Case Report

Cutaneous Lymphoepithelioma-Like Carcinoma: Report of Three Cases

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Background: *Cutaneous lymphoepithelioma-like carcinoma (cutaneous LELC) is an extremely rare malignant neoplasm with unclear histogenesis. Its histopathologic features are like those of lymphoepithelioma-like carcinoma occurring in the nasopharynx and in visceral organs especially salivary glands.*
Material and Method: *The authors reported on one male and two female patients of cutaneous LELC with immunohistochemical and electron microscopic study. All patients were of old age. All cutaneous LELCs in this report occurred on the patient's face, one of each on the eyelid, conjunctiva, and cheek.*
Results: *All resection specimens showed the typical histopathologic features of those of LELC, i.e. well-defined tumor lobules mainly located in the dermis and extending into the panniculus. These tumor lobules typically displayed ill-defined clusters/nests of large epitheloid cells with pale eosinophilic cytoplasm, atypical vesicular nuclei possessing prominent nucleoli and were surrounded by dense lymphoplasmacytic infiltration. Immunocytohistochemically, these epitheloid cells showed epithelial differentiation by the expression of epithelial membrane antigen (EMA), P63, CK5/6 and CAM5.2 but were negative to CK20, CEA and Ebstein-Barr virus (EBV). Squamous cell differentiation by the presence of desmosomes by electron microscopic study was also noted in two patients (case 1 and 3).*
Conclusion: *The findings described above indicated that cutaneous LELC was a malignant neoplasm exhibiting squamous cell differentiation.*

Keywords: *Lymphoepithelioma-like carcinoma, Squamous cell differentiation*

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Cutaneous LELC, firstly described by Swanson et al in 1988[1], is an extremely rare epithelial neoplasm. It is less common than LELC. Furthermore, it is occurring in the nasopharyngeal area and in the visceral organs, especially the salivary glands. The histogenesis of cutaneous LELC is still in debate. In the past, it has been reputed to be unclassified epithelial neoplasm[2-5], squamous cell neoplasm[6-8], folliculo-sebaceous[9], adnexal[10,11] and sweat gland neoplasm[12]. Most cutaneous LELCs were located on the face and scalp of the middle-aged and elderly patients, affecting both sexes equally[2]. Recurrence and metastasis sometimes occurred[2]. The diagnosis of LELC depended on its unique histopathologic features, *i.e.* it consisted of well-defined tumor lobules mainly located in the dermis and usually extending into the panniculus. These tumor lobules were composed of predominant lymphocytes in which containing clusters/nests of large epitheloid cells or, sometimes, in the midst of these lobules, analogous to LELCs of the visceral organs. The present study aimed to determine the enigmatic histogenesis of this malignancy by immunohistochemical studies as well as by electron microscopic study. The authors reported on three patients, one male and two females with tumor mass on the conjunctiva, eyelid and cheek. All possessed the typical histopathologic features of LELC. The epitheloid cells in our LELCs were constantly positive for AE1/3, CK5/6, epithelial membrane antigen (EMA), P63 and CAM5.2 (2 cases) but did not express carcinoembryonic antigen (CEA), smooth muscle actin (SMA) and Epstein-Barr virus (EBV). By electron microscopic study, two LELCs

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(case 1 and 3) exhibited squamous differentiation by the presence of desmosomes. The findings, described above, made the authors believe cutaneous LELC as a malignant neoplasm that might possess squamous cell differentiation.

Cutaneous LELCs and LELCs of the nasopharynx and of the visceral organs, especially the salivary glands, displayed the same histopathologic features. Therefore, before the diagnosis of cutaneous LELC was established, the possibility of cutaneous metastasis from those previously described areas should be excluded by nasopharyngeal examination and by the completed systemic work-up. LELCs of the nasopharynx and of many visceral organs had been described to be related to EBV infection[13], whereas cutaneous LELCs usually were not associated with EBV[2,3,7,8,14,15]. In this instance, the study of EBV may be helpful in the differential diagnosis of cutaneous LELCs from LELCs of the nasopharynx and of the visceral organs.

Case Report

Case 1

A 66-year-old male patient had a mass on medial aspect of his left eye for three years. Clinical examination revealed a 2 x 1 cm lobulated, infiltrative conjunctival mass. Wide excision as well as reconstruction of the soft tissue around the tumor mass was performed.

Case 2

A 95-year-old female patient presented with a 2 x 1.4 x 1 cm infiltrative mass on her upper eyelid for many years. She was referred from the provincial hospital and the clinical diagnosis at that time was sebaceous carcinoma. Computed tomographic studies of the skull revealed multiple hyperdensity, metastatic areas at right frontal, temporal regions. She underwent wide excision of her upper eyelid mass.

Case 3

An 86-year-old female patient presented with a mass on her right cheek for more than one year. Physical examination revealed an infiltrative, ill-defined dermal mass, 2 x 1 cm with overlying slightly verrucous, hyperpigment plaque, akin to those of senile keratosis. Incisional biopsy specimen displayed histopathologic features typical of LELC and subsequent wide-excision of the lesion was performed. Her history was otherwise unremarkable except there was squamous cell carcinoma on her right hand that was completely excised six years previously without any evidence of recurrence or metastasis.

After the diagnosis of cutaneous LELC was established, all of the presented patients underwent a complete physical examination, paranasal roentgenograms as well as otolaryngoscopic examination in order to rule out LELC of the nasopharynx and of the visceral organs that could metastasize to the skin, all of which revealed no abnormal findings in these areas. In the present study, one patient (case 2) although her physical health deteriorated through aging, lived well with her metastatic brain lesions for three years after removal of the eyelid mass, one patient (case 1) was lost to follow-up and one (case 3) had no recurrence or metastasis two months after excision.

Results

All resection specimens displayed the same histopathologic features, typical of cutaneous LELC, *i.e.*, well-defined lobulated masses in the dermis and often extending into the subcutaneous fat. The epidermis appeared to be normal (Fig. 1). These tumor lobules were composed of predominant lymphocytes and plasma cells associated with ill-defined, epitheloid cell aggregations within or in the midst of the tumor lobules (Fig. 1). These large cells exhibited ill-defined cell border and usually contained large vesicular nuclei and distinct nucleoli (Fig. 2). Mitosis as well as atypical mitosis was frequent (Fig. 3). Pleomorphism also was prominent (Fig. 3). Sebaceous, glandular, or squamous differentiation was not obvious.

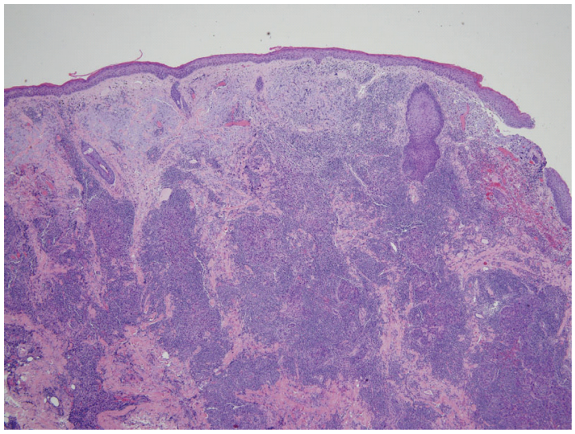

Fig. 1 It usually presented as well-defined lobulated masses in the dermis and the panniculus (original magnification x4)

Immunohistochemically, these large epitheloid cells showed strong expression of epithelial membrane antigen (EMA) (Fig. 4), broad spectrum cytokeratin (AE1/3), P63, CK5/6 (Fig. 5), CAM5.2 (case 2 and 3), and were non-reactive to carcinoembryonic antigen (CEA), smooth muscle actin (SMA) and gross cystic disease fluid protein (GCDFP-15). All of the presented LELCs were also EBV negative, By electron microscopic study, the presented 2 LELCs (case1, 3) exhibited squamous cell differentiation by the scatter presence of two dense plaques, 10-15 nm thick, resembling desmosomes on adjacent cell membrane of these epitheloid cells (Fig. 6A, B).

Discussion

Cutaneous LELC is an extremely rare epithelial neoplasm. This neoplasm usually affected elderly patients and was equal in both sexes. The predicted sites were the head, face, and neck region[2]. Lesions on the back and forearm sometimes occurred[6,14]. Although cutaneous LELC is a malignant neoplasm, it possessed a paradoxically indolent course and could easily be treated by wide excision or by Mohs micrographic surgery[9,10,16]. Recurrence sometimes occurred but metastasis was rare[1,2,6].

The histogenesis of cutaneous LELC is still in controversy. According to the constant positive

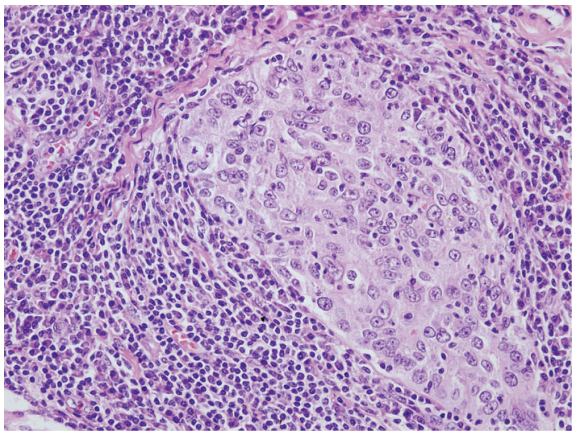

Fig. 2 The tumor lobules were composed of predominant lymphocytes containing ill-defined groups/clusters of large epitheloid cells with ill-defined cell borders, large vesicular nuclei and distinct nucleoli (original magnification x40)

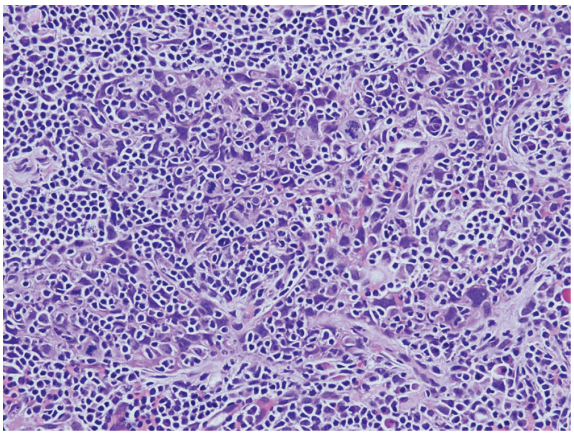

Fig. 3 Mitosis as well as atypical mitosis was frequent. Pleomorphism also was prominent (original magnification x40)

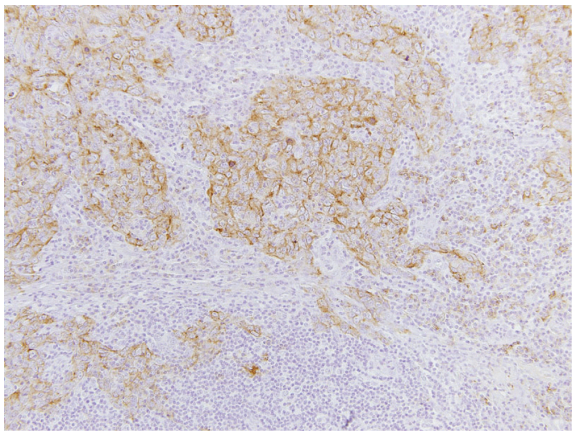

Fig. 4 These large epitheloid cells expressed epithelial membrane antigen (original magnification x20)

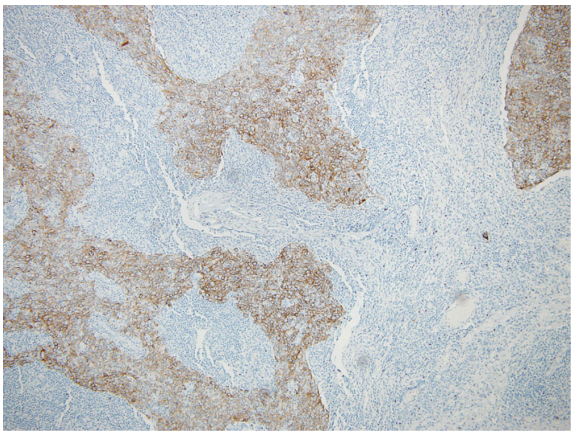

Fig. 5 Positive reactivity for CK5/6 was constant (original magnification x20)

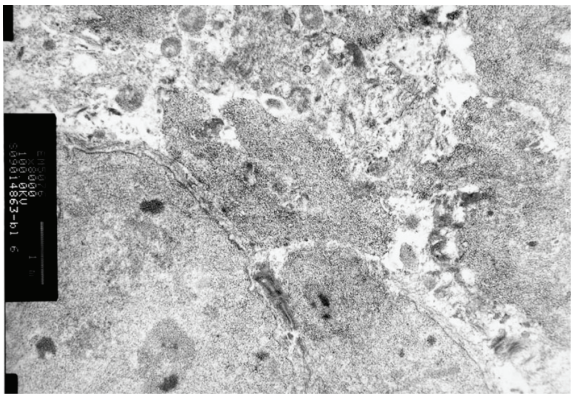

Fig. 6A Scatter electron dense structures, resembling desmosomes, on adjacent cell membrane were noted (original magnification x17,600)

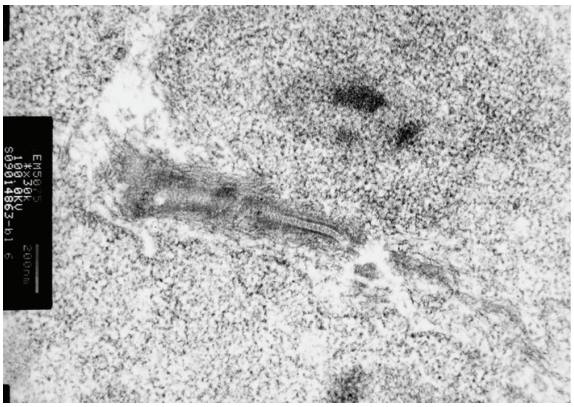

Fig. 6B High magnification revealed two parallel dense plaques, 10-15 nm thick resembling desmosomes (original magnification x66,000)

staining for cytokeratins and EMA[2,4,6,12,14,16], it has been generally accepted to be epithelial neoplasm. Shek et al[8] found tonofilaments, desmosomes in the cytoplasm of the tumor cells. Lind[7], as well, noted the connection of the tumor lobules to the epidermis and the positive staining of the tumor cells for CK5/6[6,12]; these evidences made them believe cutaneous LELC to be a variant of squamous cell carcinoma. Some authors regarded cutaneous LELC as adnexal neoplasm or pilosebaceous neoplasm[9,10]. Cutaneous LELC in the present study, concordant to the previous study, were highlighted by cytokeratins and EMA. Most cutaneous LELCs in the reviewed literature did not express CAM5.2[3, 6, 15] except Shek[8] who noted CAM5.2 positivity in one of two patients in his report.

As mentioned earlier, the present study aimed to determine the enigmatic histogenesis of this malignant neoplasm. By electron microscopic study, two of our LELCs (case 1 and 3) showed squamous cell differentiation by the presence of two dense plaques of 10-15 nm in thickness, resembling desmosomes, on the adjacent cell membrane of the epitheloid cells. Although cutaneous LELCs, as well as in the present study, often displayed the malignant histopathologic features, to wit, asymmetric, poorly circumscribed tumor lobules, the epitheloid cells inside the tumor lobules showed atypical features with increase in mitosis including atypical mitosis and invasion into the subcutis was also frequent but most cutaneous LELCs possessed indolent clinical course by the usual absence of recurrences or metastases. In the present study, the authors noted brain metastasis at the time of the diagnosis in one patient (case 2), however, she lived well with her metastatic brain lesion after excision of her cutaneous LELC. No recurrence was noted in any of the authors' three cases.

The histopathologic features of cutaneous LELCs were the same as LELCs of the nasopharynx and of the visceral organs but cutaneous LELCs were far less common. For instance, before the diagnosis of cutaneous LELCs was established, the possibility of cutaneous metastasis from occult LELCs of those previously described areas, especially the nasopharynx, should be excluded. The notable difference between LELCs of the visceral organs and the skin is the presence of EBV in the former[2,3,7,8,14,15] while it is usually absent in the latter until recently it had been reported that cutaneous LELC could possess EBV[17]. However, EBV may be the helpful marker in the differential diagnosis of cutaneous LELCs from LELCs of the nasopharynx and of the visceral organs.

In conclusion, the diagnosis of LELCs of the skin, nasopharynx and of visceral organs depends on their distinct, unique histopathologic findings. Despite their aggressive histopathologic features, most cutaneous LELCs possessed relatively good prognosis[2] and could be easily treated by wide excision or by Mohs micrographic surgery[2,9,10,16]. Recurrence and metastasis were infrequent. Although the histogenesis of cutaneous LELCs, to date, was uncertain, the authors agreed with the previous reports that cutaneous LELCs are malignant neoplasms that might possess diverse, bewildering histogenesis, *i.e.* squamous cell differentiation, pilosebaceous neoplasm, adnexal neoplasm and as in the present study, exhibiting squamous cell differentiation by

the electron microscopic detection of desmosomes. Furthermore, studies of other eruptive patients of cutaneous LELCs will be necessary to find the definite histogenesis of this malignancy.

Potential conflicts of interest

None.

References

1. Swanson SA, Cooper PH, Mills SE, Wick MR. Lymphoepithelioma-like carcinoma of the skin. Mod Pathol 1988; 1: 359-65.
2. 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 the stroma reaction. J Cutan Pathol 2000; 27: 306-11.
3. Requena L, Sanchez YE, Jimenez E, Roo E. Lymphoepithelioma-like carcinoma of the skin: a light-microscopic and immunohistochemical study. J Cutan Pathol 1994; 21: 541-8.
4. Walker AN, Kent D, Mitchell AR. Lympho-epithelioma-like carcinoma in the skin. J Am Acad Dermatol 1990; 22: 691-3.
5. Wade TR, Finan MC, Stahr BJ, White WL, Troy JL. Self assessment. J Cutan Pathol 1993; 20: 513-24.
6. 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; 28: 211-5.
7. 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; 85: 884-90.
8. Shek TW, Leung EY, Luk IS, Loong F, Chan AC, Yik YH, et al. Lymphoepithelioma-like carcinoma of the skin. Am J Dermatopathol 1996; 18: 637-44.
9. Robins P, Perez MI. Lymphoepithelioma-like carcinoma of the skin treated by Mohs micrographic surgery. J Am Acad Dermatol 1995; 32: 814-6.
10. Dozier SE, Jones TR, Nelson-Adesokan P, Hruza GJ. Lymphoepithelioma-like carcinoma of the skin treated by Mohs micrographic surgery. Dermatol Surg 1995; 21: 690-4.
11. 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.
12. Otsuki T, Watanabe D, Yano K, Tamada Y, Matsumoto Y, Yokoo K. Lymphoepithelioma-like carcinoma of the skin with potential for sweat glandular differentiation. J Dermatol 2005; 32: 393-6.
13. Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. Am J Clin Pathol 1995; 103: 308-15.
14. Gillum PS, Morgan MB, Naylor MF, Everett MA. Absence of Epstein-Barr virus in lympho-epitheliomalike carcinoma of the skin. Polymerase chain reaction evidence and review of five cases. Am J Dermatopathol 1996; 18: 478-82.
15. Carr KA, Bulengo-Ransby SM, Weiss LM, Nickoloff BJ. Lymphoepitheliomalike carcinoma of the skin. A case report with immunophenotypic analysis and in situ hybridization for Epstein-Barr viral genome. Am J Surg Pathol 1992; 16: 909-13.
16. 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.
17. Aoki R, Mitsui H, Harada K, Kawamura T, Shibagaki N, Tsukamoto K, et al. A case of lymphoepithelioma-like carcinoma of the skin associated with Epstein-Barr virus infection. J Am Acad Dermatol 2010; 62: 681-4.

การรายงานของมะเร็งชนิด lymphoepithelioma-like carcinoma ของผิวหนังจำนวน 3 ราย

เจน มโนนุกุล, ชนกพรรณ โชติรัตน์, วรัญญา บุญชัย, นุชศรา ช่อมณี, นารี ชูศรีโฉม

ภูมิหลัง: *Lymphoepithelioma-like carcinoma เป็นมะเร็งของผิวหนังที่มีพยาธิกำเนิดไม่ชัดเจนและพบน้อยมาก ลักษณะทางพยาธิวิทยาคล้ายคลึงกับมะเร็งชนิด lymphoepithelioma-like carcinoma ที่บริเวณ nasopharynx และอวัยวะภายในโดยเฉพาะต่อมน้ำลาย*

วัสดุและวิธีการ: *ผู้นิพนธ์ได้ศึกษาลักษณะทางอิมมูโนวิทยาและทางจุลทรรศน์อิเล็กตรอนของมะเร็งชนิด lymphoepithelioma-like carcinoma ที่พบบนผิวหนังบริเวณใบหน้า (เปลือกตา เยื่อบุตา แก้ม) ในผู้ป่วยหญิง 1 ราย และชาย 2 ราย ทั้งหมดเป็นผู้ป่วยสูงอายุ*

ผลการศึกษา: *การศึกษาชิ้นเนื้อจากการผ่าตัดพบลักษณะเฉพาะทางพยาธิวิทยาของมะเร็งชนิด lymphoepithelioma-like carcinoma โดยภายในชั้นหนังแท้และชั้นไขมันพบเซลล์ชนิดลิมโฟไซท์ และ plasma cell รวมกันเป็นกลุ่มขอบเขตชัดเจน โดยภายในพบเซลล์มะเร็งชนิด epitheloid cells ที่มีขนาดใหญ่ และซัยโตพลาสมติดสีชมพูจาง ๆ รวมกันเป็นกลุ่มไม่ชัดเจน ภายในเซลล์ชนิดหลังพบนิวเคลียสลักษณะใสแบบ vesicular ที่มีลักษณะผิดปกติ และมักพบ nucleoli ขนาดใหญ่ชัดเจนเช่นกัน จากการศึกษาทางอิมมูโนวิทยาพบว่าเซลล์ชนิดหลังนี้แสดงผลบวกต่อ epithelial membrane antigen (EMA), P63, CK5/6 และ CAM5.2 แต่แสดงผลลบต่อ CK20, CEA และ Ebstein-Barr virus (EBV) นอกจากนี้จากการศึกษาทางจุลทรรศน์อิเล็กตรอนยังพบ desmosome ที่บ่งชี้การพัฒนาเปลี่ยนแปลงแบบ squamous (ในผู้ป่วยรายที่ 1 และ 3)*

สรุป: *ลักษณะดังกล่าวข้างต้นบ่งชี้ว่า lymphoepithelioma-like carcinoma ของผิวหนังเป็นมะเร็งที่มีการพัฒนาเปลี่ยนแปลงแบบ squamous*