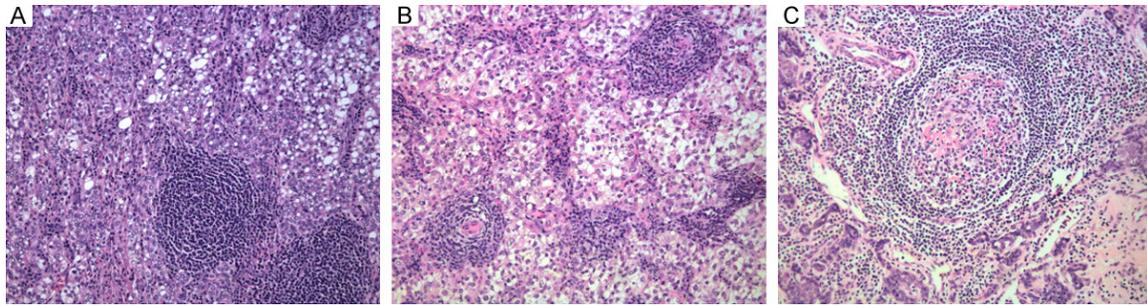


Figure 1. A. HCC with fatty change and increased fibrous and inflammatory stroma between the cell plates. Follicular structure was note. B. Germinal center were small and artrophy. C. The germinal centers were enlarged with massive hyaline degeneration in CHC. (hematoxylin and eosin, $\times 200$).

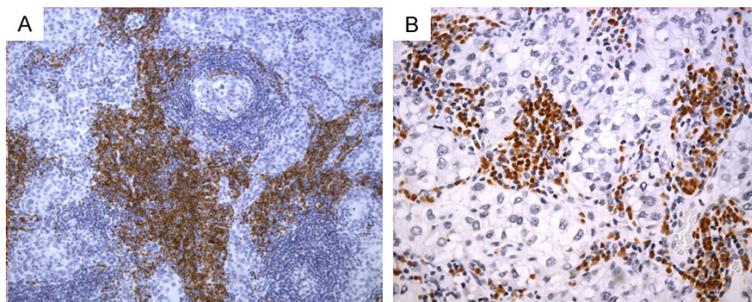


Figure 2. Immunohistochemical analysis showed TdT positive small immature lymphocytes infiltration in the interfollicular areas (A) and between the cords of the carcinoma (B).

seventh edition of AJCC TNM staging, 5 patients were classified as stage I, 2 patients as stage II. The main tumor size was 2.4 cm. All HCC were moderately differentiated. 5 patients had a solitary tumor and 4 patients had histologically confirmed cirrhosis.

The median duration of follow-up of the cohort was ranged from 0.8 to 8 years post operation (median 4.0 years). During follow-up, none of patients developed any hematolymphoid disorder. 4 patients are alive and without evidence of recurrence. 3/4 cirrhotic patients (no. 2, 4, 5) developed HCC recurrence 8, 2 months and 4.5 year postoperatively, and one patient (no. 4) died with tumor progression 10 months post operation, one patient (no. 2) received orthotopic liver transplantation (OLT). The 4-y disease free survival rate was 100% in non-cirrhosis HC with iT-LBP.

Pathologic findings

According to the WHO classification, the architecture of the HC with iT-LBP was mainly trabecular (n=6) in HCC and showed stem cell

features in CHCC (n=1). Fatty change of the tumor cells was present in 6 cases. The tumor grade was moderated differentiation. Lymphoid infiltration was present in all tumors, and account for 10%-40% of total tumor volume. The trabecular were separated by increased amounts of fibrous and small lymphocytes (**Figure 1A**). Although scattered lymphoid follicles showed a preserved germinal center, some centers were only denoted after follicular dendritic cell (FDC) immunostaining or was shown by the presence of small-hyalinized vessel (present in 4 cases), in others the follicular centers were enlarged with lymphocytes depletion and massive eosinophilic hyaline material deposition (present in 2 cases) (**Figure 1B, 1C**). Plasma cells and polymorphonuclear leucocytes were inconspicuous.

In lymphoid tissues, some TDT⁺ cells were highlighted in the CD3⁺ area. These lymphoblasts localized predominantly between the cords of the carcinoma (**Figure 2A**) and inter follicular regions (**Figure 2B**), diffused (4 cases) or only focal (3 cases) presented more than 50 TdT⁺ lymphoblasts/HPF. These cells were small with immature blastic chromatin. Cells atypia and nucleoli were inconspicuous. Only 1 mitosis was present in one case. But high proliferation fractions were shown when stained for Ki67 in these immature T-cells (>70%). No EBV expression was detected.

T-cell antigen receptor gene rearrangement studies were performed. No clonal rearrangement was detected.

Discussion

7 cases of two different types HC with iT-LBP have been described. Although it has been more than 15 years since Velankar et al described the first case of iT-LBP [2], there were only 2 HCC case reports with iT-LBP reported in the literature. They showed a peak age of diagnosis in the fourth and fifth decades. All patients had a clinical history of chronic hepatitis B viral infection and most with high serum AFP level. Different with other non-carcinoma iT-LBP cases, the past medical history of autoimmune disease i.e. rheumatoid arthritis, myasthenia gravis was not found [6, 9, 10]. The clinical course of the cirrhosis patients was more aggressive [12], but non-cirrhosis iT-LBP patients had a favorable prognosis [11]. Although immature T-lymphoblasts proliferated in HC, the risk of developing lymphoma is not increased.

The occurrence of iT-LBP does not seem to be associated with a specific HCC type. The background lesion was represented by a typical HCC component. But sclerosis (often of a hyaline quality) was common in lymphoid area. The germinal centers showed regressive changes and featured prominent capillary, the resulting picture being reminiscent of Castleman’s disease of the vascular hyaline type. The immature cells only located within the carcinoma, it is possible that this is the secondary effect to the carcinoma. Previous study revealed bone marrow-derived CD117+ precursors are able to migrate and home to the liver during fetal development or adulthood [14, 15]. And CD117+ progenitor cells are capable to give rise to extrathymic T-lymphocytes under certain pathological conditions, i.e. infection, autoimmune disease and malignancy [16, 17]. Additionally, it is worth mentioning that this hyperplastic lymphoid tissue with the microscopic features of Castleman’s has been described in association with iT-LBP [6-8]. The local microenvironment, i.e. fibrous scaffold [6, 18], hyperplastic FDCs seem to be associated with iT-LBP.

The differential diagnosis of HC involvement by indolent T-lymphoblasts includes HCC with reactive lymphoid hyperplasia, HCC with co-existing lymphoma, reactive lymphoid hyperplasia (pseudolymphoma), and chronic hepatitis with cirrhosis and lymphocytic infiltration et al.

Distinguishing between these benign lymphoid proliferated disease and T-lymphoblastic lymphoma is more than an academic exercise because they showed confused histologic appearance, manifest different patterns of clinical behavior and dictate different treatment strategies. In direct contrast to reactive lymphoid hyperplasia, These T cells are lymphoblasts and showed high Ki67 index. While the absence of cytologic atypia and the absence of clonality as detected by molecular genetic analysis, against these dense T lymphoblasts representing T cell lymphoma [19].

Additional, it seemed that HC cases with iT-LBP here described expand the range of diagnosis of HC with lymphoid stroma, which currently prefer to lymphoepithelioma-like HCC, which have better prognosis than conventional HCC [20].

In conclusion, we have described the clinical, pathologic, and immunophenotypic features of 7 HC patients with iT-LBP. It is a rare unusual lymphoid proliferation and easily be misdiagnosed in HC cases. It does not seem to be associated with a specific HCC type. If HC accompanied with numerous small lymphocytes infiltration and showed high Ki67 index, a primary HC with iT-LBP should be considered in the list of diagnosis.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Lisong Teng, Department of Oncology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, 79 Qinchun Road, Hangzhou 310003, China. Tel: 86-057187236878; E-mail: lsteng@zju.edu.cn

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