Chapter 8
Kidney and Adrenal Gland

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Kidney

Introduction

In the past, clinical management of patients was based on characteristic radiologic features; hence there was no clear role for fine needle aspiration (FNA) of renal tumors [1]. The great majority of renal lesions are radiologically benign cysts, which require no treatment. All solid renal cortical lesions, except metastases, were subject to surgical resection. More recently, FNA has been of increasing value. It is helpful in preventing unnecessary surgeries in patients with benign lesions such as oncocytoma, in patients with malignant lesions who are otherwise nonsurgical candidates, in patients with radiologically indeterminate cysts, and in other patients for whom partial nephrectomy rather than radical nephrectomy may be a preferred alternative treatment, especially in patients with tumors such as papillary renal cell carcinoma (papillary RCC), chromophobe RCC, and mucinous tubular and spindle cell carcinoma, which have a good prognosis [1–4]. Current management of small renal masses involves ablating the masses using cryotherapy, radiofrequency, or ethanol injections. FNA is done in this category of patients to confirm malignancy before the ablation procedure [5]. Advances in neoadjuvant targeted therapies for RCC have made the knowledge of the histological subtype critical for tailoring clinical trials and follow-up strategies [6, 7].

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Specimen Adequacy Assessment

Virtually all kidney aspirations are performed percutaneously by radiologists using ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI) for guidance. However, there is increasing use of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) [8]. Rapid on-site evaluation (ROSE) for assessment of specimen adequacy is very important because it helps in decision-making such as whether additional passes are needed and whether additional tissue such as needle core biopsy is needed. It has been suggested that core biopsy and FNA are complementary and the combination of these techniques is better than either alone [9]. There are no established criteria for adequacy requirement in terms of specimen cellularity. A renal FNA specimen is considered adequate if a specific diagnosis can be made or if there is sufficient cellularity to suggest a limited differential diagnosis [10]. Aspiration of a cystic lesion composed exclusively of macrophages is reported as nondiagnostic rather than negative because a cystic RCC cannot be entirely excluded. The success of a renal FNA is largely dependent on the technique of aspiration, the skill of the aspirator, and the motivation and expertise of the pathologist and cytotechnologist.

Normal Elements in Kidney Cytology

Normal renal parenchymal components are occasionally encountered especially when a small renal mass is targeted and the needle misses the lesion and samples the adjacent normal renal parenchyma. Glomeruli are large, highly cellular globular structures, with sharply demarcated, multilayered clusters of epithelial and endothelial cells. They are much more dense in the center than at the periphery and there are distinctive capillary loops at the edges. Glomeruli may mimic the papillae of papillary RCC.

Proximal convoluted tubules have abundant granular, eosinophilic cytoplasm, and large oval nuclei with small, inconspicuous nucleoli. The cells have ill-defined cell borders, with the granules appearing to be spilling out of the cells. The cells may mimic those of oncocytoma or chromophobe RCC.

The cells of distal convoluted tubules are much smaller than cells from the proximal tubules and they have less cytoplasm. The cytoplasm is clear to slightly granular, and they have a small, round nucleus with an inconspicuous nucleolus. The cell borders are well-defined. The cells may mimic those of a low-grade clear cell or papillary RCC.

Cystic Lesions of the Kidney

Diagnostic Considerations

It has been estimated that up to 85% of asymptomatic renal masses detected by various imaging studies are at least partially cystic [11]. The majority of renal cysts appear radiographically as unilocular cysts with homogeneous watery content and regular, thin, smooth walls. Most of these can be reliably diagnosed as simple benign cysts

[12, 13]. The remainder, however, display atypical imaging features such as multilocularity; mural nodules; shaggy, irregularly thickened, or calcified cyst wall; or heterogeneous or high-density cyst content [11, 14–16]. For this group, diagnostic possibilities other than simple cysts should be considered. The gross appearance of the aspirated fluid is a poor diagnostic indicator, since fluid from benign cysts and cystic carcinomas may be clear, cloudy, or bloody. Cystic degeneration of tumor tissue, substantial enough to be visible by imaging, is frequently seen in clear cell RCC and papillary RCC [16, 17]. The tumor may be solid with extensive cystic change or it may represent a mural tumor nodule arising from cyst epithelium [14].

1. Cytomorphologic features

   - Macrophages are almost always present, and in most cases, it represents the predominant or the only cell type present.
   - In benign cysts, macrophages display nuclei without atypical features and abundant, uniformly vacuolated, or granular cytoplasm with or without hemosiderin pigment (Figs. 8.1 and 8.2).

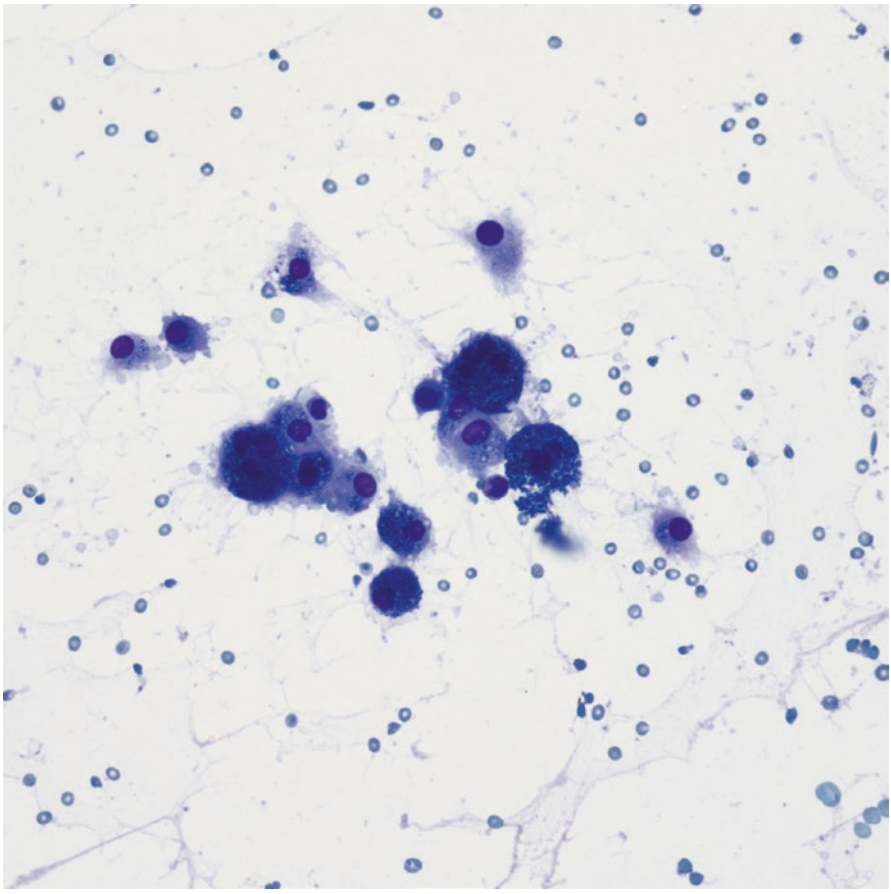

Fig. 8.1 Renal cyst. Macrophages are the predominant cells present, some with hemosiderin pigment (Diff-Quik stain, ×400)

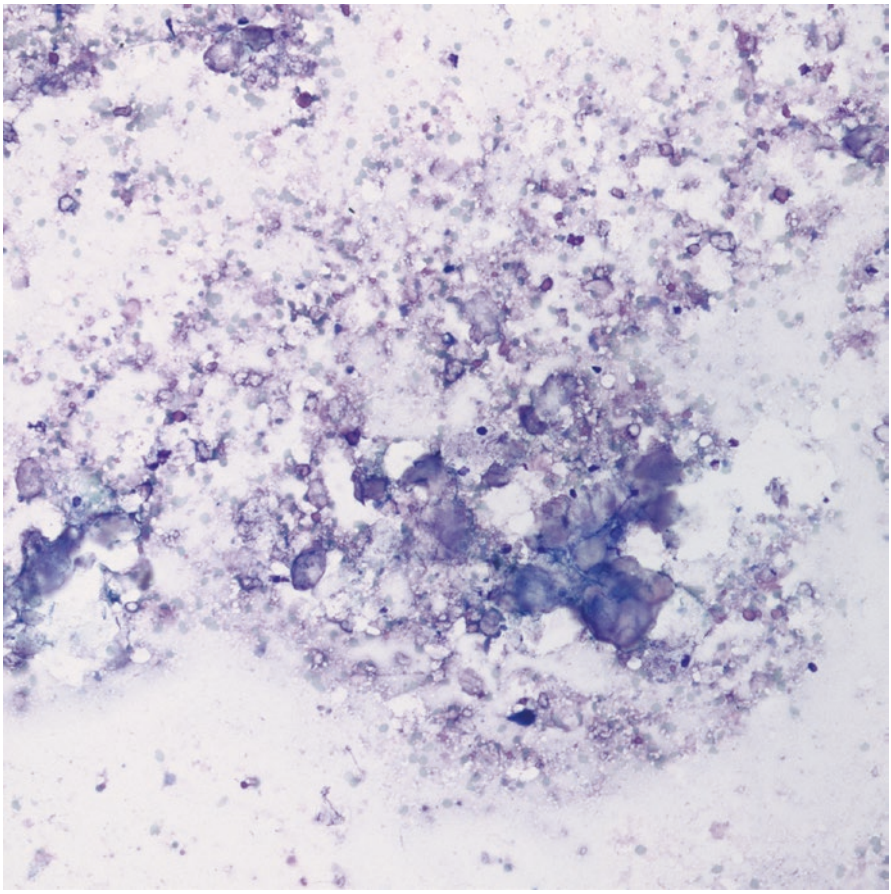

Fig. 8.2 Renal cyst. Predominantly crystals and scattered macrophages (Diff-Quik stain, ×200)

- Macrophages mostly present as single cells but they may be aggregated into cohesive clusters.
- Cyst-lining epithelial cells appear as rare 2-dimensional clusters or isolated epithelial cells with mild nuclear atypia, reticulated or granular cytoplasm, and ill-defined cell borders [11].
- Tubular cells are often seen, consisting mostly of proximal tubular cells, which appear as small, orderly, oriented, 2-dimensional cell clusters with abundant, finely granular, homogeneous cytoplasm and uniform, round nuclei with small nucleoli. Aspirated proximal tubular cells present as naked nuclei or as 2-dimensional tubular fragments.
- Cystic renal cell carcinoma is characterized by abundant clusters and isolated tumor cells with ample, vacuolated, fluffy, or reticulated cytoplasm. Tumor cell clusters are mostly large, irregular, and three-dimensional [11].

2. Tips and pitfalls

- When macrophages are aggregated into cohesive clusters, they may simulate cells of renal cell carcinoma. Immunohistochemistry is very helpful in this scenario as macrophages are positive for CD68, while the cells of renal cell carcinoma will be positive for cytokeratin AE1/AE3.
- The presence of numerous epithelial cells, even with mild atypia, or of few epithelial cells with significant atypia should raise the possibility of a malignant neoplasm or complex cystic lesions.
- Repeated aspiration of any residual solid areas that are visible after evacuation of the cyst usually yields abundant tubular cells, which may be misinterpreted as tumor cells.
- Calcium oxalate crystals are frequently seen in the acquired cystic disease-associated renal cell carcinoma.

Benign or Uncertain Behavior Neoplasms

Oncocytoma

A. Diagnostic considerations

Oncocytoma, a benign tumor of oncocytes, is composed of large epithelial cells with abundant eosinophilic cytoplasm. Grossly, the tumor is usually well-circumscribed and encapsulated with mahogany brown color and a central fibrous scar.

B. Cytomorphologic features

- Cellular specimen with numerous isolated cells with abundant, eosinophilic granular cytoplasm and small, round nuclei with finely granular chromatin and inconspicuous, tiny nucleoli [18].
- Tumor is arranged in rounded nests with well-demarcated cell borders.
- Isolated pleomorphic or bizarre cells consistent with degenerative atypia may be present.

C. Tips and pitfalls

- Hepatocytes from inadvertent sampling of the liver can mimic oncocytes. Although hepatocytes have abundant granular cytoplasm similar to cells of oncocytoma, they show more variation in nuclear and cellular size and they often contain lipofuscin pigment.
- Eosinophilic variant of clear cell RCC and several other different subtypes of RCC can have eosinophilic granular cytoplasm and therefore mimic an oncocytoma. It is essential that additional pass should be collected for cell block preparation for immunohistochemistry to differentiate between oncocytoma and these neoplasms.

- Oncocytic papillary RCC has a similar appearance to oncocytoma, but it also has papillae and abundant macrophages, which are not features of oncocytoma.
- Distinction between chromophobe RCC and oncocytoma can be very difficult on smears alone and additional cell block material is needed for morphology assessment and immunohistochemistry. The neoplastic cells in oncocytoma are arranged in rounded nests, while cells in chromophobe RCC have a trabecular arrangement. Chromophobe RCC is typically positive for CK7 and shows diffuse cytoplasmic staining for Hale's colloidal iron, whereas oncocytoma is negative for CK7 and mostly negative or show focal apical staining for Hale's colloidal iron.
- Hybrid oncocytic tumors comprise of oncocytoma and chromophobe RCC components and the FNA findings depend on the areas sampled. Because of this potential pitfall, it is advisable that these cases should be diagnosed as "oncocytic renal neoplasm." A particular lesion can be favored if possible, but a note should be added that a partial nephrectomy should be considered, if clinically indicated.

Renal Cortical Adenoma

A. Diagnostic considerations

Papillary adenomas are small lesions less than 1.5 cm, which arise in the renal cortex and are often subcapsular. They are usually unencapsulated and histologically, immunohistochemically, and cytologically indistinguishable from type 1 papillary RCC.

B. Cytomorphologic features

- Lesion is composed of densely packed tubules lined by small, regular cuboidal cells with round, uniform, bland nuclei. Pure papillary and tubulopapillary patterns as well as microcyst formation can also be seen [19].

C. Tips and pitfalls

- A diagnosis of papillary adenoma based on FNA should be made with extreme caution, because the presence of capsule or grade heterogeneity may not be visualized.

Metanephric Adenoma

A. Diagnostic considerations

Metanephric adenoma is an uncommon benign neoplasm of the kidney derived from metanephric blastema and composed of well-differentiated epithelial nephroblastic cells [20]. The majority of cases are found during imaging studies for other complaints. There is a close association between metanephric adenoma and polycythemia.

B. Cytomorphologic features

- Cellular smears with cells arranged as short tubules, tight balls, and loose sheets.
- Conspicuous basement membrane-type material surrounds neoplastic cells.
- Tumor cells are small and uniform, with round nuclei, fine chromatin, absent nucleoli, and scant cytoplasm [21].
- Psammoma bodies are common.
- Mitoses are absent or very infrequent.

C. Tips and pitfalls

- Differentiating metanephric adenoma from monophasic Wilm's tumor can be very challenging. Additional passes for cell block material and immunohistochemistry is key. Metanephric adenoma is positive for CD57 and may show nuclear reactivity for WT-1 while negative for CD56, whereas Wilm's tumor is positive for WT-1 and CD56 and may be positive for CD57 in up to 50% of cases.
- Papillary RCC can also be confused with metanephric adenoma. Unlike papillary RCC, metanephric adenoma is negative for epithelial membrane antigen.

Angiomyolipoma

A. Diagnostic considerations

Angiomyolipoma, a benign neoplasm, is regarded as a hamartoma or benign mesenchymoma, and it consists of a mixture of mature adipose tissue, tortuous thick-walled blood vessels, and fascicles of smooth muscle [22, 23]. There is a strong association with tuberous sclerosis, and these patients tend to have multiple small and bilateral angiomyolipomas, and they also demonstrate extrarenal manifestations of tuberous sclerosis complex [10].

B. Cytomorphologic features

- The vascular component is characterized by thick-walled blood vessels lined by endothelial cells.
- The smooth muscle component is composed of clusters of bland small spindle cells, which vary in size and shape, with granular cytoplasm [24].
- The lipomatous component is composed of mature adipose tissue. Areas of fat necrosis, comprising of histiocytes and multinucleated giant cells may be found [23].
- The cells of epithelioid angiomyolipoma are round and range from medium to large cells with prominent nucleoli and abundant cytoplasm, resembling ganglion cells.

C. Tips and pitfalls

- The smooth muscle cells of angiomyolipoma often show atypia and this may be confused with sarcoma or sarcomatoid differentiation in renal cell carcinoma [24].

- Highly cellular smooth muscle cells with predominantly round cell pattern with granular cytoplasm may be confused with RCC with granular cytoplasm.
- Fat-predominant angiomyolipoma can mimic well-differentiated liposarcoma.
- Cells of epithelioid angiomyolipoma, especially in the presence of necrosis and mitoses, can mimic clear cell RCC [25].
- The smooth muscle cells as well as the fat cells are positive for melanoma markers such as HMB-45 and Melan A.

Renal Abscess

A. Diagnostic considerations

Localized bacteria pyelonephritis and renal abscess can have the appearance of a mass on radiologic examination. Both intrarenal and perinephric abscess can be aspirated under US guidance.

B. Cytomorphologic features

- Aspirates yield necrotic material and abundant neutrophils.
- Rare atypical cells may be present.

C. Tips and pitfalls

- If the aspiration yields turbid fluid or frank pus, material should be sent for microbiologic studies.
- The atypical cells can mimic renal cell carcinoma with abundant necrosis. Hence, in the presence of abundant acute inflammation, atypical cells in renal FNA, especially when they are very few, should be interpreted with caution.

Xanthogranulomatous Pyelonephritis

A. Diagnostic considerations

Xanthogranulomatous pyelonephritis is a chronic inflammatory disease of the kidney and is thought to be an atypical host reaction to a bacterial infection, which usually presents as a mass lesion. It is associated with recurrent urinary tract infection and may present as a mass lesion, thereby mimicking carcinoma [26].

B. Cytomorphologic features

- The lesion is composed of histiocytes and multinucleated giant cells [24].
- Histiocytes have foamy, granular, or eosinophilic cytoplasm and small uniform nuclei (Fig. 8.3).
- Necrosis, cholesterol clefts, and lymphocytes are commonly seen.

C. Tips and pitfalls

- Clusters of histiocytes can resemble the cells of clear cell RCC. The histiocytes of xanthogranulomatous pyelonephritis, however, lack nuclear atypia

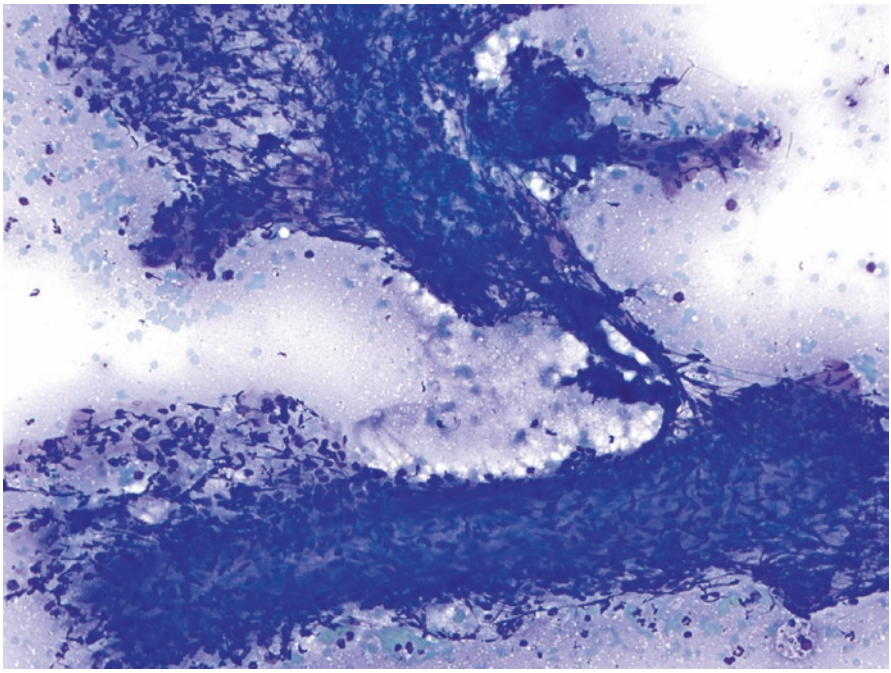

Fig. 8.3 Xanthogranulomatous pyelonephritis. Clusters of histiocytes with small uniform nuclei and foamy cytoplasm. The histiocytes form aggregates resembling clear cell RCC, but they lack nuclear atypia (Diff-Quik stain, ×200)

and have a cytoplasm that has a more microvacuolated appearance than that of typical clear cell RCC.

- Immunohistochemical stains will be helpful in difficult cases, hence the need for additional passes for cell block material. The histiocytes show immunoreactivity for CD68 and negative for cytokeratin AE1/AE3, the precise opposite of the immunoprofile that is seen in clear cell RCC.

Malignant Neoplasms

Clear Cell Renal Cell Carcinoma

A. Diagnostic considerations

Clear cell renal cell carcinoma is the most common variant of RCC, accounting for 75–80% of all RCCs. The tumor cells have a rich network of delicate, thin-walled blood vessels, which accounts for the contrast enhancement pattern on imaging studies and the frequent bloodiness of FNA samples [10]. Grossly, most clear cell RCCs are solitary and randomly distributed in the renal cortex. Multicentricity in the same kidney as well as bilaterality can also be seen and

these are often associated with familial and associated conditions such as von Hippel-Lindau disease [27, 28]. The tumor is typically golden yellow in appearance due to the rich lipid content of its cells.

B. Cytomorphologic features

- Aspirates tend to be hypercellular (Fig. 8.4), with bloody and/or necrotic background.
- Cells are interspersed with abundant, thin-walled blood vessels.
- Cells tend to be large with a low to moderate nuclear-cytoplasmic ratio.
- Nuclei tend to be round or slightly irregular, with finely granular, evenly distributed chromatin [29].
- Depending on the degree of differentiation, nucleoli may be absent, sparse, large, or prominent.
- The cytoplasm is abundant, can be clear and foamy, or may be granular and eosinophilic or a mixture of both (Fig. 8.5). Cytoplasm is thin and wispy and

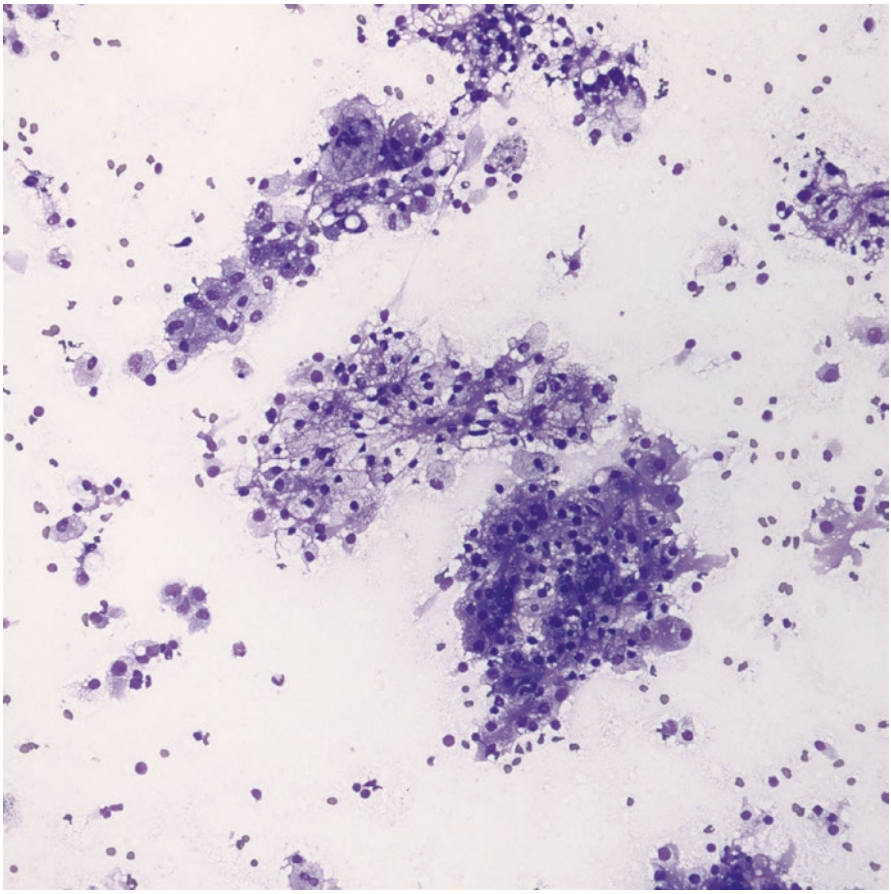

Fig. 8.4 Clear cell RCC. Hypercellular aspirate (Diff-Quik stain, ×200)

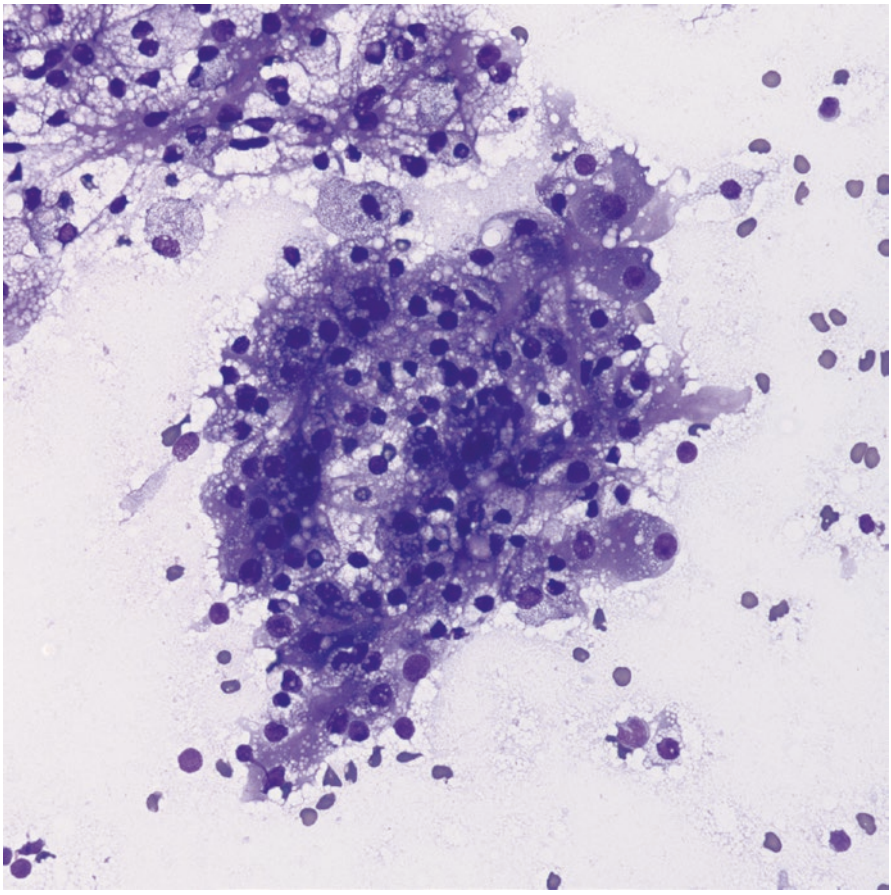

Fig. 8.5 Clear cell RCC. Abundant foamy cytoplasm with peripherally placed small cytoplasmic vacuoles (Diff-Quik stain, ×400)

cell membranes are poorly defined. Small cytoplasmic vacuoles are often peripherally placed [10, 24, 29, 30].

- Necrosis, hemorrhage, cystic degeneration, and calcifications are common.

C. Tips and pitfalls

- Higher-grade tumors have more isolated cells and less vacuolated cytoplasm (Fig. 8.6).
- A small proportion of tumors can have focal or extensive areas of cells with rhabdoid differentiation (Fig. 8.7). This should not be confused with rhabdoid tumor of the kidney.
- Aspirates of benign renal tubular cells can mimic low-grade clear cell RCC. The aspirate is usually flat and shows small groups of cells without vacuolated cytoplasm or branching vessels.

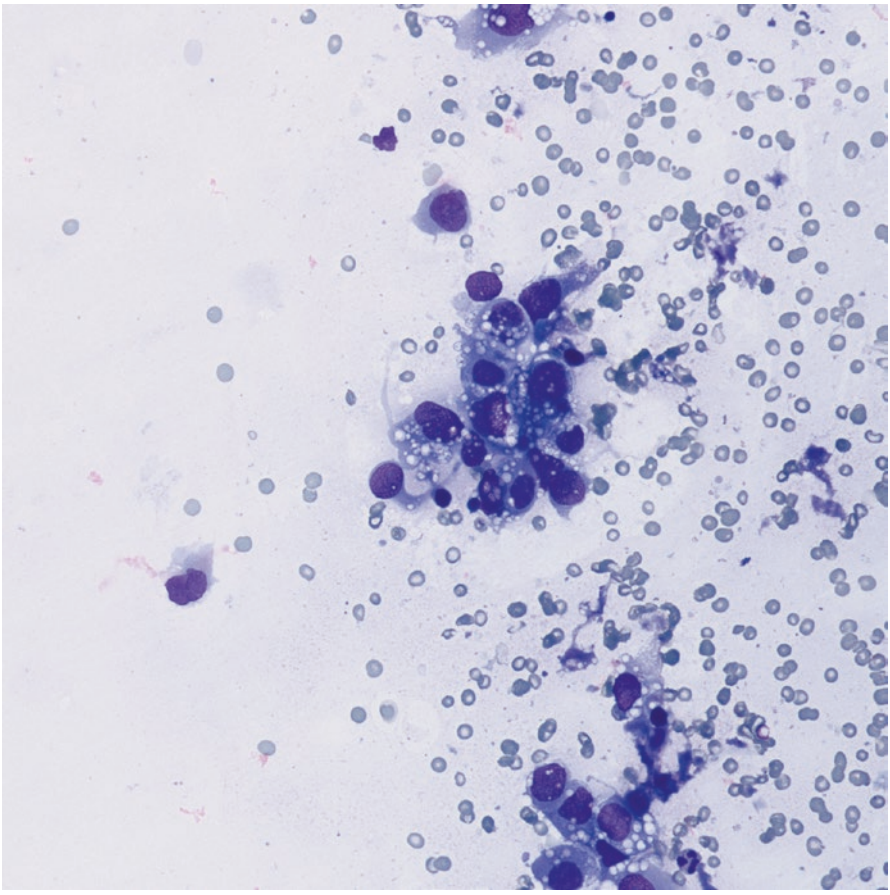

Fig. 8.6 Clear cell RCC. High-grade tumor with more isolated cells and less vacuolated cytoplasm (Diff-Quik stain, ×400)

- Adrenal cortical cells can simulate cells of clear cell RCC. However, the cells of the adrenal cortex are smaller and have a fine bubbly cytoplasm and are frequently stripped of their cytoplasm.
- Predominance of clear cells is also seen in clear cell tubulopapillary RCC and this may be impossible to distinguish from low-grade clear cell RCC based on cytology alone. It is important to collect cell block material for immunohistochemistry. Clear cell RCC typically demonstrates diffuse membranous staining for carbonic anhydrase IX while negative for CK7. In contrast, clear cell tubulopapillary RCC is negative for CK7 and shows cup-like staining for carbonic anhydrase IX.
- Other renal neoplasms with clear cell features such as epithelioid angiomyolipoma and translocation RCC should be considered in the differential diagnosis and immunohistochemical stains should be ordered accordingly.

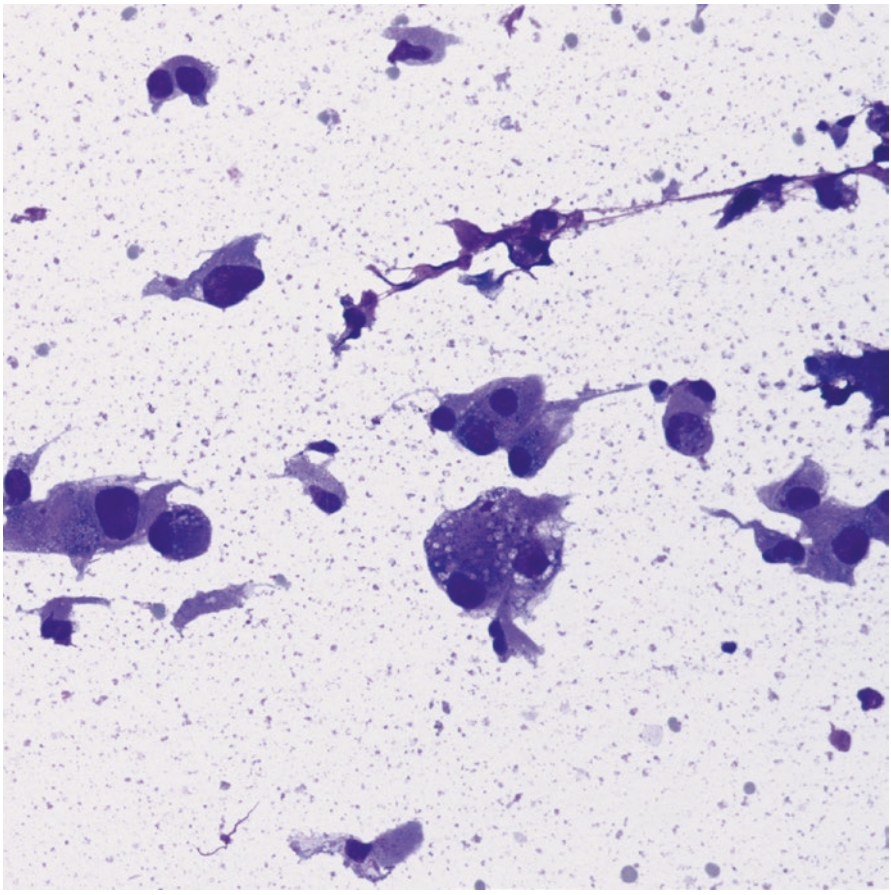

Fig. 8.7 Renal cell carcinoma with rhabdoid features (Diff-Quik stain, ×400)

Epithelioid angiomyolipoma is positive for HMB-45 and negative for carbonic anhydrase IX, while clear cell RCC demonstrates diffuse membranous staining for carbonic anhydrase IX and negative for HMB-45. Translocation RCC is positive for cathepsin K and has a variable but focal positivity for carbonic anhydrase IX, while clear cell RCC is negative for cathepsin K.

Papillary Renal Cell Carcinoma

A. Diagnostic considerations

Papillary RCC accounts for 7–15% of all RCCs [10, 31, 32]. It is associated with renal cortical adenomas and multifocality. Papillary RCC is divided into two morphologic subtypes – types 1 and 2 – which correlate with tumor grade.

Patients with a low-grade/low-stage papillary RCC have an excellent prognosis, while those with a high-grade/high-stage papillary RCC have a poor prognosis [32, 33].

B. Cytomorphologic features

- Aspirates are hypercellular with abundant papillary structures with true fibrovascular cores, spherules, and tubules.
- Type 1 tumors show papillae covered by a single layer of small bland cuboidal cells with uniform round, small nuclei, inconspicuous nucleoli, and scant cytoplasm.
- Type 2 tumors show papillae covered by large eosinophilic cells with enlarged nuclei, prominent nucleoli, and abundant granular cytoplasm.
- Cytoplasm may be clear, eosinophilic, or granular.
- Fibrovascular cores are distended with foamy macrophages.
- Abundant intracytoplasmic hemosiderin and psammoma bodies may be present.

C. Tips and pitfalls

- Type 1 papillary RCC is histologically, immunohistochemically, and cytologically indistinguishable from papillary adenoma. Radiological correlation is essential as the difference between the 2 entities is the size. Papillary adenomas are less than 1.5 cm in diameter.
- Type 1 papillary RCC can be confused with metanephric adenoma. Unlike papillary RCC, metanephric adenoma is negative for epithelial membrane antigen, so obtaining material for cell block for immunohistochemistry is important at the time of on-site evaluation.

Chromophobe Renal Cell Carcinoma

A. Diagnostic considerations

Chromophobe renal cell carcinoma is derived from the intercalated cells of the cortical collecting duct system and it consists of 4% of all RCCs [34]. Patients usually have an excellent prognosis as this entity has a much higher 5-year survival than clear cell RCC [35]. Grossly the cut surface shows a tan brown tumor which may closely mimic an oncocytoma. There are two distinct morphologic variants – the classic and eosinophilic variants.

B. Cytomorphologic features

- Aspirates are cellular with polygonal cells.
- Cells have eccentrically placed nuclei with inconspicuous nucleoli and well-defined cell borders.
- There is marked variation in the size of the nuclei, which have dark chromatin and raisinoid nuclei [36, 37].
- Cells may be binucleated or multinucleated and multiple fused nuclei may also be arranged peripherally (Fig. 8.8).

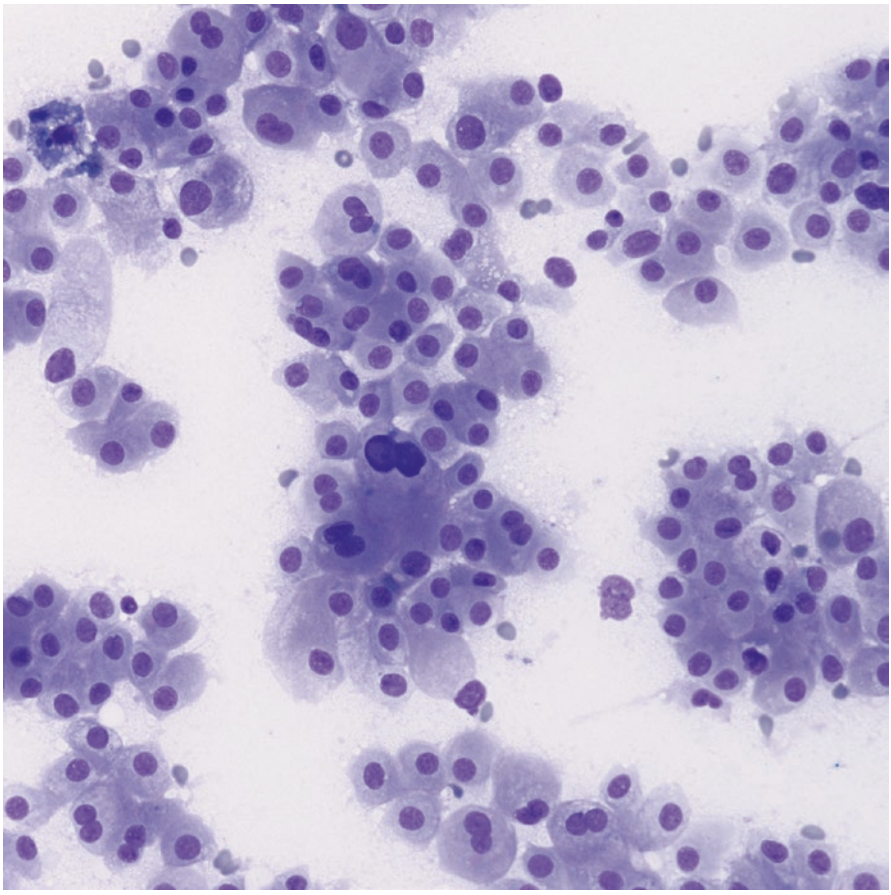

Fig. 8.8 Chromophobe renal cell carcinoma. Cells show frequent binucleation and prominent cell borders (Diff-Quik stain, ×400)

- Cytoplasm is granular and finely reticulated with perinuclear cytoplasmic clearing (Fig. 8.9). In classic variant, the cytoplasm is pale, while it is eosinophilic in the eosinophilic variant [10].
- The cells are reminiscent of koilocytes due to the nuclear features and perinuclear halo.

C. Tips and pitfalls

- Eosinophilic variant of chromophobe RCC can mimic oncocytoma. It has less dense granular cytoplasm than oncocytoma, and it is also characterized by perinuclear cytoplasmic clearing and marked anisonucleosis, features that are not typically seen in oncocytoma. Additional material for cell block preparation is very important as the morphology of tumor cells is better appreciated. In addition, immunohistochemical stains may be helpful in difficult

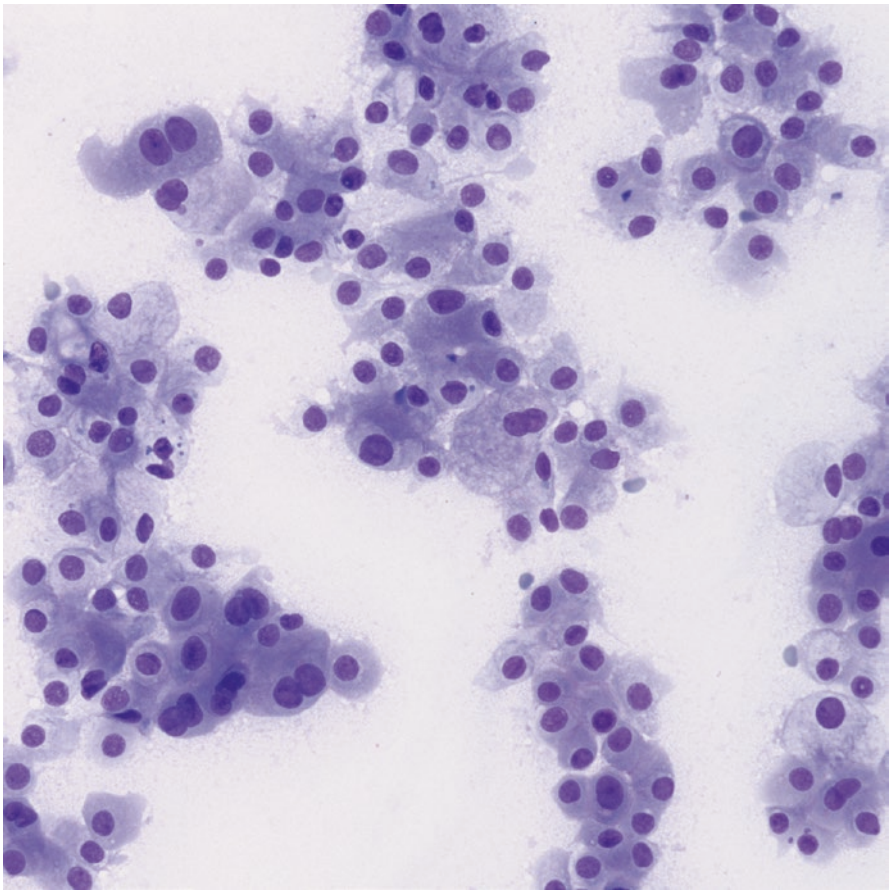

Fig. 8.9 Chromophobe renal cell carcinoma. Granular and finely reticulated cytoplasm with perinuclear cytoplasmic clearing (Diff-Quik stain, ×400)

cases. Chromophobe RCC is positive for CK7, while negative in oncocytoma. Hale's colloidal iron shows a diffuse cytoplasmic staining in chromophobe RCC, while it is usually negative or shows focal apical staining in oncocytoma. In equivocal cases, it is reasonable to interpret the specimen as "oncocytic neoplasm" and defer to partial nephrectomy for definitive classification, if clinically indicated.

- Clear cell RCC can also mimic chromophobe RCC. Clear cell RCC has abundant finely vacuolated cytoplasm with round centrally located nuclei and prominent nucleoli in contrast to the hyperchromatic raisinoid nuclei of chromophobe RCC. Chromophobe RCC is usually positive for CK7 and CD117, two stains that are negative in clear cell RCC.

Sarcomatoid Renal Cell Carcinoma

A. Diagnostic considerations

Sarcomatoid transformation in renal cell carcinomas is considered to be a poor prognostic sign and these tumors are usually highly aggressive [38, 39]. For a tumor to be diagnosed as sarcomatoid RCC, it must consist of a typical RCC component associated with a definite sarcomatoid component. In most cases, sarcomatoid transformation is associated with clear cell RCC, but it has also been documented in papillary, chromophobe, and collecting duct RCCs [40–42]. The greater the proportion of the sarcomatoid component, the worse the prognosis [39]. These tumors are ideal candidates for FNA as many are unresectable at the time of presentation.

B. Cytomorphologic features

- Aspirates are cellular with dimorphic cell population.
- The epithelial component is characterized by individual or small clusters of round cells with moderate to abundant cytoplasm. The nuclei are usually round with prominent nucleoli and nuclear membrane irregularity [43].
- The second population consists of single spindle cells or large clusters of spindle-shaped cells with elongated nuclei, prominent nucleoli, fine chromatin, and little to moderate cytoplasm [43].

C. Tips and pitfalls

- If an epithelial component is not identified, the tumor can be misdiagnosed as a true sarcoma. So, the preparation of cell block material may be of great benefit, especially in equivocal cases. The evaluation of tissue sections from cell blocks makes it easier to assess the sarcomatoid component and also provide a good source of material for immunohistochemical stains. The positivity for keratin and epithelial membrane antigen helps distinguish the tumors from true sarcomas.
- If only the epithelial area is sampled and no sarcomatoid component is represented, the tumor may be indirectly classified as a typical RCC.

Collecting Duct Carcinoma

A. Diagnostic considerations

Collecting duct carcinoma is a rare subtype of renal carcinoma that comprises 1–2% of all RCCs [44]. Unlike most RCCs, it arises in the renal medulla. It occurs in a younger age group than classical RCC and has an aggressive biologic behavior [44, 45].

B. Cytomorphologic features

- Smears have variable cellularity with cells arranged as well-demarcated groups or tightly packed cohesive cells with tubulopapillary growth pattern [44].
- Background is loose and shows loose scattered single cells and fragments of dense connective tissue.
- Nuclei are large, with eccentric or central placement, coarse chromatin, prominent nucleoli, and irregular nuclear contours [44, 46].
- Cytoplasm is scant, eosinophilic granular, or vacuolated.
- Nuclei of tubular cells may protrude into the luminal ends of the cells, giving a hobnail appearance [45].

C. Tips and pitfalls

- In the presence of prominent papillary architecture, it may be difficult to distinguish collecting duct carcinoma from type 2 papillary RCC. These two entities can be distinguished from each other by their location, architecture and immunohistochemical expression. Collecting duct carcinoma is positive for high molecular weight keratin and negative for AMACR, while the converse is true for papillary RCC.
- The cells of collecting duct carcinoma can closely resemble those of urothelial carcinoma. Cells of collecting duct carcinoma are positive for PAX-8 while negative for p63 and GATA-3, which helps distinguish it from urothelial carcinoma.
- Metastatic adenocarcinoma to the kidney can mimic collecting duct carcinoma. With a history of malignancy in other sites, metastasis should be considered and ruled out. Immunohistochemical stains are helpful in this scenario and cell block material should be obtained at the time of on-site assessment. The absence of extrarenal primary neoplasm should prompt consideration of an unusual primary renal tumor.

Mucinous Tubular and Spindle Cell Carcinoma

A. Diagnostic considerations

Mucinous tubular and spindle cell carcinoma (MTSCC) is a low-grade renal cell carcinoma, which is characterized by interconnecting tubular and spindle cells with low-grade nuclei within myxoid/mucinous stroma. Proper classification is important because this tumor behaves in a benign fashion and has excellent prognosis in overwhelming majority of cases [47], although aggressive cases have been reported [48].

B. Cytomorphologic features

- Cellular aspirates showing cohesive tissue fragments, with thick, broad trabecular arrangements as well as branching, pseudo-papillary formations [47] (Fig. 8.10).

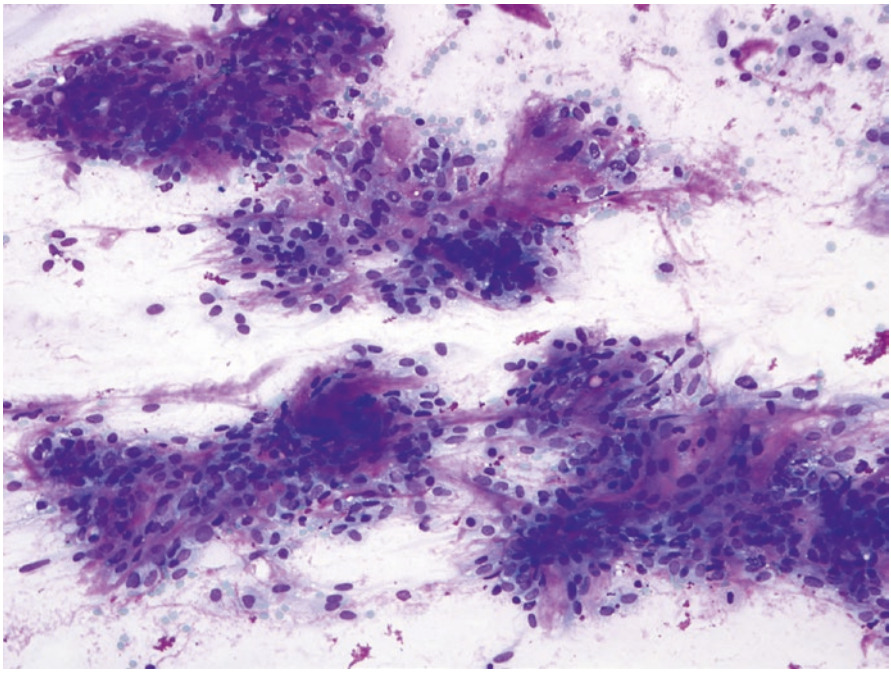

Fig. 8.10 Mucinous tubular and spindle cell carcinoma. Cohesive tissue fragments with branching, pseudo-papillary formations. Cells are uniform, oval to spindled shaped, with abundant myxoid matrix (Diff-Quik stain, ×200)

- Tumor is composed of a mixture of tubular cells and spindle cells.
- Tubular cells are uniform, usually low cuboidal with bland round to oval to slightly elongated nuclei [47, 49].
- Focal moderate nuclear pleomorphism and prominent nucleoli may be present.
- Cytoplasm is delicate with indistinct cell borders. Scattered fine intracytoplasmic vacuoles may be present.
- Metachromatic myxoid/mucinous stroma with linear, basement membrane-like arrangements is also commonly seen but occasional tumors can be mucin-poor [50]. The myxoid stroma stains magenta on Diff-Quik stain, while it stains pale blue on Papanicolaou stain.

C. Tips and pitfalls

- In the absence of myxoid matrix, MTSCC can be confused with papillary RCC because of the pseudo-papillary structures. However, MTSCC lacks true vascular cores and foam cells, two features which are the hallmark features of papillary RCC.
- Branching pseudo-papillary arrangements can also be seen in clear cell RCC but clear cell RCC will be expected to have more cells with vacuolated cytoplasm and perivascular nesting of tumor cells.

- MTSCC can also be confused with sarcomatoid RCC because of the presence of abundance of spindled cells. The spindled cells of MTSCC usually lack significant anisonucleosis and atypia and they also lack necrosis, unlike sarcomatoid carcinoma.

Urothelial Carcinoma

A. Diagnostic considerations

Urothelial carcinoma accounts for 5–10% of all renal tumors. It is similar to its bladder counterparts clinically, histologically, and cytologically. Urothelial carcinoma of the kidney has a significant association with synchronous or metachronous urothelial tumors of other sites. Distinguishing urothelial carcinoma from RCC is important because the management of urothelial carcinoma requires the resection of the ureter along with the kidney.

B. Cytomorphologic features

- The cytologic appearance depends on the grade of the tumor [30, 51, 52].
- Smears from low-grade tumors are usually cellular and are composed of aggregates of cells appearing as sheets, papillae, and single cells. The cells are columnar to polygonal with minimal nuclear atypia. Cells with elongations or cytoplasmic tails may be seen (Fig. 8.11), with occasional intracytoplasmic vacuole at the end of the tail. These are called cercariform cells [53, 54] and are said to be characteristic of low-grade urothelial carcinoma.
- Smears from high-grade tumors are cellular and are composed of large columnar or polygonal cells with dense cytoplasm (Fig. 8.12). The nuclei are large and hyperchromatic, with coarse chromatin, irregular nuclear contours, and high nuclear-to-cytoplasmic ratios. Bizarre multinucleated forms and single cells may be seen (Fig. 8.13).
- Focal squamous differentiation and glandular differentiation with or without production of mucin may be seen.

C. Tips and pitfalls

- High-grade urothelial carcinoma with sarcomatoid transformation may be confused with sarcomatoid RCC. In the absence of recognizable epithelial component, it may be difficult or even impossible to distinguish one from the other and additional material for immunohistochemical stains should be requested at the time of on-site evaluation.
- Urothelial carcinoma with either squamous or glandular differentiation may be confused with metastatic tumors to the kidney. Metastasis should always be ruled out especially when there is a history of extrarenal malignancy.
- It may be difficult to distinguish urothelial carcinoma from papillary RCC especially when there is predominance of papillary architecture. Distinction is made based on the distinctive nuclear features of each entity as well as the

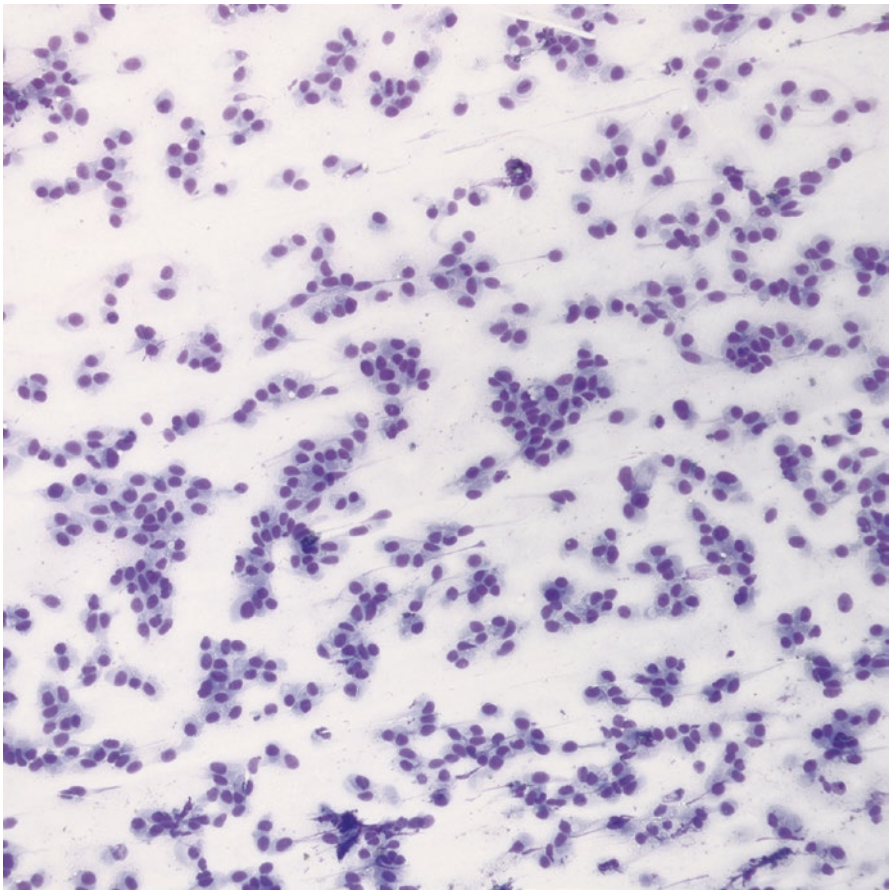

Fig. 8.11 Low-grade urothelial carcinoma. Cellular smear, showing cells with elongated cytoplasm (Diff-Quik stain, ×200)

characteristic features of papillary RCC such as abundant foamy macrophages and psammoma bodies.

- The cells of urothelial carcinoma can closely resemble those of collecting duct carcinoma. This has been discussed earlier.

Metastatic Tumor

A. Diagnostic considerations

Metastases to the kidney account for about 11% of renal tumors [55]. It is extremely uncommon for a kidney metastasis to be the initial manifestation of malignancy. Most tumors that are thought to be metastases in the kidney without a known primary most likely represent unusual primary renal tumors. Metastatic

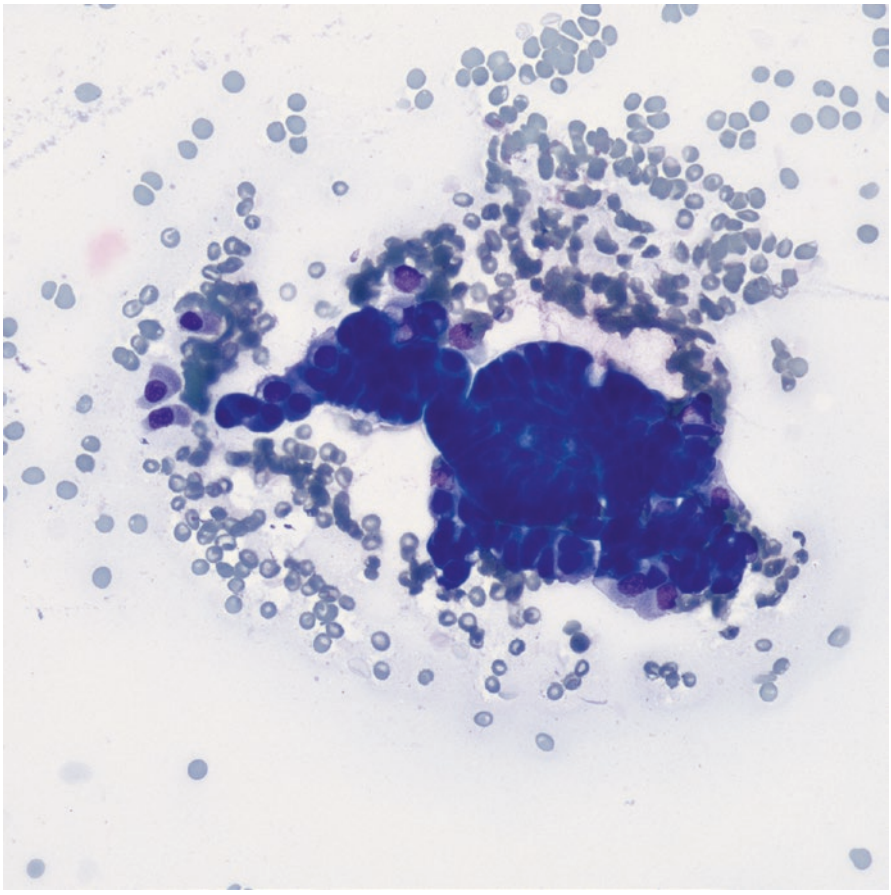

Fig. 8.12 High-grade urothelial carcinoma. Papillary cluster of large columnar cells (Diff-Quik stain, ×400)

tumors are often multifocal and bilateral. The lung is the most common primary site, while other common sites include the stomach, breast, pancreas, and contralateral kidney [55]. Malignant tumors of the adrenal may directly invade the kidney. Lymphomas are almost always metastatic from other sites although they may originate in the kidney.

B. Cytomorphologic features

- Metastatic carcinomas have three-dimensional clusters of tumor cells [56].
- Most metastatic lung tumors show cells with dark nuclei and irregular nuclear outlines, but some may have abundant clear cytoplasm and prominent nucleoli, thereby mimicking high-grade clear cell RCC [10].

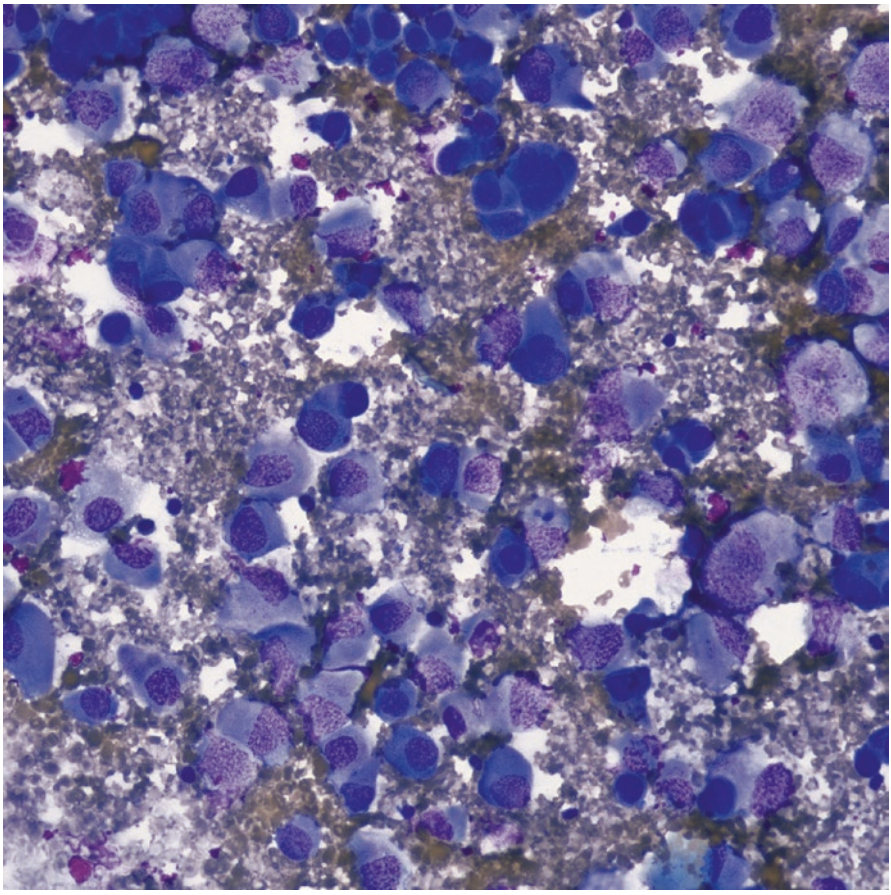

Fig. 8.13 High-grade urothelial carcinoma. Single cells with large, hyperchromatic nuclei, coarse chromatin, and irregular nuclear contours. The nuclear-to-cytoplasmic ratio is high (Diff-Quik stain, ×400)

- For most of the other metastatic tumors, the cells are usually either pleomorphic, large cells or undifferentiated small cells.

C. Tips and pitfalls

- Knowledge of the clinical history as well as judicious use of immunohistochemistry are key to the diagnosis. Although metastatic tumors differ from primary renal cell carcinoma on cytologic smears, the diagnosis is often made by the combination of cytomorphologic features, immunohistochemical stains, radiological appearance, and clinical history.

Adrenal Gland

Introduction

Fine needle aspiration (FNA) is an important procedure in the workup of patients with adrenal gland masses. It is a very effective method for distinguishing between adrenal tumors arising from the cortex and those arising from the medulla. It is also effective in distinguishing benign adrenal nodules from metastatic tumors during staging workup for cancer elsewhere in the body [57, 58]. Its value in the assessment of incidental adrenal nodules in patients without a history of malignancy remains unclear. FNA is generally avoided when a pheochromocytoma is suspected because of episodic hypertension resulting from the procedure.

Specimen Adequacy Assessment

Virtually all aspirations of the adrenal gland are performed by radiologists percutaneously using CT or US imaging guidance; however, endoscopic ultrasound-guided FNA is also becoming increasingly popular [59, 60]. The performance of this procedure requires a skilled operator especially if the lesion is small. To ensure adequate sampling of the suspected lesion, it is recommended that rapid on-site evaluation (ROSE) of direct smears be performed. Depending on the initial impression, additional material may be obtained for cell block. This is needed for subsequent immunohistochemical stains, special stains, or ultrastructural studies. Adrenal FNA has an accuracy of 96–98% and very good negative predictive value, especially for lesions larger than 3 cm [61, 62].

Normal Elements in Adrenal Cytology

Adrenal cortical cells are similar in size to hepatocytes. They are usually arranged in small clusters or cords, and they are polyhedral cells with small, round, vesicular nuclei with evenly distributed chromatin and small but distinct nucleoli (Fig. 8.14). The cytoplasm is faintly vacuolated or granular eosinophilic. Cells from the zona glomerulosa and zona fasciculata show either single prominent or multiple finely dispersed lipid inclusions. The cells from the zona reticularis contain golden-brown lipofuscin pigment. Small spindle-shaped stromal cells are occasionally present.

The cells of normal adrenal medulla are rarely encountered in aspirates of adrenal cortical lesions.

Hepatocytes can be sampled inadvertently during FNA of right adrenal gland. Hepatocytes usually do not have markedly vacuolated cytoplasm or delicate frayed cytoplasmic borders and there is no bubbly lipid-rich background.

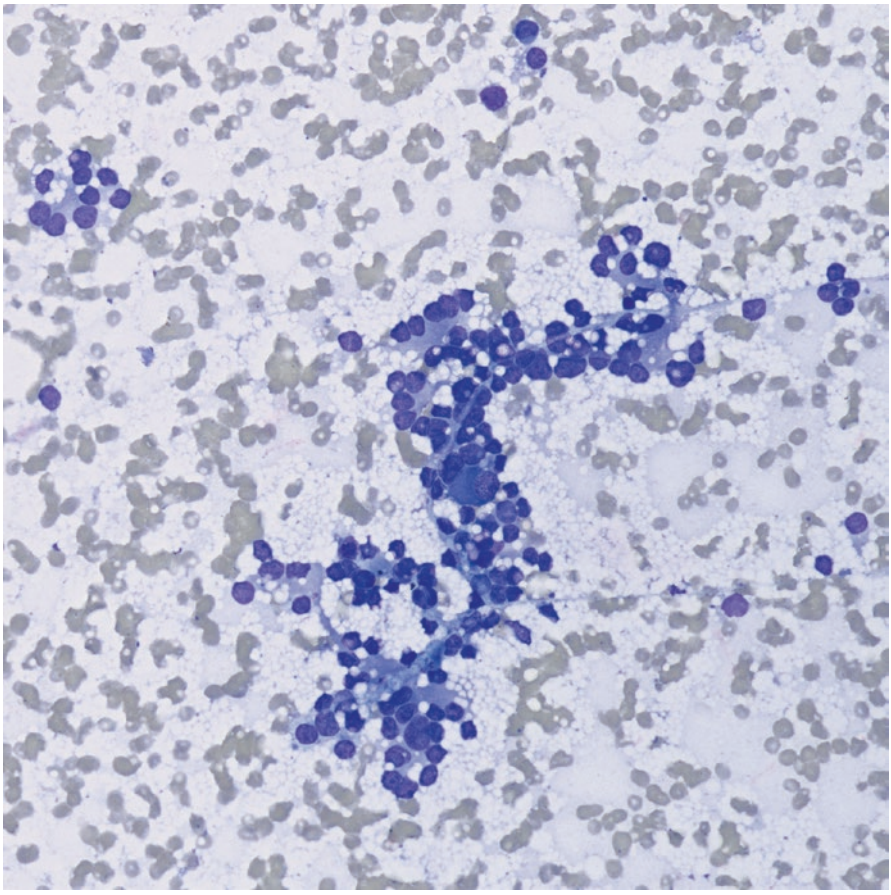

Fig. 8.14 Normal adrenal cortex. Cells with small, round, vesicular nuclei and vacuolated cytoplasm (Diff-Quik stain, ×400)

Benign or Uncertain Behavior Neoplasms

Myelolipoma

A. Diagnostic considerations

Myelolipoma is an uncommon benign neoplasm of the adrenal gland, which consists of mature fat containing normal hematopoietic cells. They are usually incidental findings.

B. Cytomorphologic features

- Smears show mature adipose tissue with immature hematopoietic cells of myeloid and erythroid origin, lymphocytes and megakaryocytes [63] (Fig. 8.15).

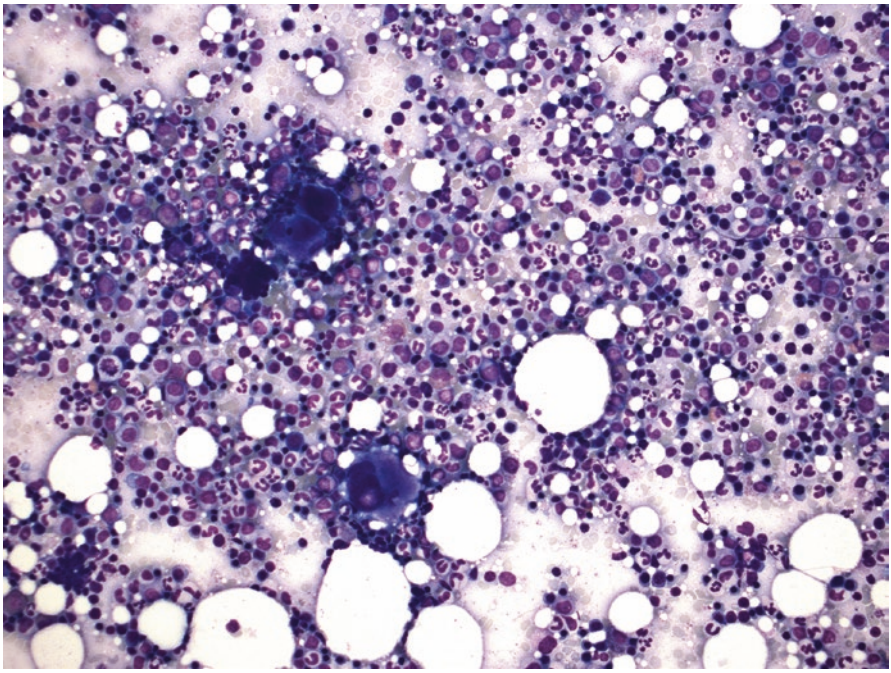

Fig. 8.15 Myelolipoma. Mature adipose tissue with immature hematopoietic cells of myeloid and erythroid origin, lymphocytes and megakaryocytes (Diff-Quik stain, ×200)

C. Tips and pitfalls

- The major differential diagnosis is angiomyolipoma of the kidney. The presence of hematopoietic elements as well as absence of prominent vessels and smooth muscle cells are helpful to make a diagnosis of myelolipoma.
- Retroperitoneal lipoma and liposarcoma should also be considered in the differential diagnosis. These entities also lack hematopoietic components.

Pheochromocytoma

A. Diagnostic considerations

Pheochromocytomas arise from the cells of the adrenal medulla. They are associated with familial neoplastic syndromes such as multiple endocrine neoplasia syndromes 2a and 2b (MEN 2) in 10–20% of cases [10]. Fine needle aspiration of suspected pheochromocytoma should be avoided as this may induce a fatal hypertensive crisis. No single cytologic pattern is diagnostic of this lesion.

B. Cytomorphologic features

- Highly cellular smears with cells arranged in loose clusters and as isolated cells.

- Small polygonal cells are often admixed with large spindled and epithelioid cells.
- Cells show pleomorphic nuclei with irregular nuclear membrane, finely stippled chromatin, prominent nucleoli, and intranuclear cytoplasmic pseudoinclusions [10].
- Cytoplasm is intensely granular and Diff-Quik stain shows red cytoplasmic granules.

C. Tips and pitfalls

- The cytologic features of pheochromocytoma overlap with those of metastatic high-grade malignant neoplasms, and ancillary tests such as immunohistochemistry will be helpful in differentiating this entity from metastatic neoplasms.
- The cytologic picture of pheochromocytoma is rarely conclusive in FNA specimens, and the diagnosis must be supported by clinical, imaging, and biochemical data.

Adrenal Cortical Adenoma

A. Diagnostic considerations

Adrenal cortical adenomas are thought to be very common, occurring in approximately 6% of adults, and their frequency increases with age [64]. They are usually unilateral and solitary masses, which distinguishes them from adrenal cortical hyperplasia which tends to be diffuse and bilateral. The majority of adenomas are nonfunctioning.

B. Cytomorphologic features

- Smears are very cellular and are composed of loose monolayered sheets or discohesive numerous small, round, moderately homogeneous naked nuclei on a pink granular or bubbly background of fragile and ill-defined vacuolated cytoplasm with frayed cellular borders [65].
- Nuclei are evenly spaced and are small and round, with smooth contours, even granular chromatin, and small nucleoli.
- Some of the nuclei may be enlarged but there is no nuclear pleomorphism.

C. Tips and pitfalls

- It is not possible to distinguish adrenal cortical adenoma from a hyperplastic nodule on cytology; hence they are referred to as benign adrenal cortical nodules/adenomas.
- It is often impossible to distinguish adrenal cortical adenoma from well-differentiated adrenal cortical carcinoma. The presence of necrosis and mitoses favor carcinoma. Correlation with radiology is also important as carcinomas tend to be fast growing and infiltrative.

- Clear cell RCC should be considered in the differential diagnosis of adrenal cortical adenoma. Clear cell RCC typically has abnormal nuclear features including the presence of prominent nucleoli and cell pleomorphism.
- Inadvertent sampling of liver tissue may occur during FNA of right adrenal gland. Hepatocytes are generally large polygonal cells with well-defined cell borders. They have prominent nucleoli and granular cytoplasm, which may contain bile pigment as opposed to the microvesicular cytoplasm of adrenal cortical adenoma.
- Superimposition of naked nuclei can mimic nuclear molding seen in small cell carcinoma. The true nuclear molding in small cell carcinoma is associated with necrosis and active mitosis.

Malignant Neoplasms

Adrenal Cortical Carcinoma

A. Diagnostic considerations

Adrenal cortical carcinomas are rare, highly malignant tumor with an annual prevalence estimated at 2–4 cases per million [66, 67]. Most tumors are functional with excess production of glucocorticoid, mineralocorticoid, or sex hormones. Up to 40% of cases have metastases at presentation.

B. Cytomorphologic features

- Cytomorphologic features range from well-differentiated to poorly differentiated tumors.
- Smears of well-differentiated tumors are cellular, and they show uniform tumor cells in loose clusters or single cells, with abundant, eosinophilic granular cytoplasm and large, uniform nuclei with coarse chromatin and prominent nucleoli [68, 69].
- Capillary vessels may be occasionally observed within the cell clusters.
- Smears of poorly differentiated tumors show large anaplastic malignant tumor cells with marked anisocytosis, large pleomorphic nuclei, prominent nucleoli, multinucleation, and abnormal mitoses [68, 69].

C. Tips and pitfalls

- It is often impossible to distinguish adrenal cortical adenoma from well-differentiated adrenal cortical carcinoma (discussed above).
- Clear cell RCC can be confused with adrenal cortical carcinoma. Additional material for immunohistochemistry is necessary. Clear cell RCC typically stains positive for PAX-8 and carbonic anhydrase IX, while adrenal cortical carcinoma is positive for Melan A and inhibin.
- The cells of adrenal cortical carcinoma can closely resemble those of metastatic tumor to the adrenal gland. Metastatic tumors are most likely to be bilateral and multiple. Correlation with history and immunohistochemistry is essential.

Metastatic Tumors

A. Diagnostic considerations

Adrenal gland is the fourth most common site of extranodal metastasis [70]. Metastases are far more common than primary malignant tumors of the adrenal gland [71]. Lung tumors account for the majority of metastases to the adrenal gland. Other common tumors that metastasize to the adrenals include melanoma, lymphoma and RCC [62, 70, 71]. Metastasis to the adrenals correlate with aggressive behavior and widespread dissemination of the primary tumor. Although most metastatic adrenal tumors are multifocal and bilateral, lung tumors and RCC have a tendency to produce a solitary adrenal metastasis. In such cases, FNA plays a key role in distinguishing a primary adrenal lesion from a solitary metastasis.

B. Cytomorphologic features

- Cytologic features depend on the primary tumor (Figs. 8.16, 8.17, 8.18, 8.19, and 8.20).

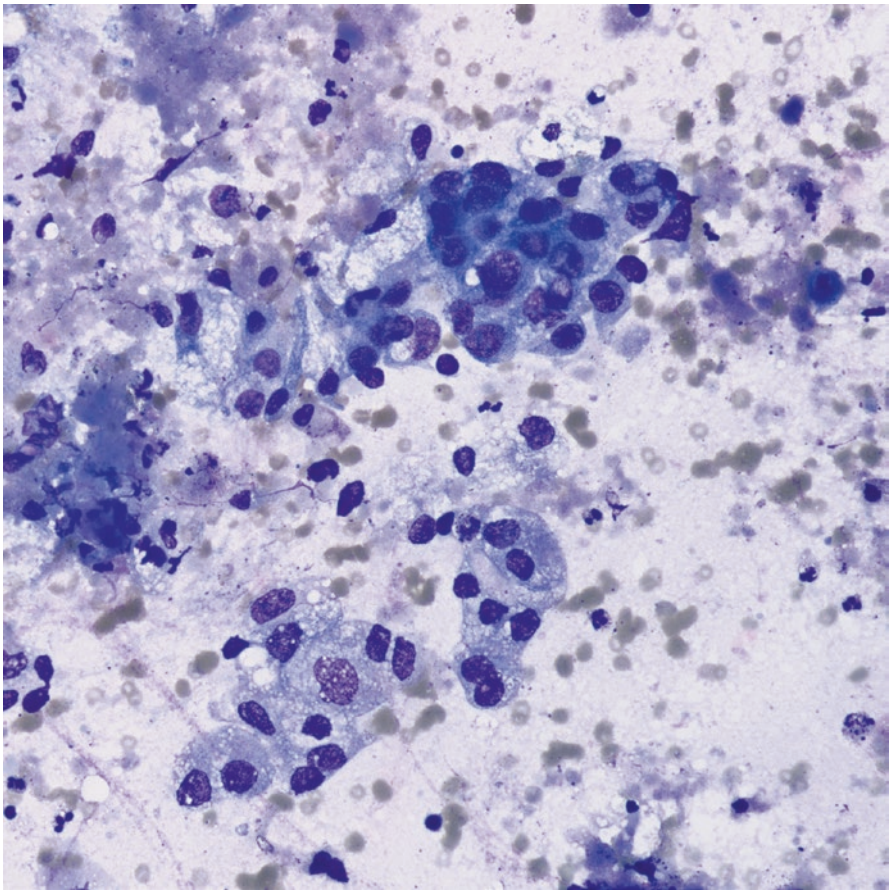

Fig. 8.16 Metastatic adenocarcinoma from the lung (Diff-Quik stain, ×400)

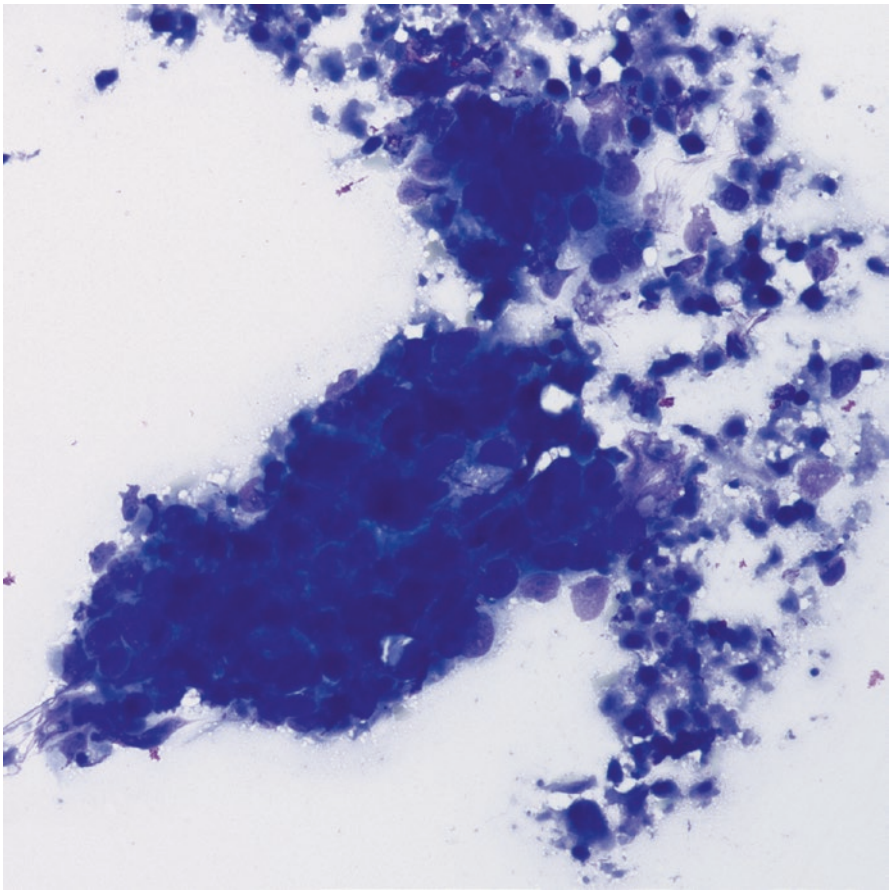

Fig. 8.17 Metastatic squamous cell carcinoma from the lung (Diff-Quik stain, ×400)

- Metastatic adenocarcinoma is the most common.
- Background necrosis or mucin may be seen.

C. Tips and pitfalls

- Cytologic diagnosis of metastasis to the adrenal gland rely on a constellation of clinical history, comparison with previous cytologic or histologic materials, and appropriate additional immunohistochemical stains.

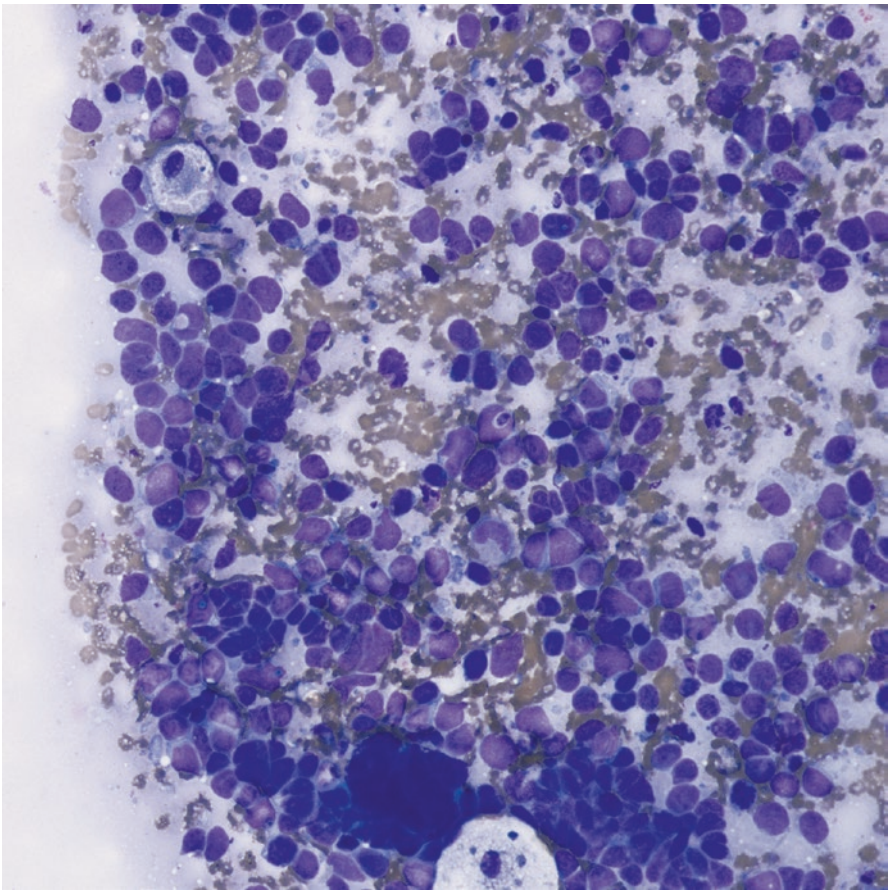

Fig. 8.18 Metastatic small cell carcinoma (Diff-Quik stain, ×400)

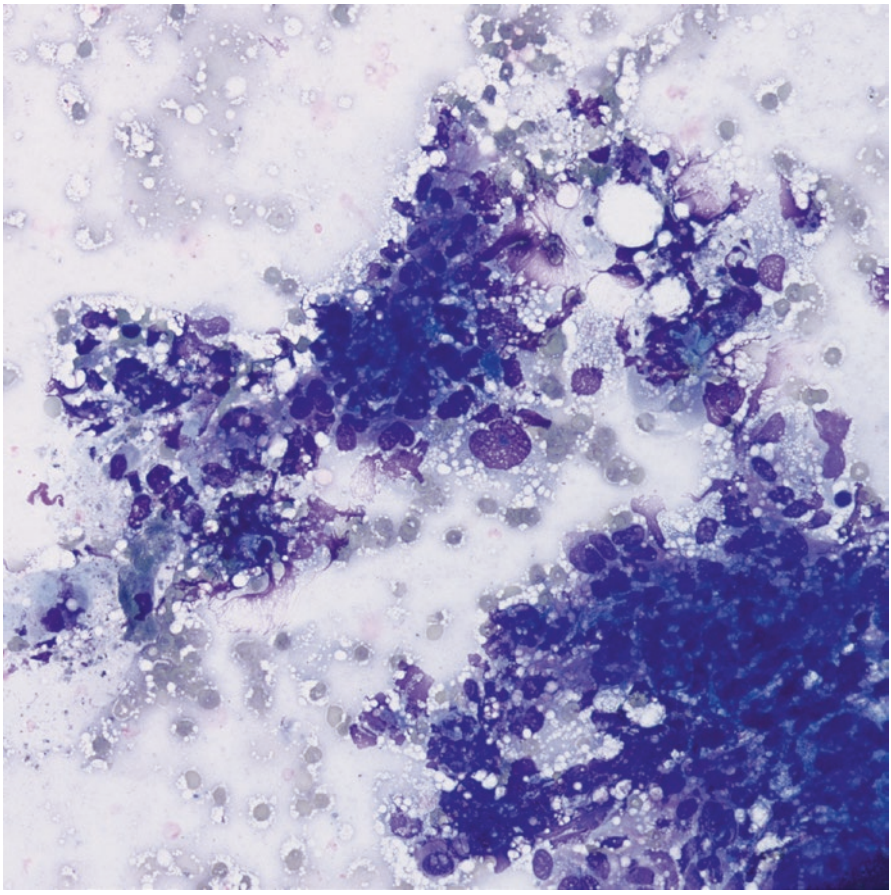

Fig. 8.19 Metastatic clear cell renal cell carcinoma (Diff-Quik stain, ×400)

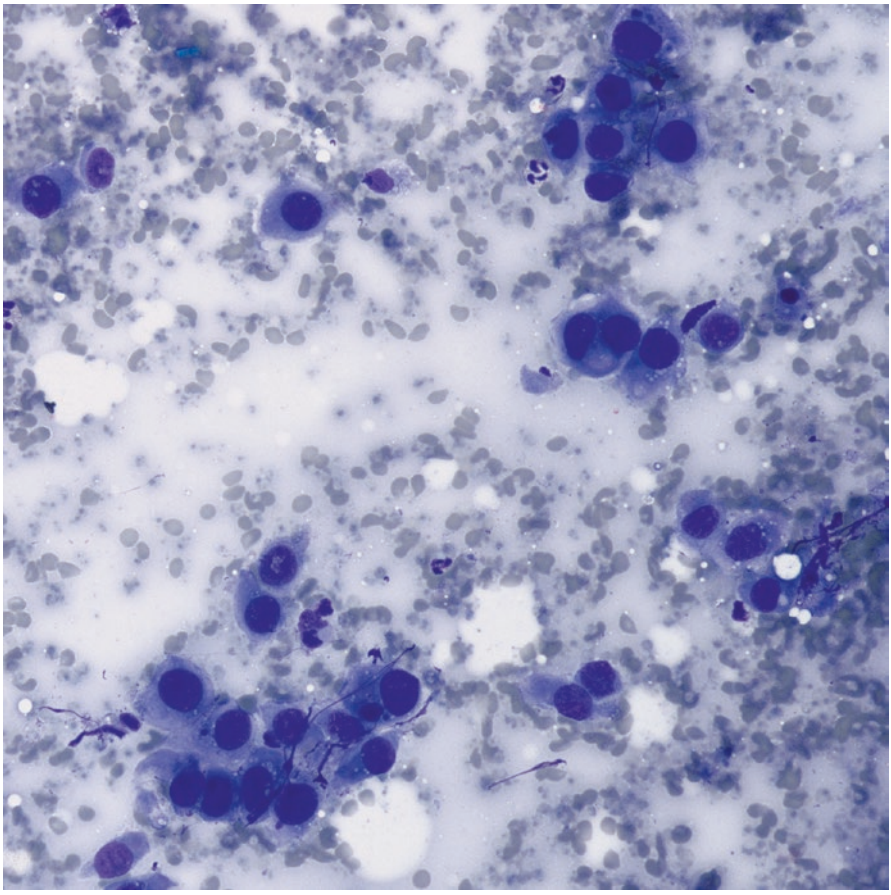

Fig. 8.20 Metastatic high-grade urothelial carcinoma (Diff-Quik stain, ×400)

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