Cutaneous Metastases of Unusual Tumor Types: Retrospective Single-Institution Analysis and Literature Review

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Abstract: Cutaneous metastasis (CM) is a rare manifestation of internal malignancy. We analyzed the incidence, clinical features, and patterns of metastatic spread among 408 CMs from 15 primary sites, excluding skin, breast, lung, colorectum, and hematolymphoid primary sites, in a 34-year (1990–2024) single-institution retrospective review (88 cases) and literature review (320 cases). CMs from thyroid were most common in the single-institution review. A young median age was observed in patients with CMs from soft tissue (14 years) and bone (32 years) tumors. Male predilection was most observed in CMs from esophagus, mesothelium, and kidney. CMs from 9 of 15 primary sites favored the head and neck region. CMs most presented as solitary lesions from bile duct (72%), thyroid (69%), and pancreas (67%) primary sites. In total, 45% of CMs from the bile duct were due to catheter-related tumor seeding. The primary sites with the highest percentage of CMs at initial presentation were neuroendocrine (55%), esophagus (45%), and pancreas (40%). The time interval between primary cancer diagnosis and development of CM ranged from 0 to 429 months. The shortest median time interval was observed in CMs arising from pancreas (1 month) and esophagus (2 months), while the longest median time interval was observed in those from prostate (80 months) and kidney (46 months). In summary, CM may be the initial clinical presentation of underlying malignancy from uncommon primary sites and can exhibit distinctive patterns of cutaneous spread based on the primary cancer type and anatomic location.

Key Words: cutaneous metastases, uncommon tumor, thyroid, kidney, prostate, bladder, esophagus, pancreas

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LEARNING OBJECTIVES

After completing this CME activity, physicians should be better able to:

1. Describe the clinical presentation and histologic features of cutaneous metastases from uncommon primary sites.
2. Explain how to apply immunohistochemical algorithm in the work-up of cutaneous metastases.

INTRODUCTION

Cutaneous metastasis (CM) is a rare manifestation of internal malignancy, comprising approximately 2% of all diagnosed skin cancers. In individuals with a known internal malignancy, the overall incidence of CM is 5.3%.[1] However, the risk of developing a CM largely depends on the primary organ and type of cancer, with breast cancer, lung cancer, and colorectal cancer being the most common visceral organ sources.[2] CMs can be further stratified by patient demographics. With the exclusion of melanoma, the most common origins of CMs in males are lung and colon, while females more often show CMs arising from breast and ovarian cancers.[2] The difference in frequency between sexes is largely attributed to the overall incidence of these cancers in each sex and the proximity of sex-specific organs to the skin.[3] The clinical presentation of CMs vary, with most presenting as single or multiple dome-shaped nodules, papules, plaques, or ulcerations.[3]

From a clinical perspective, CMs require urgent workup, because they often signify an advanced stage of internal malignancy. At time of diagnosis, most patients have metastases to other anatomical sites, including lymph nodes and other internal organs. In this regard, CMs confer a poor prognosis, with an average length of survival of 7.5 months after time of diagnosis.[4]

Previous studies have provided insight into the patterns of metastatic spread to the skin from internal primary malignancies.[5–7] Common sites of CM include the head and neck region, and trunk and extremities. In contrast, metastasis to the back tends to be a rarer presentation. Patterns of spread are dependent on the primary cancer type and adjacent anatomic structures, because they may spread through lymphatic and vascular channels, and through direct tissue invasion, seeding, and implantation.[3]

Determining the origin of a CM can be challenging for both clinicians and pathologists, however, it is important for prognostic evaluation and appropriate

management. Understanding the cutaneous presentations, clinical courses, and demographics of affected patients is essential for timely recognition of CMs and their primary malignancies. Furthermore, it is essential to understand patterns of metastatic spread by cancer type, because the cutaneous site and presentation of metastasis may provide further insight into the behavior of the primary neoplasm. Although clinical presentations and patterns of spread have been closely studied in CMs from common primary sites, few studies have examined the characteristics and workup of CMs from rarer sites. Through a retrospective chart review at a large teaching hospital and review of the literature, we aim to describe the patterns of cutaneous spread among metastases from uncommon internal primary malignancies. In addition, we aim to classify these CMs from uncommon sites by patient demographics and clinical presentations.

MATERIALS AND METHODS

The study has been approved by the Mass General Brigham Institutional Review Board (2022P001314). A retrospective review of electronic medical records from Massachusetts General Hospital in Boston, MA, spanning 1990 to 2024, was conducted to identify patients with CMs originating from uncommon internal primary sites. CMs arising from skin, breast, lung, colorectum, and hematolymphoid primary sites were excluded because of their higher incidence and well-studied clinical features. CMs from 12 primary internal sites were identified in the institutional review: mesothelium, thyroid, bone, kidney, prostate, pancreas, ovary, bile duct, bladder, stomach, esophagus, and endometrium. A literature review was conducted to supplement institutional cases and gather case information for 3 additional primary sites: cervix, soft tissue, and neuroendocrine. Using online full-text archives of scientific journal articles (eg, PubMed), additional case information was gathered from peer-reviewed case reports, case studies, and institutional analyses of CM.

Case information extracted from the institutional database and literature review was combined for analysis. CMs from each primary site were grouped into 6 categories based on anatomic regions of metastasis, designated as "head and neck," "extremities," "chest," "abdomen and pelvis," "back," and "inguinal, anal, and gluteal." The presence of a single or multiple metastases was evaluated, with localized plaque, induration, and rash presentations considered as solitary. Cases with multiple CMs at different anatomic sites were listed in all appropriate anatomic region categories. The time interval between primary cancer diagnosis (ie, date set by histopathologic diagnosis) and CM diagnosis was recorded in months. Cases with an unknown primary cancer diagnosis because of deficits in clinical history were omitted from initial diagnosis and time interval calculations. Macroscopic presentations of CMs were grouped into categories based on available clinical descriptions and images, designated as "nodule," "papule," "ulcer/abscess," "plaque," vesicle/bulla," "rash," "polypoid," and "macule/patch." "Nodule" referred to a raised mass $\geq$1.0 cm and "papule" referred to a raised mass $<$1.0 cm. "Rash" included telangiectatic and inflammatory patches, while "macule/patch" excluded rashes (see **Figures 1 and 2, Supplemental Digital Content 1**, http://links.lww.com/AJDP/A179).

RESULTS

Patient demographics and clinical presentations of CMs are listed by primary site in Table 1. Within the Massachusetts General Hospital database in a period of 34 years, 88 cases from 12 primary sites were found to have CMs from primary sites other than skin, breast, lung, colorectum, and hematolymphoid tissue. CMs were most often observed from the thyroid (25 cases) and kidney (19 cases) (Fig. 1). An additional 320 CM cases were identified from literature review for a total of 408 examined cases from 15 primary sites. Patient ages ranged from 1 month to 95 years. The lowest median ages were observed in patients with CMs from soft tissue (14 years) and bone (32 years) tumors, while the highest median ages were observed in patients with CMs from bladder (68 years) and prostate (73 years). Excluding CMs from examined sex-specific primary sites (ie, prostate, ovary, endometrium, and cervix), 63% of all CMs were identified in males. CMs from the esophagus, mesothelium, and kidney had the strongest male predilection at 90%, 88%, and 84%, respectively, while CMs from the soft tissue, thyroid, and pancreas showed the strongest female predilection at 55%, 52%, and 52%, respectively.

CMs from 9 of 15 primary sites favored spread to the head and neck region (mesothelium, thyroid, bone, kidney, pancreas, bile duct, esophagus, soft tissue, and neuroendocrine), with kidney (78%) and thyroid (71%) showing the strongest predilection. CMs from ovary, bladder, stomach, endometrium, and cervix showed greatest spread to the abdomen and pelvis, while those from prostate had a predilection for the inguinal, anal, and gluteal region (Fig. 2). In total, 45% of metastases from the bile duct were present at surgical scar sites from drainage catheter use. CMs presented as solitary lesions in 48% of all cases, with CMs from bile duct, thyroid, and pancreas most often favoring solitary presentation at 72%, 69%, and 67%, respectively (Fig. 3). Alternatively, a multilesional CM presentation was most common in soft tissue, bladder, and cervical cancers at 90%, 76%, and 70%, respectively. CMs most presented as nodules from all primary sites except for soft tissue, which showed a predilection for papules (Fig. 4). Plaque presentations were frequently observed in CMs from mesothelium (21%) and prostate (20%) compared with other sites, and rash presentation was more common in CMs from pancreas (13%) and ovary (13%) (Fig. 5).

CM was observed at initial presentation of malignancy in 19% of all cases and was observed in all primary sites except for prostate and soft tissue (Fig. 6). The primary sites with the highest percentage of CMs at initial cancer presentation were esophagus (45%), pancreas (40%), and neuroendocrine (36%). The time interval between initial cancer diagnosis and identification of CM ranged from 0 to 429 months among all cases. Metastases arising from the pancreas and esophagus had the shortest median time interval between diagnosis and CM at 1 and 2 months, respectively, while those arising from prostate

TABLE 1. Summary of Clinical Features of 88 Institutional Cases and 320 Cases From Literature Review

Primary Tumor Site	Total Cases	Literature Review	Institutional Cases	Age (Years)	Sex		Anatomic Site					Size Range (cm)	Presentation		Skin as Initial Diagnosis	Interval From Diagnosis (Months)	Most Common Tumor Type
				Median (Range)	Male	Female	Head & Neck	Extremities	Chest	Abdomen & Pelvis	Back	Inguinal, Anal, & Gluteal	Solitary	Multiple		Median (Range)	
All Sites	408	320	88														
Thyroid	88	63	25	64 (26–95)	42 (48%)	46 (52%)	65 (71%)	2 (2%)	16 (18%)	2 (2%)	6 (7%)	0 (0%)	0.2–16	61 (69%)	27 (31%)	18/89 (20%)	3 (0–48)	Papillary thyroid carcinoma
Kidney	19	0	19	58 (42–71)	16 (84%)	3 (16%)	14 (78%)	3 (17%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	0.2–7.5	11 (58%)	8 (42%)	1/19 (5%)	36 (0–429)	Clear cell renal cell carcinoma
Pancreas	21	12	9	62 (43–90)	10 (48%)	11 (52%)	8 (40%)	0 (0%)	2 (10%)	7 (35%)	1 (5%)	2 (10%)	0.2–3.5	14 (67%)	7 (33%)	8/20 (40%)	17 (0–115)	Adenocarcinoma
Ovary	20	13	7	64 (24–73)	0 (0%)	20 (100%)	2 (8%)	3 (12%)	5 (19%)	14 (54%)	1 (4%)	1 (4%)	0.5–6	9 (45%)	11 (55%)	1/20 (5%)	46 (0–214)	Papillary serous cystadenocarcinoma
Prostate	20	14	6	73 (55–88)	20 (100%)	0 (0%)	3 (15%)	2 (10%)	3 (15%)	3 (15%)	1 (5%)	8 (40%)	0.2–7.8	9 (45%)	11 (55%)	0/20 (0%)	80 (10–273)	Adenocarcinoma
Stomach	20	15	5	61 (29–91)	11 (55%)	9 (45%)	9 (25%)	1 (3%)	5 (14%)	13 (37%)	6 (17%)	1 (3%)	0.5–12	7 (35%)	13 (65%)	4/20 (20%)	1 (0–54)	Adenocarcinoma
Mesothelium	24	20	4	65 (25–93)	21 (88%)	3 (12%)	11 (35%)	2 (6%)	10 (31%)	3 (10%)	2 (6%)	3 (10%)	0.6–13.8	9 (37.5%)	15 (62.5%)	8/24 (33%)	27 (0–324)	Pleural mesothelioma
Endometrium	20	16	4	62 (45–82)	0 (0%)	20 (100%)	4 (13%)	3 (10%)	5 (17%)	10 (33%)	2 (7%)	6 (20%)	0.5–5.5	7 (35%)	13 (65%)	1/20 (5%)	3 (0–108)	Endometrioid adenocarcinoma
Esophagus	20	17	3	60 (32–81)	18 (90%)	2 (10%)	11 (38%)	4 (14%)	5 (17%)	2 (7%)	7 (24%)	0 (0%)	0.8–10	11 (55%)	9 (45%)	9/20 (45%)	6 (0–276)	Adenocarcinoma
Bone	33	30	3	32 (7–85)	21 (64%)	12 (36%)	17 (34%)	14 (28%)	5 (10%)	5 (10%)	2 (4%)	7 (14%)	0.2–5	10 (32%)	21 (68%)	1/24 (4%)	12 (0–156)	Chondrosarcoma
Bladder	34	32	2	68 (48–83)	27 (79%)	7 (21%)	8 (17%)	4 (8%)	6 (13%)	15 (31%)	7 (15%)	8 (17%)	0.9–8	8 (24%)	26 (76%)	4/34 (12%)	2 (0–36)	Transitional cell carcinoma
Bile duct	29	28	1	63 (35–77)	20 (69%)	9 (31%)	10 (34%)	1 (3%)	8 (28%)	9 (31%)	1 (4%)	0 (0%)	0.2–4	21 (72%)	8 (28%)	8/29 (28%)	12 (0–273)	Cholangiocarcinoma
Cervix	20	20	0	52 (23–78)	0 (0%)	20 (100%)	1 (3%)	4 (13%)	7 (23%)	9 (30%)	1 (3%)	8 (27%)	0.5–8	6 (30%)	14 (70%)	1/20 (5%)	6 (0–69)	Squamous cell carcinoma
Soft tissue	20	20	0	14 (0.1–71)	9 (45%)	11 (55%)	9 (26%)	4 (12%)	5 (15%)	7 (21%)	5 (15%)	4 (12%)	0.3–2	2 (10%)	18 (90%)	0/4 (0%)	21 (3–120)	Rhabdomyosarcoma
Neuroendocrine	20	20	0	43 (0.1–89)	12 (60%)	8 (40%)	13 (34%)	6 (16%)	7 (18%)	5 (13%)	4 (11%)	3 (8%)	0.5–2.5	9 (50%)	9 (50%)	4/11 (36%)	7 (0–180)	Neuroblastoma

and kidney had the longest median time interval at 80 and 46 months, respectively (Fig. 7).

DISCUSSION

In our single-institution review of 88 CMs originating from uncommon primary sites, CMs from thyroid and kidney were most frequently observed and together accounted for 50% of the institutional CMs among 12 examined primary sites (Fig. 1). Despite the relatively high prevalence of bladder and prostate cancers among the examined primary sites, they showed proportionately fewer CMs than thyroid and kidney malignancies.[8]

Combining institutional review and literature review to examine CMs from 15 total primary sites, CMs from soft tissue and bone were detected in a younger population. This may be partially explained by the peak incidence of malignant bone tumors in adolescence and prevalence of both soft tissue and bone sarcomas in childhood and adolescence.[8,9] However, the increased availability of case reports describing rare pediatric metastases may have affected this group. Alternatively, CMs arising from the prostate were detected in an older population, likely because of the sharp increase in incidence in men above age 50 years.[8] Excluding sex-specific primary cancers, the sex distribution of cutaneous metastases roughly aligned with the population incidence of malignancies from the examined primary sites.[8] Interestingly, CMs from thyroid only showed a slight female predominance (52%), despite thyroid carcinomas having a strong female predilection in the general population.

CMs most commonly involved the head and neck region in 9 of 15 primary sites, likely because of the high vascularity of the scalp and the tendency of metastases to spread through the bloodstream (Fig. 2). Despite its anatomic distance, CMs from the kidney presented in the head and neck region more than any other primary site. This may be explained by the highly vascularized nature of kidney tumors that often metastasize, most notably clear cell renal cell carcinoma. However, across all primary sites, CMs frequently localized to nearby skin regions (Fig. 2), as noted in previous studies.[2,3] Although approximately half of all CM cases presented as solitary lesions, the percentage of solitary CMs varied widely between primary sites (Fig. 3). CMs from the bile duct presented as solitary lesions in 72% of cases, which could be explained by their preference for cutaneous scars overlying biliary drainage sites. In these settings, malignant cells may reach the scar site through direct extension and tumor seeding before presenting elsewhere. CMs from the pancreas also commonly presented as solitary lesions, often as a nodule within or adjacent to the umbilicus.

Although most CMs presented as nodules or papules, other manifestations of CM should be noted (Figs. 4 and 5). Notably, plaques were seen as a clinical presentation of CM from 11 primary sites, and rashes were observed from 8 primary sites. Several CMs also showed an ulcerative component. The variety of cutaneous presentations among CMs makes their recognition a clinical challenge, and the diagnosis of CM should not be excluded based on macroscopic findings.

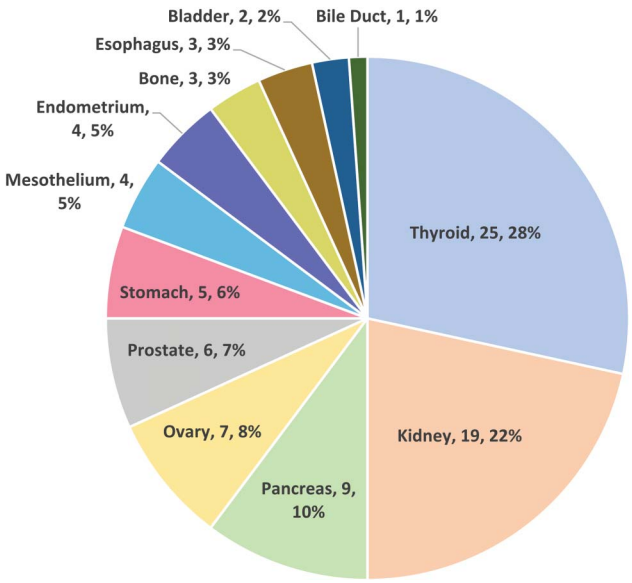

FIGURE 1. Institutional cases of cutaneous metastasis by primary site. In total, 88 cases from 12 primary sites were identified. For each primary site, number of cases and percentage of all cases are included.

The shortest median time interval between primary diagnosis and CM diagnosis was observed in CMs arising from the pancreas, with those arising from the esophagus, mesothelium, and bile duct also showing short intervals (Fig. 7). Not surprisingly, these primary malignancies were also among the most frequently associated with CMs at time of initial diagnosis (Fig. 6). Pancreatic adenocarcinoma, mesothelioma, and cholangiocarcinoma have long posed diagnostic challenges because of their tendency to present with minimal, nonspecific symptoms until metastasis occurs. Early detection is further hindered by the lack of reliable serum tests and the necessity for extensive histologic evaluation to confirm tumor presence.[8,10,11]

CMs frequently exhibit morphologic characteristics that can assist in their diagnosis (Fig. 8). Although they typically present as well-circumscribed lesions confined to the dermis, CMs may also extend into the subcutaneous tissue. At low magnification, CMs often display a "bottom-heavy" pyramidal distribution with a broad, rounded base situated in the deeper dermis.[4] Furthermore, CMs generally preserve the architectural and cytologic characteristics of their primary malignancies and may exhibit regions of inflammation and necrosis.[12] Although the epidermis is usually unaffected, the lesional cells can closely approach or abut the dermal–epidermal junction. The epidermis may also exhibit an ulcerated or vesiculobullous presentation. Vascular invasion is a common feature of CMs that can help differentiate the lesion from primary skin tumors.[4]

Despite these characteristic histologic features, distinguishing CMs from primary cutaneous lesions remains a significant diagnostic challenge because both entities can

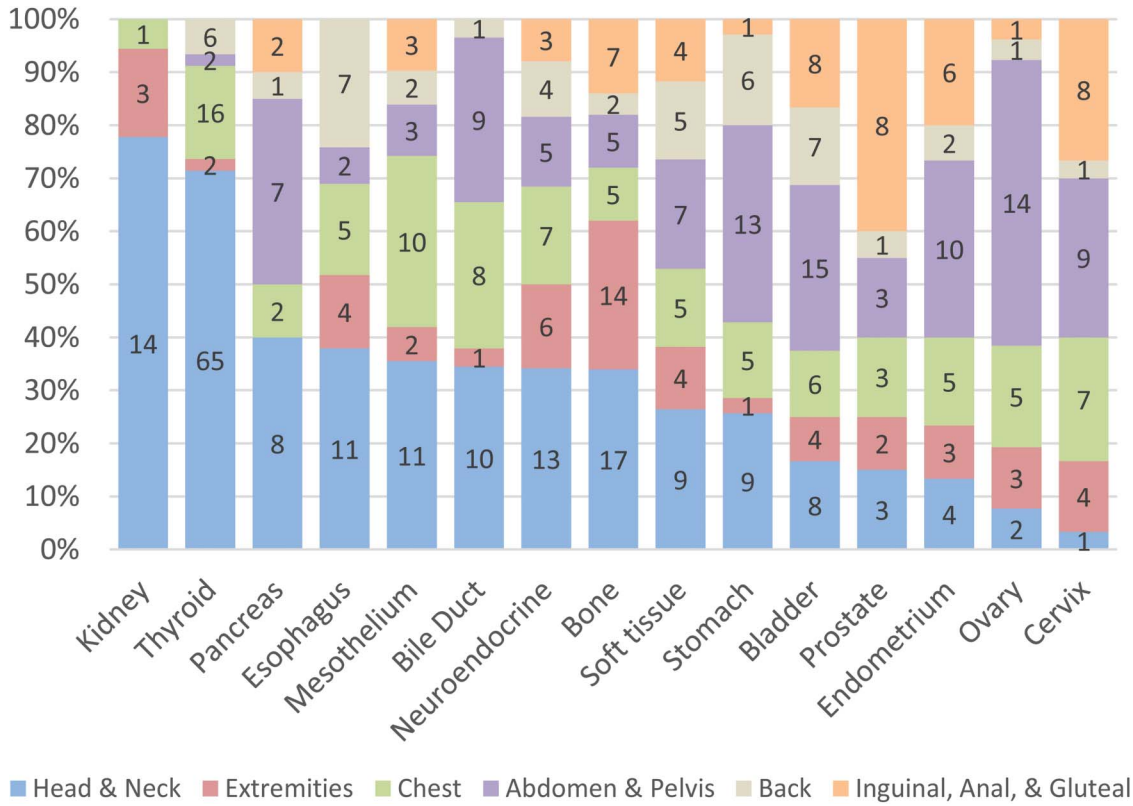

FIGURE 2. Distribution of cutaneous metastases from uncommon primary sites by anatomic region. Data include both institution cases and published case reports. The number of cutaneous metastases for each anatomic region is marked within primary site plot bars.

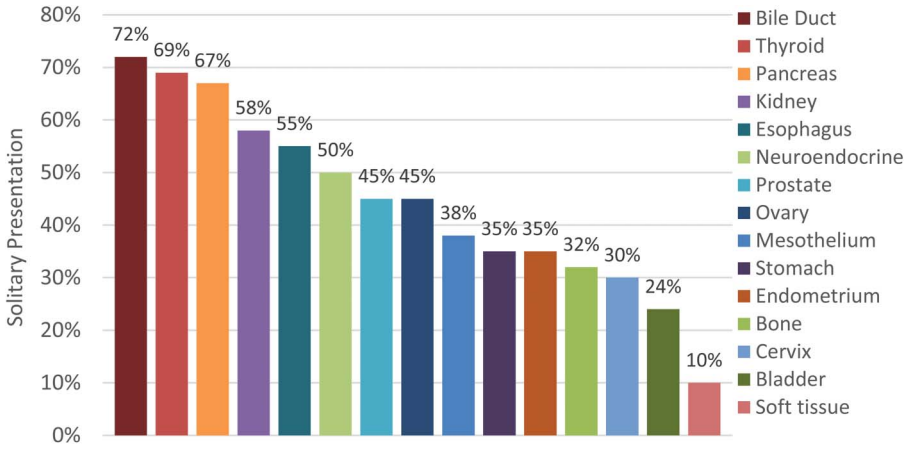

FIGURE 3. Percentage of cutaneous metastases presenting as solitary lesions from uncommon primary sites. Data include institutional cases and supplemental case reports.

exhibit overlapping characteristics. Primary adnexal neoplasms, in particular, often share architectural features with CMs. For example, endometrioid adenocarcinoma can share histologic features with cutaneous adnexal carcinoma, and clear cell renal cell carcinoma may show morphologic overlap with hidradenomas and sebaceous tumors.[13,14] When considering a primary cutaneous tumor, it is essential to look for an in situ component or surrounding non-neoplastic component adjacent to the lesion, because these features suggest a primary tumor origin. Moreover, close involvement with the epidermis or native dermal structures serves as evidence supporting a primary cutaneous lesion.[15]

Although distinguishing CMs from primary cutaneous lesions based on morphologic features alone can be challenging, the use of ancillary testing, particularly immunohistochemistry (IHC), is commonly used to differentiate the 2 groups (Figs. 8 and 9). p63 and p40 are especially helpful in distinguishing CMs from primary adnexal carcinoma with p63 being more sensitive (89%–100%) and p40 more specific.[16–18] p40 is also more specific than p63 in excluding cutaneous metastases from tumors of the breast, lung, endometrium, stomach, and thyroid, because p63 expression can be seen in 11%–22% of cutaneous metastases from these sites.[16] D2-40 and keratin 15 can help further differentiating primary cutaneous lesions from metastatic lesions, staining positive in several primary adnexal carcinomas and negative in metastatic adenocarcinomas.[17,19] However, caution must be taken when primary cutaneous apocrine carcinoma and primary cutaneous mucinous carcinoma are in consideration, because they often show weak or negative staining for p63, p40, CK5/6, and D2-40.[15–17,20] Alternatively, CMs from urothelial carcinoma often retain both p63 and keratin 5/6 and may be easily confused with a primary cutaneous carcinoma without additional immunostains.[21,22] Differentiating primary and metastatic squamous cell carcinomas is also a diagnostic challenge, because the entities often share similar immunohistochemical profiles (eg, keratin 5/6 and p63 positive). In these cases, their differentiation relies on clinical assessment and further ancillary testing.

Cancer of unknown primary (CUP), accounting for approximately 3%–5% of all cancer diagnoses, is characterized by the presence of metastatic disease without an identifiable primary tumor site. After ruling out the possibility of primary cutaneous adnexal carcinoma, determining the primary site

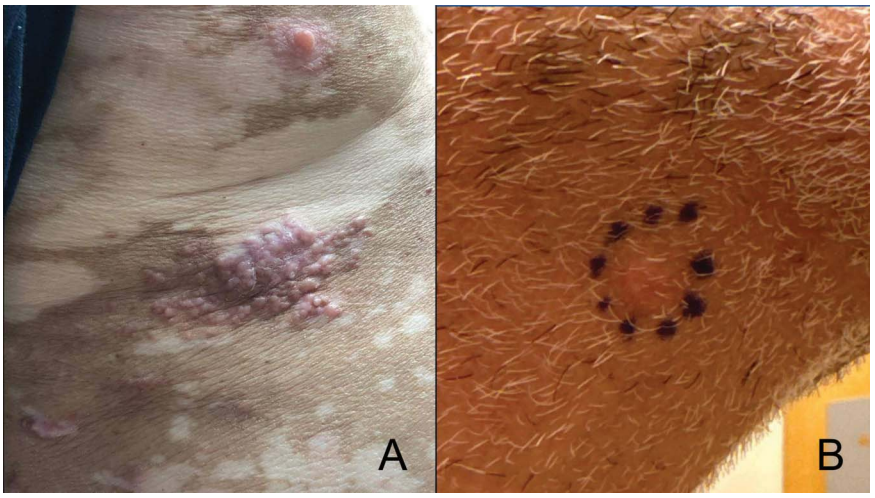

FIGURE 4. A, Metastatic mesothelioma. A 69-year-old man presented with painful infiltrative nodules on his right chest. One year prior the patient had a diagnosis of epithelioid mesothelioma. B, Metastatic pancreatic adenocarcinoma. A 55-year-old man with a history of pancreatic adenocarcinoma presented with nodule on right anterior neck.

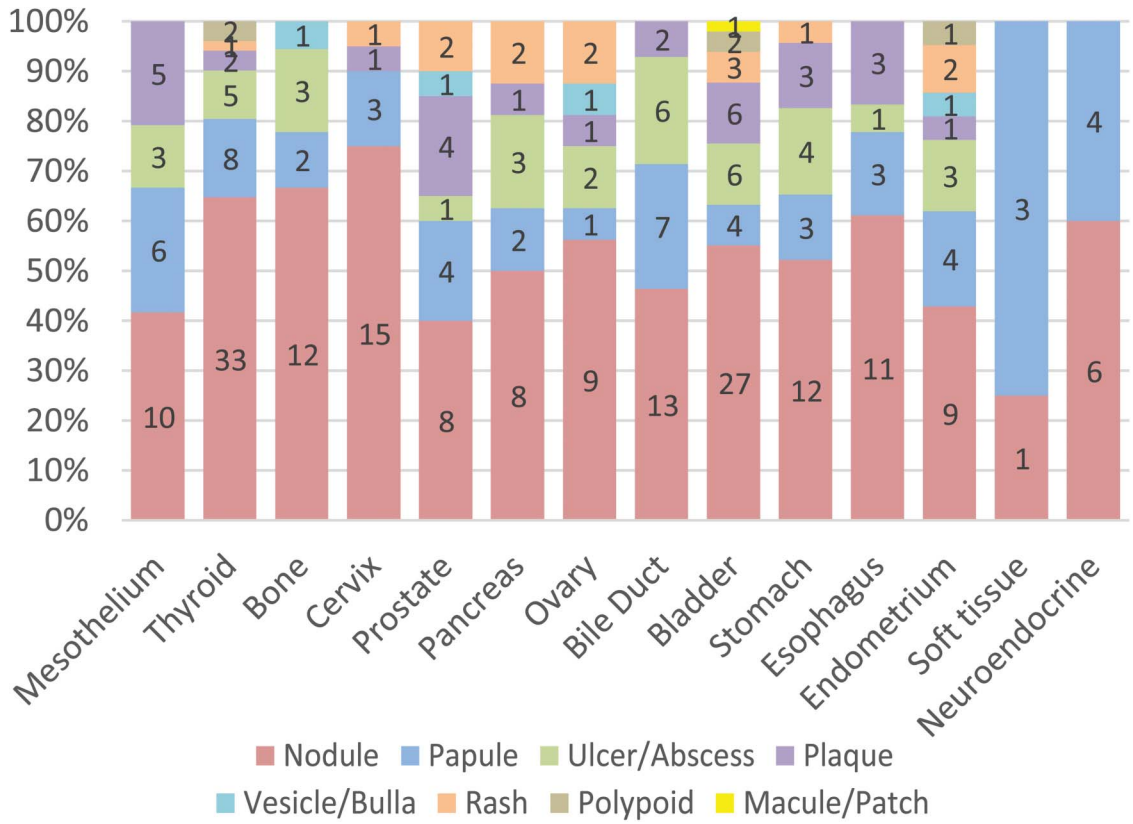

FIGURE 5. Clinical presentations of cutaneous metastases from uncommon primary sites. The number of cutaneous metastases with each clinical presentation is marked within primary site plot bars.

through clinical workup can be expensive. Therefore, IHC serves as a cost-effective method for identifying the tumor's origin. After the IHC algorithm illustrated in Figure 9, broad-spectrum keratin stains and histopathologic findings can help group the lesion into a broad category (carcinoma, neuroendocrine, sarcoma, lymphoma, and melanoma) and guide further

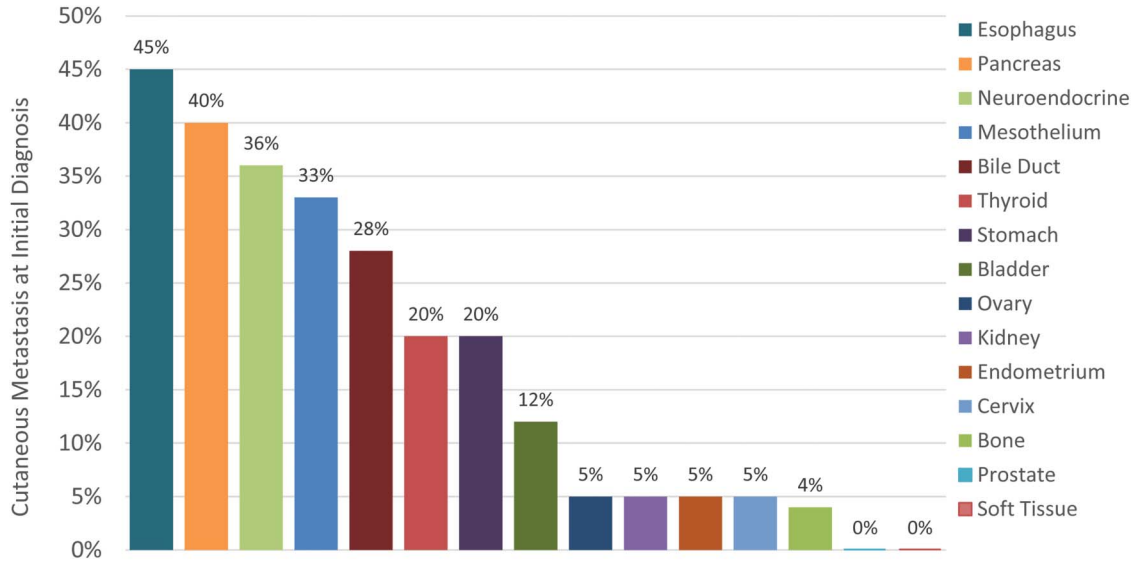

FIGURE 6. Percentage of cutaneous metastases identified at initial diagnosis from uncommon primary sites. Data include institution cases and supplemental case reports.

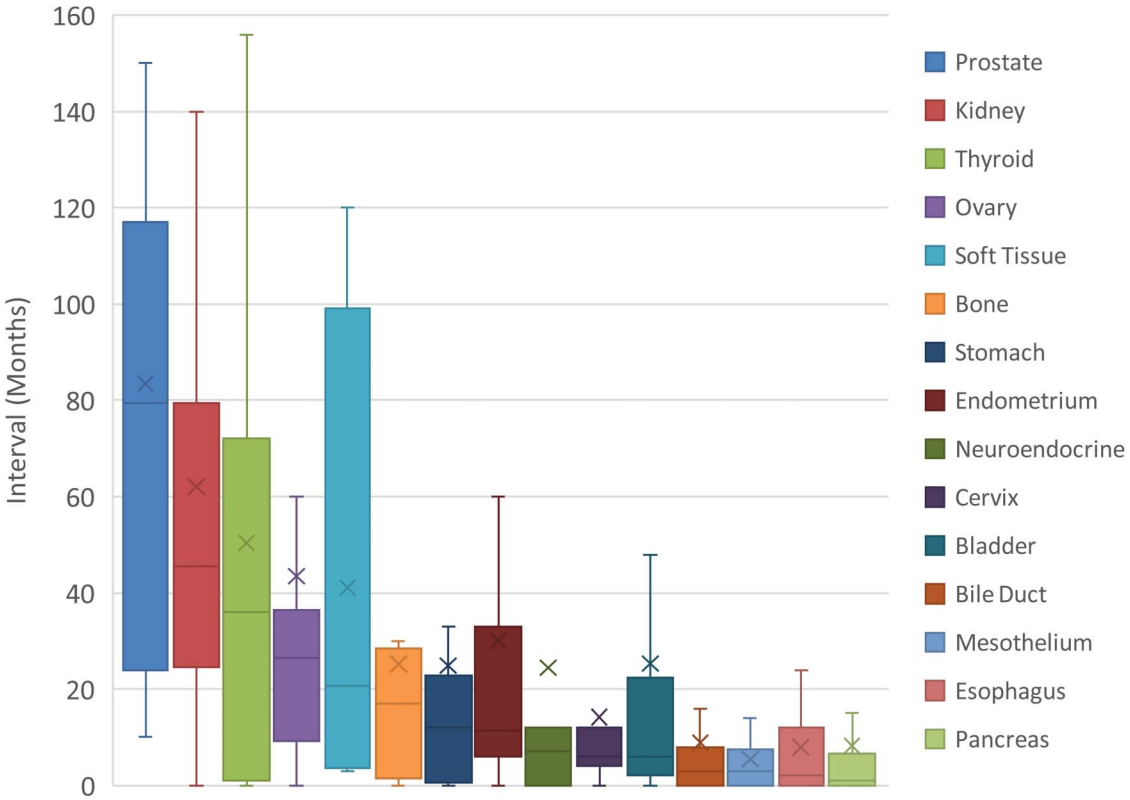

FIGURE 7. Time interval between primary cancer diagnosis and development of cutaneous metastasis from uncommon primary sites. Data include Massachusetts General Hospital cases and supplemental case reports. The box is limited by the 25th and 75th percentile and the horizontal bar represents the median line. "X" represents the mean. The top and bottom bars of the whisker plot represent the upper and lower outlier boundaries. Outlier points are included in calculations but omitted from the plot.

immunostaining.[23] Most CUP cases are adenocarcinomas or undifferentiated carcinomas.[24] Possible carcinomas can be further classified with keratin 7 and keratin 20 immunostains.[25] Although keratin 7 is expressed in glandular epithelium such as cutaneous appendages, breast, lung, ovary, and endometrium, keratin 20 is expressed in gastrointestinal epithelium, urothelium, and Merkel cells. An initial panel of keratin 7 and keratin 20 can separate the cutaneous metastases into 4 subgroups: keratin 7+ keratin 20− (breast carcinoma, lung carcinoma, endometrial carcinoma, endocervical carcinoma, cholangiocarcinoma, ovarian serous carcinoma, gastric adenocarcinoma, thyroid carcinoma, mesothelioma), keratin 7− keratin 20+ (colonic adenocarcinoma, Merkel cell carcinoma), keratin 7− keratin 20− (prostatic adenocarcinoma, renal cell carcinoma, hepatocellular carcinoma, adrenocortical carcinoma, germ cell tumor), and keratin 7+ keratin 20+ (pancreatic adenocarcinoma, ovarian mucinous carcinoma, urothelial carcinoma) (Fig. 9).[12,22,26] Further classification can be done with additional immunostains (Fig. 9).[3,27–29] The following sarcomas express keratin that can result in diagnostic pitfalls: epithelioid sarcoma, epithelioid angiosarcoma synovial sarcoma, desmoplastic small round cell tumor, and rhabdoid tumor.[30]

Although tissue diagnosis is key for determining the tumor origin, IHC studies may only narrow down the differential diagnosis, ultimately relying on clinicopathologic correlation. In approximately 15% of CUP cases, the tumor origin cannot be identified.[31] However, in recent years, advances in molecular methods have played an important role in predicting the primary tumor origin and guiding treatment decisions (Fig. 9).[32] Studies have demonstrated that combining IHC with molecular studies improves the identification of primary tumor sites.[33] Emerging molecular tests in CUP identification include (1) next-generation sequencing (NGS) assays, (2) gene expression profiling, (3) gene microarrays, (4) DNA methylation analysis, and (5) liquid biopsy.[33–38]

Site-specific genomic variants identified by NGS can help define the putative site of origin, and comprehensive NGS analyses enable the identification of oncogenic drivers with actionable targeted therapies (Fig. 9).[32,34,35] In a study of 200 CUP specimens by Ross et al,[35] a 236-gene NGS panel revealed *TP53*, *KRAS*, and *CDKN2A* mutations in 55%, 20%, and 19% of specimens, respectively, with mutations in *KRAS*, *CDKN2A*, *MCL1*, *PTEN*, *PIK3CA*, *ERBB2*, *RICTOR*, *BRAF*, and *NF1* being the most frequent "potentially druggable" molecular alterations. However, the molecular findings must be correlated with histologic and IHC findings because the effectiveness of therapy cannot be based on molecular findings alone. For example, colonic cancer harboring *BRAF*V600E does not respond to BRAF inhibitors as observed in melanoma.[39]

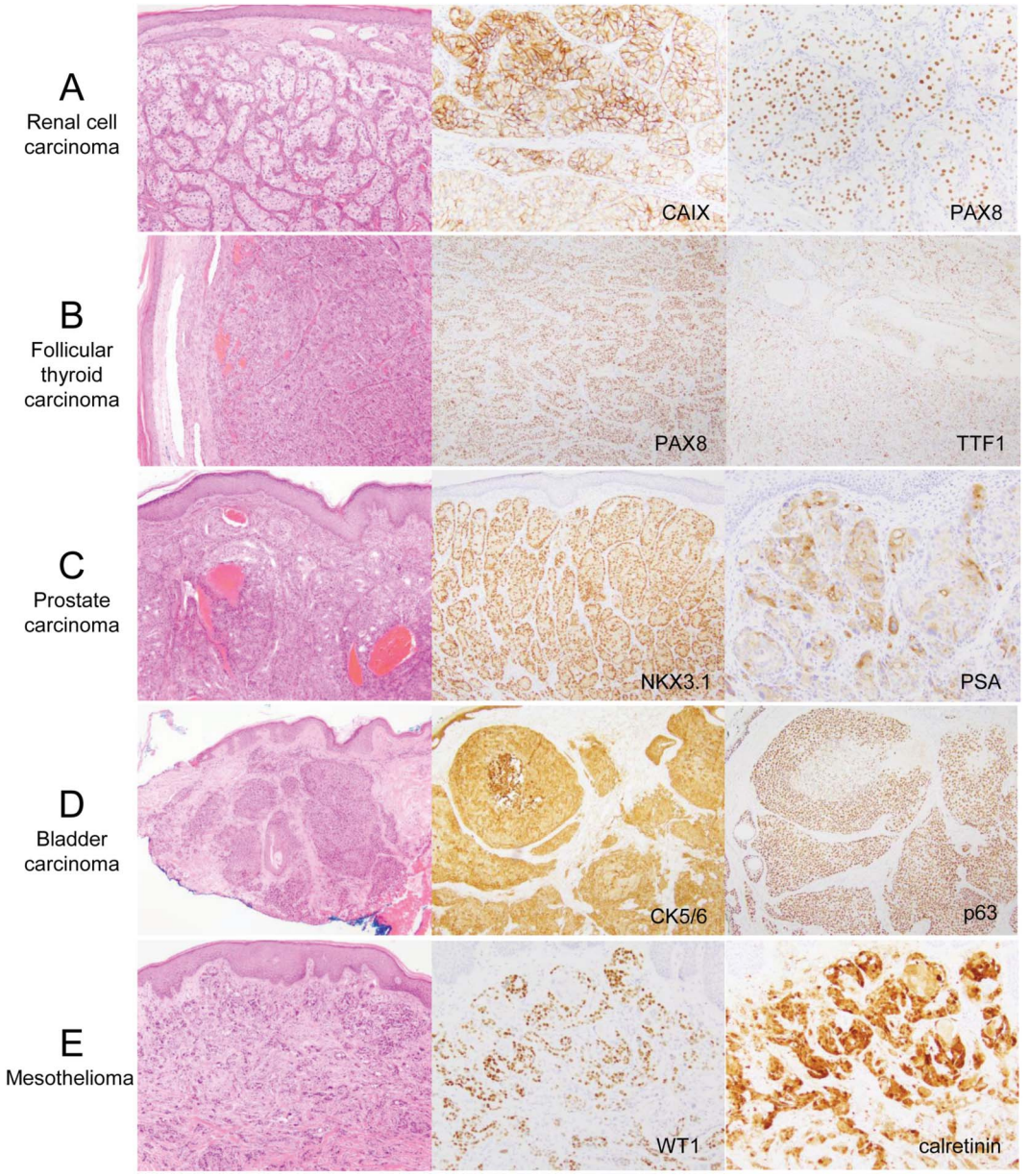

FIGURE 8. Histology of cutaneous metastases of uncommon tumors. A, A 65-year-old man with a history of renal cell carcinoma presented with multiple nodules on his foot and scalp. A skin biopsy showed clear cell carcinoma in the dermis that was diffusely positive for CAIX and PAX8. B, A 79-year-old man presented with a 0.5 × 0.5 cm nodule on his right scalp. He had a thyroidectomy performed 17 years prior for invasive follicular thyroid carcinoma. A skin biopsy showed a tumor positive for PAX8 and TTF1, supporting the diagnosis of metastatic follicular thyroid carcinoma. C, A 55-year-old man presented with nodules in his left medial and lateral inguinal fold. He had a prostatectomy performed 9 years prior for prostatic adenocarcinoma. A skin biopsy showed adenocarcinoma in the dermis exhibiting strong nuclear NKX3.1 and cytoplasmic prostatic specific antigen (PSA) staining, supporting the diagnosis. D, An 83-year-old woman with a history of urothelial carcinoma diagnosed 1 year earlier presented with a solitary scalp nodule. A skin biopsy showed an epithelial neoplasm in the dermis, positive for keratin 5/6, p63, and p40, and negative for keratin 7, keratin 20, GATA3, and p16. The findings were supportive of metastatic urothelial carcinoma. E, A 69-year-old man presented with painful infiltrative nodules on his right chest. One year prior the patient had a diagnosis of epithelioid mesothelioma. The primary tumor was diffusely positive for calretinin, WT1, and D2-40, focally positive for BerEP4 and MOC31, and negative for TTF1. A skin biopsy showed an infiltrative tumor in the dermis that was positive for WT1, calretinin, and D2-40, and negative for BerEP4, MOC31, and TTF1, supporting the diagnosis of metastatic mesothelioma.

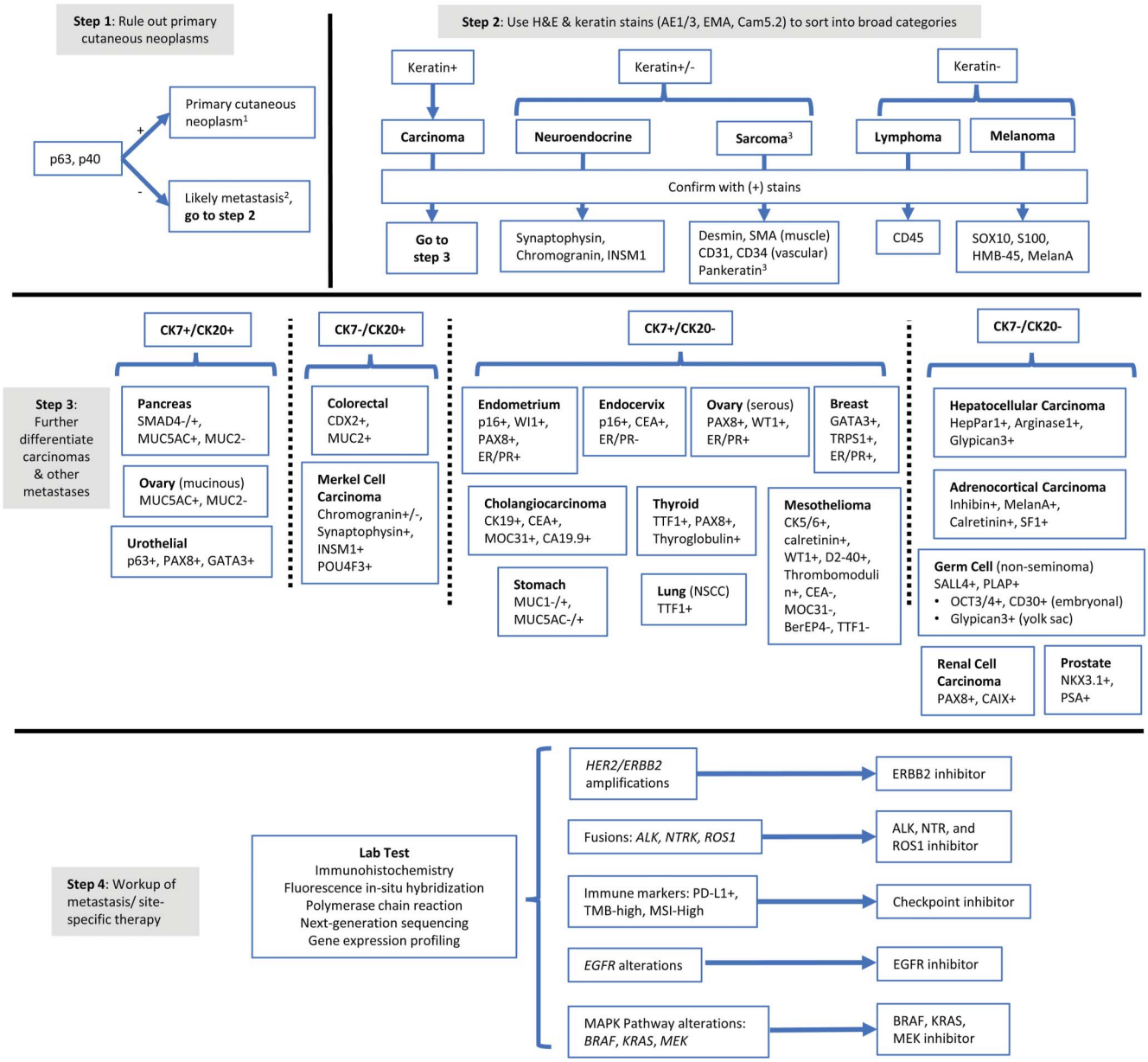

FIGURE 9. Immunohistochemical and molecular workup of cutaneous metastases. (1) Metastatic squamous cell carcinoma and urothelial carcinoma can be p63+, p40+, CK5/6+. (2) Primary cutaneous apocrine carcinomas and primary cutaneous mucinous carcinomas can be p63−, p40−, CK5/6−. (3) Most sarcomas are keratin-, but epithelioid sarcoma, epithelioid angiosarcoma, synovial sarcoma, desmoplastic small round cell tumor, and rhabdoid tumor can be keratin+.

A "liquid biopsy" is a noninvasive, cost-effective means to detect circulating tumor DNA (ctDNA), tumor microRNAs (miRNAs), platelet-derived tumor mRNA, and exosomes, as well as DNA, RNA, and protein from circulating tumor cells (CTCs) in a blood or fluid sample.[38] A single blood test can help identify tissue of origin, evaluate prognostic and predictive biomarkers, and guide treatment decisions. Subsequent blood tests can monitor response to therapy and detect minimal residual disease, resistance, and relapse. Owing to ease of collection, liquid biopsies are often convenient and have faster turnaround times than tissue biopsies. In the setting of metastasis, liquid biopsies may also allow for better assessment of tumor heterogeneity and provide tumor analysis when a tissue sample is not readily attainable.[40] In a study of 1739 patients with CUP tumors, performing a 74-75-genes NGS panel on cell-free DNA (cfDNA), at least 1 genetic alteration was detected in 90% of patients.[41] However, driver mutations can be detected in benign skin of healthy individuals, potentially affecting cfDNA studies and necessitating additional tests, such as epigenetic analyses.[42,43] Further studies can be performed by isolating CTCs, which are more frequent in treatment-naive patients.[44]

However, liquid biopsies have some limitations. Low ctDNA quantities can result in insufficient samples or false-negative results, while cfDNA from individuals with clonal hematopoiesis of uncertain clinical potential may show mutational changes that overlap with solid tumors, leading to false-positive results. Thus, liquid biopsies are recommended in conjunction with tissue testing.[40,45]

Determining the primary tumor origin in CUP using molecular profiling remains a debated topic, because CUP tumors lack histologic classification, making them more difficult to classify by molecular findings. Multiple metastatic deposits often give rise to a heterogeneous ctDNA, which can prove a diagnostic challenge. Metastases may also have a different molecular profile than the primary tumor, making CTC phenotyping difficult. Recently, machine learning algorithms, including stepwise additive logistic regressions, random forests, and convolutional neural networks, have been used to classify CUP using data from multiple sources, including clinical, radiographic, histologic, and molecular information.[46]

In summary, CMs may be the initial presentation of underlying malignancy from uncommon primary sites and can exhibit distinctive patterns of cutaneous spread based on the primary cancer type and anatomic location. The primary site can also affect the clinical and cutaneous presentation of CMs. Moreover, the use of histomorphologic examination, IHC, and molecular studies can help differentiate CMs from primary skin tumors and further narrow down the possible primary sites.

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CME EXAMINATION
June 2026

Please mark your answers on the ANSWER SHEET.

After participating in this CME activity, physicians should be better able to: 1. Describe the clinical presentation and histologic features of cutaneous metastases from uncommon primary sites. 2. Explain how to apply immunohistochemical algorithm in the work-up of cutaneous metastases.

CME Questions

1. Which of the following is a clinical feature of cutaneous metastasis from uncommon primary sites?
   a. Skin can be an initial presentation.
   b. The shortest median time interval was observed for cutaneous metastasis arising from pancreas.
   c. Head and neck is the most commonly affected site by cutaneous metastasis.
   d. Many cutaneous metastases from the bile duct were due to catheter-related tumor seeding.
   e. All of the above

2. The clinical presentation of cutaneous metastasis can be?
   a. Nodule
   b. Ulcer
   c. Vesicle or bulla
   d. Rash
   e. All of the above

3. The most common primary sites of cutaneous metastasis are?
   a. Breast and lung
   b. Thyroid
   c. Kidney and bladder
   d. Bone and soft tissue
   e. Prostate, ovary, and endometrium

4. Which of the following immunostain is helpful in distinguishing primary adnexal carcinoma from cutaneous metastasis?
   a. Keratin 19
   b. Keratin 903
   c. p63
   d. Keratin 7
   e. Epithelial membrane antigen

5. Which two immunostains are helpful in further narrowing the possible primary sites of cutaneous metastasis?
   a. Keratin 5/6 and keratin 903
   b. Keratin 7 and keratin 20
   c. PAX8 and TTF1
   d. Estrogen receptor and progesterone receptor
   e. p16 and WT1

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JUNE 2026

Please answer the questions on pages 426-427 by filling in the appropriate circles on the answer sheet below. Mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

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1. (a) (b) (c) (d) (e)
2. (a) (b) (c) (d) (e)
3. (a) (b) (c) (d) (e)
4. (a) (b) (c) (d) (e)
5. (a) (b) (c) (d) (e)

Your evaluation of this CME activity will help guide future planning. Please respond to the following questions below.

Please rate these activities 1 (minimally) to 5 (completely):	1	2	3	4	5
These activities were effective in meeting the educational objectives.	O	O	O	O	O
These activities were appropriately evidence-based.	O	O	O	O	O
These activities were relevant to my practice.	O	O	O	O	O

Please rate your ability to achieve the following objectives, both before and after this activity:
1 (minimally) to 5 (completely)

After participting in this CME activity, physicians will be better able to:	Pre 1	2	3	4	5	Post 1	2	3	4	5
1. Describe the clinical presentation and histologic features of cutaneous metastases from uncommon primary sites.	O	O	O	O	O	O	O	O	O	O
2. Explain how to apply immunohistochemical algorithm in the work-up of cutaneous metastases.	O	O	O	O	O	O	O	O	O	O

Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 — definitely will not change, 5 — definitely will change)	1	2	3	4	5
	O	O	O	O	O

How many patients are likely to be impacted by what you learned from this activity?
O <20% O 20-40% O 40-60% O 60-80% O >80%

Please list at least one (1) change you will make to your practice as a result of this activity:
_____

How will you apply what you learned from these activities? (Mark all that apply).

O In diagnosing patients	O In making treatment decisions
O In monitoring patients	O As a foundation to learn more
O In educating students and colleagues	O In educating patients and their caregivers
O As part of the quality or performance improvement project	O To confirm current practice
O For maintenance of board certification	O For maintenance of licensure

How committed are you to applying this activity to your practice in the ways you indicated above? (1 — definitely will not change, 5 — definitely will change)	1	2	3	4	5
	O	O	O	O	O

Did you perceive any bias for or against any commercial products or devices? Yes O No O
If yes, please explain:

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