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CASE REPORT

Lymphoepithelioma-like hepatocellular carcinoma: Case report and review of the literature

Andrea Cacciato Insilla, Pinuccia Faviana, Luca Emanuele Pollina, Paolo De Simone, Laura Coletti, Franco Filipponi, Daniela Campani

Andrea Cacciato Insilla, Pinuccia Faviana, Luca Emanuele Pollina, Daniela Campani, Department of Surgical, Medical, Molecular Pathology and Critical Area, Division of Surgical Pathology, University Hospital of Pisa, 56124 Pisa, Italy

Paolo De Simone, Laura Coletti, Franco Filipponi, Department of Surgical, Medical, Molecular Pathology and Critical Area, Division of Liver Surgery and Transplantation, University Hospital of Pisa, 56124 Pisa, Italy

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Correspondence to: Daniela Campani, MD, Professor of Pathology, Department of Surgical, Medical, Molecular Pathology and Critical Area, Division of Surgical Pathology, University Hospital of Pisa, Via Paradisa 2, 56124 Pisa, Italy. daniela.campani@med.unipi.it
Telephone: +39-50-995690
Fax: +39-50-996891

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Abstract

Lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC) is a rare form of undifferentiated carcinoma of the liver characterized by the presence of an abundant lymphoid infiltrate. Here, a case of LEL-HCC is described. An 81-year-old woman with a chronic hepatitis C infection was referred to the general surgery department of our hospital in August 2013 with a diagnosis of HCC. A past ultrasound examination had revealed a 60 mm-diameter nodular lesion in the third segment of the liver. After a needle biopsy, the lesion was diagnosed as HCC. The patient underwent surgery with a liver segmentectomy. Two additional nodes on the gastric wall were detected during the surgical operation. The histology of the removed specimen showed a poorly differentiated HCC with significant lymphoid stroma. Immunohistochemical studies revealed that the epithelial component was reactive for CK CAM5.2, CK8, CK18, CEA (polyclonal) and was focally positive for hepar-1 and that the lymphoid infiltrate was positive for CD3, CD4 and CD8. The tumor cells were negative for Epstein-Barr virus. The gastric nodes were ultimately determined to be two small gastrointestinal stromal tumors (GISTs).

The synchronous occurrence of HCC and GIST is another very uncommon finding rarely described in the literature. Here, we report the clinicopathological features of our case, along with a review of the few cases present in the literature.

Key words: Lymphoepithelioma; Lymphoepithelioma-like; Hepatocellular carcinoma; Gastrointestinal stromal tumors

Core tip: Here a case of Lymphoepithelioma-like hepatocellular carcinoma (HCC) described in a 81-year-old woman with a chronic hepatitis C infection. An ultrasound examination revealed a nodular lesion in the third segment of the liver, diagnosed as HCC after a needle biopsy. The patient underwent surgery with a liver segmentectomy. Histology of the removed specimen showed a poorly differentiated HCC with a significant lymphoid stroma. Here we describe the clinico-pathological features of our case with a review of the few cases reported in literature.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most frequent malignancies in the world; in particular, it is the fifth most common cancer in men and the seventh most common cancer in women, and it represents the third most frequent cause of death from cancer. Persistent infections by hepatitis B virus (HBV) and/or hepatitis C virus (HCV) are the main recognized risk factor for HCC. In addition, heavy alcohol drinking, smoking, overweight status, diabetes and familial/genetic factors play an important role, especially in high-income countries[1]. Despite all of the recent advances in diagnostic and therapeutic approaches for the treatment of HCC, the prognosis is still poor, and long-term survival after disease onset is an exception[2]. Lymphoepithelioma-like carcinomas (LELCs) are a particular form of undifferentiated carcinoma characterized by a predominant lymphoid component that was originally described in the nasopharynx. Beyond the nasopharynx, these tumors are reported to occur in several organs, such as the salivary glands[3], lungs[4], stomach[5], colon[6] and thymus[7]; less frequently, they are reported in the uterine cervix[8], vagina[9], ovaries[10], bladder and urinary tract[11], trachea[12], lacrimal glands[13], breast[14], soft tissues[15] and skin[16]. Epstein-Barr virus (EBV) has been shown to be strongly connected to LELCs at several anatomic sites, such as the stomach, salivary glands, lung, and thymus[7]. Racial and/or geographic factors seem to influence the association of EBV with LELC in several of these organs. Specifically, the association of EBV with LELC of the salivary gland and lung is restricted to Asian patients, whereas the association of EBV with gastric and thymic LELCs seems to be independent of race[7]. However, regardless of EBV status, the morphologic features and prognosis seem to be the same, except for LELCs at uncommon sites for which the prognostic information is limited[17]. In the hepatobiliary tract, primary LELCs are rare. The World Health Organization (WHO) has only recently recognized LELCs as a variant of HCC (LEL-HCC). In 2000, Emile *et al*[18] reported a case of HCC with lymphoid stroma that was characterized by a good prognosis after liver transplant and by negativity for EBV infection. These authors were the first to suggest that HCC with these aspects should be considered as a distinct clinicopathological and prognostic entity. Before 2000, several case reports described the clinicopathological features of the marked inflammatory cell infiltration in HCC, but the term "LEL-HCC" was not used, and it is not completely clear whether the features of HCC described before 2000 are distinguishable from those reported as features of LEL-HCC after that year[19]. To date, the majority of LELCs identified in the hepatobiliary tract are cholangiocarcinomas, whereas only ten cases of LEL-HCC have been described, in six reports, from 2000 to 2013[2,18-22]. In 2014, Patel *et al*[17] reviewed all cases of HCC at their institution, starting from 1988, and identified 8 cases of LEL-HCC; in a 2015 study, Chan *et al*[23] have reported 20 cases of LEL-HCC from a 9-year retrospective cohort of 409 patients who underwent surgical resection for primary HCC. Considering also these retrospective studies, to the best of our knowledge, thirty-eight cases of LEL-HCC have been described from 2000 until now, with only one LEL-HCC case being positive for EBV[20]. Here, we describe a case of LEL-HCC in an 81-year-old woman, the eldest patient to have been described, and to further understand the disease's characteristics, we review previous cases reported after the term "LEL-HCC" first appeared in 2000.

CASE REPORT

An 81-year-old woman with a chronic hepatitis C infection was referred to the general surgery department of our hospital in October 2013 with a diagnosis of HCC. Her past medical history was significant for hypertension, venous insufficiency and osteoarthrosis. An ultrasound (US) evaluation conducted in July 2013 during a periodic medical

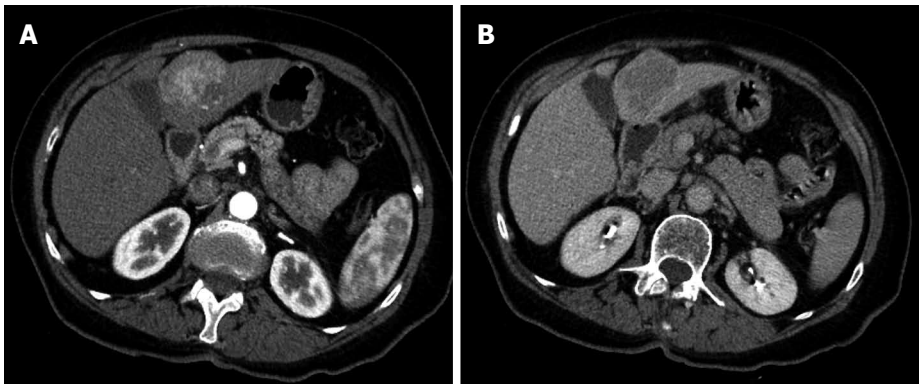

Figure 1 Computerized tomography scan. Left liver neoplasm (segments Ⅲ and Ⅳ), hypervascular (A) with rapid portal-phase wash-out (B).

investigation revealed the presence of a 60 mm, irregular pericholecystic node in the third hepatic segment, and the collateral liver parenchyma showed certain foci of steatofibrosis. The US exam was repeated after intravenous injection of 2.4 mL SonoVue, revealing a mosaic pattern in the lesion, with diffuse contrast enhancement, during the arterial phase and hypoenhancement during the portal and late phases. These findings suggested a malignant nature for the lesion. An abdominal contrast-enhanced computerized tomography (CT) scan confirmed the presence of a nodular lesion in the liver, with clear-cut enhancement in the arterial phase and rapid wash-out in the portal venous and delayed phases (Figure 1). The CT scan also revealed the presence of a second 15 mm nodular lesion involving the wall of the gastric antrum, for which the patient underwent an endoscopic examination that yielded a negative result. A subsequent examination of a biopsy sample from the hepatic lesion was performed in August 2013 confirmed the suspicion of HCC. A surgical operation was carried out on October 10th, 2013. A physical examination prior to the operation revealed mild, diffuse abdominal tenderness with normal auscultatory bowel sounds and peristaltic rushes. Pre-surgical laboratory tests revealed the following results: an alanine aminotransferase level of 23 IU/L (normal range 2-34 IU/L), an aspartate aminotransferase level of 29 IU/L (normal range 2-31 IU/L), a gamma-glutamyl transferase level of 22 IU/L (normal range 9-40 IU/L), an alkaline phosphatase level of 44 IU/L (normal range 35-105 IU/L) and a total bilirubin level of 0.75 mg/dL (normal range 0.50-1.20 mg/dL). The serum level of alpha-fetoprotein was 80.5 kU/L (normal range < 6.0 kU/L), of CEA was 1.1 microg/L (normal range 0-5.0 microg/L), and of CA19-9 was 13 kU/L (normal range 0-27 kU/L). Serological tests were positive for anti-HCV antibodies, HCV RNA and also for anti-HAV IgG but were negative for anti-HBV antibodies. The patient underwent a surgical operation with resection of the third hepatic segment and removal of the 15 mm nodule on the gastric wall, identified thanks to the CT scan. During the surgical operation, another 2 mm nodule on the gastric wall, close to the lesser curvature, was detected and removed. Macroscopically, the hepatic tumor was a 72 mm, yellowish, encapsulated solid mass 15 mm from the nearest resection margin. Microscopically, the neoplasm was composed of poorly differentiated, atypical, large epithelial cells characterized by an eosinophilic cytoplasm, large nuclei, and prominent nucleoli. The epithelial cells were surrounded by dense lymphoid stroma extending inside the tumor. The collateral liver parenchyma showed morphological aspects of HCV-related chronic hepatitis. Immunohistochemical analyses revealed that the neoplastic cells were positive for CK CAM5.2, CK8, CK18, and CEA (polyclonal, with a canalicular expression pattern) and had only focal positivity for hepar-1. The lymphocytes in the lymphoid stroma were predominantly positive for CD3, with the majority of them also positive for CD4 and fewer for CD8 (Figure 2). The carcinoma cells were negative for EBV. As a consequence of these results, we classified this poorly differentiated HCC with heavy lymphoid infiltration as LEL-HCC. The two gastric nodules were ultimately identified as gastrointestinal stromal tumors (GISTs) that were positive for CD117 and CD34, and a specific mutation in exon 11 of the c-Kit gene was identified in both of the two nodules. PDGFRA mutations were absent. The patient has been alive and disease free during the 15 mo since the operation.

DISCUSSION

LELCs are undifferentiated carcinomas with prominent lymphoid stroma. LELCs in the liver have been reported, but most of these cases have instead been referred to as LEL-cholangiocarcinomas[19]. LEL-HCCs seem to have been first described in 2000 by Emile *et al*[18], who studied 162 HCCs in explanted livers, finding 5 cases of HCC with abundant lymphoid stroma. Before 2000, there were several case reports in which the clinicopathological features of marked inflammatory cell infiltration in HCC were described, but the term "LEL-HCC" was not used. Since the five cases

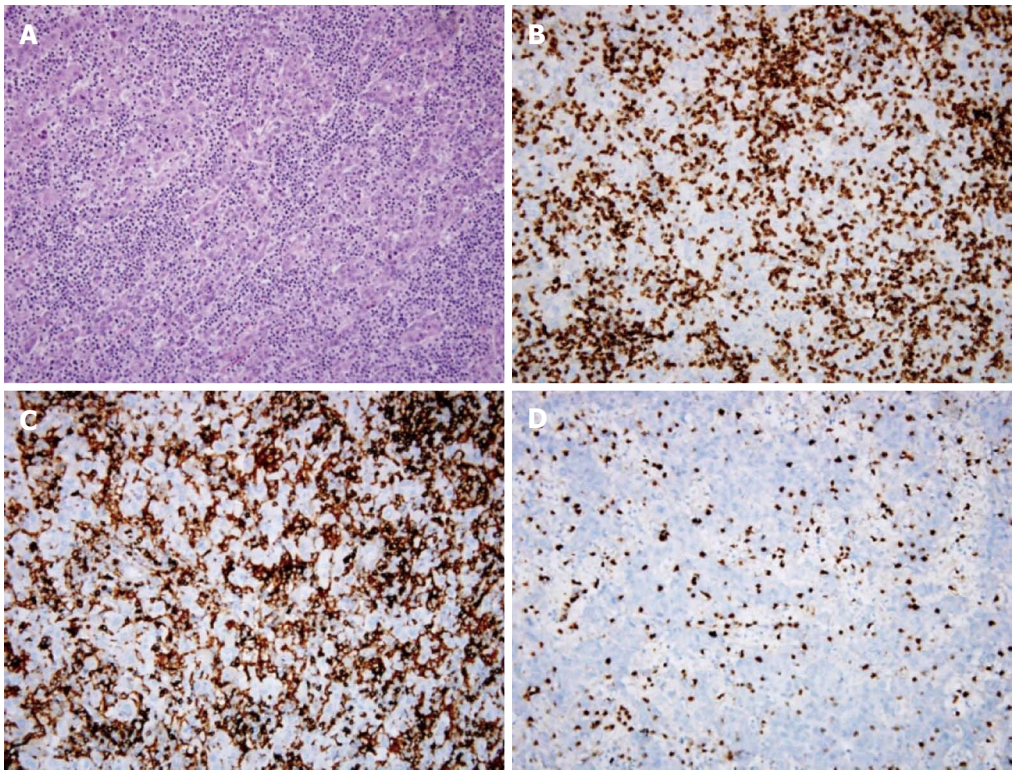

Figure 2 Neoplastic cells surrounded by a dense lymphoid infiltrate. A: Hematoxylin/eosin stain x 200; B: CD3 immunostain x 200; C: CD4 immunostain x 200; D: CD8 immunostain x 200.

were reported in 2000 by Emile, only five additional cases of HCC with marked lymphoid stroma have been documented as LEL-HCC, in five different articles[2,19-22]. In 2014, Patel *et al*[17] reviewed all cases of HCC at their institution, starting from 1988, and identified 8 cases of LEL-HCC. In a 2015 study, Chan *et al*[23] have reported 20 cases of LEL-HCC from a 9-year retrospective cohort of 409 patients who underwent surgical resection for primary HCC; considering also these retrospective studies, to the best of our knowledge, only thirty-eight cases of LEL-HCC have been described in the English-language medical literature from 2000 to date. The clinicopathological and prognostic features as well as the criteria for the diagnosis of LELCs at uncommon sites, such as the liver, are not clear. In this article, we describe a case of LEL-HCC in an 81-year-old woman, the eldest patient to have been reported, and to further understand the disease's characteristics, we review previous cases reported after the term "LEL-HCC" first appeared in 2000. In Tables 1 and 2, we have summarized the features of the ten cases reported since the proposal of Emile *et al* and, in addition, the data of the retrospective studies by Patel and Chan. Among all of the cases of LEL-HCCs reported, there were twenty-three males and sixteen females, with a mean age of 59.7 years (the youngest was 39 years old[21] and the eldest, 81, was described in the present case). Single tumors were reported in thirty-four cases, and multiple tumors were reported in five cases. The mean tumor size was 4.3 cm (range, 1 cm[21] to 13 cm[17]). HBV and HCV serology showed variable patterns: fifteen cases were negative for both, two cases were positive for both and those that remained were positive only for one of the two (in particular, four were HCV positive, and eighteen was HBV positive). Fifteen patients had cirrhosis. Alpha-fetoprotein levels were reported in thirty-seven cases, and they were elevated in eighteen of them. All of the lesions were described as undifferentiated tumors with similar morphological aspects and abundant lymphocytic infiltration. Immunohistochemical studies were performed on nearly all of the lesions to better define the characteristics of the inflammatory infiltration. All of the prior reports showed a predominance of T cells over B cells, except in one case in which the cell dominancy was not documented[21]. The T-cell markers investigated varied among the reports. In the five cases reported by Emile *et al*, the mean CD3/CD20 ratio was 11/1[18,19]. Si and colleagues investigated CD20 and CD3 in the infiltrating cells and described a mixed lymphocytic population with an excess of T cells[19,20]. In their work, Park and Nemolato also observed a prevalence of T cells, with a predominance of CD4-positive cells in the first report[20] and a predominance of CD8-positive cells in the second report[22]. In all eight cases reviewed by Patel *et al*[17], a predominance of T lymphocytes was observed, with an equal distribution of CD4- and CD8-positive cells. Finally, also Chan *et al*[23] reported a predominance of

Table 1 Clinicopathological features of lymphoepithelioma-like hepatocellular carcinoma reported in the literature until 2015

Case (ref.)	Age (yr)	Sex/ Race	Multifocal	Tumor size (cm)	HBV	HCV	EBV	Cirrhosis	AFP	Preoperative therapy	Postoperative therapy	Outcome
1 (18)	50	M/W	No	4	+	+	-	+	N	None	None	Alive w/o recurrence (10 yr)
2 (18)	54	M/W	Yes	2	-	-	-	-	N	Chemo-emb	None	DOD (7.7 yr)
3 (18)	59	M/W	Yes	5	+	+	-	+	N	None	Adj chemo	Alive w/o recurrence (8 yr)
4 (18)	45	M/W	No	2	-	+	-	+	N	None	Adj chemo	Alive w/o recurrence (4.7 yr)
5 (18)	64	M/W	Yes	4	-	-	-	+	N	Chemo-emb	Adj chemo	Alive w/o recurrence (3 yr)
6 (20)	39	F/H	No	1	-	+	+	+	-	None	None	DOD (5 mo)
7 (21)	56	M/?	No	3	-	+	-	+	N	None	Chemo for recurrence	DOD (21 mo)
8 (22)	47	F/?	No	2.2	-	-	-	-	-	None	Not describe	Alive w/o recurrence (15 mo)
9 (2)	57	M/?	No	2.7	+	-	-	+	E	None	Not describe	Alive w/o recurrence (50 mo)
10 (19)	79	M/A	No	5	-	-	-	-	E	None	Chemo for recurrence	Alive with recurrence (20 mo)
11 (17)	74	F/W	Yes	6.5	-	-	-	-	N	None	Not describe	DOD
12 (17)	65	M/W	No	4.8	-	-	-	-	N	None	Not describe	Died of unrelated cause
13 (17)	65	F/W	No	1.3	-	-	-	-	E	None	Not describe	Alive w/o recurrence
14 (17)	70	F/W	No	2.7	-	-	-	-	E	None	Not describe	Alive w/o recurrence
15 (17)	61	F/W	Yes	9.5	-	-	-	-	N	None	Not describe	Died of unrelated cause
16 (17)	78	M/W	No	10.5	-	-	-	-	N	None	Not describe	Alive with recurrence
17 (17)	78	F/W	No	6	-	-	-	-	N	None	Not describe	Alive w/o recurrence
18 (17)	57	F/W	No	13	-	-	-	-	N	Yes (unknown)	Not describe	Died of unrelated cause
19 (present case)	81	F/W	No	7.2	-	+	-	-	E	None	None	Alive w/o recurrence (15 mo)

Table 2 Clinicopathological features of lymphoepithelioma-like hepatocellular carcinoma reported by Chan *et al*[23] in March 2015 in their 9-year retrospective study

No. of cases	Age (mean)	Sex (M/F)	Multifocal	Tumor size (mean, cm)	HBV	HCV	EBV	Cirrhosis	AFP (> 20 mg/L)	Outcome (5-yr survival)
20	57.5	13/7	-	3.8	17	-	-	8	13	94.1%

HBV: Hepatitis B virus; HCV: Hepatitis C virus; EBV: Epstein-Barr virus; AFP: Alpha-fetoprotein; N: Normal; E: Elevated.

T lymphocytes with a mean CD8/CD4 ratio of 6.0/1. In our case, we observed a high predominance of T cells, many of which were CD4 positive, with only a few CD8-positive cells at the edge of the lesion. Many authors have suggested that HCC with lymphoid stroma has a favorable prognosis[17,19]. Human solid tumors are often infiltrated by lymphocytes, and the degree of the infiltration appears to be a favorable prognostic factor. As a mechanism of favorable prognosis, involvement of the antitumor effects of cellular immunity, mainly mediated by T lymphocytes, and of humoral immunity, mediated by B lymphocytes, have been considered[2]. Emile *et al*[18], for instance, suggested that HCCs with lymphoid stroma had a better prognosis than those without, possibly due to an antitumor effect related to the lymphocytic infiltration. However, Si *et al*[20] have described an aggressive case of LEL-HCC in a very young patient who died 5 mo after transplant surgery because of recurrence in the transplanted liver. Chen *et al*[21] also reported a case of LEL-HCC, in which the tumor was well encapsulated and did not have microvascular invasion, with a poor outcome[19]. Among all of the cases described after 2000, three patients died of HCC after surgery, whereas the other seven were still alive after 55.3 mo[19]. Among the eight cases described by Patel *et al*[17] in their retrospective study, three were still alive, without disease, after a mean period of 68 mo; one was alive with recurrence 48 mo after surgery; one died because of the disease after 24 mo; and the last three died of causes not related to the disease. Finally, all the cases described by Chan *et al* were associated with a 2-year survival rate of 100% and a 5-year survival rate of 94.1%[23,24]. Although many authors have highlighted that LEL-HCCs have a better prognosis than conventional carcinomas with less marked lymphocytic infiltrate do[22,23], the few reports present in the English-language medical literature supply poor clinical information and show a variable course for the disease, suggesting that further accumulation of cases and studies is needed to determine the real biological behavior of LEL-HCC. An additional point of interest discussed in every report is the possible association between LEL-HCC and EBV. EBV is a lymphotropic virus that belongs to the Herpesviridae family and that infects over 90% of adults worldwide. This virus is closely associated with a variety of human neoplasms, such as Burkitt's lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma and a subset of gastric carcinoma that is defined as EBV-associated gastric carcinoma[19,25]. EBV has been shown to be strongly connected to LELCs at

several anatomic sites, such as the stomach, salivary glands, lung, and thymus[7]. With regard to neoplasms in the hepatobiliary system, a strong relationship between EBV and LEL-cholangiocarcinomas has been demonstrated. In contrast, only one case of EBV-positive LEL-HCC has been described in the literature, by Si *et al* in 2004; in particular, the patient was the youngest patient described, with the worst clinical course, multiple recurrences three mo after liver transplantation and death of the patient within several weeks. This is the only such case described in the literature, so we do not have enough information to posit a possible role for EBV infection in the poor outcome of the patient. It is unlikely that an association exists between LEL-HCC and EBV with respect to tumorigenesis. The biological implications of lymphoid infiltration in LEL-HCC are currently under debate, and the causes and consequences of this disease remain poorly understood[19]. In all of the cases reported after 2000, inflammatory infiltrates were predominantly composed of T cells, but certain discordances were present: certain authors reported the prevalence of CD4 over CD8 cells, several others reported a co-existence of CD4 and CD8 cells, and the prevalence of CD8 over CD4 cells has been reported in only one case. In conclusion, given all of these considerations, further studies are needed to better understand the genesis and behavior of LEL-HCCs. Finally, it should be highlighted that the synchronous occurrence of HCC with GISTs, another very uncommon finding, has been rarely described in the literature[26].

COMMENTS

Case characteristics

A 81-year-old woman with a Lymphoepithelioma-like hepatocellular carcinoma (HCC) and synchronous gastrointestinal stromal tumor (GIST) of the stomach, a very unusual finding.

Clinical diagnosis

An ultrasound evaluation conducted during a periodic medical investigation in a patient with chronic hepatitis C infection revealed the presence of an irregular pericholecystic node.

Differential diagnosis

Classic HCC.

Laboratory diagnosis

Normal levels of transaminase, gamma-glutamyl transferase, alkaline phosphatase and bilirubin. High levels of α-fetoprotein and CEA.

Imaging diagnosis

An ultrasound evaluation revealed the presence of an irregular pericholecystic node. The ultrasound exam was repeated after intravenous injection of 2.4 mL SonoVue and the result suggested a malignant nature for the lesion. An abdominal contrast-enhanced computerized tomography scan confirmed the presence of a nodular lesion in the liver and the suspect for malignant nature.

Pathological diagnosis

Microscopically, the neoplasm was composed of poorly differentiated, atypical, large epithelial cells characterized by an eosinophilic cytoplasm, large nuclei, and prominent nucleoli. The epithelial cells were surrounded by dense lymphoid stroma extending inside the tumor.

Treatment

Surgical operation with resection of the third hepatic segment.

Experiences and lessons

The biological implications of lymphoid infiltration in lymphoepithelioma-like HCC (LEL-HCC) are currently under debate, and the causes and consequences of this disease remain poorly understood. This case report underline the fact that further studies are needed to better understand the genesis and behavior of LEL-HCCs. We also report the very unusual and uncommon association between two different kinds of neoplasia such as LEL-HCC and GIST.

Peer-review

This case report reported in detail all the cases of LEL-HCC described in the English literature within the time of the submission.

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