Case Report

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P53 and Nuclear Unrest: Biological Driver's Suggesting Poor Prognosis in Anaplastic Wilm's Tumor

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Abstract

In the early era, survival from Wilm's tumor (WT) was less than 10% compare to today's date which has a 90% chance of survival. Multimodal therapy, enhanced surgical techniques, effective chemotherapy regimens and radiation therapy in treatment protocols have revolutionized the survival rates. As the advancement continues, molecular basis and targeted therapies are being considered for risk stratification and better treatment. Particularly important is evaluation of molecular abnormalities that confer to poor prognosis, so that intensification of chemotherapy and radiotherapy can be done to achieve maximum remission. The aim of this article is to highlight the importance of p53 and a morphological spectrum that have been associated with prognosis in WT.

Keywords: Wilm's tumor; Malignancy; Child; WT; Prognosis.

Conflict of interest: The author declares no conflict of interest.
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Introduction

Wilm's tumor (WT) or nephroblastoma, represents approximately 95% of childhood kidney tumors, with an incidence of approximately 7 cases per million children aged 15 years or younger (1). WTs show a molecular resemblance to the embryonic kidney. Research efforts are now focusing on the more lethal variants of WT, including anaplastic histology, relapse and bilateral disease that account for most treatment morbidity and mortality. Wilms tumors historically were risk stratified by histology, defined as favorable (FHWT) or unfavorable histology (UHWT) (2). The molecular dynamics came into the picture and have widened the concept of anaplasia in a Wilms tumor. Morphologically, Nuclear unrest represents an intermediary in the spectrum from favorable histology to anaplastic histology and nuclear unrest grade III is a very close station to anaplastic morphology especially if associated with p53 overexpression (3). p53 which is associated with anaplasia and poor prognosis.

We here present two cases of Wilm's tumor in different age group suggesting the aggressiveness of p53 expression and nuclear unrest in an Anaplastic Wilm's tumor.

Case Reports

Case one was a 6-year-old female patient who presented in the OPD with a large swelling in right side of abdomen. Swelling was gradually progressive in size. There was no history of fever, pain, vomiting, hematuria and constipation. The patient had no congenital anomaly. Birth history revealed an uncomplicated full-term vaginal delivery.

On physical examination, patient had low-grade fever (99 degrees Fahrenheit) and Blood pressure was 130/90 mmHg. On abdominal examination, a mass of 8x5 cm with regularly shaped margins was palpated in the right upper quadrant. The mass was smooth, firm, non-mobile, and did not cross the

midline. All other systemic examination were within normal limits. The CECT revealed a Heterogeneous enhancing echogenic mass of size 10x10cm seen in left renal fossa at upper and interpolar regions with internal areas of cystic necrosis with internal vascularity. Radical Nephrectomy was done and the specimen was sent for histopathological evaluation. Grossly, the kidney with its attached capsule measured 10x10x4cms, along with an attached ureter. The capsule showed a breech and the cut section showed a tumor occupying almost the entire kidney. There was compressed renal parenchyma identified at the periphery of the tumor (figure 1).

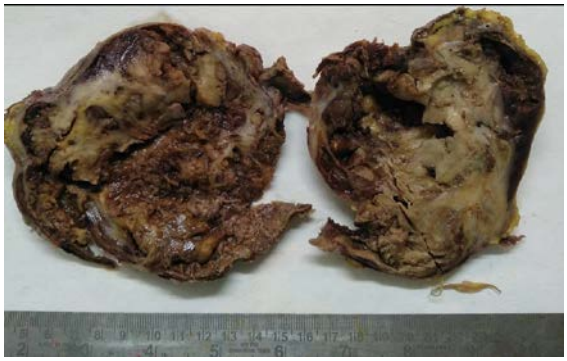

Figure 1. Tumor is occupying whole of kidney, 10x10x4cm, weighing 230gms. Cut section shows grey-white to brown with areas of necrosis.

Tumor showed variegated appearance with areas of hemorrhage and necrosis. Histopathological analysis of multiple sections revealed the presence of a tumor with a triphasic pattern showing epithelial, stromal and blastemal components (Figure 2, 3).

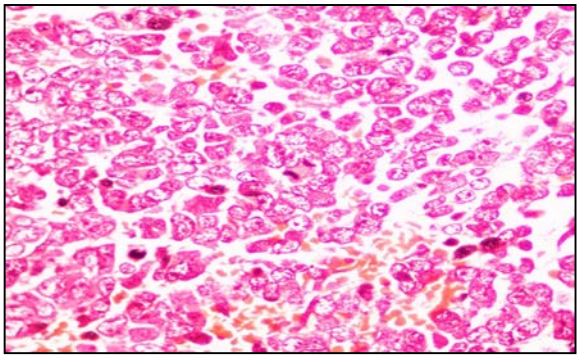

Figure 2. H&E, 400x: Blastemal component comprising of small round cells, some showing nuclear abnormalities and atypia.

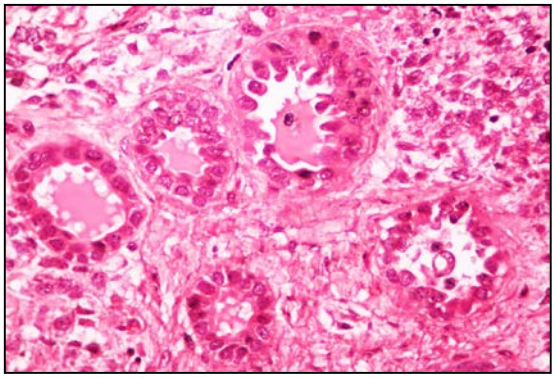

Figure 3. H&E, 400x: Epithelial component comprising of abortive tubules with lining epithelium showing nuclear atypia and enlargement.

The blastemal component showed many areas with features of nuclear unrest and few foci of anaplasia in the form of significant nuclear enlargement, hyperchromasia and atypical mitotic figures. A panel of immunohistochemical markers were put and it revealed strong and diffuse p53 positivity along with WT1 positive cells (Figure 4,5).

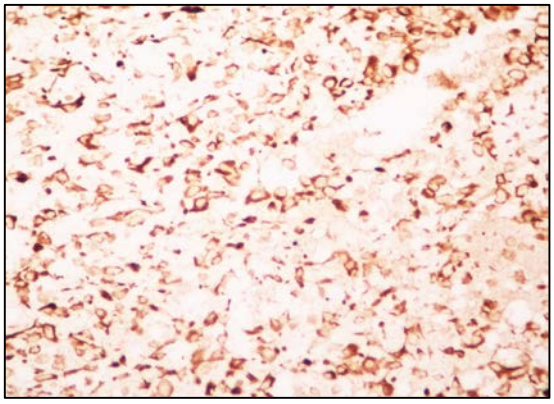

Figure 4. IHC, 400x: tumor cells showing WT1 positivity

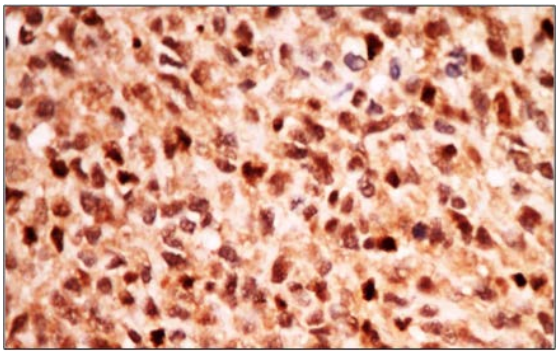

Figure 5. IHC, 400x: tumor cells showing p53 positivity, some cells showing darker staining and some showing less. Feature characteristically seen in anaplastic wilm's tumor.

A diagnosis of Triphasic Wilms with Anaplasia was given. The patient was intensified on the chemotherapeutic regimen but was lost within 3 months of chemotherapy.

Case two was a 9-month-infant presenting in the OPD with abdominal swelling, fever and cough. There was no history of vomiting, hematuria or constipation. The patient had no congenital anomaly. Birth history revealed an uncomplicated full-term vaginal delivery. On abdominal examination, a mass of 4x3 cm palpated in the right upper quadrant. The mass was smooth, firm, non-mobile, and did not cross the midline. All other systemic examination were within normal limits. FNAC was suggestive of a small round cell tumor. A CECT was done and it revealed a heterogeneous enhancing mass of size 11.5 × 9.5 × 5.5cm seen in right renal fossa areas of cystic necrosis. A radiological diagnosis of a mesenchymal tumor (or Rhabdoid?) was considered. Radical Nephrectomy was done was sent for histopathological examination. Cut surface of the kidney showed a variegated appearance with large necrotic areas, grey white with hemorrhage and necrosis (Figure 6).

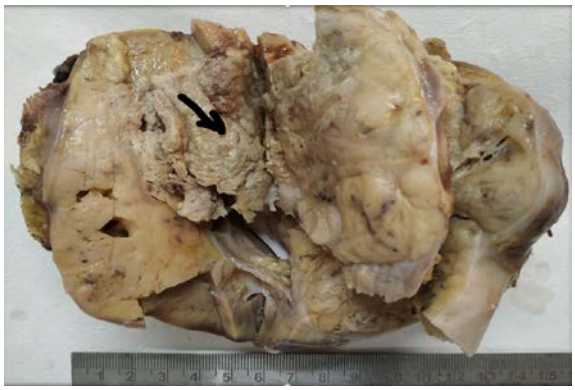

Figure 6. Tumor is occupying whole of kidney, 11.5 × 9.5 × 5.5cm, weighing 385 gms. Cut section shows grey-white to brown with areas of necrosis (black arrow) .

Histopathological examination of multiple sections revealed the presence of spindled cells showing nuclear enlargement, cytological atypia, atypical mitotic figures and areas of necrosis (Figure 7). On extensive sampling, few abortive tubules were identified (Figure 8). A panel of immune histochemical markers were put and revealed diffuse p53 positivity along with WT1 positive cells (Figure 9,10). A histopathological diagnosis of Anaplastic Wilms Tumor was made. The patient was again intensified on the chemotherapeutic regimen but the patient was lost within one month of therapy.

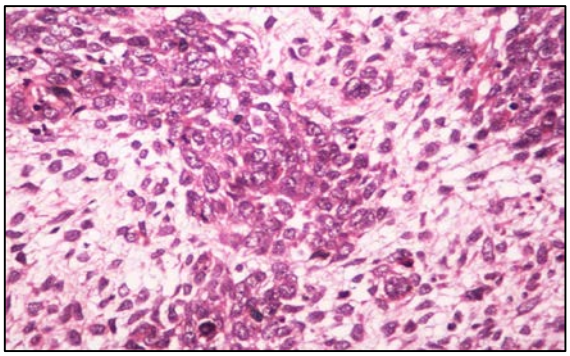

Figure 7. H&E, 400x: section showing anaplastic blastemal component with cells showing variation in nuclear size, hyperchromasia, cytological atypia and many mitotic figures.

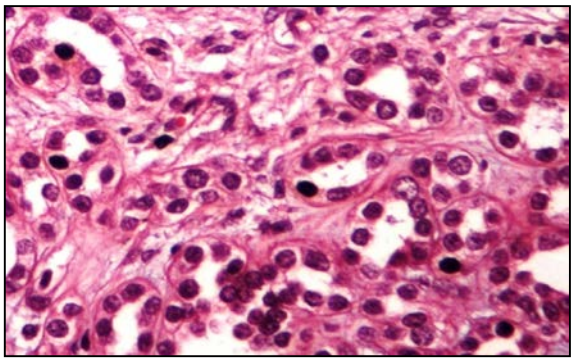

Figure 8. H&E, 400x: section showing epithelial component with lining cells showing hyperchromasia and cytological atypia

Discussion

This is a retrospective study of 2 patients who presented at Kalawati Saran Children's Hospital with Wilms' tumors, and underwent preoperative chemotherapy followed by nephrectomy. Histopathologic morphological assessment and p53 immunohistochemistry were done. Stage of the tumor and the dominant blastemal morphology are potent prognostic factors. p53 is linked to blastema dominant morphology. A grade III nuclear unrest in a wilm's tumor resembles closely to an anaplastic WT. Appropriate treatment hence warrants stratification of these tumors with nuclear unrest grade III with anaplastic histology. Childhood renal tumors account for ~7% of all childhood cancers, and most cases are Wilms tumors (WT) or nephroblastomas (~90%), affecting one in 10,000

children under the age of fifteen (4). The peak incidence is between the ages of 2 and 3 years (4), but bilateral cases and those associated with congenital syndromes (5 to 10% of the cases) are diagnosed earlier (5). WT develops from primitive renal cells incapable of completing kidney differentiation, which results in a tumor that recapitulates nephrogenesis, with morphology, methylation, and gene expression similar to the fetal kidney (6). WT is usually composed of varying proportions of three histological distinct cell types: undifferentiated blastemal cells, epithelial cells structured into different primitive structures, and stromal cells, all of which are related to the clinical behavior (7).

Salama et al (3) suggested that tumor stage and morphologic subtypes were found to be the most important determinants of prognosis of Wilms' tumor and they deserve priority in precise and meticulous sampling of the nephrectomy specimen for proper assessment of stage and assessment of chemotherapy induced changes for better categorization of the patients regarding postoperative treatment. Their study pointed out that, this also helps in defining anaplasia and various grades of nuclear unrest in larger number of patients for further studies to clarify exactly the weight of nuclear unrest in Wilms' tumor (3).

The role of p53 in the pathogenesis and progression of Wilms tumors is only partly understood (8). Several studies including one by Malkin et al. found p53 mutations in Wilms tumor (9). Cheah et al. in their study mentioned that the immunohistochemical expression of p53 protein in Wilms tumor was presumably a result of mutation in the p53 tumor suppressor gene and correlates with the histological classification (10). Lahoti et al suggested that the accumulation of p53 in these tumors may not only be due to mutations but it also could be, due to stabilization of normal p53 with other proteins, histological categorization being one of the useful features in the prognostic assessment of Wilms tumor (8). Ooms et al studied p53 expression in diffuse anaplastic wilms tumor and concluded the key role of TP53 loss in the development of anaplasia in WT (11).

Few Wilms tumors with morphologically favorable histology show disturbing nuclear enlargement, cytologic atypia, and histologic disarray. This is known as *nuclear unrest*. Zuppan et al (12) in a study suggested that Wilms tumors with nuclear unrest show tumor cells with enlarged, hyperchromatic nuclei but do not have the enlarged multipolar mitotic figures required to meet the criteria for anaplasia. Salama et al (3) in their study of cases described nuclear unrest in an intermediary position in the spectrum from favorable histology to anaplastic histology. They suggested that nuclear unrest grade III is a very close station to anaplastic morphology especially if associated with p53 overexpression. p53 is hence linked to a blastemal dominant morphology, anaplastic histology showing a nuclear unrest grade III. A Blastemal dominant morphology is associated with poor survival. Ashley et al (13) also proposed nuclear unrest as an intermediary and that the tumors which showed nuclear unrest subsequently incur *p53* mutations and convert to bona fide anaplasia.

Conclusion

WT with nuclear unrest shows a spectrum that leads to an anaplastic histology, both clinically and pathogenetically. The use of these morphological parameters and immunohistochemical analysis of p53 expression may potentially provide the treating oncologist with a biological rationale in identifying patients at high risk and to guide the adjuvant chemotherapy and/or radiotherapy.

Key Message

Patients with favourable histology may show an aggressive clinical course. This confers a need for complete histological assessment of tumor as well as immunohistochemical staining with prognostic markers like p53 for judgement of patient prognosis. We advocate the routine use of p53 in assessment of Wilm's tumor histology showing features of nuclear unrest.

Conflict of Interest

There are no conflicts of interest.

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