Nonlymphoid Tumors Mimicking Lymphoma

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Introduction

No book on cutaneous hematopathology would be complete without a chapter dedicated to non-hematolymphoid tumors that routinely or on occasion masquerade as hematologic malignancies. Mimickers of lymphoma or other hematopoietic infiltrates in the skin are not uncommon and have the potential to pose a major diagnostic challenge to the pathologists. Cutaneous lymphoma mimics include benign entities such as infection, hypersensitivity reactions, drug reactions, and inflammatory dermatoses, as well as neoplasms, including melanoma, sarcoma, and undifferentiated carcinomas. Many of the inflammatory dermatoses that can be histologically confused with a malignant hematolymphoid proliferation have been discussed elsewhere in this book (see Chaps. 5, 7, and 8); this chapter will therefore concentrate on the neoplasms that can mimic hematopoietic malignancies.

Undifferentiated neoplasms in the skin require a broad differential diagnosis. Clinical characteristics of the lesion and pertinent history are helpful but not always available. When confronted with a cutaneous lesion with ambiguous morphologic characteristics, immunohistochemistry is often necessary to arrive at a final diagnosis, although histologic clues to a non-hematopoietic etiology may usually be detected with careful examination. As a rule, histologic findings should be evaluated in the context of clinical information in order to carefully select a panel of stains that will aid in the accurate diagnosis of a tumor. Cutaneous infiltrates can be broadly generalized into categories based on morphology; a few pertinent examples of such categories include small round cell, spindle cell, epithelioid, and pleomorphic neoplasms (Wick 2008). As cutaneous hematolymphoid neoplasms can fall within many of these morphologic categories, these should not be neglected when forming a differential diagnosis. A strategically selected panel of immunohistochemical stains can then be utilized to support a suspected diagnosis or at the least to narrow the differential diagnosis. In general, molecular testing is secondary to immunohistochemistry, and its use is left to the discretion of the pathologist (Wick 2008). This chapter will focus on entities that may be histologically confused with hematopoietic neoplasms. Each entity will be briefly discussed with a particular concentration on patterns that overlap with cutaneous hematolymphoid infiltrates and the valuable ancillary techniques to distinguish them.

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Table 18.1 Melanoma incidence by race and gender

Race/ethnicity	Male (per 100,000)	Female (per 100,000)
All races	27.4	16.7
White	31.9	20.0
Black	1.1	1.0
Asian/Pacific Islander	1.6	1.1
American Indian/native Alaskan	4.1	3.5
Hispanic	4.7	4.4

Adapted from the National Cancer Institute Surveillance Epidemiology and End Results.
Rates based on cases diagnosed in 2006–2010 from 18 SEER geographic areas.

Melanoma

Epidemiology

Melanoma is one of the deadliest cutaneous malignancies, with an age-adjusted incidence rate of 21.1 per 100,000 persons per year and an age-adjusted death rate of 2.7 persons per 100,000 per year. The lifetime risk of developing melanoma for Americans is estimated at 2 %, and males are affected slightly more than females (SEER 2012). The average age of presentation is 61 years, although the range of those affected by melanoma is broad and encompasses all ages. Melanoma is extremely rare in infants and young children, although such cases have been reported (Marghoob et al. 1996; Richardson et al. 2002). As with other cutaneous malignancies, Caucasians and fair-skinned individuals have a higher incidence of disease than those of darker pigmentation, a statistic which reflects the significance of ultraviolet (UV) radiation as a contributing factor to the development of melanoma (Table 18.1).

Clinical Features

Classically, melanoma presents as a new or changing darkly pigmented macule, papule, or nodule. Lesions may arise on sun-exposed or sun-protected skin, as well as mucosal sites. Characteristics of concern include large size, asymmetry or irregular borders of the lesion, and uneven or multiple variations in color. Ulceration may or may not be present. Biopsies of clinically concerning lesions should attempt to sample the entire lesion by way of primary excision or deep shave biopsy. Alternatively, a partial biopsy, especially when the lesion is large, generally gives accurate staging information and carries no increased risk of local recurrence, nodal metastasis, or death from disease (Bagley et al. 1981).

Histology and Differential Diagnosis

Different subtypes of melanoma, although not useful as a prognostic indicator of disease, do offer a scaffold by which to conceptualize clinical presentations and classic histologic findings. Melanocytic lesions, not unlike lymphoma, are notorious for their heterogeneity, and indeed, melanoma has been termed "the great mimicker," which derives from its range of histologic patterns and cytologic features. On occasion, the conventional histologic clues that point toward melanoma as a diagnosis, such as melanin production or an intraepidermal component, are absent. For this reason, melanoma should remain on the differential diagnosis of almost any undifferentiated tumor encountered by the pathologist. While a detailed discussion of all of the encountered histologic patterns is beyond the scope of this book, the following section will focus on histologic variants of melanoma that are most likely to demonstrate overlap with hematolymphoid tumors.

Amelanotic Melanoma

While pigmented melanocytic lesions often lead to a clinical differential diagnosis encompassing benign and malignant melanocytic entities, non-pigmented melanomas can be readily mistaken for benign dermatitis or a non-melanocytic neoplasm, including solitary lymphoproliferative processes. Amelanotic melanoma, as the name implies, is a melanoma lacking melanin pigment (Fig. 18.1). The majority of these tumors have been shown to exhibit epithelioid morphology (72 %), with a minority exhibiting spindle cell (18.7 %), desmoplastic (5.3 %), or rhabdoid

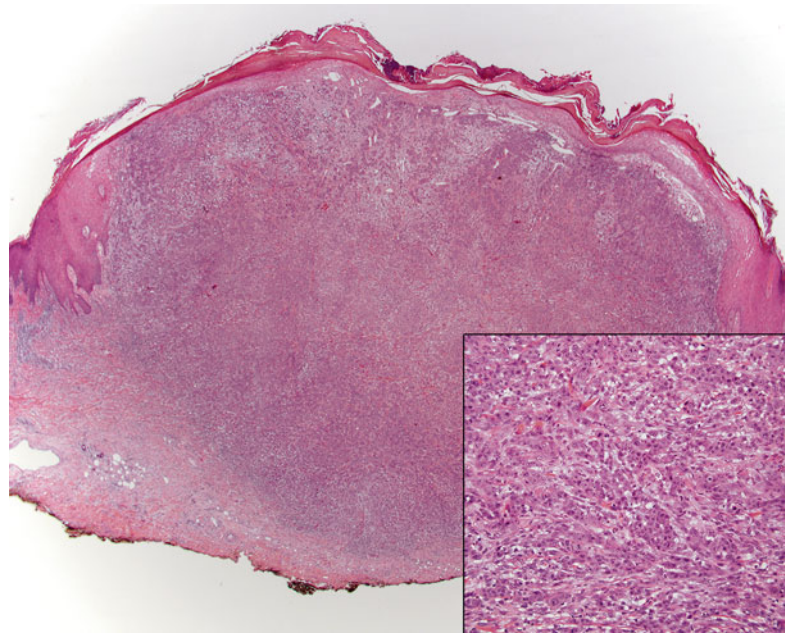

Fig. 18.1 Amelanotic melanoma. This nodular tumor extends deeply into the dermis and does not have a classic melanoma in situ component. Higher power (*inset*) shows focal clustering of tumor cells, but pigment production is lacking. Tumor cells expressed S100 protein and MART-1

morphologies (4 %) (Cheung et al. 2012). Lesions with epithelioid cytomorphology are more likely to display other unusual features, such as signet ring cells, multinucleated giant cells, or monster cells. When such a variety of atypical cells are present, especially in the absence of melanin pigment or an in situ component in the epidermis, a diagnosis of melanoma is not entirely straightforward; in particular, these tumors may mimic large cell lymphomas, such as anaplastic large cell lymphoma or diffuse large B-cell lymphoma. Fortunately, the absence of melanin pigment does not appear to correlate with expression of melanocytic markers, and examined cases of amelanotic melanoma have reliably retained expression of such markers by immunohistochemistry. This preserved antigenicity also argues the case that amelanotic melanoma is a subtype of melanoma with phenotypic variation rather than a dedifferentiated melanoma (Cheung et al. 2012).

Melanoma with Small Cell Morphology

Small cell melanoma is an uncommon variant of nevoid melanoma with a differential diagnosis encompassing a spectrum of benign and malignant melanocytic lesions as well as non-melanocytic tumors. The constituent tumor cells resemble those that would typically be seen at the base of an otherwise conventional melanoma. The tumor cells are small with a high nuclear to cytoplasmic ratio, nuclear atypia, hyperchromasia, and prominent nucleoli (Fig. 18.2) (Blessing et al. 2000). In this regard, clusters of small tumor cells on scanning power may mimic small round blue cell tumors, Merkel cell carcinoma, and hematolymphoid neoplasms such as non-Hodgkin lymphoma. Overlying nests of in situ melanoma cells and melanin pigment are useful clues to the diagnosis, but are not always present. The diagnosis is made more challenging in cases of metastases of unknown primary origin, in which pathologists may not consider melanoma within the initial differential diagnosis given the small size and scant cytoplasm of tumor cells (Hanson et al. 2002). Features which help distinguish small cell melanoma from a benign nevus include expansile and often asymmetric growth, deep dermal extension, disorganized growth pattern, monotony without evidence of maturation, and readily identifiable dermal mitoses (Fig. 18.3) (Hanson et al. 2002). Small cell melanomas

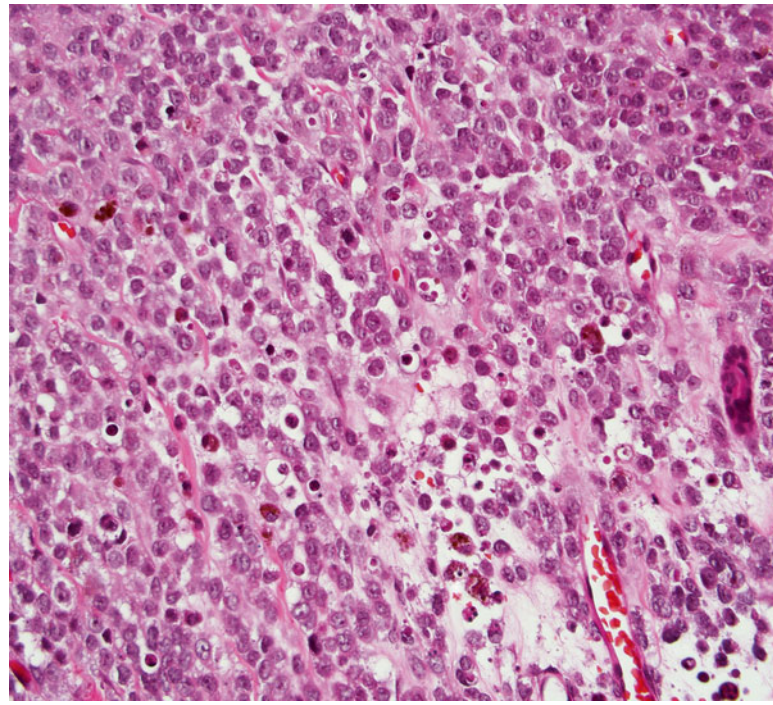

Fig. 18.2 Small cell melanoma. Dispersed tumor cells show a high nuclear to cytoplasm ratio and are relatively small (compare to erythrocytes). Individual cell necrosis and mitotic figures are seen, and some of the tumor cells contain pigment

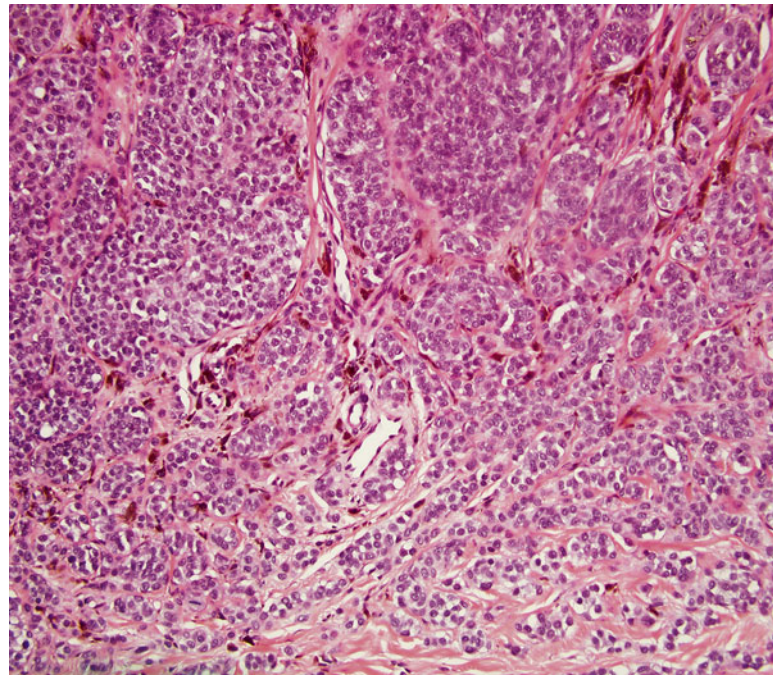

Fig. 18.3 Small cell melanoma. In this case, despite the small cell size and pseudomaturation of melanocytic nests, deep dermal mitoses were evident (*bottom left*), and focally there was sheetlike architecture

typically maintain expression of melanocytic markers and lack expression of traditional lymphoid markers such as CD45/LCA, so the derivation of the tumor becomes apparent as soon as appropriate immunohistochemical staining is utilized.

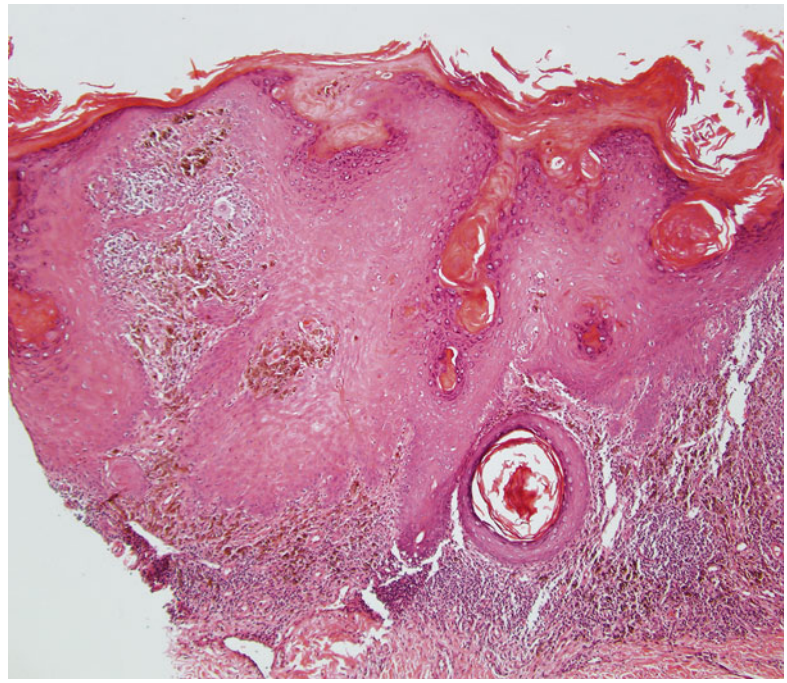

Fig. 18.4 Regressing melanoma. Epidermal hyperplasia and a dense lichenoid infiltrate obscure scattered tumor cells (*upper left*). The melanophages are a clue to the regression taking place

Melanoma with Regression

Active regression of melanoma is thought to represent a host immune response leading to the loss or degeneration of tumor cells. This host response is reflected by a prominent lymphocytic infiltrate (McGovern 1975), whereby tumor cells are likely removed by lymphocyte-mediated apoptosis. Established regression is characterized by a mixed lymphocytic population, vascular fibrosis, and often associated melanophages (Weedon 2010). On occasion, the dense lymphocytic infiltrate of active regression can mask remaining tumor cells and be confused with a reactive or neoplastic hematolymphoid infiltrate, as lymphocytes involved in regression may show nuclear irregularity and epidermotropism (Fig. 18.4). Regressing melanoma has been reported to mimic both mycosis fungoides and cutaneous nodular sclerosing Hodgkin lymphoma. Regressing melanoma can simulate the epidermotropism and Pautrier microabscesses of mycosis fungoides, and residual melanoma cells admixed in a sea of inflammation can mimic the binucleated Reed-Sternberg cells of Hodgkin lymphoma (Menasce et al. 2005). In fact, Reed-Sternberg-like cells are not unique to Hodgkin lymphoma and are not infrequently reported in melanomas and a variety of other tumors (Strum et al. 1970). In general, regressing melanoma will demonstrate a lymphoid infiltrate primarily composed of CD8-positive cytotoxic T cells, and T-cell gene rearrangement will fail to demonstrate monoclonality. Any remaining atypical dermal cells will prove to be of melanocytic derivation (Menasce et al. 2005).

As an incidental note, it should be remembered that benign nevi can also undergo spontaneous regression. This correlates clinically with a "halo" phenomenon, whereby a pale rim (or halo) surrounds the involuting pigmented lesion. Microscopically, the melanocytic proliferation is engulfed in a dense inflammatory infiltrate which, as in regressing melanoma, can occasionally obscure melanocytes (Fig. 18.5). As in melanoma with regression, the lymphocytic infiltrate associated with a benign nevus undergoing regression is predominantly CD8 positive (Musette et al. 1999; Tokura et al. 1994).

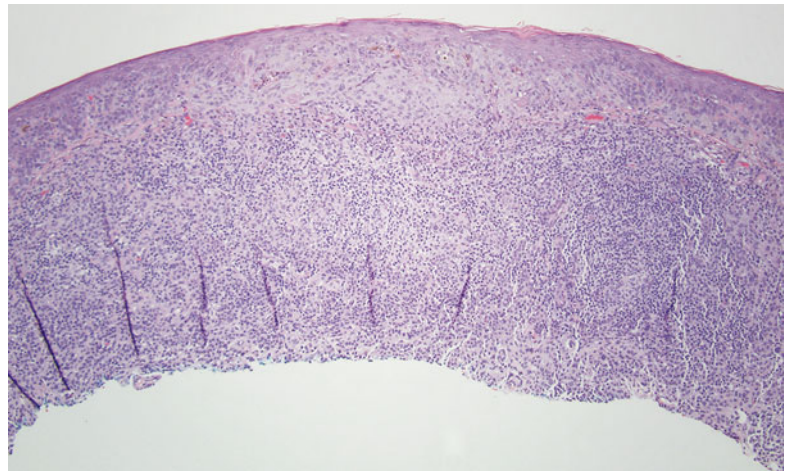

Fig. 18.5 Halo nevus. A brisk lymphocytic infiltrate obscures the dermal component of this nevus from a 15-year-old female. Clinically, the lesion displayed a "halo"

Melanoma on Cytologic Preparations

When applicable, fine-needle aspirate (FNA) is a rapid, minimally invasive technique for diagnosis. Although FNA is considered a procedure with high diagnostic accuracy for melanoma (published sensitivity and specificity values for FNA in metastatic melanoma have ranged between 86.5 % and 100 %), accurate diagnosis of melanoma can be challenging due to the varied morphologic appearances of this disease in cytologic preparations (Basler et al. 1997; Cangiarella et al. 2000; Hafstrom et al. 1980; Murali et al. 2007; Perry et al. 1986b; Rodrigues et al. 2000; Voit et al. 2000). In the absence of tissue architecture, the cytologic features of melanoma cells may be confused with atypical lymphocytes, particularly when the lymph nodes are aspirated with concern for unexplained lymphadenopathy. Care should be taken not to mistake these cells for unusual plasma cells or atypical lymphocyte forms as would be encountered in anaplastic large cell lymphoma or diffuse large B-cell lymphoma (Fig. 18.6). In aspiration smears, melanoma cells are often plasmacytoid and relatively discohesive; upon further investigation, however, foci of more cohesive cell clusters are usually identified, distinguishing melanoma from lymphoma, in which the tumor cells are highly dissociated (Murali et al. 2007). Additional hints that suggest a diagnosis of melanoma are binucleation and the lack of lymphoglandular bodies (Perry et al. 1986a). Interestingly, the presence of pigment is identified in only one-quarter of melanoma aspirates (Murali et al. 2007). If there is doubt as to the diagnosis, creation of a cell block with subsequent immunohistochemical stains should resolve the dilemma (see immunohistochemistry section discussed below).

Metastatic Melanoma

Clinical history often guides the approach to working up an undifferentiated cutaneous neoplasm and is particularly important in a patient with a history of invasive melanoma. Cutaneous metastasis of melanoma is not uncommon and can be diagnostically challenging, as tumor cells may become undifferentiated, may lose expression of melanocytic markers, and may even acquire aberrant expression of other antigens. If available, review of slides from the original biopsy of the primary tumor can be useful. In some cases, however, an extensive immunohistochemical panel may prove necessary.

Pleomorphic and epithelioid melanoma cells can mimic either Reed-Sternberg cells, as previously discussed, or tumor cells of anaplastic large cell lymphoma. The reverse is also true: primary

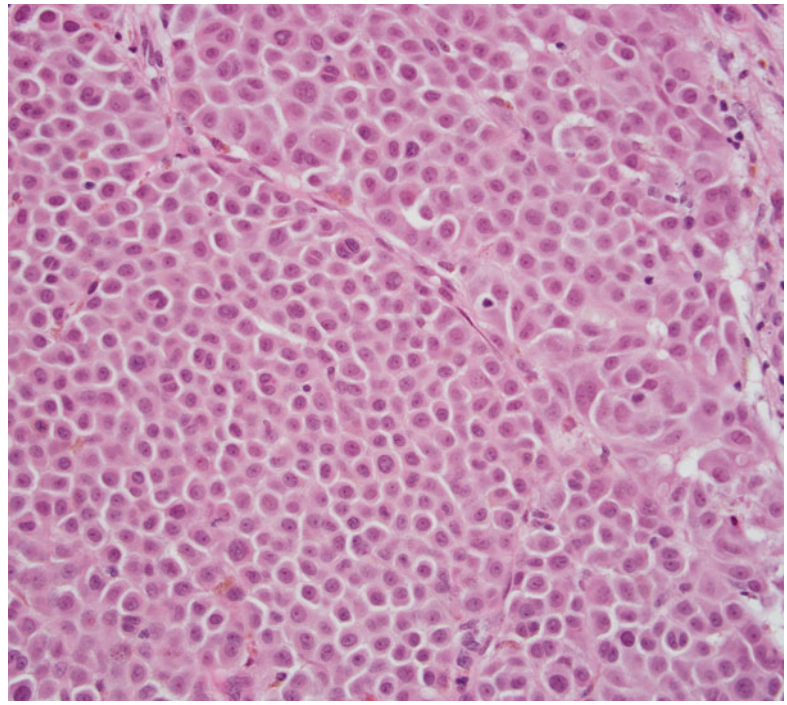

Fig. 18.6 Melanoma with plasmacytoid features. This high-power micrograph demonstrates melanoma tumor cells with plasmacytoid morphology, including eccentrically placed nuclei, occasional perinuclear clearing, and prominent nucleoli

cutaneous anaplastic large cell lymphoma (cALCL) has been reported as a morphologic mimic of metastatic melanoma. In a case report, a man with a remote history of melanoma presented with a new lesion presumed clinically and, at first glance, histologically, to be metastatic melanoma. The absence of expression of melanocytic markers led to an expanded immunohistochemical panel and ultimately a diagnosis of primary cutaneous anaplastic lymphoma, illustrating a pitfall in evaluating poorly differentiated tumors in patients with a known history of melanoma (Pulitzer et al. 2013). Both types of tumors may have a nodular configuration on low-power microscopic examination. Additional overlapping cytologic features of cALCL and metastatic melanoma include abundant cytoplasm, bizarre nuclei, and angulated basophilic nucleoli (Fig. 18.7). However, in cALCL, lymphocytes are more likely to aggregate around the small vessels and to demonstrate classic wreath-shaped "hallmark cells." Although melanoma may lose expression of melanocytic markers and gain anomalous expression of other antigens, it typically remains negative for CD45/LCA, which makes this stain a fairly reliable screening tool to differentiate hematopoietic from melanocytic lineages (Pulitzer et al. 2013). As a subset of anaplastic large cell lymphomas will lack CD45 expression, the addition of CD30 immunohistochemical staining is worthwhile if this entity is within your differential diagnosis (Falini et al. 1990).

In addition to cutaneous metastases, metastatic melanoma within lymph nodes may be challenging to detect. Lymph node metastasis of melanoma, especially when consisting of only a small focus or single cells, may be mistaken for subcapsular/sinusoidal histiocytes. The mitotically active, enlarged lymphocytes comprising germinal centers of lymph nodes may also be a source of diagnostic confusion, especially for those with limited knowledge about normal lymph node architecture (Fig. 18.8). For this reason, the use of immunohistochemistry in the evaluation of sentinel lymph node biopsies has become commonplace and has been shown to be essential in the detection of metastatic disease (Fig. 18.9) (Lobo et al. 2012).

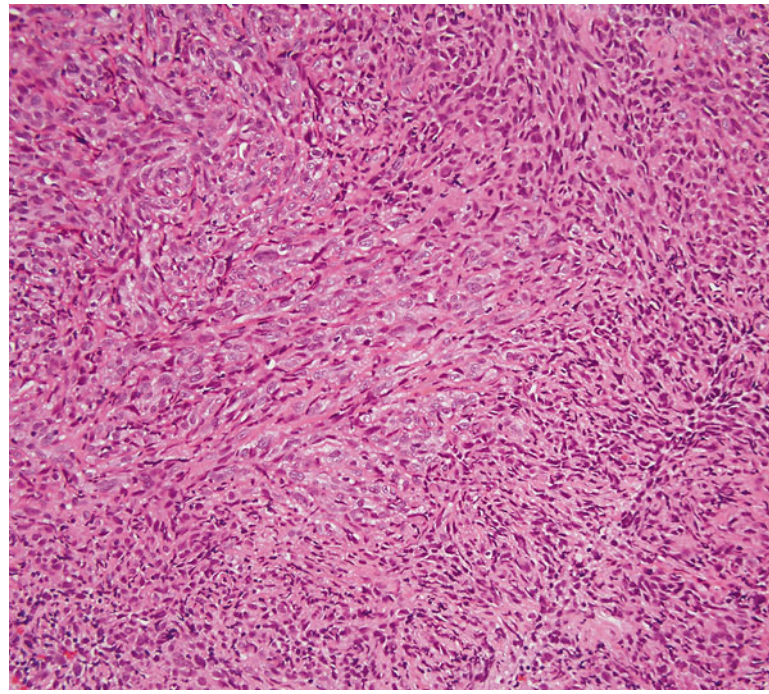

Fig. 18.7 Melanoma. This melanoma demonstrates sheetlike architecture and large pleomorphic tumor cells with admixed inflammatory cells. The lack of clear differentiation and the lack of pigment in this tumor raise a broad differential diagnosis, including anaplastic large cell lymphoma. In this case, tumor cells expressed melanocytic markers

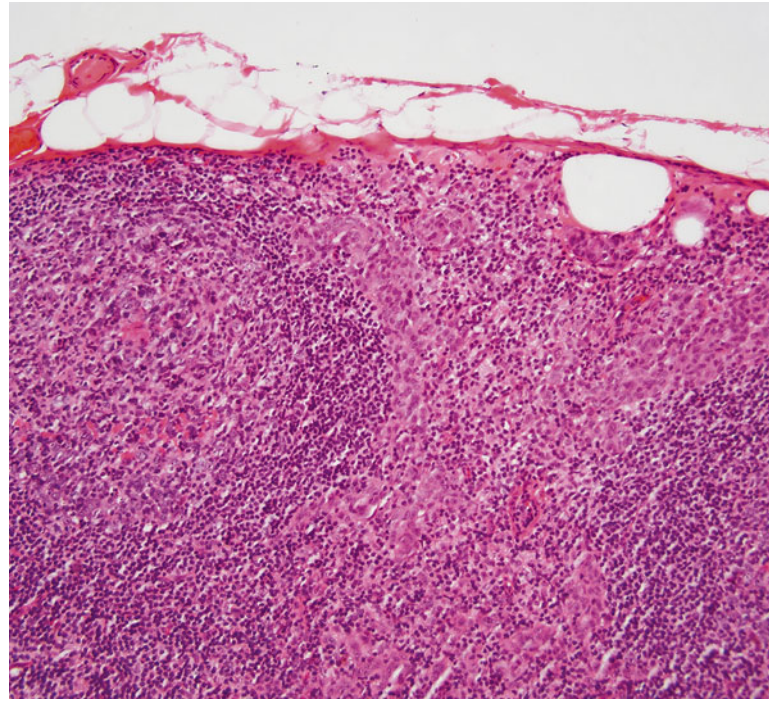

Fig. 18.8 Melanoma metastatic to a sentinel lymph node. Lymph node involvement by melanoma is often subtle. Tumor cells can be seen infiltrating the sinusoidal space adjacent to a lymphoid follicle with germinal center

Immunohistochemistry

Evaluation of melanocytic neoplasms may require the use of immunohistochemical stains. The most commonly used antibodies include MART-1/MelanA, HMB-45, S100, and MiTF. MART-1 (melanoma antigen recognized by T cells 1) and MelanA are two separate names for the protein

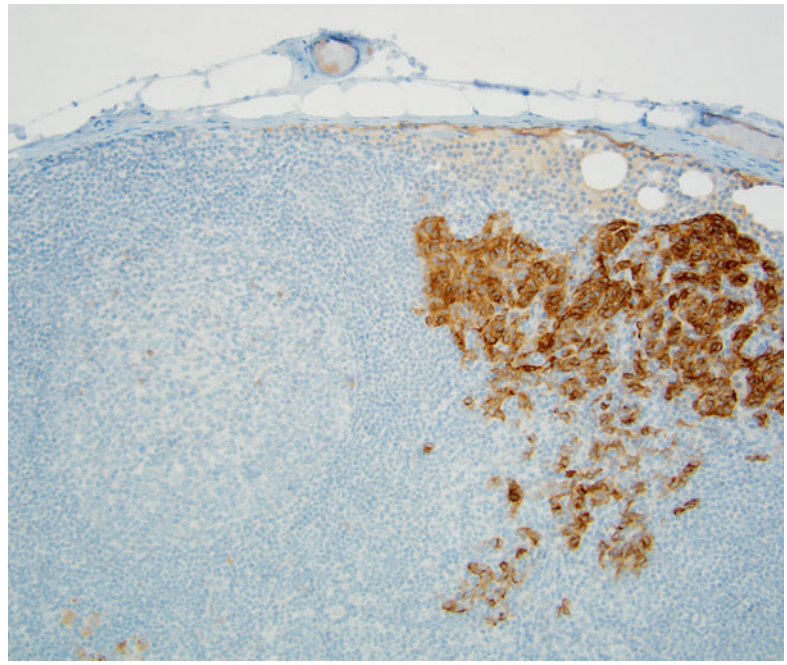

Fig. 18.9 Melanoma metastatic to a sentinel lymph node. MART-1 immunoreactivity of melanoma tumor cells can assist in confirming or detecting small metastatic deposits

encoded by the human *MLANA* gene and represent a highly specific melanocytic marker. HMB-45, or anti-gp100, is a monoclonal antibody that identifies immature melanosomes and is, therefore, frequently expressed in melanomas that maintain pigment production. S100 protein remains a highly sensitive, albeit not entirely specific, marker of melanocytes. It is particularly useful in the diagnosis of spindle cell or desmoplastic melanomas, as this subtype of melanoma is less likely to express the more specific melanocytic markers. However, S100 is positive in a wide variety of non-melanocytic cell types, including neural-derived cells, adipocytes, chondrocytes, and myoepithelial cells, thereby limiting its specificity. MiTF (microphthalmia transcription factor) is directed against the transcription factor involved in melanocytic development and, as such, represents a nuclear stain for melanocytes. Additional markers for melanocytic neoplasms include tyrosinase, which lacks specificity, and Sox10, a transcription factor and relatively novel nuclear stain which shows promise in providing a more specific marker for the diagnosis of desmoplastic melanoma (Mohamed et al. 2012; Ramos-Herberth et al. 2010). Ki-67 and phosphohistone H3 are markers that serve as surrogates for cell cycle engagement and mitotic activity and are sometimes useful in determining the proliferative index of a melanocytic lesion. While typically not useful in thin lesions, these markers may be of assistance when encountering a thick melanocytic tumor in which considerations include (benign) nevus versus nevoid melanoma.

Electron Microscopy

Ultrastructural analysis of melanocytic tumors will demonstrate the presence of melanosomes and premelanosomes. Due to the widespread availability and use of immunohistochemical stains, electron microscopy no longer plays a major role in routine diagnosis, although it may be useful in the rare setting of an undifferentiated neoplasm.

Molecular/Genetics

Routine use of molecular studies is not necessary for the diagnosis of straightforward melanocytic lesions. However, molecular techniques are increasingly being employed to aid in the diagnosis

of challenging melanocytic lesions, with the assumption that molecular aberrations will be more prevalent and widespread in malignant tumors than in benign ones. Specifically, a 4-probe fluorescent in situ hybridization (FISH) panel (targeting regions on chromosomes 6 and 11) has been designed to detect chromosomal amplifications and deletions of loci that are often mutated in melanoma but are unaltered in benign nevi. This technique was shown to classify melanoma with 86.7 % sensitivity and 95.4 % specificity in initial validation studies (Gerami et al. 2009). Array comparative genome hybridization (aCGH) is another technique by which the entire genome of a tumor is examined for widespread chromosomal gains or losses, with melanomas characteristically demonstrating more aberrations than benign tumors (Bauer and Bastian 2006). Using aCGH performed on human cell lines derived from metastatic melanoma, many genetic alterations specific to melanoma have been identified, including deletions of the *CDKN2A* and *PTEN* loci and amplifications of loci encoding genes previously implicated in melanoma such as *BRAF*, *NRAS*, *EGFR*, *MITF*, *NOTCH2*, *CCND1*, *MDM2*, *CCNE1*, and *CDK4* (Gast et al. 2010). In addition, mass spectroscopy represents a novel field whereby the specific protein expression within a lesion gives clues to its biological potential. For instance, imaging mass spectrometry has been reported to correctly differentiate Spitz nevus from Spitzoid melanoma with 97 % sensitivity and 90 % specificity (Lazova et al. 2012).

A thorough discussion of all of the specific genetic mutations associated with melanoma is beyond the scope of this chapter, and the reader is referred to one of many excellent reviews on the subject (Nelson and Tsao 2009). However, special mention to the *BRAF* mutation seems warranted, as the presence of this mutation in metastatic lesions confers eligibility for treatment with the recently FDA-approved BRAF inhibitor. Approximately 40–60 % of melanomas exhibit a point mutation in BRAF kinase, in which glutamic acid (most commonly) is substituted for a valine at amino acid position 600 (V600E) on chromosome 7, leading to increased kinase activity of the protein and thereby driving malignancy (Chapman et al. 2011, Rubinstein et al. 2010). BRAF inhibitors are specifically formulated against the mutated BRAF kinase and represent targeted drug therapy that has been associated with relatively prolonged survival in patients with metastatic melanoma, compared to prior treatment regimens (Chapman et al. 2011).

Prognosis/Course

In the absence of identifiable regional or distant metastases, the prognosis of patients with melanoma depends predominantly on the depth (Breslow's measurement) of the primary tumor. Additional features that inversely correlate with prognosis include ulceration of the primary tumor, increased mitotic activity (measured per millimeter squared), and extensive regression (Edge et al. 2010). Thin melanomas, generally considered to be less than 1 mm in Breslow's depth, have an overall favorable prognosis and are treated surgically with wide local excision. Thicker tumors are treated with wide local excision with generous (1–2 cm) margins, as well as sentinel lymph node sampling, which is usually followed by completion lymphadenectomy if metastatic deposits are identified within the sentinel node. The medical benefit of these procedures remains debated in the literature, and clinical studies are ongoing (Essner 2010; van Akkooi et al. 2010). Chemotherapy, immunomodulatory therapy, and targeted drug therapies, as described above, are utilized in metastatic disease.

Most recurrences from primary cutaneous melanoma occur within 10 years of initial diagnosis, and the majority of these occur within 3 years. However, patients require lifelong surveillance as second primary melanomas and late-occurring metastases can occur. Colloquial terms to describe delayed metastases include "late" metastases that occur 10 years following diagnosis and "ultralate" metastases that occur 15 years following diagnosis. As such, the pathologist should maintain a degree of suspicion for metastatic melanoma in any biopsy from a patient with a clinical history of melanoma.

Merkel Cell Carcinoma

Epidemiology

Merkel cell carcinoma (MCC), or primary cutaneous neuroendocrine carcinoma, is an uncommon, albeit not rare, cutaneous neoplasm that occurs primarily on sun-exposed skin. Caucasians comprise approximately 95 % of all cases of MCC, with a mean age at diagnosis of 76.2 years for women and 73.6 years for men (Penn and First 1999). In addition to ultraviolet radiation exposure, risk factors for the development of MCC include immunosuppression (Penn and First 1999; Samarendra et al. 2000; Ziprin et al. 2000) and infection with the recently discovered Merkel cell polyomavirus (Feng et al. 2008). The role of the Merkel cell polyomavirus as an independent prognostic factor in MCC has been widely debated and remains unclear (Hall et al. 2012, Higaki-Mori et al. 2012; Sihto et al. 2009).

Clinical Features

Merkel cell carcinoma most often presents as a firm, painless, and rapidly enlarging red to violaceous nodule on the face (27 %), upper extremities (22 %), lower extremities (15 %), or scalp and neck (9 %) (Penn and First 1999). The lesion may ulcerate and may have a more plaque-like, rather than nodular, appearance (Goessling et al. 2002). Most patients present with localized skin involvement; however, some patients have regional lymph node metastases at the time of initial presentation, and a few patients diagnosed with MCC present with distant metastatic disease (Calder and Smoller 2010; Goessling et al. 2002). The diagnosis of MCC is rarely made by clinical account alone, as it may be mistaken for angiosarcoma, basal cell carcinoma, melanoma, or cutaneous lymphoma (Calder and Smoller 2010).

Histology and Differential Diagnosis

Despite the early theory that MCC arose from Merkel cells, slow-acting cutaneous mechanoreceptors (and thus, where it derived its namesake), MCC is now thought to originate from a totipotent stem cell capable of heterogeneic differentiation, most notably neuroendocrine and epithelial differentiation (Calder and Smoller 2010; Smith and Patterson 2001; Tilling and Moll 2012). As such, MCC displays histologic and immunophenotypic features characteristic of both neuroendocrine and epithelial lineages. Similar to other small round blue cell tumors of the dermis and hematolymphoid neoplasms, MCC is composed of monotonous, round to ovoid basophilic cells with sparse cytoplasm (Fig. 18.10). Epidermotropism is not an uncommon finding in MCC; it is estimated that 10–30 % of MCC cases demonstrate epidermal infiltration by tumor cells (D'Agostino et al. 2010; Kanitakis et al. 2006). Furthermore, the pattern of epidermal infiltration may occasionally assume a Pagetoid configuration or may even resemble the Pautrier microabscesses of mycosis fungoides (D'Agostino et al. 2010; Donner et al. 1992; Hashimoto et al. 1998; Kanitakis et al. 2006; LeBoit et al. 1992; Rocamora et al. 1987). Unlike lymphoma cells, MCC tumor nuclei have finely dispersed chromatin typical of neuroendocrine cells, also known as a vesicular or "salt and pepper" chromatin, and prominent nucleoli are absent (Fig. 18.11). MCC may display other neuroendocrine features such as molding, crush artifact, and pseudorosette formation. Molding is particularly useful in distinguishing MCC, as it gives a clue to the cohesive nature of the cells, in comparison to hematopoietic tumor cells, which are discohesive; these features are likely the result of the presence (in MCC) or lack of (in lymphoid cells) cell surface adhesion molecules. Apoptotic debris and mitotic figures are often plentiful in MCC (Pulitzer et al. 2009). Architecturally, MCC cells may be arranged in the dermis as trabeculae, sheets, or ribbons or may be scattered as single diffuse cells. Again, these patterns usually hint at the epithelial nature of the tumor (Calder and Smoller 2010; Pulitzer et al. 2009). Giant tumor cell aggregates have been reported in one case of MCC, a finding that was described as a potential mimic of diffuse large B-cell lymphoma (Smith and Patterson 2001). However, with closer examination, the giant tumor cells in MCC displayed identical nuclear features and an immunohistochemical

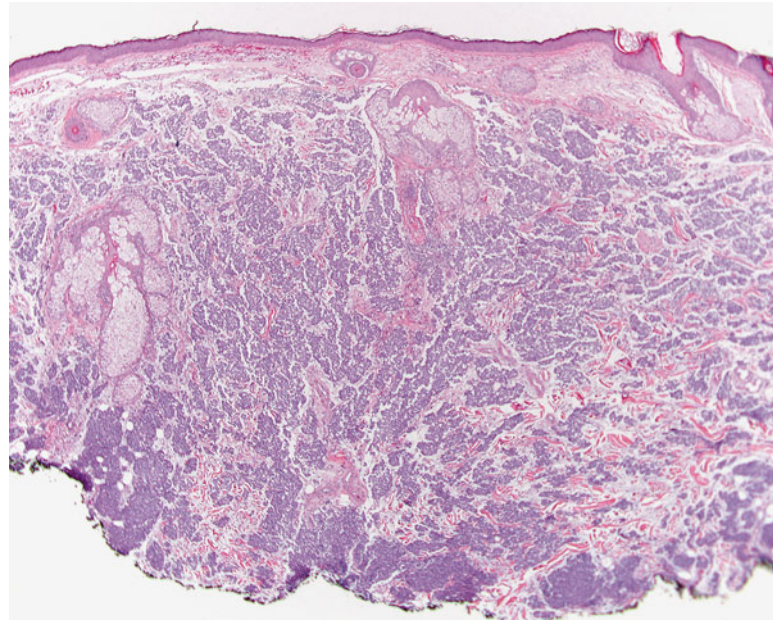

Fig. 18.10 Merkel cell carcinoma. The superficial and deep dermis is involved by sheets, nests, and focally trabeculae of monotonous blue cells

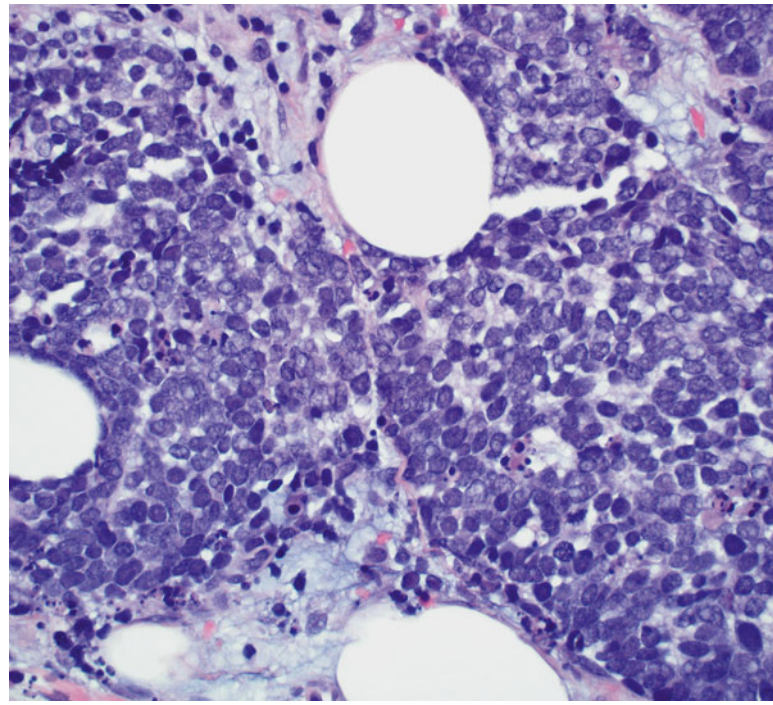

Fig. 18.11 Merkel cell carcinoma. High-power examination of tumor cells reveals nuclei with finely dispersed, "salt and pepper" chromatin and scant cytoplasm. As in other neuroendocrine tumors, nuclear molding is characteristic. Abundant apoptotic debris and frequent mitotic figures are also commonly encountered

staining pattern belonging to conventional MCC tumor cells. Squamous, adnexal, and sarcomatous differentiation have been observed within MCC, prompting the idea of phenotypic transformation and further supporting the theory that MCC derives from a totipotent stem cell (Calder

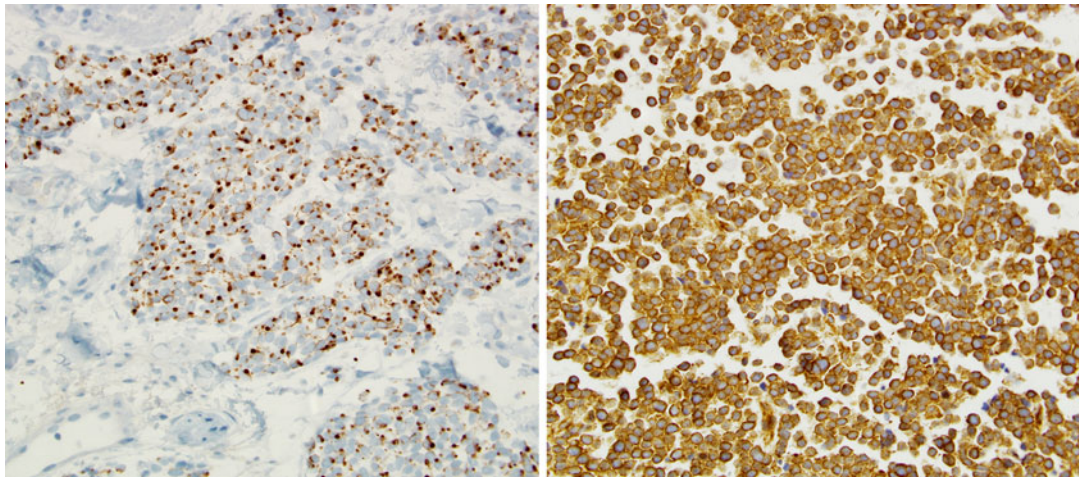

Fig. 18.12 Merkel cell carcinoma. Cytokeratin 20 staining in Merkel cell carcinoma classically highlights malignant cells in a perinuclear "dot-like" pattern (*left image*). Other times, cytokeratin 20 staining can be more diffuse throughout the cytoplasm (*right image*)

and Smoller 2010; Pulitzer et al. 2009; Smith and Patterson 2001). Moreover, lymphocytic aggregates may surround and/or infiltrate a focus of MCC, thereby further obscuring the diagnosis.

Immunohistochemistry

The use of immunohistochemistry can assist in distinguishing MCC from hematolymphoid malignancies and other small round blue cell tumors. Epithelial markers that are expressed in MCC include the low-molecular-weight cytokeratins CK8/CK18 (CAM 5.2), CK19, CK20, MNF116, and epithelial membrane antigen (EMA). The pattern of CK20 staining (often also mirrored in pancytokeratin stains) is particularly useful in identifying MCC. Thought to highlight the perinuclear intermediate filaments seen on electron microscopy, CK20 classically (but not always!) displays a perinuclear dot-like positivity in tumor cells (Fig. 18.12). Additionally, although a minority of MCC will express CK7, cytokeratins CK5/CK6 and CK17 are invariably negative. Neuroendocrine markers that are positive in MCC include neuron-specific enolase (NSE), CD56, synaptophysin, and chromogranin. Tumor cells may also show positivity for vasoactive intestinal peptide (VIP), calcitonin, and somatostatin (Smith and Patterson 2001). Importantly, unlike lymphoma tumor cells, MCC tumor cells do not express leukocyte common antigen (LCA/CD45). MCC is also negative for S100 protein, distinguishing it from melanoma, and while a subset may be positive for CK7, there should be absence of thyroid transcription factor (TTF)-1 expression, distinguishing MCC from metastatic small cell carcinoma of the lung. Interestingly, there are recent reports regarding a subset of MCCs that express terminal deoxynucleotidyl transferase (TdT), PAX5, and anaplastic lymphoma kinase (ALK), markers that have been traditionally described in lymphoblastic lymphomas. These findings potentially induce diagnostic confusion and add to the debate regarding the origin of MCC (Buresh et al. 2008; Filtenborg-Barnkob and Bzorek 2013; Kolhe et al. 2013; Zur Hausen et al. 2013). Moreover, owing to the expression of CD56 in both neuroendocrine tumors and natural killer (NK) cell lymphoma, one may be mistaken for the other, particularly in biopsies with prominent crush artifact or inflammation. CD56 appears to be expressed more strongly in MCC than in NK cell lymphoma, though this

finding is subjective and requires a reference threshold (McNiff et al. 2005). Other more reliable histologic features for distinguishing NK cell lymphoma from MCC include the lack of expression of epithelial markers with concurrent expression of CD2 and CD7 surface antigens, along with cytoplasmic – but not surface – CD3 expression. Reactive lymphocytes in MCC demonstrate a mixed phenotype, with both surface CD3- and CD20-positive cells identified. In addition, NK cell lymphomas will often display angiocentricity and angiodestruction, along with significant eccrine infiltration and/or destruction, features which are typically lacking in MCC (Ansai et al. 1997; McNiff et al. 2005).

Electron Microscopy

Ultrastructural studies reveal characteristic membrane-bound electron-dense core granules and perinuclear intermediate filament aggregates; however, the widespread availability of immunohistochemical staining generally supersedes the use of electron microscopy in aiding in the diagnosis of MCC (Pulitzer et al. 2009; Smith and Patterson 2001).

Molecular/Genetics

Multiple cytogenetic abnormalities have been identified in MCC, particularly within chromosomes 1, 11, and 13. These aberrations include gains and losses of genetic material, as well as chromosomal rearrangements. In fact, several mutations identified in MCC have also been detected in small cell carcinoma of the lung. This finding, along with the presence of multiple and diverse genetic abnormalities in MCC, currently does not support the use of cytogenetics studies as an ancillary diagnostic tool for MCC.

Prognosis/Course

A particularly aggressive tumor, MCC has a propensity for rapid enlargement, local recurrence, and early regional lymph node involvement, as well as distant metastatic potential (Goessling et al. 2002; Smith and Patterson 2001). The presence of nodal involvement at the time of presentation, along with immunocompromised status, correlates with poor clinical outcomes, including decreased survival rates and increased risk for the development of distant metastatic disease (Tarantola et al. 2013). Histologic prognostic indicators in MCC have been widely debated and remain somewhat controversial, although features such as size of the primary tumor, depth of tumor invasion, and degree of inflammation are thought to correlate with clinical outcome (Mott et al. 2004; Tarantola et al. 2013). The presence of bcl-2 expression in tumor cells is reported to convey a better clinical prognosis, while p63 expression in tumor cells is thought to correlate

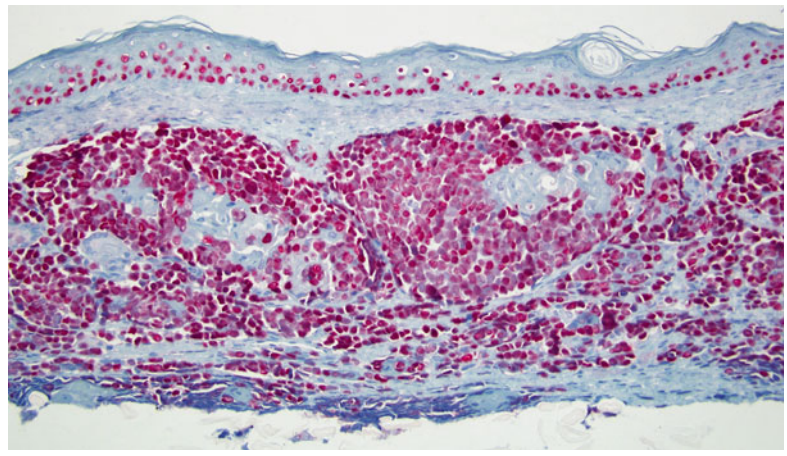

Fig. 18.13 Merkel cell carcinoma. P63 expression in Merkel cell carcinoma has been associated with a more aggressive clinical course and worse prognosis. This Merkel cell carcinoma shows diffuse nuclear immunoreactivity for p63

with adverse outcome (Fig. 18.13) (Hall et al. 2012; Sahi et al. 2012). Current treatment recommendations include wide local excision with sentinel lymph node biopsy, followed by adjuvant radiotherapy of the tumor bed and regional lymph nodes. Systemic chemotherapy is typically reserved for stage 4 metastatic disease, though its use is controversial in localized disease (NCCN 2013, Poulsen et al. 2006; Tai et al. 2000a, b).

Carcinomas

Primary and Metastatic Lymphoepithelioma-Like Carcinoma

Epidemiology

Cutaneous lymphoepithelioma-like carcinoma (LELC) is a remarkably rare dermal neoplasm. Lymphoepithelioma-like carcinoma is a histologically undifferentiated carcinoma that is not unique to the skin; in fact, LELC has been described in nearly every organ, particularly within the head and neck region. The World Health Organization's preferred terminology for tumors with this histologic appearance is "lymphoepithelial carcinoma" (Barnes et al. 2007); however to date, the majority of tumors originating in the skin have been reported in the literature as "lymphoepithelioma-like carcinoma." Unlike its extracutaneous counterparts and sinonasal lymphoepithelial carcinoma, however, lymphoepithelioma-like carcinoma of the skin has not shown an association with Epstein-Barr virus (EBV) (Arsenovic 2008; Carr et al. 1992; Gillum et al. 1996; Weiss et al. 1989) with the exception of one rare case (Aoki et al. 2010). Although its exact histogenesis remains unclear, the tumor is likely derived from epithelial or adnexal origin (Arsenovic 2008; Lopez et al. 2011; Wick et al. 1991).

Clinical Features

Clinically, LELC presents as a slow-growing, flesh-colored or red plaque or nodule arising on the head or neck of middle-aged to elderly patients; there is no gender predilection. It may be clinically mistaken for a basal cell carcinoma or Merkel cell carcinoma, and, in some cases with epidermal ulceration, it has been mistaken for squamous cell carcinoma (Lopez et al. 2011).

Histology

Histologically, LELC is composed of large, cohesive, epithelioid cells arranged singly or in well-delineated dermal lobules or small nests and surrounded and infiltrated by a mixed population of reactive T and B lymphocytes (Fig. 18.14). The neoplastic cells contain large nuclei with a vesicular chromatin pattern and prominent nucleoli; mitotic activity may be abundant (Fig. 18.15). In cases with a florid lymphocytic infiltrate, the epithelioid component of the tumor may become obscured, making diagnosis particularly more challenging. They key to diagnosis is, therefore, to recognize the neoplastic cells amidst the associated inflammatory infiltrate and to correctly identify them as epithelial in origin (Fig. 18.16).

Immunohistochemistry

Epithelial markers, including cytokeratins, p63, and epithelial membrane antigen (EMA), will highlight inconspicuous epithelioid tumor cells (Fig. 18.17). Primary LELC can be differentiated from metastatic lymphoepithelial carcinoma from other organs by the absence of detection of EBV by either in situ hybridization studies (EBV-encoded RNA, or EBER) or polymerase chain reaction (PCR) on fixed tissues (Gillum et al. 1996). Furthermore, the absence of a separate primary tumor following thorough clinical examination negates the possibility of metastasis.

Differential Diagnosis

Within the differential diagnosis of LELC are squamous cell carcinoma with florid lymphocytic reactivity, Merkel cell carcinoma, poorly differentiated melanoma, and cutaneous lymphoma. Squamous cell carcinoma with reactive lymphocytic infiltrate often reveals a connection to the epidermal surface, and/or epidermal dysplasia. LELC lacks the characteristic CK20 staining pattern and neuroendocrine differentiation of Merkel cell carcinoma, and LELC is negative for melanocytic markers, distinguishing this entity from melanoma. To differentiate LELC from lymphoid malignancies, the polyclonal nature of the

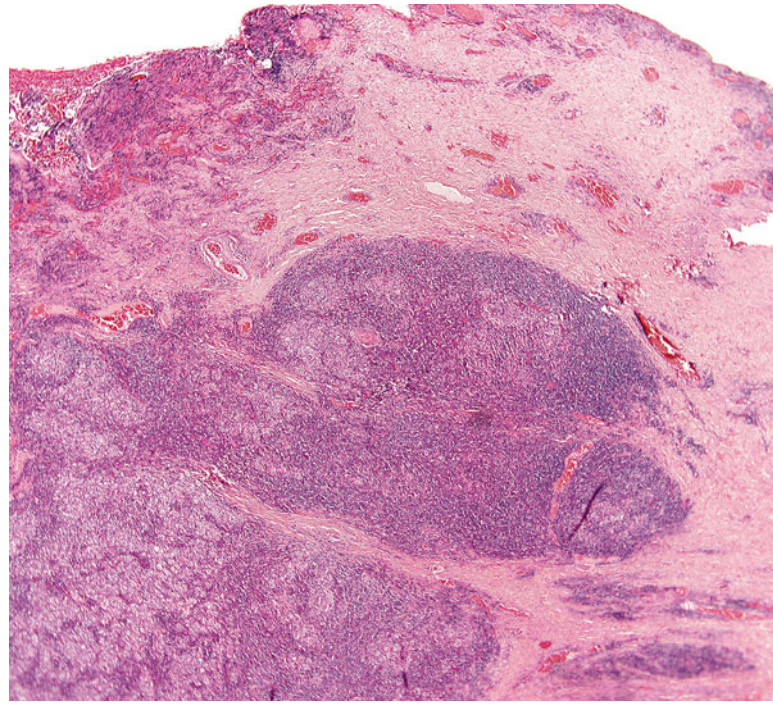

Fig. 18.14
Lymphoepithelioma-like carcinoma. On low-power examination, dermal lobules of tumor cells are obscured by a dense lymphocytic infiltrate, almost simulating the formation of lymphoid follicles

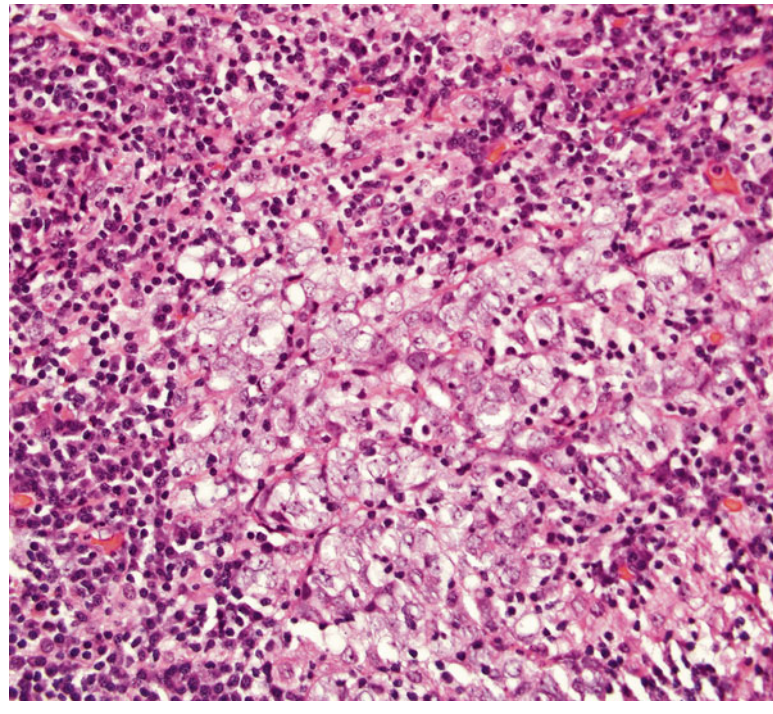

Fig. 18.15
Lymphoepithelioma-like carcinoma. On high power, large epithelioid tumor cells with abundant cytoplasm, vesicular nuclei, and prominent nuclei are appreciated within the background of small round lymphocytes and plasma cells

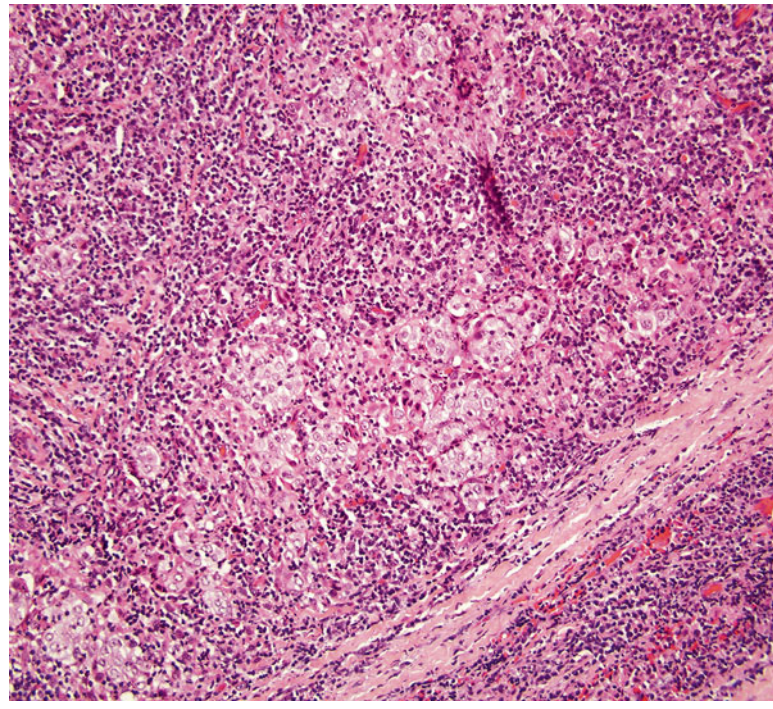

Fig. 18.16
Lymphoepithelioma-like carcinoma. Focal nesting of the neoplastic cells provides a clue to the epithelial nature of their origin

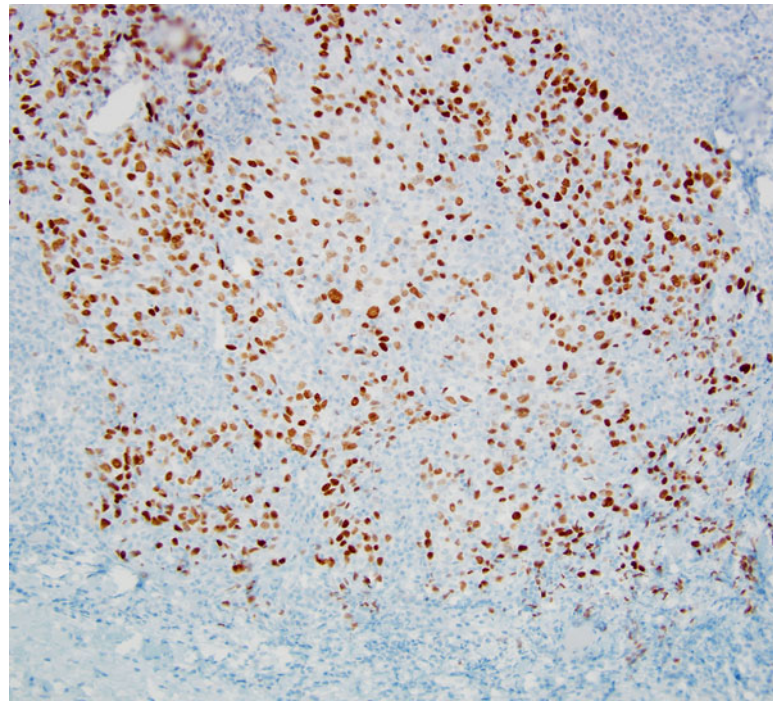

Fig. 18.17
Lymphoepithelioma-like carcinoma. Immunohistochemical staining of the tumor reveals strong diffuse nuclear p63 immunoreactivity in the neoplastic cells. Pancytokeratin stain (not shown) was also positive in the tumor cells

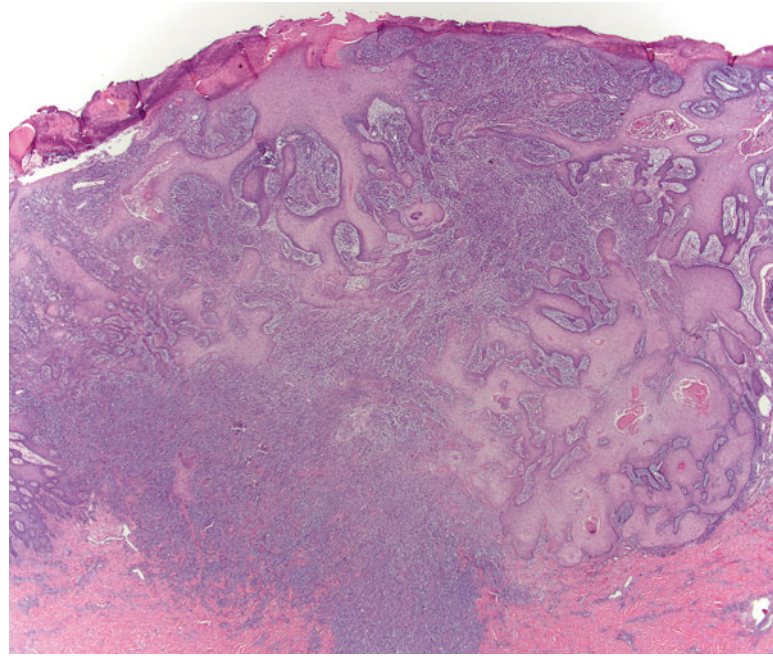

Fig. 18.18 Cutaneous anaplastic large cell lymphoma with pseudoepitheliomatous hyperplasia. On occasion, epithelial changes can overshadow the atypical dermal infiltrate and be mistaken for a squamous cell carcinoma (Slide for photography provided by Dr. Richard Cheney, Roswell Park Hospital, Buffalo, NY)

lymphocytic infiltrate can be confirmed by demonstrating a mixed population of CD20- and CD3-positive lymphocytes with mixed kappa and lambda light chain expression of B cells. Any gene rearrangement studies would also be expected to be negative.

As a side remark regarding the capacity of carcinomas and lymphoma to mimic one another, it should also be noted that pseudoepitheliomatous hyperplasia (epidermal hyperplasia resembling squamous cell carcinoma) has been reported overlying cases of cutaneous anaplastic large cell lymphoma (Biswas et al. 2008). Pseudoepitheliomatous hyperplasia is not associated with LELC; however, the presence of florid pseudoepitheliomatous hyperplasia combined with atypical epithelioid cells in the dermis and an inflammatory infiltrate can easily be misinterpreted as an invasive, poorly differentiated squamous cell carcinoma (Figs. 18.18 and 18.19). Alternatively, lesional cells may be completely overlooked as they are overshadowed by the epidermal proliferation (Biswas et al. 2008). In such cases, dermal epithelioid cells can be evaluated for pancytokeratin and/or p63 (positive in carcinoma) and CD30 expression (positive in at least 75 % of cells in a membranous and perinuclear pattern in cALCL) to determine the cellular lineage. Conversely, poorly differentiated squamous cell carcinoma consisting of pleomorphic, discohesive dermal cells without obvious epidermal connection or clear keratinocytic atypia may simulate cALCL (Figs. 18.20 and 18.21). Once again, immunohistochemistry easily distinguishes these two entities.

Molecular/Genetics

Routine use of molecular testing is not necessary in cases of LELC. For cases in which lymphoma is considered within the differential diagnosis, T-cell or B-cell clonality studies for gene rearrangement will be negative.

Prognosis/Course

Cutaneous LELC has a tendency for local recurrence when not completely excised (Hall et al. 2006; Lopez et al. 2011). While not often widely metastatic, some case reports document regional lymph node involvement and perineural invasion (Hall et al. 2006; Robins and Perez 1995). Only one death has been reported, which occurred

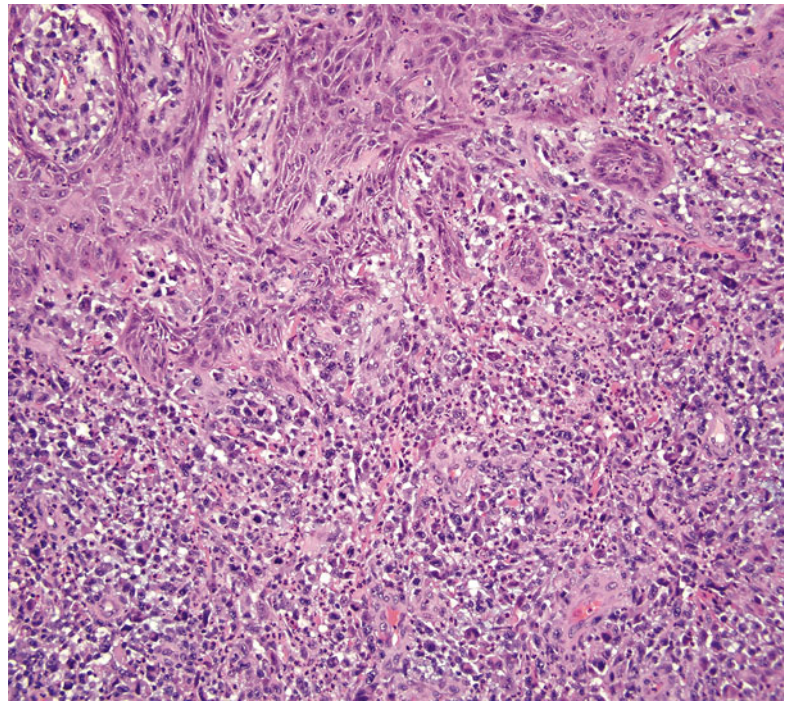

Fig. 18.19 Cutaneous anaplastic large cell lymphoma with pseudoepitheliomatous hyperplasia. On higher power, pleomorphic, atypical cells are seen within the dermis. The tumor cells expressed CD30 and were negative for pancytokeratin (Slide for photography provided by Dr. Richard Cheney, Roswell Park Hospital, Buffalo, NY)

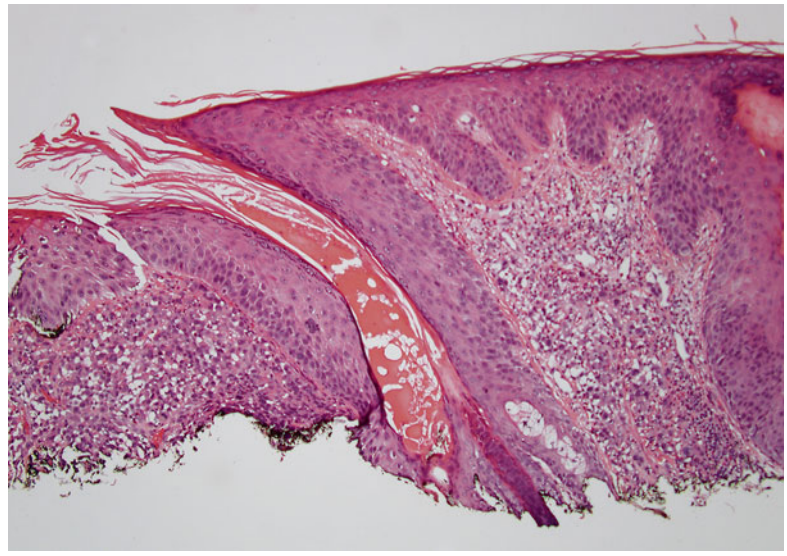

Fig. 18.20 Poorly differentiated squamous cell carcinoma. This case shows a dermal infiltrate of singly dispersed, pleomorphic cells without connection to the overlying epidermis. There is an associated inflammatory infiltrate including eosinophils. Basilar squamous atypia gives a clue to the epithelial nature of the dermal cells

57 months following diagnosis (Swanson et al. 1988). Current treatment strategies include wide local excision or Mohs micrographic surgery (Jimenez et al. 1995; Lopez et al. 2011; Robins and Perez 1995).

Metastatic Carcinoma

Epidemiology

Overall, the skin is an uncommon site for visceral carcinomatous metastasis. When cutaneous

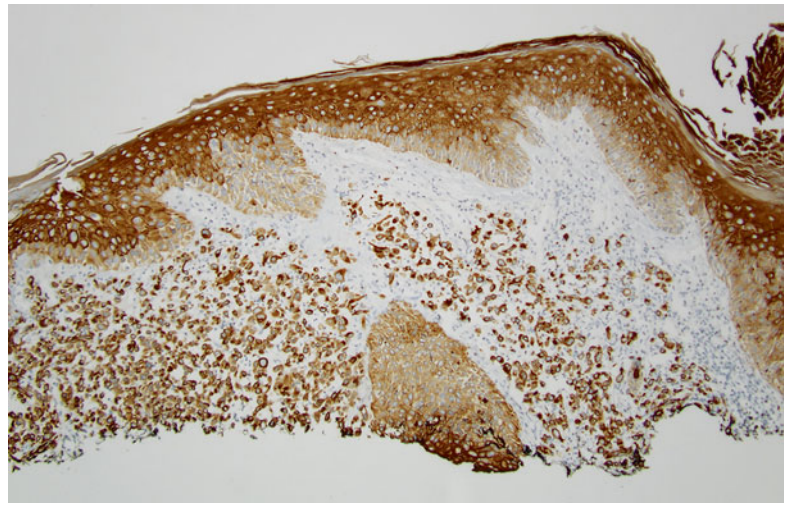

Fig. 18.21 Poorly differentiated squamous cell carcinoma. Pancytokeratin highlights the individual tumor cells in the dermis

metastasis does occur, it is secondary to hematogenous or lymphatic spread from the primary site, direct extension by an underlying tumor, or iatrogenic deposition following a surgical procedure. A seminal study in the 1970s determined that cutaneous metastases most commonly originated from the lung and colon in males and from the breast, colon, and ovary in females (Brownstein and Helwig 1972). More recent studies have reaffirmed that lung carcinoma remains overall the most common source of cutaneous metastatic carcinoma (Rosen 1980; Saeed et al. 2004). Rarely, a cutaneous metastasis may be the presenting sign of malignancy, with lung, kidney, and ovarian carcinomas being the most commonly reported (Brownstein and Helwig 1972).

Clinical Features

Cutaneous carcinomat metastases typically present as painless, firm, flesh-colored to pink papules or nodules. Lesions may be solitary or multiple and may mimic benign dermal-based skin lesions. Heavily vascularized tumors, such as renal cell carcinoma, may masquerade as vascular tumors clinically. Anatomic location is an important clue to the origin of the neoplasm, as tumors tend to metastasize in the vicinity of the primary tumor. For example, breast and lung cancers have a propensity to metastasize to the chest wall, while cancers of the colon, ovary, kidney, and bladder often metastasize to the abdomen (Gul et al. 2007).

Histology and Immunohistochemistry

Clinical correlation with a history of malignancy is essential in the evaluation of skin metastases. Often the morphology of the cutaneous metastasis will correspond to the morphology of the primary tumor, and, therefore, review of the original case is elemental to the metastatic work-up. For instance, the presence of glandular structures points to an adenocarcinoma (Fig. 18.22). Particular variants of metastatic carcinoma may impart a histologic appearance that mimic lymphomatoid or leukemic infiltrates; these are given specific mention with their immunophenotypes below.

In general, identifying carcinoma in the dermis in the absence of a clinical history of malignancy requires a panel of immunohistochemical stains for accurate diagnosis. Some authors cite CK7 and CK20 as the most helpful initial screening immunostains (Chu et al. 2000). In another study of 44 cases of skin metastases from unknown origin, CK20, estrogen receptor (ER), and progesterone receptor (PR) were found to be the useful first-line markers in determining primary tumor site by identifying tumors of colorectal and breast origin, respectively (Azoulay et al. 2005).

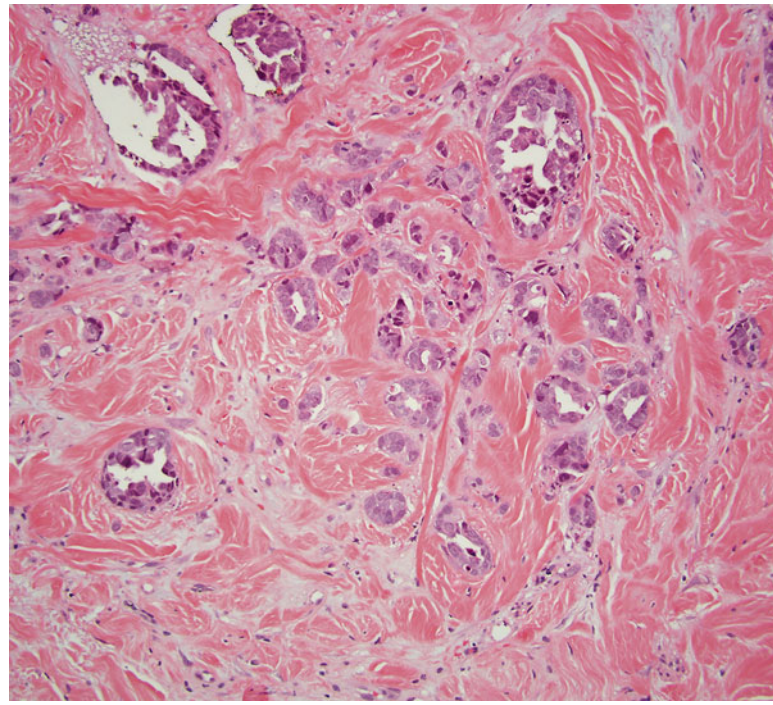

Fig. 18.22 Metastatic adenocarcinoma. Irregularly shaped glands, some with central necrosis, are deposited in the dermis. In this case, the primary tumor was from the breast

Table 18.2 Immunohistochemical profile of metastatic carcinoma

	CK7	CK20	TTF-1	CDX2	GCDFP15	ER/PR	PAX8
Breast	+	–	–	–	+	+	–
Lung (adenocarcinoma)	++	–/+	+	–	–	–	–
Lung (small cell carcinoma)	+/–	–	+	–	–	+/–	–
Colorectal	–/+	++	–	++	N/A	–	–
Renal	–/+[a]	–	–	–	N/A	–	++
Ovarian	++	+/–	–	–	–	–	++

Note: Exceptions for staining patterns in each of these entities do exist, and this table represents the most commonly observed patterns of staining (Chu et al. 2000; Jagirdar 2008; Nonaka et al. 2008; Park et al. 2007; Saad et al. 2011; Saeed et al. 2004)

++ (almost always positive), + (usually positive), +/– (often positive), –/+ (usually negative)

CK cytokeratin, *TTF* thyroid transcription factor, *GCDFP* gross cystic disease fluid protein, *ER* estrogen receptor, *PR* progesterone receptor, *PAX8* paired box gene 8

[a]CK7 positivity depends on subtype (clear cell RCC is classically CK7 negative; papillary, chromophobe, and collecting duct RCCs are typically CK7 positive)

The addition of S100 can detect melanoma as well (Saeed et al. 2004). Supplementary immunohistochemical stains that are valuable in the investigation of metastatic cutaneous carcinomas are summarized in Table 18.2. This table may be used as a guide; however, as can be expected, many exceptions for staining patterns in each of these entities do exist.

Metastatic Breast Carcinoma

Tumors originating from the breast may metastasize with many different patterns, several of which may be confused with hematolymphoid infiltrates. An undifferentiated, sheetlike pattern is not uncommon (Weedon 2010) and may be readily confused with cutaneous lymphoma.

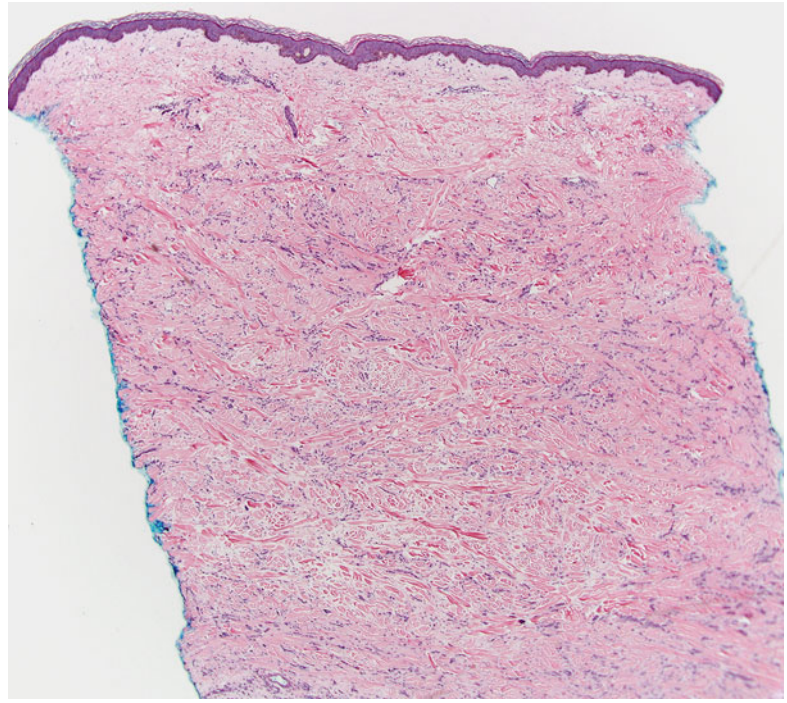

Fig. 18.23 Metastatic breast cancer. Metastatic breast cancer cells are seen throughout the dermis, dispersed in a single-file pattern. Leukemia cutis can also infiltrate through the dermis in this pattern

Moreover, metastatic breast carcinoma (particularly of the lobular variant) classically infiltrates in a linear pattern through sclerotic collagen bundles in the dermis (Fig. 18.23). This pattern of infiltration can be similar to the pattern of leukemia cutis, whereby immature myeloid cells infiltrate the skin as sheets, cords, or linear arrays. Additionally, both entities tend to display a Grenz zone, an area of the papillary dermis that is spared from tumor involvement. The presence of intracytoplasmic vacuoles, glandular formation, and lymphatic permeation are helpful clues to the diagnosis of mammary adenocarcinoma (Fig. 18.24), while perivascular and periappendageal "layering" of cells favors a leukemic infiltrate (Weedon 2010). On occasion, metastatic breast cancer may permeate the dermis as individual single cells and may be mistaken for a (nonneoplastic) inflammatory infiltrate (Weedon 2010). Primary lymphoma of the breast, a rare entity, has been described as presenting clinically as inflammatory breast carcinoma, an entity constituting 0.04–0.5 % of breast neoplasms and characterized by plugging of dermal lymphatics by a poorly differentiated ductal carcinoma with an associated mixed population of inflammatory cells (Anne and Pallapothu 2011).

Differentiating metastatic breast carcinoma from leukemia cutis often necessitates the use of immunohistochemistry. Cytokeratin 7 is expressed by breast metastases in the majority (approximately 2/3) of cases, while estrogen and progesterone receptor positivity, although less sensitive, offer greater specificity to the diagnosis (Azoulay et al. 2005). Gross cystic disease fluid protein-15 (GCDFP15) and mammaglobin are also potential markers of metastatic breast carcinoma, the former of which demonstrates greater specificity and the latter of which confers greater sensitivity (Ormsby et al. 1995). Because the breast is a modified apocrine gland, it is no surprise that primary adnexal neoplasms of the skin and benign adnexal glands also stain with the markers mentioned above, so caution is necessary if such neoplasms are also within the differential diagnosis (Wallace et al. 1995). Additionally, GATA3 is a new and potentially useful marker for metastatic breast carcinoma

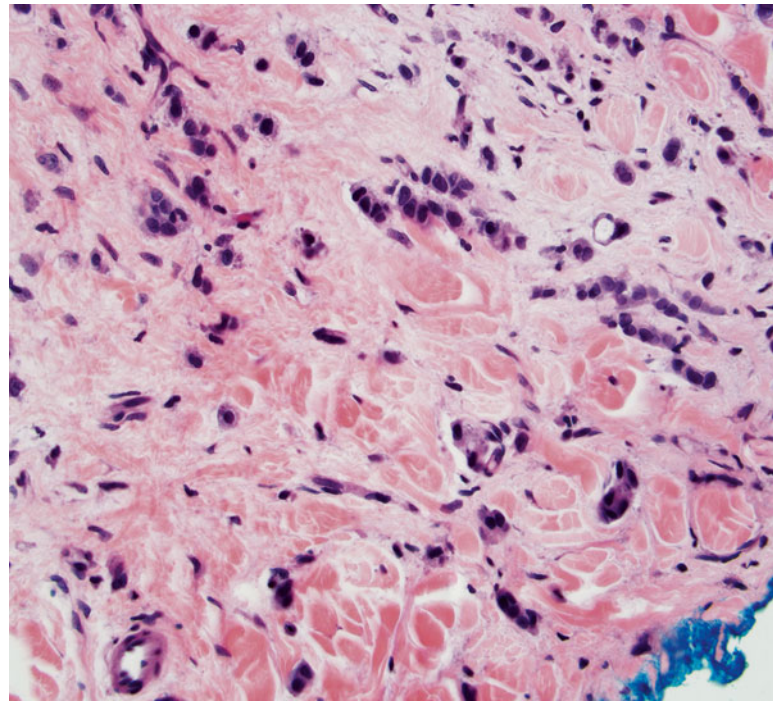

Fig. 18.24 Metastatic breast cancer. On higher power examination, the tumor cells are hyperchromatic, atypical, and relatively cohesive. There is focal abortive glandular formation and rare intracytoplasmic vacuoles

(Cimino-Mathews et al. 2013). The immunophenotype of leukemia cutis varies depending on the degree of cytologic differentiation and cytogenetic abnormalities; CD68 and lysozyme are reported to have the highest sensitivity in the detection of myeloid leukemia cutis, regardless of subtype. Myeloperoxidase is also frequently useful but is less commonly positive in cases of leukemia cutis with monocytic differentiation, which is the most common subtype leukemia involving the skin (Cibull et al. 2008). B- and T-cell specific markers will be useful in confirming a diagnosis of primary breast lymphoma.

Metastatic Small Cell Lung Cancer

Small cell lung cancer is a neuroendocrine carcinoma that only rarely metastasizes to cutaneous sites (Marcoval et al. 2012; Terashima and Kanazawa 1994). Given its neuroendocrine differentiation, it shares histologic similarity to the previously discussed Merkel cell carcinoma. Architecturally, tumor cells invade the dermis in trabeculae, sheets, or ribbons or as single, diffusely scattered cells (Fig. 18.25). Features typical of neuroendocrine tumors include molding and pseudorosette formation, both of which may hint at the epithelial derivation of the tumor. Tumor nuclei display a vesicular, finely dispersed chromatin pattern, and nucleoli are inconspicuous (Fig. 18.26). As in MCC and aggressive hematolymphoid infiltrates, apoptotic debris, crush artifact, and brisk mitotic activity are often plentiful in small cell carcinoma.

The classic immunophenotype of small cell lung carcinoma is CK7 positive, CK20 negative, and TTF-1 positive (Figs. 18.27 and 18.28). In contrast, although a minority of MCC expresses CK7, MCC is invariably negative for TTF-1 and usually positive for CK20. Similar to MCC, small cell carcinoma can express neuroendocrine markers including synaptophysin, chromogranin, neuron-specific enolase, and CD56. Furthermore, as in MCC, expression of TdT in a subset of small cell lung carcinomas has been identified, leading to a potential for diagnostic confusion with lymphoblastic lymphoma (Kolhe et al. 2013). CD45/LCA is uniformly negative in these tumors, however, and represents a sensitive

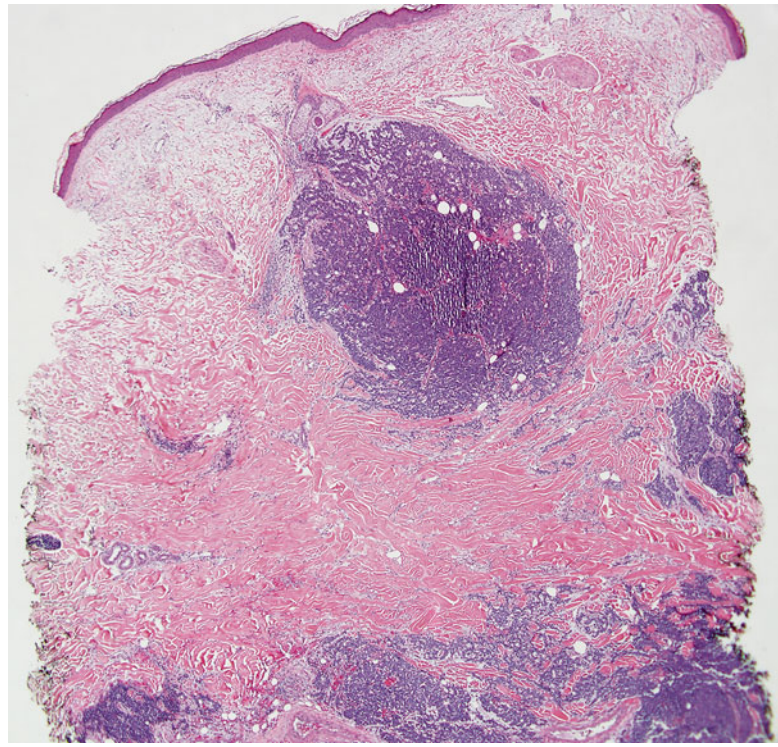

Fig. 18.25 Metastatic small cell lung carcinoma. Nodular deposits of blue tumor cells with a nested to sheetlike pattern is present in the dermis

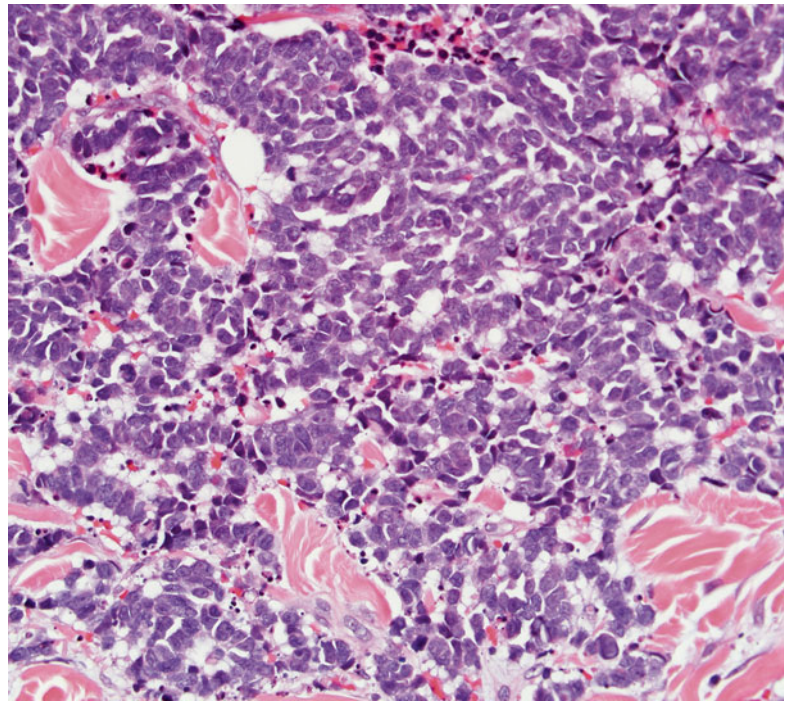

Fig. 18.26 Metastatic small cell lung carcinoma. The tumor cells demonstrate a high nuclear to cytoplasmic ratio and molding. The cells show scant eosinophilic cytoplasm, neuroendocrine-type chromatin, and readily identifiable mitotic figures

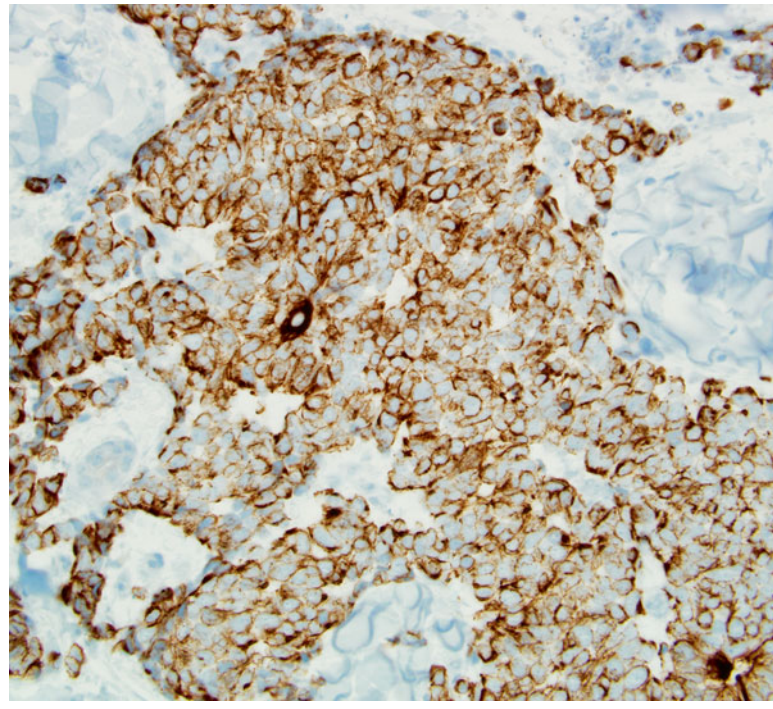

Fig. 18.27 Metastatic small cell lung carcinoma. In metastatic small cell lung carcinoma, tumor cells express cytokeratin 7

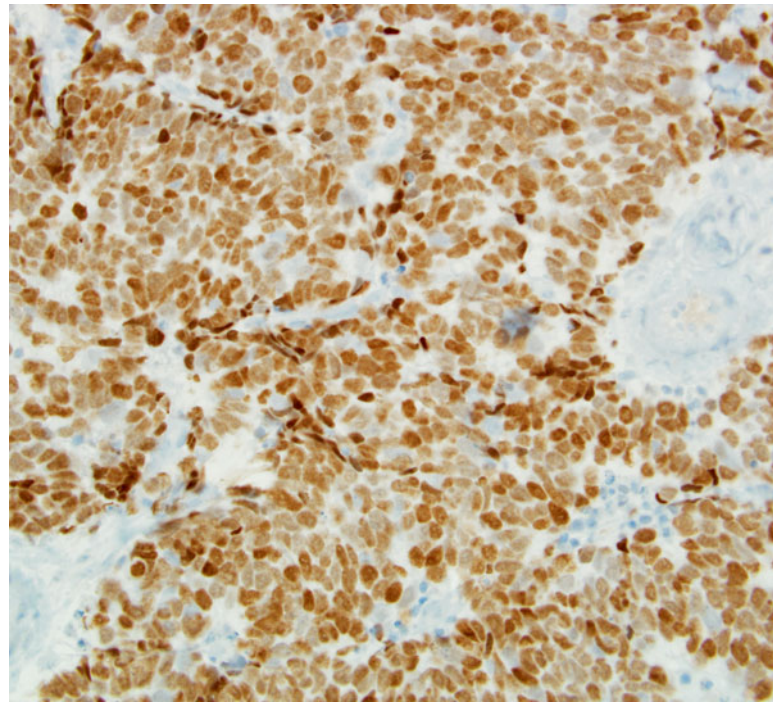

Fig. 18.28 Metastatic small cell lung carcinoma. In metastatic small cell lung carcinoma, tumor cells show nuclear immunoreactivity for thyroid transcription factor-1

stain to distinguish small cell carcinoma from a malignant lymphoid infiltrate.

Molecular/Genetics

Molecular and genetic studies are typically not useful in the evaluation of cutaneous metastases.

Prognosis/Course

Cutaneous metastases typically arise late in disease progression and signify advanced disease with a poor outcome. Survival following the detection of cutaneous carcinoma metastases has been estimated between 5 and 7.5 months (Saeed et al. 2004; Sariya et al. 2007). Metastatic disease can be treated with a combination of surgery, radiation, and/or chemotherapy.

Sarcomas/Other

Like Merkel cell carcinoma and the variants of melanoma and carcinomas described above, some sarcomas and other malignancies can occasionally be mistaken for hematolymphoid neoplasms. Most of these tumor types include those that fall within the "small round blue cell" differential. They may arise either as primary dermal neoplasms or as metastases from non-cutaneous sites. Key histologic and clinical features, as well as immunohistochemical profiles, are useful in distinguishing these entities from cutaneous lymphoma or leukemia.

Primary Cutaneous Ewing Sarcoma/ PNET

Epidemiology

Primary Ewing sarcoma (EWS) of the skin is a remarkably rare neoplasm that was first described in 1975 by Angervall and Enzinger (1975). Like conventional Ewing sarcoma, cutaneous Ewing sarcoma most often affects teenagers and young adults (Boland and Folpe 2013). Whereas mesenchymal Ewing sarcomas display a clear male predominance, the cutaneous variant is identified twice as frequently in women than in men (Ehrig et al. 2007).

Clinical Features

Primary cutaneous EWS often presents as a painless superficial nodule. It is most frequently encountered on the extremities, followed by the trunk and the head and neck (Boland and Folpe 2013; Collier et al. 2011). Cutaneous metastases from deep-seated Ewing sarcoma are rare but have been described (Izquierdo et al. 2002).

Histology, Immunohistochemistry, and Differential Diagnosis

Histologically, the features of cutaneous Ewing sarcoma are identical to its skeletal and deep soft tissue equivalents. The tumors are composed of dense sheets or nests of monomorphic cells containing scant clear to eosinophilic cytoplasm and round nuclei with fine, open chromatin (Fig. 18.29) (Hasegawa et al. 1998). There may be hemorrhagic or necrotic foci within the tumor, and mitotic figures are often easily identified (Collier et al. 2011, Hasegawa et al. 1998). The strong membranous expression of CD99 (MIC2) that is characteristic of extracutaneous Ewing sarcoma is also present in cutaneous EWS tumor cells (Hasegawa et al. 1998; Terrier-Lacombe et al. 2009). A pitfall of CD99, however, is that its expression is not entirely specific for Ewing sarcoma; not only may it be present in other non-Ewing sarcomas, but it is invariably and diffusely expressed in lymphoblastic lymphomas. To further complicate the diagnosis, lymphoblastic lymphomas are frequently negative for CD45, and sometimes negative for CD10, CD20, and CD3 (Boland and Folpe 2013; Hsiao and Su 2003). In these cases, the presence of terminal deoxynucleotidyl transferase (TdT) and CD43 expression may be the most useful antibodies to correctly identify lymphoblastic lymphoma and to distinguish it from other CD99-positive entities (Hsiao and Su 2003). Approximately 25 % of cutaneous EWS demonstrate positivity for the low-molecular-weight cytokeratins (Boland and Folpe 2013).

Molecular/Genetics

Like its deep-seated counterparts, cutaneous EWS derives from a chimeric fusion of the *EWSR1* gene located on chromosome 22q12

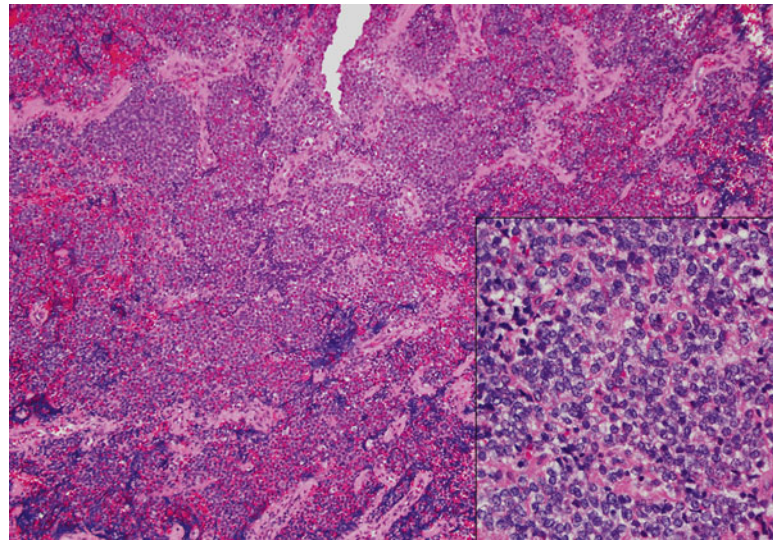

Fig. 18.29 Ewing sarcoma. On scanning magnification, the tumor is composed of sheets and nests of small round blue cells. On higher power, the tumor cells are monomorphic, with round nuclei and open chromatin (*inset*)

with a member of the E 26 (ETS) family of transcription factors that include *FLI-1* (chromosome 11q24), *ERG* (chromosome 21q22), *ETV1* (chromosome 7p22), *ETV4* (chromosome 17q21), and *FEV* (chromosome 2q36) (Boland and Folpe 2013; Terrier-Lacombe et al. 2009). Immunohistochemical stains for FLI-1 and ERG are commercially available and may be useful in the microscopic work-up of this tumor (Folpe et al. 2000). Additionally, the fusion gene transcripts can be demonstrated via tumor cytogenetics, fluorescence in situ hybridization (FISH), or reverse transcriptase-polymerase chain reaction (RT-PCR). The advantage of performing FISH using break-apart EWSR1 probes is that it is easily carried out on archival, paraffin-embedded tissues and is sensitive, although not specific, in detecting any EWSR1 rearrangement. RT-PCR is particularly helpful in distinguishing cutaneous EWS from other sarcomas that also demonstrate EWSR1 translocations, including clear cell sarcoma, myoepithelioma, and angiomatoid fibrous histiocytoma. Currently, however, RT-PCR can only detect the EWSR1-FLI-1 and EWSR1-ERG fusion products (Boland and Folpe 2013).

Prognosis/Course

Cutaneous EWS carries a better overall prognosis when compared to its osseous and soft tissue counterparts, with less likelihood to locally recur or metastasize. It is therefore thought to represent a more favorable subtype of Ewing sarcoma (Boland and Folpe 2013; Collier et al. 2011; Delaplace et al. 2012; Ehrig et al. 2007; Hasegawa et al. 1998; Terrier-Lacombe et al. 2009).

Cutaneous Rhabdomyosarcoma

Epidemiology

Rhabdomyosarcoma (RMS) is a malignant small round blue cell tumor with skeletal muscle differentiation and is the most common soft tissue tumor of childhood. While the majority of RMS found in the skin represents metastatic deposits or dermal extension of tumors arising from the deep soft tissues, primary cutaneous RMS has been documented, with the largest series in the literature comprising 11 cases (Brecher et al. 2003; Cobanoglu et al. 2009; Lima et al. 2011; Marburger et al. 2012; Scatena et al. 2012). Both primary and metastatic RMS of the skin demonstrate a bimodal age distribution, and gender predilection is controversial (Marburger et al. 2012; Scatena et al. 2012).

Clinical Features

Three unique subtypes of rhabdomyosarcoma exist: alveolar RMS, embryonal RMS (further divided into botryoid and spindle cell subtypes),

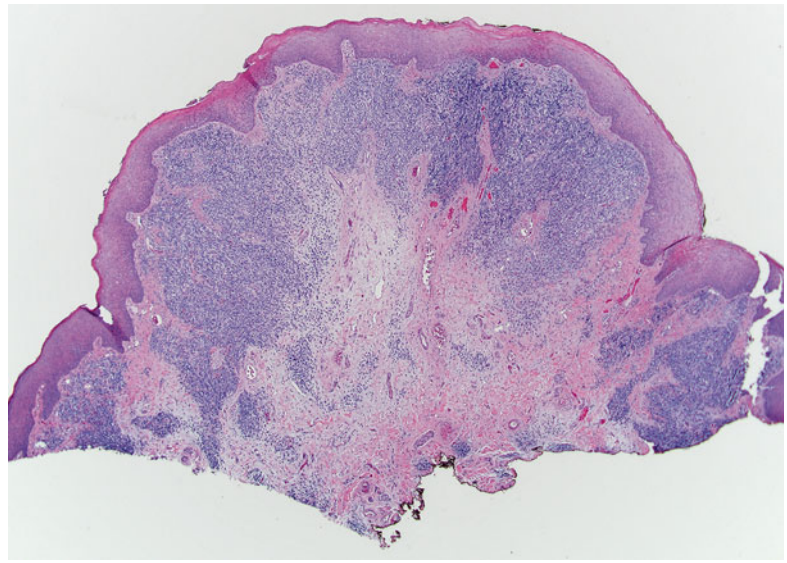

Fig. 18.30 Cutaneous rhabdomyosarcoma. Sheets of monomorphic blue cells fill the dermis. This was classified as alveolar type and may be the most common type to see in the skin

and pleomorphic RMS. With regard to extracutaneous disease, alveolar and embryonal rhabdomyosarcoma subtypes predominate in the pediatric population, the former of which has a proclivity for the extremities and the latter of which involves either the head and neck region or the genitourinary organs. The pleomorphic type arises almost exclusively in adults, which, like alveolar RMS, has a predilection for the extremities. Overall, embryonal RMS is the most common extracutaneous subtype, but alveolar RMS may be the most common subtype to arise in the skin (Setterfield et al. 2002). Primary cutaneous RMS appears to parallel the clinical patterns of its deep-seated counterpart, with alveolar and embryonal RMS being observed in the younger population and pleomorphic RMS occurring in older adults (Marburger et al. 2012). Neonatal alveolar RMS with cutaneous metastases has been reported in association with Beckwith-Wiedemann syndrome (Kuroiwa et al. 2009).

Histology

Histologically, RMS varies broadly in architectural and cytologic appearance depending on the subtype. Alveolar rhabdomyosarcomas are composed of classic small round blue cells with scant cytoplasm and monotonous, hyperchromatic, round to ovoid nuclei (Fig. 18.30). The tumor cells are aggregated between dense fibrous septa with fibrovascular cores. They often become discohesive, creating central, acellular spaces and resembling pulmonary alveoli (Fig. 18.31). The solid variant of alveolar rhabdomyosarcoma poses a particular challenge, as this variant lacks the characteristic fibrous septa and cellular discohesion seen in conventional alveolar RMS and may be confused with cutaneous lymphoma (Fig. 18.32) (Marburger et al. 2012). The tumor cells of embryonal RMS display varying degrees of myogenic differentiation, ranging from small round blue cells like those seen in alveolar RMS to more differentiated "strap cells," which are larger and oblong in shape and contain brightly eosinophilic cytoplasm. Striations, when present, are helpful clues to the diagnosis. Architecturally, embryonal-type RMS is composed of hypercellular areas alternating with hypocellular, myxoid areas (Cobanoglu et al. 2009). Pleomorphic rhabdomyosarcoma, in contrast to the other two subtypes, is composed of cells with varying morphologies, overall with more prominent cytoplasm, eccentrically placed nuclei, and large, conspicuous nucleoli (Fig. 18.33) (Marburger et al. 2012). Given the

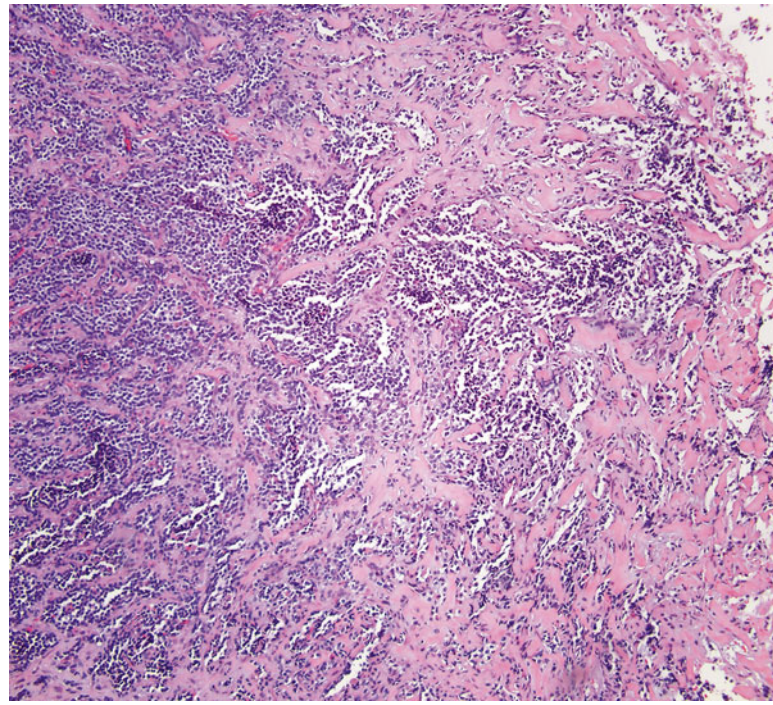

Fig. 18.31
Rhabdomyosarcoma, alveolar pattern. This example of alveolar rhabdomyosarcoma demonstrates hyperchromatic tumor cells cling to vascular cores, resulting in central discohesion and resembling pulmonary alveoli

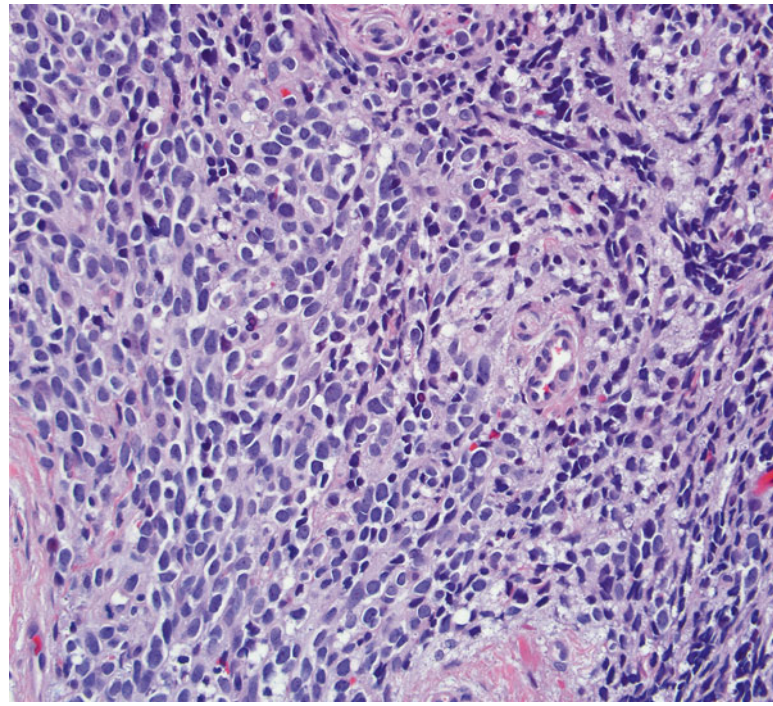

Fig. 18.32
Rhabdomyosarcoma, alveolar type with solid pattern. The tumor cells are enlarged and hyperchromatic and show brisk mitotic activity but lack clear differentiation

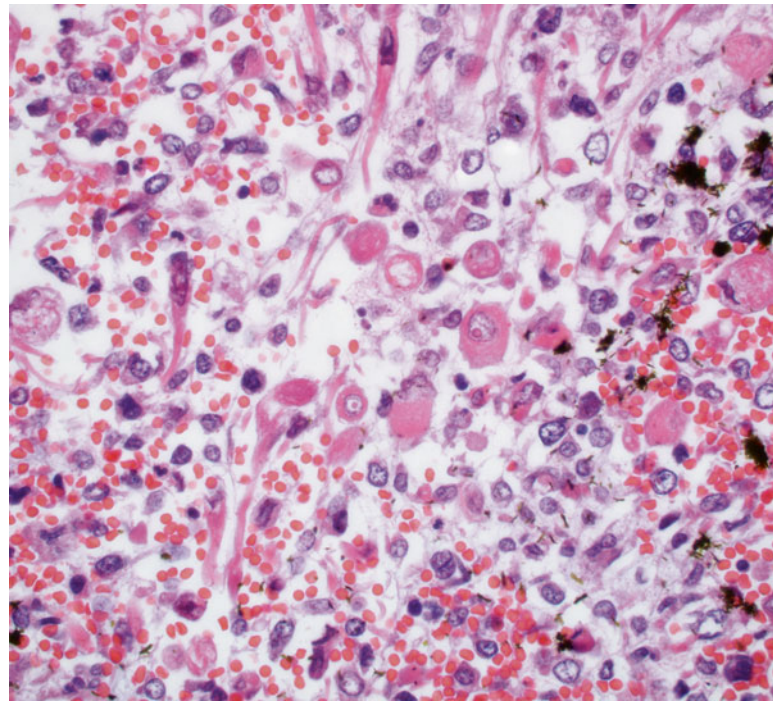

Fig. 18.33 Rhabdomyosarcoma, pleomorphic type with striations. The tumor cells are large and atypical, containing abundant eosinophilic cytoplasm and displaying prominent eosinophilic nucleoli. These large cells are admixed with small, primitive cells and spindle cells

eccentrically located nuclei, the pleomorphic type may be mistaken for plasma cell myeloma or plasmacytoma.

Immunohistochemistry and Differential Diagnosis

Regardless of subtype, rhabdomyosarcoma tumor cells express markers of skeletal muscle differentiation. These markers include desmin, muscle-specific actin (MSA), myogenin, and MYOD1. Marburger and colleagues recommend employing a battery of stains, including desmin, myogenin, and MYOD1, in the work-up of RMS, as single cases may lack expression of one or more markers (Marburger et al. 2012). Myogenin and MYOD1 are nuclear stains, and it should be remembered that even patchy focal nuclear staining (a pattern frequently observed in embryonal-type RMS) should still be interpreted as positive staining (Fig. 18.34). It is not uncommon to observe anomalous expression of cytokeratin, CD56, and NSE in RMS (Marburger et al. 2012; Scatena et al. 2012; Setterfield et al. 2002). Furthermore, anaplastic lymphoma kinase (ALK) positivity has been observed in rhabdomyosarcoma, particularly in the alveolar subtype, although it is reported to occur in an unusual, dot-like cytoplasmic pattern (Corao et al. 2009). The pattern of ALK staining and CD30 negativity are important in distinguishing RMS from anaplastic large cell lymphoma.

Molecular/Genetics

The translocations t(2;13)(q35;q14) and t(1;13)(p36;q14) are characteristic of conventional alveolar RMS, resulting in the fusion of transcription factors PAX3 or PAX7, respectively, to the transcription factor FOX01 (also known as FKHR). These fusion gene products have been detected in some cases of primary cutaneous alveolar RMS (Nakagawa et al. 2008; Setterfield et al. 2002). Interestingly, however, these translocations are absent in many cases of neonatal alveolar RMS with metastasis to the skin. Therefore, clinical and histologic features must be considered in adjunct to molecular profiles in neonates when cutaneous metastases of RMS are suspected (Kuroiwa et al. 2009; Marburger et al. 2012).

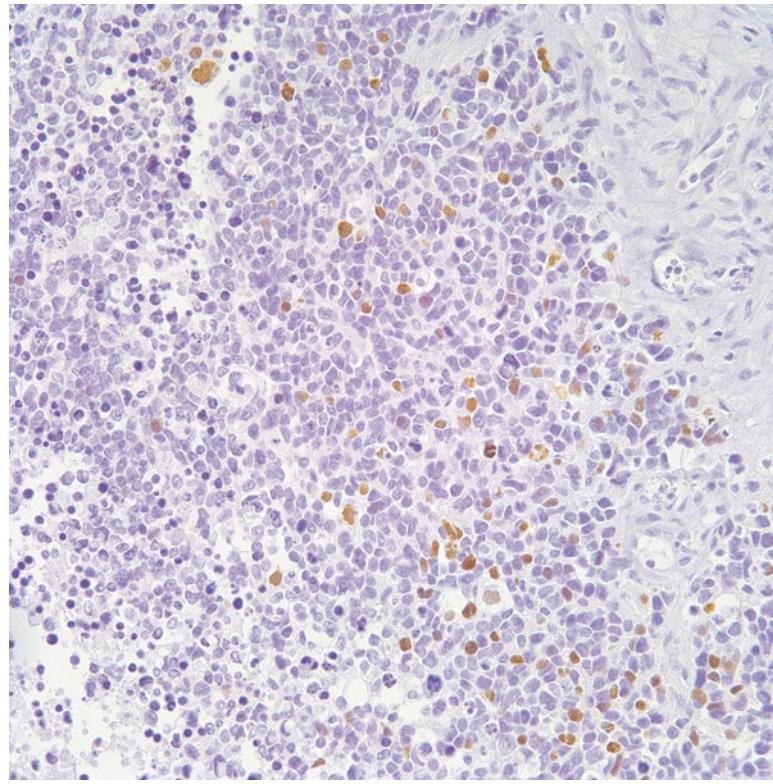

Fig. 18.34
Rhabdomyosarcoma. Nuclear myogenin immunoreactivity, even when patchy as in this embryonal type, secures the diagnosis (Photograph courtesy of Dr. Jerad Gardner, University of Arkansas for Medical Sciences, Little Rock, AR)

Prognosis/Course

Unlike the more favorable outcomes observed when some other soft tissue tumors present as primary cutaneous neoplasms, the prognosis of cutaneous RMS mirrors that of the soft tissue forms. In fact, it is not uncommon for cutaneous RMS to result in local recurrence, distant metastasis, and even death (Marburger et al. 2012; Nakagawa et al. 2008; Scatena et al. 2012).

Cutaneous Osteosarcoma

Epidemiology

Primary skeletal osteosarcoma (OS), although rare overall, is the most common primary malignant bone tumor, most frequently involving the metaphyses of long bones in children and young adults. While approximately 95 % of skeletal OS metastasize to the lung, metastases to the skin do occur, either exclusively or – more commonly – in addition to pulmonary metastases (Collier et al. 2003; Ragsdale et al. 2011; Setoyama et al. 1996). Extraskeletal osteosarcomas (ESOS) comprise a small fraction of all osteosarcomas (approximately 2–4 %), and only 1–2 % of all soft tissue sarcomas collectively (Riddle et al. 2009; Salamanca et al. 2008). Case reports of ESOS arising as a primary neoplasm from the dermis and subcutis exist (Drut and Barletta 1975; Kobos et al. 1995; Kuo 1992; Llamas-Velasco et al. 2013; Massi et al. 2007; Park et al. 2011; Riddle et al. 2009; Salamanca et al. 2008). Risk factors for primary cutaneous osteosarcoma are similar to those for deep-seated ESOS and include a history of prior irradiation, chemotherapy, and trauma; several cutaneous OS, in fact, have arisen within remote scars (Drut and Barletta 1975; Kuo 1992; Park et al. 2011; Riddle et al. 2009).

Clinical Features

Both primary and metastatic cutaneous OS present as firm, flesh-colored to red or violaceous

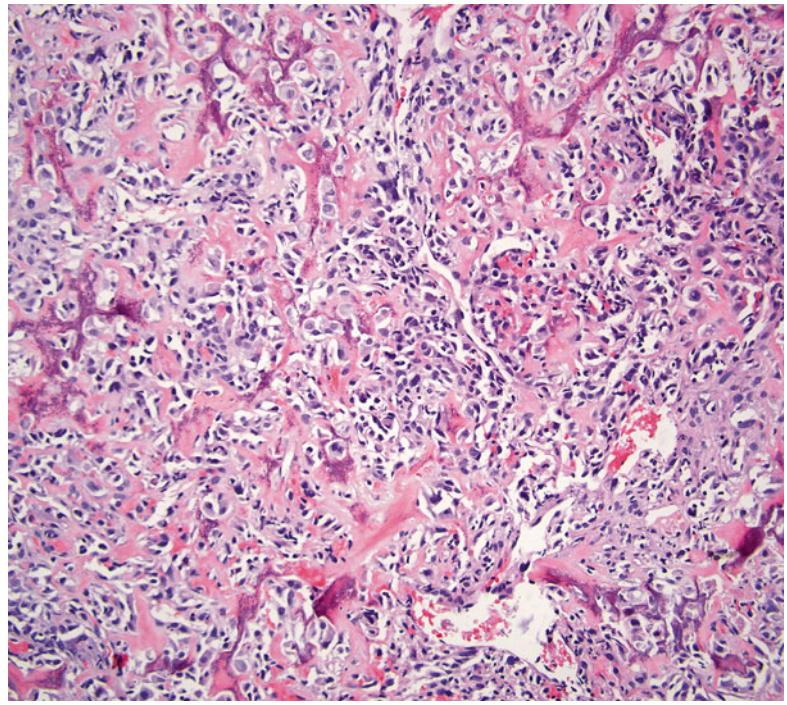

Fig. 18.35 Osteosarcoma. Tumor osteoid production is characterized by eosinophilic, fibrillary, immature-appearing deposits between individual tumor cells in a lacelike pattern

subcutaneous nodules (Collier et al. 2003; Larsen et al. 2010; Llamas-Velasco et al. 2013; Massi et al. 2007; Park et al. 2011). ESOS most commonly occurs within the deep soft tissues of the extremities, and unlike its skeletal counterpart, ESOS primarily affects middle-aged to elderly adults (Park et al. 2011; Riddle et al. 2009). Like deep-seated ESOS, primary cutaneous OS have also been identified in the extremities of older adults (Drut and Barletta 1975; Kobos et al. 1995; Kuo 1992; Park et al. 2011; Riddle et al. 2009; Salamanca et al. 2008). Interestingly, cutaneous OS, whether metastatic or primary in origin, demonstrates a particular proclivity for the scalp (Collier et al. 2003; Massi et al. 2007; Park et al. 2011; Ragsdale et al. 2011).

Histology, Immunohistochemistry, and Differential Diagnosis

Skeletal OS is commonly categorized according to predominant histologic features, and subtypes include osteoblastic OS, osteoclastic/giant cell OS, chondroblastic OS, telangiectatic OS, fibroblastic OS, and small cell OS. The small cell variant is the most likely OS type to resemble other small round blue cell tumors and lymphoproliferative disorders. No particular subtype appears to be more likely to metastasize to or develop as a primary tumor in the skin (Fernandez-Pineda et al. 2011; Park et al. 2011).

Histologically, cutaneous OS is composed of poorly defined sheets of spindled to pleomorphic tumor cells with hyperchromatic nuclei and little cytoplasm. Neoplastic cells are often admixed with and surrounded by a lacelike, amorphous osteoid matrix and/or immature bony trabeculae (Fig. 18.35). One must be cautioned that osteoid deposition is seen in a variety of other reactive and neoplastic processes, including myositis ossificans, osteoma cutis, ossifying fibromyxoid tumor, and sarcomas or melanomas with osseous metaplasia; the presence of osteoid alone, therefore, must not reflexively give rise to a diagnosis of osteosarcoma (Riddle et al. 2009). Conversely, evidence of bone formation may be absent, particularly in biopsies, and in these cases, immunohistochemistry may be useful (see below) (Salamanca et al. 2008). Mitotic activity is typically brisk and atypical mitotic figures can be seen, but necrosis is usually absent (Massi et al. 2007).

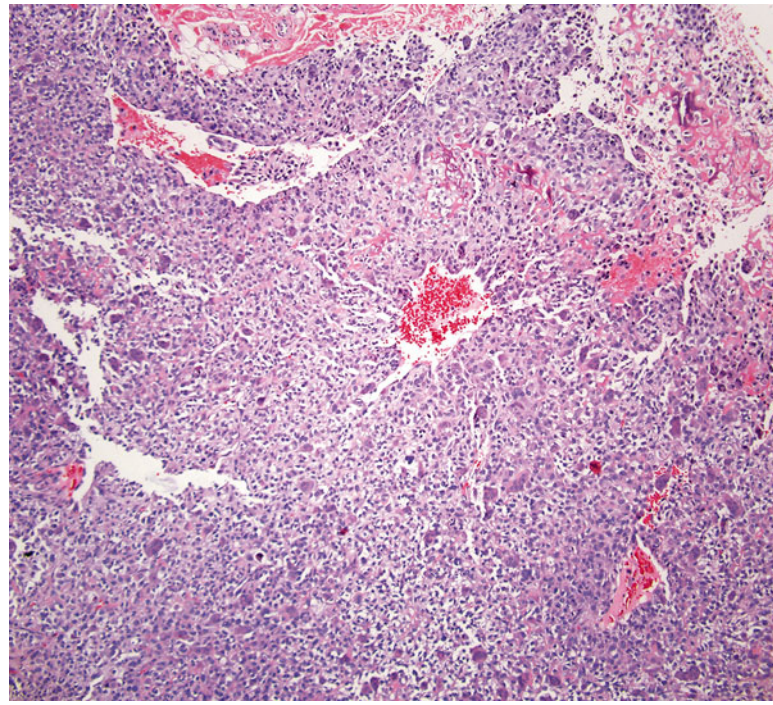

Fig. 18.36 Osteosarcoma. Sheets of pleomorphic cells are admixed with multinucleated giant osteoclasts and anastamosing vascular spaces. Osteoid deposition here is focal

Other features, including multinucleated giant osteoclasts, chondroid differentiation, large anastomosing vascular spaces, and fibroblastic proliferation, may variably be present or predominate the histologic picture (Fig. 18.36).

Tumor cell negativity for CD43, CD45/LCA, and other hematolymphoid markers will exclude the possibility of lymphoma. Tumor cells of osteosarcoma stain positively with vimentin, alkaline phosphatase, anti-osteonectin, and anti-osteocalcin (Covello et al. 2003; Fanburg-Smith et al. 1999; Massi et al. 2007). Osteonectin is sensitive but lacks specificity, as it is also expressed in fibroblasts, pericytes, endothelial cells, chondrocytes, basal epidermal cells, nerves, and osteoclasts. Osteocalcin demonstrates greater specificity. Unfortunately, neither stain is routinely available in all immunohistochemistry laboratories (Fanburg-Smith et al. 1999). If present, chondroid areas may stain with S100.

Molecular/Genetics

Molecular studies are of little utility in the work-up of osteosarcoma, as there are currently no well-established molecular markers of diagnostic or prognostic significance.

Prognosis/Course

ESOS has a 5-year mortality rate approaching 75 % (Covello et al. 2003; Riddle et al. 2009). The clinical behavior of primary OS arising in the skin appears to parallel that of extracutaneous ESOS, in that local recurrence, as well as metastasis and death, may result (Kobos et al. 1995; Park et al. 2011; Riddle et al. 2009; Salamanca et al. 2008). Tumor size appears to most closely correlate with clinical outcome, however, this feature along with other prognostic indicators, including tumor histology, remain controversial (Larsen et al. 2010; Park et al. 2011). Like skeletal OS, extracutaneous ESOS can metastasize to the skin, and often metastasizes to the scalp (Covello et al. 2003; Fernandez-Pineda et al. 2011; Park et al. 2011; Ragsdale et al. 2011).

Cutaneous Angiosarcoma

Epidemiology

Angiosarcoma is a rare but aggressive neoplasm of vascular derivation accounting for approximately 1 % of soft tissue sarcomas. It typically affects older individuals with light skin color,

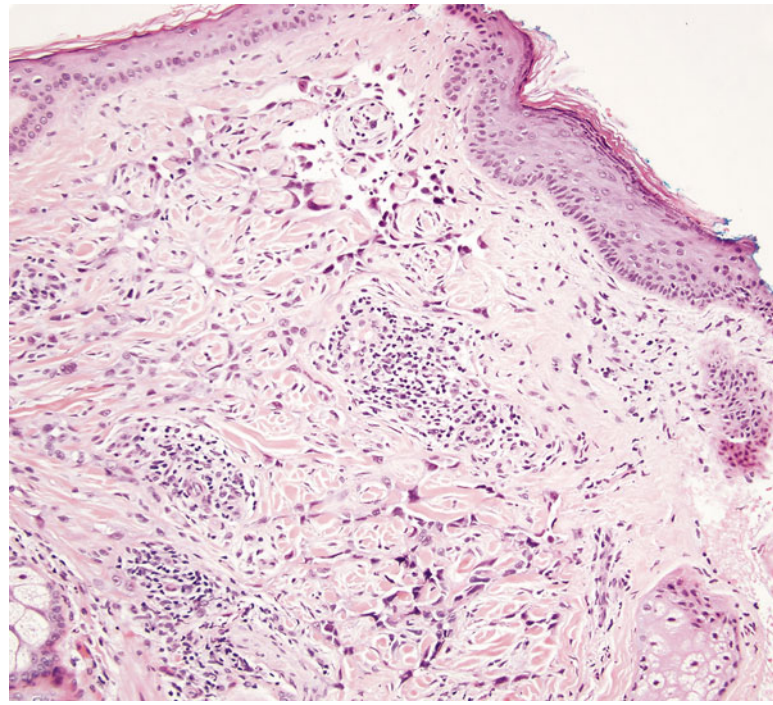

Fig. 18.37 Angiosarcoma, well differentiated. Vasoformative areas, as demonstrated by the slit-like, irregular vascular spaces lined by hyperchromatic endothelial cells, are fundamental to the diagnosis

but there is no well-established gender predilection (Albores-Saavedra et al. 2011). These tumors may arise in soft tissues and also in the skin, where they occur most frequently on head and neck sites in elderly individuals. Cutaneous angiosarcoma also has a well-established association with radiation and chronic lymphedema, with tumors presenting after long intervals following irradiation as a treatment modality or after many years of chronic lymphedema; classically, this phenomenon can be seen as the Stewart-Treves syndrome following mastectomy (Requena et al. 2007). Exceptionally, angiosarcoma is reported in children, in which case it appears to more frequently affect the extremities (Bacchi et al. 2010).

Clinical Features

Cutaneous angiosarcoma, given its vascular derivation, usually presents as a violaceous patch or indurated plaque, often resembling a bruise or hematoma. The tumor frequently has ill-defined borders, and an early lesion can be extraordinarily subtle, consisting of only slight erythema and edema (Requena et al. 2007). Idiopathic cutaneous angiosarcomas typically arise on the scalp or facial region of older individuals, while angiosarcomas related to irradiation or lymphedema arise in patients with relevant history, often on the breast, chest wall, or inner arm. Lesions may be multifocal and/or ulcerated. Angiosarcomas arising from extracutaneous sites may metastasize to the skin (Hart and Mandavilli 2011).

Histology, Immunohistochemistry, and Differential Diagnosis

Angiosarcoma may have a variety of histologic patterns. Well-differentiated variants will show a poorly circumscribed proliferation of irregular, anastamosing vascular channels dissecting through dermal collagen with deep extension. Endothelial cells are hyperchromatic and pleomorphic and will protrude into the lumen of the vascular spaces (hobnailing) (Requena et al. 2007). These vasoformative foci are fundamental to the diagnosis but may be difficult to discern in more poorly differentiated tumors (Fig. 18.37).

Epithelioid angiosarcoma in particular has the capacity to mimic other tumors, including lymphoma, melanoma, and certain carcinomas (Bacchi et al. 2010). Epithelioid angiosarcoma

tumor cells tend to aggregate as broad sheets or islands of large, polygonal to round cells (Fig. 18.38). There is typically mild pleomorphism of tumor cells, with enlarged and often eccentrically placed nuclei and prominent nucleoli. The nuclei often have amphophilic to steel grey coloration (Bacchi et al. 2010), and margination of chromatin may lead to a vesicular appearance (Fig. 18.39) (Hart and Mandavilli 2011). Individual cell necrosis or apoptosis is more likely to be identified than frank necrosis (Bacchi et al. 2010). Vasoformative foci may be only focal in this tumor type but should be searched for on microscopic examination. The presence of erythrocytes around tumor cells may be useful. An additional helpful clue is the presence of focal cytoplasmic vacuolization of tumor cells, which is thought to correlate with primitive vascular lumen formation (Hart and Mandavilli 2011; Requena et al. 2007). Rarely, cutaneous angiosarcoma is accompanied by an obscuring inflammatory infiltrate including lymphoid follicles with germinal center formation, thereby mimicking follicle center cell lymphoma or reactive cutaneous lymphoid hyperplasia (Requena et al. 2007).

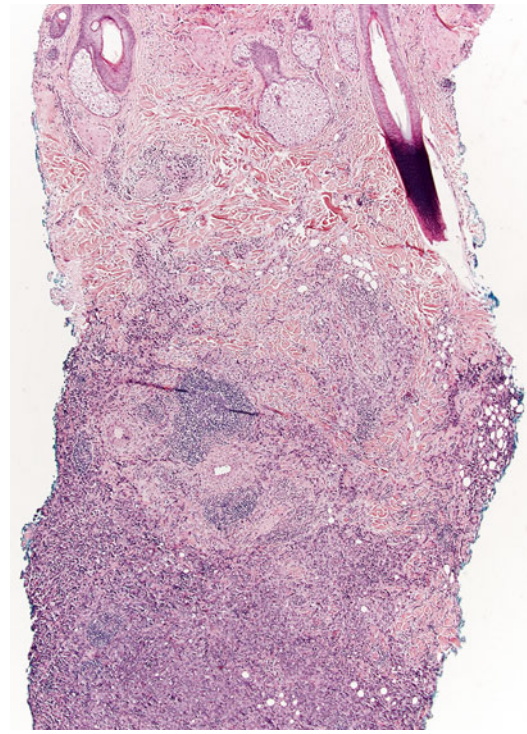

Fig. 18.38 Angiosarcoma, epithelioid variant. On low power, there is a prominent, diffuse infiltrate of blue cells with several interspersed lymphoid aggregates, reminiscent of the sheets of blue cells seen in diffuse large B-cell lymphoma

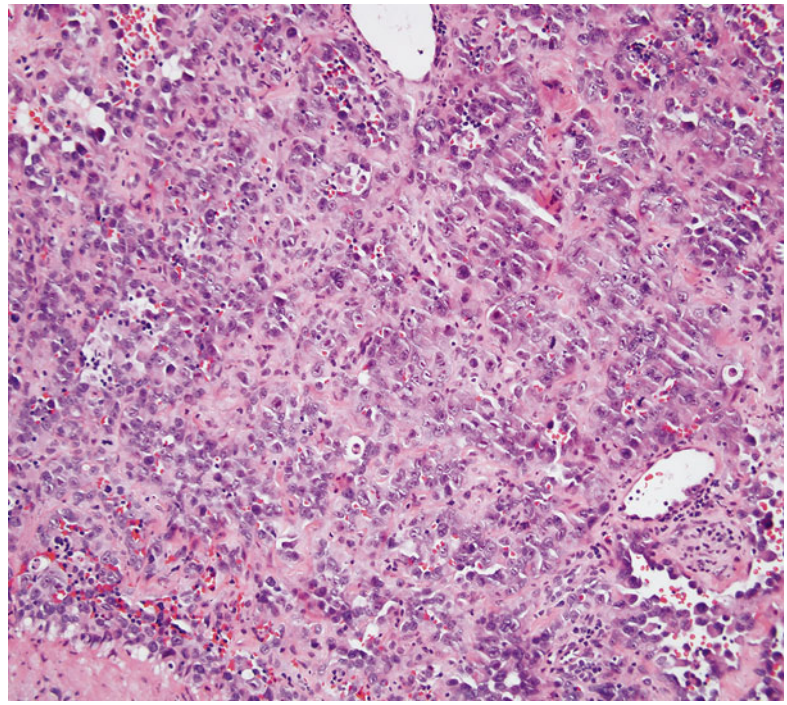

Fig. 18.39 Angiosarcoma, epithelioid variant. High-power examination shows sheets of polygonal epithelioid tumor cells with amphophilic cytoplasm, prominent nucleoli, and mitotic figures. Vasoformative foci are evident in the upper left and lower right

Angiosarcomas express endothelial markers, namely, CD31, CD34, factor VIII-related antigen (von Willebrand factor), FLI-1 protein, and podoplanin (D2-40) (Hart and Mandavilli 2011, Weed and Folpe 2008). CD31 represents a specific marker and demonstrates approximately equivalent sensitivity to some of the other, less specific stains (Bacchi et al. 2010). Recently, the use of the nuclear immunohistochemical stain ERG has been described as having superior sensitivity and specificity in the diagnosis of cutaneous angiosarcoma (McKay et al. 2012). Epithelioid angiosarcoma may express pancytokeratin and, less frequently, epithelial membrane antigen, although the exact frequency of co-expression ranges widely depending on the case series (Bacchi et al. 2010; McCluggage et al. 1995; Meis-Kindblom and Kindblom 1998; Suchak et al. 2011). Aberrant CD30 expression has been reported in an angiosarcoma arising in an irradiated site, thereby mimicking anaplastic large cell lymphoma (Weed and Folpe 2008). In the so-called pseudolymphomatous variant of cutaneous angiosarcoma, the lymphoid infiltrate was composed of a mix of predominantly CD4-positive T cells, with CD20-positive, Bcl-6-co-expressing germinal center cells that demonstrated the expected high proliferative index by MIB-1 (Ki-67) staining for a reactive follicle (Requena et al. 2007). The distinction of this variant from reactive cutaneous lymphoid hyperplasia requires careful evaluation of the tumor for the presence of vasoformative foci which express the previously discussed endothelial markers.

Electron Microscopy

While now uncommonly utilized as a diagnostic modality, ultrastructural examination of angiosarcoma will reveal endothelial cells and associated pericytes. Red blood cells may be identified between and within tumor cells, and Weibel-Pelade bodies may be visualized, assisting with the identification of vascular differentiation (Hart and Mandavilli 2011).

Molecular/Genetics

Cutaneous angiosarcoma associated with prior radiation has been shown to demonstrate MYC amplification as detected by FISH or by strong nuclear immunoreactivity using immunohistochemical staining (Fernandez et al. 2012; Mentzel et al. 2012). Angiosarcomas unassociated with radiation do not seem to exhibit this amplification (Mentzel et al. 2012).

Prognosis/Course

Survival rates for cutaneous angiosarcoma are generally unfavorable and appear to be related to multiple factors, including patient age, site of tumor, and disease stage. Younger patients (less than 50 years old) and those with truncal disease have increased survival rates at 10 years (approximately 75 %) compared to older patients (37 %) or patients with tumors on the head and neck (14 %) (Albores-Saavedra et al. 2011). Predictably, patients with localized cutaneous disease have improved survival compared to those with regional or distant disease (Albores-Saavedra et al. 2011). The presence of a prominent lymphoid infiltrate in angiosarcoma has been proposed as a potential predictor of improved survival; however, additional studies are required (Requena et al. 2007).

Cutaneous Neuroblastoma

Epidemiology

Like some of the previous entities mentioned, cutaneous neuroblastoma (NB) is both exceedingly rare and more likely to occur as a metastatic implant from a primary visceral source than as a primary cutaneous neoplasm. The adrenal gland is the most common primary site for tumor development, but neuroblastoma may develop at any site along the sympathetic nervous system chain (Argenyi and Jokinen 2011; Klapman and Chun 1991; Van Nguyen and Argenyi 1993). Of soft tissue sarcomas, neuroblastoma is one of the most likely to metastasize to the skin; in fact, approximately one-third of patients with congenital neuroblastoma present with cutaneous metastases, and cutaneous metastases are particularly more prevalent in neonates than in any other patient population (Hawthorne et al. 1970; Kao and Yu 1991; Lucky et al. 1982; Wyatt and Hansen 2000).

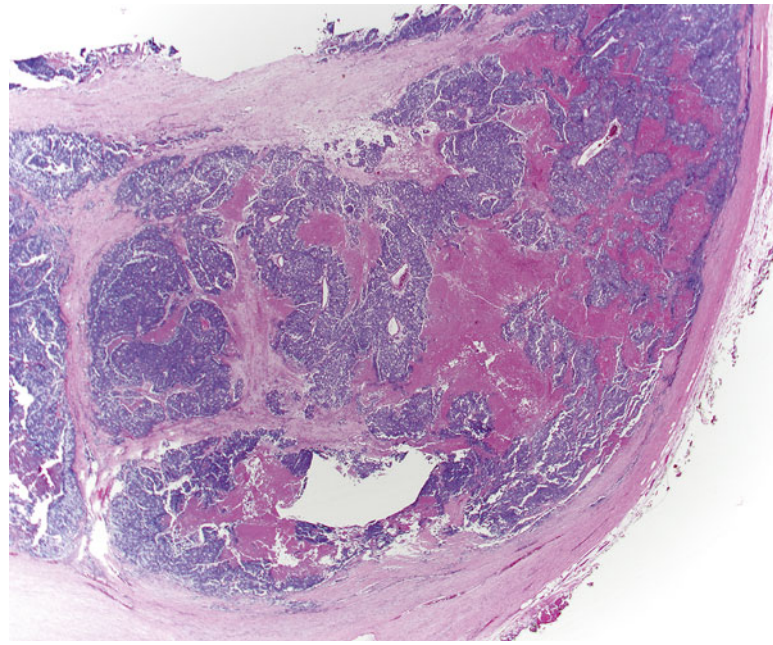

Fig. 18.40 Neuroblastoma. Sheets of monotonous blue cells are arranged in nests

Unlike metastatic NB, cutaneous neuroblastomas of primary origin are recognized almost exclusively in the adult population (Argenyi and Jokinen 2011, Van Nguyen and Argenyi 1993).

Clinical Features

Whether primary or secondary in origin, cutaneous neuroblastoma presents as a rapidly growing blue or purple nodule with characteristic protracted blanching behavior following the application of pressure, a feature of which is likely due to vasoconstriction secondary to the local release of catecholamines (Argenyi and Jokinen 2011; Hawthorne et al. 1970; Lucky et al. 1982). Clinically, mesenchymal neuroblastomas are unique, and, therefore, one may find a review of the patient's history particularly useful when presented with a potential metastatic NB. First, the tumor is associated with increased levels of the serum catecholamines dopamine and norepinephrine and the urine catecholamine metabolites homovanillic acid (HVA) and vanillylmandelic acid (VMA). Visceral neuroblastoma may be confirmed by scintigraphy, a test in which radio-iodinated metaiodobenzylguanidine (^{123}I-MIBG) is administered and then monitored for its uptake by tumor foci (Dabbs 2010). Similar laboratory and imaging studies are not generally performed in cases of primary cutaneous neuroblastoma.

Histology, Immunohistochemistry, and Differential Diagnosis

Whether primary or metastatic in origin, cutaneous neuroblastoma appears microscopically as a poorly demarcated aggregate of tumor cells arranged in infiltrative sheets, nests, or trabeculae (Fig. 18.40) (Argenyi and Jokinen 2011). The neoplastic cells are epithelioid to ovoid in shape with a vesicular chromatin pattern and scant cytoplasm. The tumor cells often assimilate to form Homer Wright rosettes, which are ringlike structures characterized by a rim of palisading neoplastic cells and a central area containing fine, pink fibrillary material (Argenyi and Jokinen 2011). Like in visceral NB, Homer Wright rosettes are pathognomonic for cutaneous NB and, when present, are fundamental clues in differentiating this tumor from the other small round blue cell neoplasms (Fig. 18.41). The presence of ganglion cells, schwannoma-like stroma, and neuropil vary depending on the degree of maturation of the tumor.

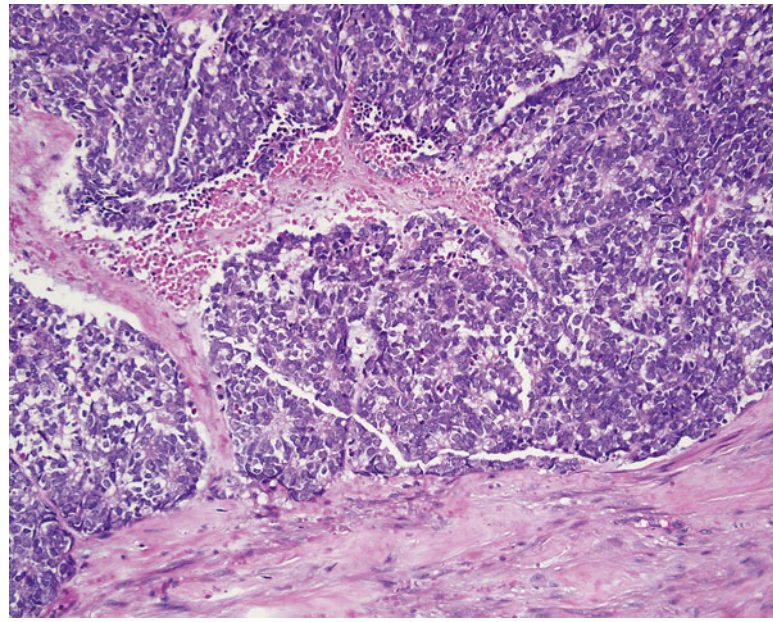

Fig. 18.41 Neuroblastoma. On higher examination, rosette formation can be appreciated and karyorrhectic debris is plentiful

NB tumor cells express neuroblastic markers such as neuron-specific enolase (NSE), CD56, synaptophysin, chromogranin, and neurofilament protein. More recent markers for NB appear to be more specific but less sensitive and include anti-neuroblastoma antibody (NB84), protein gene product 9.5 (PGP 9.5), and anti-GD2, a cell membrane glycolipid identified on neuroblastoma cells (Dabbs 2010; Sariola et al. 1991). A promiscuous stain, ALK 1, is also positive in greater than 90 % of neuroblastomas, and as discussed previously with rhabdomyosarcoma and Merkel cell carcinoma, discretion must be used in its interpretation (Dabbs 2010). Ganglioneuroma-like differentiation has been identified in Merkel cell carcinoma; CK20 stain is helpful in distinguishing this rare variant from cutaneous neuroblastoma (Vanchinathan et al. 2009). Schwannoma-like stroma, when present, stains positively for S100 protein.

Molecular/Genetics

Ancillary studies are primarily of prognostic rather than diagnostic utility: NBs that express TRK-A, a neurotrophic tyrosine kinase receptor important in sympathetic neuronal development, have a more favorable prognosis, while tumors that express TRK-B and/or that demonstrate N-*myc* oncogene amplification are associated with lack of response to therapy and rapid tumor progression, respectively (Brodeur et al. 2009). Currently, molecular tests for the detection of the neurotrophic tyrosine kinase receptors are not widely available. Identification of N-*myc* amplification, however, has been made relatively straightforward through the use of fluorescence in situ hybridization studies (FISH). DNA indexing via flow cytometry is also a useful prognostic indicator in young patients with disseminated neuroblastoma; triploid and hyperdiploid tumors are associated with a more favorable prognosis, while those with near diploid states are associated with more aggressive tumor behavior (Brodeur et al. 2009).

Prognosis/Course

Visceral neuroblastomas display significant prognostic heterogeneity, with survival rates varying from 15 % to 90 % based on the age of the patient and the extent of disease burden. Two staging systems have been proposed for NB. According to the International Neuroblastoma Staging System (INSS), the presence of cutaneous metastases in children upstages the tumor to stage 4 disease,

although children less than 1 year of age have substantially greater survival rates than children older than 1 year of age. Importantly, however, if all of the following are true – (1) the primary tumor consists of a single focus that can be completely excised; (2) there are no distant metastases other than dermal metastases; and (3) the patient is less than 1 year of age – then the patient's disease is categorized as stage 4S, and survival rates are comparable to those of stage 1 or 2 disease (75–90 % at 3 years) (ASCO 2012). The more recent International Neuroblastoma Risk Group Staging System (INRGSS) takes into account not only the tumor stage but also the molecular and histologic features of the tumor to classify patients into low-, intermediate-, or high-risk disease categories (ASCO 2012, Cohn et al. 2009). As reports of primary cutaneous neuroblastoma are rare, generalizations about patient outcome are not available, although adult patients appear to have an unfavorable prognosis with rapid disease progression (Klapman and Chun 1991).

Current treatment options range from careful observation to neoadjuvant chemotherapy, surgical excision, and postsurgical chemoradiation therapy, depending on the determined disease risk level (Cohn et al. 2009).

Conclusion

This chapter has sought to describe nonlymphoid malignancies that demonstrate histologic overlap with hematolymphoid infiltrates of the skin. We acknowledge that no such chapter – however broad – can be entirely exhaustive. When presented with a cutaneous infiltrate without clear lineage, one must often go beyond the basic H&E-stained slide evaluation to exploit available supplementary tools and methods of investigation. As is evident in this chapter, diagnostic precision often necessitates the use of immunohistochemistry, molecular testing, and clinical information. However, sometimes simply thinking outside the box and remembering to include a rare entity within one's differential diagnosis will lead down the path to an accurate diagnosis.

References

Albores-Saavedra J, Schwartz AM, Henson DE, Kostun L, Hart A, Angeles-Albores D, et al. Cutaneous angiosarcoma. Analysis of 434 cases from the Surveillance, Epidemiology, and End Results Program, 1973-2007. Ann Diagn Pathol. 2011;15(2):93–7.

Angervall L, Enzinger FM. Extraskeletal neoplasm resembling Ewing's sarcoma. Cancer. 1975;36(1):240–51.

Anne N, Pallapothu R. Lymphoma of the breast: a mimic of inflammatory breast cancer. World J Surg Oncol. 2011;9:125. doi:10.1186/1477-7819-9-125.

Ansai S, Maeda K, Yamakawa M, Matsuda M, Saitoh S, Suwa S, et al. CD56-positive (nasal-type T/NK cell) lymphoma arising on the skin. Report of two cases and review of the literature. J Cutan Pathol. 1997;24(8):468–76.

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(4):681–4. doi:10.1016/j.jaad.2008.07.024.

Argenyi Z, Jokinen CH. Cutaneous neural neoplasms : a practical guide. New York: Humana Press; 2011. xiv, 135 p.

Arsenovic N. Lymphoepithelioma-like carcinoma of the skin: new case of an exceedingly rare primary skin tumor. Dermatol Online J. 2008;14(8):12.

ASCO. Neuroblastoma-childhood. [Internet]. 2012. [Updated Oct 2012]. Available from: http://www.cancer.net/cancer-types/neuroblastoma-childhood/staging

Azoulay S, Adem C, Pelletier FL, Barete S, Frances C, Capron F. Skin metastases from unknown origin: role of immunohistochemistry in the evaluation of cutaneous metastases of carcinoma of unknown origin. J Cutan Pathol. 2005;32(8):561–6. doi:10.1111/j.0303-6987.2005.00386.x.

Bacchi CE, Silva TR, Zambrano E, Plaza J, Suster S, Luzar B, et al. Epithelioid angiosarcoma of the skin: a study of 18 cases with emphasis on its clinicopathologic spectrum and unusual morphologic features. Am J Surg Pathol. 2010;34(9):1334–43. doi:10.1097/PAS.0b013e3181ee4eaf.

Bagley FH, Cady B, Lee A, Legg MA. Changes in clinical presentation and management of malignant melanoma. Cancer. 1981;47(9):2126–34.

Barnes L, Eveson JW, Reichart R, Sidransky D, World Health Organization, Cancer IAfRo. WHO classification of tumours: Pathology and Genetics of Head and Neck Tumours. 2nd ed. Lyon: IARC Press; 2007. 430 p.

Basler GC, Fader DJ, Yahanda A, Sondak VK, Johnson TM. The utility of fine needle aspiration in the diagnosis of melanoma metastatic to lymph nodes. J Am Acad Dermatol. 1997;36(3 Pt 1):403–8.

Bauer J, Bastian BC. Distinguishing melanocytic nevi from melanoma by DNA copy number changes:

comparative genomic hybridization as a research and diagnostic tool. Dermatol Ther. 2006;19(1):40–9. doi:10.1111/j.1529-8019.2005.00055.x.

Biswas A, Gey van Pittius D, Stephens M, Smith AG. Recurrent primary cutaneous lymphoma with florid pseudoepitheliomatous hyperplasia masquerading as squamous cell carcinoma. Histopathology. 2008;52(6):755–8. doi:10.1111/j.1365-2559.2008.03013.x.

Blessing K, Grant JJ, Sanders DS, Kennedy MM, Husain A, Coburn P. Small cell malignant melanoma: a variant of naevoid melanoma. Clinicopathological features and histological differential diagnosis. J Clin Pathol. 2000;53(8):591–5.

Boland JM, Folpe AL. Cutaneous neoplasms showing EWSR1 rearrangement. Adv Anat Pathol. 2013;20(2):75–85. doi:10.1097/PAP.0b013e31828625bf.

Brecher AR, Reyes-Mugica M, Kamino H, Chang MW. Congenital primary cutaneous rhabdomyosarcoma in a neonate. Pediatr Dermatol. 2003;20(4):335–8.

Brodeur GM, Minturn JE, Ho R, Simpson AM, Iyer R, Varela CR, et al. Trk receptor expression and inhibition in neuroblastomas. Clin Cancer Res. 2009;15(10):3244–50. doi:10.1158/1078-0432.CCR-08-1815.

Brownstein MH, Helwig EB. Metastatic tumors of the skin. Cancer. 1972;29(5):1298–307.

Buresh CJ, Oliai BR, Miller RT. Reactivity with TdT in Merkel cell carcinoma: a potential diagnostic pitfall. Am J Clin Pathol. 2008;129(6):894–8. doi:10.1309/R494HQ9VRDJWDY30.

Calder KB, Smoller BR. New insights into merkel cell carcinoma. Adv Anat Pathol. 2010;17(3):155–61. doi:10.1097/PAP.0b013e3181d97836.

Cangiarella J, Symmans WF, Shapiro RL, Roses DF, Cohen JM, Chhieng D, et al. Aspiration biopsy and the clinical management of patients with malignant melanoma and palpable regional lymph nodes. Cancer. 2000;90(3):162–6.

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(9):909–13.

Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507–16. doi:10.1056/NEJMoa1103782.

Cheung WL, Patel RR, Leonard A, Firoz B, Meehan SA. Amelanotic melanoma: a detailed morphologic analysis with clinicopathologic correlation of 75 cases. J Cutan Pathol. 2012;39(1):33–9. doi:10.1111/j.1600-0560.2011.01808.x.

Chu P, Wu E, Weiss LM. Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. Mod Pathol. 2000;13(9):962–72. doi:10.1038/modpathol.3880175.

Cibull TL, Thomas AB, O'Malley DP, Billings SD. Myeloid leukemia cutis: a histologic and immunohistochemical review. J Cutan Pathol. 2008;35(2):180–5. doi:10.1111/j.1600-0560.2007.00784.x.

Cimino-Mathews A, Subhawong AP, Illei PB, Sharma R, Halushka MK, Vang R, et al. GATA3 expression in breast carcinoma: utility in triple-negative, sarcomatoid, and metastatic carcinomas. Hum Pathol. 2013;44(7):1341–9. doi:10.1016/j.humpath.2012.11.003.

Cobanoglu B, Kandi B, Okur I. Primary cutaneous rhabdomyosarcoma in an adult. Dermatol Surg. 2009;35(10):1573–5. doi:10.1111/j.1524-4725.2009.01278.x.

Cohn SL, Pearson AD, London WB, Monclair T, Ambros PF, Brodeur GM, et al. The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. J Clin Oncol. 2009;27(2):289–97. doi:10.1200/JCO.2008.16.6785.

Collier 3rd AB, Simpson L, Monteleone P. Cutaneous Ewing sarcoma: report of 2 cases and literature review of presentation, treatment, and outcome of 76 other reported cases. J Pediatr Hematol Oncol. 2011;33(8):631–4. doi:10.1097/MPH.0b013e31821b234d.

Collier DA, Busam K, Salob S. Cutaneous metastasis of osteosarcoma. J Am Acad Dermatol. 2003;49(4):757–60.

Corao DA, Biegel JA, Coffin CM, Barr FG, Wainwright LM, Ernst LM, et al. ALK expression in rhabdomyosarcomas: correlation with histologic subtype and fusion status. Pediatr Dev Pathol. 2009;12(4):275–83. doi:10.2350/08-03-0434.1.

Covello SP, Humphreys TR, Lee JB. A case of extraskeletal osteosarcoma with metastasis to the skin. J Am Acad Dermatol. 2003;49(1):124–7. doi:10.1067/mjd.2003.297.

D'Agostino M, Cinelli C, Willard R, Hofmann J, Jellinek N, Robinson-Bostom L. Epidermotropic Merkel cell carcinoma: a case series with histopathologic examination. J Am Acad Dermatol. 2010;62(3):463–8. doi:10.1016/j.jaad.2009.06.023.

Dabbs DJ. Diagnostic immunohistochemistry : theranostic and genomic applications. 3rd ed. Philadelphia: Saunders/Elsevier; 2010. xviii, 941 p.

Delaplace M, Lhommet C, de Pinieux G, Vergier B, de Muret A, Machet L. Primary cutaneous Ewing sarcoma: a systematic review focused on treatment and outcome. Br J Dermatol. 2012;166(4):721–6. doi:10.1111/j.1365-2133.2011.10743.x.

Donner LR, Speights VO, Trompler RA. Merkel cell carcinoma with pagetoid spread. Ultrastruct Pathol. 1992;16(1–2):25–8.

Drut R, Barletta L. Osteogenic sarcoma arising in an old burn scar. J Cutan Pathol. 1975;2(6):302–6.

Edge SB, American Joint Committee on Cancer., American Cancer Society. AJCC cancer staging handbook : from the AJCC cancer staging manual. 7th ed. New York: Springer; 2010. xix, 718 p.

Ehrig T, Billings SD, Fanburg-Smith JC. Superficial primitive neuroectodermal tumor/Ewing sarcoma (PN/ES): same tumor as deep PN/ES or new entity? Ann Diagn Pathol. 2007;11(3):153–9. doi:10.1016/j.anndiagpath.2006.12.019.

Essner R. Lymphatic mapping and sentinel lymphadenectomy in primary cutaneous melanoma. Expert Rev

Anticancer Ther. 2010;10(5):723–8. doi:10.1586/era.10.65.

Falini B, Pileri S, Stein H, Dieneman D, Dallenbach F, Delsol G, et al. Variable expression of leucocyte-common (CD45) antigen in CD30 (Ki1)-positive anaplastic large-cell lymphoma: implications for the differential diagnosis between lymphoid and nonlymphoid malignancies. Hum Pathol. 1990;21(6):624–9.

Fanburg-Smith JC, Bratthauer GL, Miettinen M. Osteocalcin and osteonectin immunoreactivity in extraskeletal osteosarcoma: a study of 28 cases. Hum Pathol. 1999;30(1):32–8.

Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science. 2008;319(5866):1096–100. doi:10.1126/science.1152586.

Fernandez-Pineda I, Bahrami A, Green JF, McGregor LM, Davidoff AM, Sandoval JA. Isolated subcutaneous metastasis of osteosarcoma 5 years after initial diagnosis. J Pediatr Surg. 2011;46(10):2029–31. doi:10.1016/j.jpedsurg.2011.06.011.

Fernandez AP, Sun Y, Tubbs RR, Goldblum JR, Billings SD. FISH for MYC amplification and anti-MYC immunohistochemistry: useful diagnostic tools in the assessment of secondary angiosarcoma and atypical vascular proliferations. J Cutan Pathol. 2012;39(2):234–42. doi:10.1111/j.1600-0560.2011.01843.x.

Filtenborg-Barnkob BE, Bzorek M. Expression of anaplastic lymphoma kinase in Merkel cell carcinomas. Hum Pathol. 2013. doi:10.1016/j.humpath.2012.11.021.

Folpe AL, Hill CE, Parham DM, O'Shea PA, Weiss SW. Immunohistochemical detection of FLI-1 protein expression: a study of 132 round cell tumors with emphasis on CD99-positive mimics of Ewing's sarcoma/primitive neuroectodermal tumor. Am J Surg Pathol. 2000;24(12):1657–62.

Gast A, Scherer D, Chen B, Bloethner S, Melchert S, Sucker A, et al. Somatic alterations in the melanoma genome: a high-resolution array-based comparative genomic hybridization study. Genes Chromosomes Cancer. 2010;49(8):733–45. doi:10.1002/gcc.20785.

Gerami P, Jewell SS, Morrison LE, Blondin B, Schulz J, Ruffalo T, et al. Fluorescence in situ hybridization (FISH) as an ancillary diagnostic tool in the diagnosis of melanoma. Am J Surg Pathol. 2009;33(8):1146–56. doi:10.1097/PAS.0b013e3181a1ef36.

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;18(5):478–82.

Goessling W, McKee PH, Mayer RJ. Merkel cell carcinoma. J Clin Oncol. 2002;20(2):588–98.

Gul U, Kilic A, Gonul M, Kulcu Cakmak S, Erinckan C. Spectrum of cutaneous metastases in 1287 cases of internal malignancies: a study from Turkey. Acta Derm Venereol. 2007;87(2):160–2. doi:10.2340/00015555-0199.

Hafstrom L, Hugander A, Jonsson PE, Lindberg LG. Fine-needle-aspiration cytodiagnosis of recurrent malignant melanoma. J Surg Oncol. 1980;15(3):229–34.

Hall BJ, Pincus LB, Yu SS, Oh DH, Wilson AR, McCalmont TH. Immunohistochemical prognostication of Merkel cell carcinoma: p63 expression but not polyomavirus status correlates with outcome. J Cutan Pathol. 2012;39(10):911–7. doi:10.1111/j.1600-0560.2012.01964.x.

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(3):211–5.

Hanson IM, Banerjee SS, Menasce LP, Prescott RJ. A study of eleven cutaneous malignant melanomas in adults with small-cell morphology: emphasis on diagnostic difficulties and unusual features. Histopathology. 2002;40(2):187–95.

Hart J, Mandavilli S. Epithelioid angiosarcoma: a brief diagnostic review and differential diagnosis. Arch Pathol Lab Med. 2011;135(2):268–72. doi:10.1043/1543-2165-135.2.268.

Hasegawa SL, Davison JM, Rutten A, Fletcher JA, Fletcher CD. Primary cutaneous Ewing's sarcoma: immunophenotypic and molecular cytogenetic evaluation of five cases. Am J Surg Pathol. 1998;22(3):310–8.

Hashimoto K, Lee MW, D'Annunzio DR, Balle MR, Narisawa Y. Pagetoid Merkel cell carcinoma: epidermal origin of the tumor. J Cutan Pathol. 1998;25(10):572–9.

Hawthorne Jr HC, Nelson JS, Witzleben CL, Giangiacomo J. Blanching subcutaneous nodules in neonatal neuroblastoma. J Pediatr. 1970;77(2):297–300.

Higaki-Mori H, Kuwamoto S, Iwasaki T, Kato M, Murakami I, Nagata K, et al. Association of Merkel cell polyomavirus infection with clinicopathological differences in Merkel cell carcinoma. Hum Pathol. 2012;43(12):2282–91. doi:10.1016/j.humpath.2012.04.002.

Hsiao CH, Su IJ. Primary cutaneous pre-B lymphoblastic lymphoma immunohistologically mimics Ewing's sarcoma/primitive neuroectodermal tumor. J Formos Med Assoc. 2003;102(3):193–7.

Izquierdo MJ, Pastor MA, Carrasco L, Requena C, Farina MC, Martin L, et al. Cutaneous metastases from Ewing's sarcoma: report of two cases. Clin Exp Dermatol. 2002;27(2):123–8.

Jagirdar J. Application of immunohistochemistry to the diagnosis of primary and metastatic carcinoma to the lung. Arch Pathol Lab Med. 2008;132(3):384–96. doi:10.1043/1543-2165(2008)132[384:AOITTD]2.0.CO;2.

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(5 Pt 2):878–81.

Kanitakis J, Euvrard S, Chouvet B, Butnaru AC, Claudy A. Merkel cell carcinoma in organ-transplant recipients: report of two cases with unusual histological features and literature review. J Cutan Pathol. 2006;33(10):686–94. doi:10.1111/j.1600-0560.2006.00529.x.

Kao CH, Yu HS. Cutaneous neonatal neuroblastoma: report of a case. J Formos Med Assoc. 1991;90(4):422–5.

Klapman MH, Chun D. Cutaneous and subcutaneous neuroblastoma in children and adults: case reports and population study. J Am Acad Dermatol. 1991;24(6 Pt 1):1025–7.

Kobos JW, Yu GH, Varadarajan S, Brooks JS. Primary cutaneous osteosarcoma. Am J Dermatopathol. 1995;17(1):53–7.

Kolhe R, Reid MD, Lee JR, Cohen C, Ramalingam P. Immunohistochemical expression of PAX5 and TdT by Merkel cell carcinoma and pulmonary small cell carcinoma: a potential diagnostic pitfall but useful discriminatory marker. Int J Clin Exp Pathol. 2013;6(2):142–7.

Kuo TT. Primary osteosarcoma of the skin. J Cutan Pathol. 1992;19(2):151–5.

Kuroiwa M, Sakamoto J, Shimada A, Suzuki N, Hirato J, Park MJ, et al. Manifestation of alveolar rhabdomyosarcoma as primary cutaneous lesions in a neonate with Beckwith-Wiedemann syndrome. J Pediatr Surg. 2009;44(3):e31–5. doi:10.1016/j.jpedsurg.2008.12.010.

Larsen S, Davis DM, Comfere NI, Folpe AL, Sciallis GF. Osteosarcoma of the skin. Int J Dermatol. 2010;49(5):532–40. doi:10.1111/j.1365-4632.2010.04315.x.

Lazova R, Seeley EH, Keenan M, Gueorguieva R, Caprioli RM. Imaging mass spectrometry – a new and promising method to differentiate Spitz nevi from Spitzoid malignant melanomas. Am J Dermatopathol. 2012;34(1):82–90. doi:10.1097/DAD.0b013e31823df1e2.

LeBoit PE, Crutcher WA, Shapiro PE. Pagetoid intraepidermal spread in Merkel cell (primary neuroendocrine) carcinoma of the skin. Am J Surg Pathol. 1992;16(6):584–92.

Lima LL, Rodrigues CA, Pereira PM, Schettini AP, Tupinamba WL. Primary cutaneous alveolar rhabdomyosarcoma in a pediatric patient. An Bras Dermatol. 2011;86(2):363–5.

Llamas-Velasco M, Rutten A, Requena L, Mentzel T. Primary cutaneous osteosarcoma of the skin: a report of 2 cases with emphasis on the differential diagnoses. Am J Dermatopathol. 2013. doi:10.1097/DAD.0b013e31827f0a6f.

Lobo AZ, Tanabe KK, Luo S, Muzikansky A, Sober AJ, Tsao H, et al. The distribution of microscopic melanoma metastases in sentinel lymph nodes: implications for pathology protocols. Am J Surg Pathol. 2012;36(12):1841–8. doi:10.1097/PAS.0b013e31826d25f9.

Lopez V, Martin JM, Santonja N, Molina I, Ramon D, Monteagudo C, et al. Lymphoepithelioma-like carcinoma of the skin: report of three cases. J Cutan Pathol. 2011;38(1):54–8. doi:10.1111/j.1600-0560.2009.01458.x.

Lucky AW, McGuire J, Komp DM. Infantile neuroblastoma presenting with cutaneous blanching nodules. J Am Acad Dermatol. 1982;6(3):389–91.

Marburger TB, Gardner JM, Prieto VG, Billings SD. Primary cutaneous rhabdomyosarcoma: a clinicopathologic review of 11 cases. J Cutan Pathol. 2012;39(11):987–95. doi:10.1111/cup.12007.

Marcoval J, Penin RM, Llatjos R, Martinez-Ballarin I. Cutaneous metastasis from lung cancer: retrospective analysis of 30 patients. Australas J Dermatol. 2012;53(4):288–90. doi:10.1111/j.1440-0960.2011.00828.x.

Marghoob AA, Schoenbach SP, Kopf AW, Orlow SJ, Nossa R, Bart RS. Large congenital melanocytic nevi and the risk for the development of malignant melanoma. A prospective study. Arch Dermatol. 1996;132(2):170–5.

Massi D, Franchi A, Leoncini G, Maio V, Dini M. Primary cutaneous osteosarcoma of the scalp: a case report and review of the literature. J Cutan Pathol. 2007;34(1):61–4. doi:10.1111/j.1600-0560.2006.00562.x.

McCluggage WG, Clarke R, Toner PG. Cutaneous epithelioid angiosarcoma exhibiting cytokeratin positivity. Histopathology. 1995;27(3):291–4.

McGovern VJ. Spontaneous regression of melanoma. Pathology. 1975;7(2):91–9.

McKay KM, Doyle LA, Lazar AJ, Hornick JL. Expression of ERG, an Ets family transcription factor, distinguishes cutaneous angiosarcoma from histological mimics. Histopathology. 2012;61(5):989–91. doi:10.1111/j.1365-2559.2012.04286.x.

McNiff JM, Cowper SE, Lazova R, Subtil A, Glusac EJ. CD56 staining in Merkel cell carcinoma and natural killer-cell lymphoma: magic bullet, diagnostic pitfall, or both? J Cutan Pathol. 2005;32(8):541–5. doi:10.1111/j.0303-6987.2005.00378.x.

Meis-Kindblom JM, Kindblom LG. Angiosarcoma of soft tissue: a study of 80 cases. Am J Surg Pathol. 1998;22(6):683–97.

Menasce LP, Shanks JH, Howarth VS, Banerjee SS. Regressed cutaneous malignant melanoma mimicking lymphoma: a potential diagnostic pitfall. Int J Surg Pathol. 2005;13(3):281–4.

Mentzel T, Schildhaus HU, Palmedo G, Buttner R, Kutzner H. Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by MYC amplification in contrast to atypical vascular lesions after radiotherapy and control cases: clinicopathological, immunohistochemical and molecular analysis of 66 cases. Mod Pathol. 2012;25(1):75–85. doi:10.1038/modpathol.2011.134.

Mohamed A, Gonzalez RS, Lawson D, Wang J, Cohen C. SOX10 expression in malignant melanoma, carcinoma, and normal tissues. Appl Immunohistochem Mol Morphol. 2012. doi:10.1097/PAI.0b013e318279bc0a.

Mott RT, Smoller BR, Morgan MB. Merkel cell carcinoma: a clinicopathologic study with prognostic implications. J Cutan Pathol. 2004;31(3):217–23.

Murali R, Doubrovsky A, Watson GF, McKenzie PR, Lee CS, McLeod DJ, et al. Diagnosis of metastatic melanoma by fine-needle biopsy: analysis of 2,204 cases. Am J Clin Pathol. 2007;127(3):385–97. doi:10.1309/3QR4FC5PPWXA7N29.

Musette P, Bachelez H, Flageul B, Delarbre C, Kourilsky P, Dubertret L, et al. Immune-mediated destruction of melanocytes in halo nevi is associated with the local

expansion of a limited number of T cell clones. J Immunol. 1999;162(3):1789–94.

NakagawaN,TsudaT,YamamotoM,ItoT,FutaniH,YamanishiK. Adult cutaneous alveolar rhabdomyosarcoma on the face diagnosed by the expression of PAX3-FKHR gene fusion transcripts. J Dermatol. 2008;35(7):462–7. doi:10.1111/j.1346-8138.2008.00503.x.

NCCN. Clinical Practice Guidelines in Oncology: merkel cell carcinoma. [Internet]. 2013. [Updated May 14 2013]. Available from: http://www.NCCN.org/professionals/physician_gls/pdf/mcc.pdf

Nelson AA, Tsao H. Melanoma and genetics. Clin Dermatol. 2009;27(1):46–52. doi:10.1016/j.clindermatol.2008.09.005.

Nonaka D, Chiriboga L, Soslow RA. Expression of pax8 as a useful marker in distinguishing ovarian carcinomas from mammary carcinomas. Am J Surg Pathol. 2008;32(10):1566–71. doi:10.1097/PAS.0b013e31816d71ad.

Ormsby AH, Snow JL, Su WP, Goellner JR. Diagnostic immunohistochemistry of cutaneous metastatic breast carcinoma: a statistical analysis of the utility of gross cystic disease fluid protein-15 and estrogen receptor protein. J Am Acad Dermatol. 1995;32(5 Pt 1):711–6.

Park SG, Song JY, Song IG, Kim MS, Shin BS. Cutaneous extraskeletal osteosarcoma on the scar of a previous bone graft. Ann Dermatol. 2011;23 Suppl 2:S160–4. doi:10.5021/ad.2011.23.S2.S160.

Park SY, Kim BH, Kim JH, Lee S, Kang GH. Panels of immunohistochemical markers help determine primary sites of metastatic adenocarcinoma. Arch Pathol Lab Med. 2007;131(10):1561–7. doi:10.1043/1543-2165(2007)131[1561:POIMHD]2.0.CO;2.

Penn I, First MR. Merkel's cell carcinoma in organ recipients: report of 41 cases. Transplantation. 1999;68(11):1717–21.

Perry MD, Gore M, Seigler HF, Johnston WW. Fine needle aspiration biopsy of metastatic melanoma. A morphologic analysis of 174 cases. Acta Cytol. 1986a;30(4):385–96.

Perry MD, Seigler HF, Johnston WW. Diagnosis of metastatic malignant melanoma by fine needle aspiration biopsy: a clinical and pathologic correlation of 298 cases. J Natl Cancer Inst. 1986b;77(5):1013–21.

Poulsen MG, Rischin D, Porter I, Walpole E, Harvey J, Hamilton C, et al. Does chemotherapy improve survival in high-risk stage I and II Merkel cell carcinoma of the skin? Int J Radiat Oncol Biol Phys. 2006;64(1):114–9. doi:10.1016/j.ijrobp.2005.04.042.

Pulitzer M, Brady MS, Blochin E, Amin B, Teruya-Feldstein J. Anaplastic large cell lymphoma: a potential pitfall in the differential diagnosis of melanoma. Arch Pathol Lab Med. 2013;137(2):280–3. doi:10.5858/arpa.2011-0532-CR.

Pulitzer MP, Amin BD, Busam KJ. Merkel cell carcinoma: review. Adv Anat Pathol. 2009;16(3):135–44. doi:10.1097/PAP.0b013e3181a12f5a.

Ragsdale MI, Lehmer LM, Ragsdale BD, Chow WA, Carson RT. Cutaneous metastasis of osteosarcoma in the scalp. Am J Dermatopathol. 2011;33(6):e70–3. doi:10.1097/DAD.0b013e318214a7ea.

Ramos-Herberth FI, Karamchandani J, Kim J, Dadras SS. SOX10 immunostaining distinguishes desmoplastic melanoma from excision scar. J Cutan Pathol. 2010;37(9):944–52. doi:10.1111/j.1600-0560.2010.01568.x.

Requena L, Santonja C, Stutz N, Kaddu S, Weenig RH, Kutzner H, et al. Pseudolymphomatous cutaneous angiosarcoma: a rare variant of cutaneous angiosarcoma readily mistaken for cutaneous lymphoma. Am J Dermatopathol. 2007;29(4):342–50. doi:10.1097/DAD.0b013e31806f1856.

Richardson SK, Tannous ZS, Mihm Jr MC. Congenital and infantile melanoma: review of the literature and report of an uncommon variant, pigment-synthesizing melanoma. J Am Acad Dermatol. 2002;47(1):77–90.

Riddle ND, Bowers JW, Bui MM, Morgan MB. Primary cutaneous osteoblastic osteosarcoma: a case report and review of the current literature. Clin Exp Dermatol. 2009;34(8):e879–80. doi:10.1111/j.1365-2230.2009.03637.x.

Robins P, Perez MI. Lymphoepithelioma-like carcinoma of the skin treated by Mohs micrographic surgery. J Am Acad Dermatol. 1995;32(5 Pt 1):814–6.

Rocamora A, Badia N, Vives R, Carrillo R, Ulloa J, Ledo A. Epidermotropic primary neuroendocrine (Merkel cell) carcinoma of the skin with Pautrier-like microabscesses. Report of three cases and review of the literature. J Am Acad Dermatol. 1987;16(6):1163–8.

Rodrigues LK, Leong SP, Ljung BM, Sagebiel RW, Burnside N, Hu T, et al. Fine needle aspiration in the diagnosis of metastatic melanoma. J Am Acad Dermatol. 2000;42(5 Pt 1):735–40.

Rosen T. Cutaneous metastases. Med Clin North Am. 1980;64(5):885–900.

Rubinstein JC, Sznol M, Pavlick AC, Ariyan S, Cheng E, Bacchiocchi A, et al. Incidence of the V600K mutation among melanoma patients with BRAF mutations, and potential therapeutic response to the specific BRAF inhibitor PLX4032. J Transl Med. 2010;8:67. doi:10.1186/1479-5876-8-67.

Saad RS, Ghorab Z, Khalifa MA, Xu M. CDX2 as a marker for intestinal differentiation: Its utility and limitations. World J Gastrointest Surg. 2011;3(11):159–66. doi:10.4240/wjgs.v3.i11.159.

Saeed S, Keehn CA, Morgan MB. Cutaneous metastasis: a clinical, pathological, and immunohistochemical appraisal. J Cutan Pathol. 2004;31(6):419–30. doi:10.1111/j.0303-6987.2004.00207.x.

Sahi H, Koljonen V, Kavola H, Haglund C, Tukiainen E, Sihto H, et al. Bcl-2 expression indicates better prognosis of Merkel cell carcinoma regardless of the presence of Merkel cell polyomavirus. Virchows Arch. 2012;461(5):553–9. doi:10.1007/s00428-012-1310-3.

Salamanca J, Dhimes P, Pinedo F, Gomez de la Fuente E, Perez Espejo G, Martinez-Tello FJ. Extraskeletal cutaneous chondroblastic osteosarcoma: a case report. J Cutan Pathol. 2008;35(2):231–5. doi:10.1111/j.1600-0560.2007.00785.x.

Samarendra P, Berkowitz L, Kumari S, Alexis R. Primary nodal neuroendocrine (Merkel cell) tumor in a patient with HIV infection. South Med J. 2000;93(9):920–2.

Sariola H, Terava H, Rapola J, Saarinen UM. Cell-surface ganglioside GD2 in the immunohistochemical detection and differential diagnosis of neuroblastoma. Am J Clin Pathol. 1991;96(2):248–52.

Sariya D, Ruth K, Adams-McDonnell R, Cusack C, Xu X, Elenitsas R, et al. Clinicopathologic correlation of cutaneous metastases: experience from a cancer center. Arch Dermatol. 2007;143(5):613–20. doi:10.1001/archderm.143.5.613.

Scatena C, Massi D, Franchi A, De Paoli A, Canzonieri V. Rhabdomyosarcoma of the skin resembling carcinosarcoma: report of a case and literature review. Am J Dermatopathol. 2012;34(1):e1–6. doi:10.1097/DAD.0b013e31822381fas.

SEER. SEER Stat Fact Sheets: melanoma of the skin. [Internet]: National Cancer Institute; 2012. [Updated Nov 2012]. Available from: http://www.seer.cancer.gov/statfacts/html/melan.html

Setoyama M, Kanda A, Kanzaki T. Cutaneous metastasis of an osteosarcoma. A case report. Am J Dermatopathol. 1996;18(6):629–32.

Setterfield J, Sciot R, Debiec-Rychter M, Robson A, Calonje E. Primary cutaneous epidermotropic alveolar rhabdomyosarcoma with t(2;13) in an elderly woman: case report and review of the literature. Am J Surg Pathol. 2002;26(7):938–44.

Sihto H, Kukko H, Koljonen V, Sankila R, Bohling T, Joensuu H. Clinical factors associated with Merkel cell polyomavirus infection in Merkel cell carcinoma. J Natl Cancer Inst. 2009;101(13):938–45. doi:10.1093/jnci/djp139.

Smith PD, Patterson JW. Merkel cell carcinoma (neuroendocrine carcinoma of the skin). Am J Clin Pathol. 2001;115(Suppl):S68–78.

Strum SB, Park JK, Rappaport H. Observation of cells resembling Sternberg-Reed cells in conditions other than Hodgkin's disease. Cancer. 1970;26(1):176–90.

Suchak R, Thway K, Zelger B, Fisher C, Calonje E. Primary cutaneous epithelioid angiosarcoma: a clinicopathologic study of 13 cases of a rare neoplasm occurring outside the setting of conventional angiosarcomas and with predilection for the limbs. Am J Surg Pathol. 2011;35(1):60–9. doi:10.1097/PAS.0b013e3181fee872.

Swanson SA, Cooper PH, Mills SE, Wick MR. Lymphoepithelioma-like carcinoma of the skin. Mod Pathol. 1988;1(5):359–65.

Tai PT, Yu E, Tonita J, Gilchrist J. Merkel cell carcinoma of the skin. J Cutan Med Surg. 2000a;4(4):186–95.

Tai PT, Yu E, Winquist E, Hammond A, Stitt L, Tonita J, et al. Chemotherapy in neuroendocrine/Merkel cell carcinoma of the skin: case series and review of 204 cases. J Clin Oncol. 2000b;18(12):2493–9.

Tarantola TI, Vallow LA, Halyard MY, Weenig RH, Warschaw KE, Grotz TE, et al. Prognostic factors in Merkel cell carcinoma: analysis of 240 cases. J Am Acad Dermatol. 2013;68(3):425–32. doi:10.1016/j.jaad.2012.09.036.

Terashima T, Kanazawa M. Lung cancer with skin metastasis. Chest. 1994;106(5):1448–50.

Terrier-Lacombe MJ, Guillou L, Chibon F, Gallagher G, Benhattar J, Terrier P, et al. Superficial primitive Ewing's sarcoma: a clinicopathologic and molecular cytogenetic analysis of 14 cases. Mod Pathol. 2009;22(1):87–94. doi:10.1038/modpathol.2008.156.

Tilling T, Moll I. Which are the cells of origin in merkel cell carcinoma? J Skin Cancer. 2012;2012:680410. doi:10.1155/2012/680410.

Tokura Y, Yamanaka K, Wakita H, Kurokawa S, Horiguchi D, Usui A, et al. Halo congenital nevus undergoing spontaneous regression. Involvement of T-cell immunity in involution and presence of circulating anti-nevus cell IgM antibodies. Arch Dermatol. 1994;130(8):1036–41.

van Akkooi AC, Voit CA, Verhoef C, Eggermont AM. New developments in sentinel node staging in melanoma: controversies and alternatives. Curr Opin Oncol. 2010;22(3):169–77. doi:10.1097/CCO.0b013e328337aa78.

Van Nguyen A, Argenyi ZB. Cutaneous neuroblastoma. Peripheral neuroblastoma. Am J Dermatopathol. 1993;15(1):7–14.

Vanchinathan V, Marinelli EC, Kartha RV, Uzieblo A, Ranchod M, Sundram UN. A malignant cutaneous neuroendocrine tumor with features of Merkel cell carcinoma and differentiating neuroblastoma. Am J Dermatopathol. 2009;31(2):193–6. doi:10.1097/DAD.0b013e31819114c4.

Voit C, Mayer T, Proebstle TM, Weber L, Kron M, Krupienski M, et al. Ultrasound-guided fine-needle aspiration cytology in the early detection of melanoma metastases. Cancer. 2000;90(3):186–93.

Wallace ML, Longacre TA, Smoller BR. Estrogen and progesterone receptors and anti-gross cystic disease fluid protein 15 (BRST-2) fail to distinguish metastatic breast carcinoma from eccrine neoplasms. Mod Pathol. 1995;8(9):897–901.

Weed BR, Folpe AL. Cutaneous CD30-positive epithelioid angiosarcoma following breast-conserving therapy and irradiation: a potential diagnostic pitfall. Am J Dermatopathol. 2008;30(4):370–2. doi:10.1097/DAD.0b013e31817330ff.

Weedon D. Weedon's skin pathology. 3rd ed. China: Elsevier; 2010. 1041 p.

Weiss LM, Movahed LA, Butler AE, Swanson SA, Frierson Jr HF, Cooper PH, et al. Analysis of lymphoepithelioma and lymphoepithelioma-like carcinomas for Epstein-Barr viral genomes by in situ hybridization. Am J Surg Pathol. 1989;13(8):625–31.

Wick MR, Swanson PE, LeBoit PE, Strickler JG, Cooper PH. Lymphoepithelioma-like carcinoma of the skin with adnexal differentiation. J Cutan Pathol. 1991;18(2):93–102.

Wick MR. Immunohistochemical approaches to the diagnosis of undifferentiated malignant tumors.

Ann Diagn Pathol. 2008;12(1):72–84. doi:10.1016/j.anndiagpath.2007.10.003.

Wyatt AJ, Hansen RC. Pediatric skin tumors. Pediatr Clin North Am. 2000;47(4):937–63.

Ziprin P, Smith S, Salerno G, Rosin RD. Two cases of merkel cell tumour arising in patients with chronic lymphocytic leukaemia. Br J Dermatol. 2000; 142(3):525–8.

Zur Hausen A, Rennspiess D, Winnepenninckx V, Speel EJ, Kurz AK. Early B-cell differentiation in Merkel cell carcinomas: clues to cellular ancestry. Cancer Res. 2013. doi:10.1158/0008-5472.CAN-13-0616.