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Lymphoepithelioma-like carcinoma of head and neck skin: a systematic analysis of 11 cases and review of literature

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Lymphoepithelioma-like carcinoma of the skin (LELCS) is a rare tumor of unknown etiology, low malignant potential, and microscopic resemblance to undifferentiated nasopharyngeal carcinoma. Clinically, it presents as a flesh-colored firm nodule or plaque on the face, scalp, or shoulder of middle-aged to elderly individuals. Histologically, LELCS is composed of islands of enlarged epithelial cells with large vesicular nuclei surrounded and permeated by a dense lymphoplasmacytic infiltrate. LELCS exhibits immunoreactivity with high-molecular-weight cytokeratins and epithelial membrane antigen, indicating the epithelial origin. The differential diagnosis includes basal cell carcinoma, squamous cell carcinoma, lymphoma, pseudolymphoma, and Merkel cell carcinoma. We report 11 cases of LELCS of the head and neck region with discussion of the clinical, histopathologic, immunohistochemical, and therapeutic aspects of this rare cutaneous neoplasm. In addition, we systematically review and compare the findings with the previously published cases of LELCS. This study is the largest case series of LELCS reported in the English-language literature. It attempts to more clearly define the diagnostic criteria for LELCS. Its histomorphologic and immunophenotypic features help distinguish this tumor from similar-appearing malignancies, including metastatic nasopharyngeal carcinoma. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:78-86)**

Undifferentiated carcinoma of the lymphoepithelial type is a well defined epithelial malignancy of the nasopharynx. Histologically and immunophenotypically identical neoplasms have been described in the salivary glands, larynx, thymus, stomach, uterine cervix, and skin.[1,2] Lymphoepithelioma-like carcinoma of the skin (LELCS) was first described by Swanson et al.[1] in 1988 as a distinctive primary malignant neoplasm with remarkable microscopic similarity to undifferentiated carcinoma of the nasopharynx. There have been only 54 reported cases of primary LELCS of the head and neck in the English-language literature (Table I). Clinically, LELCS has a predilection for sun-exposed skin of the head and neck in elderly individuals. There is a tendency toward local recurrence and very limited metastatic potential.[3] The clinical appearance of LELCS is varied and ranges from a solitary flesh-colored nodule or plaque to an erythematous or indurated lesion with a keratotic center.[1,4] Histologically, LELCS is composed of a neoplastic epithelial component associated with a reactive lymphoid infiltrate.[1,5] Tumor cells are arranged in nodules, isolated or anastomosing islands, trabeculae, narrow cords, or round to oval nests. The epithelial component of the tumor is represented by atypical polygonal cells with vesicular nuclei and prominent nucleoli.[1,6] The histologic diagnosis of LELCS may be complicated by the variable architectural and cytologic appearance of the epithelial

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Table I. Summary of the literature review of head and neck lymphoepithelioma-like carcinoma of the skin (LELCS)

Study	*No. of patients*	*Gender*	*Age, y*	*Location*	*Clinical presentation*	*Treatment*
Swanson et al.,[1] 1988	4	M	50	Scalp	Lump	Local excision
		M	62	Forehead	Nodule	Surgical excision
		M	68	Cheek	Nodule	Surgical excision, radiotherapy
		F	81	Cheek	Nodule	Surgical excision
Malhotra et al.,[32] 1989	2	M	67	Nose	Papule	N/A
		M	71	Scalp	Nodule	N/A
Walker et al.,[28] 1990	1	F	83	Zygoma	Nodule	Radiotherapy
Kutzner et al.,[19] 1991	1	F	56	Upper lip	Pearly papule	Surgical excision
Wick et al.,[18] 1991	3	F	51	Forehead	Papule	Electrodissection
		M	52	Face	Nodule	Local excision
		F	71	Eyelid	Nodule	Local excision
Carr et al.,[5] 1992	1	F	84	Cheek	Nodule	Surgical excision
Ortiz-Frutos et al.,[33]1993	1	M	70	Nose	Nodule	Surgical excision, radiotherapy on recurrence
Stahr,[34] 1993	1	M	63	Forehead	N/A	N/A
Requena et al.,[20] 1994	1	F	83	Temple	Nodule	Surgical excision
Clarke and Ioffreda,[7] 1995	1	M	72	Forehead	Nodule	Surgical excision
Dozier et al.,[35]1995	1	F	91	Nose	Nodule	Electrodissection, curettage; Moh's surgery at recurrence
Jimenez et al.,[11] 1995	1	M	68	Nasal ala	Plaque	Moh's surgery
Leung et al.,[25] 1995	1	M	78	Orbit angle	Nodule	Surgical excision
Maruyama et al.,[36] 1995	1	F	89	Eyelid	Papule	Surgical excision
Robins and Perez,[10] 1995	1	F	74	Cheek	Nodule	Mohs surgery
Gillum et al.,[22] 1996	4	F	64	Chin	N/A	N/A
		F	74	Cheek	N/A	N/A
		M	39	Forehead	N/A	N/A
		M	69	Cheek	N/A	N/A
Shek et al.,[3] 1996	2	F	81	Forehead	Nodule	Surgical excision
		M	78	External orbital angle	Nodule	Surgical excision
Takayasu et al.,[24] 1996	1	F	62	Nasal ala	Nodule	Surgical excision, radiotherapy
Ko et al.,[23] 1997	1	M	67	Cheek	Nodule	Surgical excision
Dudley et al.,[13] 1998	1	M	81	Mandible	Nodule	Moh's surgery
Bornhövd et al.,[26] 1999	1	F	87	Cheek	Nodule	Surgical excision
Chen,[6] 1999	1	M	71	Forehead	Nodule	Surgical excision
Lind et al.,[2] 1999	1	F	96	Nasal ala	Nodule	Surgical excision
Ferlicot et al.,[17] 2000	3	M	61	Nasal ala	Nodule	Surgical excision
		M	88	Ear	Nodule	Surgical excision
		M	87	Cheek	Nodule	Surgical excision
Ahmadi et al.,[30] 2001	1	M	45	Forehead	Nodule	Surgical excision, radiotherapy
Ho et al.,[37] 2005	2	M	79	Lower eyelid	Nodule	Surgical excision
		M	67	Lower eyelid	N/A	Surgical excision
Otsuki et al.,[38] 2005	1	M	77	Cheek	Nodule	Surgical excision
Fenniche et al.,[39] 2006	1	F	78	Cheek	Nodule	Surgical excision
Glaich et al.,[12] 2006	1	F	97	Cheek	Nodule	Moh's surgery
Cavalieri et al.,[9] 2007	1	F	92	Cheek	Violaceous nodule	Surgical excision
Kazakov et al.,[31] 2007	7	4 M	57-86	Face	N/A	N/A
		2 F		Face	N/A	N/A
		1 N/A		Face	N/A	N/A
				Face	N/A	N/A
				Scalp	N/A	N/A
				Scalp	N/A	N/A
				Auricle	N/A	N/A
Arsenovic et al.,[40] 2008	1	F	89	Cheek	Brown beige plaque like non ulcerated lesion	Surgical excision
Lyle et al.,[41] 2008	1	F	68	Forehead	Papule	Mohs surgery
Mahomed et al.,[42] 2008	1	M	73	Lower lip	Ulcer with indurated edges	Surgical excision
Hinz et al.,[43] 2009	1	F	91	Temple	Erythematous with central erosion, peripheral telengectasia	Surgical excision

M, male; *F,* female; *N/A,* not available.

Table II. Summary of the findings of the present cases of LELCS

Case no.	*Age, y*	*Gender*	*Location*	*Clinical appearance*	*Clinical impression*	*Contributor's microscopic differential*	*Treatment*
1	84	M	Cheek	Irregular nodule	BCC	Malignant adnexal tumor	Surgical excision
2	74	F	Zygoma	Flesh colored nodule with telangiactasia	Sarcoidosis	Granulomatous rosacea	Surgical excision
3	78	M	Forehead	Red nodule with ulceration	Atypical fibroxanthoma	Atypical lymphoid proliferation/lymphoma	Surgical excision
4	80	M	Forehead	Irregular nodule	H/O carcinoma of hypopharynx, R/O metastasis	ALHE	Surgical excision
5	79	M	Scalp	Irregular ulcerated white plaque	N/A	Trichilemmal carcinoma	Surgical excision
6	47	F	Cheek	Pearlescent nodule	BCC	Lymphoid hyperplasia	Surgical excision
7	60	M	Ear	Raised pale brown nodule with ulceration	Cyst	Squamous cell carcinoma(poorly differentiated)	Surgical excision
8	70	M	Temple	Red-purple scaly nodule	BCC	LELCS	Surgical excision
9	82	M	Eyebrow	Irregular ulcerated nodule	BCC	Atypical lymphoid proliferation/lymphoma	Surgical excision
10	80	F	Ear	Pearly papule	BCC	LELCS	Surgical excision
11	80	M	Upper lip	Red firm nodule	Calcified cyst	Atypical lymphoid & squamous epithelial proliferation	Electrocautery with deep shave

BCC, basal cell carcinoma; *H/O,* history of; *R/O,* rule out; *ALHE,* angiolymphoid hyperplasia with eosinophilia; other abbreviations as in Table I.

cells and the dense lymphoplasmacytic infiltrate which may obscure the epithelial component.[7] Immunohistochemical evaluation may serve to exclude other histologically similar lesions. Owing to the close histologic similarity to nasopharyngeal lymphoepithelioma, patients with suspected LELCS should have a thorough otolaryngologic examination, including indirect laryngoscopy to rule out a metastatic nasopharyngeal lymphoepithelioma. Although the skin metastasis of nasopharyngeal lymphoepithelioma is extremely rare, with only 16 cases documented in the literature, they are associated with a worse prognosis, with patients succumbing within a year.[8]

Eleven new LELCS cases are reviewed along with previously reported cases from the English-language literature.

MATERIALS AND METHODS

Eleven cases of LELCS of head and neck were identified in the Armed Forces Institute of Pathology (AFIP) files. The clinical findings, including presentation, patient age, gender, location, and clinical differential diagnosis, were reviewed. Histomorphologic features were evaluated regarding architecture, cellular and nuclear atypia, mitotic rate, growth pattern, and lymphoid stroma. The immunophenotypic features were evaluated with a panel of antibodies on the paraffin-embedded sections by using a modified avidin-biotin complex technique with appropriate controls. When necessary, the contributors were contacted for additional material and follow-up information. Additionally, a review of the available English-language literature was performed.

RESULTS

Clinical findings

Eight patients (72%) were male and 3 (28%) female (Table II). Patients ranged in age from 47 to 84 years, with a median of 79 years and a mean of 74 years, which is similar to the previously reported cases (Table I). As in the previously reported cases, all lesions were located on sun-exposed areas of head and neck, involving forehead (2), cheek (2), ear (2), zygoma (1), scalp (1), temple (1), eyebrow (1), and upper lip (1). Most cases presented as a solitary flesh-colored pearlescent or erythematous firm nodule or plaque, often roughened or hypopigmented with or without telangiactasia and ulceration. The most commonly offered clinical differential diagnosis was basal cell carcinoma. The treatment modalities for the cases included local surgical excision, reexcision of residual tumor after incomplete removal, and deep shave followed by electrocautery (Table II). The clinical follow-up was available for 8 patients: 5 patients were alive without evidence of recurrent disease, and 3 died of unrelated causes with no evidence of disease.

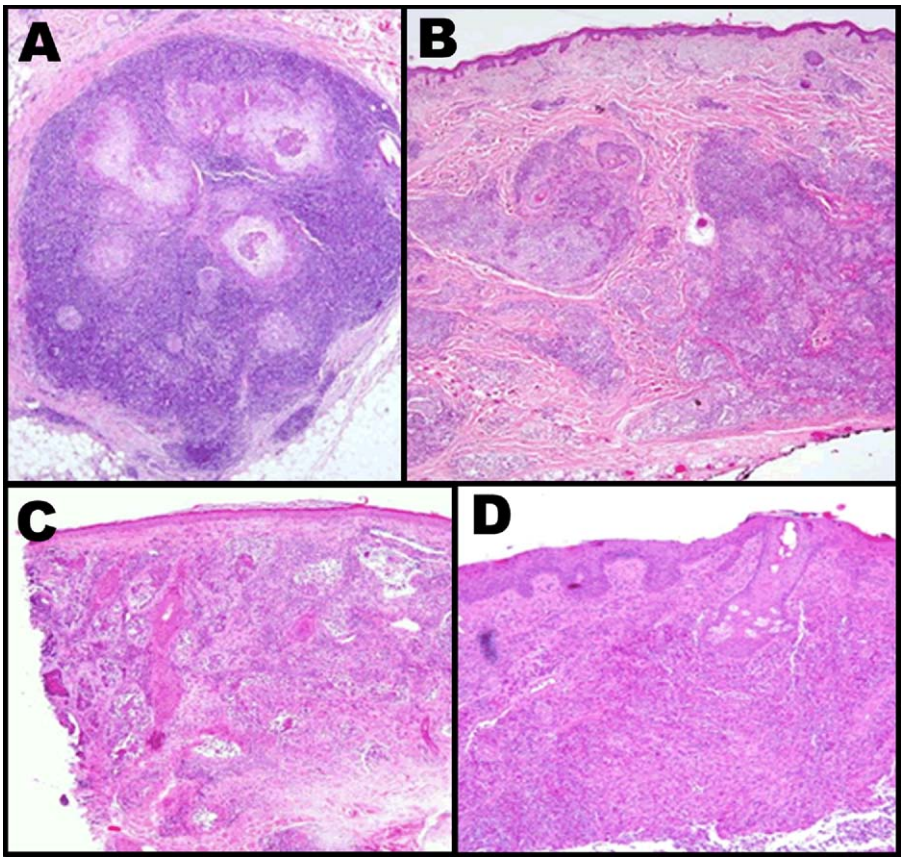

Fig. 1. Composite histologic images. **A, B,** Nodular growth of neoplastic epithelial cells immersed in a dense lymphoid stroma (hematoxylin-eosin [HE], ×10). **C, D,** Diffuse pattern exhibiting a cohesive arrangement of neoplastic cells with less lymphoid stroma and closer to the surface (HE, ×10).

Histologic findings

The 11 cases revealed 2 distinct histologic growth patterns. Seven cases were characterized by nodular growth of syncytial sheets, islands, and/or nests of atypical epithelioid cells in the middle and deep dermis associated with a dense lymphoid infiltrate with a variable plasma cell component (Fig. 1, *A* and *B*). Four cases exhibited diffuse growth of a cohesive more sheet-like atypical epithelioid cells with scant lymphoid component approximating surface epidermis (Fig. 1, *C* and *D*). The tumor cells appeared to be of moderate size with vesicular, monotonous, and polymorphic nuclei, 1-2 nucleoli, and variable amount of eosinophilic cytoplasm. Mitotic figures ranged from 1 to 8 per high-power field (Fig. 2, *A* and *B*). The borders of the atypical epithelioid component were often indistinct, blending with the lymphoid stroma (Fig. 2, *C*). No connection to the overlying epidermis was evident in any of the cases (Fig. 3). Two of the present cases displayed evidence of squamous differentiation (Fig. 4, *A*), and a sebaceous differentiation was independently observed in another (Fig. 4, *B*). Reed-Sternberg–like cells were noted in 1 case (Fig. 5, *A*). The stromal fibrosis was not uniform, and 1 case demonstrated prominent collagenized fibroblastic stroma dividing the tumor cells into compartments (Fig. 5, *B*). "Pseudorosettes" were observed on rare occasion (Fig. 5, *C*).

Immunohistochemical findings

The neoplastic cells showed strong positive reaction with pancytokeratin (Fig. 6, *A*). The surrounding lymphoid infiltrate exhibited a positive reaction with the T-cell and B-cell markers CD3 and CD20, respectively (CD3 > CD20; Fig. 6, *B* and *C*). All tumors exhibited strong p63 protein reactivity (Fig. 6, *D*). Stains for Epstein-Barr virus (EBV) latent membrane protein 1 (Fig. 6, *E*) cytokeratin (CK) 7, CK-20, neuron-specific enolase, and carcinoembryonic antigen were negative in all of the cases studied (Table III).

DISCUSSION

LELCS is a distinctive tumor of low malignant potential that is morphologically similar to undifferentiated

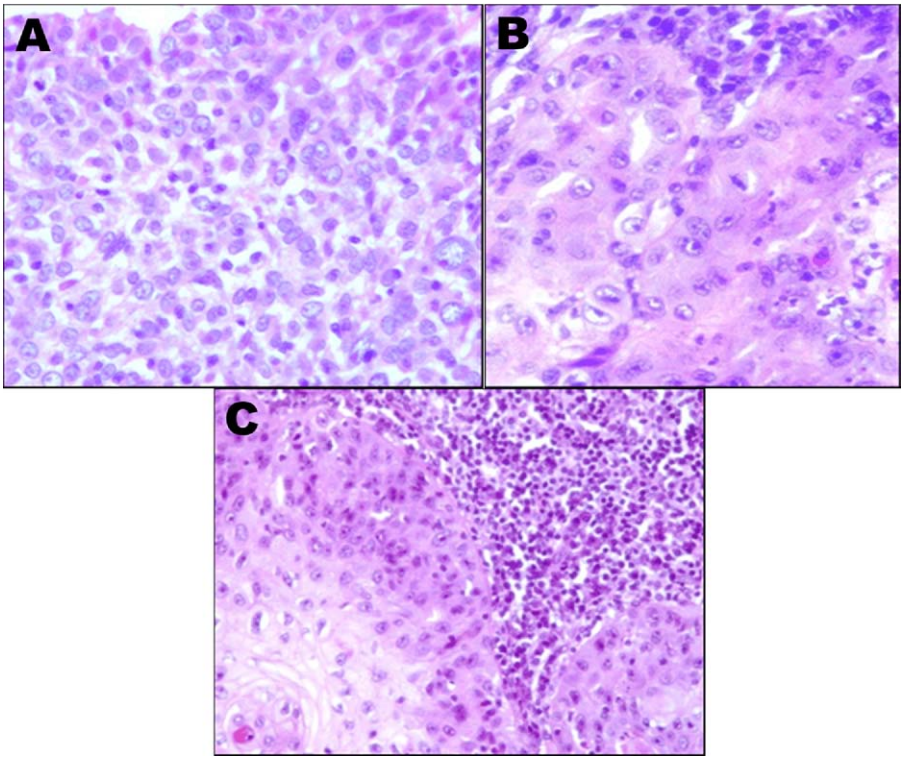

Fig. 2. Composite histologic images. **A, B,** Dense neoplastic proliferation of moderately sized cells with polymorphic nuclei, 1-2 nucleoli, eosinophilic cytoplasm, and atypical mitotic figures (hematoxylin-eosin [HE], ×40). **C,** Indistinct borders of the tumor nests owing to heavy lymphocytic infiltrate (HE, ×40).

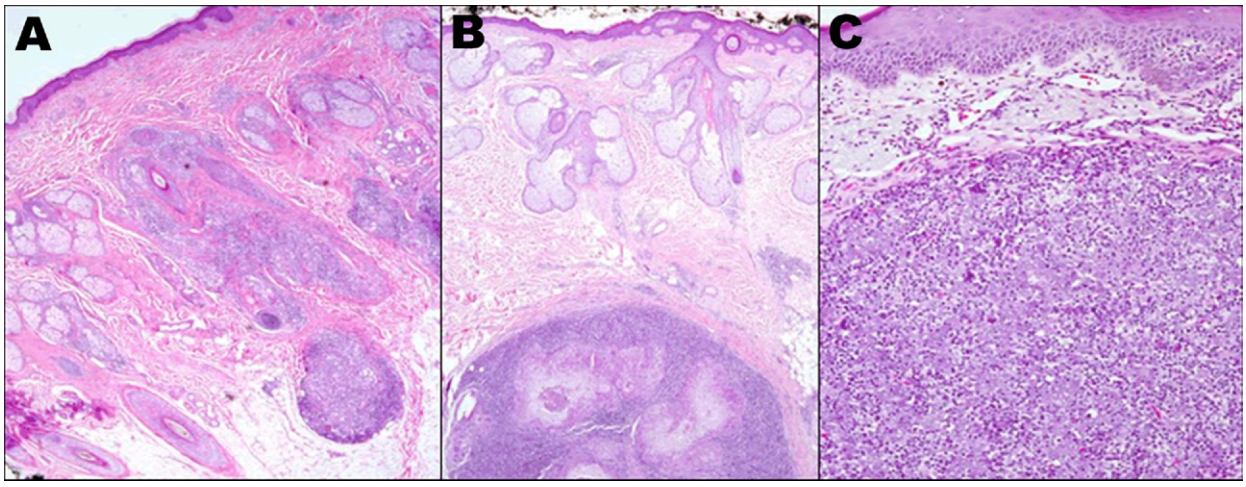

Fig. 3. Composite histologic images. No evidence of connection to the overlying epidermis (HE, ×20).

nasopharyngeal carcinoma and lymphoepithelioma-like carcinoma occurring in other anatomic sites, such as salivary glands, tonsils, larynx, thyroid, thymus, lungs, stomach, breasts, and uterine cervix.[2,5] LELCS is usually seen in older individuals and has a male predilection.[9] Our study of 11 cases demonstrated a definite male bias similarly to the data collected from the published literature (Table II). The most frequent location for LELCS is sun-exposed skin of the head and neck region, although it has also been reported to occur on the trunk.[1,10]

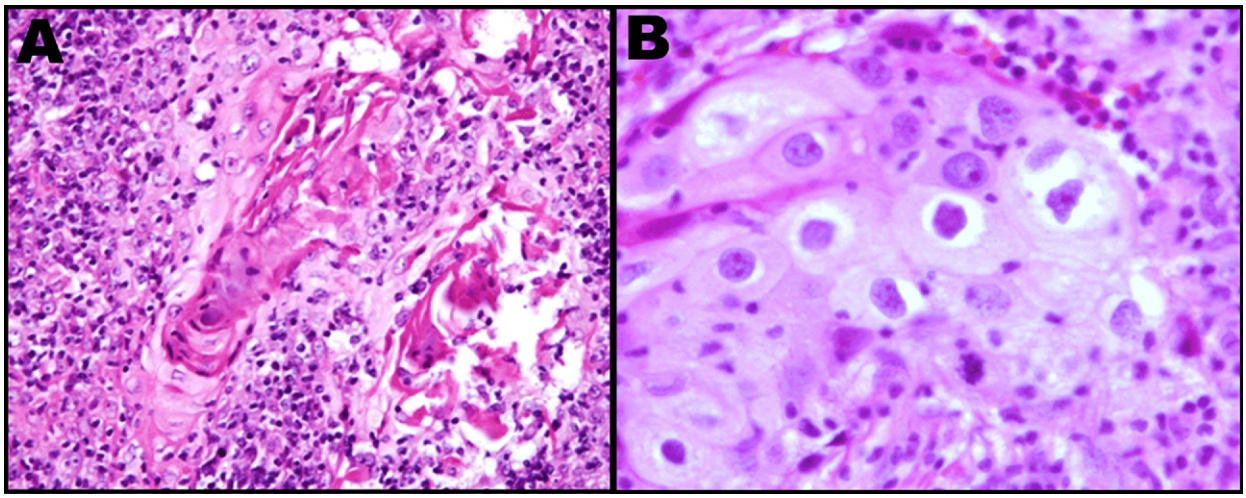

Fig. 4. Composite histologic images. **A,** Evidence of squamous differentiation (hematoxylin-eosin [HE], ×40). **B,** Evidence of sebaceous differentiation (HE, ×40).

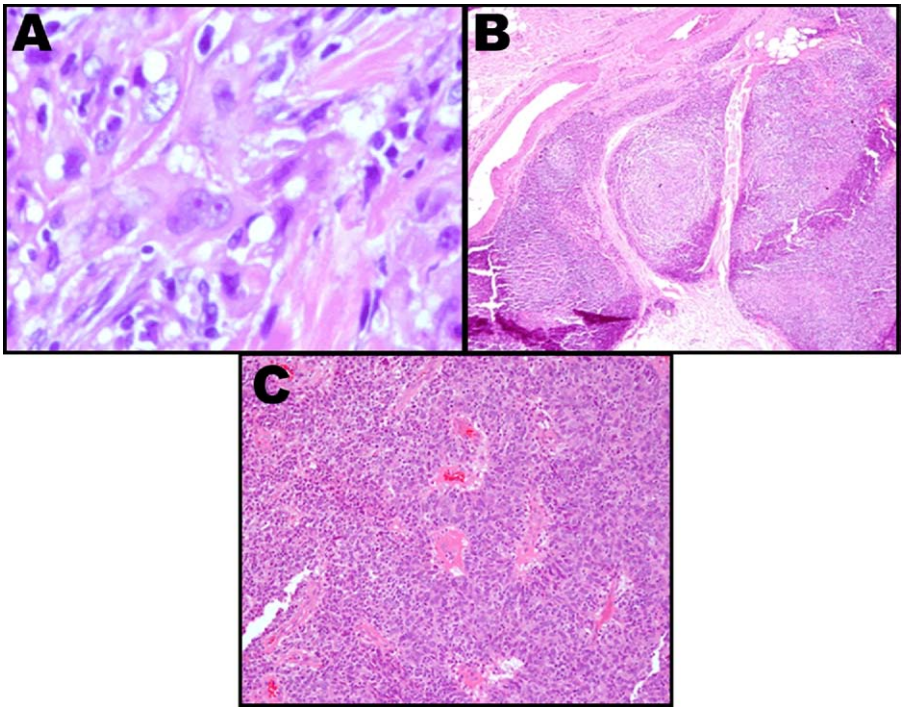

Fig. 5. Composite histologic images. **A,** Binucleated tumor cells resembling Reed-Sternberg cells (hematoxylin-eosin [HE], ×40). **B,** Collagenized fibroblastic stroma dividing the tumor cells into compartments (HE, ×20). **C,** Evidence of pseudorosettes formation (HE, ×20).

Clinically, LELCS appears as an asymptomatic, slowly enlarging, solitary, flesh- or red-colored, firm nodule or plaque.[11-13] The clinical differential diagnosis of LELCS includes basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, and Merkel cell carcinoma (MCC). Histomorphologically, LELCS is characterized by nests, cords, or sheets of mitotically active polygonal epithelioid cells with scant amphophilic to eosinophilic cytoplasm, hyperchromatic nuclei, coarse chromatin granules, and 1 or 2 prominent nucleoli.[1,4,11,14] The tumor

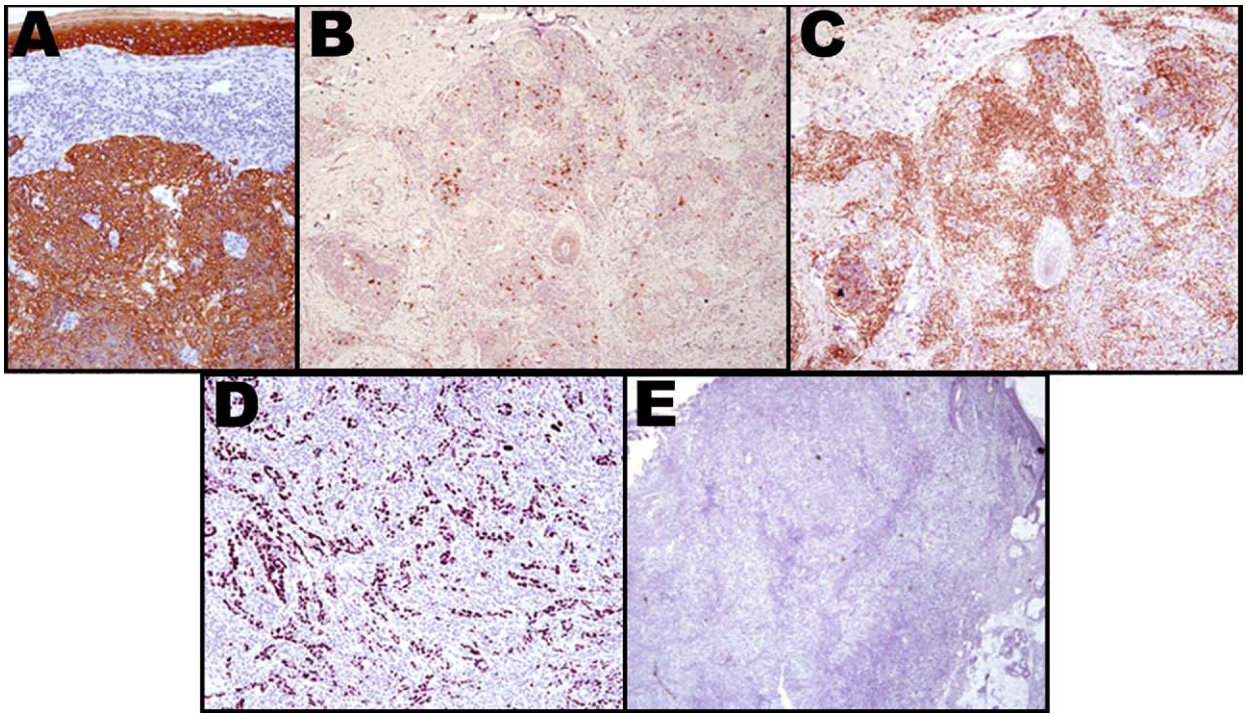

Fig. 6. Composite immunohistochemical photomicrographs. **A,** Strong positivity with pancytokeratins (×20). **B,** Positive staining with CD20 (×20). **C,** Strong positivity with CD3 (×20). **D,** Positive reactivity to p63 protein (×20). **E,** Negative reactivity to Epstein-Barr virus–associated antibodies (×20).

Table III. Immunohistochemical reagents* and their reactivity in the present cases

Antibody	*Clone*	*Dilution*	*Reactivity*
CD3	F7.2.38	1:400	+
CD20	L26	1:100	+
Pancytokeratin	AE1/AE3	1:200	+
EBV LMP-1	CS1234	1:300	−
p63	4A4	1:400	+

EBV LMP-1, Epstein-Barr virus latent membrane protein 1.
*Source: Dako Corp., Carpinteria, CA.

cells display a syncytial or cohesive growth pattern surrounded by variable amounts of a lymphoid stroma composed predominantly of small lymphocytes with occasional plasma cells.[7,11] The cytologic features of LELCS are similar to those found in the fine-needle aspirations of metastatic nasopharyngeal carcinoma in cervical lymph nodes[15] and lymphoepithelial carcinomas of the lung.[16]

The most frequent submitted microscopic differential diagnoses for the present cases were LELCS and atypical lymphoid proliferation (Table I). The histologic differential diagnosis of LELCS is wide, including entities such as cutaneous lymphadenoma, metastatic nasopharyngeal carcinoma, metastatic lymphoepithelial carcinoma from other organs, follicular dendritic cell tumor, MCC, melanoma, Hodgkin disease, and lymphoma.[1,4,13,17-20] The immunohistochemical profile of LELCS aids in differentiating it from other histologic mimics. LELCS expresses high-molecular-weight cytokeratins and epithelial membrane antigen reactivity, favoring an epidermal, follicular, or sudoriferous differentiation. The tumor cells are negative for carcinoembryonic antigen, S-100 protein, CK-20, CK-7, and neuron-specific enolase.[10] Surrounding lymphoid cells show reactivity with T-cell and B-cell markers.[12]

Cutaneous lymphadenoma also exhibits a dense lymphocytic infiltrate similar to that of LELCS which surrounds the neoplastic lobules. But unlike LELCS, the neoplastic cells of cutaneous lymphadenoma are monomorphous, there is no mitotic activity, and a peripheral layer of basal-like cells is generally observed.[17] The most complex differential diagnosis of LELCS is a metastatic nasopharyngeal carcinoma. The histopathologic features of metastatic nasopharyngeal carcinoma are akin to those of LELCS, and the only reliable method to differentiate the two lesions is by testing for EBV. LELCS stains negative to EBV, in contrast to the EBV-positive staining of nasopharyngeal carcinoma.[17]

Follicular dendritic cell tumor (FDCT) is histologically characterized by the presence of syncytial-appearing plump cells in a background of reactive lymphoid cells similar to LELCS. The diagnosis of FDCT is confirmed by immunohistochemical studies. In contrast to LELCS, the tumor cells of FDCT stain negative for cytokeratins. FDCT stains positive for FDC markers, namely Ki-M4, CD21, and CD35.[3]

Metastatic lymphoepithelial carcinoma from other organs and primary LELCS are identical both histogically and immunophenotypically, but are different in their association with EBV. Metastatic LELCS are positive for EBV.[21]

Merkel cell carcinoma is histologically characterized by closely approximated hyperchromatic cells containing coarse chromatin. Unlike LELCS, MCC may demonstrate connection to the surface epithelium. The other important histologic criterion that separates these 2 entities is the absence of lymphocytic infiltrate in MCC. MCC shows negativity for cytokeratin and immunopositivity for neuroendocrine markers such as neuron-specific enolase, synaptophysin, and chromogranin.[17,22]

Microscopically, LELCS may also bear resemblance to Hodgkin lymphoma owing to the presence of occasional binucleated cells resembling Reed-Sternberg cells. Negativity for cytokeratin and positivity for CD30 and CD15 support a diagnosis of Hodgkin lymphoma.[3,7] Lymphoma also is considered to be a possible differential diagnosis of LELCS. The cells of malignant lymphoma exhibit unevenly shaped nuclei with coarser chromatin and smaller basophilic or amphophilic nucleoli, whereas the lymphocytes in LELCS show no cellular atypia. Additionally, depending on the type of lymphoma, the cells are either positive to CD20 (B-cell) or CD3 (T-cell) and negative for cytokeratins.[22]

In addition to these entities, one of the cases reported by Clarke and Ioffreda[7] displayed a spindle cell component, thereby including mesenchymal spindle cell lesions, especially the spindle cell variant of melanoma, in the spectrum of histologic differential diagnosis of LELCS. The immunohistochemical profile of melanoma is used to distinguish it from LELCS. The neoplastic cells of melanoma stain positively with S-100 and HMB-45 and negatively with cytokeratins.[7]

Although LELCS represents a distinct pathologic entity, its histogenesis still remains unclear.[11,17] There have been competing opinions regarding the origin of LELCS among different reviewers. Adnexal origin is favored by many authors because of its location in the dermis, its lack of continuity with the surface epidermis, and the reported presence of cytoplasmic acid epithelial mucin vacuoles[1,23] with possible follicular,[10,11,18,24] glandular,[22] or sebaceous differentiation.[20] All of our cases exhibited strong p63 protein reactivity, supporting the epithelial origin with a putative adnexal histiogenesis. It is possible that newer isoforms of p63 may in the future reliably distinguish between basilar cells of the skin and basilar-myoepithelial cell of the adnexa. Some authors favor epidermal origin based on the presence of keratinocytic atypia and epidermal involvement.[2,3,13,23,25,26] None of the present 11 cases exhibited these features. Like undifferentiated nasopharyngeal carcinoma, LELCS may be a squamous cell carcinoma variant.[2,27]

In spite of the high-grade histologic features of LELCS, the prognosis is good. There have been reports of recurrences after incomplete excision.[1] The treatment of choice is complete surgical removal. Radiotherapy is a useful adjunctive therapy for aggressive or unresectable tumors and for those patients who are not surgery candidates.[1,12,28] To prevent local recurrence, some reports also recommend Mohs micrographic surgery.[11,23] It is imperative to properly diagnose and adequately treat this type of malignancy with complete excision of the tumor. Close clinical follow-up of the patient is recommended. Metastasis to lymph nodes and internal organs (liver, lungs, and bone), though exceptionally uncommon (only 5 cases), have been reported.[1,29-31]

In conclusion, LELCS is an uncommon neoplasm that is rarely suspected at the time of presentation. It displays distinctive histologic features and similarities to nasopharyngeal carcinoma. Awareness can serve to prevent a diagnostic and therapeutic misadventure.

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