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CASE REPORT

Coexistence of Two Epstein-Barr Virus–associated Malignancies: Lymphoepithelioma-like Cholangiocarcinoma in a Patient with a History of Undifferentiated Nasopharyngeal Carcinoma

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ABSTRACT

Undifferentiated nasopharyngeal carcinoma is particularly common in Southern China and is consistently associated with Epstein-Barr virus. In contrast, lymphoepithelioma-like carcinoma of the bile duct is a rare disease and not always associated with Epstein-Barr virus. We report the first case of coexisting Epstein-Barr virus–associated nasopharyngeal carcinoma and lymphoepithelioma-like carcinoma of the bile duct in a Chinese patient.

Key Words: *Cholangiocarcinoma; Epstein-Barr virus infections; Nasopharyngeal neoplasms*

中文摘要

兩種Epstein-Barr病毒相關惡性腫瘤並存：一名有未分化鼻咽癌病史的病人併發淋巴上皮瘤樣膽管癌

戴燕萍、顏繼昌、丁信顯

未分化鼻咽癌在南中國地區特別常見，發病通常與Epstein-Barr病毒相關。相反，淋巴上皮瘤樣膽管癌是一種罕見疾病，且不一定與Epstein-Barr病毒相關。本文報告首個併發Epstein-Barr病毒相關性鼻咽癌和淋巴上皮瘤樣膽管癌的華籍病例。

INTRODUCTION

Undifferentiated nasopharyngeal carcinoma (NPC) has a distinctive ethnic and geographical distribution. It is particularly common in Southern China, reaching a peak incidence of around 20 to 30 cases per 100,000 population.[1] Unlike World Health Organization types I and II NPC, undifferentiated NPC is consistently associated with Epstein-Barr virus (EBV).[2]

Carcinomas with morphological features similar to undifferentiated NPC are often referred to as lymphoepithelioma-like carcinoma (LELC). LELC has been described in a number of different anatomical locations such as the salivary glands, oropharynx, larynx, trachea, lung, thyroid gland, thymus gland, skin, oesophagus, stomach, liver, bile duct, urinary bladder, cervix, and vagina.[3-15] The morphological similarities

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between undifferentiated NPC and LELC have prompted investigators to look for an association with EBV. Some studies have shown that EBV is frequently associated with LELC arising from foregut-derived structures, but not the oral cavity, skin, or urogenital structures.[16]

LELC of the bile duct is a rare entity. Only 23 cases have been reported in the literature to date[17-28]; 74% of which were EBV-positive. The latest and largest series consisted of seven Chinese patients who all had EBV-associated LELC of the bile duct.[28]

In this paper, we report on a Chinese man with lymphoepithelioma-like cholangiocarcinoma (LELCC) with a history of undifferentiated NPC; both of which were associated with EBV.

CASE REPORT

In 1996, a 38-year-old Chinese man with unremarkable past health was diagnosed with T3N2M0 biopsy-confirmed undifferentiated NPC. His mother also had a history of NPC diagnosed at the age of 48 years. Staging computed tomography (CT) showed a mass at the left nasopharyngeal recess with left posterior nasal, parapharyngeal space, ethmoid involvement, and retropharyngeal involvement and cervical lymphadenopathy. Immunoglobulin A antibody to EBV viral capsid antigen was done, but the result could not be traced.

The patient was treated with one cycle of neoadjuvant chemotherapy before radical radiotherapy to the nasopharynx and neck of up to 66 Gy in 33 fractions with additional boost to the left parapharyngeal space.

Nasopharyngoscopy done 8 weeks after the radiotherapy showed no residual disease in the nasopharynx. The patient has achieved sustained clinical remission since then. He developed left 12th cranial nerve palsy, hypothyroidism, and left vocal cord palsy with aspiration pneumonia as complications of the radiotherapy.

In April 2014, 18 years later, he presented with significant weight loss. Blood tests — including complete blood counts, liver and renal function tests, and tumour markers (alpha-fetoprotein, carcinoembryonic antigen, and cancer antigen 19-9) — were normal. EBV DNA was 31 copies/ml, within the range of low positivity specified by the reference range of 20-1000 copies/ml. Hepatitis B surface antigen was negative.

Contrast CT and positron emission tomography (PET)–CT showed a solitary hypermetabolic liver lesion of 1.8 x 2.4 cm in size in segments II and III with a maximum standardised uptake value of 4.2 (Figure 1). There were also some patches of uptake over the bilateral lung bases suggestive of infection, otherwise there was no evidence of locoregional or distant recurrence of NPC.

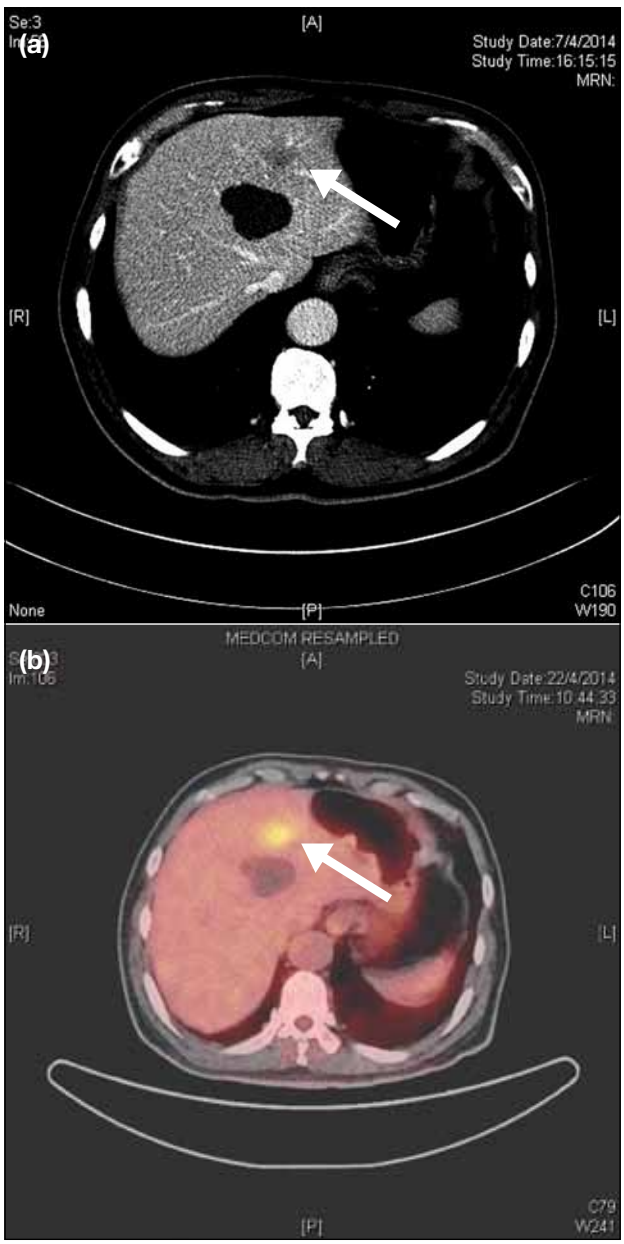

Figure 1. (a) Computed tomography and (b) positron emission tomography images of the patient show a hypermetabolic liver lesion at segments II and III (arrows).

Nasopharyngoscopy and bronchoscopy did not show any nasopharyngeal or endobronchial lesions. Bronchial aspirate, bronchial biopsy, and sputum for cytology, culture, and acid-fast bacillus smears were all negative. Sputum cultures grew *Staphylococcus aureus*. The bilateral lower zone consolidations on chest radiography improved after a 1-week course of oral amoxicillin and clavulanate potassium 1 g twice daily.

The PET-CT images were reviewed with the radiologists at a multidisciplinary meeting. The overall features suggested a diagnosis of primary cholangiocarcinoma rather than a metastatic tumour in view of the delayed central contrast enhancement over the hepatic lesion.

As a result, laparoscopic bisegmentectomy of segments II and III of the liver was performed. Intra-operatively a 2.5 x 2.0 cm tumour was identified at the left lateral section of the liver; no peritoneal deposit was found. The patient had a smooth recovery from the operation. The latest CT scan done 3 months after the operation did not show any evidence of recurrence. The postoperative EBV DNA level has not yet been checked.

Pathological Examination

The bisegmentectomy specimen measured 9.0 x 12.0 x 5.5 cm. A firm whitish tumour measuring 2.3 x 2.0 x 2.2 cm was identified abutting a portal area. The tumour was located 7 mm away from nearest bile duct margin. The background parenchyma was normal.

On microscopy, the tumour was shown to comprise two distinct components, both being invasive (Figure 2a). Most of the tumour displayed small branching tubules and glands lined by monotonous cuboidal epithelium. In smaller areas, there were sheets of anaplastic carcinoma cells with large vesicular and pleomorphic nuclei, rich eosinophilic cytoplasm, and sometimes a spindly

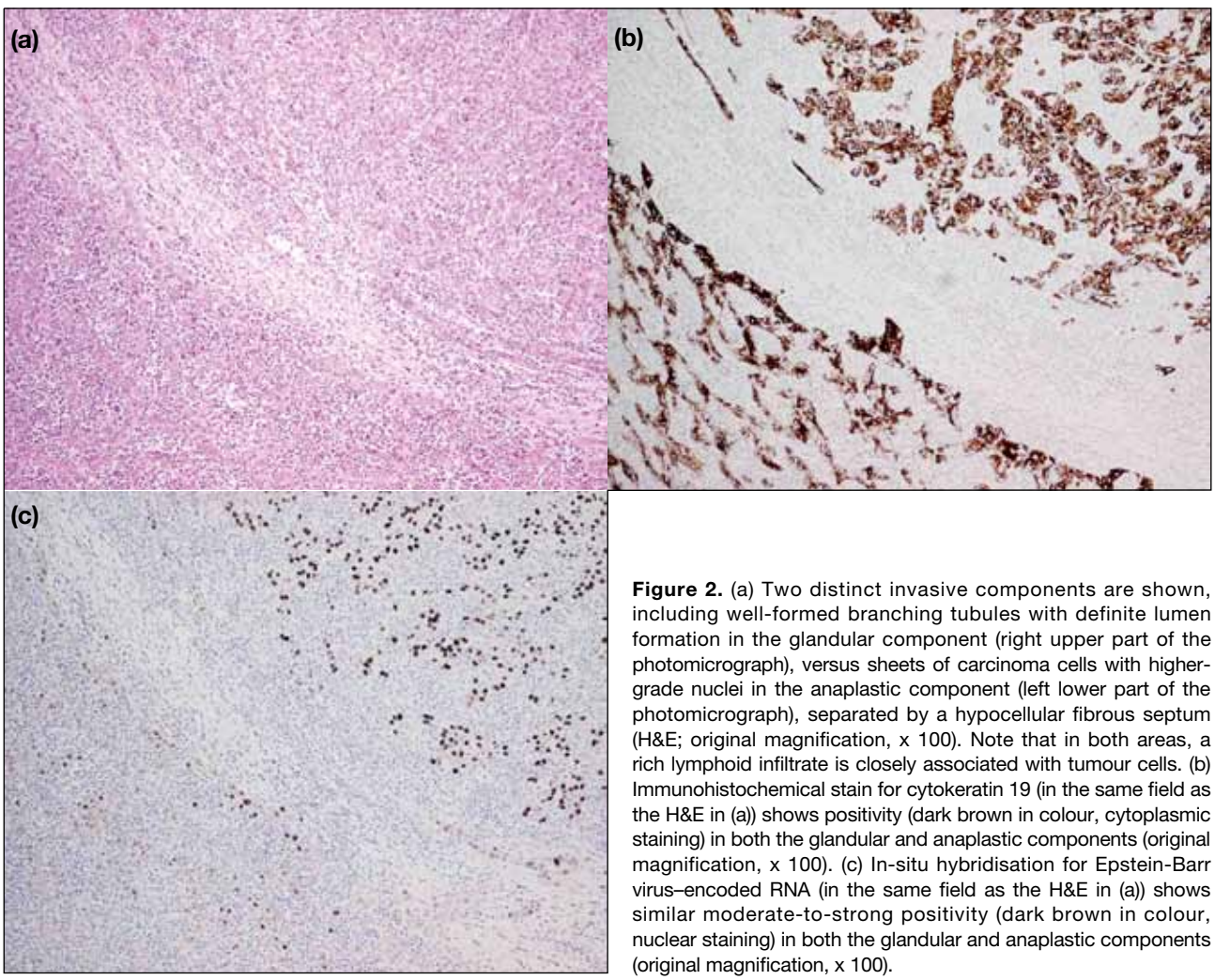

Figure 2. (a) Two distinct invasive components are shown, including well-formed branching tubules with definite lumen formation in the glandular component (right upper part of the photomicrograph), versus sheets of carcinoma cells with higher-grade nuclei in the anaplastic component (left lower part of the photomicrograph), separated by a hypocellular fibrous septum (H&E; original magnification, x 100). Note that in both areas, a rich lymphoid infiltrate is closely associated with tumour cells. (b) Immunohistochemical stain for cytokeratin 19 (in the same field as the H&E in (a)) shows positivity (dark brown in colour, cytoplasmic staining) in both the glandular and anaplastic components (original magnification, x 100). (c) In-situ hybridisation for Epstein-Barr virus–encoded RNA (in the same field as the H&E in (a)) shows similar moderate-to-strong positivity (dark brown in colour, nuclear staining) in both the glandular and anaplastic components (original magnification, x 100).

outline. Both components were associated with a rich lymphoplasmacytic infiltrate. Perineural invasion and portal venous invasion were identified, but there was no tumour perforation through the liver capsule. Resection margins were not involved.

On immunohistochemical staining, carcinoma cells in both the glandular and undifferentiated areas were positive for cytokeratin 19, a marker supporting biliary epithelial differentiation (Figure 2b), and were negative for arginase 1, a hepatocyte marker. In-situ hybridisation for EBV-encoded RNA showed moderate-to-strong positivity in most tumour cells (Figure 2c).

The dense lymphoid infiltrate associated with the tumour showed follicles of B cells (CD20+) with interspersed small reactive T cells (CD3+). Staining for kappa and lambda light chains demonstrated a mixed pattern. These results were in keeping with a reactive lymphoid proliferation.

Diagnosis

In view of the long disease-free interval from the first diagnosis of NPC 18 years previously, the presence of a solitary lesion located close to a large portal tract, diagnostic radiological enhancement pattern, presence of definite glandular component, and positivity for cytokeratin 19 (favouring a biliary origin over a nasopharyngeal primary), this newly developed malignant tumour was diagnosed as LELCC rather than a metastasis from NPC.

Management

Due to the rarity of LELC of the bile duct and hence a lack of strong evidence for adjuvant chemotherapy after complete resection, observation was suggested.

DISCUSSION

The EBV is a herpes virus that causes a persistent infection in over 90% of the adult population worldwide. It has been classified as a group 1 carcinogen due to its association with a variety of lymphoid and epithelial malignancies, including undifferentiated NPC, which is most prevalent in Southern China and some other regions. As EBV infection is almost ubiquitous throughout the world, the development of NPC in a subset of the infected population suggests that there are certain contributing factors in the tumourigenesis, including genetic and environmental co-factors. Studies have postulated that certain Chinese-related human leukocyte antigen profiles conferred genetic susceptibility leading to reduced efficiency in activating the host immune response to EBV infection.[29] Childhood consumption of salted fish has also been shown to be related to an increased risk of NPC in southern Chinese people.[1]

There have been 23 patients with LELCC reported in the literature to date.[17-28] Of them, 20 (87%) were Asian and 17 (74%) were EBV-positive. This echoes the geographical prevalence and virological aetiology of undifferentiated NPC.

According to Chan et al,[29] LELCC is associated with a favourable overall survival (100% at 5 years), which is much better than that for the more common intrahepatic cholangiocarcinoma or NPC counterparts. In that study, six out of seven patients were alive at the time of analysis, with the longest follow-up at 165 months. One patient died of liver metastasis after 69 months of follow-up.

In view of the paucity of cases described so far, there is no consensus on the standard adjuvant treatment for this patient after primary surgery. However, regular follow-up is necessary to detect possible recurrence. For patients with NPC, circulating EBV DNA in the blood plasma has been employed to predict prognosis and monitor disease recurrence. However, this patient only had a low positive level of EBV DNA at presentation, which might be explained by the relatively small tumour load in the early stage of disease. Nevertheless, regular monitoring of EBV DNA is still recommended in this patient as a raised EBV DNA level, regardless of the magnitude, may warrant detailed investigation for early recurrence of both malignancies.

To the best of our knowledge, this is the first report of the coexistence of two EBV-associated malignancies involving the nasopharynx and the bile duct in a single patient. Coincidentally, these two EBV-associated malignancies are more commonly reported in Asian population, which suggests that they may share similar aetiological factors. In this particular patient, both he and his mother had NPC at a relatively young age. This may be related to a particular genetic susceptibility or other environmental factors that are crucial to the development of these two disease entities.

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