CASE REPORT

Peri-Ampullary Lymphoepithelioma-Like Carcinoma: Case Report and Review of the Literature

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ABSTRACT

Context Lymphoepithelioma-like carcinomas are rare, non-keratinizing and undifferentiated carcinomas, with a distinctive syncytial growth pattern, and with associated numerous non-neoplastic lymphocytes admixed with the tumor cells. The majority of tumors with this appearance are Epstein Barr virus-associated. **Case report** We report a case of a forty-one-year-old male patient who had a pancreatoduodenectomy for a peri-ampullary lymphoepithelioma-like carcinoma. Epstein-Barr Virus-Encoded RNA *in situ* hybridization was positive. Immunohistochemistry for mismatch repair proteins showed that the tumor cells were positive (normal staining pattern) for MSH-2, MSH-6, MLH-1 and PMS-2. **Conclusion** Peri-ampullary lymphoepithelioma-like carcinomas have not been previously described in the published English literature. We review the morphological, immunohistochemical and molecular features of lymphoepithelioma-like carcinomas.

INTRODUCTION

Carcinomas that are disposed in broad sheets, usually with exiguous gland formation, and accompanied by a lymphoid infiltrate have been likened to an Epstein–Barr virus-associated nasopharyngeal carcinoma (so-called lymphoepithelioma carcinoma). In the extra-nasopharyngeal setting, similar appearing carcinomas have been called lymphoepithelioma-like carcinomas and have been encountered in a plethora of sites including the gastrointestinal tract. Here, they may be associated with EBV or mismatch repair protein loss.

In this paper we describe a rare lymphoepithelioma-like carcinoma occurring in the peri-ampullary region. To the best of our knowledge, this appears to be the first such case described in the English language literature.

CASE REPORT

Clinical

A forty-one-year-old gentleman was referred to our institution for investigation of melena and shortness of breath. There was no significant past medical history. An esophagogastroduodenoscopy (EGD) revealed a malignant-appearing stricture in the second part of the duodenum (D2). A staging CT of abdomen and pelvis showed slight thickening of the duodenal wall at D2. There was no evidence of distant disease. As the disease was locally confined, a Whipple pancreatoduodenectomy was performed.

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Keywords Ampulla of Vater; Carcinoma; Pancreas
Abbreviations EBV epstein barr virus; EBER Epstein-Barr Virus-Encoded RNA; EGD esophagogastroduodenoscopy; LEC lymphoepithelioma-like carcinoma
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Pathology

Macroscopically, a 3.5 cm well-circumscribed, peri-ampullary solid mass was identified, which appeared to be confined to the peri-ampullary region. A 2.7 cm regional lymph node was grossly positive for tumor.

Histological examination disclosed an invasive moderately to poorly differentiated adenocarcinoma, with an infiltrative growth pattern, comprising glands and irregular nests, composed of large epithelioid cells with vesicular chromatin and prominent nucleoli. The tumor involved the ampullary region and the duodenal wall, and, given that the bulk of the tumor was located surrounding the ampulla, it was considered to represent a peri-ampullary LEC (AJCC pTNM 7th edition pT2). Lymphovascular and perineural invasion were present. A marked mixed inflammatory infiltrate was present, at the periphery of the tumor and admixed with the tumor cells, and comprised mainly small, mature lymphocytes, but also plasma cells and occasional eosinophils. Intra-epithelial lymphocytes were conspicuous within tumor cells **(Figure 1)**.

Four of fifteen (4/15) regional lymph nodes were positive for metastatic carcinoma (pN1). All resection margins were negative for dysplasia or malignancy (R0).

Epstein-Bar Virus-Encoded RNA (EBER) *in situ* hybridization was positive in the malignant epithelial cells (**Figure 2)**. Immunohistochemistry for mismatch repair

proteins showed that the tumor cells retained (normal nuclear staining pattern) MSH-2, MSH-6, MLH-1 and PMS-2, indicating that the mismatch repair genes were intact.

The morphological and immunohistochemical features were of an EBV-positive peri-ampullary lymphoepithelioma-like carcinoma.

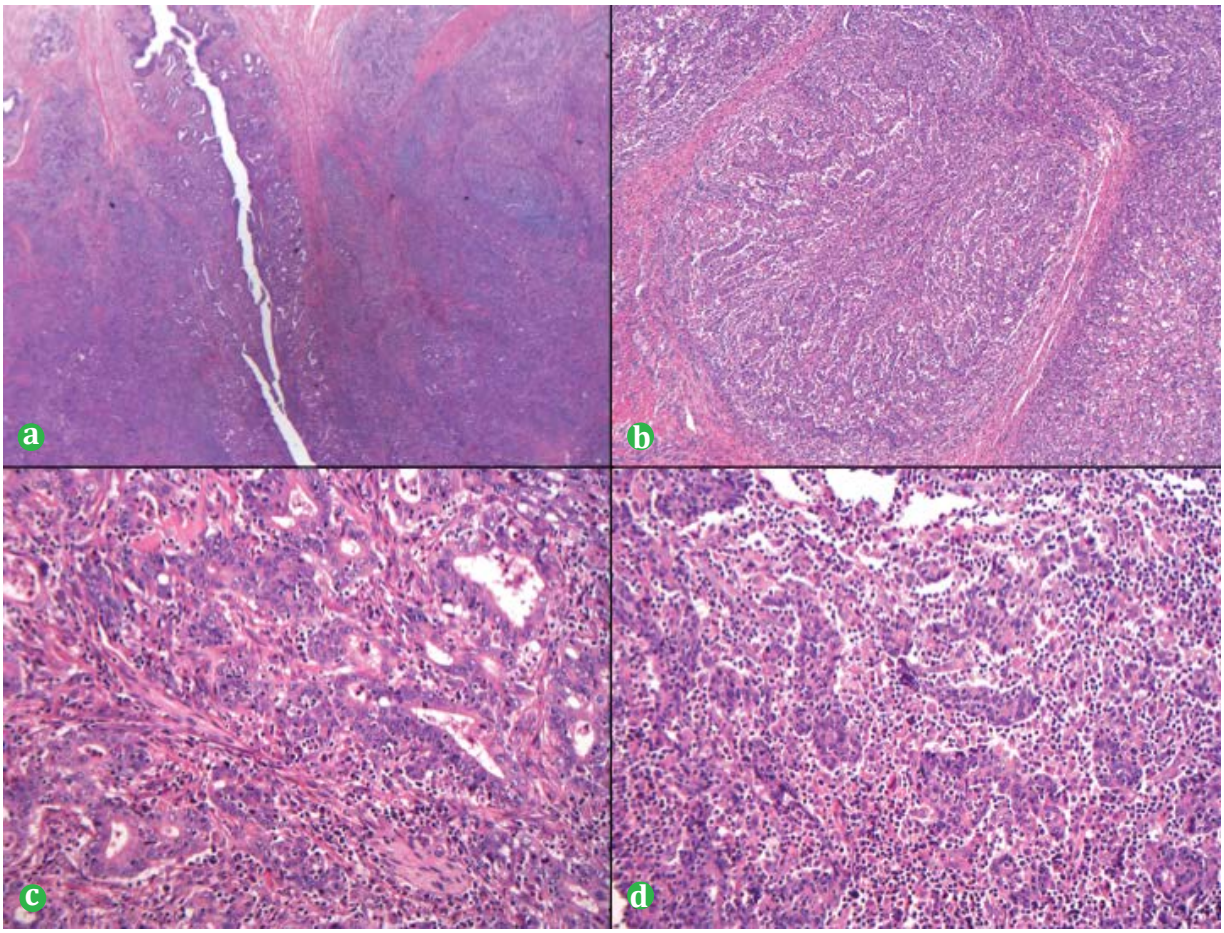

Figure 1. (a). The tumor was centered around the ampulla and had an infiltrative growth pattern (16X magnification). **(b).** It was an invasive poorly differentiated carcinoma, with a marked peri-tumoral inflammatory infiltrate (50X magnification). **(c).** Occasional glandular structures were seen and a marked intra-tumoral inflammatory infiltrate comprising predominantly small, mature-appearing lymphocytes was present (200X magnification). **(d).** The tumor cells were large epithelioid cells, with vesicular chromatin and prominent nucleoli (200X magnification). Intra-epithelial lymphocytes were conspicuous within tumor cells (200X magnification).

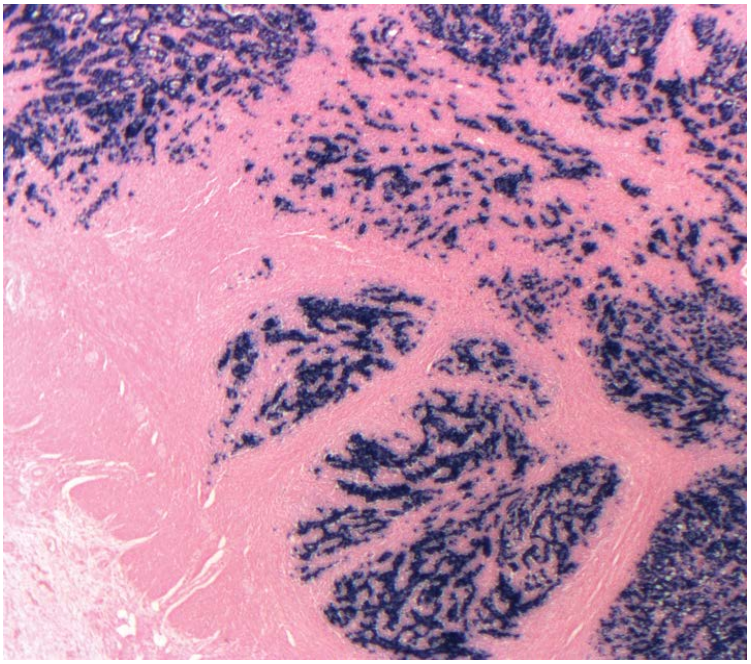

Figure 2. Epstein-Bar Virus-Encoded RNA (EBER) *in situ* hybridization was positive in the malignant epithelial cells (25X magnification).

Follow-up

The patient underwent 10 cycles of FOLFOX chemotherapy (folinic acid, fluorouracil and oxaliplatin). He was followed for 5 years by yearly CT scans, and, as he was well and there was no evidence of local or metastatic disease, he was discharged from follow-up.

DISCUSSION

A review of the published English literature using recognized search engines, PubMed and Google, was performed, with the keywords: "ampulla", "lymphoepithelial carcinoma", "lymphoepithelioma-like", "lymphoid infiltrate", "pancreas" and "peri-ampullary".

The term lymphoepithelioma-like carcinoma (LEC) is used to describe non-keratinizing and undifferentiated carcinomas, with a distinctive growth pattern, and with associated numerous non-neoplastic lymphocytes admixed with the tumor cells [1]. It was first described by Regaud and Reverchon, and by Schmincke in 1921, and has also been termed Schmincke-Regaud's tumor, lymphoepithelioma and lymphoepithelial carcinoma [2, 3, 4].

LEC typically develops in the nasopharyngeal area and represents the undifferentiated variant of non-keratinizing nasopharyngeal carcinoma. Extra-nasopharyngeal LECs have been described, in the lung, breast, renal pelvis, bladder and female genital tract [5, 6, 7, 8, 9], but they are exceedingly rare tumors. LEC has been reported in the gastrointestinal tract, specifically in the esophagus, stomach, sigmoid colon and rectum [10, 11, 12, 13, 14, 15, 16, 17, 18], and in the hepatobiliary tract [19, 20, 21, 22, 23, 24, 25, 26]. Recently, Vanoli et al. reported a single case of distal ileal Epstein–Barr virus (EBV)-positive LEC [27], however, LEC of the ampulla, duodenum or peri-ampullary region has not been described previously.

Kekis *et al*. reported an EBV-related LEC of the pancreas, occurring in a patient several years after an EBV-related LEC of their stomach. However, although the authors favored that two independent EBV-related carcinomas developed in the pancreas and in the stomach of their patient, they could not exclude the possibility that the LEC observed in the pancreas was a metastasis from the EBV-associated gastric carcinoma (2). In a series describing 13 medullary carcinomas of the pancreas, one tumor exhibited lymphoepithelioma-like features morphologically and contained EBV-encoded RNA-1 (EBER1) [28].

Histologically, LEC characteristically is composed of single cells, small clusters of cells and small glands, with an infiltrative growth pattern [13]. The tumor cells have large vesicular nuclei, single prominent nucleoli and indistinct cell borders. LEC has an attendant lymphoplasmacytic inflammatory component, which tends to be more intra-tumoral than peri-tumoral [13, 29].

Immunohistochemistry with pan-cytokeratin and/or epithelial membrane antigen (EMA) highlights the malignant epithelial tumor cells, which can sometimes be obscured by the dense inflammatory infiltrate. They are negative for neuroendocrine markers (e.g. neuron-specific enolase (NSE), chromogranin A, synaptophysin, CD56) and lymphoid markers. The lymphoid cells consist of a mixture of CD3-positive T lymphocytes and CD20-positive B lymphocytes. Admixed plasma cells are positive for CD38 and CD138. There is no evidence of light chain restriction of the lymphoid or plasma cells.

With respect to the etiology of LEC, as alluded to previously, the most important link to their development is EBV [30], a herpes virus causing ubiquitous infection by adulthood worldwide. With the use of EBER-*in situ* hybridization (ISH) (the gold standard for detecting the virus in tissue) and PCR, EBV genomic components have been detected in 75%–100% of LECs [31], with EBV infection thought to represent an early event in the carcinogenic pathway [32]. In addition, EBV has been detected in dysplastic and normal epithelium adjacent to LECs of the nasopharynx and of the stomach, and expression of EBV latent proteins has been shown to lead to genetic instability, epigenetic changes, and eventual cell transformation [33]. Thus, tumorigenesis seems to be related to latent EBV infection, which may be facilitated by genetic alterations in the host cells [33].

In contrast to nasopharyngeal LECs, LECs occurring in other organs have been shown to express EBV-related RNA to a variable extent. EBV-associated gastric carcinomas have been shown to occur as either typical appearing adenocarcinomas or as LECs. Not all gastric LECs are associated with EBV; some are microsatellite instability high carcinomas, and these two associations have been shown to be mutually exclusive [34, 35]. EBV *in situ* hybridization and/or PCR have been reported to be negative in LEC of the breast, renal pelvis, and uterine cervix [6, 7, 8]. The association with EBV has been inconsistent in reported cases of LEC of the colon, with the majority of cases showing no association with EBV [15, 16, 17, 36]. LECs of the colon unrelated to EBV, may be due to sporadic epigenetic silencing of *MLH-1* (15). Thus, it has been suggested that perhaps these tumors with a prominent intra- or peri-tumoral lymphoid component should be descriptively designated as adenocarcinomas with lymphoid stroma, with or without associated EBV, with or without microsatellite instability (MSI) [13]. Of particular relevance to our case report, Samdani *et al*. and Kekis *et al.* each reported a case of EBV–associated LEC in the pancreas [2, 37]. The rate of latent EBV infection in conventional adenocarcinomas in the pancreatobiliary tract is not well understood. A case of EBV-positive ileal LEC has recently been described in the literature by a group in Italy [27].

Multiple chromosomal abnormalities (e.g. copy number changes on chromosomes 3p, 9p, 11q, 12p, and 14q), epigenetic changes (e.g. *RASSF1A*, *CDKN2A* and *TSLC1* methylation) and gene alterations (e.g. *p16* deletion and *LTBR* amplification) and have been identified in nasopharyngeal LECs [33, 38]. Lin *et al*. reported frequent alterations in genes involved in chromatin modification

pathways (*ARID1A, BAP1, KMT2D/3, TSHZ3,* and *TET1/2/3*) in nasopharyngeal LECs [38]. According to The Cancer Genome Research Network data, EBV-associated gastric cancers have a distinct genomic profile, which includes extreme CpG-island methylation of the promoter region, frequent mutations of *PIK3CA*, *ARID1A*, *JAK2* and *BCOR*, and amplification of *ERBB2* [9].

Recently, Samdani et al. reported a case of EBV-associated LEC of the pancreas, on which they performed next generation sequencing via a custom hybrid capture assay (MSK-IMPACT) targeting all exons of 341 genes. They detected somatic mutations in the following genes: *BARD1*, *BCOR*, *FAT1*, *HIST1H1C*, *INPP4*, and *PARP1*. These results support the hypothesis that pancreatic LEC is distinct from conventional pancreatic ductal adenocarcinoma (which usually harbors variants in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4)* [37].

Recently, a study by Zhou *et al*. concluded that programmed cell death-ligand (PD-L1) might be a potential prognostic biomarker for patients with nasopharyngeal carcinoma, irrespective of EBV-DNA load [39]. Chang et al. showed that PD-L1 expression is a common feature in EBV-associated LEC of lung, and suggested that expression of this protein might lead to enhanced immune evasion by the tumor [40]. Thus, it has been proposed that clinical trials targeting PD-1 and/or PD-L1 may benefit patients with LECs of lung [40, 41]. It has also been shown that EBV-positive gastric cancers as well as gastric carcinomas with dense lymphocyte infiltration are more likely to express PD-L1 [42, 43]. Wang *et al*. demonstrated PD-L1 expression in both the tumor cells and tumor-infiltrating immune cells in intrahepatic lymphoepithelioma-like cholangiocarcinoma at higher levels than in conventional intrahepatic cholangiocarcinoma [24]. It remains to be seen if there is high expression of PD-L1 in EBV-associated LECs of other sites, including pancreas and ampulla, and if this expression may provide an attractive rationale for immunotherapy in LECs.

The histological differential diagnosis of peri-ampullary LEC includes medullary carcinoma, poorly differentiated carcinoma (not otherwise stated, NOS) and high grade neuroendocrine carcinoma (NEC). Medullary carcinomas exhibit a syncytial, organoid and sheet-like growth pattern with a pushing, rather than infiltrative, border, poor differentiation and extensive necrosis. They demonstrate frequent MSI and wild-type *KRAS* [28, 44]. Features suggesting MSI are important to recognize to identify patients with potential germline mutations of mismatch repair protein genes. In general, peri-ampullary and pancreatic medullary carcinomas do not have as large a number of intra-tumoral lymphocytes as LECs [28], and when there is a prominent lymphocytic infiltrate, it tends to be more peri-tumoral than intra-tumoral (with the converse being true for LEC) [13]. An association between true medullary carcinoma (in any site) and EBV has not been described in the literature, therefore EBER-ISH positivity is useful to exclude medullary carcinoma [13]. Poorly differentiated carcinoma NOS lacks an infiltrate of lymphoid cells and is EBER-ISH negative. In the absence of unequivocal morphological features, determining MSI and EBV status via ancillary testing appears to be a practical approach to distinguishing between LEC, medullary carcinoma and poorly differentiated carcinoma (NOS). Similar to poorly differentiated carcinoma (NOS), high grade NECs lack a dense infiltrate of lymphoid cells and demonstrate EBER-ISH negativity. In addition, NECs express neuroendocrine immunohistochemical markers (chromogranin-A, synaptophysin, CD56).

CONCLUSION

In conclusion, we report a case of a peri-ampullary lymphoepithelioma-like carcinoma, associated with EBV, in a 41-year old man. Only a handful of cases of pancreatic lymphoepithelioma-like carcinoma have been reported and, to our knowledge, peri-ampullary lymphoepithelioma-like carcinomas have not been previously described.

Confilct of Interest

Authors are declared that there is no conflict of interest.

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