



Extensive chondroid differentiation in a Wilms tumor following chemotherapy: Clinical relevance and implications

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ABSTRACT

Wilms tumor (WT) is the most common childhood tumor of the kidney, which histologically mimics various stages of nephrogenesis. Spectrum of chemotherapy induced histopathological changes has been described in literature, and is one of the most important predictors of disease outcome and survival rates. Extensive chondroid differentiation and absence of necrosis in a post-chemotherapy nephrectomy specimen of a radiologically proven Wilms tumor is an unusual finding. Herein, we present the case of 6-year-old girl from South Africa who received a 10-week course of chemotherapy upon radiological diagnosis of WT, and post-surgery nephrectomy specimen revealed extensive mature cartilage island formation on histology raising diagnostic dilemma. Reporting of such cases is extremely important to recognize tumor morphological heterogeneity, particularly post-chemotherapy, and developing consensus for selecting further treatment and clinical follow-up.

Key Words: Wilms tumor, chondroid, post-chemotherapy, stromal.

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Introduction

Wilms tumor (WT) is the most common childhood tumor of the kidney, constituting 6 to 7% of childhood cancer in developed countries, [1] and accounts for approximately 12% of all childhood cancers in the underdeveloped countries [2]. WT mimics

normal nephrogenesis, and histologically is composed of a variable admixture of epithelial, blastemal and stromal components [3]. Heterologous components i.e. striated and smooth muscle, cartilage, bone, adipose tissue, etc. are present in only 10% of WT [4]. Recently, studies have shown that two-hit inactivation of the *WT1* gene is more prevalent in stromal-predominant WT [4]. Currently, pre-chemotherapy/ up-front surgery-based system developed by the National Wilms Tumor Study Group (NWTSG) and post-chemotherapy- based system developed by the

International Society of Pediatric Oncology (SIOP) are the treatment strategies selected based on individual patient risk of tumor spillage, rupture and recurrence [5]. Patients following SIOP protocol usually do not undergo a biopsy prior to starting therapy [5]. Preoperative chemotherapy is known to affect original tumor histology, sometimes drastically, resulting in reduced or enhanced individual tumor components, and often inducing maturation [6,7]. WT has good prognosis with survival rate of 90% in developed countries following either regime [1,2]. Tumor stage and histopathological features following neoadjuvant chemotherapy as well as after upfront surgery are the most important predictors of disease outcome and survival rates [5]. Herein, we present a case of 6-year-old girl from South Africa who received 10 weeks course of chemotherapy upon radiological diagnosis of WT, and post-surgery nephrectomy specimen revealed extensive mature cartilage island formation on histology raising diagnostic dilemma. Reporting of such cases is extremely important to recognize tumor morphological heterogeneity and assess response following chemotherapy. Indeed, requires developing consensus for selecting further treatment course for such cases.

Case report

A 6-year-old girl from South Africa presented to the pediatric surgery out-patient department with a complaint of swelling in the right flank. The swelling was first noticed by her parents 8 months ago, when the size was that of a lemon. However, they found a rapid increase in the size of the swelling. History of fever, pain abdomen, hematuria, and hypertension was absent. Past medical history was non-contributory. Contrast enhanced CT revealed a

large heterogeneously enhancing mass measuring 17 X 16 X 11 cm with well-defined margins arising from lower pole of the right kidney. The mass extended from T11 to S1 vertebral body, crossing the midline. Right renal vein and inferior vena cava (IVC) were free of thrombus (Fig. 1; A, B & C). A radiological diagnosis of Wilms tumor was suggested. Pre-operative fine needle aspiration cytology (FNAC) was not done. With this diagnosis patient was started on chemotherapy. DD4A regimen (vincristine, dactinomycin, and doxorubicin) was administered for 10 weeks. Post-chemotherapy CECT revealed reduction in size of the tumor to 15X9 cm with change in the internal attenuation and enhancement pattern (Fig. 1; D, E & F). Right nephrectomy and hilar lymph node dissection was undertaken.

On histopathological examination, the right nephrectomy specimen measured 20X13X10 cm, weighing 1325 grams (Fig. 2). Attached ureter measured 10.5 cm in length and 0.6 cm diameter. External surface of the kidney was bosselated with a thick, adherent capsule. Serial slicing showed a large well encapsulated mass replacing almost the entire renal parenchyma, with a thin rim of normal renal tissue at the lower pole. Cut surface of the tumor was lobulated, firm, pearly white to myxoid, with intervening pin-point yellowish areas. Focal fleshy areas were also identified. Microscopic examination from different tumor areas predominantly showed islands of mature cartilage lacking nuclear atypia (approximately 80% of tumor area), surrounded by nondescript mesenchyme with focal myxoid stroma (approximately 15%). At places, skeletal muscle differentiation was noted (approximately 5%), along with areas of hyalinization. Epithelial, blastemal or malignant stromal component were not seen.

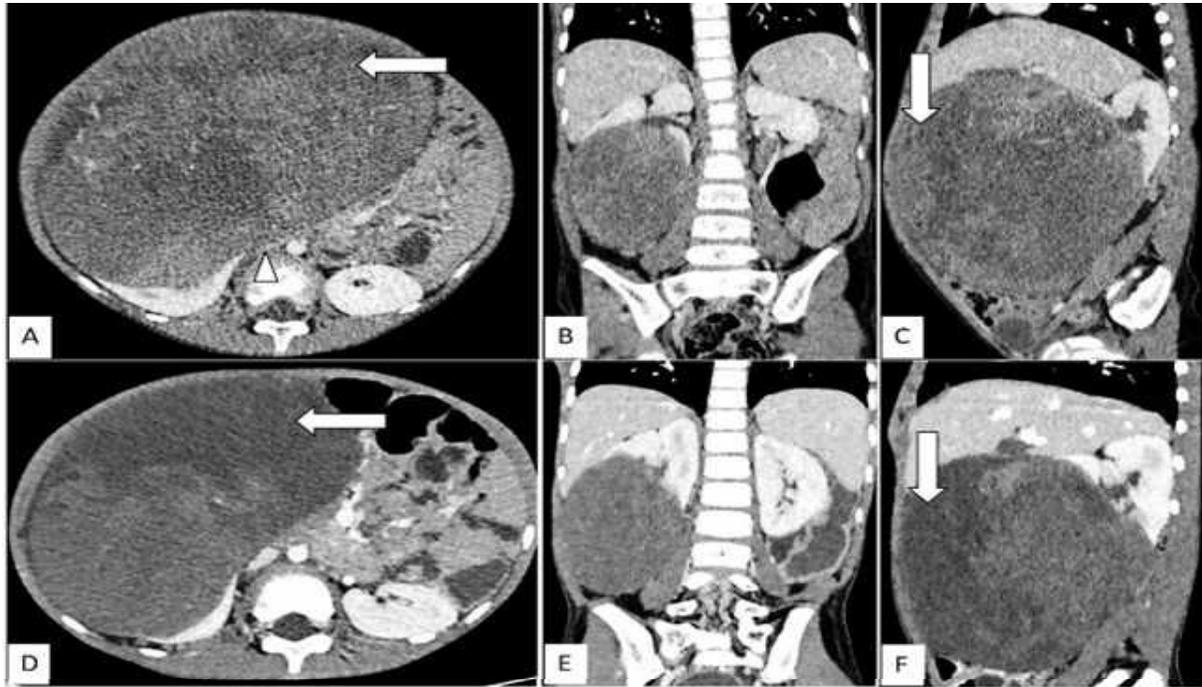


Fig. 1. Contrast enhanced CT images displaying large, well defined mass arising from lower pole of the right kidney and showing heterogeneously enhancing areas (arrows). IVC was compressed by the mass with no thrombosis (arrowhead) Axial (A), coronal (B) and sagittal (C). Post chemotherapy CT shows mild decrease in the size of the mass with altered internal characteristics; Mass showed significant low attenuation [HU 35-40 and not cystic or necrotic], hypoenhancing areas (arrows) (D, E, F).

Necrosis was present in less than 1% of the total area sampled. MIB-1 labeling index was negligible in the chondroid islands (Fig. 3). Differential diagnoses considered were stromal-predominant WT with heterologous elements, ossifying renal tumor of infancy and intrarenal teratoma. Immunohistochemistry (Fig. 4a, b) for WTI showed cytoplasmic and nuclear staining in the skeletal muscle component and helped to confirm the diagnosis. Non-descript stroma showed negative staining for smooth muscle actin, desmin, myogenin and S100. Based on the post-chemotherapy induced histological changes in form of predominance of chondroid elements and WT1 staining in the skeletal muscle component, a final diagnosis of stromal-predominant WT with extensive chondroid differentiation was made. Thereafter, patient received radiotherapy to the

flank 10.8 Gy/6 cycle for six days and adjuvant chemotherapy planned upto 24 weeks as per DD4A regimen.

Discussion

Histologically, WT mimics various stages of nephrogenesis [4]. Depending upon the components present, it can be mesenchymal predominant, epithelial or mixed. WT containing heterologous elements are considered to arise from intralobar nephrogenic rests (ILNRs) rich in stroma [4]. Fetal rhabdomyomatous WT containing abundant skeletal muscle are chemoresistant and often shows poor volumetric response has been described in literature [7,8]. Presence of extensive cartilaginous differentiation along with foci of rhabdomyomatous differentiation, and the complete absence of necrosis, tubules, blastema and epithelial component in the index



Fig. 2. Gross photomicrograph: Nephrectomy specimen depicting large well circumscribed tumor with small portion of normal renal tissue at the upper pole. Cut section is lobulated, firm, pearly white to myxoid, with intervening pin-point yellowish areas.

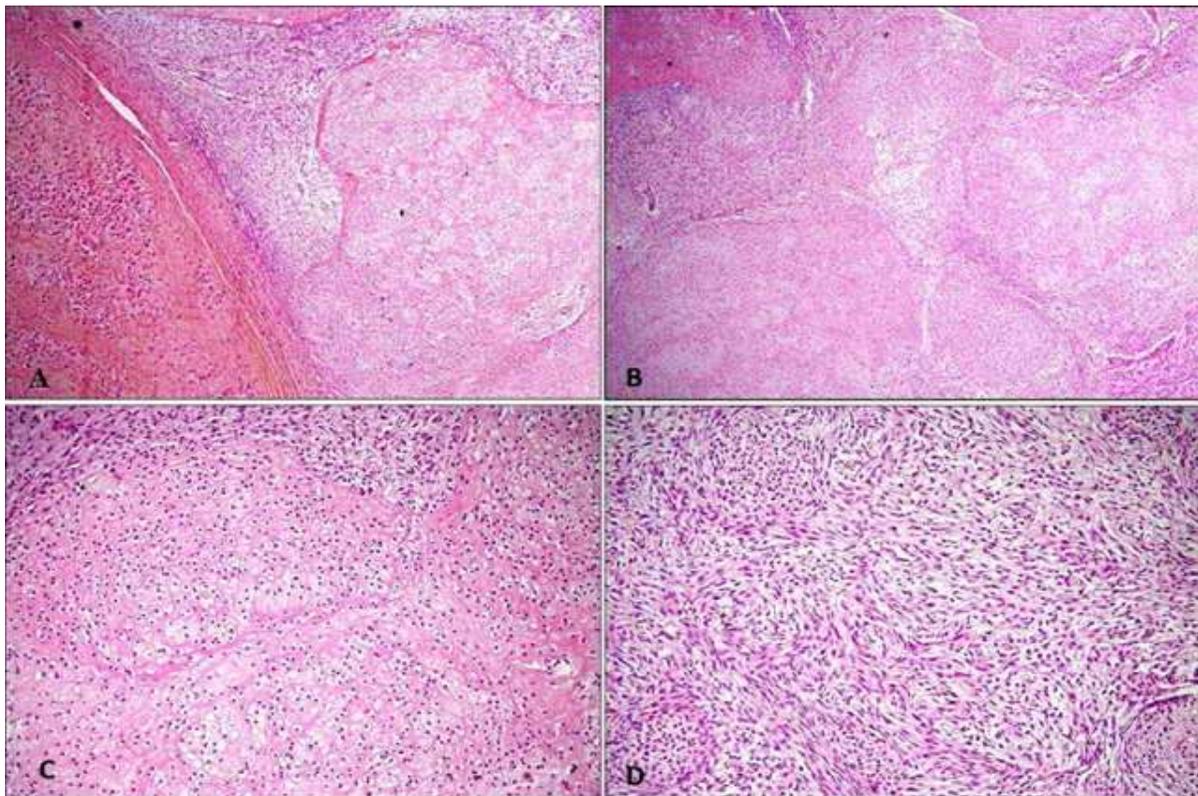


Fig. 3. Photomicrograph depicting lobules of cartilage islands separated by well demarcated areas showing skeletal muscle differentiation (A, H&E, x100). Extensive chondroid islands with intervening stromal component. Necrosis absent (B, x100). Cartilage islands displaying benign appearing chondrocytes (C, x200). Non-descript stroma lacking atypia (D, x200).

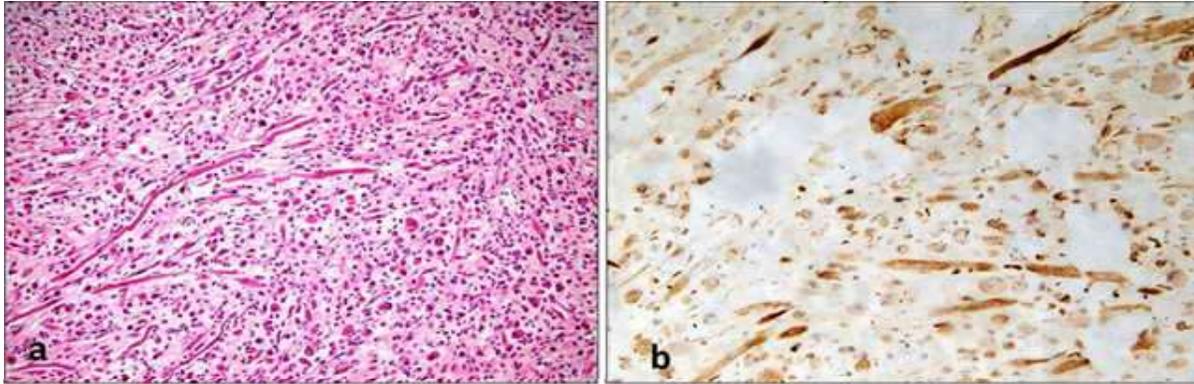


Fig. 4. Photomicrograph displaying areas showing skeletal muscle differentiation with atrophied nuclei and cell body (**a, x200**). Immunohistochemistry for WT1 showing cytoplasmic staining (**b, x200**).

case is an unusual type of tumor response to chemotherapy in a radiologically proven WT. In routine practice, the diagnosis of Wilms tumor relies on classical morphological features supplemented by nuclear staining for WT1 on immunohistochemistry [9]. WT1 shows strong nuclear expression in majority of cases, particularly in epithelial and blastemal components, while it may be extremely low or even absent in stromal components [4]. WT1 gene mutation is present in approximately 15 to 20% of WT [9]. However, recently, germline mutations have also been described in the majority of stromal-predominant WTs, leading to ectopic myogenesis [4]. In such a setting, the gene product of WT1 is aberrantly expressed in the cytoplasm of tumor cells, indicating arrest of mesenchymal to epithelial lineage transformation, and this can be detected by immunohistochemistry using an antibody against the N-terminus of WT1 [4]. Cytoplasmic WT1 expression in the skeletal muscle component in the present case thus supported the diagnosis of WT, although only focal nuclear staining was seen.

Studies have shown that chemotherapeutic agents used in treatment of WT induce necrosis of immature and actively proliferating cells i.e. the blastemal component, and cell maturation in other components [6,9,10]. The

differentiated component appears histologically benign with negligible proliferating index [10]. However, rate at which the therapeutic agents induce differentiation process i.e. rhabdomyomatous and chondromatous is still unknown [7,10]. In the present case, extensive cartilaginous differentiation presumably represents a maturation response following chemotherapy, or survival of well differentiated component in the original tumor population. The lack of evidence of chondroid differentiation on preoperative imaging favors the former over the latter. Absence of necrosis after chemotherapy is also suggestive of a stromal predominant WT lacking blastemal or other rapidly proliferating components. Reduction in tumor volume after chemotherapy is a measure of clinical response for determining postoperative treatment. Stromal predominant WTs are known not to reveal volume reduction post-chemotherapy [6,10]. In the index case, there was only slight reduction in tumor volume, suggesting poor volumetric response and need for further therapeutic intervention, and further supporting our hypothesis that extensive cartilaginous differentiation in the present case occurred as a maturation of stromal component following chemotherapy. However, studies have supported that poor

volumetric response may not represent treatment failure or aggressive tumor behavior [10,11].

Conclusion

Extensive presence of heterologous elements may confound the histological diagnosis in absence of classical triphasic appearance of WT. Volumetric response is not the only measure of response to chemotherapy; maturation and terminal differentiation to benign stromal derivatives without volume reduction can also be considered a response to chemotherapy, limiting its metastatic potential.

Compliance with ethical statements

Conflicts of Interest: None.

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Consent: All photos were taken with parental consent.

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