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CASE REPORTS

Epstein–Barr Virus-Associated Lymphoepithelial Carcinoma Arising in a Salivary Sebaceous Lymphadenoma

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Abstract

Background Lymphadenomas are rare benign tumors of the major salivary glands that are further classified as sebaceous and non-sebaceous. No association with viruses has been reported so far. Little is known about the mechanisms that allow lymphadenomas to undergo malignant transformation. Among these rare instances, there has never been a malignant transformation to Epstein–Barr virus (EBV)-associated lymphoepithelial carcinoma.

Methods Clinical data of the reported case were retrieved from the patient's electronic medical record. Hematoxylin & eosin-stained slides, immunohistochemical tests, and in situ hybridization performed for routine diagnostic purposes were reviewed.

Results We report a salivary gland sebaceous lymphadenoma in which the luminal components were mostly replaced by malignant epithelial cells with markedly atypical nuclear features. Presence of EBV was demonstrated in all components by EBER. The morphological and immunohistochemical findings were consistent with a lymphoepithelial carcinoma arising from a sebaceous lymphadenoma.

Conclusion We report the first case of an Epstein–Barr virus-associated lymphoepithelial carcinoma arising from a sebaceous lymphadenoma.

Keywords Salivary gland tumor · Parotid tumor · Lymphadenoma · Lymphoepithelial carcinoma · Epstein–Barr virus

Introduction

Sebaceous and non-sebaceous lymphadenomas (LAD) are rare benign tumors of the major salivary glands first described in 1960 by McGravan, et al. [1]. Little is known about the mechanisms that allow LADs to undergo malignant transformation. Among these rare instances, transformation to lymphoepithelial carcinoma (LEC) has never been reported. LECs are histologically similar to nasopharyngeal non-keratinizing squamous cell carcinoma (NPC), and they are associated with Epstein–Barr virus (EBV) in endemic areas [2]. We report the first case of an EBV-associated lymphoepithelial carcinoma arising from a sebaceous LAD.

Materials and Methods

Clinical data of the reported case were retrieved from the patient's electronic medical record. Hematoxylin & eosin-stained slides, immunohistochemical tests, and in situ hybridization performed for routine diagnostic purposes were reviewed and diagnosis was reconfirmed in accordance with the WHO classification of head and neck tumors [3–5].

Results

Case Report

We report the case of a 51-year-old non-smoking male without significant medical history who presented with a left preauricular mass. Imaging revealed a 1.3-cm well-delimited

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lesion of the superficial parotid lobe without metastasis. No nasopharyngeal or other suspicious masses were found on head and neck CT scan or PET scan (Fig. 1). A superficial parotidectomy was performed.

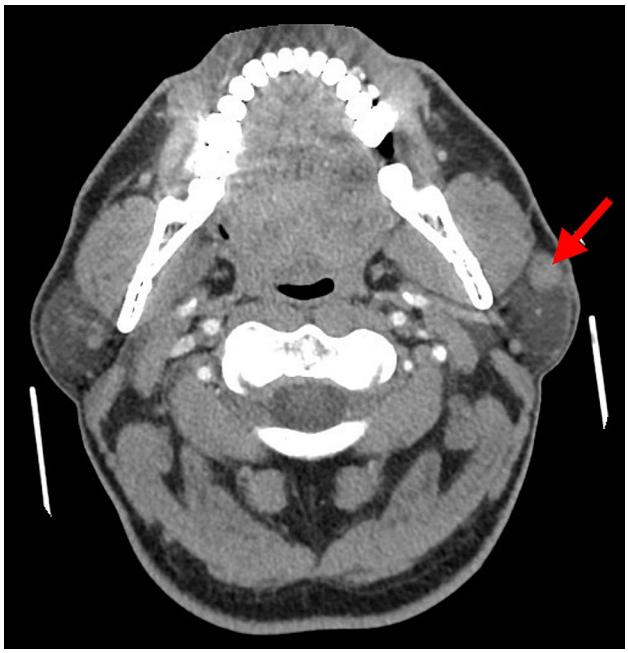

Fig. 1 Computed tomography scan shows a solid and well-demarcated lesion of the left superficial parotid lobe measuring 1.3 cm in diameter (arrow)

Grossly, the lesion consisted of a beige 1.4-cm well-encapsulated nodule without extraparenchymal extension. Microscopically, the tumor was well demarcated and it was composed of epithelial tubules and trabeculae within a background of lymphoid tissue exhibiting germinal centers. The epithelial foci consisted of peripheral monotonous basaloid cells without atypia. In the center of these foci, the epithelial cells showed focal squamous and sebaceous differentiation, consistent with the epithelial component of a sebaceous lymphadenoma. However, in most of the lesion, the luminal component was replaced by malignant epithelial cells with indistinct cytoplasmic borders, markedly enlarged nuclei, prominent nucleoli, and a high nuclear-to-cytoplasmic ratio (Fig. 2). Lymphovascular invasion and perineural invasion were absent.

Immunohistochemistry and in situ Hybridization

By immunohistochemistry, the peripheral and the luminal components of the lymphadenoma showed an intercalated duct phenotype and the cells were positive for cytokeratin 7, p40, p63, and SOX10. In contrast, the central malignant cells were weakly positive for cytokeratin 7 and Ki67 showed a high proliferation index of up to 60%, while p40, p63, and SOX10 were negative. The presence of EBV was demonstrated in both the malignant and benign lymphadenoma components with an EBV in situ hybridization probe (EBER) (Fig. 3). Smooth muscle actin and p16 were

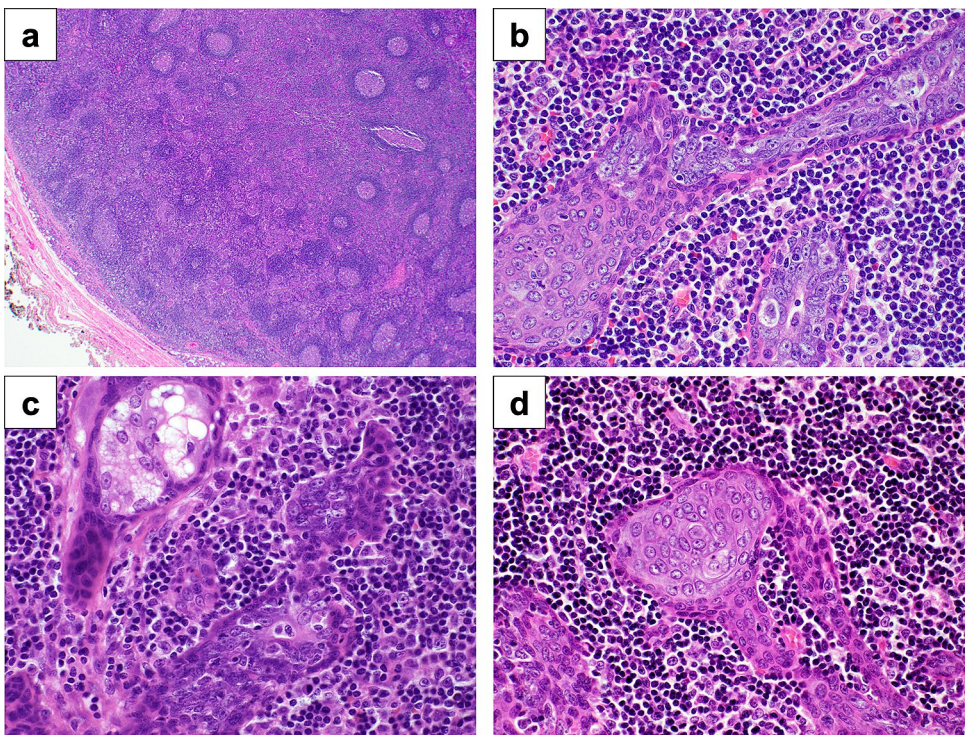

Fig. 2 **a** The tumor is well demarcated and is composed of epithelial cells within a lymphoid stroma (H&E 20X), **b** Monotonous abluminal cells surround the luminal carcinoma component (H&E 100X), **c** Sebaceous lymphadenoma in relation to malignant component (H&E 100X), **d** Squamous differentiation (H&E 100X)

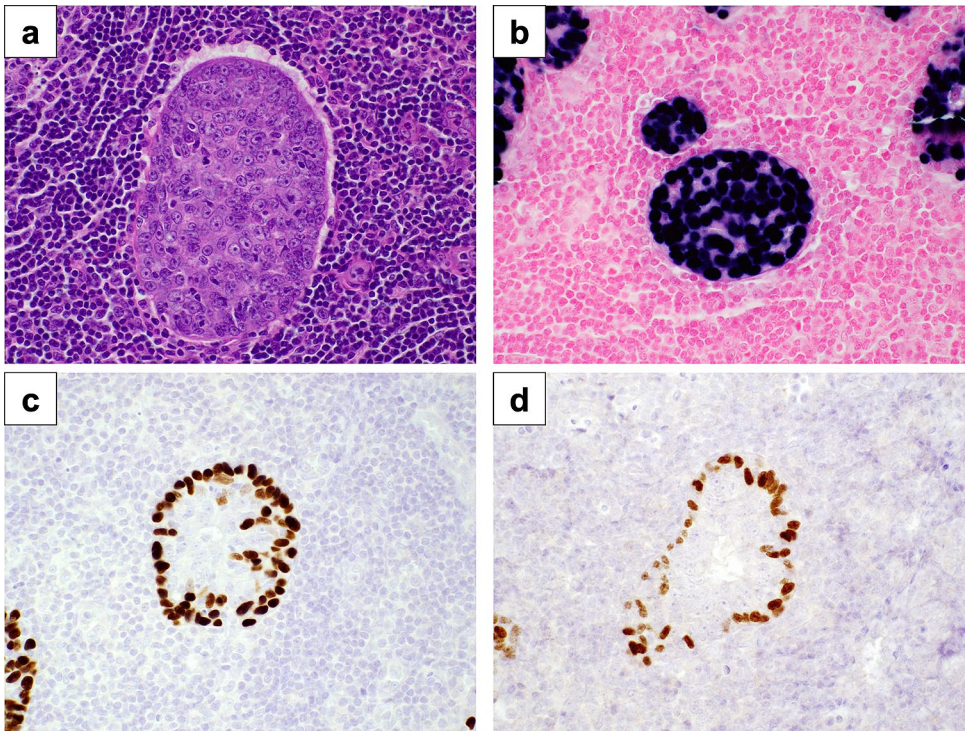

Fig. 3 **a** Tumor (H&E, 400X), **b** Epstein–Barr Virus in situ hybridization shows positivity in the luminal carcinoma and abluminal lymphadenoma components, **c** The abluminal component shows positivity for p40, **d** SOX10 is expressed in abluminal cells

negative. The changes were consistent with a lymphoepithelial carcinoma, EBV-related, arising from a sebaceous lymphadenoma.

Follow-Up

The patient was treated with local adjuvant radiation therapy and no suspicious lesion was identified on follow-up imaging. There was no evidence of disease after 24 months.

Discussion

LADs are rare benign tumors of the major salivary glands that are further subclassified according to the presence or absence of sebaceous differentiation. Sebaceous LADs occur in patients over 50 years old with a predilection for the parotid glands [6]. Histologically, LADs are characterized by a well-circumscribed proliferation of epithelial cells accompanied by a dense background of reactive lymphocytes [3]. The epithelial component shows anastomosing cords and nests of basaloid cells that can be solid or cystic with a varying degree of squamous differentiation [6].

Even though the vast majority of LADs are benign and do not recur after complete surgical excision, cases of carcinoma ex LAD have been described. Including the present case, there are only 12 reports of LAD with malignant transformation, all of which are summarized in Table 1. Mean age of presentation is 64 years old with a slight male preponderance [6–14]. Except for two patients who died of unrelated causes, all the patients were alive and showed no evidence of recurrence after follow-up periods ranging between 4 months and 6 years [6–14]. Malignant transformation predominantly arises in sebaceous LADs. Reported subtypes of carcinoma ex sebaceous LAD include sebaceous lymphadenocarcinoma, basal cell adenocarcinoma, and sebaceous carcinoma [6, 14]. The only case of malignancy arising in a non-sebaceous LAD was an undifferentiated carcinoma [7].

LAD has never been reported in association with LEC, which is a rare EBV-associated undifferentiated carcinoma characterized by a syncytial growth pattern of malignant epithelial cells accompanied by a dense background of non-neoplastic lymphocytes [3]. LEC typically occurs in the sixth decade without sex predilection [3]. Most cases occur in North American Inuit people and in EBV-endemic regions such as South-East Asia, Japan, and North Africa [3]. Salivary LEC is undistinguishable from nasopharyngeal non-keratinizing squamous cell carcinoma, EBV-associated, and from LECs of other sites of the upper aero-digestive tract [15]. Treatment consists of surgical resection with neck dissection followed by adjuvant radiation therapy [2]. Nodal metastases are observed in up to 40% of cases, while 3-year and 5-year overall survival are reported to be 93% and 86%, respectively [16].

Our case represents the first instance of a LEC arising in a sebaceous LAD. Both the carcinoma and the LAD components were EBV-positive by in situ hybridization. Until now,

Table 1 Reported cases of lymphadenoma with malignant transformation

Author	Patient	Clinical	Diagnosis of malignant component (Histology)	EBV	Treatment	Course
Kara et al. [7]	F 54	R parotid. 2 cm. Present for 12 months, enlarging over past 3 months	Undifferentiated carcinoma from non-sebaceous LAD	–	Excision and postoperative locoregional radiotherapy	NED at 10 months
Seethala et al. [6]	F 74	R parotid. 1.5 cm	Basal cell adenocarcinoma from Sebaceous LAD	N/A	N/A	N/A
Seethala et al. [6]	M 76	R parotid. 5.5 cm	Sebaceous carcinoma	N/A	N/A	N/A
Linhartova [8]	F 68	Parotid. 5 cm. Slow growth over 2.5 years	Sebaceous carcinoma from sebaceous LAD	N/A	Excision and postoperative radiotherapy	NED at 6 years
Gnepp and Brannon [9]	M 7th decade	Periparotid lymph node. Asymptomatic. Present for 1 month	Sebaceous lymphadenocarcinoma from sebaceous LAD	N/A	Excision and superficial parotidectomy	NED at 14 months
Gnepp and Brannon [9]	M 7th decade	Parotid. Asymptomatic. Present for at least 20 years	Sebaceous lymphadenocarcinoma from sebaceous LAD	N/A	Excision and superficial parotidectomy	Died of other causes at 18 months. (cardiovascular disease)
Croitoru, et al. [10]	M 55	L parotid. 6 cm. Present for 3 years. Rapidly enlarging over 3 months	Sebaceous lymphadenocarcinoma from sebaceous LAD	N/A	Excision and postoperative radiotherapy	NED at 4 months
Ahn and Park [11]	F 36	L parotid. 1.2 cm. Present for at least 10 years. Enlarging over 4 months	Sebaceous lymphadenocarcinoma from sebaceous LAD	N/A	Superficial parotidectomy and postoperative radiotherapy	NED at 24 months
Claudius et al. [12]	M 87	L parotid. 2.7 cm. Reddish violet plaques on left cheek and neck. Infraauricular mass. Palpable cervical lymph nodes	Sebaceous lymphadenocarcinoma from sebaceous LAD with cervical lymph node metastasis and lymphangiosis carcinomatosa	N/A	Skin excision, neck dissection, and postoperative radiotherapy	Died of other causes at 8 months (respiratory failure)
Vazmitsel et al. [13]	N/A	Parotid	Sebaceous lymphadenocarcinoma arising within Sebaceous LAD	N/A	N/A	N/A
Hao, et al.[14]	F 82	R parotid. 2.8 cm. Rapidly enlarging over 4 months	Sebaceous lymphadenocarcinoma with lymph node metastasis	–	Extended resection and neck dissection	NED at 10 months
Reported case	M 51	L Parotid	Lymphoepithelial carcinoma arising in sebaceous lymphadenoma	+	Superficial parotidectomy and postoperative radiotherapy	NED at 12 months

R right; *L* left; *LAD* lymphadenoma; *NED* no evidence of disease

sebaceous LADs have never been associated with viruses such as EBV and human papilloma virus (HPV) [6, 7, 17–20]. Our differential diagnosis included metastatic NPC, but no nasopharyngeal lesion or other suspicious masses were found on imaging and clinical examination. Also, in our case, the carcinomatous component was confined within the tubules and trabeculae of the lymphadenoma, which argues against a metastasis. The presence of EBV and absence of myoepithelial cells ruled out other basaloid salivary carcinomas such as sebaceous lymphadenocarcinoma, basal cell adenocarcinoma, epithelial myoepithelial carcinoma, adenoid cystic carcinoma, and sebaceous carcinoma.

In summary, we report a novel case of EBV-associated LEC arising in a sebaceous LAD. In addition, the LEC component remained confined in the LAD, which may suggest a more indolent course than traditional LEC. Our patient shows no evidence of disease recurrence after 24 months, which mirrors the absence of recurrence in other reported cases of carcinoma ex LAD [6–14]. Additional cases are required to truly evaluate the clinical evolution of EBV-associated LEC arising in LAD.

Author Contributions JW performed literature review and wrote the manuscript. JB supervised the project, substantially edited the manuscript, and provided images. OG, KA, and RRS reviewed the manuscript. All authors read and approved the final manuscript.

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Data Availability All material included in manuscript. No supplementary data to provide.

Declarations

Conflict of interests The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent For this type of study informed consent is not required.

Consent for Publication For this type of study consent for publication is not required.

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