Neuropathology of brain metastases

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Abstract

Metastatic tumors are the most common neoplasms encountered in the central nervous system (CNS), and continue to be major cause for mortality and morbidity. Macroscopic features and corresponding radiological findings can be diagnostic in majority of the cases, however, microscopic evaluation would be necessary when the differential diagnosis includes a primary CNS tumor, unknown primary tumor site, and when the resection of the tumor is either considered therapeutic or palliative. The first step in the diagnosis of a metastatic brain lesion is to exclude a primary CNS tumor, followed by verification or identification of the primary tumor and the site. Although general approach to a metastatic lesion from an unknown primary tumor is the same everywhere else, there are slight variations for the metastatic lesions in the CNS versus other regions. When morphological features are not enough to establish a definitive diagnosis, additional studies including immunohistochemical stains are applied. With the expending immunohistochemical armamentarium for pathologists, more accurate assessments are possible even in cases of unknown primary tumor. This review summarizes the diagnostic approach to CNS metastases, immunohistochemical assessment of neoplasm of unknown primary, and primary CNS lesions entering in the differential diagnosis of metastases.

Key words: Brain metastases, central nervous system metastases, metastasis

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GENERAL ASPECTS-EPIDEMIOLOGY

Metastatic tumors are the most common neoplasms encountered in the central nervous system (CNS), and continue to be a major cause of morbidity and mortality. Most CNS lesions are symptomatic at the time of diagnosis, with seizures, localized motor deficits, dysphasia, and headaches the most common signs and symptoms.[22,26] Only a small percentage of brain metastases, almost exclusively from melanoma and clear cell renal cell carcinoma (RCC), are asymptomatic and diagnosed during routine imaging.[26] The exact incidence is mostly unknown due to variable sources of data ranging from preimaging era autopsy studies to single institution surgical series. Incidence rates of brain metastases in population-based studies range from 8.3 to 14.3 per 100,000 people.[34] There has been an increase in the incidence of brain metastases over time, possibly as a result of increased survival times for cancer patients overall, more sensitive diagnostic methods, and a relative increase in cancer incidence as the population ages.[52] However, there has not been much improvement in overall survival for patients with brain metastases throughout the time interval included in that study. Intracerebral metastases were the immediate or contributing cause of death in 50% of the patients in an older series.[65] Patients

at greater risk of dying of intracerebral metastases included those in whom the brain was the first site of distant metastasis, those with an intracerebral metastasis from an unknown primary site, and those who already had evidence of brain metastasis at first presentation.

The most common primary sites for brain metastases are lung, breast, skin, kidney, and gastrointestinal tract with incidence proportions of 20%, 5%, 6.5%, 6.8%, and 1.8%, respectively.[2] CNS metastasis typically occurs late during the course of the systemic malignancies.[65] In a large retrospective study of metastatic brain tumors, median interval between diagnosis of primary tumor and brain metastases was 8.5 months and showed significant variation ranging from 4 months in lung carcinomas to 37 months in melanomas.[26] However, the signs and symptoms of brain metastasis may be the first evidence of malignancy and require clinical, radiographic, and/or pathological work-up for an unknown primary. Such cases constitute up to 16% of CNS metastases and the overwhelming majority of them turn out to be of pulmonary origin.[26,30] Metastatic sarcomas are usually not in the differential of unknown primary, since they tend to form bulky disease at primary location before they metastasize, although a rare, but notable exception is alveolar soft part sarcoma.[18,47,56] The incidence of metastases also varies by the histologic subtype of the tumors. Nonsmall cell lung carcinomas are more likely to metastasize to brain as compared with small cell carcinomas, and among the former, adenocarcinomas are more likely to metastasize than squamous cell and large-cell carcinomas.[19,36,55] A retrospective study reported that only 3% of the patients with sarcoma developed CNS metastasis and the most common types were alveolar soft part sarcoma and osteosarcoma.[7]

SITES

The majority of the neoplasms reach to the CNS via hematogenous spread; however, in rare cases retrograde spread via cranial nerves is possible especially in squamous cell carcinomas of the head and neck region and malignant salivary gland neoplasms.[36,53] Most tumor cells ultimately spread to the brain via the pulmonary arterial circulation, either as a primary lung cancer or a metastasis to the lung from other systemic primaries. The majority of the brain metastases are parenchymal; however, metastases to leptomeninges/subarachnoid space, dura and skull are not uncommon. Direct extension of tumor from adjacent skull occurs mostly in tumors prone to bony metastases such as breast and prostate carcinomas. Within the brain, metastases are most commonly found in the corticomedullary gray/white junction due to narrowing and acute angle branching of vessels at that point [Figure 1].[13,20] The corticomedullary regions within the middle cerebral

artery distribution are especially common given that this is the straightest route to the brain. Nevertheless, brain metastases also tend to be more common at the terminal "watershed areas" of arterial circulation, with the territory between the middle and posterior cerebral arteries being most common.[13] Approximately 80% of brain metastases are located in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem.[44] This is correlated with the amount of blood flow to each area. However, there is a disproportionately high incidence of posterior fossa metastases from pelvic and gastrointestinal tumors, suggesting that these primaries more often gain CNS access through the posterior circulation.[13] Leptomeningeal spread is more typical of small cell lung carcinoma and melanoma; however, leptomeningeal metastases are most frequently associated with breast carcinomas due to its higher overall incidence.[6] Other rare sites include choroid plexus, pineal gland, pituitary, and optic nerve. There are also case reports of metastases to primary CNS tumors. Tumor to tumor metastasis most commonly occurs from a rapidly proliferating systemic malignancy such as melanoma and lung or breast carcinoma to an indolent primary CNS tumor such as pituitary adenoma or meningioma.[59]

NUMBER OF METASTASES

The number of the metastatic foci varies among the cases from solitary or single to miliary (innumerable). In a retrospective surgical review, 45.6% of the patients had solitary brain metastasis (one CNS lesion without other systemic metastases), 26.5% had single brain metastasis (one CNS lesion with other systemic metastases), and the rest had two or more brain metastases.[55] Although, the finding of multiple CNS lesions renders the diagnosis of metastasis more likely, fully 36% of the patients who initially presented with neurological symptoms due to a single brain lesion were also diagnosed with metastasis from a systemic cancer.[30]

In general, lung cancers and melanoma are more likely to be associated with multiple metastases, whereas breast, renal, and colorectal carcinomas are more likely to present with a solitary brain metastasis.[13,36] Presence of multiple metastatic tumor foci surrounding blood vessels without parenchymal invasion is described as one pattern of miliary brain metastasis, and has been reported most often with nonsmall cell lung carcinomas.[37] In contrast, meningeal carcinomatosis [Figure 2], which represents subarachnoid dissemination with widespread meningeal studding, is mostly seen in lung and breast carcinomas.[58]

MACROSCOPIC FEATURES

Macroscopically, metastatic lesions are usually sharply demarcated, spherical masses that often do not infiltrate

the surrounding brain parenchyma, but cause edema due to mass effect. Softening of the surrounding brain parenchyma is prominent and sometimes disproportional to the size of the lesions. Especially larger tumors tend to have necrotic centers. Hemorrhage is not uncommon and most often seen with metastases from melanoma [Figure 3], choriocarcinoma, and clear cell RCC.[62,63] Occasionally, metastases from lung and breast carcinomas appear cystic. Some metastatic lesions may show characteristic features of the primary tumor such as a shiny mucoid appearance of mucin-secreting adenocarcinomas or the gray-to-black pigmented lesions of melanoma [Figures 1 and 3]. Importantly, however, lack of pigmentation does not exclude melanoma, since some examples are amelanotic. Meningeal carcinomatosis may present with multiple small nodules or with focal opacification of the leptomeninges, particularly over craniospinal nerve roots and the base of the brain [Figure 4].

MICROSCOPIC FEATURES

Microscopic evaluation of metastatic brain lesions occurs when the differential diagnosis includes a primary CNS tumor in a patient with or without known systemic malignancy, and when the resection of the tumor is either considered therapeutic or palliative in nature for increased intracranial pressure or impending cerebral herniation. Patients with single intracerebral lesions are more likely to undergo resection even in the presence of other systemic lesions suspicious for primary cancer.[30] The majority of metastases are sharply demarcated from the surrounding brain and show similar histological features to those of the primary tumor [Figure 5]. Surrounding brain shows tissue rarefaction, neovascularization and gliosis, manifesting as vasogenic edema on imaging. Meningeal carcinomatosis [Figure 2] consists of neoplastic cells filling the subarachnoid
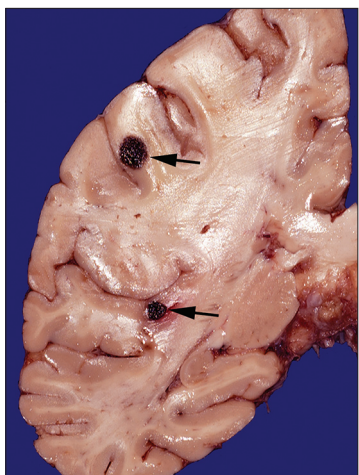

Figure 1: Autopsy brain at level of the hippocampus showing the typical sharp demarcation and corticomedullary location for two foci of metastatic melanoma (arrows)
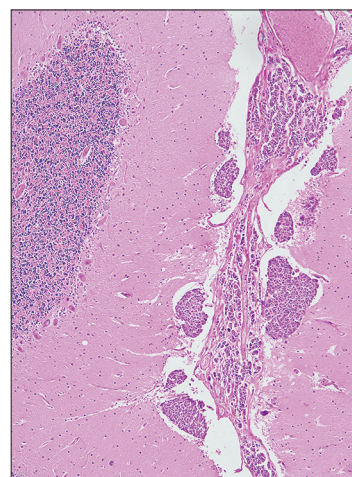

Figure 2: Example of leptomeningeal carcinomatosis pattern in a patient with breast carcinoma. Clusters of tumor cells are invading the meninges and filling the subarachnoid space between two folia of cerebellar cortex
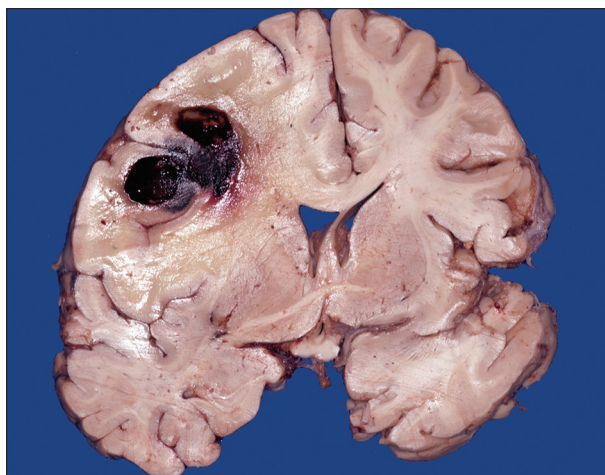

Figure 3: Focus of metastatic melanoma involving frontal lobe at level of the anterior commissure (same case as Figure 1) with associated hemorrhage and surrounding edema
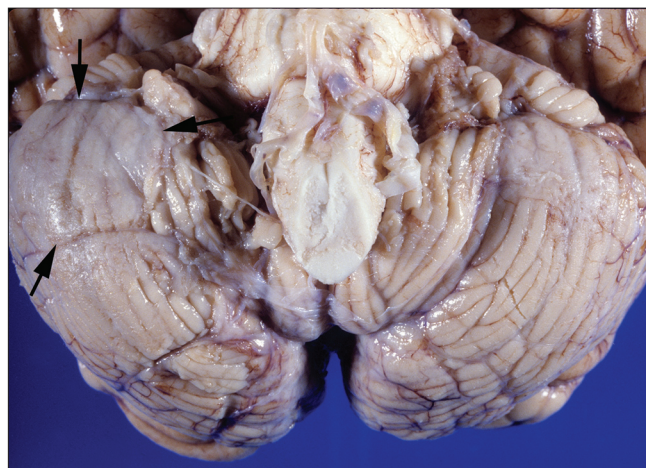

Figure 4: Autopsy brain involved by leptomeningeal carcinomatosis (same case as Figure 2). Note the leptomeningeal opacification, best seen at the base of the left cerebellum (arrows)

space, often with further spread along the perivascular Virchow–Robin spaces.

PRIMARY CNS NEOPLASMS IN THE DIFFERENTIAL DIAGNOSIS OF METASTASES

The first step in the diagnosis of a metastatic brain lesion is to exclude a primary CNS tumor. Knowledge of a systemic malignancy, especially one with tissue diagnosis is extremely helpful. However, even among the patients with known cancer, 11% of the single brain lesions represent something other than metastasis, the majority of which turn out to be high-grade gliomas.[45] The microscopic features of the metastatic tumors are usually similar to their primary, and when the metastatic tumor is well differentiated, diagnosis is rarely a problem. However, poorly differentiated neoplasms in the brain parenchyma, especially when solitary, almost always trigger a differential diagnosis with high-grade gliomas, such as glioblastoma.

In contrast to metastases, high-grade gliomas typically feature an invasive border with surrounding brain parenchyma. However, limited and mostly perivascular brain invasion can also be seen in some metastases, especially those from small cell lung carcinoma, melanoma, and lymphoma. In metastatic lesions, surrounding brain parenchyma shows reactive astrocytosis, proliferation of microglia, and vascular proliferation, all of which might be misinterpreted as glioblastoma in a small biopsy from this region. This is an especially difficult pitfall for solitary brain metastases in patients with an absence of known systemic malignancy. In a similar vein, predominantly epithelioid or rhabdoid glioblastoma may resemble metastatic carcinomas or melanomas. While negative stains for melanoma and carcinoma may suggest glioma, addition of glial markers, such as glial fibrillary acidic protein (GFAP), OLIG2, and SOX2 resolves this dilemma in nearly all cases.

Another primary CNS tumor that may enter in the differential diagnosis, especially for metastatic RCC is hemangioblastoma. Hemangioblastomas have foamier cytoplasm and darker nuclei with degenerative atypia. Metastatic RCC, clear cell type often has clear (but not typically foamy) cytoplasm, vesicular nuclei with prominent nucleoli, and shows high grade features including mitoses and necrosis. RCCs are generally positive for epithelial membrane antigen (EMA), CD10, and RCC protein, whereas hemangioblastomas are positive for inhibin A, D2-40, neuron-specific esterase (NSE) and S-100 protein.[50] Hemangioblastomas are also negative for transcription factors expressed by the cells of nephric and mullerian duct origin such as PAX2 and PAX8.[5]

True epithelial differentiation is rare in the CNS but such tumors may enter into the differential diagnosis of a metastatic carcinoma. For instance, choroid plexus tumors are variably positive for GFAP, S100, and transthyretin, unlike the most common metastatic carcinomas that enter in the differential such as breast, lung, ovary, and biliary tract.[14] Unfortunately, both choroid plexus tumors and these carcinomas are usually CK7-positive, CK20-negative, and therefore, other organ-specific markers are necessary to exclude a metastasis. Fortunately, the great majority of choroid plexus carcinomas occur in infants, where metastatic carcinoma is not a realistic differential diagnostic consideration, but rare examples have also been reported in adults; in these rare cases, newly identified choroid plexus markers, such as Kir7.1 and stanniocalcin-1 may be of additional aid.[17] Carcinomas metastatic to the sellar region may similarly require exclusion from primary epithelial neoplasms, such as pituitary adenoma and craniopharyngioma, especially the papillary variant.

Dural and intraventricular metastases often raise the alternate possibility of anaplastic meningioma. When there is a component of classical meningioma present, diagnosis is straightforward, except in rare cases of metastasis to a meningioma. Unfortunately there are no absolutely specific markers for meningiomas. Although most are positive for EMA, this marker is also expressed in almost all carcinomas. Moreover, high-grade meningiomas may show positivity for various cytokeratins, further complicating the diagnostic workup. Another marker that may potentially help is vimentin since it is strongly positive in meningiomas and negative in the majority of carcinomas. However, more specific makers are required when metastatic neoplasm is suspected to be RCC or melanoma, which are also commonly positive for vimentin. Fortunately, most melanomas will express at least one of several specific markers, such as HMB-45, Melan A (melanoma antigen recognized by T-cells-1, or MART-1), tyrosinase, and microphthalmia-associated transcription factor (MITF).[39] Organ specific markers for kidney such as the RCC antibody and PAX8 may be similarly useful in the differential of metastatic RCCs and clear cell meningiomas.[48]

Germ cell neoplasms, primary or metastatic, are more commonly seen in children and young adults. Although considerably rarer, this category is particularly important to consider given its much greater likelihood of response to radiation and chemotherapy. Metastatic carcinoma is rarely a consideration in this age group; however, immunohistochemical (IHC) studies may help since germ cell tumors stain with various specific markers, such as CD117 (c-kit), OCT4, alpha fetoprotein (AFP), beta human chorionic gonadotropin (β-HCG), and CD30 [Figure 6]. The majority of primary CNS germ cell tumors are located in the midline, unlike metastatic
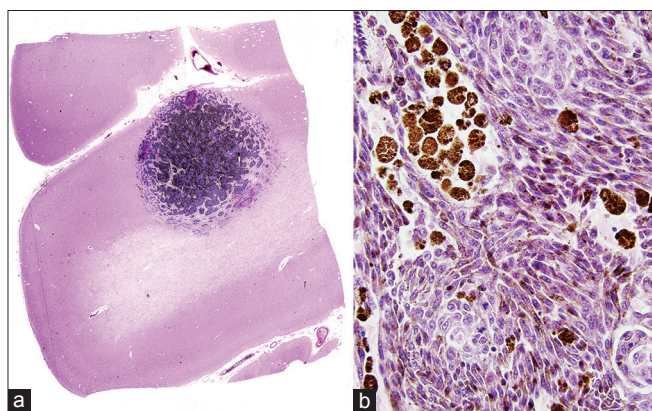
Figure 5: Metastatic melanoma (same case as Figure 1). (a) At low magnification, there is relatively sharp demarcation, except for limited peripheral spread along perivascular spaces. The adjacent white matter appears pale and edematous. (b) Higher magnification reveals a variably pigmented spindled and epithelioid neoplasm with prominent nucleoli, mitotic activity, and scattered melanophages, typical of melanoma
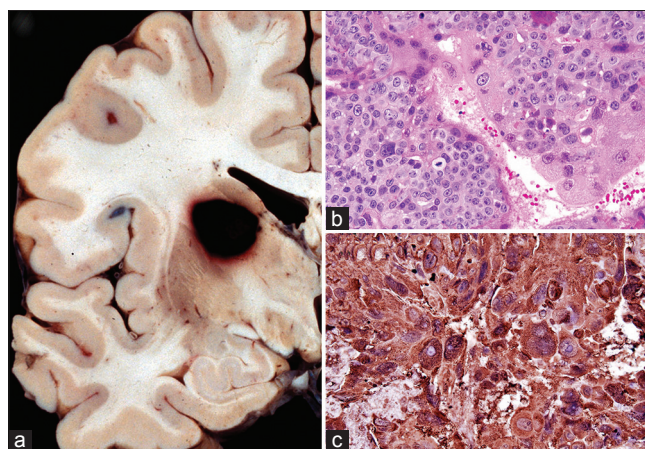

Figure 6: Metastatic choriocarcinoma. (a) Gross pathology reveals a hemorrhagic, well-demarcated mass involving basal ganglia and internal capsule. (b) Histology shows mononucleated epithelioid cells consistent with cytotrophoblast, covered by larger multinucleated syncytiotrophoblasts. (c) The tumor cells strongly express beta HCG

germ cell tumors that are predominantly seen in cerebral hemispheres. However, there is extensive overlap and knowledge of a prior or synchronous systemic neoplasm is therefore critical.

The second step in the diagnosis of metastatic brain tumors is to either verify or identify the primary tumor and the site. When the microscopic features of the metastatic tumors are similar to the known primary tumor, the diagnosis is straightforward. However, the grade and degree of differentiation may vary, with more anaplastic tumors often requiring ancillary IHC studies for confirmation. Ancillary studies become even more important in the evaluation of a metastatic neoplasm of unknown primary (NUP).

There is an extensive literature on the evaluation of NUPs, including antibody sensitivities and specificities, diagnostic staining patterns, cross-reactivity patterns, and potential pitfalls for each stain.[40] Positive stains supporting a diagnosis are generally more reliable than the negative stains excluding a diagnosis. Also as a general principle, more than one stain should be evaluated to control for aberrant expression patterns, technical artifacts, and spurious findings. The general goal is to subtype the tumor, so that the site of origin is established and tumor specific therapy may be initiated. Although the main principles are same, there are slight variations in the approach to the NUP in the CNS versus other regions.

APPROACH TO NUP IN CNS

Diagnostic Approach Based on Histologic Type
Often the distinction between carcinoma, sarcoma, lymphoma, and melanoma is possible based on morphology alone. Carcinoma cells are cohesive, round,

cuboidal, or columnar cells arranged in sheets, tubules and acinar structures, and usually have moderate to abundant cytoplasm. Sarcomas are composed of cohesive, generally elongated spindle cells, arranged in fascicles that may have diagnostic elements such as cartilage or fat. Melanoma has been dubbed "the great mimicker" since it can resemble carcinomas, sarcomas, lymphomas, and even nonneoplastic considerations occasionally. Identification of brown melanin pigment is useful for the diagnosis, but is not found in amelanotic forms. Lymphomas are generally discohesive cellular proliferations, often with a combined angiocentric and infiltrative growth pattern when primary or dural/meningeal localization when secondary.

When morphology is not enough, ancillary studies are applied. A basic IHC panel including melanocytic and lymphoid markers and cytokeratins is a widely accepted initial step in cases of NUP in any site. However, the selection of antibodies is slightly different for the NUP in the CNS. The most useful markers are summarized in Table 1, often starting with a few general markers such as cytokeratin (carcinoma), S-100 (melanoma, glioma), and leukocyte common antigen (lymphoma). Lack of staining with these markers may suggest a sarcoma, other less common tumors such as germ cell tumors, or a primary CNS tumor. Nonetheless, a battery of more specific markers is often applied in the second round of staining based on the initial findings.

Malignant melanoma
CNS metastases can be seen any time during the course of a melanoma. Diagnostic challenge arises when the CNS lesion precedes the systemic diagnosis, the tumor is amelanotic, or the primary melanoma diagnosis was so remote that it does not come up in the initial history.

Table 1: Common immunohistochemical profiles in metastatic neoplasms and primary CNS neoplasms in the differential diagnosis

	CK5/6	CD56	CK7	CK20	TTF1	Napsin A	GCDFP15	CDX2	RCC	PSA	EMA	PAX8	Vimentin	MelanA	Inhibin	S100	GFAP
Squamous cell carcinoma	+	-	+	-	-	-	-	-	-	-	+	-	-	-	-	-	+
Small cell carcinoma of lung	-	+	+	-	+	-	-	-	-	-	+	-	-	-	-	-	-
Urothelial carcinoma	+	-	+	+	-	-	-	-	-	-	+	-	-	-	-	-	-
Lung adenocarcinoma	-	-	+	-	+	+	-	-	+/–	-	+	-	-	-	-	-	-
Breast adenocarcinoma	+/–	-	+	-	-	-	+	-	-	-	+	-	-	-	-	+/–	-
Prostate adenocarcinoma	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	-
Colorectal adenocarcinoma	-	-	-	+	-	-	-	+	-	-	+	-	-	-	-	-	-
Stomach adenocarcinoma	-	-	+	+	-	-	-	+	-	-	+	-	-	-	-	-	-
Renal cell carcinoma	-	-	-	-	-	-	-	-	+	-	+	+	+	-	-	-	-
Melanoma	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	+	-
Hemangioblastoma	-	+/–	-	-	-	-	-	?	-	-	-	?	+	-	+	+	+/–
Meningioma	-	-	+/–	-	?	?	-	?	-	-	+	?	+	-	+/–	+/–	-
Choroid plexus carcinoma	-	-	+	-	-	?	?	-	+	-	+/–	?	+	-	-	+/–	+/–
High-grade glioma	-	+	-	-	-	-	-	-	?	-	+/–	?	+	-	+/–	+	+

This table represents the most common patterns of expression for individual tumors, though many exceptions exist. + : Usually positive; – : Usually negative; +/– : Positive in a significant subset; ? : Unknown; CNS: Central nervous system

Melanoma is most often composed of epithelioid cells with abundant pink cytoplasm, large nuclei and giant cherry-red nucleoli [Figure 5b]. It may also be composed of spindle cells, mimicking a sarcoma.

S-100 is a low-molecular weight calcium binding protein that stains all melanomas including the desmoplastic/spindle cell variant.[39] The initial IHC panel therefore includes S-100 due to its very high sensitivity; however, its use is limited in CNS metastases due to low specificity with widespread expression in neurons, astrocytes, Schwann cells, and gliomas. SOX10, a nuclear transcription factor expressed in neural crest, melanocytes, and glial and Schwann cells, also has high sensitivity for melanoma with limited expression in CNS lesions.[51] Other specific markers include HMB-45, Melan-A, tyrosinase, and MITF; however, they have lower sensitivities especially for metastatic lesions.[39] A combination of variably sensitive and specific markers therefore seems to be the best approach in the diagnosis of a CNS melanoma of unknown primary.

Sarcoma

Intracranial metastases are usually late events in the course of sarcomas, and can be as long as 10 years after initial diagnosis especially for alveolar soft part sarcomas. Microscopic features will be similar to the tumor of origin and ranges from bundles of spindle cells with blunt ended elongated nuclei in leiomyosarcoma to nests of large polygonal cells with abundant granular eosinophilic cytoplasm and uniform round nuclei with single prominent nucleoli in alveolar soft part sarcoma. The former may enter in the differential of primary tumors such as gliosarcoma or malignant meningioma, and the latter may be considered in the differential of melanoma or metastatic RCC. As stated earlier, this also becomes a particular pitfall in the rare cases where metastatic alveolar soft part sarcoma to the CNS presents prior to recognition of the soft tissue primary [Figure 7].[18,47,56]

Carcinoma

The vast majority of the CNS metastases are carcinomas. Carcinoma cells are cohesive, round, cuboidal, or columnar cells arranged in sheets, tubules or acinar structures, and usually have moderate-to-abundant cytoplasm. Most of the carcinomas can be identified and even subtyped by morphology alone.

Squamous tumors are composed of flattened cells with dense pink cytoplasm, forming sheets. Desmosomes or intercellular bridges can be identified with light microscopy and are diagnostic of squamous differentiation. Another diagnostic finding is the presence of keratin, formed by accumulation of fully differentiated anucleate squamous cells. Urothelial carcinoma represents

a rarer consideration for such tumors when definitive squamous features are not found.

The formation of ducts, glands, and acinar structures is diagnostic of adenocarcinoma. Carcinomas originating from solid organs such as liver, kidney, or thyroid might also be included in the general group of adenocarcinomas; however, they usually include their own unique architectural patterns. Neuroendocrine carcinomas may broadly include differentiated carcinoid tumors and paragangliomas (rare subtypes for CNS metastasis), both of which have organoid morphology composed of uniform, cuboidal cells with pink granular cytoplasm, small bland nuclei, and salt-and-pepper chromatin. Much more common are poorly differentiated neuroendocrine carcinomas, including small cell carcinomas composed of small cells with scant cytoplasm, hyperchromatic nuclei that often show "molding," and increased mitotic and apoptotic figures, representing high cell turnover.

Differential cytokeratin expression

Cytokeratins are the intermediate filaments relatively specific to epithelial cells; therefore, they are used as IHC markers of carcinomas. They can be categorized as high or low molecular weight, and acidic or basic keratins. Each epithelial cell type expresses only a subset of the cytokeratins, and this "differential" expression is therefore exploited to identify the specific cell type in NUP.

Widely used keratin antibody cocktails include AE1, which reacts with CK10, CK15, CK16 and CK19, and AE3, which reacts with cytokeratins 1-6 and CK8; thus staining virtually all carcinomas. However, positivity of AE1 in normal or neoplastic astrocytes, possibly due to cross-reactivity with GFAP limits its use in CNS lesions.[38] Therefore, a more useful cocktail antibody in this setting is CAM 5.2, which recognizes low-molecular weight keratins CK8 and CK18, which are similarly

expressed in the majority of metastatic carcinomas, but not in primary glial neoplasms.[10]

Reactivity with individual cytokeratins is used to further subtype carcinomas. High molecular weight cytokeratins such as 5 and 6 are found in all squamous epithelia, and almost all squamous cell carcinomas including skin, lung, and head and neck region.[10] Almost half of all urothelial carcinomas, and only a small percentage of adenocarcinomas, mainly those with focal squamous differentiation, are similarly CK5/6 positive.[9] CK7 and CK20 are also of great use for narrowing the site of origin and are discussed below under adenocarcinomas.

Small cell carcinomas

Small cell carcinoma shows features of both primitive epithelial and neuroendocrine differentiation [Figure 8a]. They are composed of small primitive cells with scant eosinophilic cytoplasm, oval to spindle-shaped nuclei with dark smudgy nuclear chromatin, and inconspicuous nucleoli. Mitotic figures and necrosis are frequently prominent. The most common primary site is lung, although extrapulmonary sites should also be considered, including but not limited to urinary bladder, larynx, gall bladder, and rectum. In a retrospective study, brain metastasis was the first presentation of small cell lung carcinoma in 11% of the cases, while brain metastases from extrapulmonary small cell carcinomas were typically later events.[11] Small cell carcinomas are positive for neuroendocrine markers such as chromogranin, synaptophysin, and CD56. Thyroid transcription factor 1 (TTF-1) is generally a useful marker for carcinomas of lung origin, although it was shown that small cell carcinomas of other sites are also frequently positive for TTF1 [Figure 8b].[23,42] Presence of small cells in a brain biopsy should also prompt the differential of other small blue round cell tumors including primary CNS primitive neuroectodermal
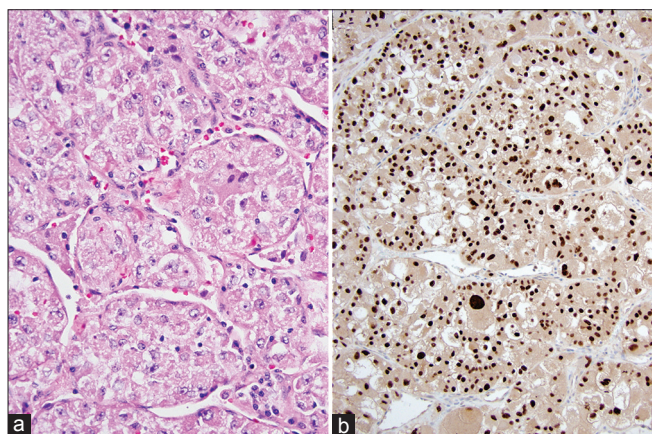

Figure 7: Metastatic alveolar soft parts sarcoma. (a) This lobulated, hypervascular neoplasm with large epithelioid cells and prominent nucleoli often engenders a differential diagnosis with melanoma, renal cell carcinoma, and paraganglioma. **(b)** Nuclear immunoreactivity for the transcription factor, TFE3 is diagnostically helpful
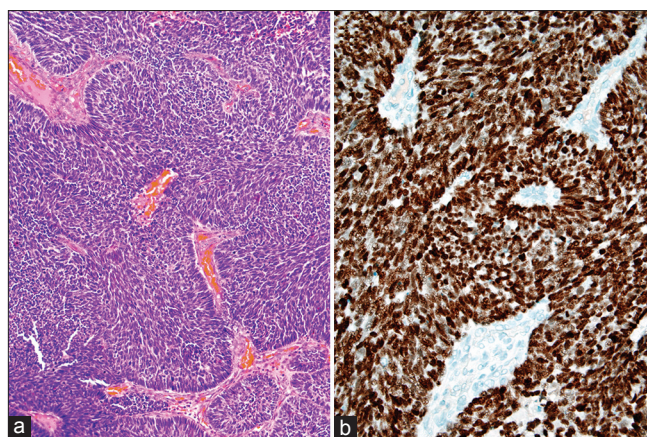

Figure 8: Metastatic pulmonary small cell carcinoma. (a) Typical histopathology includes nests of small primitive appearing cells with hyperchromatic nuclei, high nuclear to cytoplasmic ratio, and nuclear molding. **(b)** Nearly all cases are strongly positive for TTF-1

tumor or medulloblastoma, though these tumor types typically occur in a much younger patient.

Squamous cell carcinomas

The majority of CNS metastases are adenocarcinomas, and the diagnosis of squamous cell carcinoma is rarely an issue when the tumor is well differentiated. Nevertheless, ancillary studies are occasionally necessary to differentiate a squamous cell carcinoma from an adenocarcinoma, and CK5/6 and p63 are the most useful initial markers. As mentioned earlier, CK5/6 labels almost all squamous cell carcinomas from the lung or head and neck region. In contrast, p63 is a member of the *TP53* tumor suppressor gene family, and is positive in the nuclei of basal cells of squamous epithelium and urothelium, basal/myoepithelial cells of breast and lung, and the majority of the squamous cell and urothelial carcinomas. Both CK5/6 and p63 show very limited expression in adenocarcinomas, and expression of both in a poorly differentiated metastatic tumor strongly predicts a primary tumor of squamous origin.[24]

Urothelial carcinomas

CNS metastases from primary urothelial carcinoma are rare comprising only 1% of the brain metastases.[29] Generally, there is already a known history of urothelial carcinoma, and identifying the primary site is not a concern. Similar to squamous cell carcinomas, the majority of urothelial carcinomas are CK5/6 and p63 positive, although they differ by being positive for both CK7 and CK20. If there is a real concern for urothelial carcinoma in the setting of negative CK7 and CK20, however, more specific markers such as uroplakin III and thrombomodulin may be used.[43]

Adenocarcinomas

Use of differential cytokeratin expression can also help to identify the site of adenocarcinomas. CK7, an intermediate-sized basic cytokeratin, is present in normal simple glandular epithelium including breast and pancreas, pseudostratified respiratory epithelium, and urothelium. Accordingly it labels lung adenocarcinomas, carcinomas of breast, ovary, pancreas, biliary tract, endometrium, prostate, thyroid, salivary gland, and urinary bladder.[8,10,49] Nonetheless, strong and widespread immunoreactivity for CK7 in the setting of a CNS NUP is most suggestive of lung or breast origin. To lesser extents, it also labels nonconventional RCCs, some neuroendocrine tumors, and a portion of squamous carcinomas arising from noncornified squamous epithelium such as uterine cervix.

CK20, an intermediate-sized acidic cytokeratin, is present in normal and neoplastic colorectal epithelium, the majority of urothelial carcinomas, and some gastric and pancreatic carcinomas. [8,10,31] Carcinomas of breast, thyroid and lung, and squamous cell carcinomas of head and neck origin are essentially negative for CK20.

SITE SPECIFIC OR RESTRICTED MARKERS

Lung adenocarcinoma

Lung is the most common primary site for both systemic and CNS metastases presenting as NUP.[30,46] TTF-1 is expressed in the nuclei of normal thyroid cells, and respiratory epithelium in lung. TTF-1 is positive in majority of carcinomas of lung origin including adenocarcinoma, small cell carcinoma, poorly differentiated nonsmall cell carcinomas, and neuroendocrine carcinoma, whereas pulmonary squamous cell carcinomas are typically negative.[32,41,54] There are reports of TTF-1 positivity in primary CNS neoplasms, although in most diagnostic considerations for metastatic NUP, TTF-1 is negative or only weakly and focally positive.[25] A greater specificity is obtained by combining markers, with most primary lung adenocarcinomas being CK7-positive, CK20-negative, and TTF-1-positive [Figure 9].[21] Thyroid carcinomas have a similar expression profile; however, they have distinct architectural features and are rarely included in the differential of CNS NUP. Another pulmonary specific and relatively sensitive marker is napsin A, which is positive in the cytoplasm of pulmonary adenocarcinomas.[32,57,64]

Breast carcinoma

Like pulmonary adenocarcinomas, breast carcinomas are CK7-positive and CK20-negative [Figure 10]; however, they are negative for TTF-1 and napsin A.[64] Gross cystic disease fluid protein 15 (GCDFP-15) is expressed in normal and neoplastic breast, skin adnexa, salivary gland, and prostate.[61] Other markers to verify breast origin of a metastasis include mammaglobin and estrogen receptor, the latter of which is less specific. All these markers are imperfect, however, and may even be expressed occasionally in pulmonary carcinomas.[64]

Colon and other gastrointestinal carcinomas

Colon adenocarcinomas are CK7-negative and CK20-positive [Figure 11], making them easily distinguishable from pulmonary and breast adenocarcinomas, even when poorly differentiated. CDX2 is a transcription factor normally expressed in the intestine, biliary tract, and represents a highly sensitive and specific marker for intestinal adenocarcinomas.[60] It shows strong nuclear expression in up to 90% of colorectal and duodenal adenocarcinomas. Gastric adenocarcinomas are also CDX2-positive, although their dual CK7/CK20-positive profile may facilitate their diagnoses. Ovarian mucinous carcinomas and some urinary bladder adenocarcinomas may be strongly positive for CDX2; however, they only rarely metastasize to the CNS, typically well after the primary diagnosis has been established.[60]

Renal cell carcinoma

The majority of the RCCs are conventional clear cell carcinomas, and other subtypes rarely present

with metastases. Despite the distinctive morphology of well-differentiated RCC, tumors with less typical morphology or other tumors with clear cells may create a diagnostic challenge. RCCs are well known to coexpress keratin and vimentin; however, this profile is not entirely specific.

CD10 (common acute lymphoblastic leukemia antigen–CALLA) is a cell surface metalloendopeptidase, which can be positive up to 85% of RCCs.[15] However, it is also present in numerous hematological malignancies, melanomas and some sarcomas, and is therefore not specific to kidney. The RCC antibody reacting with the brush border of the proximal tubules is also a marker of RCCs with 99% specificity and 86% sensitivity [Figure 12].[1,15] More recent transcription factors such as PAX2 and PAX8 are positive in tumors of renal, thyroid, and mullerian duct origin; and can be of further aid in the differential diagnosis.[5,27]

Ancillary testing
The evaluation of the metastatic brain lesions is not only limited to provide a diagnosis and site of origin, but also includes assessment of prognostic and predictive factors
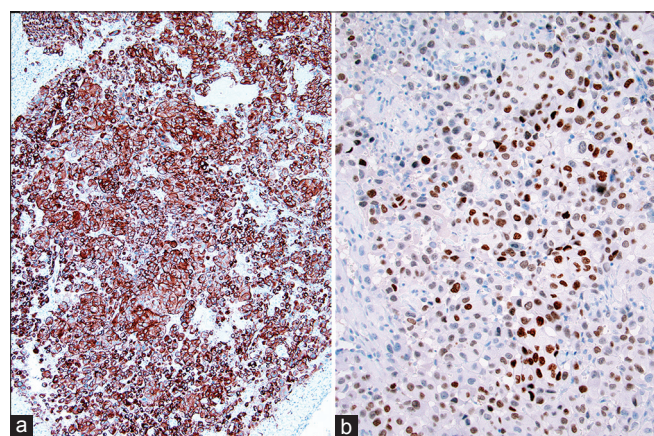
for certain targeted treatments in some neoplasms. Although the most "theranostic" studies would be performed on the primary tumor, there is ample evidence in the literature that the metastases might have different expression profiles requiring modifications in treatment regimens.

One of the best-studied predictive factors in cancer treatment is the hormone receptor expression profile of breast carcinomas. Commonly, there is a significant difference between the estrogen and progesterone receptor profile of the recurrent and metastatic lesions as compared with the primary.[35] In these cases, negative conversion of hormone receptor expression may prompt the clinicians for alternative treatments, rather than continuing with tamoxifen. Similar results were also reported for the human epidermal growth factor receptor 2 (HER2) overexpression.[33] Negative conversion of HER2 overexpression may provide an opportunity to reconsider the treatment strategy, and the presence of newly identified HER2 overexpression [Figure 10c] or gene amplification [Figure 10d] provides a new treatment

Figure 9: Metastatic poorly differentiated pulmonary adenocarcinoma with immunoreactivity for both CK7 (a) and TTF-1 (b)
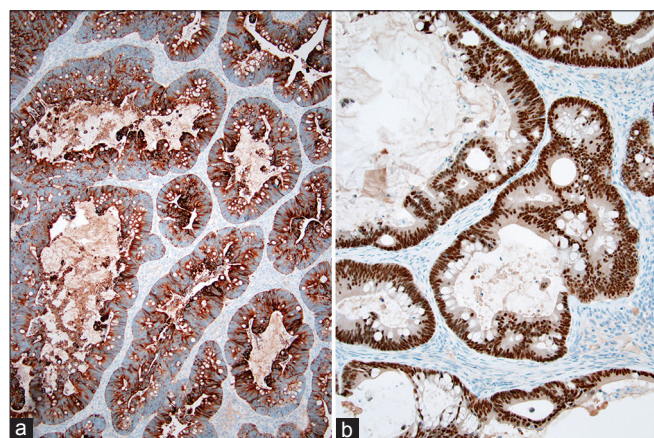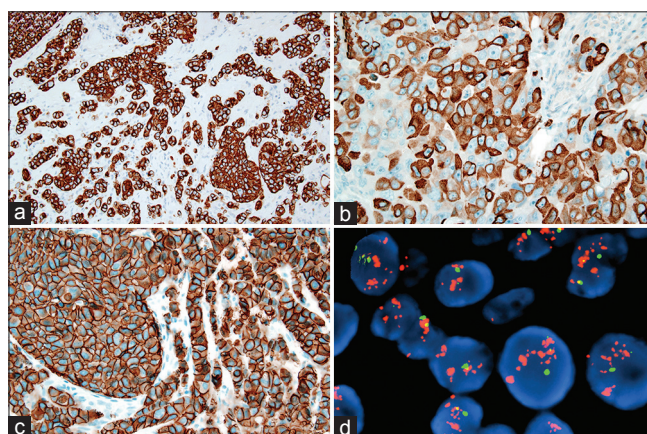

Figure 10: Metastatic breast carcinoma with strong CK7 positivity (a), mammaglobin expression (b), membrane pattern immunoreactivity for HER2 (c), and high-level HER2 gene amplification by fluorescence *in situ* hybridization (d; centromere 17 in green and HER2 in red)
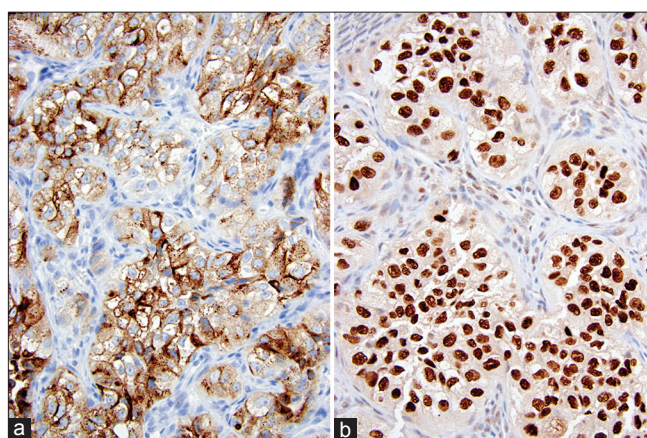

Figure 11: Metastatic colorectal adenocarcinoma, coexpressing CK20 (a) and CDX2 (b)

Figure 12: Metastatic clear cell renal cell carcinoma, expressing the RCC protein (a) and PAX8 (b)

option with trastuzumab, although the poor blood–brain barrier permeability of trastuzumab remains a potential limitation.

Activating epidermal growth factor receptor (EGFR) mutations are present up to 25% of nonsmall cell carcinomas, mainly in adenocarcinomas. The oral EGFR tyrosine kinase inhibitors gefitinib and erlotinib are Food and Drug Administration (FDA)-approved and routinely used in current management of lung carcinomas. There are few studies with limited sample size comparing the EGFR status of the primary lung tumor with associated metastatic lesions, including those to the CNS; similar to breast cancer, some discordance has been reported, which could potentially be significant for individual patient treatment.[12,16] Nonetheless, such testing has not become routine to date.

Other relatively well-studied molecular testing in human neoplasms is BRAF, most commonly V600E mutations. The BRAF mutation status can be tested with DNA-based methods and immunohistochemistry using a V600E mutation-specific antibody.[4] In general patients with brain metastases have been excluded from clinical trials for BRAF inhibitors; however, some studies have shown promising responses in such cases, suggesting that testing of metastatic melanomas could become important in the future.[28] BRAF mutations can be detected in and thus far, there has been good concordance between primary tumors and their metastases.[3] As such, samples of brain metastases could be tested for BRAF mutations when metastatic tissue is the only available tissue.

Summary

Just as radiologists have developed new tools for identifying primary sites of origin for metastatic disease, the IHC armamentarium for pathologists has expanded greatly over the past two decades. This allows for more accurate assessments, even in cases where a primary is not identified radiologically or where multiple primary sites are possible. The role of individualized therapy is also increasing beyond just the identification of the primary tumor type, such that ancillary testing for ER, PR, and HER2 status is now common in metastatic breast carcinoma to the brain. To a lesser extent, molecular testing may be useful in select cases of metastatic lung carcinoma and in metastatic melanoma. Nevertheless, it is likely that molecular subtyping of CNS metastases by neuropathologists will continue to play an increasing role in the future.

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