Collecting Duct Carcinoma and Renal Medullary Carcinoma

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Introduction

Collecting duct carcinoma (CDC), also called "carcinoma of collecting ducts of Bellini," is a rare renal epithelial malignancy first described in 1949 and later recognized as a distinct subtype of renal cell carcinoma (RCC) in 1986. Renal medullary carcinoma (RMC) was initially described in 1995 as a rare and unique renal malignancy occurring in a distinct population of patients, specifically in young African American patients with sickle cell hemoglobinopathy, thus prompting the authors to call it the "seventh sickle cell nephropathy" [1]. These two tumors are similar in that both are rare and aggressive neoplasms that are thought to arise from the distal segment of the collecting ducts in the renal medullary pyramids, yet some distinct clinical and pathologic features can aid in distinguishing these two entities.

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Epidemiology, Clinical Features, and Radiographic Features of Collecting Duct and Renal Medullary Carcinoma

Epidemiology and Clinical Features

CDC accounts for <1 % of renal malignancies [2] and occurs in patients with a median age of 63 years (range 53–72.5), with a male predominance of about 2:1, and more frequently in Caucasians (71 %) than in African Americans (23 %) based on recent analysis of the Surveillance, Epidemiology, and End Results (SEER) database [3]. Over 50 % of patients are symptomatic at presentation with gross hematuria, abdominal/back pain, or general malaise [4, 5]. Patients with CDC generally present at higher stage than patients with clear cell RCC, as evidenced by a higher rate of locally advanced (T3–T4) disease (33 % vs. 18 %, respectively), nodal involvement (15 % vs. 2 %, respectively), and distant metastasis (28 % vs. 17 %, respectively) [6]. One and 3-year disease-specific survival rates for CDC are 70 % and 58 %, respectively, which is significantly worse when compared to patients with clear cell RCC [6].

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RMC is a rare tumor with less than 200 cases reported in the literature since its original description in 1995 by Davis [1]. The mean age at diagnosis is 19 years (range 5–69) with a male predominance of about 2:1. The overwhelming majority of patients are African American, with few cases occurring in Caucasian, Hispanic, and Asian Indian patients [5, 7]. Almost all patients have a sickle cell hemoglobinopathy, most commonly sickle cell trait and less commonly SC disease or sickle cell disease (SS disease), with only very rare cases reported in Caucasian patients without hemoglobinopathy [5, 8]. Most patients present with symptoms such as hematuria, flank pain, and weight loss and have evidence of metastatic disease at presentation, which can involve lymph nodes, lungs, liver, bones, or adrenal glands [5, 9]. Median cancer-specific survival for RMC is reported to be about 5 months (Fig. 8.1) [3, 5].

When patient and tumor characteristics between CDC and RMC are compared, RMC patients are significantly younger, more often African American, and more likely to have lymph node involvement and distant metastatic disease at presentation, and median cancer-specific survival is significantly shorter [3]. Distinguishing clinical features in CDC and RMC are summarized in Table 8.1.

Radiographic Features

The usual CT findings of CDC are of a solid renal mass located in the medulla with involvement of the renal sinus, infiltrative growth, preserved renal contour, and a cystic component [10]. Weak and heterogeneous enhancement due to areas of necrosis, hemorrhage, and calcification can be seen [11]. RMC is also characterized by an infiltrative, medullary-based solid renal mass with heterogeneity due to areas of hemorrhage and necrosis, and caliectasis is often present [11, 12]. Regional lymphadenopathy and metastasis are frequently seen in both CDC and RMC at initial diagnosis. These findings are nonspecific and do not allow for differentiation from more common types of RCC by imaging.

Pathologic Characteristics of Collecting Duct and Renal Medullary Carcinoma

Collecting Duct Carcinoma

Gross Pathology

On gross examination, CDCs are white to grey, firm, multinodular tumors with infiltrative borders and focal areas of tumor necrosis (Fig. 8.2), but without significant areas of hemorrhage, making them grossly distinct from the more usual types of RCCs. When small, the tumors appear centered in the renal medulla; however, this may be difficult to appreciate in larger tumors, which can extend into the renal cortex, renal pelvis, perinephric fat, or renal hilum [7, 13]. Tumors average about 6 cm in diameter and can range from 1 to 15 cm [4].

Microscopic Pathology

Histologically, CDC is essentially a high-grade poorly differentiated adenocarcinoma and most commonly shows tubules or tubulopapillary structures with irregular, angulated glands infiltrating the renal parenchyma (Fig. 8.3). However, other architectural patterns may be admixed in varying proportions, including solid cords, sheets, papillary formations with fibrovascular cores, a "hobnail" pattern, cystically dilated spaces, and cribriform histology [13]. At higher power, tumor cells have moderate to abundant eosinophilic cytoplasm with large hyperchromatic, pleomorphic nuclei and prominent nucleoli (Fig. 8.4) [2, 13]. As in other types of RCC, sarcomatoid differentiation and rhabdoid change can be seen (Fig. 8.5). Mitotic figures are frequently present. Both intraluminal and intracytoplasmic mucin may be seen, which can be highlighted with mucicarmine or Alcian blue stains. An additional characteristic feature of CDC is the presence of a pronounced desmoplastic stromal reaction, which can range in appearance from loose, myxoid, and collagenous to dense, eosinophilic, and fibrosclerotic. Associated inflammatory infiltrates, which are predominantly lymphocytic but occasionally mixed, are seen within the areas of desmoplasia (Fig. 8.6)

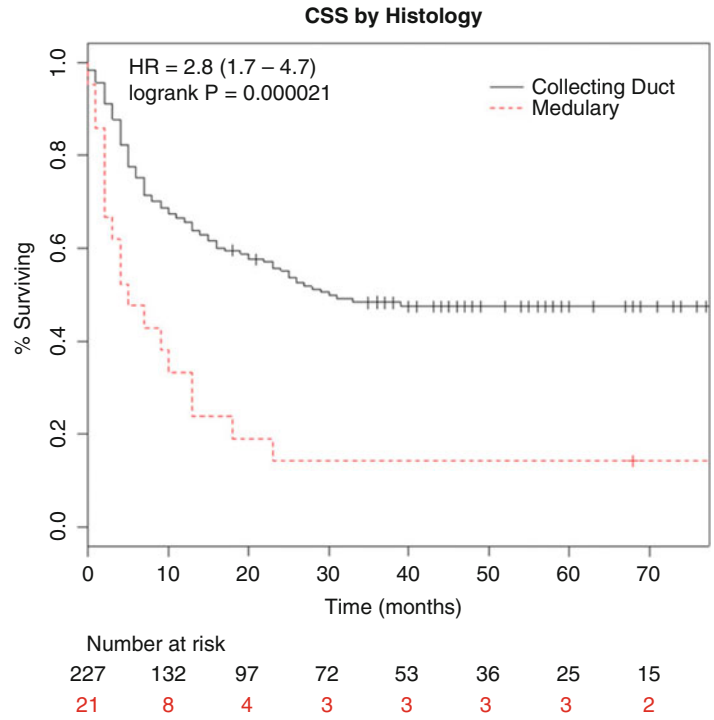

Fig. 8.1 Cancer-specific survival among patients diagnosed with CDC or RMC as reported by Abern et al. The *x*-axis represents the proportion of patients surviving and the *y*-axis represents time in months. Patients with RMC had nearly three times the hazard of dying compared to CDC patients [3]. *CSS* cancer-specific survival (permission granted by Elsevier. Abern et al. [3])

Table 8.1 Distinguishing clinical features in collecting duct carcinoma versus renal medullary carcinoma

Feature	Collecting duct carcinoma	Renal medullary carcinoma
Average age	63 years	19 years
Race		
Caucasian	71 %	5 %
African American	23 %	90 %
Association with sickle cell hemoglobinopathy	No	Yes
Metastatic at presentation	28 %	71 %
Median survival	30 months	5 months

[13]. Areas of geographic tumor necrosis and microscopic angiolymphatic invasion are also frequently present.

Dysplasia of the adjacent renal tubular epithelium is another feature of CDC that can be helpful in making the diagnosis (Fig. 8.7), but can also occasionally be seen in urothelial carcinomas of the renal pelvis and in renal tubules adja-

Fig. 8.2 Grossly, collecting duct carcinomas are firm, white-grey tumors with ill-defined, infiltrative borders, often with multinodularity. Note the separate tumor nodules in the hilar fat

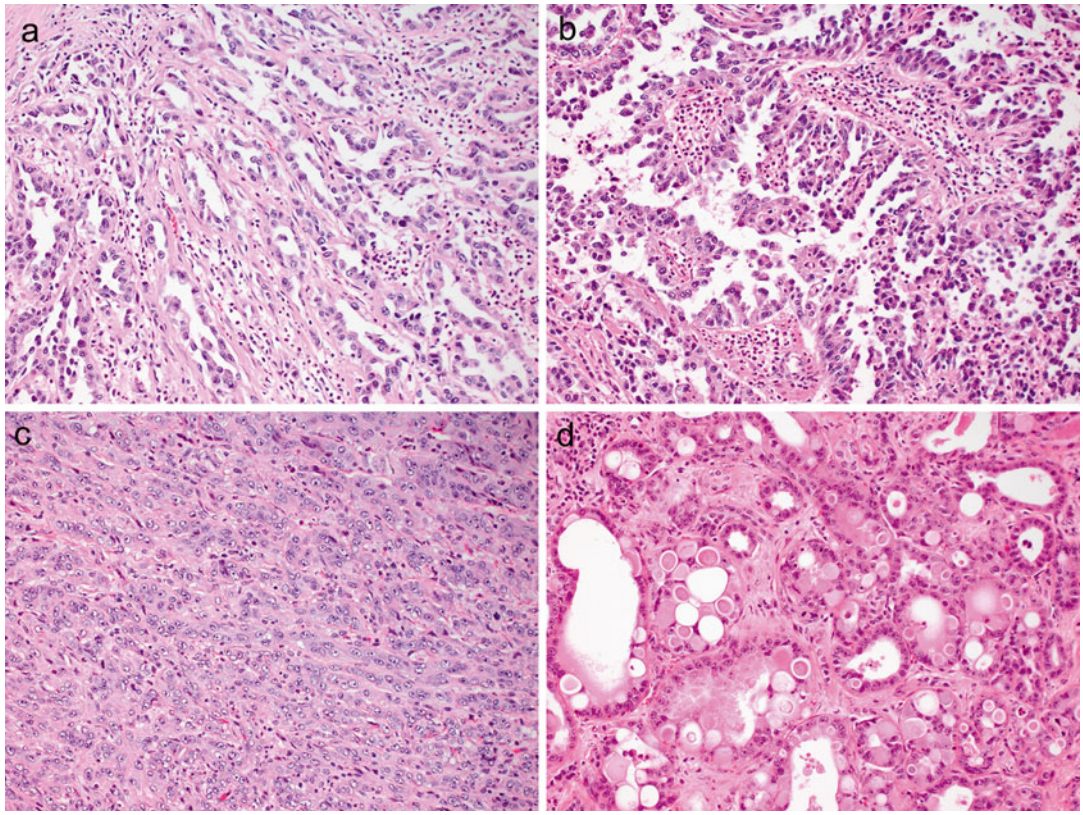

Fig. 8.3 Histologically, collecting duct carcinomas commonly show tubular (**a**) or tubulopapillary architecture with other admixed patterns, including papillary with true fibrovascular cores (**b**), solid cords and sheets (**c**), and cribriform (**d**)

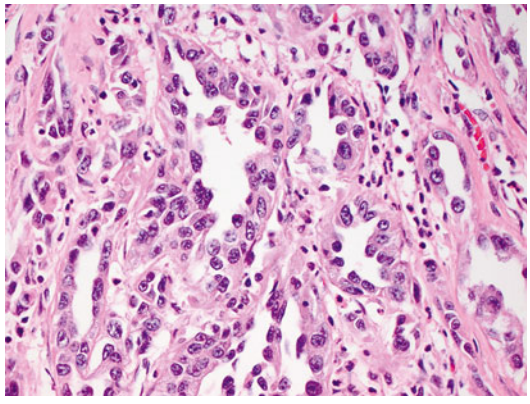

Fig. 8.4 High-grade cytologic features in collecting duct carcinoma, including high nuclear to cytoplasmic ratio, nuclear enlargement and irregularity, pleomorphism, and prominent nucleoli

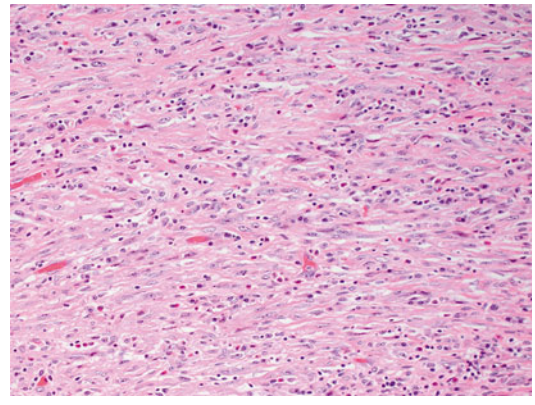

Fig. 8.5 Sarcomatoid differentiation as evidenced by high-grade, malignant spindle cells can also be seen in collecting duct carcinoma

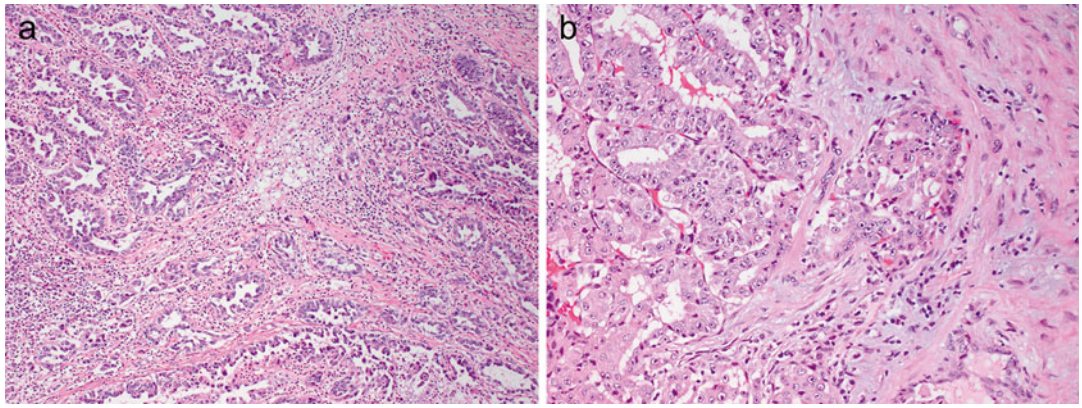

Fig. 8.6 Pronounced desmoplastic stromal response in collecting duct carcinoma, which can be dense and fibrosclerotic (**a**) to myxoid (**b**). Associated lymphocytic inflammatory infiltrates are also present

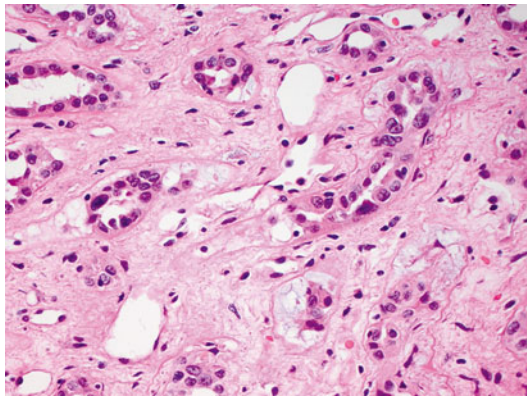

Fig. 8.7 Dysplastic tubules in areas adjacent to a collecting duct carcinoma can be a helpful diagnostic feature

cent to other types of RCC [7, 14]. Other more typical RCC patterns, urothelial carcinoma, or urothelial carcinoma in situ of the renal pelvis should not be present and would exclude the diagnosis of CDC [7].

Recently, the International Society of Urological Pathology (ISUP) has recommended the following histologic criteria for the diagnosis of CDC: (1) at least some of the lesion involves the medullary region; (2) there is a predominant formation of tubules; (3) a desmoplastic stromal reaction should be present; (4) cytologic features are high grade; (5) growth pattern is infiltrative; and (6) there is an absence of other typical RCC subtypes or urothelial carcinoma [15]. Because CDCs are by definition high-grade tumors, it has also been recommended that CDCs should not be assigned a grade (i.e., Fuhrman grade).

Immunohistochemistry

The immunohistochemical profile of CDC is reflective of the tumor's origin from the cells of the collecting ducts in the renal medulla. Tumors are usually positive with lectins such as *Ulex europaeus* agglutinin-1 (UEA1) and peanut lectin. CDCs are also generally positive for low molecular weight cytokeratin (LMWCK), epithelial membrane antigen (EMA), PAX8, c-KIT/CD117, and vimentin, and a smaller number are positive for high molecular weight cytokeratin (HMWCK), CK7, CK20, and PAX2 [13, 16, 17]. In contrast, markers typically positive in proximal renal tubules such as CD10, alpha-methylacyl-CoA racemase (AMACR), and RCC antigen are negative [18], as is p63, a commonly used marker of urothelial differentiation [17].

In contrast to RMCs, which show complete loss of staining for INI1 by immunohistochemistry (discussed below), only 15 % (3 of 20 cases) of CDC showed complete loss of INI1 staining in one study, and only 5 % (1 of 22 cases) in another study [19, 20]. Loss of INI1 staining in CDC does not portend a worse clinical outcome [19].

Cytogenetic and Molecular Findings

There are only limited data on the cytogenetic abnormalities seen in CDC, with no consistent genetic abnormality being identified to date. By conventional cytogenetics, CDCs show complex karyotypes with numerical and structural abnormalities involving multiple chromosomes [21–24]. More common abnormalities include loss of chromosomes 1, 13, 14, and 22. Loss of heterozygosity of 1q, 6p, 8p, 13q, and 21q by microsatellite analysis has also been reported in CDC [25, 26], while the characteristic loss of chromosome 3p commonly seen in clear cell RCC is not seen in CDC. Her2neu amplification was seen in about 50 % of CDC in a small series of cases [27].

Differential Diagnosis

The histologic differential diagnosis of CDC includes invasive urothelial carcinoma, papillary RCC, metastatic adenocarcinoma, unclassified RCC, and renal medullary carcinoma (summarized in Tables 8.2 and 8.3).

Urothelial carcinoma involving the renal pelvis can be challenging to differentiate from CDC, especially if glandular differentiation and invasion of the renal parenchyma with desmoplasia are present. Identification of an associated urothelial papillary surface component, urothelial carcinoma in situ (CIS), squamous differentiation, or a predominance of other more typical patterns of urothelial carcinoma such as nested growth would essentially exclude the diagnosis of CDC [13, 18]. Immunohistochemistry can be helpful in this distinction, with PAX8 positivity seen in virtually all CDCs and only in 9 % of upper tract urothelial carcinomas [17]. Additionally, p63 positivity is seen in almost all upper tract urothelial carcinomas and in 14 % of CDCs. Further, when these two markers are interpreted together, the PAX8+/p63− profile gives a 100 % positive predictive value for CDC, and the PAX8−/p63+ profile gives a 100 % positive predictive value for urothelial carcinoma [17]. It should be noted that CK20 can be positive in a small number of CDC [13] and UEA1 is positive in both CDC and urothelial carcinoma [16]. Distinguishing between these two tumors has significant clinical implications, since CDC generally has an unfavorable prognosis, and patients with urothelial carcinoma generally require further evaluation of their urinary tract for additional urothelial lesions.

Papillary RCC may mimic CDC because of its predominant papillary or tubulopapillary architecture, especially if it is of high grade (papillary RCC, type 2). However, papillary RCCs are usually well circumscribed and encapsulated, in contrast to CDCs, which are grossly and histologically infiltrative. Papillary RCC also does not exhibit the desmoplastic stroma and angulated tubules of CDC. Immunohistochemistry can also distinguish between these two entities, as papillary RCC is usually positive for CD10, RCC antigen, and AMACR, while CDC is usually negative for these markers.

Metastatic adenocarcinoma, most commonly of colorectal or lung origin, is an important consideration in the differential diagnosis of CDC, as it also displays a marked desmoplastic stromal reaction. Generally, metastatic lesions tend to be multifocal, small, and relatively circumscribed. A previous history of malignancy would obviously be helpful in this distinction and could guide the selection of lineage-specific immunohistochemical markers such as TTF-1 and CDX2 to prove the metastatic nature of these lesions.

If a tumor of renal origin with infiltrative growth and desmoplasia is proven not to be urothelial or metastatic carcinoma and shows an absence of angulated glands with high-grade nuclear cytologic features, the diagnosis of unclassified RCC should be made [13]. Generally, these high-grade unclassified carcinomas are predominated by sheetlike, nested, and solid patterns. However, if there is any component of the tumor that meets the ISUP criteria for CDC (see above), it is recommended that the diagnosis should be “poorly differentiated CDC” and not “unclassified RCC” [15].

Renal medullary carcinoma shows overlapping histologic features with CDC and is considered by some to represent an especially aggressive variant of CDC [7]. However, there are subtle features that can help differentiate between the two (summarized in Table 8.3; also see below for detailed description of RMC). First, CDC typically shows angulated tubules, glands, and tubulopapillary structures, while RMC commonly demonstrates a reticular pattern composed of anastomosing tubules and cords with irregular microcystic spaces. Both

Table 8.2 Features helpful in distinguishing collecting duct carcinoma from other entities in the differential diagnosis

Feature	Collecting duct carcinoma	Urothelial carcinoma	Papillary renal cell carcinoma	Metastatic carcinoma
Circumscription/encapsulation	No	No	Often both	Often circumscribed
Focality	Unifocal	Unifocal	Unifocal	Multifocal
Multinodularity	Often	Sometimes	No	No
Desmoplastic stroma	Yes, prominent	Yes	No	Yes
Other	Associated lymphocytic inflammation	Associated papillary lesion, urothelial CIS	Sometimes foam cells in papillary cores	Clinical history of other malignancies
Immunohistochemistry				
Positive	PAX8, UEA1	p63, UEA1, CK20	PAX8, CD10, RCC, AMACR	Possibly other lineage markers (e.g., TTF1, CDX2)
Negative	p63, CK20 (rare +), CD10, RCC, AMACR	PAX8	UEA1	PAX8, RCC

Table 8.3 Distinguishing histologic features in collecting duct carcinoma versus renal medullary carcinoma

Feature	Collecting duct carcinoma	Renal medullary carcinoma
Dominant histologic pattern	Tubular, tubulopapillary architecture with angulated glands	Reticular composed of tubules, cords, and microcysts; irregular cribriform structures
Inflammatory infiltrate	Predominantly lymphocytic to mixed	Predominantly neutrophilic to mixed
Necrosis	Coagulative, geographic	Microabscess-like foci
Sickled red blood cells in tissue	No	Yes

tumors show desmoplastic stroma with associated inflammatory infiltrates, but the inflammatory infiltrates in CDC are predominantly lymphocytic, in contrast to the neutrophilic to polymorphous infiltrates seen in RMC [13]. Additionally, CDC often shows areas of coagulative necrosis, while RMC will occasionally show distinctive microabscess-like areas of suppurative necrosis. Importantly, RMC clinically affects younger patients with sickle cell hemoglobinopathy who are commonly African American. Immunohistochemistry appears to have a limited role in distinguishing these two tumors since both are consistently positive for vimentin and UEA1 and variably positive for HMWCK, CK7, and PAX2 [13]. RMC consistently shows complete loss of immunohistochemical staining with INI1, but since a minority of CDC also shows this pattern of staining, it appears that INI1 immunohistochemistry cannot reliably distinguish these two tumors [15].

Renal Medullary Carcinoma

Gross Pathology

RMC shows a similar gross appearance to CDC, as these tumors are also white-grey to tan, firm to rubbery, poorly circumscribed with infiltrative borders, and centered in the renal medulla with variable hemorrhage and necrosis. There are often satellite nodules in the adjacent renal parenchyma corresponding to areas of lymphovascular invasion in large caliber vessels, as well as diffuse infiltration into the renal parenchyma, perinephric fat, or renal hilum [1, 7]. Tumors average 7 cm in diameter and can range from 4 to 18 cm [1, 28, 29]. Interestingly, RMC occurs more commonly in the right kidney (>75 %), but the reason for this is unclear [1, 18].

Microscopic Pathology

The most distinct and consistent histologic growth pattern seen in RMC is a reticular pattern formed

by anastomosing tubules and cords with irregular microcystic spaces, imparting a resemblance to testicular yolk sac tumor (Fig. 8.8) [1, 13]. Often there is an admixture of architectural growth patterns including infiltrating cords, solid sheets, trabeculae, cribriform structures, and papillary with true fibrovascular cores [13]. Compact cribriform structures with rigid round spaces simulating adenoid cystic carcinoma can also be present. Tumor cells have moderate to abundant eosinophilic cytoplasm and high-grade nuclear features with prominent nucleoli. Areas demonstrating rhabdoid and sarcomatoid features may be present focally. Intracytoplasmic or intraluminal mucin is seen in a majority of cases.

A prominent desmoplastic stromal reaction is also a characteristic and tends to have a myxoid, edematous, hypocellular, loose, basophilic appearance. Focal areas with dense, eosinophilic, collagenous desmoplastic stroma are usually also appreciated. The associated inflammatory infiltrate can be quite striking and ranges from predominantly neutrophilic to polymorphous, including a mixture of neutrophils, lymphocytes, and eosinophils [7, 13]. Geographic and microabscess-like areas of necrosis can be seen.

As RMC almost invariably occurs in patients with sickle cell hemoglobinopathy, most commonly sickle cell trait, sickled red blood cells are frequently seen, both in the main tumor and within capillaries in the adjacent renal parenchyma (Fig. 8.9). In addition, the red blood cells may appear clustered or agglutinated within capillaries [14].

Immunohistochemistry

By immunohistochemistry, RMC is consistently positive for cytokeratin AE1/AE3, LMWCK, EMA, vimentin, cytokeratin 7, CEA, and PAX8 [9, 13, 28–31]. Tumors also show variable positivity with HMWCK, cytokeratin 20, UEA-1, OCT3/4, and PAX2.

Complete loss of INI1/SMARCB1 expression in RMC by immunohistochemistry was first reported in 5 cases by Cheng et al. and has now been confirmed in 13 additional cases of RMC [20, 30] (details and significance discussed below). In RMC, INI1 is completely negative in tumor cells, while moderate to strong staining is present in inflammatory, stromal, and adjacent nonneoplastic collecting duct epithelial cells. Although this pattern of INI1 staining is not necessarily associated with rhabdoid cytologic features in RMC, most urothelial carcinomas and RCC are positive for immunohistochemical expression for INI1 even when rhabdoid features are present [31]. As mentioned above, a minority of CDC cases also show complete loss of INI1 expression. Thus, INI1 immunohistochemistry can be useful in distinguishing RMC from urothelial carcinomas and other RCCs, but is of more limited value in distinguishing RMC from CDC [15].

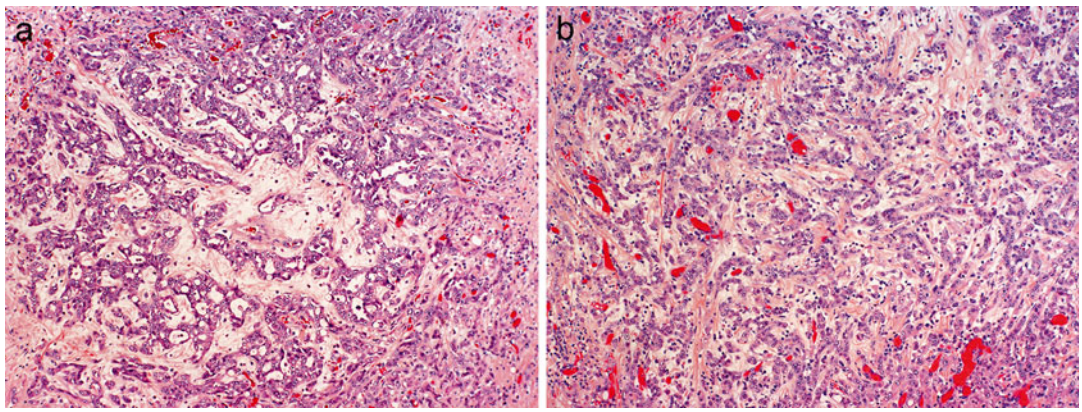

Fig. 8.8 Histologic patterns in renal medullary carcinoma include reticular with anastomosing cords, tubules, and microcystic spaces (**a**), infiltrating cords (**b**), solid nests, and cribriform. Note associated hypocellular, hyalinized desmoplastic stroma (photos provided by Dr. Liang Cheng, Indiana University)

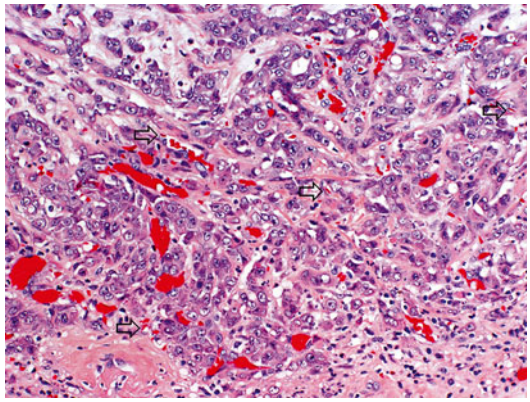

Fig. 8.9 Sickled red blood cells (*arrows*) are seen in capillaries of renal medullary carcinoma, as well as clusters of agglutinated red blood cells (photo provided by Dr. Liang Cheng, Indiana University)

Cytogenetic and Molecular Findings

A small number of RMCs have been studied by conventional cytogenetics, which have generally shown complex karyotypes with a variety of insertions, deletions, and/or balanced translocations, but no recurrent genetic abnormalities have been identified [8]. Of note, one case showed the presence of a t(9;22) bcr-abl translocation, which was confirmed by fluorescence in situ hybridization (FISH) [32], and a subsequent study demonstrated *ABL* amplification in three tumors by FISH, but no bcr-abl translocation [5]. Comparative genomic hybridization analysis has shown an overall lack of genetic gains and losses in RMC, with only one case demonstrating loss of chromosome 22 [29].

Based on the results of immunohistochemistry studies, it has been suggested that TP53, hypoxia inducible factor (HIF), and vascular endothelial growth factor (VEGF) may play a role in the pathogenesis of RMC [29]. Molecular analysis of two RMC cases occurring in Caucasian patients without hemoglobinopathy has shown mutations in *fumarate hydratase* and *von Hippel-Lindau* (*VHL*) genes [8]. These findings suggest that a common underlying hypoxic cellular environment, either due to sickle cell trait/disease or mutations affecting hypoxia-sensing pathways, may subsequently lead to activation of HIF pathways and contribute to the development of RMC.

Two small studies have demonstrated that topoisomerase II alpha (TopoII), a nuclear enzyme involved in cell cycle progression and DNA repair, is overexpressed in RMC based on immunohistochemistry and whole-genome microarray analysis [33, 34]. However, there was no evidence of TopoII gene amplification by FISH, suggesting that some other mechanisms such as transcriptional or posttranslational modification are responsible for this overexpression [34].

Most recently, absence of INI1 (known also as SMARCB1) expression has been reported in all tested cases of RMC. *INI1* is a tumor suppressor gene located on 22q11.23 that encodes a component of the SWI/SNF complex, which regulates transcription of target genes in an ATP-dependent manner. Loss of INI1 expression is seen in tumors with rhabdoid histology, such as pediatric renal and extrarenal malignant rhabdoid tumors and atypical teratoid/rhabdoid tumors of the central nervous system, and is now also reported in RMC. In addition to complete absence of INI1 expression by immunohistochemistry (described above), hemizygous *INI1* gene deletions detected by comparative genomic hybridization [20] and loss of heterozygosity of INI1 with polymerase chain reaction-based microsatellite analysis [30] have been documented in RMC, suggesting that inactivation of the *INI1* gene may have an important role in RMC pathogenesis. Interestingly, the presence or absence of rhabdoid histology in RMC does not appear to influence the pattern of INI1 staining, as both areas with rhabdoid and non-rhabdoid histology are negative for INI1 [31].

Differential Diagnosis

The histologic differential diagnosis for RMC includes invasive urothelial carcinoma and CDC. Since RMC is known to occur in a specific patient population (young African American patients with sickle cell trait), clinical information such as age, race, and hemoglobinopathy status are invaluable; sickle cell trait is not known to be associated with either urothelial carcinoma or CDC. In the absence of relevant clinical information, identification of some histologic features may distinguish RMC from other entities. As discussed previously, findings that would support the diagnosis of urothelial carcinoma include identification of a papillary urothelial lesion

involving the renal pelvis, urothelial CIS, or other more conventional growth patterns of urothelial carcinoma. The differential between RMC and CDC is discussed above and summarized in Table 8.3.

Clinical Management of Patients with Collecting Duct and Renal Medullary Carcinoma

Due the relative rarity of CDC and RMC, most of the data related to treatment are limited to small case series and case reports. Furthermore, most series are retrospective in nature, and strong conclusions related to survival associated with various treatments are limited by selection bias. In the next section, we will review the treatment options for patients with tumors having these two histology types.

Collecting Duct Carcinoma

Surgical Management

As described above, CDC typically presents in an advanced stage, with nodal involvement and metastatic spread present at the time of diagnosis. Nevertheless, most patients with CDC undergo surgical excision of the primary tumor (either by radical or partial nephrectomy) [3, 6, 35, 36]. In rare cases when a CDC is localized to the kidney, radical nephrectomy alone may result in cure [37]. Also, individual case reports indicate that CDC patients with localized T1 tumors can be treated with partial nephrectomy and have a prolonged cancer-specific and overall survival [38–40]. However, compared to clear cell RCC, patients with more advanced, locoregional CDC (i.e., T3a or better) treated with surgery still have over twice the risk of cancer-specific mortality [3].

There is also a paucity of data regarding performance of lymphadenectomy at the time of nephrectomy for patients with CDC. For patients with clear cell RCC, a randomized trial did not show a survival benefit associated with performance of extended lymphadenectomy [41]. Although a recent study using SEER registry data suggested a survival benefit associated with more extensive lymphadenectomy for node-positive kidney cancer patients [42], others have raised concerns that these results suffer from biases related to imputation of missing data [43]. In general, excision of enlarged lymph nodes (on radiographic imaging) would be recommended, with the decision to perform a more extended dissection left to the discretion of the surgeon.

As many patients with collecting duct carcinoma present with metastatic disease, it would be helpful to know whether cytoreductive nephrectomy (i.e., radical nephrectomy in the setting of metastases) would be beneficial for patients with CDC. Unfortunately, the data remain mixed and limited to small case series. One large retrospective series found the patients with metastatic CDC had longer cancer-specific survival when treated with cytoreductive radical nephrectomy, compared to those patients not undergoing radical nephrectomy (with or without retroperitoneal lymphadenectomy) [3]. This series suffers from possible surgical selection bias. In general, among patients with metastatic RCC and tumors amenable to nephron sparing surgery, SEER registry data suggests a survival advantage associated with treatment with partial nephrectomy [44]. However, again as with any retrospective study, these results are subject to selection bias and only included 19 patients with CDC [44]. On the other hand, at a population level, surgical removal of the primary tumor had no effect on survival among patients with metastatic CDC [6]. In addition, another series demonstrated extremely poor prognosis among five patients with metastatic CDC treated with radical nephrectomy, with 60 % of the patients experiencing death in the immediate postoperative period [45].

Systemic Therapy

Cytotoxic Chemotherapy

Metastatic CDC is typically resistant to systemic cytotoxic chemotherapy. The largest series of Japanese CDC patients showed that among 17 patients who received chemotherapy, only one patient showed a partial response to gemcitabine and carboplatin [4]. Motzer et al. reported one partial response to gemcitabine

and cisplatin among 30 patients receiving systemic chemotherapy or novel agents on a clinical trial [35]. In 2007, results from a phase II trial assessing use of gemcitabine plus a platinum-based agent (carboplatin or cisplatin) were published; they reported a 26 % response rate with a median progression-free survival of 7.1 months [46]. A number of case reports exist that describe responses to other cytotoxic agents, including salvage paclitaxel [47] or combination of paclitaxel and carboplatin [48].

Immunotherapy

Based on evidence from clinical trials, interleukin-2 (IL-2) [49] and interferon-alpha (IFN-α) [50] can have a role in metastatic clear cell RCC. However, the activity of these agents in treating metastatic CDC has not been studied extensively. In the series reported by Motzer et al., none of the 15 patients with CDC who were treated with cytokine therapy had a clinical response [35]. Furthermore, none of the 34 CDC patients in the large Japanese series had a clinical response to either IFN-α or IL-2 treatments [4]. Evidence of clinical efficacy of cytokine therapy for this disease is limited to a solitary case report of a CDC patient responding to IL-2 therapy [51].

Targeted Therapy

After phase III trials confirmed their efficacy in improving progression-free survival, a number of "targeted therapies" have been approved for the treatment of metastatic clear cell RCC, including sunitinib [52], sorafenib [53], temsirolimus [54], everolimus [55], and pazopanib [56]. However, the use of these therapies has been limited to subgroups in phase II trials or individual case reports. Within a phase II trial looking at the efficacy of sunitinib among advanced non-clear cell RCC patients, there were six patients with CDC. None of these patients had an objective response to sunitinib therapy and the median progression-free survival was just over 3 months [57]. A case series of two CDC patients who had progression after surgery and gemcitabine/cisplatin chemotherapy reported no objective response to additional sunitinib therapy [58]. However, there is one case report describing a partial response to sunitinib therapy in a CDC patient with lung and skeletal metastases [59]. Ansari et al. reported a single case of a partial response to sorafenib therapy for a patient with metastatic CDC with a durable 13-month progression-free survival [60]. Among metastatic RCC patients treated with everolimus, two patients with CDC did not exhibit a response with treatment [61]. Another case series of seven patients with metastatic CDC showed that two patients were able to have stable disease with either sequential sorafenib followed by sunitinib (for 49 months) or temsirolimus followed by sunitinib (for 19 months) [62]. Another case series did not observe any radiographic treatment response among four CDC patients treated with mTOR inhibitors [63]. Overall the quantity and quality of data limit any overall conclusion in regard to the effectiveness of any systemic therapy for this subtype.

Renal MedullaryCarcinoma

As with CDC, patients with RMC harbor an abysmal prognosis in general. Furthermore, the rarity of the disease makes it difficult to assess optimal treatment for patients with this malignancy. The two largest case series include nine patients treated in the United States, reported by Hakimi et al. [64], and seven patients treated in Brazil, described by Watanabe et al. [9]. Seven and four patients in each series underwent radical nephrectomy. Another multicenter series reported outcomes from six patients in the United States; five of six patients were treated with radical nephrectomy and overall survival ranged from 1 to 7 months [65].

A number of chemotherapy regimens have been reported in the literature, with typically poor responses. The longest reported survival after diagnosis was 24 months; this was seen in an 11-year-old who had a complete response with carboplatin, gemcitabine, and paclitaxel [66]. Another series described the use of high-dose-intensity methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) in three patients, where all three patients had partial responses and overall survival ranged from 3.5 to 16 months [67]. Outcomes from selected case reports and series are summarized in Table 8.4.

Table 8.4 Select case reports and series of patients with medullary renal carcinoma

Patient	Treatment received	Chemotherapy regimen	Objective response	Survival (months)	Reference
13 y/o F	Chemotherapy	5-FU	No	1	[68]
23 y/o M	Radical nephrectomy, radiation, chemotherapy	Vincristine + actinomycin-D; salvage doxorubicin	No	17	[69]
26 y/o F	Radical nephrectomy	None	N/A	1.7	[69]
35 y/o M	Radical nephrectomy, chemotherapy, IFN-a and IL-2	5-FU	No	4	[69]
12 y/o M	Radical nephrectomy, chemotherapy	MVAC; salvage ifosfamide, etoposide, carboplatin, topotecan	No	15	[70]
18 y/o F	Chemotherapy	MVAC	Partial	1	[71]
14 y/o M	Radical nephrectomy, chemotherapy	MVAC; salvage etoposide, carboplatin	Complete	11.5	[32]
28 y/o M	Radical nephrectomy	None	N/A	2	[72]
31 y/o F	Radical nephrectomy, chemotherapy	MVAC	No	3	[72]
21 y/o F	Radical nephrectomy, chemotherapy, bortezomib	Gemcitabine, cisplatin	Partial	6	[73]
20 y/o M	Radical nephrectomy, chemotherapy	NR	No	10	[73]
15 y/o F	Chemotherapy	Etoposide; cisplatin, gemcitabine, paclitaxel; salvage MVAC	Partial	10	[74]
17 y/o M	Radical nephrectomy, chemotherapy, radiation	Carboplatin, gemcitabine, paclitaxel	Complete	12	[74]
25 y/o M	Radical nephrectomy, chemotherapy	MVAC	NR	4	[9]
11 y/o M	Radical nephrectomy, chemotherapy	Etoposide, doxorubicin, cyclophosphamide, vincristine	NR	9	[9]
19 y/o M	Chemotherapy	Gemcitabine, cisplatin, radiation	NR	6	[9]
8 y/o M	Radical nephrectomy	None	N/A	72	[9]
17 y/o M	Radical nephrectomy, chemotherapy	High-dose-intensity MVAC	Partial	12	[67]
30 y/o M	Chemotherapy	High-dose-intensity MVAC	Partial	3.5	[67]
48 y/o F	Radical nephrectomy, chemotherapy, sunitinib	High-dose-intensity MVAC	Partial	At least 16	[67]
11 y/o M	Radical nephrectomy, chemotherapy	Carboplatin, paclitaxel, gemcitabine	Complete	24	[66]

MVAC methotrexate-vinblastine-doxorubicin-cisplatin, *N/A* not applicable, *NR* no response

Overall, it is clear that a diagnosis of either CDC or RMC imparts a poor prognosis. Although individual case reports demonstrate occasional success stories with multimodality treatment, it is clear that improvements in survival for these patient populations will require continued translational research and enrollment in clinical trials.

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