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LATE RECURRENCE OF WILMS TUMOUR WITH EXCLUSIVE SKELETAL MUSCLE PHENOTYPE, 23 YEARS AFTER PRIMARY.

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Keywords: Wilms tumour, late recurrence, relapse, skeletal muscle phenotype.

ABSTRACT

A late recurrence of Wilms tumour 23 years after the primary diagnosis is described.

The primary tumour occurred in a 10 months old girl and showed various degrees of differentiation, including skeletal muscle phenotype. A postoperative chemotherapy was performed. Twenty-three years after surgery, the tumour relapsed: the lesion was exclusively composed of mature skeletal muscle elements (diffuse and intense desmin reactivity) derived from the primary tumour, as confirmed by WT1 immunoreactivity.

Chemotherapy and radiotherapy have been reported previously to ablate the immature components of Wilms tumour; especially, chemotherapy can modify the histological type reducing the immature elements while leaving mature cells un-affected. We can hypothesise that both, the morphological and molecular features of the tumour as well as the effect of therapy can influence a tumour-relapse in Wilms tumour. The latter results in a high degree of differentiation and a long disease-free interval after the first diagnosis.

INTRODUCTION

Wilms tumour (WT) is the most common primary malignant renal tumour in children.

The association of chemotherapy and radiotherapy to radical nephrectomy has increased the overall survival rate up to 85-90% [3,6];however, in spite of these therapeutic improvements, tumour relapses in a subset of patients (15-20%) [12].Numerous studies have demonstrated that the risk of recurrence can be associated to different features such as histological tumour pattern and loss of heterozygosis (LOH) at 1p and/or 16q, as well as gain of chromosome 1 and other recently described alterations [8,18,7,14]. The recurrence risk is greater within the first 2 years after primary diagnosis (in these patients the percentage of survival approximaly ranges from 24% to 43%) but late relapses have occasionally been reported [1,10].

We here report a case of late recurrence of Wilms tumour, 23 years after primary diagnosis.

CLINICAL HISTORY

In October 2005 a 23 years-old female came to medical attention for abdominal recurrent pain and occlusive status. Physical examination revealed an abdominal soft mass in the peri-umbilical region; hematochemical analysis showed normal values for gastrointestinal cancer-associated antigens, carcinoembryonic antigen (CEA), α-phetoprotein (αFP), carbohydrate antigen 19.9 (CA 19.9) and carbohydrate antigen 125 (CA 125). Abdominal ultrasonography, computed tomography (CT scan) and magnetic resonance imaging (MRI) disclosed two masses: the first one was placed in the right peri-umbilical region whereas the second one, placed in left retroperitoneal space, caused compression of the wall of the small bowel. A tomography emission of positron (PET scan) showed no signal accumulation. The patient underwent surgical removal of the abdominal and retroperitoneal masses. Nine months after surgical removal the patient is disease-free.

A left nephrectomy with surgical removal of a Wilms tumour had been performed 23 years before (in September 1982). An histopathological diagnosis of Wilms tumour (G2, favourable histology) with differentiation towards epithelial (tubular elements), blastematous and rhabdomyoblastic features was made. No preoperative chemotherapy was performed, but following surgery the patient underwent cycles of chemotherapy with actinomicin D and vincristine. The subsequently follow-up was negative for the following 23 years.

MATERIAL AND METHODS

The surgical material was totally examined and accurately sampled. The surgical specimens of both masses were fixed in 4% buffered formaldehyde and embedded in paraffin and the routine histological sections of 3μm were prepared and stained with haematoxylin and eosin (H&E). Additional sections, collected on poly-L-lysine coated slides, were used for the immunohistochemistry analysis. Immunohistochemical reactions using antibodies anti-desmin (monoclonal antibody, clone D33, diluted 1:50, DAKO Glostrup Denmark), anti-smooth muscle actin (monoclonal antibody, clone 1A4, pre-diluted, Ventana-Diapath, Tucson, AZ, USA) and Wilms tumour 1 Protein (WT-1) (monoclonal antibody, clone 6F-H2, diluted 1:20, IMGENEX) were performed in an automated immunostainer (Ventana BenchMark AutoStainer, Ventana Medical Systems, Tucson, AZ, USA).

RESULTS

Pathological findings

A left nephrectomy with excision of the renal hilum lymph-node and the omentum was performed in September 1982. Grossly, the surgical specimen measured 14x12x8 cm and displayed a pale grey appearance with diffuse hemorrhagic areas; at the cut surface two

different nodes were present: the first one, measuring 6 cm, close to the renal hilum and the second one, measuring 9 cm, localized at the inferior renal pole. At the histological level (the slides were collected and revised in our Institute) the lesion showed various degrees of cell differentiation within the different cell components (epithelial, blastematous and stromal). The tumour cells were organized in nodes either isolated or confluent in clusters and diffusely invading the residual renal parenchyma **(fig.1 a)**; focally, epithelial cells assumed a pseudo-glandular architecture **(fig.1 b, c)**. The mesenchymal tumour cells were elongated or rounded with a scanty cytoplasm and voluminous and iper-chromatic nuclei. In some areas, representing about 10% of the tumour, skeletal muscle with elongated cells showing an intra-cytoplasmatic cross-striations was present **(fig.1 d)**. No evidence of nephrogenic rests was found. The renal capsule and the omentum appeared infiltrated by proliferating neoplastic cells. The renal hilum lymph-node examined did not display any metastatic cells. A confirmatory diagnosis of Wilms tumour (G2, favourable histology) with epithelial, blastematous and rhabdomyoblastic differentiation was made (Stage III).

The lesion removed in October 2005 was represented by two different surgical specimens: a well circumscribed mass of abdominal wall, measuring cm 14x11x2 and a retroperitoneal mass adjacent the small bowel, measuring cm 11,5x9x3,5. Macroscopically, both lesions were lobulated, encapsulated and showed a stiff-elastic consistency. At cut-surface, both lesions appeared yellow-whitish in colour and with a fasciculated appearance. Microscopically, both lesions showed an exclusive benign-appearing stroma component with mature skeletal muscle; no evidence of immature elements or nephrogenic rests was found **(fig.2 a, b)**. In the lesion adherent to the small bowel, such proliferation of mature skeletal muscle elements was not displaying any infiltrating pattern towards the bowel wall. Such elements were arranged in bundles separated by fibrous tissue and presented intra-cytoplasmatic cross-striations, an eosinophilic cytoplasm and a peripheral nuclear location

(fig.2 b). Necrosis was absent. Immunohistochemical studies showed diffuse and intense desmin **(fig.2 d)** and WT-1 **(fig. 2 c)** reactivity. Cells were negative for smooth muscle actin, (which was positive in vascular structures only) and had a low proliferation index (Ki67<1%).

Altogether, the morphological and immunohistochemical features displayed by the two lesions, together with the previous history of Wilms tumour and the lack of any infiltrating or invading growth pattern addressed to a diagnosis of late recurrence of Wilms tumour with exclusive mature skeletal-muscle component.

DISCUSSION

Approximately 15-20% of cases of Wilms tumour relapse, more frequently within the first 2-5 years following the primary diagnosis; in these cases, the risk of recurrence is mainly related to the morphological and molecular features of the previous tumour [12,8,18,7,14].

Late recurrences (>5 years after primary diagnosis) of Wilms tumour are very rare [16,11,2,15,13,4,5] and in all described cases, but one, similar histological patterns between the original and the relapsing tumour are reported with a persistence of immature cells, blastematous elements or nephrogenic rests [16,11,2,15,13,4]. In one case only, which was a late (23 years) recurrence, differentiated epithelial cells in absence of immature elements (in contrast of the original tumour showing predominantly blastematous and immature elements) were reported [5]. The case here described showed two well circumscribed lesions with a stiff-elastic consistency, exclusively composed of mature skeletal muscle elements derived from the primary tumour, as confirmed by WT1 immunoreactivity. In addition, absence of necrosis and pleomorphism and the low proliferation index (<1%) further excluded the possible differential diagnosis with a sarcomatous lesion.

Zuppan and co-workers recently stressed that preoperative chemotherapy is associated to changes of the histological features, thus creating an ambiguity on Wilms tumour staging according to tumour response [19]. They outlined that the therapy effect is variable depending on the different histological subtypes of Wilms tumour: some tumours show little therapy effects with persistence of abundant and proliferating blastema elements, others show an “atrophic pattern”. Sometimes, the loss of most embrional elements induced by therapy is accompanied by persistence of mature heterotopic elements such as mature skeletal muscle, cartilage or adipose tissue [19]. Blastematous cells usually show a dramatic response leading to necrosis, whereas mature tubular and skeletal muscle cells tend to persist [17].

We can hypothesise that since preoperative chemotherapy is able to enhance the grade of differentiation, postoperative chemotherapy as well could induce “tumour maturation” and that in our patient a maturation of residual tumour cells occurred.

Confirmatory evidence to such hypothesis is found in the literature, where a lesion entirely represented by mature skeletal muscle, similar to our relapsing tumour, was reported in the controlateral kidney in two children treated with radiotherapy for Wilms tumour following surgery [9].

Evidence is therefore accruing that chemotherapy and radiotherapy can ablate the immature components of tumour, operating a sort of selection leading, in some cases, to the exclusive persistence of mature elements [17].

In conclusion, different factors can affect a possible tumour-relapse in Wilms tumour: the morphological and molecular features of the tumour (LOH at 1p and/or 16q, gain 1q, etc.) and/or the therapy effect on the tumour itself. Also, we can consistently hypothesize that two different types of Wilms tumour recurrences can be recognised: a more undifferentiated one, which usually appears after a short disease-free interval and could be associated to a more aggressive tumour with specific genetic alterations and a worse

prognosis, and a second type, eventually related to therapy, presenting a high degree of differentiation and a long disease-free interval after the first diagnosis. The last one generally has an indolent course. The peculiarity of our case consists on the long disease-free interval from the primary tumour, as well as on its morphological well differentiated features probably induced by chemotherapy.

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LEGENDS

Figure 1: **Histological features of the primary Wilms tumour (surgical removed in September 1982).** The tumour showed the coexistence at epithelial (tubular elements) blastematous (**a** 10x**, b**40x**, c** 20x), and rhabdomyoblastic (**d** 40x) elements; areas of necrosis were also present.

Figure 2: Histological and immunophenotypical features of the Wilms tumour recurrence (surgical removed in October 2005). The late relapse of Wilms tumour showed an exclusive benign-appearing stroma with the skeletal muscle component without the evidence of immature elements or nephrogenic rests (**a** 10x**, b** 20x). The lesion was immunoreactive for WT-1 (**c** 40x) and desmin in neoplastic muscular cells (**d** 20x).