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Non-lymphoid lesions that may mimic cutaneous hematopoietic neoplasms histologically

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ABSTRACT

This review considers neoplastic lesions that originate in the skin, and which have the potential to imitate hematopoietic proliferations at a histological level. They include lymphoepithelioma-like carcinoma, Merkel cell carcinoma, benign lymphadenoma, pseudolymphomatous angiosarcoma, lymphadenoid dermatofibroma, lymphomatoid atypical fibroxanthoma, histiocytoid (epithelioid) hemangioma, and inflamed melanocytic lesions. The clinical and pathological features of those tumors are considered.

Introduction

The differential diagnosis of lesions that include many leukocytes is a difficult one. Not only is the distinction between lymphoid hyperplasias and lymphomas challenging—often requiring the use of several adjunctive laboratory studies—but several non-lymphoid neoplasms may demonstrate a morphological resemblance to *bona fide* lymphoreticular proliferations. Such imitators include thymomas, seminomas, and primary carcinomas in various sites.

This review considers comparable neoplastic lesions that originate in the skin. They include lymphoepithelioma-like carcinoma, Merkel cell carcinoma, benign lymphadenoma, pseudolymphomatous angiosarcoma, lymphadenoid dermatofibroma, lymphomatoid atypical fibroxanthoma, histiocytoid (epithelioid) hemangioma, and inflamed melanocytic lesions.

Epithelial neoplasms that may simulate lymphoma of the skin

Cutaneous lymphoepithelioma-like carcinoma (CLELC)

In 1921, Schmincke[1] and Regaud and Reverchon[2] concurrently described the same tumor type, in which cytologically-malignant epithelial cells were intermingled intimately with lymphocytes. The most common locations for such lesions were subsequently found to be the nasopharynx and oropharynx, in association with normal tonsillar tissue in those sites. As reviewed by Ewing in 1929, "lymphoepithelioma" (LE) was felt to be relatively uncommon in comparison with other carcinoma morphotypes. Moreover, its distinction from lymphomas was judged to be very difficult on purely morphological grounds. The main value for recognizing LE was felt to be its unusual susceptibility to radiotherapy.[3]

Pathological interest in LE was then relatively scant for several decades. It was briefly enhanced in the mid-1940s, owing to the fact that a famous professional baseball player, George "Babe" Ruth, had developed that tumor type in the nasopharynx.[4] His case was remarkable for the short-lived but complete remission that was achieved through the use of an early folic-acid antagonist, teropterin, in his treatment.[5]

The 1970s, and the growth that occurred then in the fields of Immunology and Virology, led to the next episode of curiosity regarding LE. Nasopharyngeal carcinoma in Asian individuals was found to show a predisposition for selected human leukocyte antigen-related genotypes.[6] In addition, integrated nucleic acid from the Epstein-Barr virus (EBV) was demonstrated in the tumor cells of some pharyngeal LEs, together with circulating antibodies to EBV-related proteins.[7] These observations were followed by the documentation of neoplasms with the LE phenotype in a substantial number of organ systems.[8]

In 1988, Swanson et al. presented a series of 5 adult patients with CLELC[9]; four were situated on the head and one lesion arose

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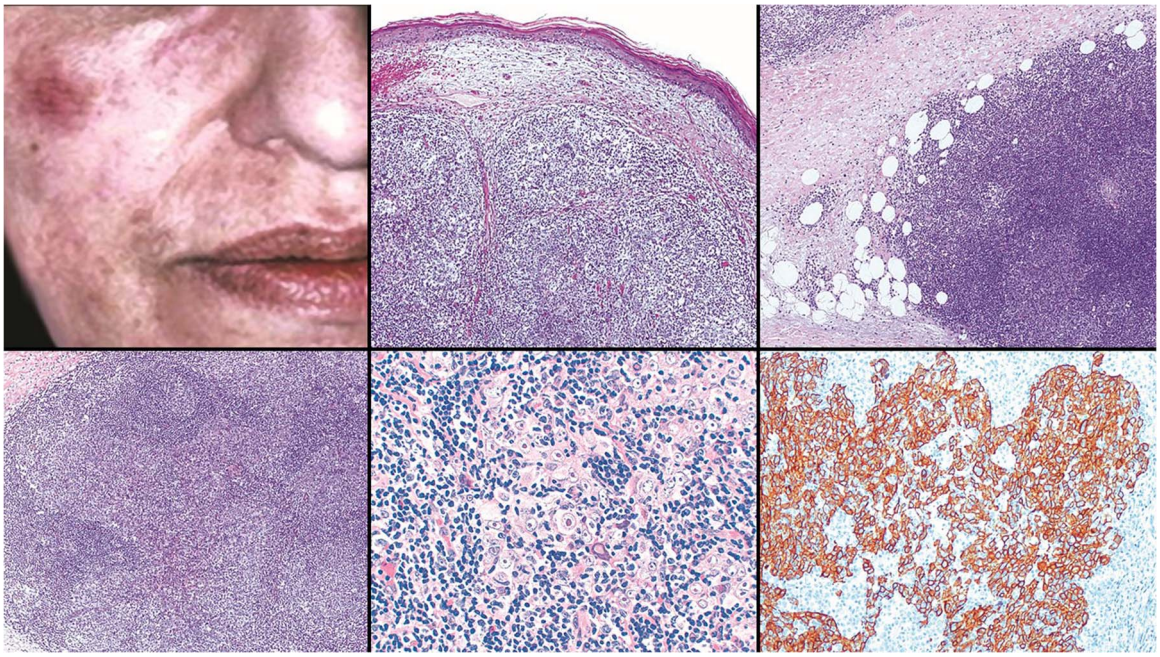

Fig. 1. Cutaneous lymphoepithelioma-like carcinoma is shown here, as a nondescript reddish nodule in the facial skin (top, left). Microscopically, the lesion comprises an intimate admixture of large atypical epithelioid tumor cells and small lymphocytes (top middle & right; bottom left & middle). An immunostain for pankeratin demonstrates diffuse reactivity among the epithelioid cells (bottom right).

on the upper trunk, as clinically-nondescript nodules. One of the tumors behaved aggressively, with metastasis, and it proved fatal 57 months after diagnosis. Since that time, less than 100 new cases of CLELC have been documented in the literature; $<10\%$ of those tumors have recurred or spread distantly.10 Accordingly, Cassarino et al. have classified this neoplasm as "intermediate" grade.[11]

Microscopically, CLELC comprises syncytia or vague clusters of large epithelioid cells in the dermis, with vesicular nuclear chromatin, prominent nucleoli, and mitotic activity. Mature lymphocytes permeate the lesions diffusely, and surround them as well (Fig. 1). Some studies have shown that eccrine or pilar features may be evident in CLELC, with the focal formation of ductal spaces or zones of trichilemmal-type keratinization.[12] Other reports demonstrated a connection by the lesion to the epidermis.[13] Therefore, it is probable that CLELC may represent a common morphologic phenotype among neoplasms with different lineages of differentiation.

Interestingly, although the histologic features of this tumor are those of a largely-undifferentiated epithelial proliferation, its behavior is indolent, as mentioned above.[14–18] Another intriguing fact is that, unlike LE of the nasopharynx, pharyngeal tonsils, salivary glands, and lungs, similar tumors of the skin only exceptionally exhibit integration of genomic nucleic acid from the Epstein-Barr virus using in-situ hybridization or polymerase chain reaction studies.[19]

In addition to the fact that CLELC itself resembles a lymphoid neoplasm, it may also coexist in the skin with authentic lymphomas. Reported examples of that concurrence have included CLELC in patients with mycosis fungoides[20] and marginal-zone lymphoma,[21] and we have also observed a case with simultaneous cutaneous small-lymphocytic lymphoma.

Merkel-cell (primary cutaneous neuroendocrine) carcinoma

Virtually from the time of its first description as "trabecular carcinoma" by Dr. Cyril Toker in 1972,[22] the tumor known as Merkel cell carcinoma (MCC) or primary cutaneous neuroendocrine carcinoma was recognized as a potential simulant of malignant lymphoma. That likeness applies to the clinical as well as the microscopic appearances of MCC.[23]

This neoplasm typically presents as a solitary, red-violet, nodular cutaneous mass, usually in sun-exposed skin areas, in middle-aged or elderly patients. It has often been present for years before a diagnosis is made.[24] Very rarely, MCC may be associated with paraneoplastic phenomena that are common to other neuroendocrine tumors, including inappropriate secretion of antidiuretic hormone, cerebellar dysfunction, and the Eaton-Lambert syndrome.[25] Behaviorally, MCC ranks behind only melanoma and angiosarcoma as a potentially-lethal cutaneous malignancy.[26,27] Pathogenetically, it is a singular neoplasm because of its association with integrated nucleic acid from a unique polyomavirus.[28,29]

The majority of MCCs are centered in the dermis, and they are separated from the surface epithelium by a "grenz" zone (Fig. 2). The tumors assume either a medullary (sheet-like) or trabecular and organoid growth pattern, with ill-defined margins, and they comprise monotonous, small, round tumor cells.[24,30,31] These have oval nuclei with evenly-distributed chromatin, inconspicuous nucleoli, and profuse mitotic activity (up to 20 division figures per high-power field). The cytoplasm is scanty and amphophilic. Supporting stroma is very vascular, and dilated intratumoral vessels likely account for the red-violet color of the lesions macroscopically. Infiltration of the underlying subcutis, with entrapment of adipocytes, is observed in many cases. Approximately 10% of MCCs involve the epidermis, in which cases a histologic resemblance to the Pautrier microabscesses of mycosis fungoides can be produced[32] (Fig. 3).

MCC also may be associated with squamous carcinoma or basal cell carcinoma in the same skin field, and divergent squamous or adnexal differentiation is also potentially seen throughout some lesions. Regional coagulative necrosis is evident in roughly one-half of MCC cases.[24,31] Peritumoral and intralesional lymphoplasmacytic inflammation may be prominent, yielding a microscopic resemblance to medullary carcinoma of the breast or malignant lymphomas containing large and small cells.[33,34]

Filamentous perinuclear whorls and neurosecretory granules can be seen ultrastructurally in MCC, even in specimens that are retrieved from paraffin blocks.[23] Such findings are absent in other differential