Chapter 4
Cerebral Parenchymal Lesions: I. Metastatic Neoplasms

After one has reasonably ruled out the possibility of a nonneoplastic diagnosis (see Chap. 3), one is left with considering a diagnosis of tumor. The first question one needs to ask along these lines is whether or not the neoplasm could represent a metastasis. Metastatic neoplasms are the most commonly encountered tumors in the central nervous system. Because the appearance of these lesions often mimic their appearance elsewhere in the body, most pathologists are relatively more comfortable with evaluating metastases. Metastases are commonly multifocal lesions that are well circumscribed (Fig. 4.1). This is in contrast to many gliomas, which tend to be infiltrative in nature and more typically unifocal. Metastases may be either parenchymal or leptomeningeal in location. This chapter briefly addresses some of the more commonly encountered metastases and potential differential diagnostic considerations (Table 4.1).

Carcinomas are probably the most common type of metastasis that is encountered. The most common sites of origin include lung, breast, kidney, skin (melanoma), and gastrointestinal tract. In many cases, the tumor is so poorly differentiated that discerning the specific tumor type is not always possible, particularly in the frozen section venue. When possible, distinction between small cell carcinoma versus nonsmall cell carcinoma should be made. Small cell carcinoma is generally marked by cells with a high nuclear to cytoplasmic ratio, no prominent nucleolation, and nuclear molding. There is a propensity for the tumor cells to be easily crushed with routine tissue handling (Fig. 4.2a, b).
Fig. 4.1 Low magnification appearance of a metastatic nonsmall cell carcinoma from the lung shows the typical sharp interface between the tumor and the adjacent gliotic parenchyma. This is in contrast to the infiltrative nature of most malignant glial neoplasms.

Table 4.1 Metastases.

Carcinoma
- Small cell
- Adenocarcinoma
- Squamous cell carcinoma
- Other
- Melanoma – great mimicker
- Sarcoma
- Lymphoma/leukemia
- Other

Differential diagnostic cautions and tips:
- Metastases are frequently multiple and have a sharp interface with the adjacent parenchyma
- Do not overdiagnose the extremely necrotic tumor
- Epithelioid glioblastoma can look like carcinoma or melanoma
- Small cell glioblastoma, lymphoma, medulloblastoma/neuroblastoma and anaplastic oligodendroglioma can resemble small cell carcinoma
- Occasional carcinomas and melanomas can be spindled; other spindle cell tumors to consider are gliosarcoma and anaplastic meningioma
Fig. 4.2 (a) A frozen section showing proliferation of cells with high nuclear to cytoplasmic ratio. A moderate degree of pleomorphism is present. A diagnosis of malignant small cell neoplasm was made in this case with the suggestion of a differential diagnosis. (b) The permanent section from the tumor in (a) shows that the lesion represents a small cell carcinoma. The cells are somewhat more homogeneous in appearance, devoid of nucleoli, and show the evidence of focal crush artifact.
Often, there are large zones of necrosis, readily identifiable mitotic activity, and evidence of apoptosis. In contrast, adenocarcinoma and squamous cell carcinoma are generally marked by cells with prominent nucleolation and more cytoplasm. Evidence of gland formation or mucin production corroborates a diagnosis of adenocarcinoma (Figs. 4.3–4.5). Evidence of keratinized cells or keratin production in the tumor favors a squamous cell cancer (Fig. 4.6). Almost any type of carcinoma may be observable as a metastasis in the brain or spinal cord. A prior history of cancer elsewhere may not be present; a significant subset of brain metastases is the initial presentation of the patient’s tumor. In many cases, the metastasis is poorly differentiated and presents few if any clues at frozen section regarding tumor type; a diagnosis of metastatic nonsmall cell carcinoma, malignant spindled cell neoplasm or malignant epithelioid neoplasm (depending on the appearance) may be appropriate (Fig. 4.7).

Care should be taken not to overdiagnose an extensively necrotic tumor. One should not presume a diagnosis of metastasis based on a history of multiple lesions and an entirely necrotic biopsy. From a differential diagnostic standpoint, an epithelioid variant of glioblastoma can mimic metastatic carcinoma or occasionally melanoma. On frozen section, the only clue may lie in finding the evidence of the more characteristic features of adenocarcinoma or squamous cancer or areas of the tumor that look like more

Fig. 4.3 Metastatic breast carcinoma demonstrating gland formation consistent with adenocarcinoma.
conventional glioblastoma. An even greater challenge is differentiating small cell carcinoma from other small cell tumors which may arise in the brain, including small cell glioblastoma, lymphoma, medulloblastoma/neuroblastoma, or anaplastic oligodendroglioma.
Fig. 4.6 A partially necrotic metastatic nonsmall cell carcinoma with keratinized cells consistent with squamous cell carcinoma.

Fig. 4.7 This patient had a known squamous cell carcinoma of the larynx. The spindled cell squamous cell carcinoma represents a metastasis from the laryngeal cancer. A diagnosis of malignant spindled cell neoplasm at the time of frozen section is appropriate with a suggestion that it may represent a metastasis from the patient’s known laryngeal carcinoma.
These are all high-grade neoplasms and may be marked by cells with high nuclear to cytoplasmic ratio, readily identifiable mitotic activity, and apoptosis. In some cases, particularly on a limited sample or extensively necrotic sample, immunohistochemistry may be needed to make the final diagnosis. In such cases, a diagnosis of malignant small cell neoplasm with a suggested list of possible diagnostic considerations is appropriate.

Metastatic malignant melanoma is a fairly commonly encountered neoplasm. The challenge with melanoma lies in the fact that it can mimic a whole host of other neoplasms, and it can be particularly difficult to diagnose in the absence of melanin pigment. Large cells with abundant cytoplasm and prominent nucleolation are classic features associated with melanoma; however, occasional tumors may be marked by spindled cells, which open up a broader differential diagnosis which includes sarcoma (Figs. 4.8 and 4.9). Occasionally, the distinction of melanoma from the metastatic nonsmall cell carcinoma or epithelioid glioblastoma may be difficult to make. Again, unless there are specific clues to indicate a particular tumor type, immunohistochemistry may be needed to resolve the differential diagnosis.

Sarcomas can arise either as primary lesions or metastases in the central nervous system (Figs. 4.10 and 4.11). Many primary sarcomas are dural based; whereas, metastases may involve either

Fig. 4.8 A spindled cell neoplasm, devoid of neuromelanin pigment. Immunostaining eventually proved this to be a malignant melanoma.
**Fig. 4.9** This example represents a more typical appearance for metastatic melanoma-discreet cells with distinct cytoplasmic boundaries, prominent nucleolation, and abundant cytoplasm.

**Fig. 4.10** Metastatic angiosarcoma in a patient with a known primary in the head and neck region.
the dura or parenchyma. Metastatic lesions often resemble the tumor from where they had come, and history is particularly useful in such cases. In a subset of these tumors, the specification of the sarcoma type is not going to be possible at frozen section. In such instances, a more descriptive diagnosis such as “malignant spindle cell neoplasm, rule out sarcoma” may be appropriate. A consideration of other spindled cell neoplasms that include gliosarcoma and anaplastic meningioma should be entertained. Gliosarcoma should have focal areas resembling a more conventional appearing glioblastoma. Anaplastic meningioma may or may not have lower grade areas that resemble a typical low-grade meningioma pattern.

Lymphomas and leukemias can metastasize and involve the central nervous system. As previously discussed in Chap. 3, metastatic lymphoma and leukemia preferentially involve the meninges and dura as compared with primary central nervous system lymphoma, which is more commonly a parenchymal-based lesion.

Less commonly, other neoplasms not discussed here may metastasize to the brain. Inquiry regarding previous history is sometimes useful in these cases.