

# Cutaneous Metastases

## A Review and Diagnostic Approach to Tumors of Unknown Origin

Gabriel Habermehl, MD; Jennifer Ko, MD, PhD

• **Context.**—Cutaneous metastases from a distant malignancy are a diagnostic challenge for pathologists. Secondary involvement of the skin by a metastatic process portends a much worse clinical prognosis than any primary cutaneous malignant mimickers. Immunohistochemical staining methods continue to evolve and are of paramount importance in diagnosis.

**Objective.**—To review the clinical, histopathologic, and immunohistochemical staining patterns for commonly encountered entities and discuss potential pitfalls in diagnosis. A practical guide useful in approaching cutaneous metastases of unknown primary is outlined.

**Data Sources.**—An extensive search and review of

literature in PubMed was performed, processed, and condensed.

**Conclusions.**—Cutaneous metastases have broad histopathologic patterns. They are nearly always dermal based, with an overall foreign appearance. They can be single papules/nodules or multiple in number, mimicking an inflammatory or infectious process. Ultimately, immunohistochemistry remains an essential diagnostic tool, and clinical correlation is paramount in the workup of these entities.

(*Arch Pathol Lab Med.* 2019;143:943–957; doi: 10.5858/arpa.2018-0051-RA)

**D**iagnosis and workup of a malignant neoplasm of unknown origin remains one of the most difficult, yet essential, skills of the practicing pathologist. In many instances, the first question is whether a neoplasm represents a metastasis from another tumor or a primary cutaneous malignancy, the latter portending a drastically better prognosis. Though more commonly the result of known widely disseminated disease, cutaneous metastases can be the first indication of an internal malignancy.<sup>1,2</sup> Given the prognostic ramifications, important staging and therapeutic information should be captured and conveyed to clinicians via these specimens, and the pathologist must maintain a high index of suspicion.<sup>3,4</sup> Here, we provide a functional review of the most commonly encountered cutaneous metastases and a guiding histopathologic and immunohistochemical framework to approach them while also avoiding potential pitfalls.

### Incidence

When examining a neoplasm where metastasis is a consideration, it helps to recall the overall incidence of certain tumors in the skin. Estimated cutaneous metastases have been reported to occur in 0.5% to 10.4% of all cancer patients.<sup>5–7</sup> Excluding melanoma—which is the most com-

mon source of cutaneous metastases (45% of cutaneous metastases)—Hu et al<sup>7</sup> listed carcinoma of the breast (51 of 124 cutaneous metastases cases; 2.42% of breast cancer patients) as the most frequent, followed by lung (23 cases; 1.78%), oropharyngeal (11 cases; 1.75%), and colon and rectal tumors (16 cases; 0.81%). Saeed et al<sup>4</sup> reviewed a total of 100 453 surgical accessions from the skin from a 10-year period (1993–2003) from the Veterans Affairs hospital system. Exclusion criteria included superficial lymph nodes involved by metastasis, recurrent melanoma within 5 cm of a surgical scar, and review cases from outside institutions. Of this total, 77 cutaneous metastases were identified, with lung being the most frequent internal malignancy (22 cases; 28.6%) followed by metastatic melanoma (nonlocal recurrence; 14 cases; 18.2%), gastrointestinal malignancy (11 cases; 14.2%), genitourinary malignancy (8 cases; 10.4%), and head and neck primary (7 cases; 9.1%). Older studies have placed breast carcinoma as most common (21.4%–26.5% of cases) followed by a mixed picture of lung (0.6%–5.9%), colorectal (2.3%–6%), and oropharyngeal (4.6%–17.3%).<sup>2,8,9</sup> In general, cutaneous metastasis occurs much more commonly in men, with some studies estimating as high as 37% in men with visceral malignancy but only 6% in women.<sup>5,6</sup> Also evident is the relative rarity of prostate cancer to involve the skin despite its high overall incidence.

### Clinical Features of Cutaneous Metastasis

Cutaneous metastases present clinically along a wide morphologic spectrum that includes papules/plaques, nodules, ulcers, and inflammatory eruptions.<sup>2,10</sup> The majority of cases present as a single lesion, are limited to a single anatomic distribution, and are painless.<sup>11–13</sup> Abdomen and chest wall, head/scalp, and umbilicus are common sites.<sup>1,14–18</sup>

Accepted for publication July 5, 2018.

Published online December 28, 2018.

From the Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio.

The authors have no relevant financial interest in the products or companies described in this article.

Corresponding author: Jennifer Ko, MD, PhD, Pathology and Laboratory Medicine Institute, Cleveland Clinic, 9500 Euclid Ave, L250, Cleveland, OH 44195 (email: koj2@ccf.org).

Brief Review of Normal Antibody Profiles and Staining Patterns of Common Cutaneous Cell Types		
Antibody Type	Normal Cell Type Stained	Common Structures Identified
LMWCK (CK7, CAM5.2) HMWCK (CK5/6) S100, SOX10	Apocrine and eccrine cells Keratinocytes, follicular adnexa Basal-layer melanocytes	Sweat ducts/glands Hair follicles, epidermis Melanocytic nests Nerves Myoepithelium Sweat glands (S100 only)
CEA, EMA CD31, CD34, ERG-1	Apocrine and eccrine cells Endothelial cells	Adnexal ducts (CEA) and sebaceous glands (CEA/EMA) Vascular endothelium

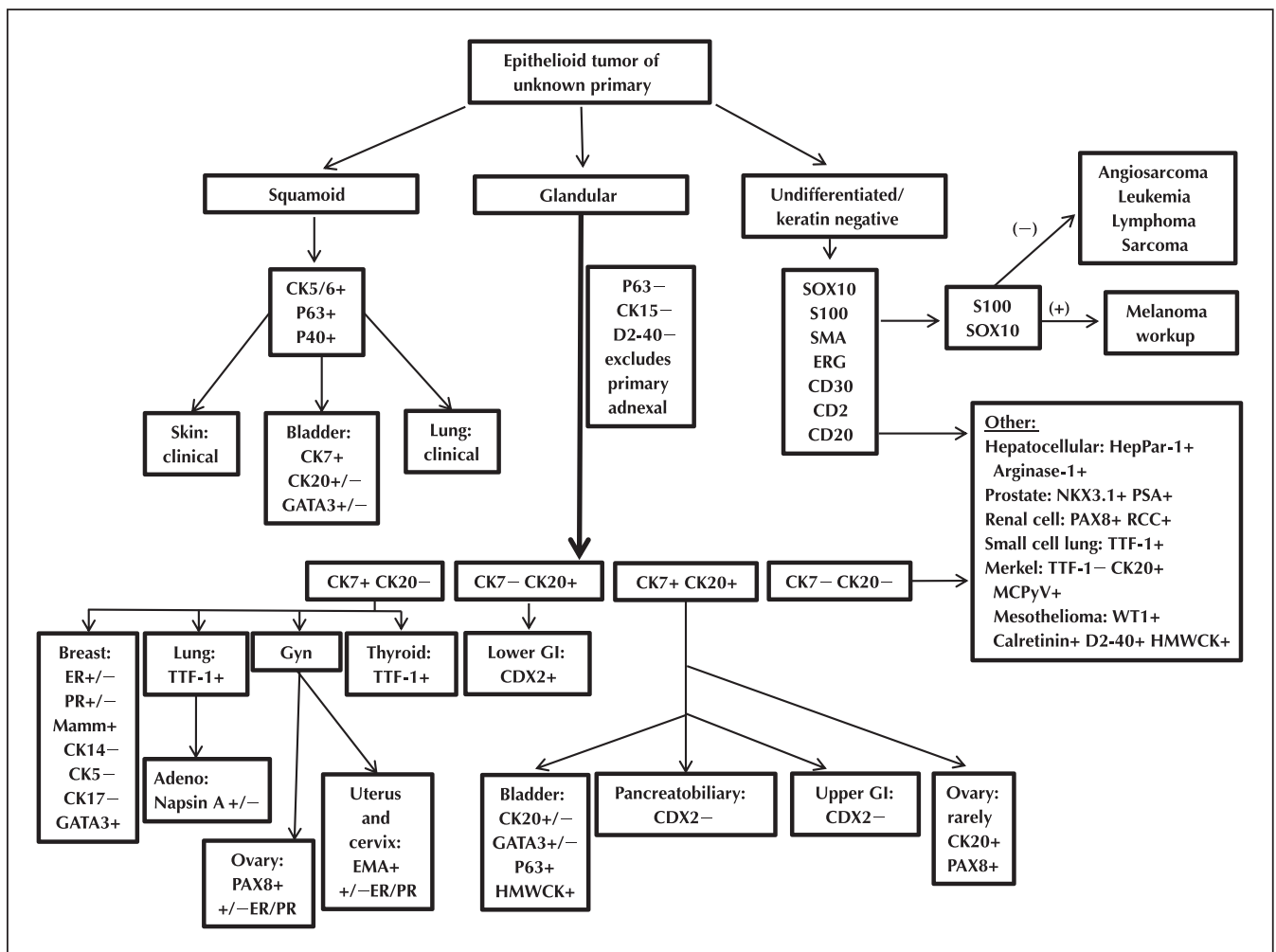
Abbreviations: CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; ERG, ETS-related gene; HMWCK, high-molecular-weight cytokeratin; LMWCK, low-molecular-weight cytokeratin; SOX10, SRY-related HMG-box 10.

Metastases can present synchronously to the primary tumor (at the same time), metachronously (months to years after; average time 33 months; range, up to 22 years), or precociously (before). Metachronous lesions are poor prognostic indicators, with 76% (59 of 77 patients) exhibiting widespread metastases at biopsy and 66% (51 patients) expiring within 6 months.<sup>4</sup> In one series of 51 patients from a single center, only 26 cases (51%) were submitted with a

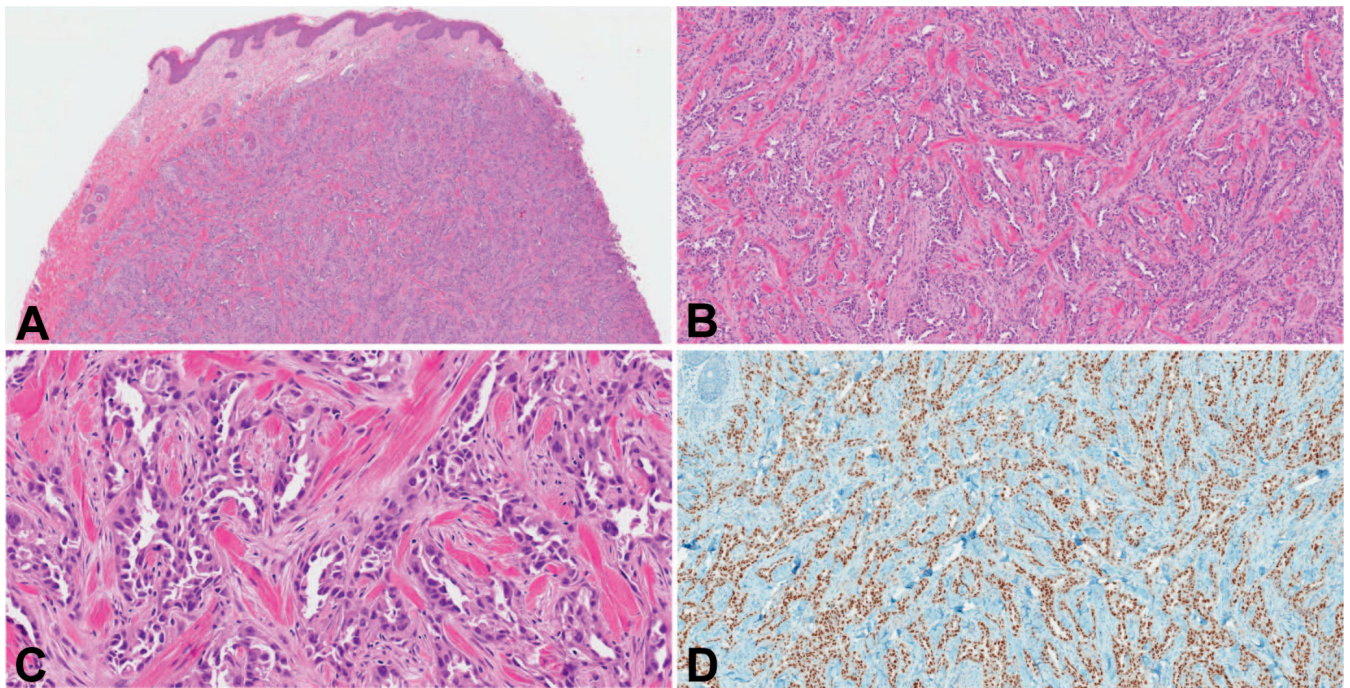
clinical diagnosis of skin metastasis, yet 47 of these cases (92%) had a history of stage III or IV disease; thus, pathologists should maintain a high index of suspicion.<sup>11</sup>

### GENERAL DIAGNOSTIC APPROACH

Morphologically, cutaneous metastases usually spare the epidermis. In the series from Saeed et al,<sup>4</sup> the majority of cases were characterized from low magnification as "bottom



**Figure 1.** Summary of the workup algorithm for epithelioid cutaneous metastases to the skin. Abbreviations: CD, cluster of differentiation; CDX2, caudal type homeobox 2; CK, cytokeratin; EMA, epithelial membrane antigen; ER, estrogen receptor; ERG, ETS-related gene; GATA3, GATA binding protein 3; HepPar-1, hepatocyte paraffin 1; HMWCK, high-molecular-weight cytokeratin; Mamm, mammaglobin; MCPyV, Merkle cell polyomavirus; PAX8, paired box gene 8; PR, progesterone receptor; PSA, prostate-specific antigen; RCC, renal cell carcinoma; SMA, smooth muscle actin; SOX10, SRY-related HMG-box 10; TTF-1, thyroid transcription factor 1; WT1, Wilms tumor 1.



**Figure 2.** Metastatic lung carcinoma. Low magnification shows a dermal infiltrate of cells forming glandular and trabecular patterns (A). Intermediate and high magnifications show atypical hyperchromatic cells with loose glandular formation infiltrating through collagen fibers (B and C). Metastatic lung adenocarcinoma in the skin will often retain strong nuclear staining for TTF-1 (D) (hematoxylin-eosin, original magnifications  $\times 40$  [A],  $\times 100$  [B], and  $\times 200$  [C]; original magnification  $\times 100$  [D]).

heavy” and often formed a pyramidal or broad-based architecture. Nodular, infiltrative, diffuse, and intravascular morphologic patterns have been described.<sup>17</sup> In general, all patterns appear to exhibit an overall dermal predominance with a foreign appearance. As such, one should think twice when considering a cutaneous metastasis in a case with a predominately superficial and epidermal-based architecture.

The most commonly considered mimickers of cutaneous metastases are primary cutaneous adnexal malignancies. Most often, malignant adnexal tumors will show at least focal well-differentiated, benign-appearing precursor areas. Initial immunohistochemical staining panels to distinguish among epithelioid entities should include cytokeratins (CKs) such as CK7 and CK20 (cytoplasmic stain, variably marks primarily glandular epithelium), SRY-related HMG-box 10 (SOX10; nuclear stain, marks melanocytic, neural, and myoepithelial cells), and p63. p63 is a well-known nuclear stain used in ruling in squamous cell carcinoma, but it will also stain positively in nearly all native carcinomas of the skin, including adnexal carcinomas. In this way, p63 negativity is very useful in excluding a primary cutaneous carcinoma.<sup>19,20</sup> Other markers helpful in this setting include CK15 and D2-40, which have been shown to be predominantly positive in primary cutaneous adenocarcinomas over metastatic adenocarcinomas (98% and 96% specificity, respectively). In one study, positive staining in a panel including p63, CK15, and D2-40 most strongly argued in favor of a primary cutaneous neoplasm.<sup>21</sup> As such, primary adnexal tumors will generally stain positively for CK7, CK15, D2-40, and p63 and negatively for CK20 and SOX10. The immunohistochemistry staining patterns of normal cutaneous structures, helpful in ruling out primary cutaneous neoplasms, are provided in the Table, and a summary of

the general diagnostic approach for most common metastatic entities is provided in Figure 1.

**Pearls and Pitfalls.**—In dermal/subcutaneous epithelioid tumors, initial immunohistochemical staining panels should differentiate carcinoma versus melanoma or myoepithelial tumors and primary cutaneous versus metastatic carcinomas.

A useful panel may include CK7/CK20, positive in adnexal ( $CK7^+CK20^-$ ) and metastatic (variable CK7/20 depending on origin) adenocarcinoma; SOX10, positive in melanoma and neural and myoepithelial tumors; and p63, CK15, and D2-40, positive in primary cutaneous adenocarcinomas.

Metastatic or primary squamous cell carcinomas are negative for CK7 (usually but not always), CK20, and SOX10 and are positive for p63 and CK5/6; distinction between metastases and primary squamous carcinomas requires clinical correlation.

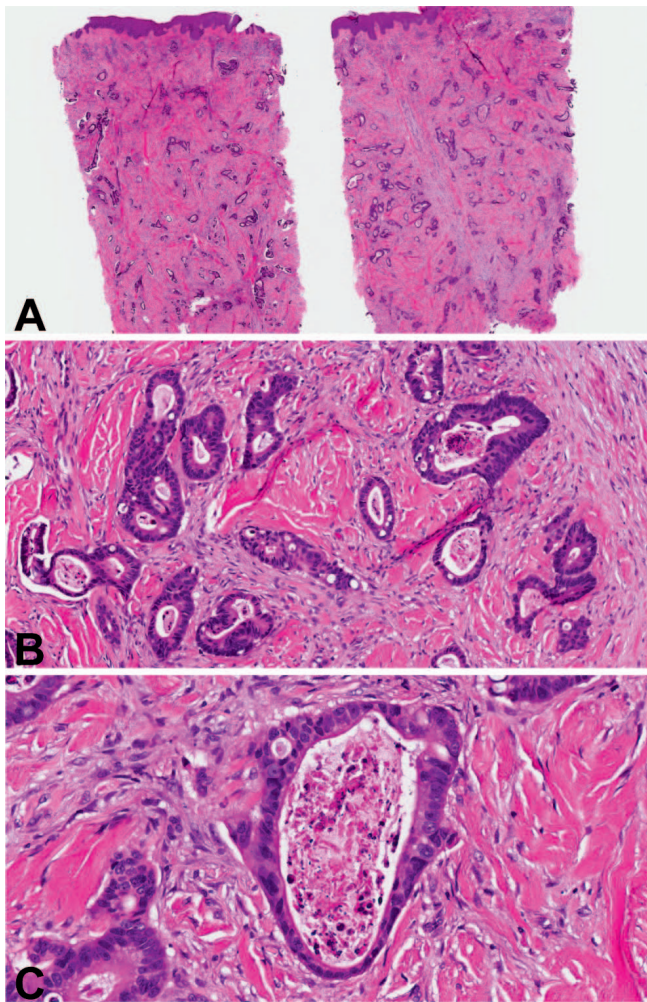
Metastatic spindle cell and vascular neoplasms are rare and are discussed later in the review.

## CARCINOMA

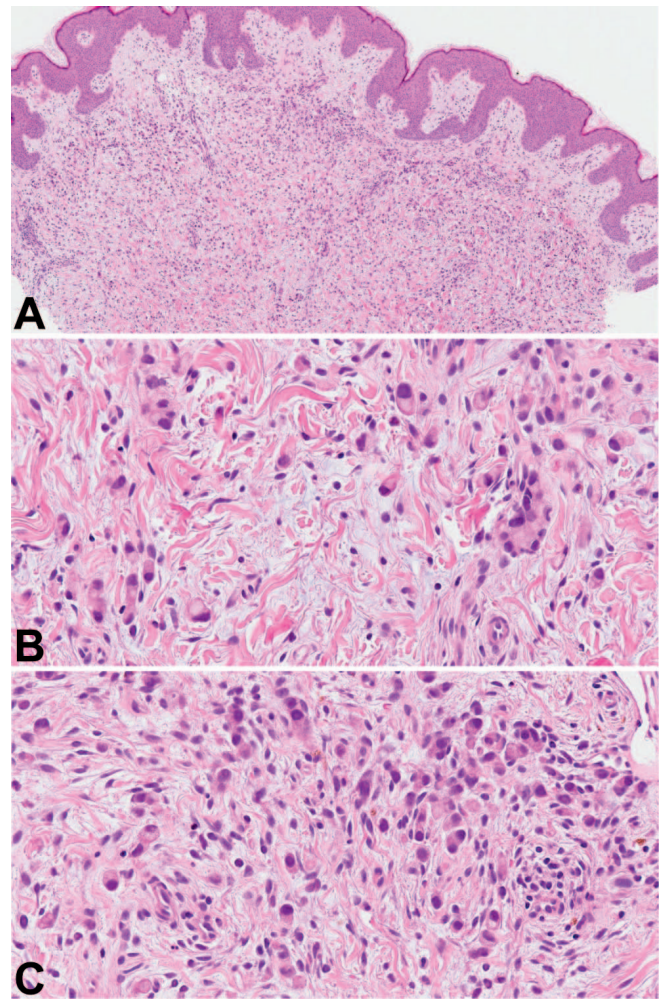
### Lung

Lung origin is one of the most frequent types of cutaneous metastases, especially in men, including non-small cell lung carcinomas (50%) and small cell lung carcinoma (30%).<sup>10,22</sup> Thoracostomy or needle aspiration sites of involvement are somewhat unique in this setting, as are crops of multiple papulonodules clinically suspicious for viral exanthem.<sup>5,23</sup>

Histologically, metastases from lung adenocarcinoma are often moderately differentiated, with solid nests, sheets, and cords of cells with no epidermal connection. Commonly retained features included mucin deposition and at least



**Figure 3.** Metastatic adenocarcinoma of the colon. Low magnification shows discrete glandular structures involving the superficial and deep dermis (A). High magnification shows well- to moderately differentiated neoplastic cells with prominent nucleoli and vacuolated cytoplasm (B). Intraluminal necrosis with neutrophilic karyorrhexis is readily identified (C) (hematoxylin-eosin, original magnifications  $\times 20$  [A],  $\times 100$  [B], and  $\times 200$  [C]).



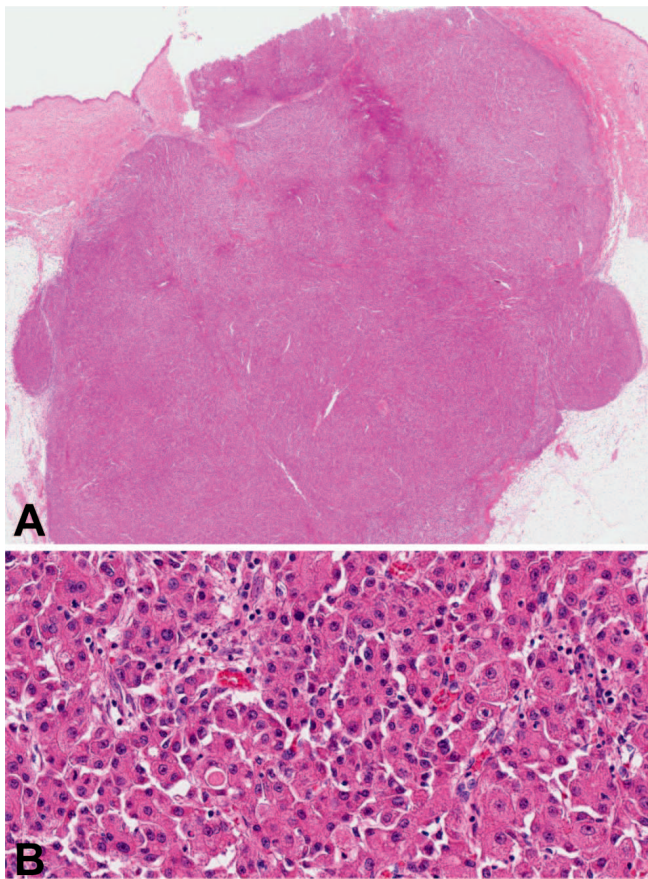
**Figure 4.** Metastatic gastrointestinal adenocarcinoma with signet-ring morphology. Low magnification shows a loosely nodular infiltrate of poorly formed glands and single cells infiltrating into the superficial to mid dermis (A). High magnification shows a predominately single-celled infiltrate of dyshesive neoplastic cells with hyperchromatic, eccentrically located nuclei and large cytoplasmic vacuoles (B and C) (hematoxylin-eosin, original magnifications  $\times 40$  [A] and  $\times 200$  [B and C]).

focal gland formation (Figure 2, A through D). Given the (at least focal) retention of a glandular component, lung origin can often be proven with immunoreactivity for thyroid transcription factor 1 (TTF-1) and CK7. Napsin A often stains lung adenocarcinoma, but is nonspecific, staining many histologic mimickers, including large cell neuroendocrine carcinomas and thyroid tumors.<sup>24</sup> Napsin A is also reduced in mucinous and sarcomatoid tumors. Another potential pitfall; lung adenocarcinoma will often stain positive for Ber-EP4 and thus could be confused for a basal cell carcinoma with insular growth pattern.<sup>25,26</sup>

Metastatic squamous carcinoma of the lung to the skin occurs less commonly than adenocarcinoma.<sup>27,28</sup> In the absence of clinical history, distinguishing metastatic lesions from primary cutaneous carcinoma can be very difficult. Likely, the most telling will be routine hematoxylin-eosin findings, including moderate differentiation and an uncharacteristic deep dermal predominance.

Metastases from small cell carcinoma can display either an infiltrative or a nodular growth pattern and commonly maintain typical neuroendocrine nuclear features of finely granular chromatin with indistinct nucleoli. Nuclear molding and crush artifact are often identifiable in the skin biopsy. Tumors maintain immunoreactivity for TTF-1 and CAM5.2 with negative staining for CK7 and CK20.<sup>29</sup> A common pitfall includes confusing a lung neuroendocrine metastasis for a primary cutaneous Merkel cell carcinoma (MCC). Though we commonly hold out for CK20 (often paranuclear dotlike) positivity in MCC, this differential is usually better resolved with TTF-1 and CK7 (both negative in MCC), given that a portion of MCCs are negative for CK20 (estimated 5%).<sup>24,30,31</sup>

Lastly, one must always consider a lung metastasis of pleural differentiation. Histologically, pleural mesothelioma typically shows epithelioid cytomorphology with glandular and tubulopapillary architecture, though sarcomatoid mor-



**Figure 5.** Metastatic hepatocellular carcinoma. Low magnification shows a prominent nodular aggregate of neoplastic cells forming solid and compact trabecular architecture, giving the impression of pseudovascular spaces (A). High magnification shows hepatoid neoplastic cells with marked nuclear hyperchromasia and ample brightly eosinophilic cytoplasm arranged in loose nests or chords (B) (hematoxylin-eosin, original magnifications  $\times 20$  [A] and  $\times 200$  [B]).

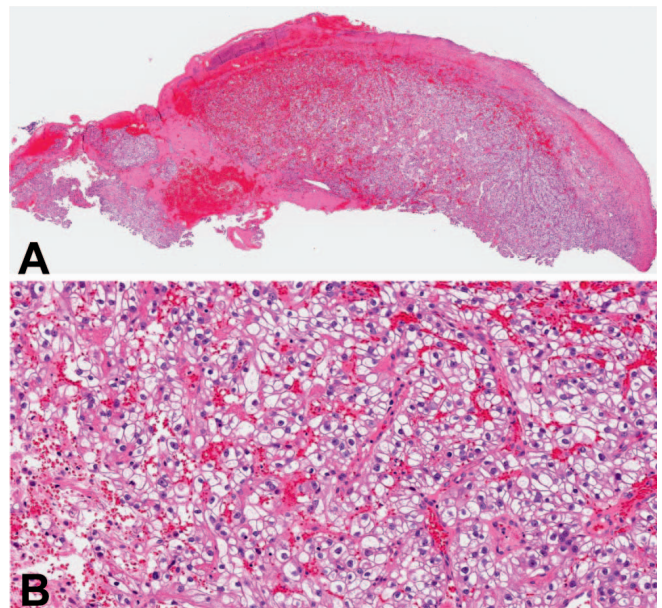
phenologies have been described.<sup>32</sup> Neoplastic cells are typically reactive with low-molecular-weight cytokeratin and are negative for carcinoembryonic antigen, TTF-1, and cluster of differentiation (CD) 31.<sup>26,33</sup> Mesothelial markers including calretinin, Wilms tumor 1, and D2-40 are positive, albeit not entirely specific.<sup>34</sup> In most cases the best “stain” to exclude this entity is a good clinical history. As such, the recommendation for clinical and radiologic correlation can be made in the diagnostic comment.

**Pearls and Pitfalls.**—Lung adenocarcinoma may mimic insular growth pattern of basal cell carcinoma and stain positively for Ber-EP4.

A significant minority of MCCs may be CK20 negative, and a differential diagnosis of MCC versus lung neuroendocrine metastases may be better resolved with TTF-1 and CK7.

### Gastrointestinal and Hepatocellular

Of the cutaneous metastases of gastrointestinal origin, the most common are from a colorectal primary, which can often be multiple large papules or plaques +/- ulceration.<sup>35,36</sup> The most frequently described locations include the abdominal wall and umbilicus (ie, Sister Mary Joseph nodule, defined as a mass involving the umbilicus on

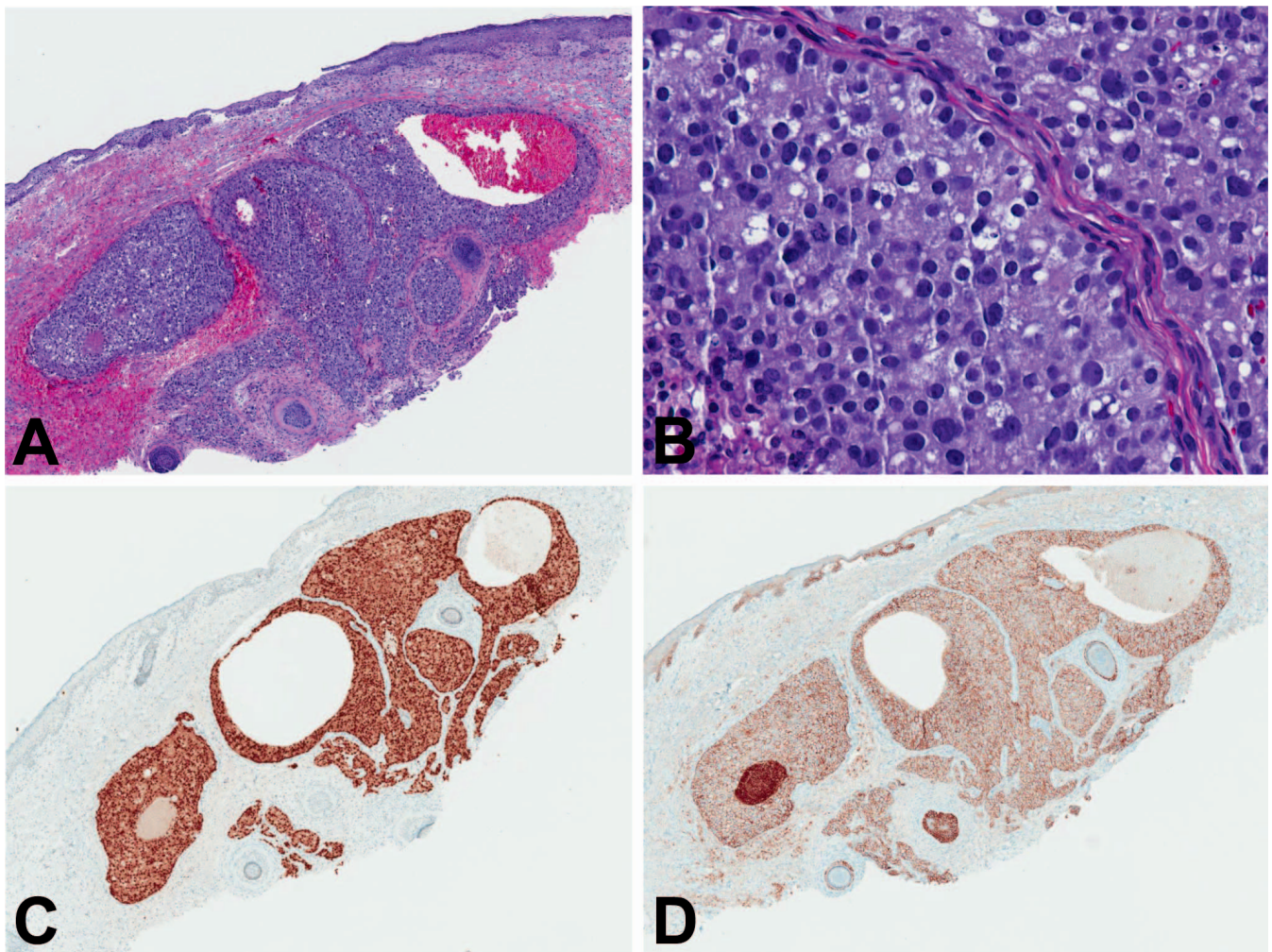


**Figure 6.** Metastatic renal cell carcinoma, clear cell type. Low magnification shows a nodular infiltrate of neoplastic cells arranged in a predominately trabecular pattern involving the superficial dermis. Epidermal ulceration as well as prominent extravasation of erythrocytes can be seen (A). High magnification shows neoplastic cells with abundant clear cytoplasm, slight nuclear angulation, and prominent nucleoli amid a prominent capillary network (B) (hematoxylin-eosin, original magnifications  $\times 20$  [A] and  $\times 200$  [B]).

physical examination). However, other forms of adenocarcinoma, including gastric, ovarian, or, less commonly, hepatobiliary types, can also present this way.<sup>37–41</sup> Interestingly, cutaneous lesions from gastric carcinoma have been reported present in patterns ranging from allergic contact dermatitis to warts to soft tissue tumors, whereas hepatocellular metastases<sup>42,43</sup> can clinically mimic vascular lesions, including lobular capillary hemangioma.<sup>44–47</sup>

Gastrointestinal skin metastases are often well to moderately differentiated and consist of mucin-producing cells arranged in glandular structures (Figure 3, A through C), though solid and single-cell patterns are possible. Colorectal tumors often retain foci of neutrophilic karyorrhexis within glandular lumina—so-called dirty necrosis. Gastric carcinomas may have smaller glandular clusters in a more fibrous stroma, and signet-ring cell morphologies are not uncommon (Figure 4, A through C).<sup>48,49</sup> Hepatocellular carcinomas can show pseudoglandular, solid, and trabecular patterns, with cells containing abundant eosinophilic cytoplasm, large round to hyperchromatic nuclei, and prominent nucleoli (Figure 5, A and B).<sup>50</sup> Foci of necrosis mimicking colonic-type dirty necrosis has been reported.<sup>50</sup> Meanwhile, cholangiocarcinomas have more angulated glands of moderately to poorly differentiated adenocarcinoma. They are associated with a marked desmoplastic stromal response but usually lack further specific features.<sup>51</sup>

Immunohistochemically, we have found a panel including CK7 (nonreactive), CK20, and caudal type homeobox 2 (CDX2) (both immunoreactive) is most useful when a colorectal primary is suspected. Carcinoembryonic antigen will stain native glandular components of cutaneous adnexa, and so is not recommended. Gastric tumors are commonly



**Figure 7.** Metastatic adenocarcinoma of the prostate. Low magnification shows a prominent infiltrate of both solid nodules and large glands involving the superficial to mid dermis with paucity of native adnexal structures (A). High magnification shows well-differentiated neoplastic cells, ample amphophilic cytoplasm, and prominent nucleoli infiltrating readily through surrounding collagen (B), with nuclear expression of NKX3.1 (C) and membranous staining for Ber-EP4 (D) (hematoxylin-eosin, original magnifications  $\times 40$  [A] and  $\times 200$  [B]; original magnification  $\times 40$  [C and D]).

reactive for both CK7 and CK20. One potential pitfall is that gastric carcinomas can exhibit CDX2 positivity, similar to colorectal primary.<sup>52,53</sup> Hepatocellular carcinomas are non-reactive for CK7 and CK20; thus, additional markers are needed: hepatocyte paraffin 1 (HepPar-1) and arginase-1. HepPar-1 has decreased sensitivity for poorly differentiated hepatocellular carcinomas (as low as 50%). As such, arginase-1 is considered the superior marker, although well-differentiated variants of hepatocellular carcinoma can be nonreactive.<sup>54</sup> Lastly, cholangiocarcinomas are typically immunoreactive for CK7 and possibly CK20. More useful, perhaps, is that they lack diffuse expression of CDX2.

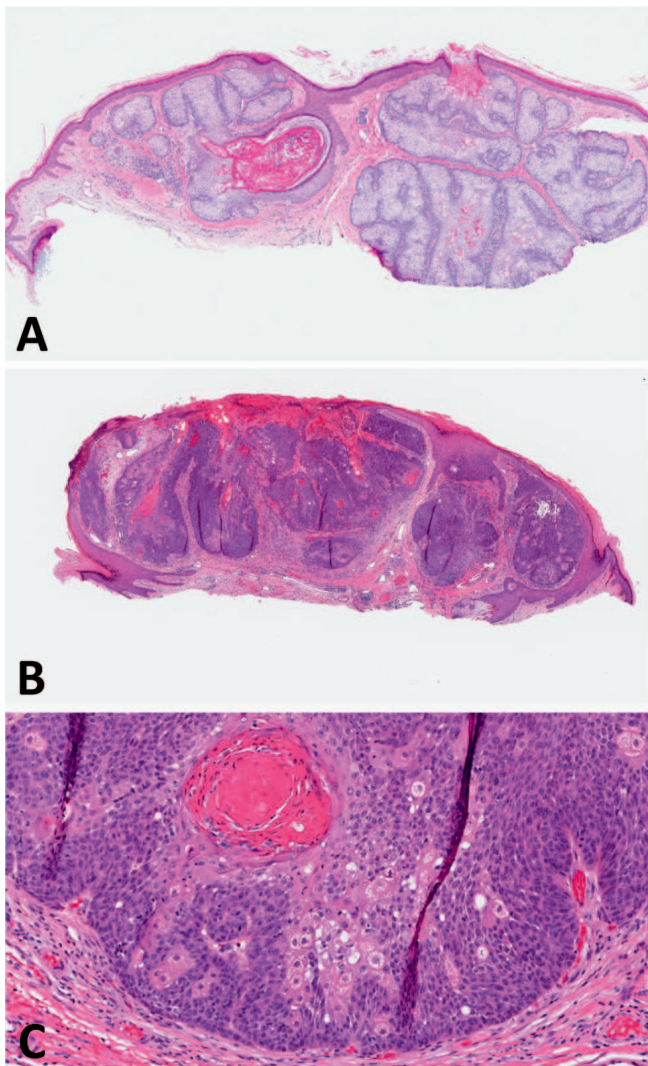
**Pearls and Pitfalls.**—CK7, CK20, and CDX2 are suggested if a gastrointestinal metastasis is suspected histologically: upper gastrointestinal, CK7<sup>+</sup>CK20<sup>+</sup>CDX2<sup>+/-</sup>; lower gastrointestinal, CK7<sup>-</sup>CK20<sup>+</sup>CDX2<sup>+</sup>; and biliary, CK7<sup>+</sup>CK20<sup>+/-</sup>CDX2<sup>-</sup>.

Arginase-1 is suggested for suspected liver metastases (CK7<sup>-</sup>CK20<sup>-</sup>). Beware the pitfall of using carcinoembryonic antigen, which will stain native adnexal structures (would be CK7<sup>+</sup>CK20<sup>-</sup>).

## Genitourinary

Estimates of genitourinary metastases to cutaneous sites are highly variable and are reported from as low as 0.22% to as high as 10.4%.<sup>4,7</sup> Some have estimated skin metastases secondary to renal cell carcinoma (RCC) specifically to be at approximately 3%.<sup>55,56</sup> Renal cell carcinomas are typically vascular clinically, like hepatic lesions, often mimicking Kaposi sarcoma or lobular capillary hemangioma.<sup>57,58</sup> Bladder, urothelial, and prostate lesions are often described as rubbery papules or nodules, and, like lung lesions, can have a viral-like or zosteriform pattern, or can have a Sister Mary Joseph nodule.<sup>59-61</sup> Cases of prostatic adenocarcinoma presenting as “lipoma,” large inflammatory plaques, or morpheaform-like lesions have been reported.<sup>62,63</sup>

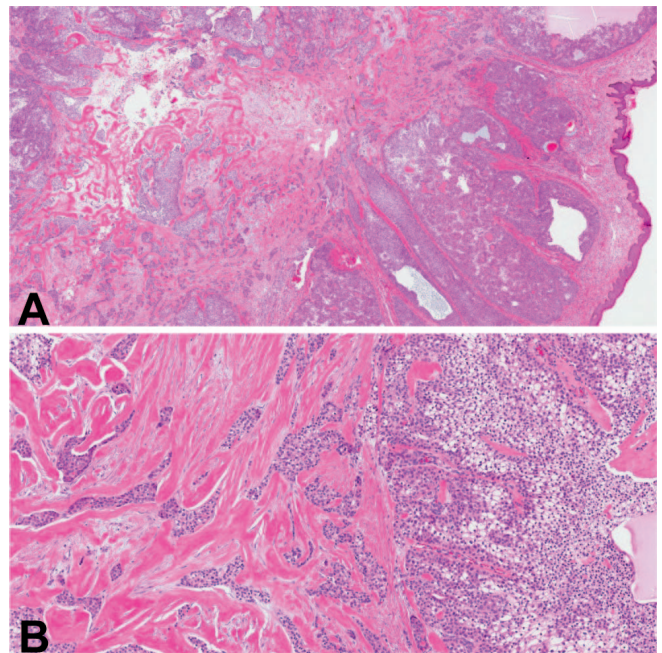
Clear cell carcinoma (the most common type of RCC) comprises the majority of cutaneous kidney metastases, and can show papillary, nested, trabecular, or cystic arrangements. A prominent capillary vasculature and clear, glycogenated cells with variably prominent nucleoli (Figure 6, A and B) are key features.<sup>64,65</sup> Urothelial metastases show broad cords and sheets of transitional-type epithelium.



**Figure 8.** Neoplasms of sebaceous differentiation. At scanning magnification, sebaceous adenoma is best identified because of its well-circumscribed nature, multilobular appearance, and attachment to the epidermal surface (A). Sebaceous carcinoma will show a large and nodular architecture with an overall basaloid proliferation of atypical cells and areas of necrosis (B). High magnification confirms cells with both basaloid and clear to vacuolated cytoplasmic features with nuclear atypia and mitotic activity (C) (hematoxylin-eosin, original magnifications  $\times 20$  [A and B] and  $\times 100$  [C]).

Marked nuclear anisocytosis and pleomorphism with abundant eosinophilic cytoplasm as well as squamitized nests can be seen.<sup>66,67</sup> Prostatic adenocarcinomas have generally bland cytomorphology and varied gland formation (Figure 7, A through D).<sup>10,63</sup>

Renal cell carcinomas are typically nonreactive for both CK7 and CK20 and positive for pancytokeratin AE1/AE3, epithelial membrane antigen (EMA), CD31, RCC (67% of metastatic tumors), and CD10. Paired box gene 8 (PAX8), if available, is a semispecific nuclear stain (also positive in thyroid, Müllerian, and thymic tumors).<sup>68,69</sup> Potential pitfalls include EMA and CD10. Although CD10 reportedly detects between 89% and 100% of metastatic RCCs, it also has overlap with several native cutaneous neoplasms with clear cell features, including those of sebaceous differentiation

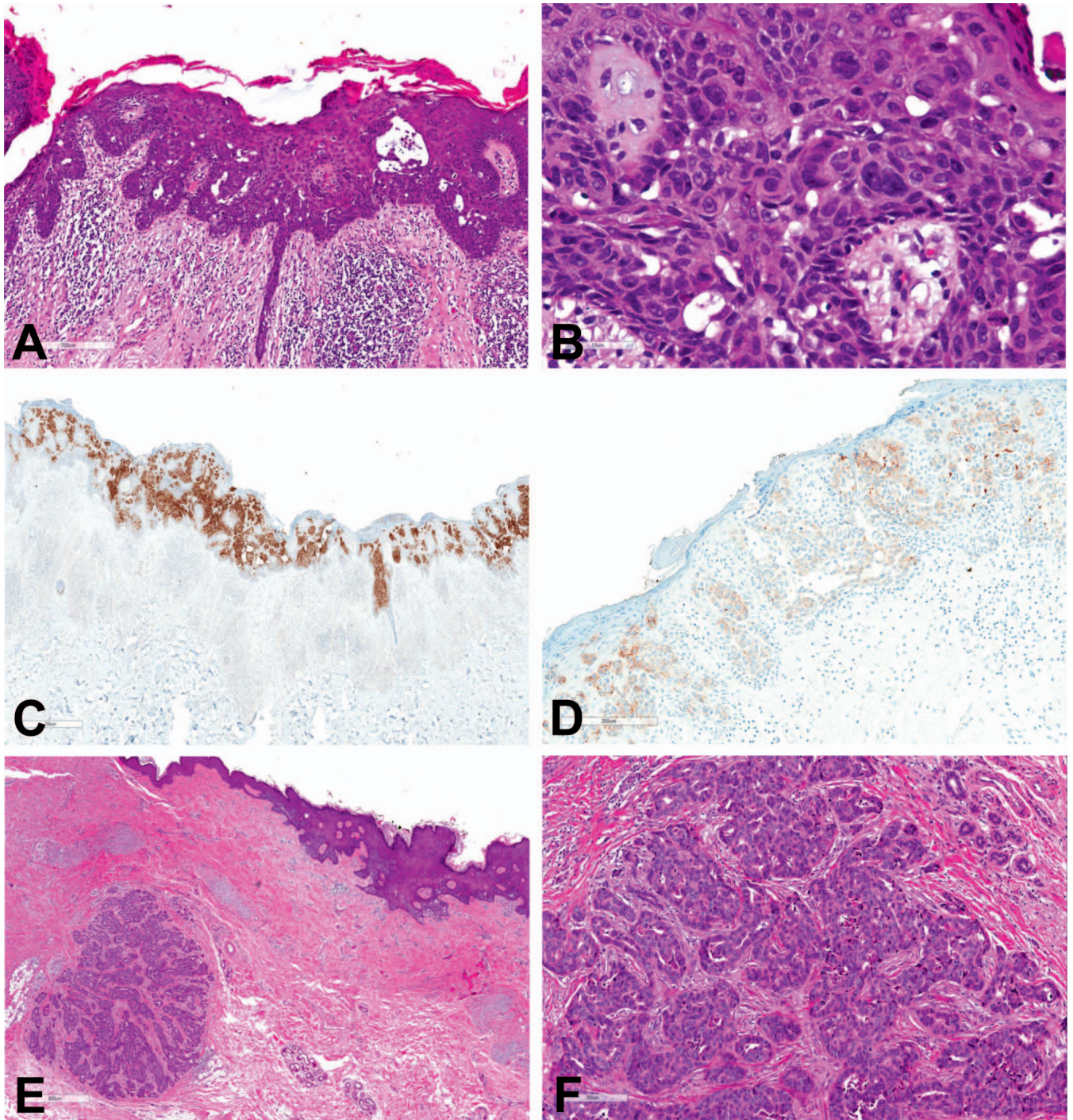


**Figure 9.** Clear cell hidradenoma. Low magnification shows a dermal-based nodule with both solid and cystic architecture surrounded by a hyalinized stroma. Though circumscribed overall, islands of clear and basaloid cells with ductal or glandular differentiation can give the false impression of invasion (A). Higher magnification of clear cell component reveals banal cells lacking mitoses or cytologic atypia (B) (hematoxylin-eosin, original magnifications  $\times 40$  [A] and  $\times 100$  [B]).

such as sebaceous adenoma, sebaceoma, and sebaceous carcinoma (Figure 8, A through C).<sup>70</sup> Both CD10 and EMA are reactive in primary cutaneous clear cell hidradenomas; thus, caution is warranted (Figure 9, A and B).<sup>71</sup> In cases of suspected chromophobe RCC, neoplastic cells will be immunoreactive for PAX8 and CD117 but negative for CD10.<sup>72</sup>

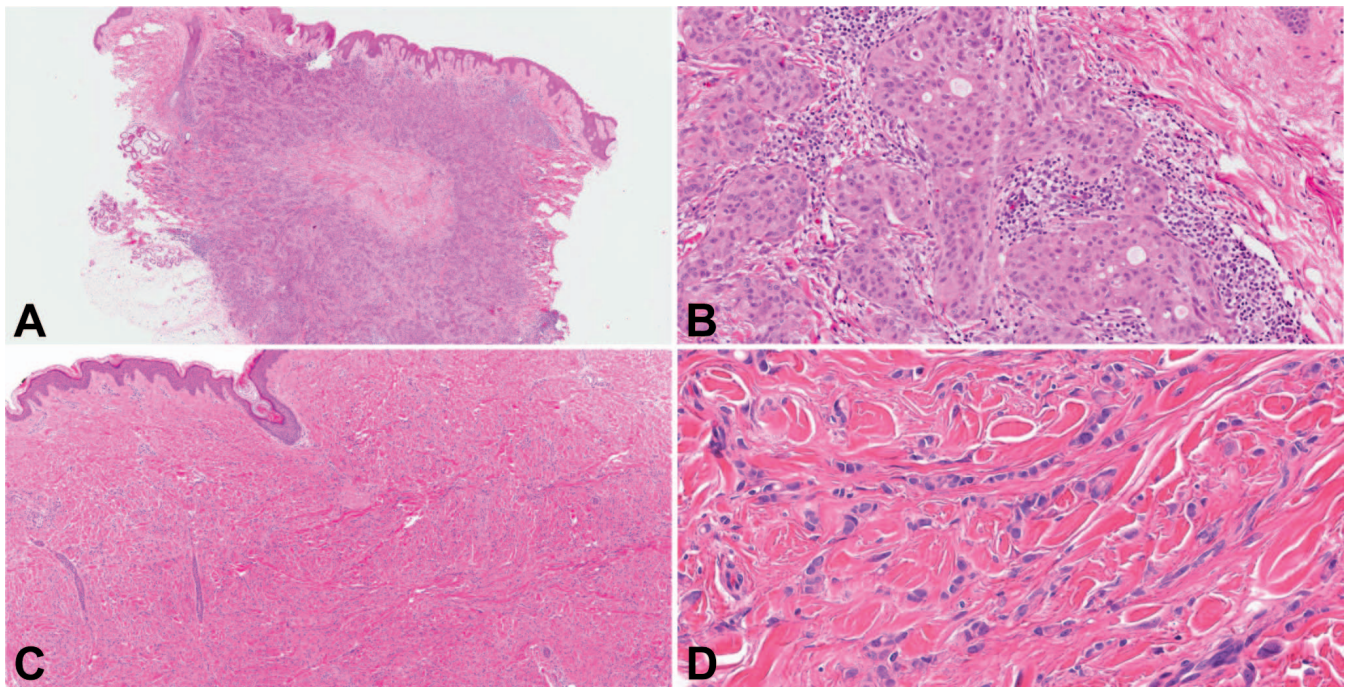
Urothelial lesions typically show positive immunoreactivity for high-molecular-weight CK, CK7, p63, and S-100P. They have variable positivity for CK20 (~55%) and GATA binding protein 3 (GATA3; ~50%). Urothelial tumors can show immunohistochemical overlap (high-molecular-weight CK, CK7, p63) with a variety of cutaneous neoplasms.<sup>73</sup> However, per our review of the literature, a study determining an optimized immunohistochemical panel to differentiate moderately to poorly differentiated metastatic urothelial carcinoma from primary cutaneous neoplasms has not been performed. Certainly uroplakin positivity, when present, would appear to be helpful in supporting a diagnosis of urothelial metastasis. Prostatic carcinomas are negative for CK7 and CK20 but stain positively for homeobox protein Nkx-3.1 (NKX3.1), CD57, and prostate-specific antigen (the last 3 of which should be negative in urothelial tumors).<sup>74</sup> A potential pitfall is that prostate carcinoma is also positive for Ber-EP4, the prototypically positive immunohistochemical stain used to confirm basal cell carcinoma of the skin.

**Pearls and Pitfalls.**—A panel for suspected genitourinary metastases could include high-molecular-weight CK, CK7, CK20, p63, and potentially PAX8, GATA3, or NKX3.1, depending on the favored entity.

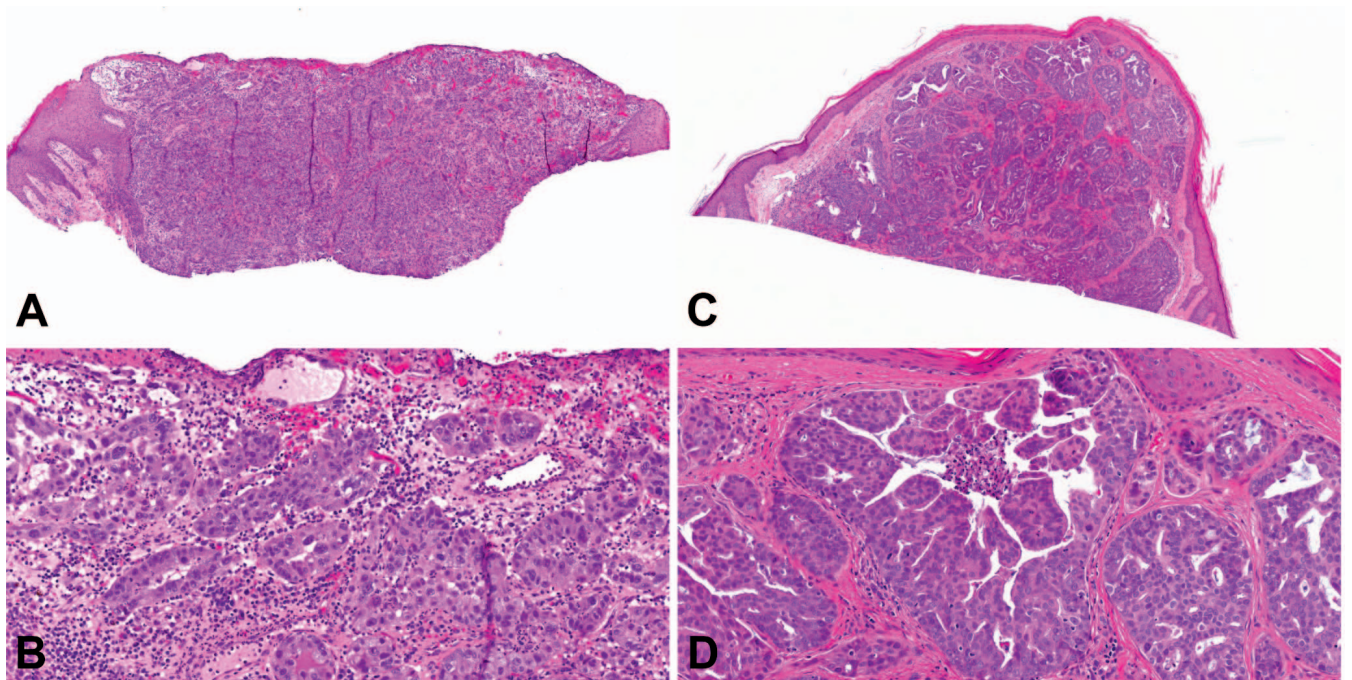


**Figure 10.** Extramammary Paget disease; pagetoid eccrine gland carcinoma. Low magnification of extramammary Paget disease shows diffuse epidermal involvement by neoplastic cells infiltrating with single cells and cluster patterns (A). Neoplastic cells stand in sharp contrast to the background epidermis because of ample amphiphilic cytoplasm and enlarged hyperchromatic nuclei with prominent nucleoli (B). Neoplastic cells in primary Paget disease will express CK7 (C) and Ber-EP4 (D), both not seen in squamous epidermis or pagetoid squamous cell carcinoma. This case originated from a common mimicker, eccrine carcinoma, present at scanning magnification as a dermal nodule surrounded by sclerotic stroma (E). Higher magnification reveals disorganized infiltrating glands with marked basophilia and mitotic figures (F) (hematoxylin-eosin, original magnifications  $\times 40$  [A and E],  $\times 100$  [F], and  $\times 400$  [B]; original magnification  $\times 40$  [C and D]).

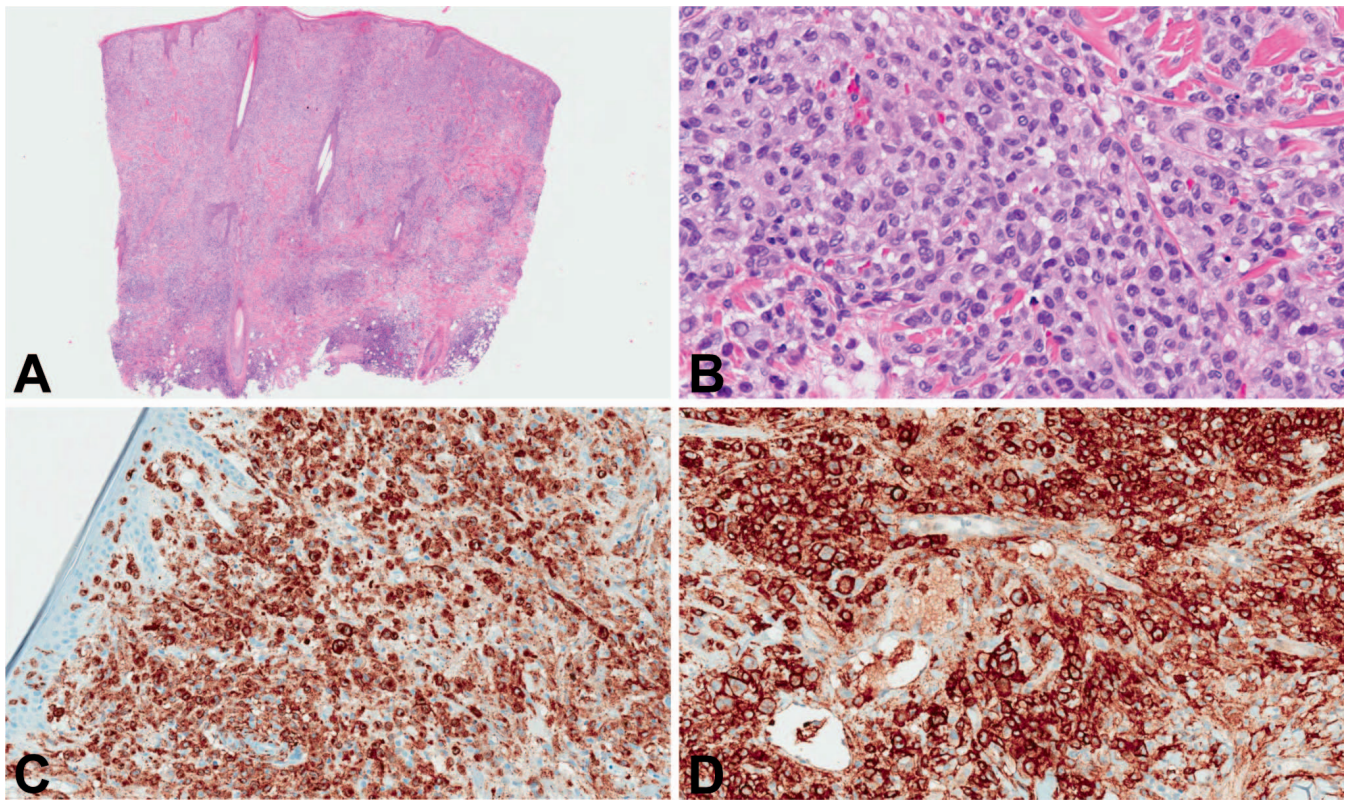




**Figure 11.** Metastatic ductal and lobular carcinoma of the breast. In the case of ductal carcinoma, low magnification shows a discrete nodular infiltrate of neoplastic cells with marked extension from the superficial dermis to the underlying subcutis and intralesional fibrosis (A), whereas lobular carcinoma maintains classic single-cell, single-file, linear, and infiltrating pattern (C). High magnification shows neoplastic cells maintain ductal (B) or lobular features (D) depending on histologic subtype of the primary cancer (hematoxylin-eosin, original magnifications  $\times 20$  [A],  $\times 40$  [C], and  $\times 200$  [B and D]).



**Figure 12.** Ovarian and endometrial carcinomas. High-grade serous ovarian carcinoma metastatic to skin presents as a broad dermal nodule at scanning magnification (A), whereas high magnification reveals poorly formed glands with marked nuclear atypia (B). Metastatic endometrial carcinoma presents similarly as a broad dermal nodule (C) of relatively well-defined glands with typical cribriform growth pattern and slight nuclear enlargement (D) (hematoxylin-eosin, original magnifications  $\times 20$  [A and C] and  $\times 200$  [B and D]).



**Figure 13.** Langerhans cell histiocytosis in a patient with prior history of systemic follicular lymphoma. Low and high magnification show a diffuse superficial and deep infiltrate of epithelioid cells with ample pale eosinophilic cytoplasm and occasional folded nuclei containing longitudinal grooves (A and B). Neoplastic cells express langerin and CD1a (C and D, respectively) confirming a Langerhans cell histiocytosis. Further workup also showed expression of BCL-2 and molecular studies supported clonal relation to the patient's prior diagnosis (hematoxylin-eosin, original magnifications  $\times 20$  [A] and  $\times 200$  [B]; original magnification  $\times 200$  [C and D]).

Common histologic mimickers of metastatic RCC include sebaceous carcinoma and clear cell hidradenoma; beware of reactivity with common RCC markers such as EMA or CD10.

### Breast

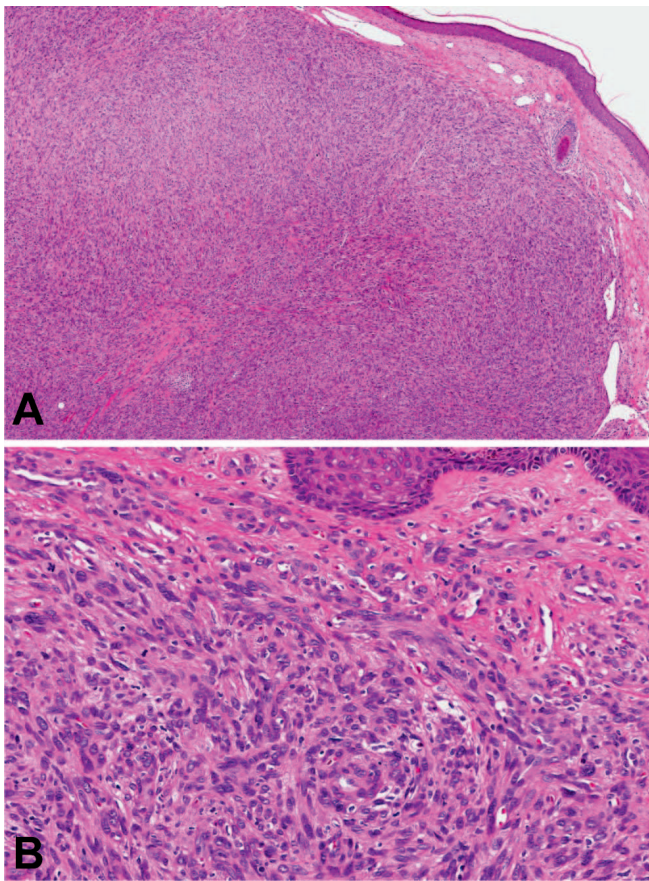
As discussed above, incidence of cutaneous metastases in patients with breast carcinoma remains extremely high (18.6%–26.5% in prior reports), and they most commonly occur on the abdomen or chest wall.<sup>8,9,74,75</sup> Another widely recognized entity is inflammatory breast carcinoma. This cutaneous finding presents in approximately 5% of all breast cancers and is often mistaken clinically as cellulitis or mastitis. The pathology of this entity involves obstruction of dermal lymphatics by neoplastic cells, leading to secondary lymphedema and possible involvement of the contralateral breast. Other entities can present similarly to an inflammatory breast carcinoma, including malignant gastrointestinal, genitourinary, and lung carcinomas.<sup>76</sup>

Another common presentation includes mammary Paget disease. This lesion appears as a sharply demarcated, erythematous patch on the nipple with scale; it is worth noting that it is seen in both men and women. The pathology of Paget disease of the nipple is multifaceted, and could represent involvement of epidermis by spread of carcinoma either through direct extension of an underlying dermal lesion or from colonization of lactiferous ducts.<sup>77</sup> In the case of the former, it is important to distinguish true

mammary Paget disease from an adnexal carcinoma with pagetoid epidermotropic involvement (Figure 10, A through F) or pagetoid squamous cell carcinoma.

Metastatic breast carcinoma typically reveals a solid, nested to infiltrative proliferation of neoplastic cells with surrounding fibrosis. Classic infiltrating ductal or lobular subtypes (Figure 11, A through D) are seen; however, irregular or occult interstitial aggregates can also present.<sup>78</sup> Concordant with its pathophysiology, inflammatory carcinoma will show neoplastic cells in dermal lymphatic spaces. Mammary Paget disease has epidermal acanthosis with expansion from neoplastic cells arranged in disorganized single cells or clusters throughout. Cells have large nuclei, prominent nucleoli, and abundant pale cytoplasm.

Breast carcinoma most closely mimics primary cutaneous adnexal malignancies, perhaps because the lactiferous ducts and glands are thought to represent modified sweat glands. Indeed, both breast carcinoma and adnexal tumors are typically CK7<sup>+</sup> and CK20<sup>-</sup>. Breast carcinoma is also classically immunoreactive for CK19, mucin 1 (MUC1), estrogen receptor (ER), progesterone receptor (PR), and mammaglobin and nonreactive for CK5/6 and TTF-1. However, rate of ER immunoreactivity in metastatic breast carcinomas is estimated to be 50%, whereas mammaglobin immunoreactivity is estimated at 65% to 70%.<sup>79–81</sup> Squamous cell carcinoma of the skin with pagetoid pattern will show positive CK5/6 and p63 expression, whereas these



**Figure 14.** *Leiomyosarcoma.* Metastatic leiomyosarcoma presents at low magnification as an expansile nodule of perpendicularly oriented fascicles with spindle cell morphology (A). High magnification demonstrates enlarged, epithelioid or blunt-ended nuclei with bright eosinophilic cytoplasm (B) (hematoxylin-eosin, original magnifications  $\times 40$  [A] and  $\times 200$  [B]).

stains will be negative in mammary and extramammary Paget disease (CK7<sup>+</sup>).<sup>82</sup>

Further, specific evaluation to separate metastatic breast tumors from adnexal tumors is difficult. Previous studies have used CK5, CK14, and CK17 in an immunohistochemical panel including p63 and mammaglobin (among other markers). Promising findings included a reproducible pattern of weak p63 expression in metastatic breast carcinoma (1 case; 8.3%) in addition to weak ancillary CK expression (0 cases expressed CK14; 2 cases [16.7%] expressed CK5 and CK17). Meanwhile, sweat gland carcinomas strongly expressed p63, CK14, CK5, and CK17 (10 cases; 90.9%). Of note, mammaglobin was expressed in only 8 cases (66.7%) of metastatic breast carcinoma.<sup>83</sup> For lesions that occur in the axilla, we tend to favor primary breast carcinoma etiology, and patients are treated as such. For lesions occurring away from the breast or axilla, when histopathologic distinction cannot be made with certainty, we recommend correlation with the clinical and radiographic findings in the breasts to aid diagnosis.

Though GATA3 shows immunoreactivity in as many as 94% of breast carcinomas, a significant pitfall is strong reactivity by many adnexal neoplasms. In one series, GATA3 was diffusely expressed in both benign and malignant

trichofollicular and sebaceous neoplasms.<sup>30,79</sup> Other possible pitfalls include other carcinomas that express GATA3 (urothelial carcinoma, parathyroid gland neoplasms, salivary gland neoplasms, and pheochromocytomas) as well as diminished expression (estimated 43% reactivity) in triple-negative breast carcinomas.<sup>84</sup>

**Pearls and Pitfalls.**—An initial immunohistochemical panel could include p63, CK5, CK14, CK17, and mammaglobin to distinguish metastatic breast from a primary cutaneous adnexal carcinoma.

A potential pitfall is the shared immunophenotype of GATA3 and CK7 positivity in both breast and adnexal neoplasms.

Estrogen receptor and mammaglobin remain negative in a significant minority of metastatic breast carcinomas.

### Gynecologic

Metastatic tumors of gynecologic origin are comparatively rare (0.31% cutaneous metastases), making exact quantification difficult. Hu et al<sup>7</sup> found 2 cases of uterine and cervical cutaneous metastases from among 646 patients with gynecologic primaries. Cutaneous metastases are estimated to occur in 2% to 5% of patients with ovarian tumors, and portend a poor prognosis.<sup>85–87</sup> In one series, the most commonly reported ovarian variant to metastasize was serous papillary cystadenocarcinoma (78%), followed by endometrioid and mucinous variants.<sup>85</sup> Clinically, the majority of patients present with crops of multiple erythematous nodules involving the chest or abdomen, with multiple reports of seeding occurring in laparotomy scars or trocar port sites.<sup>85,88,89</sup>

Ovarian, endometrial, and cervical metastases appear histologically as adenocarcinomas with potentially high-grade nuclear features (Figure 12, A through D).<sup>90–94</sup> Overall, metastatic squamous cell carcinoma from the uterine cervix, although reported, is considered less likely to metastasize when compared with adenocarcinomas of gynecologic origin.<sup>95,96</sup> Lastly, ovarian leiomyosarcoma metastatic to the skin has been described and should be considered when spindled morphology is observed in the correct clinical context.<sup>97</sup>

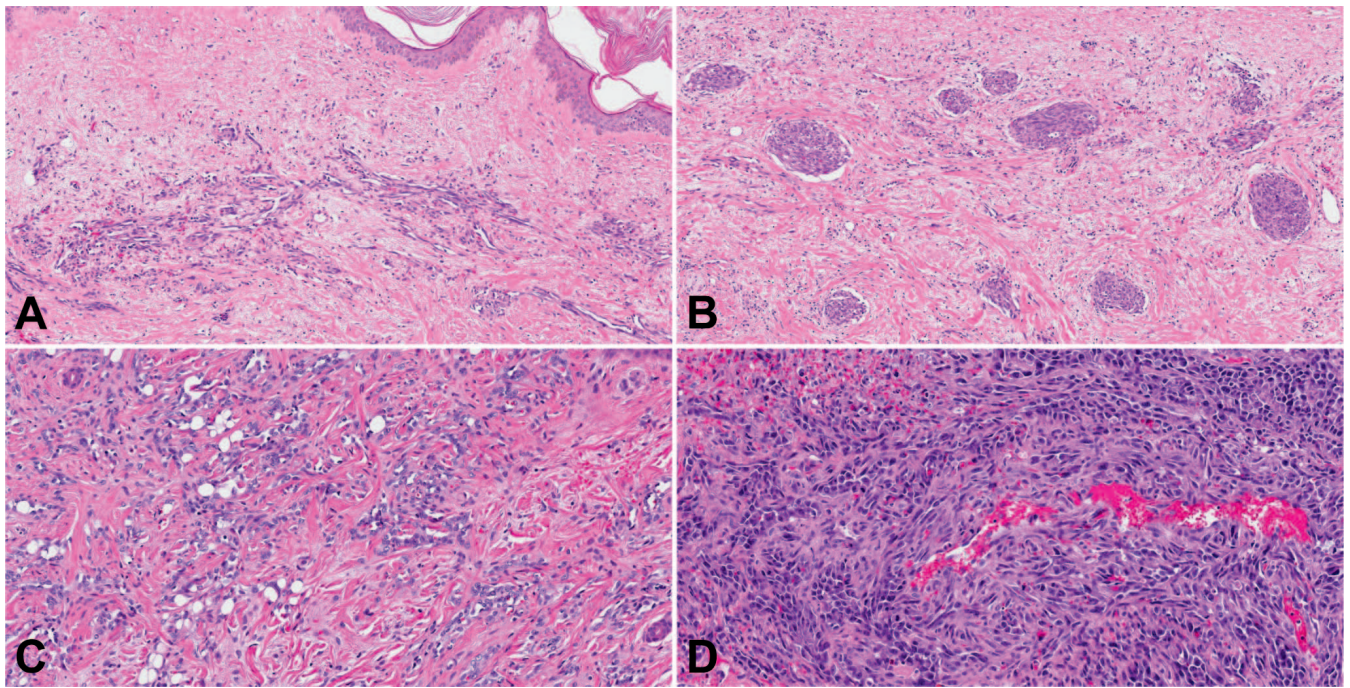
Ovarian and endometrial tumors are reactive with CK7 and PAX8, whereas adenocarcinoma of the endocervix is reactive for CK7 and potentially EMA. All 3 entities are negative for CK20 and show variable expression of ER and PR. One potential pitfall is that PAX8 will react with both renal cell and thyroid carcinomas—potentially confounding the diagnosis without judicious use.<sup>98</sup> Another is a reported architectural overlap between gynecologic neoplasms with endometrioid morphology and pilomatrical neoplasms.<sup>99</sup> In these instances, p63 may be useful, as described above, to help differentiate primary cutaneous neoplasm from metastatic gynecologic primary.<sup>49</sup>

**Pearls and Pitfalls.**—A useful initial panel could include CK7, CK20, p63, PAX8, and ER.

Beware of a potential histologic overlap between endometrioid adenocarcinomas and cutaneous entities such as pilomatrical carcinoma.

### MELANOMA

Metastatic melanoma remains the most common of all cutaneous metastatic lesions and accounts for an estimated 45% of cutaneous metastases. Melanoma may be clinically suspected if the lesion is (blue-black) pigmented. In the vast



**Figure 15.** Angiosarcoma. Metastatic angiosarcoma can show markedly differing morphologies. Well-differentiated variants demonstrate irregular and infiltrative vascular channels that infiltrate through collagen bundles (A) and, rarely, can form epithelioid nests (B). Moderately to poorly differentiated forms demonstrate less conspicuous vascular lumina (C) with an increasingly solid growth pattern and marked nuclear hyperchromasia with atypia (D) (hematoxylin-eosin, original magnification  $\times 100$  [A and B] and  $\times 200$  [C and D]).

majority of cases, tumor metastases occur in a similar distribution to the primary lesion. In the series by Saeed et al,<sup>4</sup> even after exclusion of melanomatous lesions arising within 5 cm of the primary site, approximately 84.6% of cases still occurred near the primary site. Moreover, despite exclusion of proximate metastases, melanoma remained the second most common histologic type observed (behind adenocarcinoma; 18.2% versus 40.3%).

Histologically, it can sometimes be impossible to distinguish between a cutaneous metastasis from a melanoma of unknown primary and a primary dermal-only tumor without an epidermal component. For instance, a primary nodular melanoma with previous ulceration and reepithelialization can be particularly difficult to exclude histologically from dermal metastases. However, in general, tumor cells from metastatic melanoma should be well confined to the dermis and without evidence of overlying precursor lesion in the epidermis. Other architectural features include a broad base with extension into the deep dermis or subcutis, absence of a radial growth pattern, and lymphovascular involvement with frequent mitoses. On higher magnification, the majority of melanoma subtypes will demonstrate epithelioid morphology with ample pale, amphophilic cytoplasm; oval nuclear contours; and large, prominent (cherry-red) nucleoli. Tumors will often show no or only focal pigmentation. They should have positive immunoreactivity for S100 and/or SOX10. Staining with Melan-A and human melanoma black 45 antigen (HMB-45) can be positive or negative.<sup>100</sup> In cases of suspected metastasis and no known primary tumor, it is acceptable to insert a diagnostic comment stating that absolute delineation is histologically impossible, with a recommendation to exclude another site of origin clinically. Often,

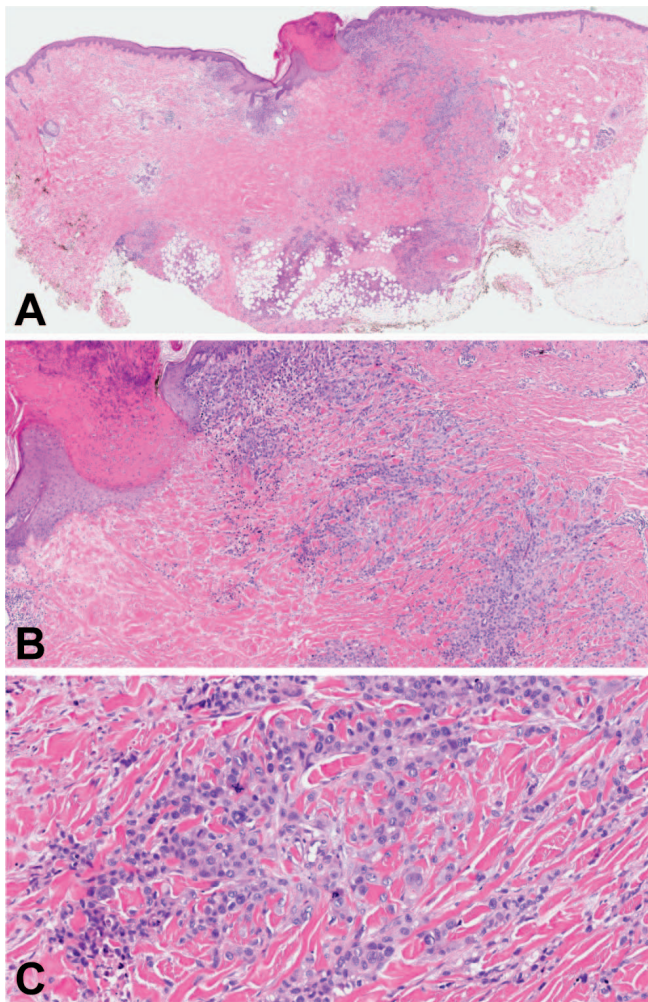
when other tumors are not identified, the dermal melanoma will be treated as a primary tumor with wide excision and sentinel lymph node biopsy.

**Pearls and Pitfalls.**—Distinguishing primary versus metastatic melanoma requires architectural histomorphologic assessment and clinical history but can be difficult.

When there is no known primary tumor, a comment detailing inability to distinguish between a primary and a metastatic tumor is often acceptable and may be more useful for continued patient care.

#### LYMPHOMA AND LEUKEMIA

The rate of systemic lymphoma presenting as cutaneous metastases is understudied, and in most larger series, lymphoma is excluded because of its inherently hematogenous nature.<sup>7</sup> One series<sup>4</sup> that did note lymphoma metastases estimated them to account for  $\sim 5\%$  of all cutaneous metastases. The workup and diagnoses of cutaneous lymphomas is beyond the scope of this paper, and in-depth discussion can be found elsewhere.<sup>101–104</sup> Generally speaking, however, there are multiple patterns of histologic involvement that should arouse suspicion, including prominent lymphoid epidermotropism, angiocentrism with angiodestruction, perifollicular or periadnexal accentuation, and diffuse sheetlike or nodular lymphoid aggregates with cytologic atypia.<sup>105</sup> Rarely, systemic lymphomas can present cutaneously as a pseudogranulomatous infiltrate in the form of a clonal histiocytic or dendritic cell transdifferentiation.<sup>106,107</sup> Thus, index of suspicion must remain high in the correct clinical context (Figure 13, A through D), and in these instances further molecular studies may be warranted.



**Figure 16.** Metastatic epithelioid sarcoma. Haphazard aggregates of histiocytoid cells give an impression of granulomatous reaction at low magnification. Some peripheral collagen trapping may be evident as well as epidermal ulceration overlying the lesion (A). Intermediate and high magnifications demonstrate neoplastic cells with epithelioid cytology, abundant eosinophilic cytoplasm, nuclear atypia, and striking mitoses, infiltrating through collagen bundles (B and C) (hematoxylin-eosin, original magnifications  $\times 20$  [A],  $\times 40$  [B], and  $\times 200$  [C]).

Interpretation of immunohistochemistry for an atypical cutaneous lymphocytic infiltrate can be extremely difficult, and expert consultation is often required in the workup of these neoplasms. An initial panel should include CD3, CD20, CD30, and muramidase to characterize the lineage of hematolymphoid tumor cells. We believe this initial panel will maximize future ability to provide accurate diagnosis while minimizing tissue waste. CD3<sup>+</sup> T-cell tumors could be next stained with CD4 and CD8 to look for an atypical ratio. CD20<sup>+</sup> would indicate a B-cell neoplasm but can be negative in rituximab-treated patients. Meanwhile, anaplastic lymphoma kinase (ALK) staining is helpful in CD30<sup>+</sup> lesions to identify CD30-positive/ALK-negative primary cutaneous anaplastic large cell lymphoma versus cutaneous involvement by systemic anaplastic large cell lymphoma (frequently ALK<sup>+</sup>).<sup>102</sup> If a myeloid sarcoma is suspected, and the clinical context is appropriate, follow-up stains with CD68, CD117, lysozyme, and myeloperoxidase will identify the majority of lesions.<sup>108</sup>

**Pearls and Pitfalls.**—A relatively simple panel including CD3, CD20, CD30, and muramidase is often best for initial evaluation of an atypical cutaneous hematolymphoid infiltrate.

Beware of the possibility of a systemic lymphoma masquerading as a pseudogranulomatous infiltrate

## SARCOMA

True metastatic sarcoma presenting as a cutaneous lesion remains extremely rare, accounting for approximately 1.3% to 3% of all cases of cutaneous metastases.<sup>1,4</sup> Usual entities presenting as primary cutaneous malignancies most commonly include leiomyosarcoma (Figure 14, A and B), angiosarcoma, rhabdomyosarcoma, Ewing sarcoma, and myxofibrosarcoma, among many more, almost all of which remain extraordinarily rare.<sup>5,10</sup> Although not a true cutaneous metastasis, angiosarcoma of the breast is often seen on biopsy via direct extension into the overlying dermis (Figure 15, A through D). Occurring in younger women of 30 to 40 years of age, this lesion presents as a mass with bluish discoloration of overlying skin and accounts for less than 0.05% of all malignant breast lesions. Likewise, true cutaneous metastases from rhabdomyosarcoma remains extraordinarily rare, with very few cases reported in the literature—the majority of which occur in children—which present as painless flesh-colored nodules on the head and neck.<sup>109</sup>

Perhaps one entity worth noting is epithelioid sarcoma, a dermal histiocytoid tumor arising in the distal extremities of young adults. With this highly aggressive lesion, metastases are noted in up to 45% of cases, many of which are cutaneous. Histologically, epithelioid sarcoma is often mistaken for reactive granulomatous inflammation. At low magnification, a prominent nodule in the deep dermis and subcutis with or without central necrosis is seen. Not uncommonly, overlying epidermal ulceration is present, and is another contributor to the potential pitfall of mistaking the lesion for an infectious process. Neoplastic cells are epithelioid and spindle-shaped with eosinophilic cytoplasm and only mild nuclear atypia (Figure 16, A through C). Occasionally, cells can be large and polygonal with occasional rhabdoid morphology. The lesion can be distinguished immunohistochemically by detection of the SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1/INI1) 22q11 deletion via loss of nuclear INI1 staining. Additionally, these lesions will express CD34 in up to 50% of cases, as well as CK AE1/3 and EMA.

**Pearls and Pitfalls.**—Sarcomas truly metastatic to skin remain extremely rare and should be entertained with caution.

One entity commonly associated with cutaneous metastases is epithelioid sarcoma, which is often confused with granulomatous inflammation.

## CONCLUSIONS

Cutaneous metastases are not uncommon and occur in a significant minority of all cancer patients. Overall, the most common metastases (aside from melanoma) remain adenocarcinomas, and of those, lung, breast, and/or gastrointestinal types prevail. Common pitfalls often involve confusing staining patterns with native cutaneous adnexa and distinguishing primary adnexal malignancies. Though cutaneous metastases can have an extremely wide clinical

presentation, most share common features on low magnification of a nodular, dermal-based infiltrate with a foreign appearance. Overall, pathologists must maintain high clinical-pathologic suspicion for both possibilities, use immunohistochemistry liberally, and yet know the limitations of immunohistochemistry in these instances. They must maintain confidence in the utmost importance of clinical correlation and must not be shy in communicating such importance.

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