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Case Report

Wilms' tumour-associated late nephrotic syndrome responsive to treatment

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Introduction

Wilms' tumour (WT) is the most common cancer of the genitourinary tract in childhood. An important feature of WT is its association with congenital anomalies, e.g. genitourinary anomalies (4.4%), hemihypertrophy (2.9%) and sporadic aniridi. A specific association of nephropathy with WT and male pseudohermaphroditism is known as Denys–Drash syndrome (DDS) [1]. Recently, DDS has been extended to include patients who have only two features of the disease, including diffuse mesangial sclerosis (DMS) [2]. Renal disease occurring later in children who had been free of renal disease for many years has also been reported. Histology showed focal segmental glomerulosclerosis (FSGS) which was interpreted as being secondary to hyperflitration [3–6]. Such FSGS was resistant to therapy and eventually progressed to renal failure [3–6].

We observed a case of WT who developed glomerulopathy after disease-free survival for 6 years. She responded to cyclophosphamide and remained in remission during the subsequent 3 years.

Case

A 10-month-old girl presented with a left flank mass 6×7 cm in diameter which her mother had noticed. The rest of the physical examination was unremarkable. Urinalysis revealed no protein but 1–2 erythrocytes per high power field. Ultrasonography and abdominal Computed tomography (CT) revealed a solid mass with cystic components in the left kidney which compressed the left ureter. According to Wilms' Tumour Study-III protocol, she was considered as having stage II WT. A left nephrectomy was performed. The histopathology of the left kidney revealed a mixed type WT with no anaplasia (Figure 1A) and no evidence of glomerulosclerosis or intrinsic anomaly of renal tissue (Figure 1B). Following the surgery, she received chemotherapy consisting of vincristine 1.5 mg/m^2 and actinomycin D 15 μg/kg. She was in remission for the next 6 years and was followed by the Oncology Department, with normal clinical findings and urinalysis. In 1995 at the age of 7 years, 3+ proteinuria with microscopic haematuria was found. The physical examination was unremarkable with normal blood pressure. Laboratory findings revealed a haemoglobin of 11.9 g/dl, WBC 8700/mm^3, with normal differential count. Urinary protein excretion was 250 mg/m^2/h, serum total protein 5.8 g/dl, albumin 3.3 g/dl and cholesterol 206 mg/dl. Serum BUN, creatinine, triglycerides, C3, C4, IgA levels and the urinary Ca/Cr ratio were normal. Anti-nuclear and anti-DNA antibodies, HBsAg and anti-HBs antibody were negative. Abdominal ultrasonography revealed a bilateral hyperechogenic cortex, compatible with glomerular disease. Abdominal tomography was normal, with no evidence of recurrence of WT. The karyotype of the child revealed 46XX. The screen for mutation of the *WT1* gene exons 8 and 9 and flanking regions by polymerase chain reaction (PCR) and direct sequencing [7] of the patient's native DNA was negative. Her parents did not give a permission for an open renal biopsy so she was put on prednisolone for 2 months without response. Then she was put on cyclophosphamide (2 mg/kg/day) with low dose prednisolone (10 mg/day) for a 3 month period. She responded to the treatment had a complete remission and remained in remission for the subsequent 3 years without treatment, not even exhibiting microalbuminuria.

Discussion

The association of nephropathy with WT and male pseudohermoaphroditism is known as DDS [8]. The

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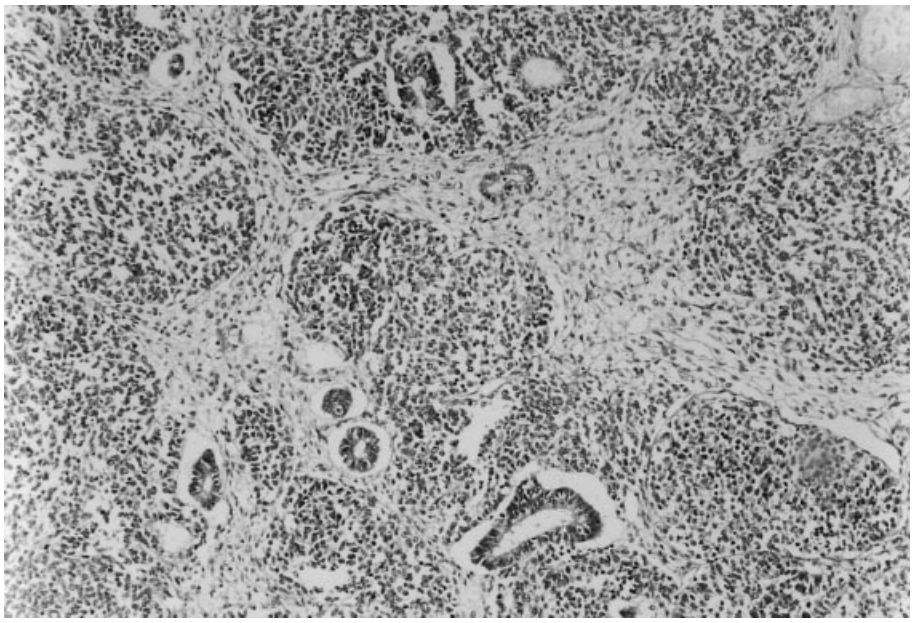
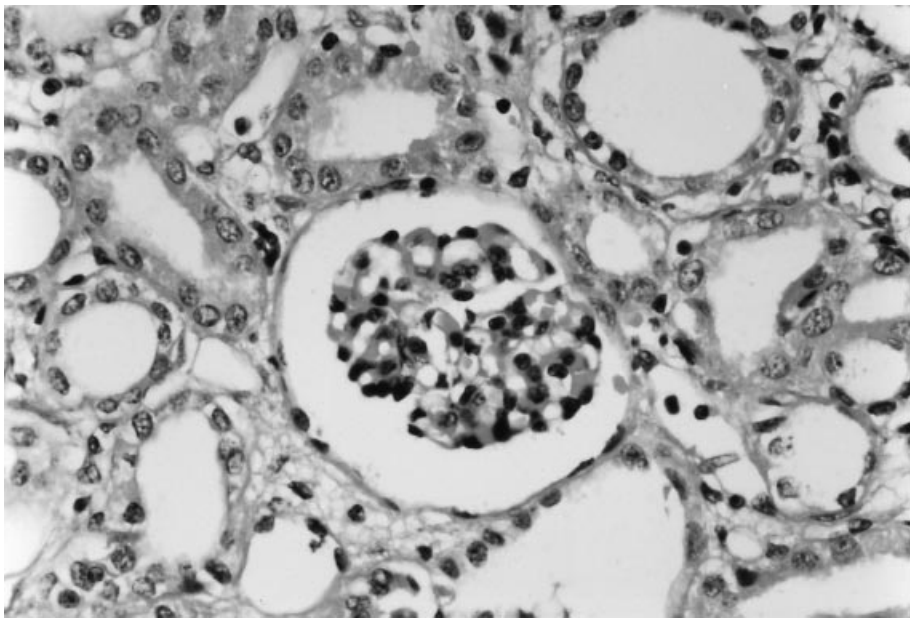


(A)



(B)

Fig. 1. (**A**) Tumour histology revealed a mixed pattern of the epithelial component represented by the round oval tumour tubules, immature mesangial elements along with undifferentiated blastemic cells. (**B**) A glomerulus from the residual normal kidney showing no anaplasia and no evidence of glomerulosclerosis or intrinsic anomaly, but congestion.

diagnosis of DDS is accepted even in the absence of either pseudohermaphroditism or WT [2]. The common denominator is the presence of nephropathy, i.e. DMS [2]. This is characterized by a nephrotic syndrome, most often occurring in the first 2 years of life and progressing rapidly to end-stage renal failure within a year [9–11]. WT is believed to arise from malignant transformation of abnormally persistent renal stem cells which retain embryonic differentiation. The *WT1* gene at 11p13 and additional genes at 11p15 and 16q have been implicated in the development of WT [12]. In DDS, missense mutations in exons 8 and 9 of *WT1* gene give rise to WT, partial gonadal dysgenesis is severe especially when WT is present [13]. Frasier syndrome (FS) is caused by donor splice site mutations in *WT1* [15]. FS and DDS have common features such as nephrotic syndrome and a 46XY karyotype. A normal female karyotype, WT and the absence of *WT1* intron 9 splice site mutation excluded FS in our patient [15].

On the other hand, renal symptoms may also be seen after the WT is removed [3–6]. In these cases,

renal lesion is mostly in the form of FSGS and in one case FSGS together with membranoproliferative glomerulonephritis (MPGN). These cases were resistant to therapy and eventually progressed to renal failure. Whether the *WT1* gene or additional genes are responsible in this association is yet to be defined.

Our patient presented with haematuria and nephrotic range proteinuria after a 6 year disease-free period. Unfortunately, as we were not able to obtain permission to perform a renal biopsy, the histopathology of the renal lesion is uncertain. The unique feature in our patient is the response of FSGS to therapy. The complete response to therapy, with long-lasting remission, normal female karyotype, and no mutation in exons 8 and 9 of the *WT1* gene make it unlikely that the diagnosis was DDS [7]. The pathogenesis of late nephropathy in WT may involve different mechanisms such as post-operative radiation therapy, deposition of immune complexes in the glomeruli or compensatory hyperperfusion of the remaining renal tissue [3,16]. Our patient did not show any evidence of associated renal histopathology of nephrectomy material, which could have facilitated FSGS along with hyperperfusion, and did not receive radiotherapy.

Although we cannot exclude FSGS along with hyperperfusion or a coincidental nephropathy such as minimal change nephrotic syndrome or membranous nephropathy, these possibilities are not likely because of the different presentation and outcome of glomerular disease in our patient compared with cases of WT and late nephropathy reported in the literature.

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