

Lessons from rare tumors: Hepatic lymphoepithelioma-like carcinomas

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Abstract

In this review we focus on lymphoepithelioma-like hepatocellular carcinomas (LEL-HCC) and lymphoepithelioma-like cholangiocarcinomas (LEL-ICC). Despite their rarity, these tumors are of general interest because of their epidemiological and clinical features, and because they represent a distinct model of interaction between the immune system

and neoplastic cells. Approximately half of LEL-HCC arise in the context of chronic hepatitis C virus (HCV) infection and have been described both in Eastern and Western patients. By contrast, LEL-ICC is associated in almost all cases with Epstein-Barr virus (EBV) infection and exhibits the same epidemiological features of EBV related malignancies. Compared with classical hepatocellular carcinoma and intrahepatic cholangiocarcinoma of corresponding stage, both LEL-HCC and LEL-ICC are characterized by lower rates of recurrence after surgery and better overall survival. How this behavior is related to distinct genetic alterations and tumor microenvironment is unclear. The pathophysiological mechanisms of lymphoid infiltrations seem to be different among the two groups of tumors. In fact, LEL-HCC frequently arises in the context of inflammatory changes driven by HCV infection, and has been recognized as a variant of classical hepatocellular carcinoma. At variance, lymphocyte recruitment of LEL-ICC is similar to that described in nasopharyngeal carcinoma and gastric LEL, and possibly depends on the expression pattern of latent EBV infection.

Key words: Lymphoepithelioma; Lymphoepithelioma-like carcinoma; Nasopharyngeal carcinoma; Lymphoepithelioma-like hepatocellular carcinoma; Lymphoepithelioma-like intrahepatic cholangiocarcinoma; Epstein-Barr virus infection

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Core tip: Despite their rarity, lymphoepithelioma-like hepatic carcinomas are of general interest because of their peculiar epidemiological and clinical features, and because they represent a distinct model of interaction between the immune system and neoplastic cells. Compared with classical hepatocellular carcinoma and intrahepatic cholangiocarcinoma of corresponding stage, lymphoepithelioma-like hepatic carcinomas are characterized by lower rates of recurrence after surgery and better overall survival. Whether these differences

are related to distinct genetic alterations or to the tumor microenvironment is unclear. Here we review the features of these tumors and the mechanisms of lymphoid infiltration.

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INTRODUCTION

The term lymphoepithelioma denotes a subgroup of nasopharyngeal carcinomas. These tumors are mostly related to Epstein-Barr virus (EBV) infection, and are characterized by the concomitance of undifferentiated carcinoma cells and polyclonal lymphocyte infiltration^[1-4]. Tumors with similar morphological features, lymphoepithelioma-like (LEL) carcinomas, have been described in salivary glands^[5], lungs^[6], thymus^[7], stomach^[8], colon^[9], uterus^[10], ovaries^[11], bladder and urinary tract^[12], breast^[13], and skin^[14]. Although the association with EBV infection was confirmed in LEL carcinomas of the digestive tract^[15], lung^[16,17], and thymus^[18], it was not found in LEL carcinomas of the breast^[19] and uterus^[20]. In the liver, this type of tumor is extremely rare. Thus far, 29 cases of LEL hepatocellular carcinoma (HCC) and 24 cases of LEL intrahepatic cholangiocarcinoma (ICC) have been described.

LEL-HCC

In 24 of 29 cases^[21-29], the diagnosis of LEL-HCC was based on the retrospective analysis of three different series: one from Japan^[21], one from France^[22], and one from the United States^[23]. These studies were conducted in different periods and differ substantially in design and patient clinicopathological features. Considering these caveats, all three of the studies suggest that patients with LEL-HCC have a better outcome compared with patients with classical hepatocellular carcinoma. The study from Japan dates back to 1994 and was aimed at evaluating the features and the long-term outcome of 11 hepatocellular carcinomas heavily infiltrated by inflammatory cells. The investigation was limited to tumors of less than 3 cm in diameter. The rate of recurrence at 5 years after surgery was 9.1 percent in these patients and 47.5 percent in 116 controls matched for the etiology of the associated liver disease and tumor size. The study from France evaluated the features and the disease course after liver transplantation in 5 patients with hepatocellular carcinoma with lymphoid infiltration. The 5-year survival was significantly better when compared with 163 patients transplanted for

hepatocellular carcinoma. Finally, the study from the United States compared 8 cases of resected tumors classified as inflammatory hepatocellular carcinoma with 18 undifferentiated hepatocellular carcinomas. The rates of local recurrence and distant metastases were 25% and 33.3% respectively, for those patients with inflammatory hepatocellular carcinoma, and 12.5% and 22.5%, respectively for those patients with undifferentiated hepatocellular carcinoma. When the survival data from all 29 patients with LEL-HCC were pooled together, it was evident that 19 patients were alive and free of disease 15 mo to 10 years after surgery (median: 43 mo). Six patients were alive with disease recurrence, and 4 patients died of recurrent disease.

The retrospective design of the above studies implicates that the pre-operative features of these patients are largely unknown. In particular, descriptions of the radiological findings are available in only two cases. In one patient, both computed tomography (CT) and magnetic resonance imaging (MRI) scans showed the features of classical hepatocellular carcinoma, as enhancement in the arterial phase and wash-out in the portal phase were observed^[24]. In the second patient, the CT scan did not show arterial enhancement, whereas the contrast phase of MRI showed peripheral rim enhancement and hyper-intensity of the nodule in T2 sequences^[25]. LEL-HCC was associated with liver cirrhosis in 13 cases, with hepatitis C virus (HCV) infection in 16 cases, hepatitis B virus (HBV) in 3 cases, and EBV in 1 case. Histopathological analysis of LEL-HCC showed that in 16 cases the tumors were poorly differentiated (Figure 1). Well-differentiated or moderately-differentiated tumors were observed in the remaining cases. Interestingly, in 3 cases the same tumor exhibited different grades of differentiation. Positivity for HepPar 1 was described in 3 of 3 tested cases. Cytokeratin 7 and 19 were positive in 4 cases. The overexpression of p16 protein was found in 2 cases. Nests of epithelial cells were surrounded by polyclonal lymphoid cells. Lymphocyte subset analysis showed that CD3-positive cells were 10 times more frequent than B cells. The majority of T cells were CD8-positive in 13 cases, whereas FoxP3 positive cells represented a minority in the single tested case. Remarkably, and similar to the metastases of undifferentiated NPC, the nodal metastatic lesions from LEL-HCC did not show lymphocytic infiltration. The molecular changes associated with LEL-HCC are unknown.

LEL-ICC

Twenty-two of the 24 patients with LEL-ICC were from South-East Asia. In seven of them, the diagnosis was made in surgically resected patients in a single center in Hong-Kong, between 1999 and 2008, and accounted for 5% of all ICC in that period^[30]. The 5-year survival rate of these patients was 100 per cent

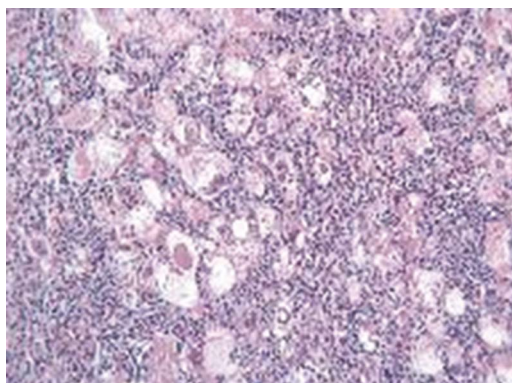


Figure 1 Histological picture of lymphoepithelioma-like hepatocellular carcinoma. Undifferentiated neoplastic cells are surrounded by lymphoid stroma (magnification $\times 250$) (Obtained from Nemolato *et al.*^[29], reprinted with permission).

and was significantly better compared with the 13.2 percent observed in 11 matched controls (classical cholangiocarcinomas). Five cases were from a single center in Taiwan^[31]. The remaining patients were from a single case report^[32-42]. At the time of writing, fifteen patients were alive without disease 2 to 165 mo after surgery (median recurrence free survival: 39 mo), and three patients were alive with recurrent disease (median survival: 56 mo). In addition, four patients died of recurrent disease (median survival: 48 mo), one patient died of post-operative complications and, in another case, no information on survival is available. Descriptions of the CT scans were available only in five cases and were limited to the unenhanced phase^[30,32,35,42]. In these cases, hypodense lesions ranging from 3 to 10 cm in diameter were described. Dynamically enhanced MR T1 imaging was available only in one case, and (similar to ICC) showed centrifugal enhancement of the neoplastic lesion^[30]. LEL-ICC was associated with cirrhosis in 6 cases. HBV infection was documented in 6 cases and HCV infection in two cases. EBV infection was found in 17 cases. Histopathology showed the features of adenocarcinoma with different grades of glandular differentiation and polyclonal lymphocytic infiltration. Interestingly, in at least seven cases, two different components were recognized within the tumor^[31,32,34,37,38,40]. One component consisted of undifferentiated lymphoepithelioma-like cholangiocarcinoma, whereas the other consisted of an adenocarcinoma without lymphocytic infiltration. CK AE1/A3, CK7, and CK19 immunoreactivity was detected in all of the cases but one. The latter tumor was in fact HepPar1 positive, raising the possibility of a misdiagnosed HCC, or a combined hepatocellular and cholangiocarcinoma^[38]. Immunolabeling for markers of stemness, such as CD133 and EpCam, was positive in 5 of 5 evaluated cases^[30]. In situ hybridization for detection of EBV non coding RNA, using antisense oligoprobes, was positive within the epithelial cells in 17 cases. Lymphocytic infiltration consisted of CD3 and CD20 positive cells,

Table 1 Characteristics of the patients with lymphoepithelioma-like hepatic carcinomas *n* (%)

	LEL-HCC (<i>n</i> = 29)	LEL-ICC (<i>n</i> = 24)
Age at diagnosis, median (range)	61 (39-79)	53 (19-71)
HBV infection (positive)	3	7
HCV infection (positive)	16	2
EBV infection (positive)	3	17
Cirrhosis	13	6
Maximum diameter of the tumor (mm)	25 (13-130)	45 (16-160)
Surgical treatment (OLT/resection)	6/23	0/24
Rate of recurrence	6 (20.6)	8 (36.3)

LEL-HCC: Lymphoepithelioma-like hepatocellular carcinomas; LEL-ICC: Lymphoepithelioma-like cholangiocarcinomas; EBV: Epstein-Barr virus; OLT: Orthotopic liver transplantation; HCV: Hepatitis C virus; HBV: Hepatitis B virus.

and was consistently negative for markers of active or latent EBV infection. One single study^[30] addressed the gene methylation status and the mutations of KRAS and EGFR genes in LEL-ICC. Loci coding for CRBP I (cellular retinol binding protein I) and CRBP IV (cellular retinol binding protein IV) showed significantly higher methylation status than in ICC. This finding is in agreement with the epigenetic changes occurring in EBV-related nasopharyngeal carcinoma. Wild-type KRAS and EGFR genes were detected in all of the cases.

INTRAHEPATIC LYMPHOEPITHELIOMA-LIKE CARCINOMA: WORKING HYPOTHESES

Hepatic LEL carcinomas, similar to gastric and lung LEL carcinomas, are characterized by a significantly better survival than classical HCC and ICC counterparts of corresponding stage. Whether the more favorable outcome of hepatic LEL carcinomas depends on distinct genetic and epigenetic changes, or whether the tumor infiltrating lymphocytes play a prominent role in improving the outcome of these patients remains unclear. In turn, the baseline features and the outcome of hepatic LEL carcinomas are also related to the clinical setting in which the tumor arises. Notably, the patients with LEL-HCC and LEL-ICC (Table 1) differ with regard to age, tumor size, presence of cirrhosis, and rate of HCV and EBV infections. The World Health Organization recently recognized LEL-HCC as a variant of HCC^[43]. Indeed, HCC is characterized by different grades of lymphoid infiltration^[44,45] and LEL-HCC represents an end of this spectrum. The molecular mechanisms linking inflammation and cancer depend on the complex network of chemokine and cognate receptor axes^[46-53]. In the setting of HCC, it has been shown that the CXCL12^[54,55] CXCL8^[56], CCL3^[57] CCL20^[58] and CCL22^[59] ligands, and the aberrant expression of their receptors affect tumor development and progression, angiogenesis and metastasis. Several

Table 2 Pathological findings in patients with lymphoepithelioma-like-hepatic carcinomas

	LEL-HCC (n = 29)	LEL-ICC (n = 24)
Histological features		
Poorly differentiated	16/29	10/24
Moderately differentiated	13/29	3/24
Combined LEL-HCC and HCC	None	
Combined LEL-ICC and ICC		9/24
Immunohistology		
HepPAR1	3/3	1/2
CK7 and CK19	4/11	24/24
EpCAM	ND	7/7
CD133	ND	7/7
EBV status		
EBERs	3/18	17/24
LMP1/2 antigens	ND	0/8
LMP1 gene	ND	2/2
EBNA2	ND	1/1
Lymphoid infiltration		
CD3/CD20 ratio > 1	29/29	4/4
CD4/CD8 ratio < 1	11/29	1/4

LEL-HCC: Lymphoepithelioma-like hepatocellular carcinomas; LEL-ICC: Lymphoepithelioma-like cholangiocarcinomas; EBV: Epstein-Barr virus; EBERs: EBV-encoded RNAs; LMP: Latent membrane protein; EBNA2: Epstein Barr nuclear antigen 2; ND: Not done.

lines of evidence, however, note that the chemokine system also has a role in tumor control. Myeloid cell infiltration is associated with a poor prognosis, whereas T helper 1 infiltration directly correlates with a reduced risk of tumor recurrence^[60]. In addition, a pro-inflammatory microenvironment characterized by high expression of the innate immune genes TNF, IL6, and CCL2 is a predictor of survival^[61]. A validated model of a 14 immune gene signature, in patients resected for early HCC, is also associated with a better prognosis^[62]. Among the genes of this signature with increased expression of particular interest include CXCL10, CCL5, and CCL2. These chemokines are related with Th1 and NK cell recruitment. Potentially tumors with the features of LEL-HCC are characterized by a similar chemokine profile.

LEL-HCC arise in nearly half of the cases in the context of HCV-related cirrhosis. In these patients, chemokine-driven inflammatory changes related to HCV chronic hepatitis may play a role in LEL-HCC development and in lymphocyte recruitment^[63-66]; however, LEL-HCC also arises in apparently normal livers. Whether lymphocyte recruitment is driven by the same genetic alterations in both groups of LEL-HCC remains unknown.

In comparison with LEL-HCC, LEL-ICC contains a higher proportion of tumorous cells with features of stemness. Indeed, 7 of 7 samples were positive for EpCam and CD133 (Table 2). In addition, in at least 2 cases the tumor exhibited the features of hepatocellular and cholangiocarcinoma. In contrast to LEL-HCC, LEL-ICC is associated in almost all cases with EBV infection and exhibits the same epidemiological features of EBV related

malignancies^[67]. Consequently, the mechanistic of LEL-ICC should be analyzed considering this background. EBV infection is detected in nearly all patients with endemic Burkitt lymphoma^[68]. By contrast, the association of EBV infection with other malignancies such as Hodgkin and non-Hodgkin lymphomas^[69], post-transplant lymphoproliferative disorders^[70], gastric adenocarcinomas^[71], leiomyosarcomas^[72], and NPC^[73] is variable and is influenced by several factors, including age of infection, ethnicity, genetic susceptibility, socio-economic status, and immune function^[74,75]. Intriguingly, EBV-related NPC has a geographical and racial distribution similar to that of intra-hepatic LEL-ICC. In contrast to LEL-ICC, the genetic alterations occurring in NPC have been extensively studied^[49-53,76-80]. Several chromosomal abnormalities, including copy number changes on chromosomes 3p, 9p, 11q, 12p and 14q, and gene alterations, such as CDKN2A deletion and LTBR (lymphotoxin beta receptor) amplification, together with epigenetic changes, such as RASSF1A and TSLC promoter hypermethylation, have been described. According to the Catalogue of Somatic Mutations in Cancer (COSMIC), the most frequent mutations in NPC affect the CDKN2A gene (11% of tested samples), which encodes for the p16INK4A protein, and PIK3CA^[81]. The prominent lymphocyte infiltration of NPC is a model of the complex interactions between tumor and immune system^[82-86]. Most of the infiltrating lymphocytes consist of CD3 positive T cells; among them, the majority show the morphology of small resting lymphocytes. The ratio of CD4 to CD8 ranges from 0.4 to 2.2. Regulatory CD4 and CD25^{high} and FoxP3 positive cells represent 12% of all T cells. Two distinct subpopulations of CD8 positive lymphocytes were described: pro-inflammatory interleukin (IL)-17 secreting cells, and regulatory CD8 cells, whereas NK and B lymphocytes represent a minority of the tumor infiltrating lymphocytes. In addition, it has been shown that malignant NPC cells constitutively produce several cytokines, including IL-1 α , IL-1 β , and IL-18^[87,88], and chemokines including CCL20 and CXCL10^[89,90]. Infiltrating leucocytes in turn further amplify the inflammatory process by positive regulatory loops. Clinical and experimental findings indicate that NPC associated lymphocytes do not control tumor growth. Conversely, inflammation promotes tumor progression, as cytokines behave as tumoral growth factors. Immune escape is related to CCL20 dependent Treg expansion^[89] and resistance to interferon γ as a result of small EBV-encoded RNAs (EBERs) and latent membrane protein (LMP) 2A and B secretion^[91]. The complex interactions described in NPC possibly differ in other types of LEL carcinomas, depending on the burden of EBV intermediates and the latent gene expression. Three forms of EBV latency have been recognized^[92,93]. Latency I is characterized by the expression of Epstein Barr nuclear antigen (EBNA) 1, EBERs, and *BamHI* A rightward transcripts (BARTs). This expression pattern is found in Burkitt

lymphoma^[94]. By contrast, latency II is characterized by the variable expression of LMP1, LMP-2A and LMP-2B, BARTs, and EBERs. This pattern is typical of NPC^[95,96]. Latency III is characterized by the expression of EBNA 1, EBNA2, EBNA3, EBNA3B, EBNA3C, EBNA LP, LMP-1/2, BARTs, and EBERs. This expression pattern is found in isolated cell lines, and in the elderly with lymphomas^[97,98]. Finally, viral reactivation from latency expresses the *BamHI* Z leftward open reading frame^[99]. In the setting of LEL carcinomas, the evidence that the lymphoid stroma is related to the pattern of EBV latency is provided by the finding that gastric LEL carcinoma, expressing EBNA1 mRNA, BARTs and LPM2, was associated with oligoclonal CD8 positive EBV specific lymphocytes^[100]. The evaluation of the EBV pattern of latency in LEL-ICC has been incompletely elucidated. EBERs were positive in 18 of 18 samples, LMP was negative in 8 of the samples by immune-histology^[30,40], and the LMP-related gene showed a 30 bp deletion in 2 of 2 cases^[35,36]. The *EBNA2* gene was found in one of one tested case. Progression of LEL-ICC is possibly associated with further molecular changes. In this respect, it is of interest that in more than one third of LEL-ICC cases, the tumor consisted of LEL-ICC and ICC with different grades of differentiation, and metastases of LEL-ICC usually lost the capacity to recruit inflammatory cells. These histological features implicate the concomitance of two different neoplastic clones. In contrast to HCC, little is known regarding the chemokines associated with ICC. Thus far, the single relevant finding in this regard is the overexpression of CXCL5^[101]. In ICC this chemokine has been associated with tumor progression and metastasis. The chemokines involved in HCC- LEL and in ICC-LEL are unknown.

The features of intrahepatic LEL carcinomas and their molecular differences compared with classical HCC and ICC warrant further study. Analysis of archival samples and prospective whole genome analysis of new cases would provide new insights into this issue. Given their rarity, addressing the above issues would be feasible only through a close cooperation between all the centers following these patients *via* the generation of a dedicated registry and the commitment of high profile basic researchers.

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