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Clinicopathological features of 11 Epstein–Barr virus-associated intrahepatic cholangiocarcinoma at a single center in China

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Abstract

To date, only 20 cases of Epstein–Barr virus (EBV)-associated intrahepatic cholangiocarcinomas (IHCCs) have been reported in the literature.

Pathology records of IHCC from January 1, 2007 to December 31, 2013 were retrieved from our hospital. Clinical information related to EBV-associated IHCC were also obtained, including gender, age at initial diagnosis, tumor size, tumor–node–metastasis stage, and follow-up duration. Surgically resected stage-matched EBV-negative IHCCs with full follow-up were selected for comparison. All liver specimens were fixed in 10% neutral-buffered formalin and paraffin-embedded tissue blocks containing cholangiocarcinoma and nonneoplastic liver tissue. Hematoxylin and eosin-stained sections were present in all cases.

Among 329 primary IHCC patients, intranuclear expression of EBV was only found in 11 patients (3.3%), with an age range of 30 to 67 years (mean, 53.2 years; median, 54 years). The group consisted of 4 male and 7 female patients (M:F ratio 1:1.8). Histopathological analysis showed 1 case (9.1%) belonged to the typical lymphoepithelioma-like carcinoma (LELC), primarily composed of undifferentiated tumor cells intimately admixed with abundant lymphoplasmacytic cells. Two cases (18.2%) belonged to the conventional-type IHCCs, showing irregularly shaped neoplastic glands and scattered lymphoplasmacytic infiltration. The remaining 8 cases (72.7%) belonged to the lymphoepithelioma-like cholangiocarcinomas (LELCCs), showing varied glandular differentiation and dense lymphoplasmacytic infiltration. The overall survival of EBV-positive IHCCs was not significantly different from that of EBV-negative IHCCs ($P = 0.512$).

Our data demonstrate that EBV-associated IHCC is very rare and may be subclassified into 3 different pathological types including LELC, conventional-type IHCC and LELCC on the basis of the tumor cellular differentiation, and host cellular immune responses in the tumors. The etiological, clinical, pathological, and molecular features are needed to be future studied by multicentric efforts in recruiting more EBV-associated IHCC patients.

Abbreviations: EBV = Epstein–Barr virus, IHCC = intrahepatic cholangiocarcinoma, LELC = lymphoepithelioma-like carcinoma, LELCC = lymphoepithelioma-like cholangiocarcinoma, LMP1 = latent membrane protein 1, EBVaGC = EBV-associated gastric carcinoma.

Keywords: clinicopathological features, Epstein–Barr virus, intrahepatic cholangiocarcinoma, lymphoepithelioma-like carcinoma, lymphoepithelioma-like cholangiocarcinoma

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KS and SX contributed equally to this work and should be considered co-first authors.

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1. Introduction

Intrahepatic cholangiocarcinoma (IHCC) is a type of primary liver cancer and accounts for 5% to 10% of the malignant tumors.[1] Chronic viral infections such as hepatitis B and C are known etiological factors for IHCC.[2] However, the role of Epstein–Barr virus (EBV) in the initiation or development of IHCC is still unclear. EBV is a ubiquitous γ-1 herpes virus usually acquired during childhood via salivary transmission. In more than 90% of EBV-infected adults, EBV establishes a lifelong persistent infection of B cells.[3] It is implicated in the etiology of undifferentiated nasopharyngeal carcinoma, NK cell malignancies, B and T lymphomas, posttransplant lymphoproliferative disorder, and a subset of smooth muscle tumors.[4] Lymphoepithelioma-like carcinomas (LELCs) are defined as tumors with morphologic features identical to undifferentiated nasopharyngeal carcinoma, and have been reported in various anatomical locations, including stomach,[5] esophagus,[6] pancreas,[7] and the salivary glands.[8] EBV-positive gastric LELC is a special subtype of EBV-associated gastric carcinoma (EBVaGC) and is subclassified into 3 histologic subtypes (typical LELC, carcinoma with Crohn disease-like lymphoid reaction, and conventional-type adenocarcinoma) according to the host cellular immune responses.[9]

In 1996, Hsu et al[10] first reported the presence of EBV genome in cholangiocarcinoma, which had both well-differentiated adenocarcinoma and lymphoepitheliomatous undifferentiated carcinoma components. Lymphoepithelioma-like cholangiocarcinoma (LELCC) was first described by Jeng et al[11] in 2001 in a small series of 5 patients whose histopathological results showed the presence of glandular differentiation, which is characteristic of hepatic LELC. In other organs, LELC most commonly presents in a pure form, without glandular differentiation. To date, only 20 EBV-associated IHCCs have been reported[10–18] and LELCC is the most reported pathological subtype. In the present study, to explore the clinicopathologic characteristics of EBV-associated IHCCs, we systematically and retrospectively studied the cases and discussed their clinical and pathological features.

2. Materials and methods

2.1. Patients and tumor samples

Pathology records of IHCC from January 1, 2007 to December 31, 2013 were retrieved from the Department of Pathology, First Affiliated Hospital, School of Medicine, Zhejiang University. Clinical information related to EBV-associated IHCC were also obtained, including gender, age at initial diagnosis, tumor size, AJCC (7th edition) tumor–node–metastasis stage, and follow-up duration. Surgically resected stage-matched EBV-negative IHCCs with full follow-up were selected for comparison. All liver specimens were fixed in 10% neutral-buffered formalin and paraffin-embedded tissue blocks containing cholangiocarcinoma and nonneoplastic liver tissue. Hematoxylin and eosin-stained sections were present in all cases. The study was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital, School of Medicine, Zhejiang University.

2.2. In situ hybridization

EBV-encoded RNAs (EBER) were detected by in situ hybridization performed with the EBV Probe ISH Kit (Tripi Fx International Biosciences, Fujian, China).

2.3. Immunohistochemical analysis

Immunohistochemistry was performed on 4-μm sections using the avidin–biotin complex method. A panel of monoclonal antibodies directed against the following antigens were used: cytokeratin 7 (1:200, clone OV-TL 12/30; Epitomics), cytokeratin 19 (1:200, clone K19.2; Lab Vision), hepatocyte paraffin-1 (1:200, clone OCH1E5; Lab Vision), glypican 3 (1:200, clone 1G12; Invitrogen), and EBV latent membrane protein 1 (LMP1) (1:100, clone CS1-CS4; Invitrogen). Appropriate positive and negative controls were run concurrently for all the markers tested.

2.4. Statistical analysis

For all statistical tests, 2 categories were analyzed in pairs as positive versus negative. The Fisher exact tests were used to determine the statistical difference between the 2 groups, and Student *t* test for those between means. Survival probabilities were calculated using the Kaplan–Meier method for different groups. The Log-rank statistics tested the equivalences of the survival curves. The statistical analysis was performed using SPSS 20.0 (IBM; Armonk, NY). P-value < 0.05 was regarded as statistically significant.

3. Results

3.1. Clinical data

Overall, 11 of the 329 tumors (3.3%) exhibited positive EBV expression. EBER was detected by in situ hybridization. Of the 11 reported patients, there were 4 males and 7 females (M:F ratio 1:1.8). All patients had normal nasopharyngoscopic finding with lung and gastrointestinal tract negative for tumor. The patients age ranged from 30 to 67 years (mean age, 53.2 years; median age, 54 years). Table 1 shows the clinical presentations of individual EBV-positive IHCCs. Full follow-up records were available in 8 out of 11 EBV-positive IHCC patients. Sixty cases were surgically resected stage-matched EBV-negative IHCC with full follow-up and were selected for comparison. Table 2 summarizes the clinical features of the 8 EBV-positive IHCC patients with full follow-up and the 60 EBV-negative IHCC patients. Gender and age were comparable to EBV-negative IHCC patients. All patients presented with AJCC stage I (i.e., solitary tumor without vascular invasion, nodal, or distant metastasis). No patient had a history of chronic hepatitis C, primary sclerosing cholangitis, or primary biliary cirrhosis. All EBV-positive IHCC patients were asymptomatic, and tumors were incidentally discovered on routine imaging studies. Imaging studies including computed tomography, magnetic resonance imaging, and ultrasonography revealed a mass in the liver of all EBV-positive IHCC patients, 4 with left lobe, and 7 located at the right lobe. Five patients (case 1, 5, 7, 8, and 10) were positive for hepatitis B surface antigen, with 1 presenting with hepatic cirrhosis (case 7). Two patients' (case 4, 11) CEA and 4 patients' (case 1, 4, 9, and 11) serum CA19-9 were elevated. Three of 11 patients were lost (case 3, 9, and 10). The remaining 8 cases received full follow-up, which ranged from 15 to 69 months. Four patients (case 1, 7, 8, and 11) survived the entire follow-up period, and 2 (case 1, 8) were disease free for the entire follow-up duration. The other 4 patients (case 2, 4, 5, and 6) were died during our follow-up due to metastatic spread. Studied patients with or without EBV infection were followed up in our hospital, with mean intervals of 40.5 and 35.7 months, respectively.

Table 1

Clinical and pathological features of 11 cases of EBV-associated intrahepatic cholangiocarcinoma.

Case	Sex/age, years	Location/size, cm	AFP	CEA, ng/mL	CA-199, U/mL	HBV/HCV	EBER	Histopathological type	LMP-1	Follow-up
1	F/35	RL/2.0 × 2.0	–	–	38.8	+/–	+	Typical LELC	–	AWOD, 69 months
2	M/66	RL/7.3 × 5.5	–	–	–	–/–	+	Conventional-type IHCC	–	DOD, 15 months
3	F/55	LL/7.0 × 5.0	–	–	–	–/–	+	Conventional-type IHCC	–	Lost
4	M/58	LL/2.9 × 1.8	–	9.1	197.4	–/–	+	LELCC	–	DOD, 23 months
5	M/54	RL/3.7 × 2.4	–	–	–	+/–	+	LELCC	–	DOD, 48 months
6	F/52	LL/4.1 × 2.8	–	–	–	–/–	+	LELCC	–	DOD, 53 months
7	M/54	LL/1.8 × 1.8	–	–	–	+/–	+	LELCC	–	AWD, 45 months
8	F/30	RL/3.0 × 2.6	–	–	–	+/–	+	LELCC	–	AWOD, 35 months
9	F/67	RL/3.2 × 2.2	–	–	–	–/–	+	LELCC	–	Lost
10	F/51	RL/3.1 × 2.6	–	–	126.9	+/–	+	LELCC	–	Lost
11	F/63	RL/7.3 × 6.7	–	8.0	458.5	–/–	+	LELCC	–	AWD, 24 months

AFP = alpha fetal protein, AWD = alive with disease, AWOD = alive without disease, CA-199 = carbohydrate antigen 199, CEA = carcino-embryonie antigen, DOD = died of disease, EBER = EBV-encoded RNA (EBV encoded small nonpolyadenylated RNA), EBV = Epstein–Barr virus, HBV = hepatitis B virus, HCV = hepatitis C virus, IHCC = intrahepatic cholangiocarcinoma, LELC = lymphoepithelioma-like carcinoma, LELCC = lymphoepithelioma-like cholangiocarcinoma, LL = left lobe of liver, LMP1 = latent membrane protein 1, RL = right lobe of liver.

Overall survival for EBV-positive IHCC was not significantly different from that for EBV-negative IHCC ($P = 0.512$) (Fig. 1). Notably, case 1 with typical LELC remains alive till date (69 months after surgery).

3.2. Pathological features

Pathological data for EBV-associated IHCC, including size, histology, and in situ hybridization are summarized in Table 1. Grossly, these tumors were well demarcated, gray-white, firm, and nonencapsulated with the sizes ranged from 1.8 to 7.3 cm in diameter. All 11 cases showed diffuse and strong EBER-positive staining in carcinoma cells by in situ hybridization and no detectable EBV was observed in nontumor hepatocytes, benign portal ductules, in inflammatory, or stromal cells (endothelial cells and fibroblasts). Apart from 1 patient (case 7) with hepatic cirrhosis, cirrhosis and intraductal papillary proliferation of the biliary duct were not observed in the other patients' tumor samples.

Microscopically, these tumors were well circumscribed and expansive growth pattern but not encapsulated. According to the tumor cellular differentiation and host cellular immune response, the tumor of case 1 was of the typical LELC, which consisted of cohesive nests of large undifferentiated cells with vesicular nuclei and prominent nucleoli, intimately admixed with abundant lymphoplasmacytic cells (Fig. 2A). Epithelioid granulomas and numerous lymphoid follicles were also seen. The morphology of case 2 and 3 was of conventional-type IHCC. In contrast to dense lymphoplasmacytic infiltration found in case 1, the 2 cases showed scattered lymphoplasmacytic infiltration and prominent desmoplasia (Fig. 2B). Necrotic tissues were seen in the center of the tumors. In case 2, some areas showed irregularly shaped neoplastic glands and dilated lumen mimicking ductal plate malformation (DPM). The tumors of the remaining 8 cases (case 4–11) were adenocarcinomas with varied glandular differentiation and extensive lymphoplasmacytic infiltration (Fig. 2C), presenting as LELCCs. Adenocarcinomas were characterized by tubular, trabecular, or cord-like patterns with variable degrees of differentiation in each case. All of the 8 cases showed a variable degree of desmoplastic reaction. In 5 cases (case 4, 6, 7, 8, and 10), lymphoid follicles could be seen. In case 6, 8, and 10, granulomatous reactions were observed. Notably, in case 8, obvious granulomatous reactions and many multinucleated giant cells coexisted (Fig. 2D). Eleven of the 329 tumors (3.3%) were EBV-positive (Fig. 3A). EBER was detected by in situ

Table 2

Summary of clinical features of EBV-positive IHCC with full follow-up and EBV-negative IHCC.

	EBV (+)	EBV (–)	*P*
Sex			0.715
Femal, %	4 (50)	25 (41.67)	
Male, %	4 (50)	35 (58.33)	
Age, years	51.5 ± 12.7	58.1 ± 9.8	0.087
AJCC stage 1 (PT1N0M0), %	8 (100)	60 (100)	
Follow-up period (mean), months	40.5	35.7	
Overall survival			0.512
Median, months	53	36	
Mean, months	48.9	44.1	

EBV = Epstein–Barr virus, IHCC = intrahepatic cholangiocarcinoma.

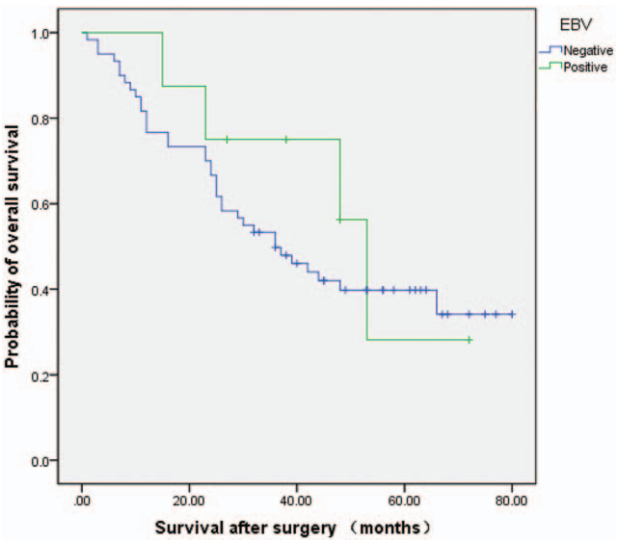

Figure 1. Survival graph of Epstein–Barr virus (EBV)-positive intrahepatic cholangiocarcinoma and EBV-negative intrahepatic cholangiocarcinoma. EBV = Epstein–Barr virus, IHCC = intrahepatic cholangiocarcinoma, LELC = lymphoepithelioma-like carcinoma, LELCC = lymphoepithelioma-like cholangiocarcinoma, LMP1 = latent membrane protein 1, EBVaGC = EBV-associated gastric carcinoma.

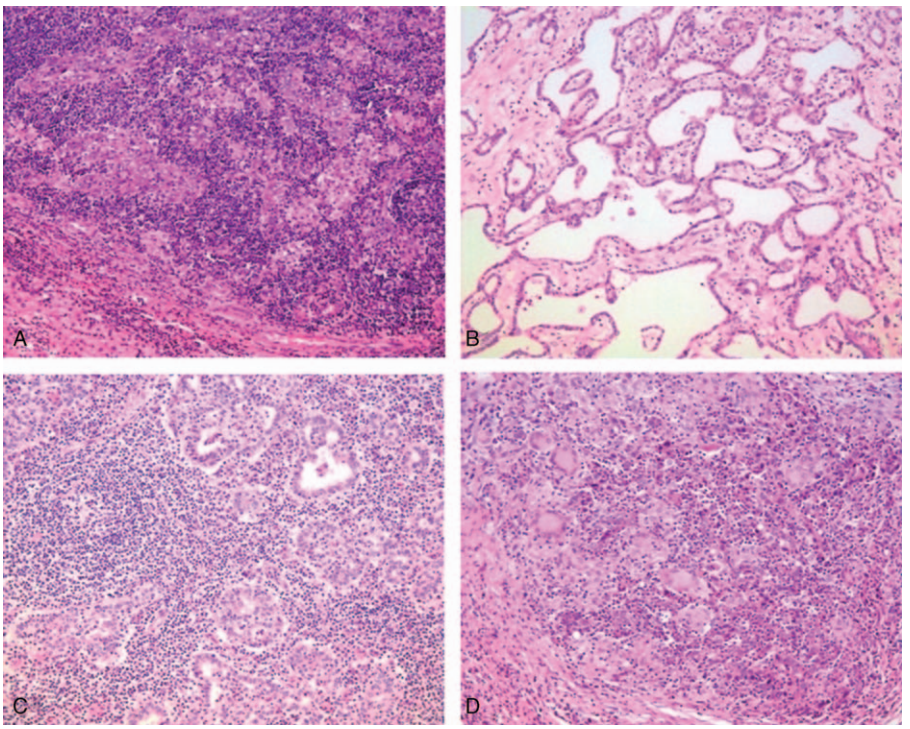

Figure 2. (A) EBV-associated lymphoepithelioma-like carcinoma, primarily composed of undifferentiated tumor cells intimately admixed with abundant lymphoplasmacytic cells. (B) EBV-associated convention-type IHCC with irregularly shaped neoplastic glands, scattered lymphoplasmacytic infiltration, and marked desmoplasia. (C) EBV-associated lymphoepithelioma-like cholangiocarcinoma with varied glandular differentiation and dense lymphoplasmacytic infiltration. (D) Obvious granulomatous reaction and many multinucleated giant cells. (H&E, magnification, ×200). EBV = Epstein–Barr virus, IHCC = intrahepatic cholangiocarcinoma.

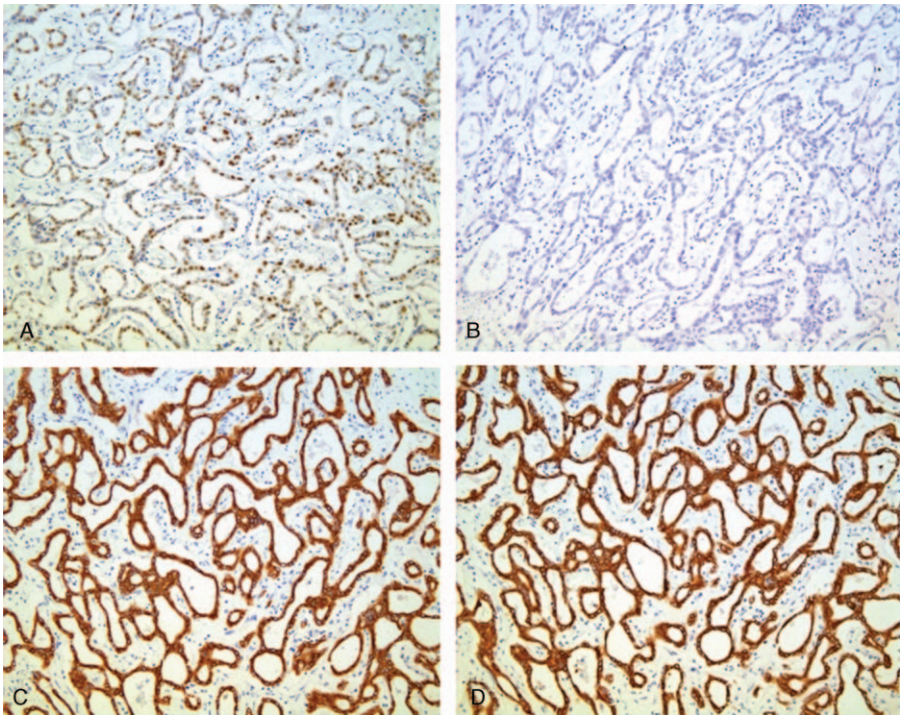

Figure 3. (A) Nuclear EBER signal is positive in EBV-associated IHCC. (B) The tumor cells are negative for EBV LMP1. (C, D) The tumor cells are positive for CK7, CK19, respectively (magnification, ×200). EBV-encoded RNA, EBV = Epstein–Barr virus, IHCC = intrahepatic cholangiocarcinoma, LMP1 = latent membrane protein 1.

Table 3

Summary of EBV-associated intrahepatic cholangiocarcinoma in the literature.

Case	Author	Sex/age	Location	Size, cm	EBV	HBV	HCV	Outcome
1	Hsu et al[10]	F/47	LL	10	+	–	–	DOD, 4 years
2	Jeng et al[11]	M/42	RL	3	+	NA	NA	AWOD, 7 years
3	Jeng et al[11]	F/67	LL	3	+	NA	NA	AWOD, 7 months
4	Jeng et al[11]	M/50	RL	4	+	+	NA	AWOD, 16 months
5	Jeng et al[11]	F/50	RL	4	+	+	NA	AWOD, 2 months
6	Vortmeyer et al[12]	F/71	Porta hepatis	5	+	NA	NA	AWD, 2 years
7	Ortiz et al[13]	F/19	LL	5.5	+	–	–	DOD, 44 months
8	Chen et al[14]	F/67	RL	5	+	–	+	DDD
9	Huang et al[15]	F/60	Caudate lobe	3.5	+	+	–	AWOD, 2 years
10	Henderson-Jackson et al[16]	F/63	LL	4	+	NA	NA	AWOD, 6 months
11	Xiao et al[17]	M/58	LL	3.2	+	–	–	Lost
12	Xiao et al[17]	F/62	RL	8.0	+	+	–	AWOD, 6 months
13	Xiao et al[17]	F/58	LL,	13	+	–	–	Recurrence, 3 months
14	Chan et al[18]	F/53	RL	1.6	+	+	–	AWOD, 165 months
15	Chan et al[18]	F/40	RL	7.5	+	+	–	AWD, 56 months
16	Chan et al[18]	F/57	LL	7.1	+	–	–	AWOD, 128 months
17	Chan et al[18]	F/56	LL	6.0	+	–	–	DOD, 69 months
18	Chan et al[18]	F/59	LL	6.0	+	+	–	AWOD, 72 months
19	Chan et al[18]	F/45	LL	3.0	+	–	–	AWD, 71 months
20	Chan et al[18]	F/57	RL	3.0	+	–	–	AWOD, 58 months

AWD = alive with disease, AWOD = alive without disease, DDD = died of different disease, DOD = died of disease, EBV = Epstein–Barr virus, HBV = hepatitis B virus, HCV = hepatitis C virus, LL = left lobe of liver, NA = not available, RL = right lobe of liver.

hybridization. None of the cases showed immunopositivity for EBV LMP1 (Fig. 3B). All tumors exhibited variable expression levels of biliary-type cytokeratins (cytokeratin 7 and cytokeratin 19) (Fig. 3C, D) with hepatic markers (hepatocyte paraffin-1 and glypican 3) negative.

4. Discussion

EBV-associated IHCC is a rare variant of IHCC, defined by the presence of EBV in cholangiocarcinoma cells. In the present study, only 3.3% of IHCC patients were positive for EBV. So far, only 20 cases of EBV-associated IHCCs have been reported in the literature[10–18] (Table 3). Combining the present cases with the already reported ones, a marked female predominance is observed (female:male ratio 3.43:1). The age range is 19 to 71 years (mean age, 53.74 years). LELCC is the most reported subtype, with distinctive clinical behavior and pathological features. Compared to patients with EBV-negative IHCCs, after surgery, patients with EBV-associated LELCCs usually have favorable outcomes.[18] However, in our study, no significant difference in the overall survival was found between EBV-positive and EBV-negative IHCCs.

Histopathologically, EBV-associated carcinomas, which do not only present as LELCs, have been reported in EBVaGCs.[9] According to the host cellular immune response, EBVaGCs can be subclassified into 3 histological subtypes: typical LELC, carcinoma with Crohn disease-like lymphoid reaction, and conventional-type adenocarcinoma.[9] Moreover, prognosis of the 3 subtypes is different.[9] Similarly, according to the tumor cellular differentiation and host cellular immune response, typical LELC and LELCC have been reported in patients with EBV-associated IHCC.[10–18] In the present study, different histopathological features were found including typical LELC, conventional-type IHCC, and LELCC. One patient presents as typical LELC and was still alive without cancer recurrence during a 69 months' follow-up, which is the longest time among the 8 patients with full follow-up. Two patients present as conventional-type IHCCs, which have never been described in EBV-associated IHCCs and could not be histologically delineated from its EBV-negative counterparts without confirming the presence of EBV within tumor cells. Among the 2 cases, 1 died after a full 15 months' follow-up, which was the shortest time among the 8 patients with complete follow-up. The other 8 cases present as LELCCs. Among the 8 cases, 6 patients received full follow-up (mean: 38 months). In addition, granulomatous reaction was found in 4 of the 11 cases. Epithelioid granulomas and multinucleated giant cells were prominent in 1 instance. To the best of our knowledge, granulomatous reaction in the stroma only has been reported in 1 case of EBV-associated IHCC.[14] The granulomatous reaction within the neoplastic tissue was believed to be the result of immune T cell-dependent response to degrade tumor particles.[19] The LMP1 gene was found with a 30 bp deletion in exon 3 in 2 cases of EBV-associated LELCC by Chen et al[14] and Huang et al.[15] However, in all 11 cases of EBV-positive IHCCs in the present study, EBV LMP1 was negative. The different types of latent EBV infection may be the reason for the result.

To date, only 20 cases of EBV-associated IHCCs have been reported in the literature. Our study presents the largest systematic and retrospective case series of 11 EBV-associated IHCCs, which account for 35.5% of all the cases. However, the patients are still too few to compare outcomes of the 3 groups with different histopathological features. These characteristics of EBV-associated IHCCs described by us need to be further studied by investigation of their etiological, clinical, and molecular features by multicentric efforts in recruiting more EBV-associated IHCC patients. Chan et al[18] found distinctively frequent DNA hypermethylation in 7 EBV-associated LELCCs. However, the underlying mechanisms of EBV infection in the initiation or development of IHCC are still unclear. Partly because the samples of EBV-associated IHCCs are too rare to study the causal relationship between EBV infection and IHCCs. Further animal and clinical studies are required to investigate the role of EBV in the carcinogenesis of IHCC.

Chronic viral infections such as hepatitis B and C are known etiological factors for IHCC.[2] However, the role of EBV in the initiation or development of IHCC is still unclear. Among the all 31 patients with EBV-associated IHCCs, 12 and 1 patients were also infected with HBV and HCV, respectively. No patient was simultaneously infected with the 3 different viruses. So far, the potential for synergism between EBV and HBV/HCV in IHCC has never been studied. The extremely low incidence of EBV-associated IHCCs maybe one of the reason. So, multicentric efforts in recruiting more EBV-associated IHCC patients are needed in the future to research the potential relationship between EBV and HBV/HCV.

5. Conclusions

EBV-positive IHCC is very rare. It is characterized by marked female predominance with no significant difference in overall survival compared with EBV-negative IHCC. According to the tumor cellular differentiation and host cellular immune response, EBV-positive IHCCs show different pathological characteristics including typical LELC, conventional-type IHCC, and LELCC. Particularly, EBV-positive conventional-type IHCC was first reported by us. The underlying mechanisms of EBV in the initiation or development of IHCC are still unclear and require further studies.

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