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Malignant Rhabdoid Tumor of the Kidney. Histopathology, Ultrastructure and Comments on Differential Diagnosis*/**

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Summary. Clinical and histopathological features of two cases of malignant rhabdoid tumor of the kidney are presented. One of these cases was also studied by electron microscopy. Histologically, both tumors consisted of an admixture of undifferentiated polygonal or elongated cells and cells with abundant eosinophilic cytoplasm frequently containing hyaline globular structures. Ultrastructurally, these cytoplasmic inclusions were composed of large masses of actin-size and intermediate-size filaments. The poor prognosis of this type of tumor is emphasized and histological criteria for differential diagnosis from other malignant renal tumors of childhood and adolescence are discussed.

Key words: Rhabdoid tumor – Histology – Ultrastructure – Prognosis

The term "malignant rhabdoid tumor of the kidney" was coined for a lesion which is predominantly composed of large polygonal cells with ample eosinophilic cytoplasm, strongly reminiscent of rhabdomyoblasts (Haas et al. 1981). This histopathologic appearance had been designated in the First National Wilms' Tumor Study (NWTS I) as "rhabdomyosarcomatoid pattern" of Wilms' tumor (Beckwith and Palmer 1978). Subsequent ultrastructural studies failed to demonstrate features suggestive of rhabdomyoblastic differentiation (Fung et al. 1981; Haas et al. 1981), and the question of the histogenetic relationship of this neoplasm remains unsettled.

The recognition of this rare tumor is important, since it has a worse outcome than typical Wilms' tumor and is frequently associated with brain metastases and second independent tumors of the posterior fossa. Character-

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istically, this type of tumor is found in young children mostly under 2 years of age. In this paper, we present the clinical and histopathological findings in two patients. One of these cases was also studied by electron microscopy and immunocytochemical techniques. Features important for differential diagnosis from other renal tumors will be discussed.

Material and Methods

Among 101 cases of Wilms' tumor or variants of Wilms' tumor from the files of the Department of Pediatric Pathology, Kiel, Federal Republic of Germany, two cases of malignant rhabdoid tumor of the kidney were identified.

The light microscopic investigation was performed on sections from paraffin-embedded tissue stained with hematoxylin-eosin, PAS, Goldner, Giemsa, and reticulin stain (Bielschowsky). Sections from at least three different areas were studied in each case. The tumors were graded using the grading procedures of Lawler et al. (1975) and Beckwith and Palmer (1978).

For immunocytochemical study sections from paraffin-embedded tumor tissue were incubated with anti-lysozyme, α_1-antitrypsin, α_1-antichymotrypsin (Dako, Copenhagen, Denmark), anti-myoglobin (Immulok, Carpinteria, CA, USA) and anti-keratin raised in rabbits (kindly provided by Dr. J. Gerdes, Institute of Pathology, Kiel, Federal Republic of Germany). Staining procedure was performed according to Sternberger et al. (1970).

For ultrastructural study, formalin-fixed tissue from one tumor was post-fixed in 1% osmium-tetroxide for 2 h and embedded in Araldite. Semithin sections were stained with methylene blue and azure II. Thin sections were cut with glassknives, stained with uranyl acetate and lead citrate, and studied in a Siemens 101 electron microscope.

Case Reports

Case 1

This 10-month-old male child presented with severe hematuria. On physical examination a large, non-tender abdominal mass was palpated in the left upper quadrant. Intravenous pyelography revealed a distorted pelvecalyceal system of the left kidney, and an $8 \times 5 \times 7$ cm solid tumor was noted by ultrasound. Chest roentgenogram and skeletal survey were normal. Ureteronephrectomy was performed, and the boy was treated with actinomycin D and vincristine. No radiotherapy was given.

One month after diagnosis the boy presented with fatigue and non-productive cough. Chest X-ray disclosed multiple bilateral pulmonary nodules which did not change in size despite aggressive combined chemotherapy with adriamycin, actinomycin D, cyclophosphamide and prednisone. The boy died 5 months after diagnosis due to respiratory failure. Permission for autopsy was not obtained.

Case 2

A rapidly growing tumor was noted in this 9-month-old female infant, who had been treated for recurrent aseptic meningitis and vomiting prior to admission. Physical examination of the weak, anemic girl revealed a firm, moveable mass of tennis-ball size in the left upper abdominal quadrant. The tumor, which was up to 12 cm in diameter, was completely resected and therapy with actinomycin D was initiated intraoperatively. Two days after surgery the infant developed two general convulsions with ensuing central respiratory dysfunction. She died 3 days later.

At autopsy, extensive metastatic deposits to the brain were found.

Results

Histopathological Findings

Using the grading procedure of Lawler et al. (1975) the tumors were classified as type 0 (no tubules). According to Beckwith and Palmer (1978), they were of "stromal predominant" type, "sarcomatous" subtype.

Histopathological examination demonstrated polygonal or elongated cells arranged in solid sheets without recognizable architectural organization (Fig. 1). Nuclei were mostly round-to-oval, containing prominent nucleoli and little chromatin. Variable numbers of cells possessed abundant eosinophilic cytoplasm, and in many of these cells large, hyaline, faintly PAS-positive globular structures were identified compressing the nuclei (Fig. 2). Cross-striations could not be detected in these cells. Hyalinization of the stromal component was apparent in one case. There were no blastematous or tubular components.

Immunocytochemical Findings

Neoplastic cells in the tumor specimen which could be investigated by immunological methods stained negatively for anti-lysozyme, α_1-antitrypsin, α_1-antichymotrypsin, anti-myoglobin and anti-keratin.

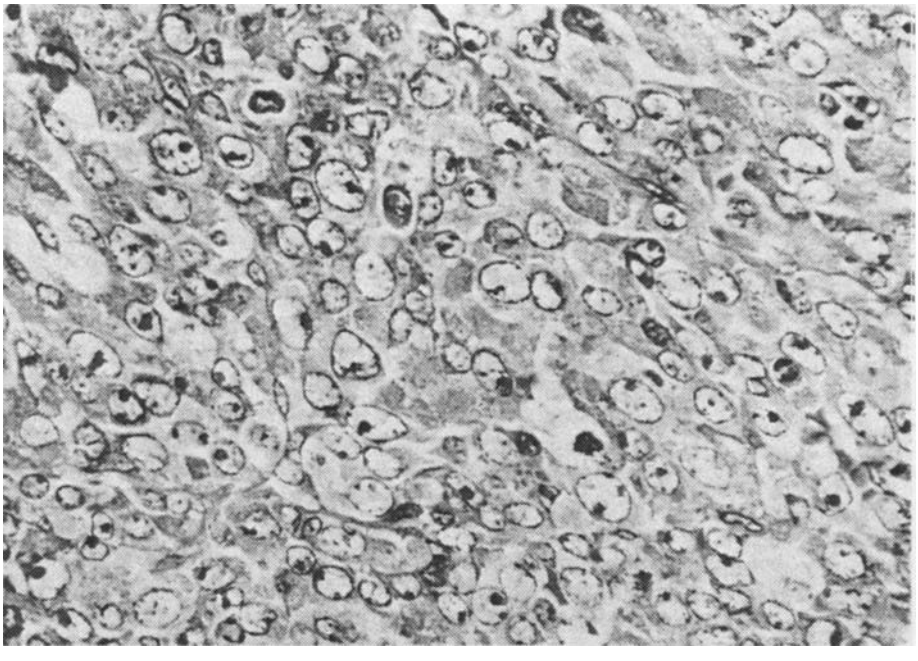

Fig. 1. Rhabdoid tumor of the kidney. Undifferentiated tumor tissue without epithelial and blastematous elements. Note paucity of chromatin of the nuclei and prominent nucleoli. Case 2, 9-month-old female infant (KT-No. 478/81). H & E × 560

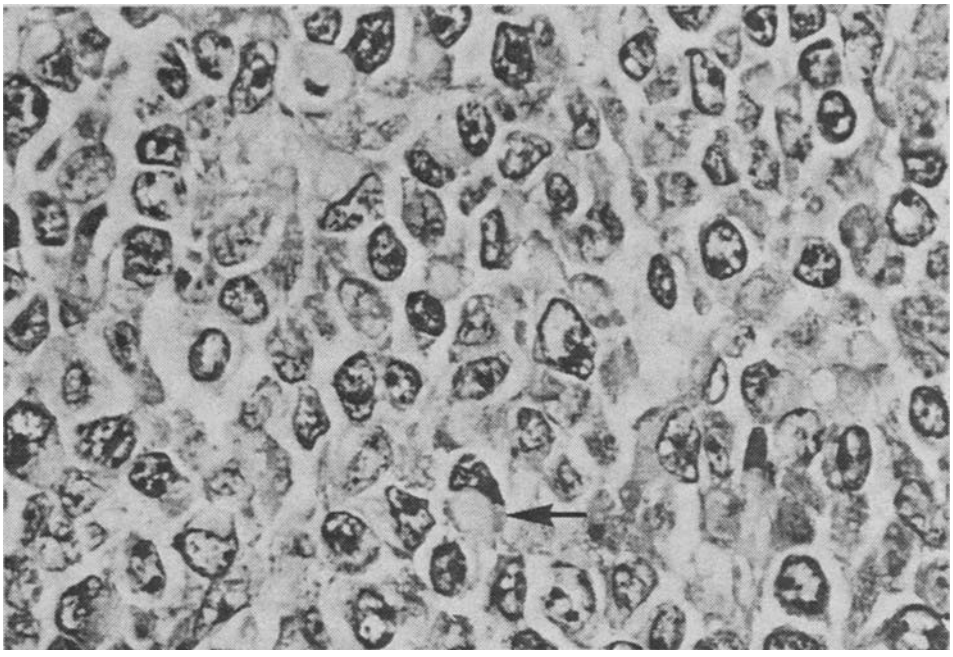

Fig. 2. Rhabdoid tumor of the kidney. Round, eccentrically located eosinophilic globules in the cytoplasm of some tumor cells (e.g. *arrow* at the bottom). Case 1, 10-month-old male infant (KT-No. 171/80). H & E ×560

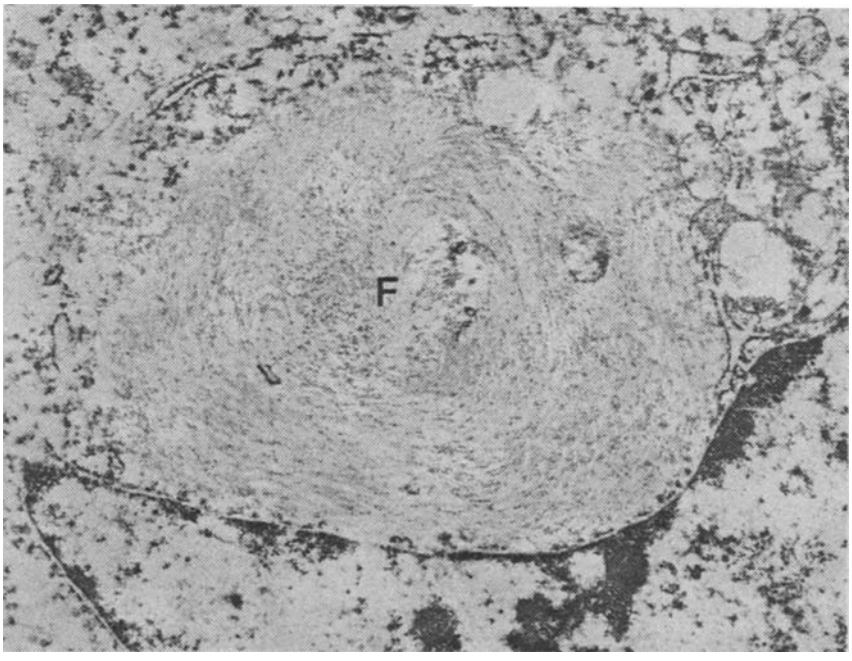

Fig. 3. Rhabdoid tumor of the kidney. Electron micrograph of an eosinophilic cytoplasmic globule. Concentric arrangement of fine filaments (*F*). Case 2, 9-month-old female infant (KT-No. 478/81). Uranyl acetate and lead citrate ×14,000

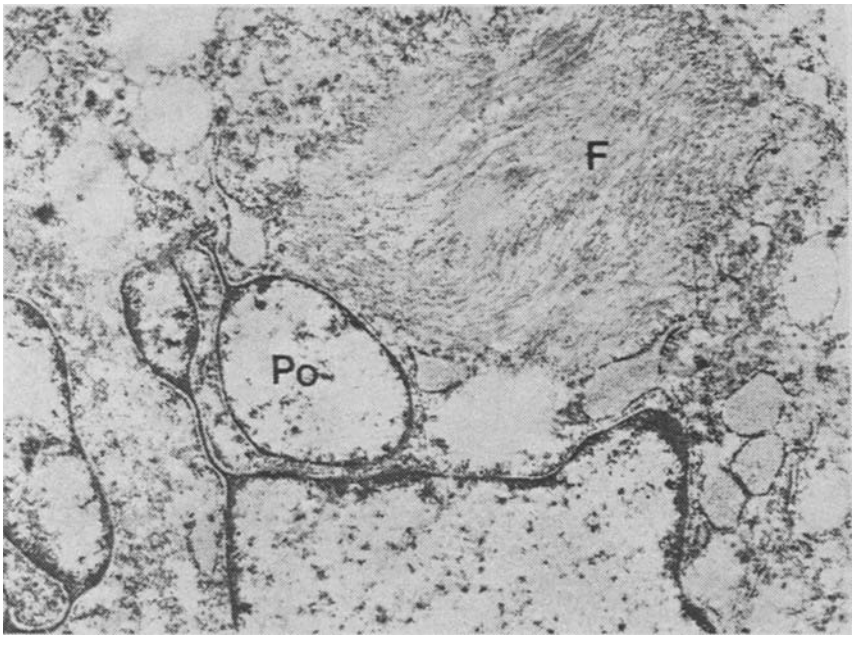

Fig. 4. Rhabdoid tumor of the kidney. Electron micrograph of an eosinophilic cytoplasmic globule. Intermediate filaments (*F*) in curved bundles (cf. filament pattern in Fig. 3). Note also nuclear pockets (*Po*). Same case as in Figs. 1 and 3. Uranyl acetate and lead citrate ×17,000

Ultrastructural Findings

The tumor that was studied ultrastructurally was composed of groups of cells with relatively large nuclei and prominent nucleoli. Nuclear pockets were frequently visible. The most striking feature in the cytoplasm was the presence of large masses of fine filaments packed in concentric whorled arrays (Fig. 3). Intermediate filaments were arranged in gently curved bundles (Fig. 4). Cytoplasmic organelles included some lipid droplets, a moderate number of mitochondria, a small number of lysosomes, and a few strands of rough endoplasmic reticulum. Small desmosome-like junctions could be observed between the neoplastic cells.

Discussion

Malignant rhabdoid tumor of the kidney is rare, comprising only 2% of all nephroblastomas (D'Angio et al. 1980). When studying the tumors, which had been classified as special variants of Wilms' tumor at our institution, we found two cases of this type of tumor among 101 Wilms' tumors. Like Wilms' tumor, rhabdoid tumor appears to be rare at birth and in adults. None of the 11 patients in the series of Haas et al. (1981) was older than 4 years of age or younger than 4 months of age. Fung et al. (1981) reported a rhabdoid tumor in a 5-week-old boy. This patient, two patients

reported by Haas et al. (1981), and one of our patients developed early metastases to the brain, which were confirmed at autopsy in the last instance. The other patient in the present series died of respiratory failure due to extensive lung metastases. Brain and lungs are uncommon metastatic sites in typical Wilms' tumor. In the present cases as well as in those reported by other authors (Roper et al. 1981) chemotherapy commonly used for typical Wilms' tumor did not influence the progressive course of the disease.

The histopathological appearance of this highly malignant renal tumor is distinctive. Light microscopic hallmarks are relatively large polygonal cells with eccentrically located nuclei and abundant acidophilic cytoplasm containing hyaline, PAS-positive globular structures. Cells presenting these histological features are readily identifiable, but their number may vary from tumor to tumor and even within the same specimen. Initially, these cells were thought to be rhabdomyoblasts, but cross-striations are consistently absent. There are also neoplastic cells in these tumors without globular structures. They are polygonal or elongated and have little cytoplasm with round-to-oval, slightly irregular nuclei containing prominent nucleoli. It has to be noted that metastatic deposits may be composed exclusively of these cells and recognition of the tumor may be severely hampered. Apparently, blastematous areas may or may not be found. Fung et al. (1981) described blastema, spindle cell areas, and focal myxoid areas, while none of these components could be identified in our tumors or in those of Haas et al. (1981).

Globular cytoplasmic inclusions can also be observed in epithelial renal tumors. We recently had the opportunity to study a malignant renal tumor in a 17-year-old female that had metastasized to the regional lymph nodes. Histological examination of this lesion revealed striking similarities to rhabdoid tumor. Many cells presented prominent cytoplasmic inclusions, which could suggest a diagnosis of malignant rhabdoid tumor (Fig. 5). The cohesive growth of the cells and their small nucleoli, however, represent features not found in rhabdoid tumor. Another argument against this diagnosis is furnished by the recurrence-free survival, $1^1/_2$ years after termination of treatment.

Differential diagnosis also includes rhabdomyosarcoma of the kidney, which is rare in children. Among 220 primary renal tumors, Gonzalez-Crussi et al. (1981) found only one case of rhabdomyosarcoma. This tumor was composed of bizzare, atypical cells and multinucleated cells without evidence of metanephrogenic differentiation. During the clinical course, the patient developed early dissemination to the skeleton. Penchansky and Gallo (1979) reported 7 cases of rhabdomyosarcoma of the kidney, in which the neoplastic cells had abundant eosinophilic cytoplasm and exhibited cross-striations.

Rhabdoid tumor must also be distinguished from "clear cell sarcoma of the kidney" (Beckwith and Palmer 1978) or "bone metastasizing renal tumor of childhood" (Marsden et al. 1978; Marsden et al. 1980). These tumors consist of undifferentiated ovoid or polygonal cells.

In rhabdoid tumor, the large hyaline, PAS-positive globules seen by light microscopy appear to consist of whorled aggregates of thin filaments

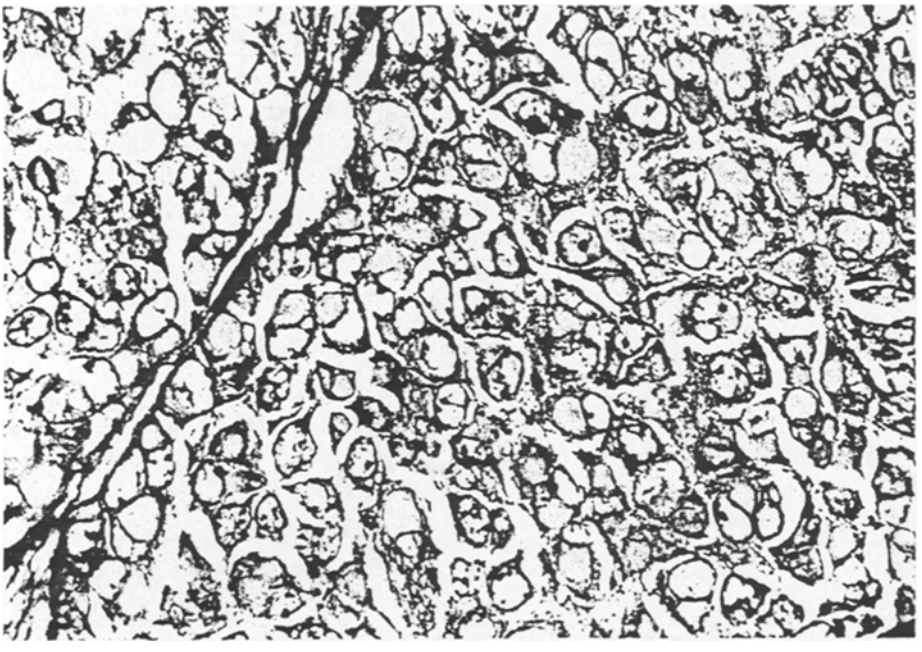

Fig. 5. Area of renal cell carcinoma with focus resembling rhabdoid tumor. 17-year-old female. Favorable outcome (follow-up $1^1/_2$ years). (KT-No. 419/80). Giemsa × 560

of 6–9 nm in diameter when studied by electron microscopy. PAS positivity is probably also caused by parallel bundles of intermediate-size filaments of 10 nm, filaments resembling tonofilaments of squamous epithelium, and a moderate amount of glycogen.

Alternating actin- and myosin-size filaments with Z-band formation cannot be identified. The histogenetic relevance of the filamentous structures has been discussed in detail by Haas et al. (1981). These authors speculate the possibility of origin from the neural crest, based on the findings of filaments of identical type and distribution in some APUD tumors. It should be borne in mind, however, that aggregates of thin filaments can occasionally be observed in undifferentiated blastemal cells of typical Wilms' tumor (Williams and Ajayi 1976; Schmidt et al. in press). A histogenetic relationship to metanephrogenic blastema could also be suspected from the finding of desmosomes or desmosome-like junctions between blastemal cells as well as between neoplastic cells in rhabdoid tumor. Further evidence of this origin is given by a rhabdoid tumor with blastemic areas reported in the literature (Fung et al. 1981).

Most recently, Gonzalez-Crussi et al. (1982) investigated four infantile sarcomas which presented a histological pattern identical to what has been described for rhabdoid tumor of the kidney. Two of these tumors occurred in the kidney and were classified as rhabdoid tumor, one was found in the liver and one in the soft tissue of the chest wall. Although variable numbers of tumor cells stained positively for muramidase, when studied

with the PAP immune complex method, there was not sufficient evidence for a histogenetic kinship to the mononuclear phagocyte system.

This contention is supported by our own findings. Negative staining was noted when tumor tissue was examined for lysozyme, α_1-trypsin and α_1-chymotrypsin. A myomatous or epithelial nature of rhabdoid tumor seems unlikely in view of negative staining against myoglobin and keratin, respectively. Additional studies including investigations on the biochemical composition of the filaments should be carried out in order to learn the nature and origin of this enigmatic tumor.

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