Metastases to the Pancreas

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Introduction

Metastasis to the pancreas is an uncommon occurrence with an incidence on fine needle aspiration (FNA) cytology ranging from 0.7% to 11.1% and comprising 1.8–10.8% of all pancreatic malignancies [1–16]. The primary tumors can arise from a diverse and wide group of organs which can include most commonly the kidney and the lung and less commonly the gastrointestinal tract, liver, breast, ovaries, and thyroid [17, 18]. In addition, metastatic melanomas, malignant lymphomas, and neuroendocrine tumors arising from different primary sources have also been diagnosed in the pancreas [17, 18]. A cytopathologist should be aware that even with these diverse groups of tumors, renal cell carcinoma and tumors arising from the lung remain the largest groups of tumors which have been reported to metastasize to the pancreas. In most instances of patient clinical workup, metastatic disease to the pancreas is usually found to be part of widespread and disseminated disease rather than being a solitary presentation [9, 14]. However, metastasis to the pancreas can also present as a solitary tumor many years after the primary malignancy was initially diagnosed [9, 14]. Hence, some of these diagnoses are rendered after a long latency period, after the primary diagnosis

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was rendered. Radiographic studies, which can include CT scan or, more commonly, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), are currently the mainstay to evaluate and diagnose these tumors [18]. EUS-FNA ensures a high degree of safety for the patients, is cost-effective, and leads to minimal morbidity in patients. EUS-FNA in experienced hands also ensures accuracy in diagnosing metastatic disease to the pancreas, which is extremely important for clinical staging and appropriate management of the patient [17, 18].

Metastatic Renal Cell Carcinoma

Renal cell carcinoma has been cited as one of the most common tumors to metastasize to the pancreas [1–16]. The prevalence rate has been found to be wide from 8% to 64% of metastatic tumors to the pancreas [2–16]. It can have a long latency period after the primary renal malignancy diagnosis and can be noted as long as 36 years after the primary diagnosis was rendered [18]. Hematogenous spread is most likely involved in metastatic renal cell carcinoma to the pancreas. The key features of metastatic renal cell carcinoma include large polygonal cells with clear, foamy, granular, or vacuolated cytoplasm (Figs. 10.1 and 10.2). The nuclei are round to oval with prominent nucleoli present (Fig. 10.3). Immunohistochemical staining (IHCS) is helpful in separating metastatic renal cell carcinoma from adenocarcinoma of primary pancreatobiliary origin. CD10 [9, 10, 14], RCC [7, 9, 11], PAX-8 [14, 16], and CAIX [16] are helpful immunohistochemical markers which will help highlight metastatic malignant cells (Figs. 10.4 and 10.5).

Metastatic Pulmonary Non-small Cell Carcinoma

The literature has initially indicated that the lung was the most common primary site of pancreatic metastases, followed by metastases from the kidney [1–18]. However, other studies have indicated that the lung as the primary site has been surpassed by the kidney [9, 13, 14]. Pulmonary non-small cell carcinomas metastasizing to the pancreas can range from well- to poorly differentiated adenocarcinomas and squamous cell carcinomas, which may make it difficult to differentiate them from primary pancreatobiliary adenocarcino-

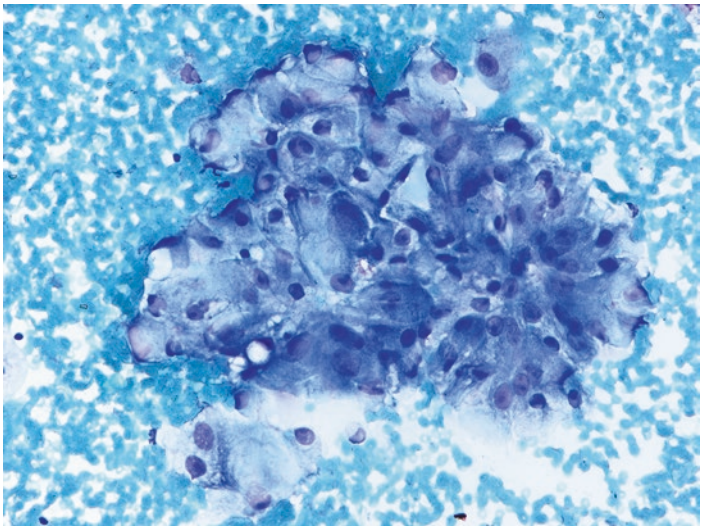

Fig. 10.1 Metastatic renal cell carcinoma with large polygonal cells with clear and granular cytoplasm (Diff-Quik stain ×40)

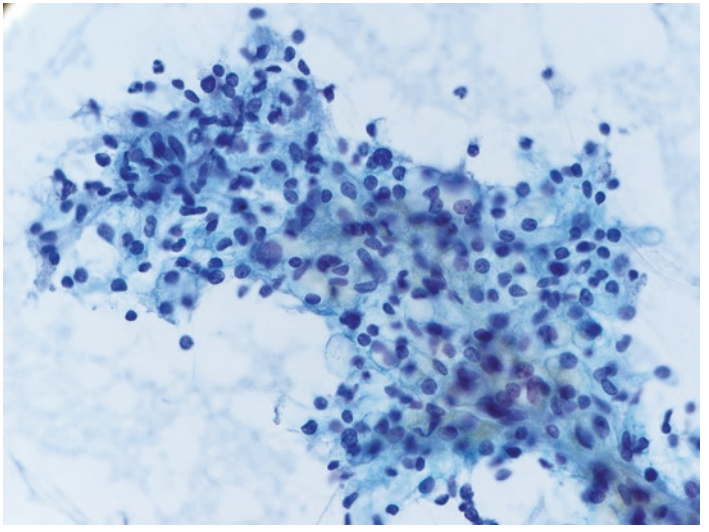

Fig. 10.2 The tumor cells show clear cytoplasm with large nuclei. Blood vessels are seen traversing in between the tumor cells (Papanicolaou stain ×40)

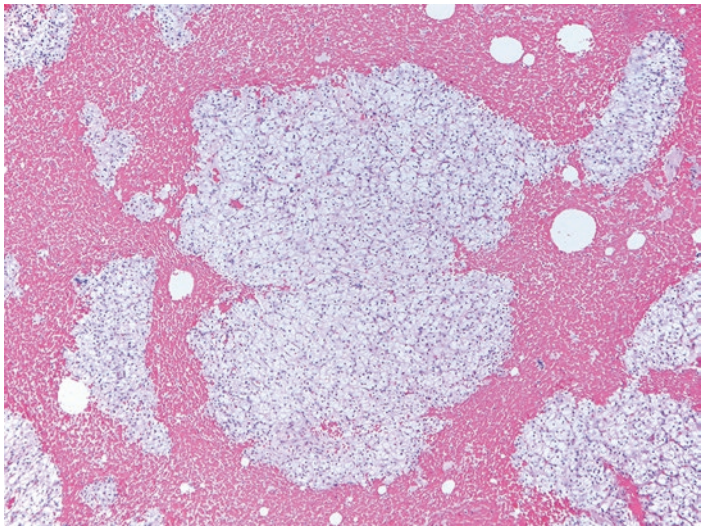

Fig. 10.3 Numerous sheets of cells representing metastatic renal cell carcinoma with clear cytoplasm in a cell block (H&E stain ×10)

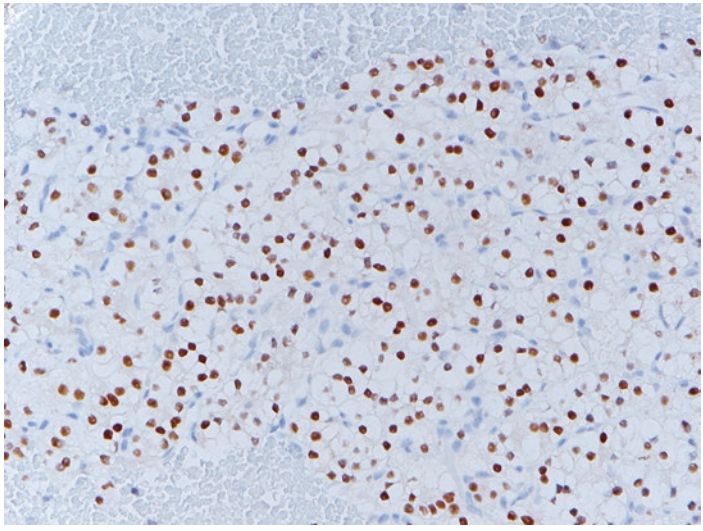

Fig. 10.4 Metastatic renal cell carcinoma showing positive nuclear staining with PAX-8 (IHCS ×40)

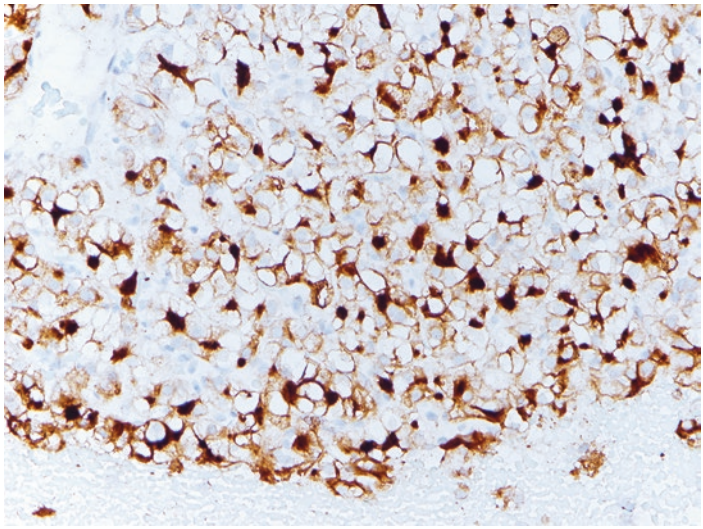

Fig. 10.5 CD10 staining shows cytoplasmic staining for metastatic renal cell carcinoma (IHCs ×40)

mas on morphology alone [3, 8, 13]. The smears will show a wide range of cytomorphologic features depending on the differentiation of the primary tumor. Well- and moderately differentiated adenocarcinoma would exhibit features of glandular differentiation, while poorly differentiated adenocarcinoma would comprise malignant cells with high nuclear to cytoplasmic ratio and prominent nucleoli (Figs. 10.6, 10.7, 10.8, and 10.9). Similarly, metastatic squamous cell carcinoma would show keratinization in well-differentiated metastases, while poorly differentiated tumors would lack keratinization and would comprise tumor cells with indistinct borders, pleomorphic nuclei, and markedly irregular nuclear membranes (Figs. 10.10, 10.11, 10.12, and 10.13). Immunohistochemical staining will be helpful in confirming the diagnosis. TTF-1 and napsin A staining will confirm a diagnosis of metastatic lung adenocarcinoma, whereas p40 staining will confirm a diagnosis of metastatic squamous cell carcinoma (Figs. 10.9 and 10.13) [8, 11, 16, 19]. It is important to recognize that the primary features of these metastatic tumors may overlap with primary pancreatobiliary malignancy; and this requires a review of clinical history, radiologic findings, and

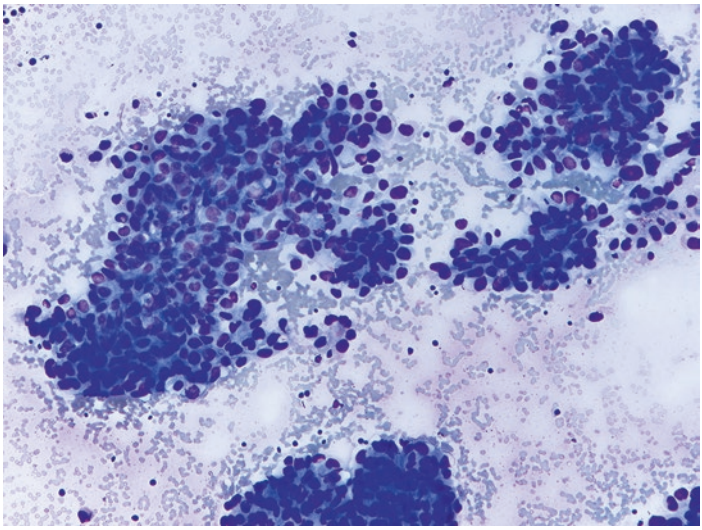

Fig. 10.6 Metastatic lung adenocarcinoma exhibiting focal gland formation and high nuclear to cytoplasmic ratio (Diff-Quik stain ×20)

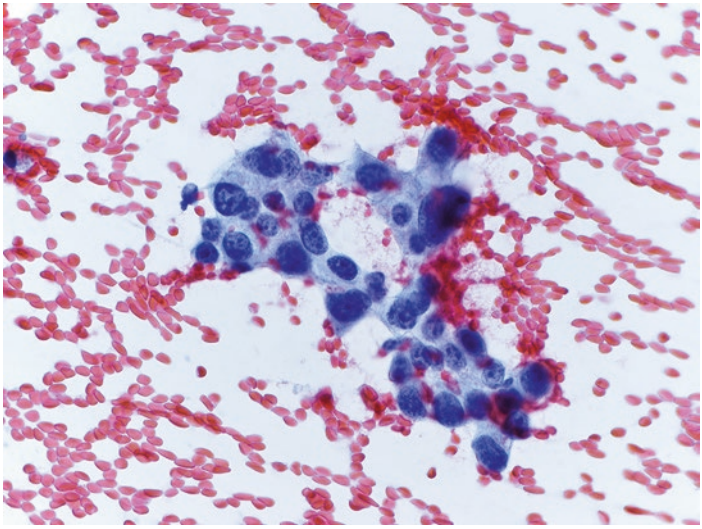

Fig. 10.7 Metastatic lung adenocarcinoma with delicate cytoplasm and high nuclear to cytoplasmic ratio. The tumor cells show nuclear hyperchromasia and prominent nucleoli (Papanicolaou stain ×40)

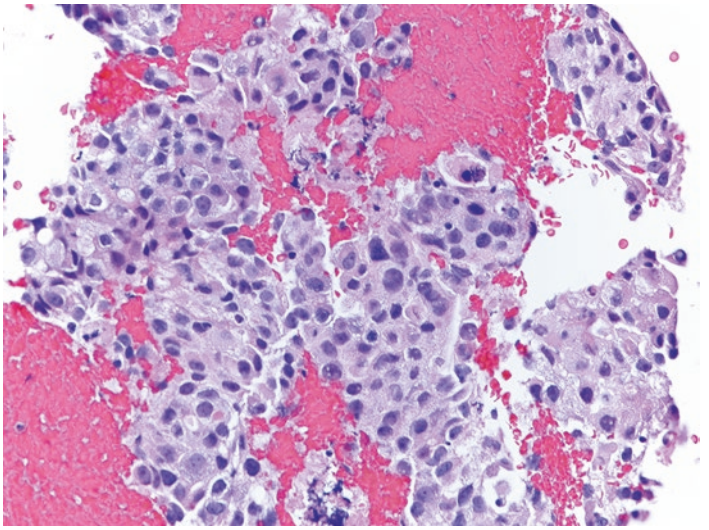

Fig. 10.8 A cell block from an aspirate with metastatic lung adenocarcinoma showing focal cytoplasmic vacuolation (H&E stain ×40)

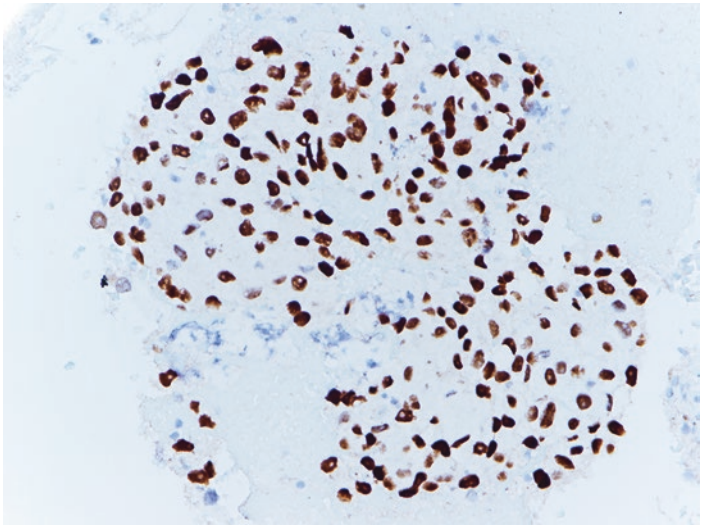

Fig. 10.9 TTF-1 staining confirms the diagnosis of metastatic adenocarcinoma. The patient had a known lung primary tumor which was also positive for TTF-1 staining (IHCS ×40)

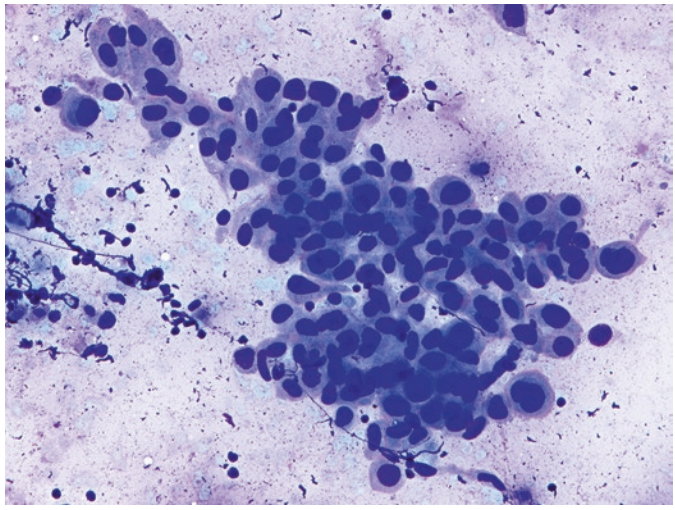

Fig. 10.10 A patient with known history of lung squamous cell carcinoma with metastatic tumor cells in the pancreas. The tumor cells show dense cytoplasm and hyperchromatic nuclei with irregular nuclear membranes. (Diff-Quik stain ×40)

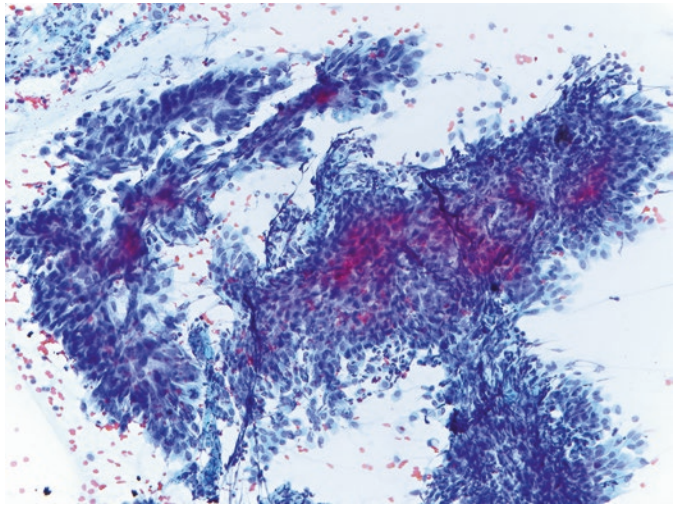

Fig. 10.11 Poorly differentiated metastatic squamous cell carcinoma lacking keratinization would comprise tumor cells with indistinct borders, pleomorphic nuclei, and markedly irregular nuclear membranes (Papanicolaou stain ×20)

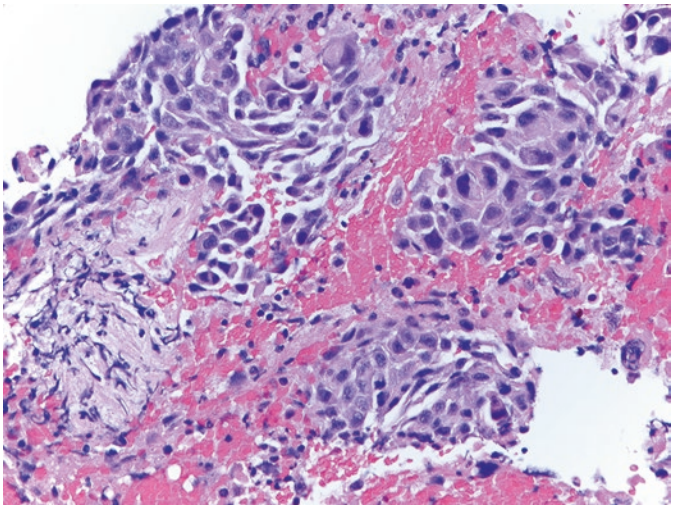

Fig. 10.12 A cell block from an aspirate with metastatic lung squamous cell carcinoma. The tumor cells are arranged in sheets with intercellular bridges apparent in between a few cells. The nuclei display characteristic hyperchromasia (H&E ×40)

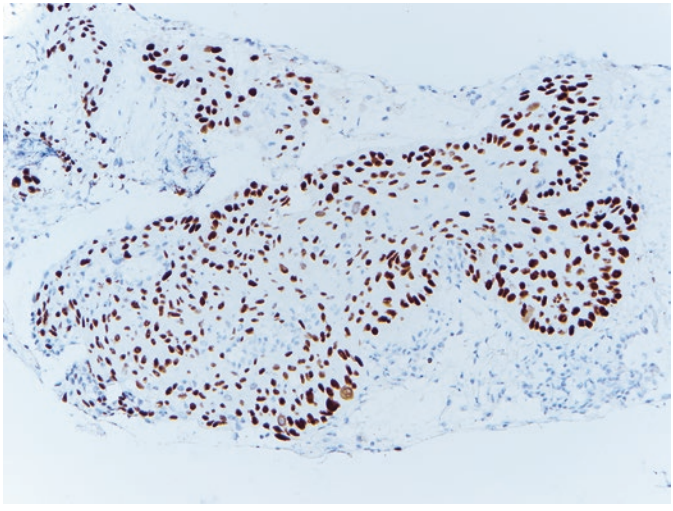

Fig. 10.13 A p40-positive nuclear stain would confirm a diagnosis of squamous cell carcinoma in a cell block (IHCS ×20)

performance of immunohistochemical staining to separate the metastasis from a primary pancreatic malignancy.

Metastatic Neuroendocrine Carcinoma

Metastatic neuroendocrine carcinoma is also a malignancy that can be encountered in the pancreas. The majority of them are small cell neuroendocrine carcinomas arising from the lung (Figs. 10.14, 10.15, 10.16, 10.17, and 10.18) [4–14, 16]. The smears will show small- to intermediate-size cells with high nuclear to cytoplasmic ratio and hyperchromatic nuclei and frequently present crush artifact due to the fragility of the cells (Figs. 10.14 and 10.15). It is difficult to distinguish metastatic lung neuroendocrine carcinoma from a primary pancreatobiliary neuroendocrine carcinoma based on cytomorphol-

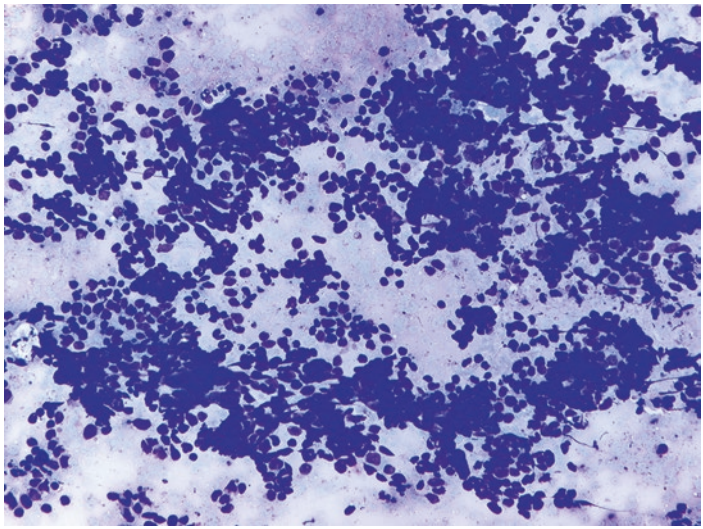

Fig. 10.14 The smears from a metastatic small cell carcinoma will show small- to intermediate-size cells with high nuclear to cytoplasmic ratio. The small cells are two to three times the size of a mature lymphocyte with rare intermediate-size cells being three to four times larger than a mature lymphocyte (Diff-Quik stain ×20)

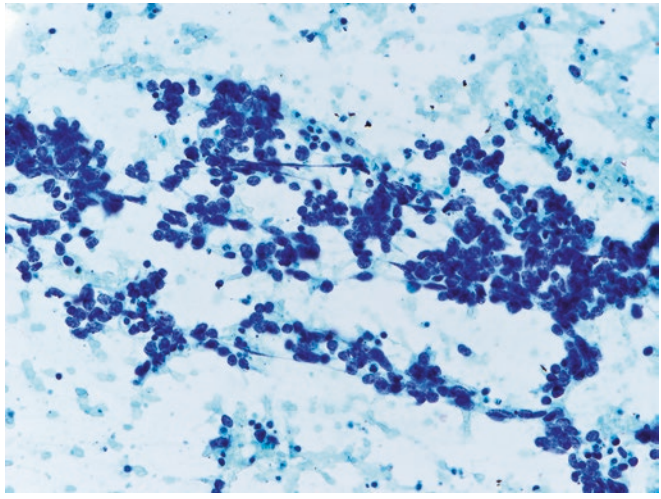

Fig. 10.15 Metastatic small cell carcinoma showing tumor cell molding and scant cytoplasm, with salt and pepper chromatin (Papanicolaou stain ×20)

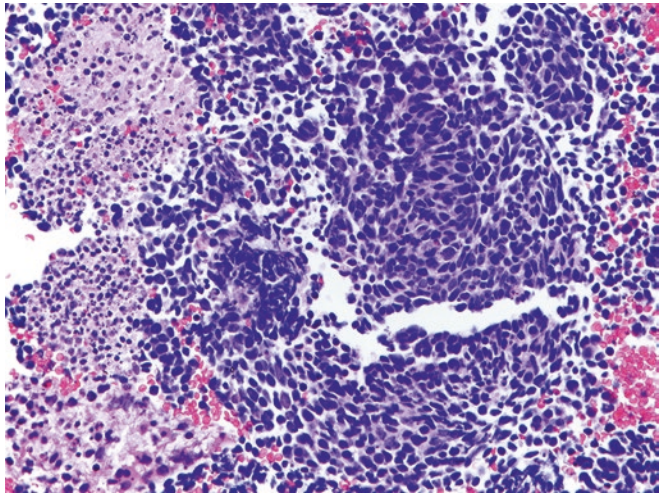

Fig. 10.16 A cell block from an aspirate showing metastatic small cell neuroendocrine carcinoma with nuclear molding and scant cytoplasm. Extensive necrosis in the background is also identified (H&E ×20)

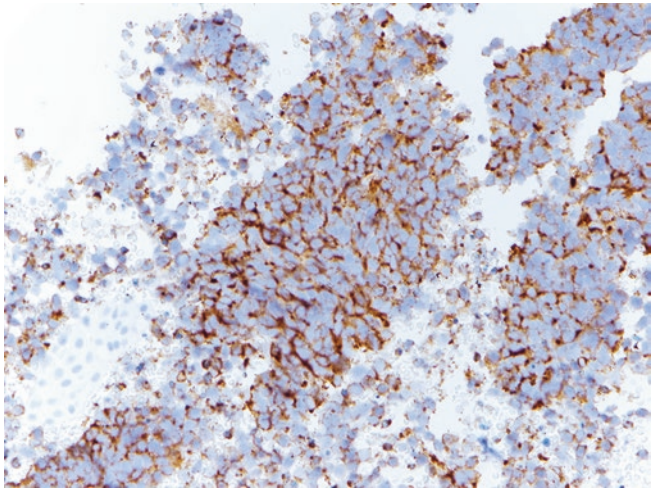

Fig. 10.17 Synaptophysin cytoplasmic staining of tumor cells from a patient with metastatic small cell neuroendocrine carcinoma from the lung (IHCS ×20)

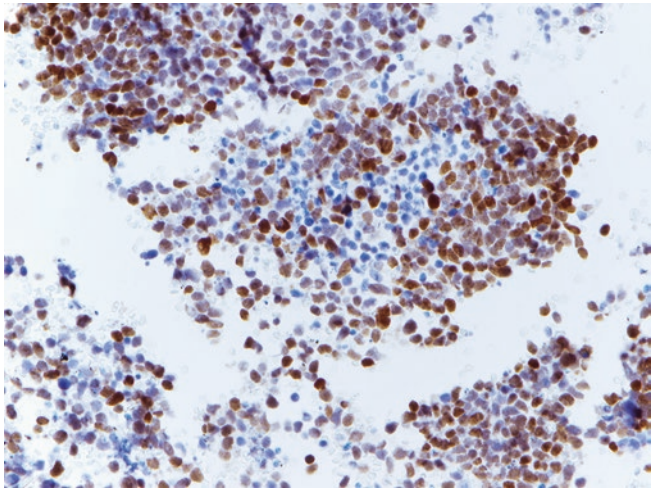

Fig. 10.18 TTF-1 nuclear staining is noted in approximately 90% of small cell neuroendocrine carcinomas of the lung. TTF-1 staining cannot be reliably used to confirm lung metastasis and would require clinical and radiologic confirmation of a primary lung tumor, since a small percentage of primary pancreatic small cell neuroendocrine carcinomas can also express it (IHCS ×20)

ogy alone. Neuroendocrine carcinoma would show a variable amount of immunoreactivity for synaptophysin, chromogranin, and CD56 staining; and these stains will help in confirming the diagnosis (Fig. 10.17) [5, 16, 17, 18]. The main cytomorphologic challenge with these tumors is distinguishing metastatic from primary neuroendocrine carcinoma of the pancreas. Lung and pancreatic neuroendocrine malignancies are sensitive to different chemotherapeutic agents due to which accurately identifying the primary site of origin is very important. TTF-1 is noted in approximately 90% of small cell neuroendocrine carcinomas of the lung; however, a small percentage of primary pancreatic small cell neuroendocrine carcinomas of the pancreas are also known to show TTF-1 immunoreactivity (Fig. 10.18) [9, 13, 14, 17, 18]. Hence, TTF-1 staining cannot be reliably used to confirm lung metastasis and would require clinical and radiologic confirmation of a primary lung tumor.

Metastatic Gastrointestinal and Hepatocellular Carcinoma

Tumors arising from the gastrointestinal tract have also been diagnosed on pancreatic fine needle aspirations [16–18]. Typically, these comprise adenocarcinomas which can arise from sites including the stomach and colon. The aspirate will comprise abundant mucin with variable cellularity [4, 5, 11]. The tumor cells can be single and signet ring-shaped in the case of a primary gastric origin, whereas colonic primary tumor cells will show sheets and clusters with a variable degree of differentiation. CDX-2 staining can be helpful in characterizing these metastatic tumors, but can lack both sensitivity and specificity [17, 18]. Clinical history and radiology features play an important role in separating these metastatic tumors from those of primary pancreatobiliary origin. Hepatocellular carcinoma can also be rarely identified in pancreatic aspirates (Figs. 10.19, 10.20, and 10.21). The tumor cells are polygonal and show a variable degree of differentiation. The cytoplasm tends to be granular with large nuclei and prominent nucleoli. A positive arginase-1 immunohistochemical staining will confirm the diagnosis of metastatic hepatocellular carcinoma in most pancreatic aspirations (Fig. 10.22).

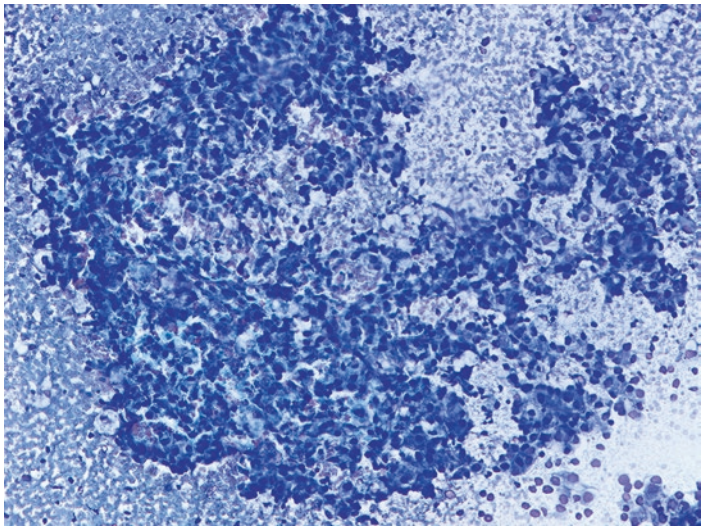

Fig. 10.19 Metastatic hepatocellular carcinoma with polygonal cells with granular cytoplasm (Diff-Quik stain ×20)

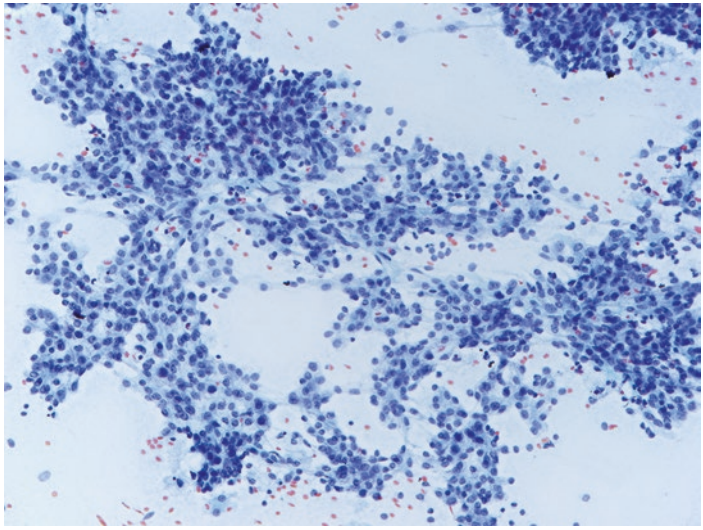

Fig. 10.20 Fine capillaries are seen separating the tumor cells from a patient with metastatic hepatocellular carcinoma. The cytoplasm of the tumor cells is granular with round and oval nuclei (Papanicolaou stain ×20)

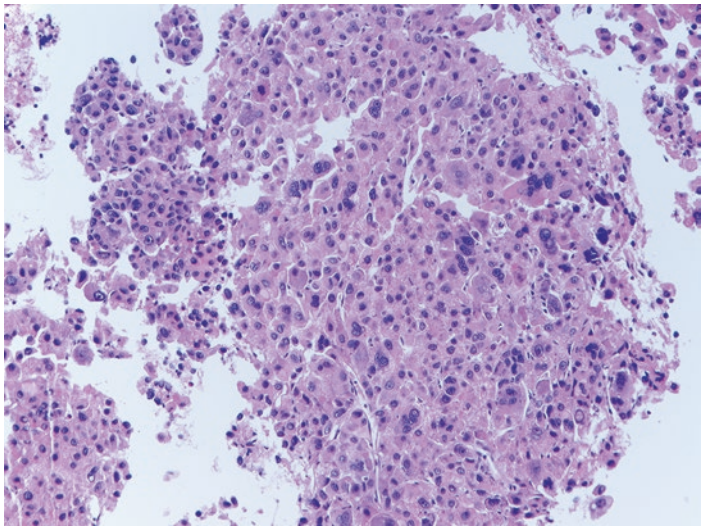

Fig. 10.21 A cell block from an aspirate with metastatic hepatocellular carcinoma. The tumor cells are intermediate to large in size. The nuclei display prominent nuclei and focal inclusions (H&E ×20)

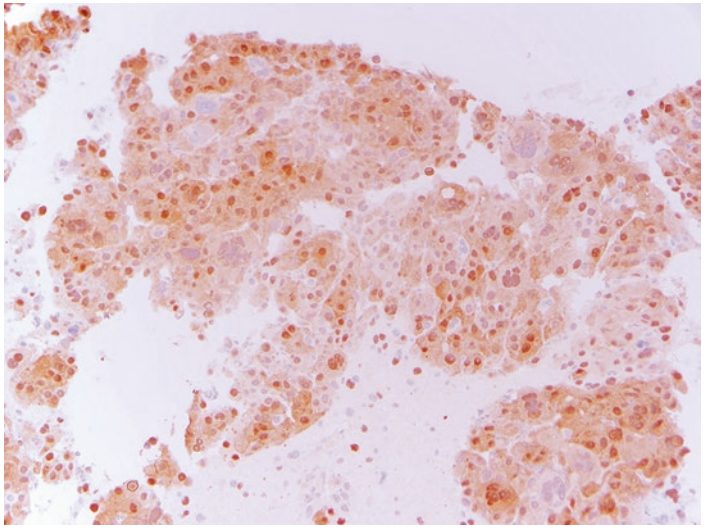

Fig. 10.22 Staining with arginase-1 will confirm a diagnosis of metastatic hepatocellular carcinoma (IHCS ×20)

Metastatic Malignant Melanoma

Metastatic malignant melanoma has also been identified as a common metastatic tumor to the pancreas [5–7, 13]. On fine needle aspiration, metastatic malignant melanomas are hypercellular and comprise dyscohesive cells, which may range from plasmacytoid to pleomorphic and round to spindle (Fig. 10.23). Large nuclei with prominent nucleoli are also present (Fig. 10.24). Intranuclear cytoplasmic pseudoinclusions can also be identified and can be helpful in diagnosing metastatic malignant melanoma. The tumor cells may also show abundant melanin pigment which may also be dispersed in the background. These cytomorphologic features and additional ancillary immunohistochemical staining with HMB-45, S-100 protein, melan-A, MART-1, and SOX-10 will help in confirming the diagnosis [6–8, 12–14, 20].

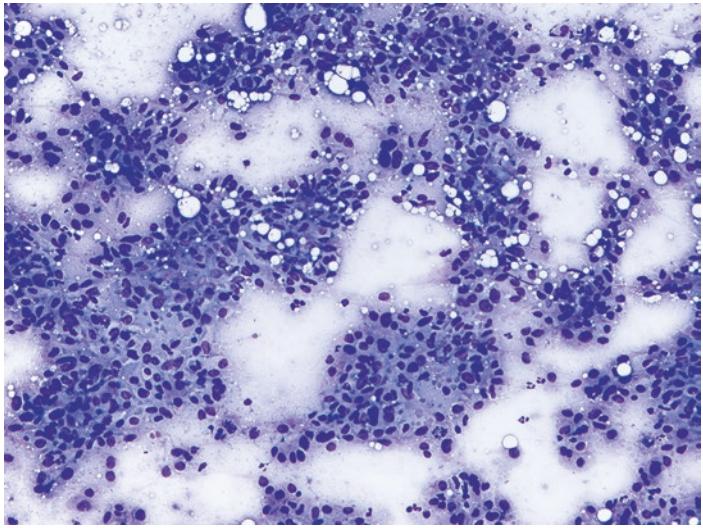

Fig. 10.23 Metastatic malignant melanoma will exhibit a variety of cell shapes and sizes. The tumor cells are round, oval, and spindle (Diff-Quik ×20)

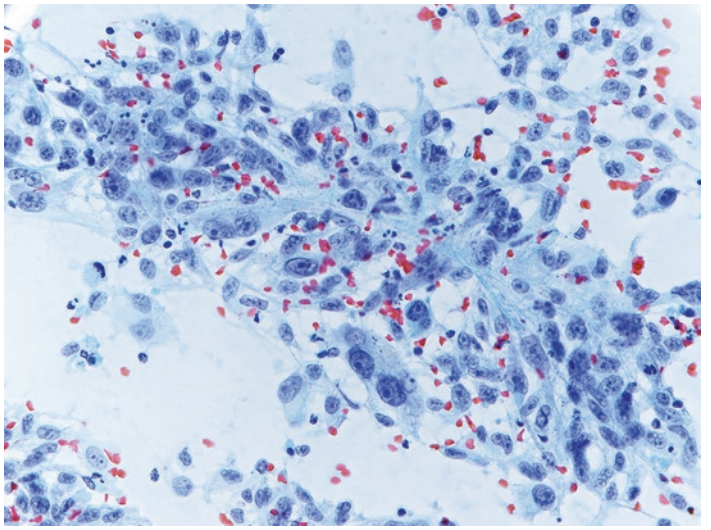

Fig. 10.24 Metastatic malignant melanoma with large prominent nuclei with enlarged prominent nucleoli is noted in this aspirate with an unknown primary site. Immunohistochemical staining with HMB-45, S-100 protein, and SOX-10 can confirm the diagnosis (IHCS ×40)

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