Lymphoepithelioma-like Carcinoma of the Skin: A Case of One Patient Presenting with Two Primary Cutaneous Neoplasms

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Abstract

Lymphoepithelioma-like carcinoma of the skin (LELCS) is a rare cutaneous neoplasm most frequently found on the head and neck of elderly patients. Debate exists regarding its histogenesis, but it's believed to be of epithelial origin. Histologically, LELCS is remarkably similar to undifferentiated nasopharyngeal carcinoma, a neoplasm associated with Epstein-Barr virus (EBV) infection. EBV reactivity is the main distinguishing factor between these two cutaneous neoplasms, with LELCS rarely documented to test positive for EBV. In general, those diagnosed with LELCS are advised to undergo evaluation of the nasopharynx as well as other internal organ systems that may harbor a lymphoepithelioma-like carcinoma to exclude cutaneous metastasis. Current treatment guidelines recommend wide local excision or Mohs micrographic surgery to prevent local recurrence of LELCS. To the best of the authors' knowledge, this case is the first to report a patient with two separate lymphoepithelioma-like carcinomas of the skin presenting simultaneously.

Introduction

Lymphoepithelioma-like carcinoma of the skin (LELCS) is a rare cutaneous neoplasm with low malignant potential. It is currently classified as a variant of squamous-cell carcinoma (SCC), although historically, its etiology has been debated. LELCS demonstrates nearly identical histologic features to undifferentiated nasopharyngeal carcinoma, also known as metastatic lymphoepithelioma of the nasopharynx, classically differentiated from LELCS by positive reactivity for an associated infection with Epstein-Barr virus (EBV).[1,2] Therefore, an evaluation of the nasopharynx with an ear, nose, and throat (ENT) examination is advised to exclude undifferentiated nasopharyngeal carcinoma.[2-4] LELCS generally is a slow-growing neoplasm with a good overall prognosis. However, due to multiple cases of recurrence after initial surgical excision, the gold standard of treatment for LELCS is wide local excision or Mohs micrographic surgery.[2,5]

Case Report

An 83-year-old Caucasian female was referred to our dermatology clinic for surgical excision of a previously biopsied lesion on her left neck reported initially as a nodular basal-cell carcinoma with focal morpheaform features. The patient also complained of an asymptomatic, slowly enlarging lesion to her left parietal scalp believed to be present for at least three months. The patient's past medical history was non-contributory, and she denied any constitutional symptoms at the time of clinical presentation.

Clinical examination revealed a solitary, 2.0 cm x 2.2 cm, tan to pink, indurated ulcerative plaque (**Figure 1**). There were no naso-oropharyngeal abnormalities or regional lymphadenopathy. A shave biopsy was performed to the left parietal scalp to exclude both basal-cell carcinoma and squamous-cell carcinoma.

The histopathological findings for both the left neck and left parietal scalp neoplasms showed a dermal proliferation of atypical epithelioid cells forming well-defined nests invested by a dense lymphocytic infiltrate (**Figure 2**). The atypical epithelioid cells were basophilic and featured enlarged nuclei with prominent nucleoli. A central ulceration was present under microscopic examination of the cutaneous biopsy on the patient's left parietal scalp. The overlying epidermis appeared uninvolved in both samples. Each specimen stained positive for cytokeratin (CK) 5/6 and epithelial

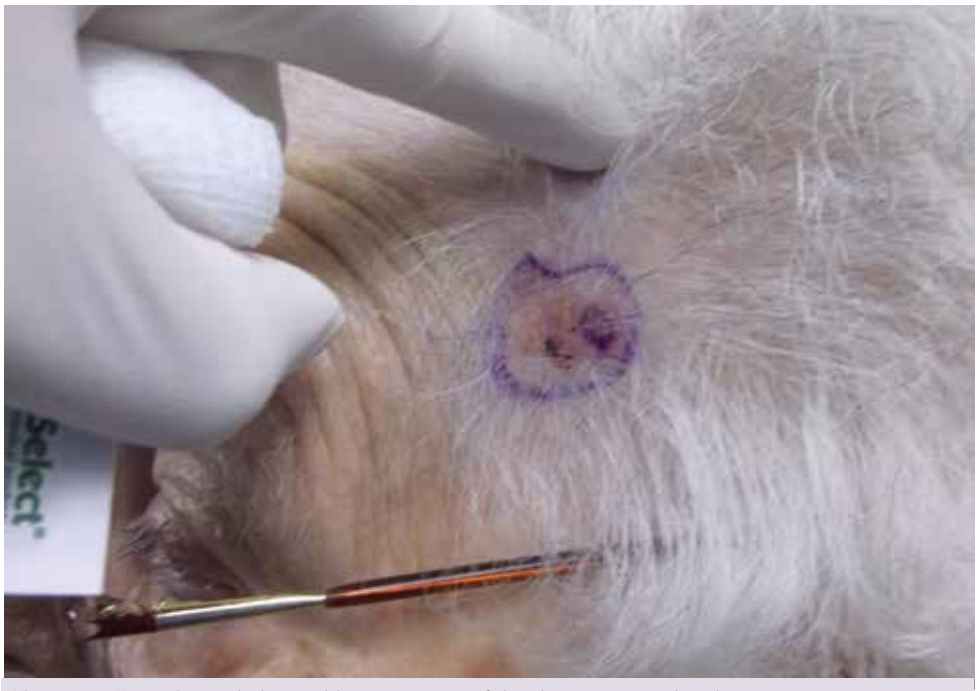

Figure 1. Lymphoepithelioma-like carcinoma of the skin on parietal scalp.

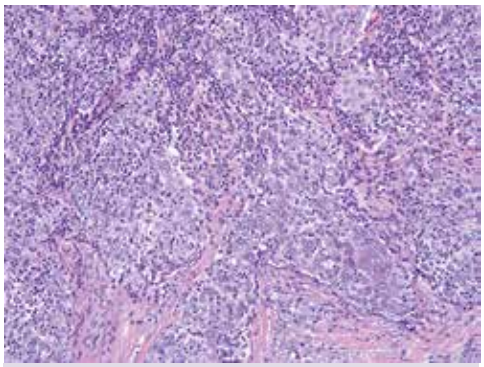

Figure 2. H&E staining of LELCS (20x).

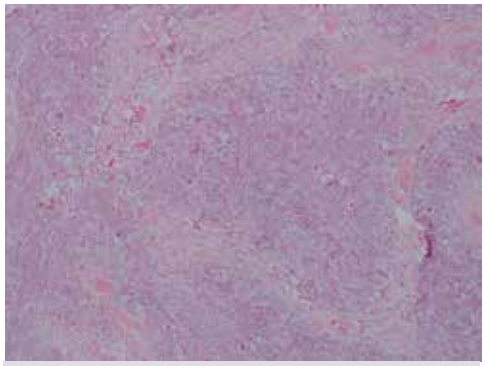

Figure 3. In situ hybridization Epstein-Barr virus encoded RNA (ISH/EBER) of LELCS on parietal scalp. Demonstrates absence of blue staining; determined to be EBV negative (20x).

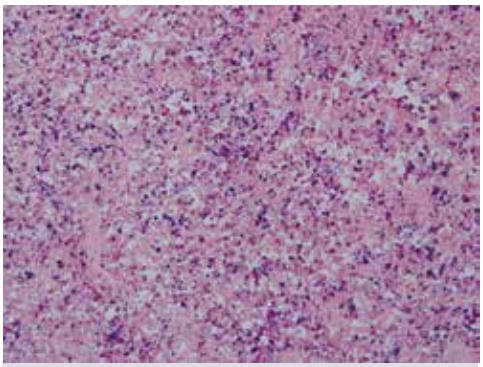

Figure 4. Control slide demonstrating positive reaction to ISH/EBER immunohistochemical stain (20x).

membrane antigen (EMA), suggesting tumors of epithelial origin. Staining for CK7 and CK20 yielded negative results, excluding Paget's disease and Merkel-cell carcinoma (MCC), respectively, from the differential diagnosis. Due to the concern for an underlying metastatic undifferentiated nasopharyngeal carcinoma or lymphoepithelioma-like carcinoma (LELC) of another internal organ, an in situ hybridization for Epstein-Barr virus-encoded RNA (ISH/EBER) was performed for detection of an active or latent EBV infection (**Figure 3**). The patient's histologic slides were compared to a control ISH/EBER immunohistochemical stain (**Figure 4**). The negative ISH/EBER stain for both lesions strongly favors two primary LELSC in our patient and does not favor a metastatic disease related to an EBV-driven undifferentiated nasopharyngeal carcinoma or internal LELC.

Our patient was referred to an oncologist for medical evaluation to exclude cutaneous metastasis of an undifferentiated nasopharyngeal carcinoma or lymphoepithelioma-like carcinoma of other internal organs. Given the patient's advanced age and frail status, the patient refused oncologic examination as she planned to decline systemic treatment if an underlying internal malignancy was discovered. Per initial consultation with the patient, the oncologist remarked that it was highly unlikely that an internal carcinoma was metastasizing to her skin. She was also referred to a plastic surgeon for evaluation and surgical removal of both LELCS.

Our patient plans to undergo surgical excision of both cutaneous neoplasms and remains free from systemic symptoms, which supports the diagnosis of two primary lymphoepithelioma-like carcinomas of the skin.

Discussion

Lymphoepithelioma-like carcinoma of the skin (LELCS) is a rare primary cutaneous neoplasm initially described in 1988 by Swanson et al.[6] Since this first report, close to 80 cases have been described in the English literature. LELCS occurs most often in elderly individuals on sun-exposed areas, primarily the head and neck.[2] However, there has been a report of LELCS occurring on the trunk and upper extremity.[7-9] The incidence is equal in men and women.[8] LELCS often presents as a solitary, flesh-colored to red, firm papule, plaque, or nodule.[2] The average size is fairly large, measuring about 2 cm to 3 cm in diameter.[3] Typically, LELSC is asymptomatic and slowly enlarges over a period of months to years.[8]

Histology

On histology, LELCS presents as a dermal proliferation of atypical polygonal epithelioid cells arranged in nests, cords, or sheets surrounded by a peripheral dense lymphocytic infiltrate.[6] Cellular atypia includes vesicular hyperchromatic nuclei and prominent nucleoli with scant amphophilic-to-eosinophilic cytoplasm.[2] The reactive lymphoid stroma is comprised of small B- and T-lymphocytes, staining positive for CD3 and CD20, with an occasional plasma cell present.[2,8] LELCS generally extends into the reticular dermis with occasional involvement into the subcutis and even skeletal muscle.[6,10] LELCS stains positively for pancytokeratin, CK5, CK6, p63 and EMA reactivity, likely indicating a neoplasm of epithelial origin.[2,7] These markers also indicate that LELCS may derive from an epidermal, follicular, glandular, sudoriferous origin.[2,5,7,11-14] In fact, the histogenesis of LELCS is controversial. Historically, LELCS was thought to derive from adnexal origin, supported by the fact that LELCS is located in the dermis and usually lacks a connection with the epidermis.[6,15] Also, within LELCS, there is often sebaceous, eccrine and trichilemmal differentiation.[8] In more recent literature, some consider LELCS to be a variant of squamous-cell carcinoma (SCC).[2,4,16-20] For instance, Wang et al. presented a case of LELCS occurring below a scar from removal of multiple recurrent, well-differentiated and subsequent moderately differentiated SCC.[19] However, SCC is typically located in the superficial dermis and maintains connectivity with the epidermis.[4] Finally, others believe that LELCS is a morphologic pattern as opposed to a distinct clinicopathologic entity.[17,21,22]

Differential

The differential diagnosis is fairly extensive and includes cutaneous metastasis of undifferentiated nasopharyngeal carcinoma, a lymphoepithelioma-like carcinoma of another internal organ, basal-cell carcinoma, squamous-cell carcinoma, keratoacanthoma, Merkel-cell carcinoma, melanoma, malignant lymphoma, Hodgkin's lymphoma, cutaneous lymphadenoma, and follicular dendritic cell tumor.[2,4] Histologic features and immunohistochemical staining distinguish LELCS from the possible differential diagnosis.

Merkel-cell carcinoma (MCC) can present clinically similar to LELCS but will stain positive for neuroendocrine markers such as synaptophysin, neuron-specific enolase, and CK20.[1] In addition, peripheral lymphocytic infiltrate is usually absent in MCC.[2,14] Clarke and Ioffreda report a case in which LELCS demonstrates spindle-shaped cells that resemble the spindle-cell variant of **melanoma**.[23] However, unlike LELCS, melanoma is positive for S100 and other neuroectodermal markers such as HMB-45 and melan-A. LELCS should be distinguished from **malignant lymphoma** by the absence of atypical lymphocytes in LELCS.[1] Epithelial markers such as epithelial-membrane antigen and cytokeratins will react positive in LELCS and negative in malignant lymphoma. LELCS has shown the presence of occasional binucleated cells resembling Reed-Sternberg cells; however, **Hodgkin lymphoma** is negative for cytokeratins and positive for CD30 and CD15.[1,2,21,23] **Basal-cell carcinoma** will demonstrate neoplastic basophilic cells extending downward from the epidermis, whereas LELCS does not typically have an epidermal connection and lacks peripheral palisading. Inflamed, poorly differentiated **squamous-cell carcinoma** (SCC) strongly resembles LELCS.[1,19] However, LELCS typically does not involve overlying epidermis, and poorly differentiated SCC usually has an area of well-differentiated carcinoma or overlying SCC in situ.[1,3,5] **Cutaneous lymphadenoma** demonstrates a similar dense lymphocytic infiltrate as LELCS, but these lymphocytes appear benign and monomorphic.[1,2] **Follicular dendritic-cell tumor** (FDCT) is similar to LELCS by way of syncytial-appearing plump cells surrounded by reactive lymphoid cells, but FDCT stains negative for cytokeratin markers.[2] FDCT will demonstrate positive reactivity to Ki-M4, CD21, and CD35.[2]

Histologically, LELCS is remarkably similar to metastatic lymphoepithelioma of the nasopharynx, also known as **undifferentiated nasopharyngeal carcinoma**.[1,3,22] Epstein-Barr virus (EBV) reactivity is the main distinguishing factor between LELCS and undifferentiated nasopharyngeal carcinoma.[1,2,4,24] In general, LELCS is negative for EBV reactivity, whereas undifferentiated nasopharyngeal carcinoma will test positive for EBV.[1,2,4,24] There has been only one reported case, that of a Japanese woman, of LELCS in a patient who tested EBV positive, but no related neoplasms were found elsewhere in the patient's body.[22] In situ hybridization for EBER, the most reliable, specific, and highly sensitive method for detecting latent EBV, was used in this case report and yielded a negative result for EBV in our patient.[22,25] Metastatic lymphoepithelioma of the nasopharynx is rare, but aggressive when it does occur.[2,4,6] LELCS secondary to metastasis of undifferentiated nasopharyngeal carcinoma appears to be very rare, as there are fewer than 20 cases currently reported in the literature.[2,6,11] Nonetheless, it is highly recommended to evaluate the patient for possible undifferentiated nasopharyngeal carcinoma by a complete otolaryngologic exam including indirect laryngoscopy of the nasopharynx.[4,26] A review of symptoms is recommended when LELCS is confirmed to exclude metastasis from a variety of internal organ systems.[2,4,5,22] Lymphoepithelioma-like carcinoma can be found in many organs besides the skin, including salivary glands, thyroid, thymus, lungs, stomach,

kidney, breasts, uterine cervix, prostate, vagina, and urinary bladder.[6,7,16,17,23,27] Histologically, EBV reactivity has been associated only with lymphoepithelioma-like carcinoma of the stomach, salivary glands, lungs, and thymus.[4,7,22,24]

Treatment

The prognosis for patients with LELCS is generally good despite its categorization as a poorly differentiated neoplasm.[2,5,6,22,27] It is a low malignant tumor with rare reports of metastasis to lymph nodes at presentation and to internal organs such as, liver, lung, and bone.[9,27] There are only two reported deaths from metastatic LELCS.[4,6] There are multiple reports of local recurrence after incomplete excision.[6] Therefore, most LELCS are treated by wide local excision or Mohs micrographic surgery to lower the risk of recurrence.[2,28] LELCS and undifferentiated nasopharyngeal carcinoma are both radiosensitive, and this treatment modality should be used for recurrent cases, nonsurgical candidates, and those with lymph-node metastasis.[3,8] There are also a few reports of perineural invasion, in which Mohs micrographic surgery, radiation, and chemotherapy were used in combination therapy without evidence of recurrence on follow-up evaluation.[3-5,7]

Conclusion

In conclusion, lymphoepithelioma-like carcinoma of the skin is a rare, slowly growing neoplasm with low malignant potential. LELCS is believed to be of epithelial origin based on immunohistochemical reactivity, although its exact histogenesis remains debatable. There are multiple dermatologic neoplasms that can clinically resemble LELCS. Therefore, it is important to conduct a histologic examination from a biopsied specimen to exclude other dermatologic entities. Undifferentiated nasopharyngeal carcinoma demonstrates identical histologic characteristics, and although it rarely occurs, it is a very aggressive neoplasm that requires a thorough otolaryngologic examination and CT scans of the head and neck if suspected. A thorough review of systems is recommended to exclude other possible organ systems that may have a lymphoepithelioma-like carcinoma metastasizing to the skin. Wide surgical excision or Mohs micrographic surgery are the recommended treatments for non-aggressive forms of LELCS to prevent local recurrence. To the best of our knowledge, this is the first case demonstrating two primary lymphoepithelioma-like carcinomas of the skin presenting in different anatomic locations on the same patient without evidence of a metastatic source.

References

1. Ferlicot S, Plantier F, Rethers L, Bui AD, Wechsler J. Lymphoepithelioma-like carcinoma of the skin: a report of 3 Epstein-Barr virus (EBV)-negative additional cases. Immunohistochemical study of stroma reaction. J Cutan Pathol. 2000;6:306-11.

2. Welch PQ, Williams SB, Foss RD, et al. Lymphoepithelioma-like carcinoma of head and neck shin: a systemic analysis of 11 cases and review of literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;111:78-86.

3. Abedi SM, Salama S, Alowami S. Lymphoepithelioma-like carcinoma of the skin: case report and approach to surgical sign out. Rare Tumors. 2013;5:157-9

4. Lassen CB, Lock-Anderson J. Lymphoepithelioma-like carcinoma of the skin: a case with perineural invasion. Plast Reconstr Surg Glob Open. 2014 Dec 5;2(11):e252

5. Gille TM, Miles EF, Mitchell AO. Lymphoepithelioma-like carcinoma of the skin treated with wide local excision and chemoradiation therapy: A case report and review of the literature. Case Rep Oncol Med. 2012;2012:241816.

6. Swanson SA, Cooper PH, Mills SE, Wick MR. Lymphoepithelioma-like carcinoma of the skin. Mod Pathol. 1988;1:359-65.

7. Robins P, Perez MI. Lymphoepithelioma like carcinoma of the skin treated by Mohs micrographic surgery. J Am Acad Dermatol. 1995;32:814-16.

8. Glaich AS, Behroozan DS, Cohen JL, Goldberg LH. Lymphoepithelioma-like carcinoma of the skin: a report of two cases treated with complete microscopic margin control and review of the literature. Dermatol Surg. 2006:2:316-19.

9. Hall G, Duncan A, Azurdia R, Leonard N. Lymphoepithelioma-like carcinoma of the skin: a case with lymph node metastases at presentation. Am J Dermatopathol. 2006;3:211-5.

10. Wick MR, Swanson PE, LeBoit PE, Strickler JG, Cooper PH. Lymphoepithelioma-like carcinoma of the skin with adnexal differentiation. J Cutan Pathol. 1991;18:93-102.

11. Luk NM, Yu KH, Choi CL, Yeung WK. Skin metastasis from nasopharyngeal carcinoma in four Chinese patients. Clin Exp Dermatol. 2004;29:28-31.

12. Ng KF, Chen TC, Chang PL. Lymphoepithelioma-like carcinoma of the ureter. J Urol. 1999;161:1277-8.

13. Gillum PS, Morgan MB, Naylor MF, Everett MA. Absence of Epstein-Barr virus in lymphoepithelioma like carcinoma of the skin. Polymerase chain reaction evidence and review of five cases. Am J Dermatopathol. 1996;5:478-82.

14. Abdelkrim SB, Dhouibi A, Moussa A, et al. Merkel cell carcinoma with lymphoepithelioma-like pattern: a case report of an exceedingly rare variant of Merkel cell carcinoma with lymph node metastases at presentation. Case Rep Pathol. 2011;2011:840575.

15. Ko T, Muramatsu T, Shirai T. Lymphoepithelioma-like carcinoma of the skin. J Dermatol. 1997;2:104-9.

16. Carr KA, Bulengo-Ransby SM, Weiss LM, Nickoloff BJ. Lymphoepithelioma like carcinoma of the skin. A case report with immunophenotypic analysis and in situ hybridization for Epstein-Barr viral genome. Am J Surg Pathol. 1992;9:909-13.

17. Lind AC, Breer WA, Wick MR. Lymphoepithelioma-like carcinoma of the skin with apparent origin in the epidermis-a pattern or an entity? A case report. Cancer. 1999;15:884-90.

18. Cassarino DS, DeRienzo DP, Barr R. Cutaneous squamous cell carcinoma: a comprehensive clinicopathologic classification. J Cutan Pathol. 2006;33:191-206.

19. Wang G, Bordeaux JS, Rowe DJ, Honda KS. Lymphoepithelioma-like carcinoma vs inflamed squamous cell carcinoma of the skin. JAMA Dermatol. 2014;150:1367-8.

20. Bolognia JL, Jorizzo JL, Rapini RP, eds. Dermatology. Edinburgh: Mosby, Inc; 2008. p. 1782-1783. Print.

21. Shek, TW, Leung EY, Luk IS, Loong F, Chan AC, Yik YH, et al. Lymphoepithelioma-like carcinoma of the skin. Am J Dermatopathol. 1996;6:637-44.

22. Aoki R, Mitsui H, Karada K, et al. A case of lymphoepithelioma-like carcinoma of the skin associated with Epstein-Barr virus infection. J Am Acad Dermatol. 2010;62(4):681-84.

23. Clarke LE, Ioffreda MD. Lymphoepithelioma-like carcinoma of the skin with spindle cell differentiation. J Cutan Pathol. 2005;6:419-23.

24. Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. Am J Clin Pathol. 1995;103:308.

25. Chang YL, Wu CT, Shih JY, Lee YC. New aspects in clinicopathologic and oncogene studies of 23 pulmonary lymphoepithelioma-like carcinomas. Am J Surg Pathol. 2002;26:715-23.

26. Dudley CM, Snow SN, Voytovich MC, Warner TF, Hartig GK. Enlarging facial nodule on an elderly patient. Lymphoepithelioma-like carcinoma of the skin (LELCS). Arch Dermatol. 1998;134:1628-9, 1631-2.

27. Kazakov DV, Nemcova J, Mikyskova I, Michal M. Absence of Epstein-Barr virus, human papillomavirus, and simian virus 40 in patients of central European origin with lymphoepithelioma-like carcinoma of the skin. Am J Dermatopathol. 2007;4:365-9.

28. Jimenez F, Clark RE, Buchanan MD, Kamino H. Lymphoepithelioma-like carcinoma of the skin treated with Mohs micrographic surgery in combination with immune staining for cytokeratins. J Am Acad Dermatol. 1995;32:878-81.

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