Rhabdoid morphology in renal cell carcinoma (RCC) resembling malignant rhabdoid tumor of kidney (MRTK) was first described in 1991, but this phenomenon should be strictly distinguished from MRTK and extrarenal malignant rhabdoid tumors because the prognosis and therapeutic strategies differ significantly [1]. Recently, rhabdoid change in RCC has been proposed to constitute a type of dedifferentiation, and as with sarcomatoid change it is associated with poor prognosis [2-8]. In this article, we review RCC with rhabdoid features with special reference to clinical and pathobiological aspects.

Introduction

Rhabdoid morphology in renal cell carcinoma (RCC) may, like sarcomatoid change, be perceived as a type of dedifferentiation, and is a poor prognostic factor. Histologically, rhabdoid neoplastic cells are round to polygonal cells with globular eosinophilic cytoplasmic inclusions and eccentric vesicular nuclei and enlarged nucleoli. All types of RCC, including clear cell, papillary, chromophobe, collecting duct carcinoma, renal medullary carcinoma, acquired cystic disease-associated RCC, ALK-positive renal cancer and unclassified RCC, may display a variably prominent rhabdoid phenotype. Immunohistochemically, the cytoplasm of rhabdoid cells shows positivity for vimentin and/or cytokeratin. Ultrastructurally, cytoplasmic whorls/aggregates of intermediate filaments correspond to light microscopically observed inclusions. Genetically, a previous report suggests that combined loss of \textit{BAP1} and \textit{PBRM1} may be associated with rhabdoid morphology. As with sarcomatoid change, pathologists should describe, estimate and state the proportion of tumor cells with a rhabdoid phenotype in the routine pathology report of RCC.

Key words: rhabdoid features, renal cell carcinoma, poor prognosis.
Epidemiology

The incidence of rhabdoid change in RCC has been estimated to be between 3% and 7% [6]. The age range of patients with RCC with rhabdoid features is between the third and eighth decade with a mean age of 52 to 63 years [2-6]. The male-to-female ratio is 2 : 1 [5, 6].

Clinical features

Patients with RCC with rhabdoid features frequently present with an abdominal mass, hematuria, flank or abdominal pain and nausea [2, 4, 5, 9-12]. However, some primary as well as metastatic lesions may be incidentally discovered on radiological examinations [4, 5, 13, 14].

Imaging findings

Reported imaging features are non-specific and consist of a complex hypervascular mass on ultrasonographic examination [9]. On computed tomography (CT) examinations, a heterogeneous, irregular mass which may invade the surrounding tissue is encountered [9, 11]. Contrast enhancement on CT is frequently observed [4]. In some tumors, lymphadenopathy may be radiologically detected [9, 10, 13].

Pathological findings

Macroscopic findings

The size of the tumor ranges from 4 to 15 cm with a mean size of 9 cm [5]. The cut surface varies; it may be homogeneously white and firm [5], but areas of hemorrhage or necrosis are often seen [4, 10, 11, 13].

Microscopic findings

Rhabdoid cells are round to polygonal with globular eosinophilic cytoplasmic inclusions and eccentric pleomorphic vesicular nuclei and large nucleoli (Fig. 1A, B) [1-7]. The architectural patterns include solid, organoid or sheet-like, and neoplastic cells exhibit a variable degree of discohesion [6, 7]. Renal cell carcinoma with rhabdoid features also demonstrate sarcomatoid change in up to 22% of cases [2, 4, 6, 7]. The proportion of rhabdoid cells ranges from 5% to 90% of total tumor volume [3, 5, 6]. The underlying types of carcinoma include clear cell RCC, papillary RCC, chromophobe RCC, collecting duct carcinoma, renal medullary carcinoma, acquired cystic disease-associated RCC, ALK-positive renal cancer and unclassified RCC [1-23]. The most common histological type of RCC with rhabdoid change is clear cell RCC and up to 35% of Fuhrman grade 4 clear cell RCCs displays rhabdoid features [2-7]. Rhabdoid morphology can be seen in 9.8% of cases with clear cell RCC consisting of all grades [24]. One case of hereditary leiomyomatosis and RCC with sarcomatoid change and rhabdoid features has been described [25]. If the tumor consists of only rhabdoid neoplastic cells, pathologists should designate such a tumor as “unclassified carcinoma with a rhabdoid component” [6]. Rhabdoid features in clear cell RCC are the most frequent histology among the metastatic clear cell RCC with non-clear cell morphology [26].

Immunohistochemical findings

Rhabdoid cells are generally positive for vimentin (Fig. 2A), epithelial membrane antigen and cytokeratins [2-6, 27]. PAX8 may be expressed in these cells [10]. No myogenic markers including desmin, myoglobin, myogenin and Myo D1 are expressed by the rhabdoid cells [2, 3]. The proliferative (Ki-67

Fig. 1. Microscopic findings. A) The tumor consists of discohesive cells with eosinophilic cytoplasm and eccentric nuclei, namely rhabdoid cells. B) In high magnification of rhabdoid cells, enlarged vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm are observed.
Renal cell carcinoma with rhabdoid features

Renal cell carcinoma with rhabdoid features

index is generally higher in rhabdoid cells, compared to non-rhabdoid tumor [3, 5, 28]. Overexpression of p53 is often observed [4]. The expression of integrase interactor 1 (INI1) is generally retained (Fig. 2B). However, loss of nuclear expression of INI1 is commonly observed in rhabdoid cells of renal medullary carcinoma [6, 17, 29]. It has been suggested that loss of Brahma (BRM) expression may be involved in the dedifferentiation of clear cell RCC exhibiting anaplastic or rhabdoid morphology [30].

Ultrastructural findings

Rhabdoid neoplastic cells ultrastructurally contain paranuclear whorls/aggregates of intermediate filaments [2, 3, 5, 6]. These whorls/aggregates of cytoskeletal intermediate filaments correspond to the cytoplasmic inclusions featuring immunohistochemical positivity for vimentin and/or cytokeratins [2, 3]. In addition, paranuclear condensation of cytoplasmic organelles with peripheral vacuolization may be observed [2].

Molecular genetic findings

Spectral karyotype analysis of primary cell culture of clear cell RCC established from skin metastasis showed hypertriploid karyotype: <3n>, –Y, +2, +der(3)t(3;5), der(5)t(5;6)x2, del(6p)x2, +6, +7x2, +iso(8)(q10)x2, +8, –9, +12, –13, –14, –15, +17, +der(19)t(19;20), +20x2, der(22)t(1;22) [31]. The G-band karyotype of ACD-associated RCC with sarcomatoid change and rhabdoid features showed the following changes: 46, X, +X, –Y[1]/43, idem, add(2)(q31), –6, –9, –14, –15, +16, –22, +mar1[6]/46, XY[2]/abnormal cell [11, 18]. These results suggest that the candidate tumor suppressor genes involving dedifferentiation in RCC such as sarcomatoid differentiation or rhabdoid change may be located on chromosomes 9, 14 and 15 [18, 51]. In RCC with rhabdoid features, the same genetic alterations including chromosome 3p loss and VHL gene mutation were observed in both clear cell RCC and rhabdoid components [21]. In chromophobe RCC with rhabdoid features, loss of heterozygosity of chromosomes 2, 10q, 13q and 17p in both chromophobe RCC and rhabdoid components was reported [22]. These results strongly suggest that both the RCC component and rhabdoid component are clonally related, i.e. have an identical clonal origin [21, 22]. Combined loss of BAP1 and PBRM1 may be associated with rhabdoid morphology, but not all tumors with rhabdoid change have shown coexistent loss of BAP1 and PBRM1 [32].

Differential diagnosis

Urologists, radiologists and pathologists should discriminate RCC with rhabdoid features from MRTK, renal synovial sarcoma, PNET/Ewing sarcoma, angiosarcoma, renal epithelioid angiomyolipoma, malignant lymphoma, Wilms’ tumor, congenital mesoblastic nephroma (CMN), renal oncocyoma, renal hemangioblastoma, malignant mixed epithelial and stromal tumor, direct invasion of urothelial carcinoma of the renal pelvis with rhabdoid features, metastasis from malignant rhabdoid tumor of central nervous system (MRT-CNS), metastasis from pleomorphic rhabdomyosarcoma and metastasis from epithelioid sarcoma, proximal type. In these settings, the identification of a non-rhabdoid component is crucial and may require extensive sampling. MRTK can occur in adult cases [33-35]. Loss of INI1 expression supports the diagnosis of MRTK [17, 29, 35]. Renal poorly differentiated synovial sarcoma may show rhabdoid phenotype [36]. The identification of either of the fusion transcripts SYT-SSX1 or SYT-SSX2 is of paramount importance in establishing the definite diagnosis. PNET/Ewing sarcoma may also contain rhabdoid morphology that displays rosette formation, and strong and diffuse immunoreactivity for CD99 and FLI-1 as well as the detection of chimeric transcripts such as EWS-FLI-1 or EWS-
ERG will aid in making the correct diagnosis [1, 37]. Epithelioid angiosarcoma may occur as a primary tumor in the kidney and it may demonstrate rhabdoid morphology and CD10 positivity. The identification of primitive vascular lumens and the positivity to CD31, CD34, factor VIII and FLI-1 support the diagnosis of epithelioid angiosarcoma [38]. A subset of renal epithelioid angiomyolipoma may show rhabdoid features, and in such cases the immunohistochemistry of alpha smooth muscle actin, melanosomes (HMB45) and melan A is helpful [39]. In RCC with extensive rhabdoid differentiation and prominent cellular discohesion, high-grade/aggressive lymphoid neoplasms may enter the differential diagnosis. Malignant lymphomas most commonly completely lack cell cohesion and infiltrating sclerosis, and in most cases display limited amounts of cytoplasm and react positively to leukocyte common antigen [1]. Wilms’ tumor may exhibit rhabdomyoblastic differentiation, but the age of patients, the presence of blastemal cells and positivity for myogenic markers are helpful diagnostic clues [1, 40]. In the distinction from CMN, the age of patients within 3 years after birth and the identification of ETV6-NTRK3 fusion are important [1, 41]. Renal oncocytoma macroscopically shows mahogany-brown color and microscopically demonstrates a nesting pattern on the background of edematous or hyalinized stroma [1, 42, 43]. Sporadic renal hemangioblastoma consist of nests of polygonal cells and an abundant capillary network. Immunohistochemical detection of inhibin-alpha and S-100 protein may be helpful [44]. Malignant mixed epithelial and stromal tumor may exhibit rhabdoid morphology. In such a situation, the identification of an epithelial component and ovarian-like stroma is vital [45]. High-grade urothelial carcinoma may rarely impart rhabdoid phenotype [46-48]. Identification of urothelial carcinoma in situ and immunohistochemical positivity for cytokeratin 5/6, cytokeratin 20, p63, GATA3 and uroplakin II will assist in reaching an accurate diagnosis [49, 50]. In patients with metastasis from MRT-CNS, the clinical information (of presence of brain tumor) and the loss of INI1 immunorexpression are crucial pieces of information [29]. Pleomorphic rhabdomyosarcoma can express CD10 and CA9 [51]. In this situation, the application of myogenic markers in the immunohistochemical study is of major diagnostic significance. Epithelioid sarcoma imparts a vaguely granulomatous appearance and central necrosis. Additionally, the loss of INI1 protein occurs in epithelioid sarcoma.

Therapy

For the treatment of primary cancer, radical nephrectomy is recommended. Some cases responding to tyrosine kinase inhibitors (TKI) (sorafenib and sunitinib) have been reported [9, 52]. Stronger expression of VEGF-A in the rhabdoid component than the clear cell RCC component may suggest a better response to TKI [52]. The increased expression of the angiogenesis-related gene in RCC with sarcomatoid change and rhabdoid features may be related to the resistance of tyrosine kinase inhibitors [31].

Prognosis

Renal cell carcinoma with rhabdoid features generally behaves in an aggressive fashion, causing a rapidly fatal outcome [2-9, 16, 25, 31]. Cancer-specific mortality is 40 to 50%, and the median survival rates are within 8 to 31 months [5, 6]. Metastasis occurs in up to 70% of cases, and distant metastasis can occur in lung, bone, soft tissue, liver, skin, adrenal gland and diaphragm [4-10, 13, 14, 16-18, 25, 31]. Metastases to lymph nodes occur in approximately 20% of cases [7, 10, 16, 18, 25].

Future perspectives

It is evident that rhabdoid phenotype in RCC is associated with aggressive clinical behavior. Therefore, pathologists should describe and state the presence and extent of rhabdoid phenotype in their pathological reports. However, a minimum proportion of rhabdoid features in the total tumor volume is unnecessary for diagnostic purposes. Recently, the expression of p53, AEG-1 and MDM2 may be associated with tumor progression or prognosis [53, 54]. Therefore, it may be interesting to study the expression of p53, AEG-1 and MDM2 in RCC with rhabdoid features. Although combined loss of BAP1 and PBRM1 seems to be closely associated with rhabdoid phenotype, the identification of new candidate tumor suppressor genes which may be located on chromosomes 9, 14 or 16 potentially opens up future targeted therapeutic strategies [18, 31, 32]. The pathological significance of cohesive rhabdoid morphology in RCC with ALK gene rearrangement remains unknown [19]. Accordingly, the accumulation of cases will be necessary in order to clarify the significance of rhabdoid morphology in this category.

The authors declare no conflict of interest.

References

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