Case Report
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Anaplastic Wilms' Tumor Mimicking a Rhabdoid Tumor: A Diagnostic Challenge

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Abstract
Rhabdoid tumor of the kidney (RTK) mimics other renal tumors histologically, but a rhabdoid tumor mimicking an anaplastic Wilms' tumor has been rarely reported. Wilms' tumor classically comprises three histological components, including a blastema, epithelium, and stroma. The degree of maturation of these components makes the histological appearance of this tumor unique. Anaplasia is defined by the presence of extreme nuclear and mitotic atypia. Most of these lesions can be differentiated on the basis of light microscopic histological investigations. Herein we report a case of pediatric anaplastic Wilms' tumor that was difficult to differentiate from a mesenchymal lesion histologically. The application of immunohistochemistry and extensive sampling of the lesion was critical for accurate diagnosis.

Keywords: Wilm's Tumor; Child; Rhabdoid Tumor.

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Introduction
Malignant rhabdoid tumor (RT) of the kidney is a rapidly progressive, highly aggressive, rare malignant neoplasm that accounts for 0.19 cases per million renal neoplasms (1). RT was previously described as a rhabdomyosarcomatoid variant of Wilms' tumor because of its occurrence in the kidney and its similarity with rhabdomyoblasts (2). However, the absence of muscular differentiation led Haas and colleagues to coin the term rhabdoid tumor of the kidney in 1981(2). Wilms' tumor is the most frequent tumor of the kidney in children and infants (3). The incidence of Wilms' tumor is 8.2 per 1 million in children younger than 15 years and 1 per 10,000 in infants (3). The anaplastic histology accounts for 10% of Wilms' tumors. This histological subtype is the single most important predictor of response and survival in patients with Wilms' tumor (4). Older patients usually have a higher incidence of anaplastic histology (4). In bilateral tumors, 12% to 14% have been reported to have anaplastic histology in one kidney (5-6). Anaplastic Wilms' tumor presents as a diagnostic difficulty as the tumor cells can mimic other malignant neoplasms of the kidney, especially if they have cytoplasmic protrusions and macronucleoli. Herein we present the case of a 9-month-old child with a similar diagnostic dilemma.

Case report
A 9-month-old child presented to the pediatric OPD with complaints of abdominal pain, cough, recurrent vomiting, and fever. The patient had no congenital anomaly, and birth and family history were unremarkable. On examination, the patient was found to have a large right-sided abdominal mass. Every other systemic examination was within normal limits. A contrast enhanced computed tomograpgy of the abdomen was done, which revealed a heterogeneous enhancing mass measuring 11.5 × 9.5 × 5.5 cm in the right renal fossa with many areas of cystic necrosis. A clinical-radiological diagnosis of a mesenchymal tumor possibly malignant rhabdoid was made. Fine needle

aspiration cytology was performed, which suggested a small round cell tumor. The patient did not receive any preoperative chemotherapy and a radical nephrectomy was planned. The specimen was sent for histopathological examination. Grossly, the kidney was enlarged and bosselated externally. On cut open, the kidney showed a variegated appearance. There were large areas of necrosis and hemorrhage along with solid areas and very few cystic regions. The tumor was soft and fleshy (Fig 1).

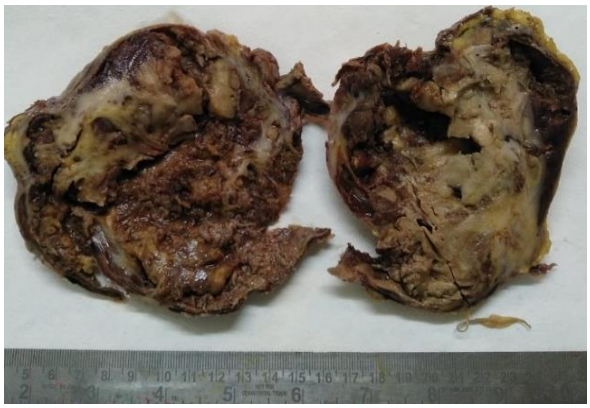

Figure 1. Tumor occupying the entire kidney, grey-white areas of necrosis and hemorrhage.

A gross diagnosis of a mesenchymal tumor was made and sections were prepared accordingly. Histopathological examination of the sections showed the presence of predominantly sarcomatoid tumor cells with no epithelial cells or structures indicative of blastema. The tumor cells were spindle shaped cells with well-defined cell boundaries, moderate eosinophilic cytoplasm, nuclear enlargement with cytological atypia, along with many cells showing a prominent nucleoli, few atypical mitotic figures, and large areas of necrosis (Fig 2).

A provisional diagnosis of a malignant rhabdoid tumor was made. A panel of immunohistochemistry was ordered, and the results showed that the cells were diffusely positive for WT1 (Fig 3) and p53 (Fig 4) and negative for pan-cytokeratin (CK). The specimen was now re-examined and more sections were prepared for an extensive sampling. On further assessment, few areas with abortive tubules were identified. These were again subjected to IHC, which showed the tubules were positive for cytokertain.

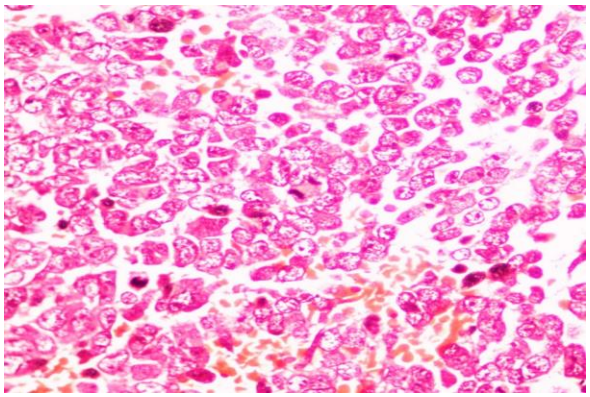

Figure 2. H&E, 400x: Sarcomatoid looking cells, with well-defined cell membrane and cytoplasmic extensions. Nuclei show prominent nucleoli with many atypical mitotic figures (arrow)

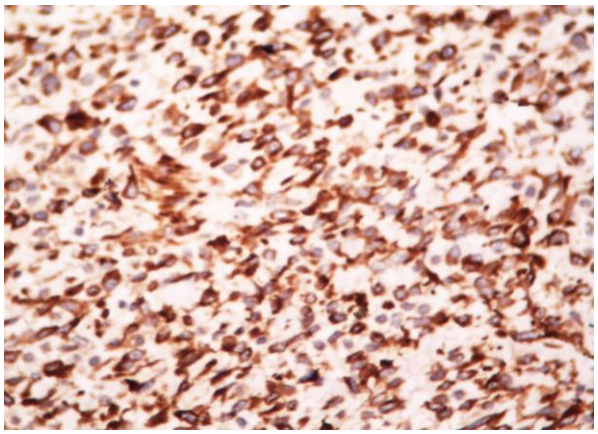

Figure 3. IHC, Ventana, 400x: WT1 positive: WT1 gene encodes for Wilms' tumor protein located on chromosome 11p13

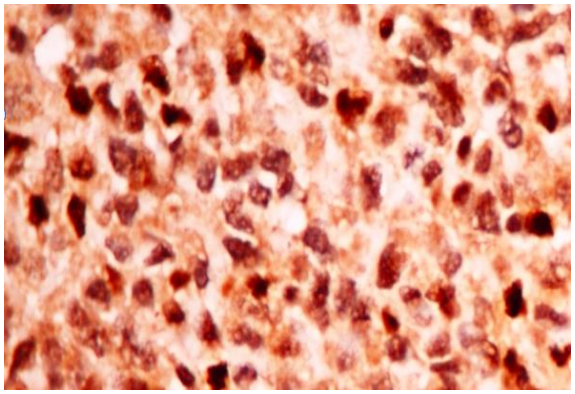

Figure 4. IHC, Ventana, 400x: diffuse positivity for P53

Hence, a histopathological diagnosis of an anaplastic Wilms' tumor was made.

The patient was started on a chemotherapeutic regimen for Wilms' tumor with an anaplastic morphology.

Discussion

Anaplastic morphology of the Wilms tumor has been recognized as a high-risk factor and is associated with a worse prognosis (7-9). Two types of anaplasia have been defined, which can occur in any component of Wilms tumors. Anaplasia can be focal or diffuse (10). According to the criterion described by Faria et al (10), three criteria need to be fulfilled to define anaplasia, including multipolar and or atypical/tripolar mitotic figures, hyperchromatic nucleus, and nuclear enlargement with the nuclear diameters at least three times those of adjacent cells (10). As defined by Faria et al, focal anaplasia is defined as the presence of one or two foci fulfilling all three criterion within the primary renal tumor without any evidence of anaplasia or prominent nuclear atypia in other areas (10). The SIOP–RTSG pathology panel defines focal anaplasia as a focus with the above-mentioned three features not exceeding 15 mm in the maximum dimension (11). Wilms tumor with focal anaplasia is regarded as an intermediate-risk tumor in this protocol (11). Diffuse anaplasia is defined as a multifocal anaplasia/focal anaplasia with marked nuclear unrest in the rest of the tumor tissue or anaplasia present outside of the kidney (tumor in intrarenal or extrarenal vessels, renal sinus, extracapsular sites or metastatic deposits). If anaplasia is seen in a biopsy sample or other incomplete tumor samples, a diagnosis of diffuse anaplasia is warranted (10). The criteria for anaplasia, both focal and diffuse, are well described; however, the diagnosis of an anaplastic Wilms' tumor can be quite challenging (12). Anaplastic Wilms' tumor must be distinguished from malignant rhabdoid tumor of the kidney. MRT is one of the most aggressive and lethal malignancies in children. This tumor is now recognized as an entity separate from a Wilms' tumor. This tumor has the worst prognosis of all renal tumors. Infants and children with rhabdoid tumors have aggressive disease, typically with extensive tumor spread, and frequently die early (within 1–2 years, 90% tumor return rate and 86% mortality) despite intense multidrug chemotherapy (13). Multimodality based and targeted treatment approaches for MRT and anaplastic Wilms' tumor are currently under trial; hence it is very important to differentiate between the two.

A careful attention to light microscopic details with an extensive sampling along with immunohistochemistry usually helps to make an accurate diagnosis. The presence of an anaplastic morphology with even a focal "typical Wilms' architecture" helps to distinguish anaplastic Wilms' from MRT (14). The IHC panel for anaplastic Wilms' tumor shows positivity for WT1, p53, and CK in the epithelial component (15).

The most distinctive morphologic features of rhabdoid tumor of the kidney (RTK) are large cells with large vesicular nuclei, a prominent single nucleolus, and the presence of globular eosinophilic cytoplasmic inclusions composed of whorled masses of intermediate filaments in at least some cells. Another distinctive feature is the extremely aggressive, invasive pattern of this lesion. RTK has a diverse immunohistochemical profile. Tumors may be positive for many supposedly incompatible epitopes for epithelial, myogenous, neural, and mesenchymal cell types (16). The loss of INI1 antibody in immunohistochemistry is useful in confirming the histologic diagnosis of renal rhabdoid tumor, especially for cases with indeterminate histologic features, equivocal immunophenotypic profiles, or uninformative molecular studies (17).

Future directions related to management of both of these aggressive cancers are under trial, with insights in possible clinical trials that consider integration of novel targeted therapies. Given the genomic instability of p53-mutation tumors, including anaplastic Wilms' tumor, the use of immune checkpoint- inhibitor therapy and investigation of CTLA4 and PD-1/PD-L1 targeting are under trial in such patients (18). Ultimately, to help develop novel therapies, cooperative group investigations and broad collaborations are

necessary to optimize treatment for infants, children, and adolescents suffering from anaplastic Wilms' tumor (18).

Conclusion

Anaplastic Wilms' tumor, clear cell sarcoma, and malignant rhabdoid tumor are currently grouped under "unfavorable histology" because they respond poorly to therapy. This case signifies the importance of thorough, extensive sampling and extended immunohistochemistry before making a diagnosis. Because this tumor is rare and pathology is still uncertain, it represents a diagnostic challenge. Knowledge of the potentially complex pathological features of this malignancy is required for accurate diagnosis, subtyping and staging to allow appropriate treatment with an intensive chemotherapy, radiotherapy and targeted therapy regardless of the extent of disease at diagnosis. Molecular biology markers play an even more important role in the tumor prognosis and differential diagnosis; however, pathological examination is the gold standard for diagnosis, subtyping and prognosis at present.

Conflict of Interest

The authors declare no conflicts of interest.

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