Familial Occurrence of Nonsyndromic Wilms Tumor—A Report in Two Siblings

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Abstract Nephroblastoma, (otherwise known as nephroblastoma) a second most common malignant neoplasm in childhood has been reported in twins, siblings & successive generations. We report two cases of Wilms tumor in female and male siblings first noticed in each at 14 months of age. No congenital anomalies were observed in these patients. Both patients were treated with surgery & histopathology of both the specimens showed a well differentiated Wilms tumor with favourable histology. On follow up both the patients are alive and in complete remission, 4 years after the diagnosis in female & 6 months after the diagnosis in the male sibling.

Keywords Nephroblastoma · WILMS tumor · Familial cancer · Childhood tumors

Introduction

Wilms tumor (otherwise known as nephroblastoma) is an embryonic tumor of the kidney that usually occurs in children less than 8 years of age [1] and constitutes 8% of all the

pediatric cancers [2]. Genetic predisposition and/or a common family environment may contribute to an increased cancer risk in families [1]. Only 1–2% of Wilms tumor cases cluster within families, but the underlying causes of these rare pedigrees are heterogeneous and complex. Furthermore, several families not linked to *WT1*, *FWT1*, or *FWT2* exist, indicating further genetic heterogeneity in familial Wilms tumor [3]. Cochran and Froggatt reported one instance of consanguinity associated with a familial occurrence of Wilms tumor [4]. Nephroblastoma has been reported in twins, siblings, and successive generations, suggesting the possibility of a monogenic determination [5]. We report two cases of Wilms tumor in a sibship in which the neoplasm first occurred in a 14-month-old female, and then 4 years later in a male sibling, also at 14 months of age. The cytogenetic examination and molecular analyses of exon 8 and 9 of *WT1* gene showed no mutation.

Case Report

A 14-month-old female child presented with complaints of mass per abdomen (Fig. 1). The patient was apparently alright till her first birthday. There was a history of consanguineous marriage of the parents, the father being married to his own niece sister's daughters (Fig. 2). There was no family history of either malignancy or renal diseases. Weight of the baby was 15 kg (>90th percentile). On examination, the only abnormality was the abdominal mass in the right lumbar region. An ultrasonography was performed and a diagnosis of Wilms tumor, which measured 65×61 mm, was given. An ultrasound-guided fine-needle aspiration cytology (FNAC) of the mass was done, which showed features consistent of Wilms tumor, a predominant blastemal component, with varying degrees of epithelial and stromal elements. Early epithelial differentiation was identified at FNAC as rosette-like and gland-like

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Fig. 1 Post operative picture of propositus

structures; stromal elements seen were fibrocytes (Figs. 3, 4, and 5).

On the basis of diagnosis, a nephrectomy was performed

Pathology

GROSS The tumor measured $9 \times 7 \times 4$ cm and was contained within the renal capsule. Surgical margin of the ureter and the vessels appeared to be clear. No tumor was seen in the renal vein or artery. Microscopy showed a triphasic pattern of tumor cells, with predominant blastemal and epithelial component. Stromal cells were in the form of fibrocytic spindle cells. No features of anaplasia were detected. The surgical margins, capsule, and renal vein were free of tumor cells. The patient was discharged and a regular follow-up for a year showed her to be doing well.

PEDIGREE ANALYSIS

Fig. 2 Pedigree analysis

Fig. 3 Cut surface of tumor showing solid, homogeneous, lobulated appearance

Second Sibling

After 4 years, the mother of the patient noticed a similar change in her second sibling—a son—since 12 months of age. On consulting a pediatric surgeon, a mass was detected in the left renal region. An ultrasonography was ordered, which showed a mass suggestive of Wilms tumor measuring 71×64 mm. Considering all the clinical and radiologi-

Fig. 4 Photomicrograph showing I) Abortive glomeruli. II) Abortive tubules. III) Blastemal component. IV) Mesenchymal component

Fig. 5 Photomicrograph showing I) Normal kidney II) Tumor

ical features, an FNAC diagnosis of Wilms tumor was made. A nephrectomy was performed and specimen was sent to the Department of Pathology.

GROSS The neoplasm in the present case measured 9×7×4 cm external surface showed an intact capsule. Surgical margins appeared to be clear. No tumor was detected in the renal vein or artery. Ureters were not received (Fig. 6). Cut surface of the tumor was grey white and was lobulated. The microscopic features were similar to that in the case of Wilms tumor of his sister. Patient is doing well 6 months

Fig. 6 I) Fibrous septa dividing the tumour in to lobules. II) Grey white solid area. III) Compressed normal kidney

Fig. 7 Photomicrograph showing triphasic components of Wilms tumor

after the surgery. A detailed family history was taken and all siblings were called up. Blood samples of both parents and step sister and brothers were sent for *WT1* gene analysis by polymerase chain reaction sequencing—no mutation on exon 8 and 9 of *WT1* gene in any of the samples was found (Figs. 7 and 8).

Discussion

Knudson and Strong claim that 62% of Wilms tumors are nonhereditary and 38% hereditary. They distinguish the nonhereditary forms as having sporadic occurrence, later age of onset, and being unilateral. Hereditary cases are characterized by anomalies such as WAGR syndrome, Denys–Drash syndrome (*WT1* gene), Beckwith–Wiedmann syndrome (*WT2* gene). Familial predisposition to tumor is rare. The present report points strongly toward some

Fig. 8 No mutations in exon 8&9 Of *WT1* gene

hereditary factors conditioned by consanguinity as operating in concert with probably yet unknown genetic events [5] other exonic mutations may be involved; the gene may be silenced due to methylation and not have any mutation; other candidate genes such as *FW1* or *FW2* may be involved. This is unlikely because in such cases the age at occurrence is higher. Environmental factor common to the family cannot be excluded. With no mutation in exon 8 and 9 of *WT1* gene in both the siblings and no other congenital anomalies, the occurrence of Wilms tumor in the two siblings, but with unaffected parents, could also be explained by gonadal mosaicism in a parent. The parent would be unaffected because only gonadal tissue contained the mutant. The gene could, however, still be transmitted and the frequency would depend in part upon the fraction of gonadal tissue involved. Histopathology of both nephrectomy specimens showed a favorable histology. In conclusion, the occurrence of nephroblastoma in siblings with consanguineous parents seems to be a genetic predisposition with heterogeneity.

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