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Original Paper

Fetal Rhabdomyomatous Nephroblastoma: a Tumour of Good Prognosis but Resistant to Chemotherapy

Ph. Maes,[1] J. Delemarre,[2] J. de Kraker[3] and J. Ninane[1]

[1]Department of Paediatric Haematology and Oncology, Cliniques Universitaires Saint-Luc, Catholic University of Louvain, Brussels, Belgium; [2]Department of Pathology; and [3]Department of Paediatric Oncology, Emma Kinderziekenhuis/AMC, Amsterdam, The Netherlands

Fetal rhabdomyomatous nephroblastoma (FRN) is a rare variant of Wilms' tumour. The tumour chiefly consists of fetal striated muscle with particularly distinct striations and central nuclei. To determine the effect of (preoperative) chemotherapy in the treatment of this subtype of nephroblastoma, a retrospective analysis was performed. By 1 November 1991, SIOP 9 had registered 852 patients (pts) from 55 centres. We report on 13 children diagnosed with FRN between 1988 and 1992 with a median age of 2 years and 1 month (range 1 month–8 years 6 months). There were 7 boys and 6 girls. 9 patients were classified as stage I, 2 as stage II, 1 as stage III and 1 as stage V. 12 patients received preoperative chemotheraphy with actinomycin-D and vincristine for 2 weeks (1 pt), 4 weeks (5 pts) and 8 weeks (6 pts) respectively. The average tumour volume at registration (determined by ultrasonography) in 12/13 patients was 965 cm^3 (range 17.3–2520 cm^3). 3/7 of the FRN patients showed no tumour regression after 4 weeks preoperative CT and 4/8 after 8 weeks preoperative chemotheraphy (compared with only 28 and 34%, after 4 and 8 weeks CT, of all trial patients). Of 13 patients, 10% are alive and free of disease with a mean follow up of 4 years. This variant of Wilms' tumour is a poor responder to preoperative chemotheraphy and is associated with a generally favourable outcome in most of all unilateral cases when treated by surgery. © **1999 Elsevier Science Ltd. All rights reserved.**

Key words: nephroblastoma, Wilms' tumour, fetal rhabdomyoma
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INTRODUCTION

NEPHROBLASTOMA (WILMS' tumour) is a well known malignant embryonic renal tumour. Classic Wilms' tumours contain three microscopic elements: tubular structures with lumina, compact undifferentiated areas consisting of blastema and areas composed of fibrous, myxoid or fibromyxoid tissue or stroma [1, 2]. There are numerous variations and deviations from this usual picture of a trimorphic nephroblastoma. Predominance of tumour areas with skeletal muscle differentiation has been found in a substantial number of nephroblastomas diagnosed below the age of 1 year [3–6]. The less aggressive clinical behaviour of the latter tumours, despite their frequent bilateral occurrence and huge size at diagnosis, justified the assignment of fetal rhabdomyomatous nephroblastoma (FRN) as a variant of nephroblastoma. They consist chiefly of fetal striated muscle with particular distinct striations and central nuclei. The present paper describes 1 such patient treated with the SIOP 93-01 protocol and reviews retrospectively the effect of (preoperative) chemotherapy in the treatment of this subtype of nephroblastoma. The patients were selected on their histopathology findings, compatible for FRN, out of 852 trial and study patients registered in the SIOP 9 protocol.

PATIENTS AND METHODS

By 1 November 1991, SIOP 9 had registered 852 patients from 55 centres. Tissue blocks were sampled from all tumours and review was performed within the SIOP nephroblastoma committee in Amsterdam, The Netherlands.

Correspondence to J. Ninane, Rue Les Brûlés 4, B 1421 Ophain, Belgium, e-mail: jacques.ninane@worldonline.be
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Thirteen of them (1.5%) were classified as FRN on their histological basis. Clinical records with operative and therapeutic reports were available and were reviewed. One case of FRN treated in the SIOP 93-01 protocol is described.

SIOP-9 trial patients

Patients' characteristics. All tumours occurred in infants and children from the age of 1 month to 8.5 years, with a median age of 2 years and 1 month (Table 1). There were 7 boys and 6 girls. 9 patients were classified as stage I, 2 as stage II, 1 as stage III and 1 as stage V. 12 patients received preoperative chemotheraphy following the SIOP 9 protocol, with Act-D and VCR for 2 weeks (1 pt), 4 weeks (5 pts) and 8 weeks (6 pts). One patient was treated by two different kinds of preoperative chemotheraphy. He was first misdiagnosed as neuroblastoma and finally diagnosed as a FRN after surgery.

Tumour regression following preoperative chemotherapy. The average tumour regression of 7/13 patients was -20.8% after 4 weeks of preoperative chemotheraphy, with a range from -59% to $+8.3\%$. After 8 weeks of preoperative chemotherapy the average tumour regression in 7/13 patients was -25.2% ranging from -69.4% to $+13.6\%$. In some cases the exact weight or tumour volume at registration and/or re-evaluation was not recorded. They were, therefore, not included in this analysis. Patient 10 who received only 2 weeks of chemotheraphy was also not included in this analysis of response. We observed no tumour regression after 4 and 8 weeks of chemotherapy in only 28% and 34% of all trial patients, compared with 43% (3/7) and 50% (4/8) of those with FRN (Table 2). These differences did not achieve statistical significance.

Pathology findings. The average tumour volume at registration was 965 cm^3 (12/13 patients), with an average weight of 476 g (11/13 patients). In spite of their great size, most tumours had remained encapsulated and were diagnosed as a stage I or II following the SIOP classification. Only one tumour was classified as stage III and one case was bilateral and staged as stage V. Microscopically, the tumours were almost exclusively of striated muscles cells in a myxoid background. Foci of blastema with tubules were present allowing the diagnosis of nephroblastoma. The monophasic predominance of striated muscle in mature fibrous tissue is diagnostic for the FRN (Table 1).

Evaluation of patients. Of 13 patients, 10 are alive and free of disease with a mean follow-up of 4 years. 2 patients were lost to follow-up, 1 after 3 months due to other causes. Another patient died almost 2 years after the first nephrectomy. She showed a bilateralisation 1 year and 5 months later. She died 6 months after the second operation due to overhydration with pulmonary oedema after haemodialysis. There was no active tumour tissue found at autopsy.

RESULTS

Case report

A 6-month-old caucasian boy was admitted to the hospital with 'digestive problems'. There was a suspicion of constipation

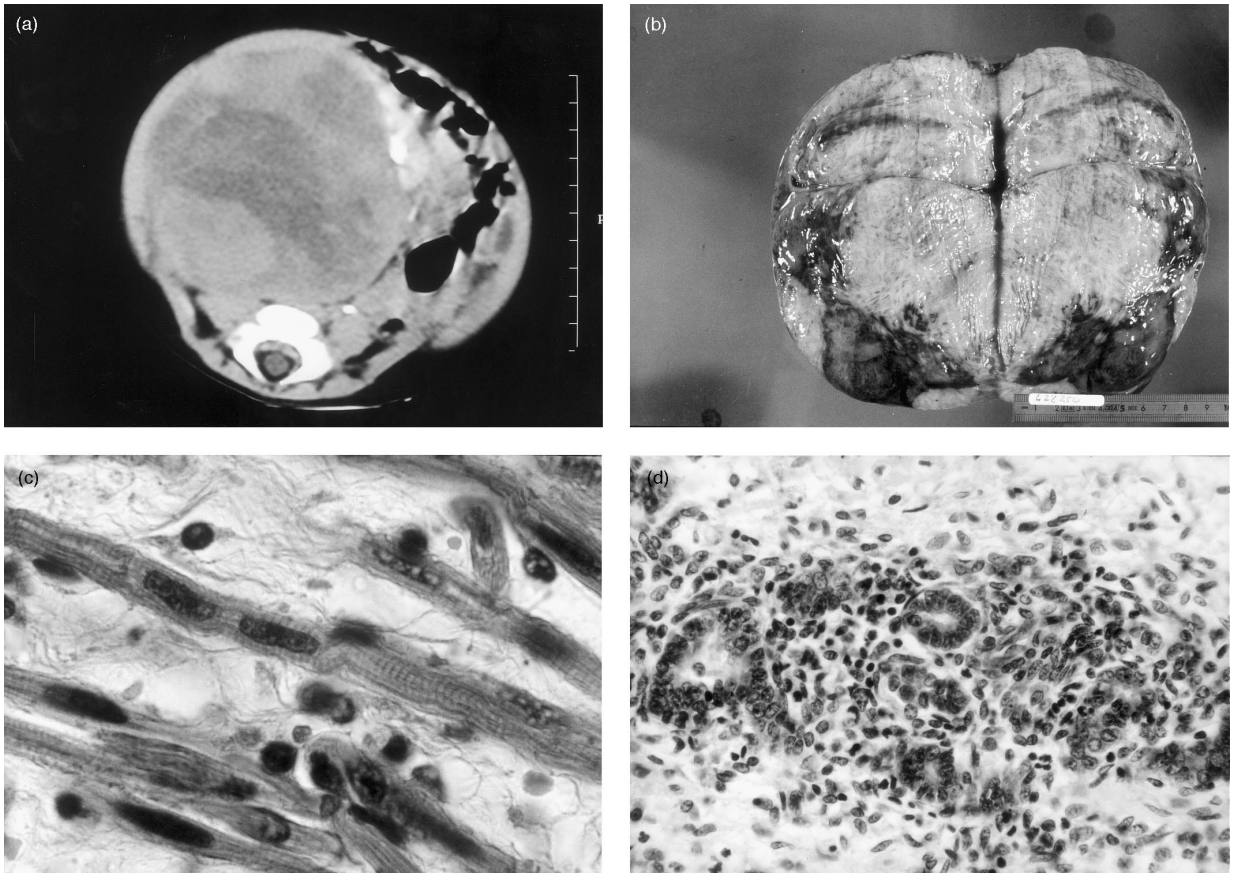

Figure 1. (a) Computed tomographic scan of the abdomen revealing a large well-demarcated tumour in the right kidney. (b) Primary tumour shown on cut section, replacing most of the kidney and of variegated appearance. The white areas were necrotic. (c) The tumour was constituted almost exclusively of striated muscle cells in a myxoid background. (H & E,×1500) (d) Rare foci of blastema with tubules were present, allowing the diagnosis of nephroblastoma. (H & E,×610).

Table 1. *Clinical and pathological features of FRN in* 13 *patients treated according to SIOP* 9 *protocol*

SIOP No: trial patients	1	2	3	4	5	6	7	8	9	10	11	12	13
Sex	F	F	M	M	M	M	M	F	M	M	F	F	F
Age at operation (months)	12	1.5	19	50	44	30	19	6	98.5	16	7.5	11.5	12.5
Side of tumour	R	L	L	R	L	R	L	L	L	R	Bilateral	L	R
Metastases at registration	—	—	—	—	—	—	—	—	—	—	—	—	—
Tumour volume at registration (cm^3)	608	680	560	2520	2058	17.3	417.5	616	2376	520	R: 4 cm diam./ L:?	165	1040
Tumour volume after 4 wks chemotherapy (cm^3)	410	680	227	ND	1157	17.3	ND	ND	ND	ND	ND	179	845
Tumour volume after 8 wks chemotherapy (cm^3)	432	ND	243	770	1112	ND	474.4	616	2640	ND	R: 7.5 cm diam./ L:?	ND	ND
Tumour evolution after 4 wks chemotherapy (cm^3)	− 32.5%	0.0%	− 59.0%	ND	− 43.80%	0%	ND	ND	ND	0 after 2 wks	ND	8.30%	− 18.70%
Tumour evolution after 8 wks chemotherapy (cm^3)	− 29.0%	ND	− 56.6%	− 69.40%	− 46.00%	ND	13.60%	0	11.00%	ND	87.50%	ND	ND
Histopathology:													
Weight (g)	320	336	168	—	700	—	400	340	1680	270	R: 80/L:2	192	750
Local stage	I	I	II	I	I	I	I	I	I	II	V (local stage R:I/L:I)	I	III
Microscopic features:													
Fetal skeletal muscle	xx	xx	xx	x	x	x	x	x	xx	xx	x/x	x	xx
Mature fibrous tissue	x	x	x	x	x	x	xx	x	x	x	xx/xx	x	xx
Blastemal tissue	x	x	x	Irregular	xx	Irregular	x	Irregular	x	x	x/x	x	x
Differentiation	epithelial	—	—	Myoblastic	Rhabdomyoid	Sclerosering glomerul ~ Drash syndrome	Rhabdomyoid and mesenchymal	Rhabdomyoid and mesenchymal	—	Fibroadenomatous	—	Rhabdomyoid and mesenchymal	—
Outcome	Alive and well 3 years postoperative	Alive and well 4.5 years postoperative	Alive and well 2.5 years postoperative	Lost to follow-up after 3 months	Lost to follow-up	Alive and well 3 years postoperative	Alive and well 6 years 2 months postoperative	Alive and well 5 years 1 months postoperative	Alive and well 5 years 5 months postoperative	Alive and well 3 years 9 months postoperative	Alive and well 5 years 8 months postoperative	Bilaterisation on 29/04/93 Dead 2 years postoperative due to pulmonary oedema	Alive and well 8 years postoperative

R, right; L, left; F, female; M, male; ND, not done.

Table 2. Tumour regression in 13 FRN patients and 382 trial patients treated according to SIOP 9 protocol

	Tumour regression			
FRN ($n=13$)	None	1–25%	26–50%	>50%
4 weeks (%) ($n=8$)	4 (50)	1 (13)	2 (25)	1 (13)
8 weeks (%) ($n=7$)	3 (43)	0 (0)	2 (29)	2 (29)
SIOP 9 ($n=382$)	None	1–25%	26–50%	>50%
4 weeks (%) ($n=193$)	53 (28)	36 (19)	29 (15)	75 (39)
8 weeks (%) ($n=189$)	63 (33)	38 (20)	25 (13)	63 (33)

FRN, fetal rhabdomyomatous nephroblastoma.

and visible swelling of the abdomen was noticed. On admission, examination revealed a well developed boy weighing 7.75 kg and measuring 68 cm. Statokinetic and mental development were normal. A firm, smooth tumour (18×8 cm) was palpable in the right upper abdominal quadrant. Arterial hypertension was detected. Laboratory analyses showed normal blood cell counts as well as normal coagulation tests. Serum concentration of creatinine was 0.45 mg/dl, urea 14 mg/dl, LDH was elevated at 2380 IU/L (normal values for age: 100–340 IU/L). Urinalysis values and urinary catecholamines were within normal limits. Neuron specific enolase was also normal. Ultrasonography and computed tomography (CT) scan of the abdomen showed a tumour mass originating from the right kidney (Figure 1a); the inferior vena cava was found to be patent. Chest X-ray was normal. Due to his age and the tumoral site, the diagnosis of nephroblastoma was suspected.

He was treated with the SIOP 93-01 preoperative protocol, which includes treatment for 4 weeks with vincristine (VCR) 1.5 mg/m^2 every week plus two cycles of actinomycin-D (Act-D) 15 μg/kg for 3 days on weeks 1 and 3. The tumour mass did not respond to preoperative chemotheraphy, and there was progression of the tumoral volume with a dramatical evolution to multiple organ failure. Therefore, tumour extirpation and right nephrectomy (weighing 1110 g and measuring 18×8×6 cm) were performed (Figure 1b). Microscopic examination confirmed a diagnosis of Wilms' tumour and more specifically a fetal rhabdomyomatous nephroblastoma due to a large predominance of fetal striated muscles (Figs 1c–d). On the basis of the histological diagnosis and the lack of response of the tumour mass to preoperative chemotherapy, chemotherapy was then applied as for stage I Wilms' tumour, High grade malignant, without radiotherapy according to the SIOP 93-01 protocol. At the time of this report cytostatic treatment has been completed. The child is free of recurrence and metastasis 15 months after his last chemotherapy course.

DISCUSSION

In 1976 Wigger reviewed 15 cases of FRN that had been initially classified as rhabdomyoma (Zenker) or myoma striocellulare (Virchow) and added 5 cases [3]. More recently Schneider and colleagues reported two cases of aniridia associated with FRN [7]. The tumours were unusually large and appeared to be encapsulated. Local recurrence without metastasis occurred in four cases and metastases were noted in 4 patients. The most important and difficult distinction is between FRN and the usual Wilms' tumour. Skeletal muscle may also occur in some Wilms' tumours, but then it is usually scattered among other tumour cells. The monophasic predominance of striated muscle, with particularly distinct striations and central nuclei, is diagnostic for FRN and responsible for the fibromyomatous gross appearance. Both FRN and Wilms' tumours are derived from the mesoblast of the nephrogenic mesoderm. These cells form the metanephric blastema of the kidney formation and have the ultrastructural characteristics of epithelial cells, similar to the neoplastic epithelial cells of the Wilms' tumour [8]. It still remains unclear which factors regulate the predominant development into either epithelial (classical Wilms' tumour) or connective tissue cell lines (FRN).

The amount of neoplastic epithelial cells has been recognised as a significant indicator for the survival of patients with Wilms' tumour [9]. The paucity of these cells in FRN seems to influence the development of local recurrence and metastases, more so than by the mode of therapy. There is a distinction between the 13 patients with FRN and patients with the classic Wilms' tumour after preoperative chemotheraphy, with less tumour regression in FRN after 4 and 8 weeks of chemotheraphy. Half of the FRN patients showed no regression at all, with tumour progression in 3 patients. This is in contrast with the trial patients of SIOP 9 protocol were 39 and 33% of patients had a tumour regression of >50% after, respectively, 4 and 8 weeks chemotherapy. Recently Saba and colleagues independently came to the same conclusion when they observed no evidence of tumour shrinkage on follow-up diagnostic imaging in 6 patients with unilateral FRN [10]. It is well established that preoperative therapy can reduce the morbidity associated with resection of very large or extensively invasive tumours. Most of the nephroblastoma studies undertaken by the International Society of Paediatric Oncology (SIOP) in Europe have involved preoperative therapy, after preliminary SIOP studies demonstrated an unacceptable high rate of intra-operative tumour rupture in conventionally managed cases [11, 12]. In the US, nephroblastomas are treated according the National Wilms' Tumor Study (NWTS), where preoperative therapy has been used less commonly.

Tumour size has also been used as a prognostic indicator. The size of nephroblastomas is inversely related to survival, i.e. tendency to recurrences and metastases [13, 14]. Some authors found that patients with volumes larger than 551 ml have a survival rate of zero. In this study, the average tumour volume in 12/13 FRN patients was 965 cm^3, ranging from 17.3 to 2520 cm^3. The usual rate and pattern of metastases of classic Wilms' tumour was not seen in these patients and their average survival rate was 4 years. There was a difference in mean age between FRN and Wilms' tumour patients. Wigger calculated the mean age of FRN patients to be 1 year 8 months and thus, lower than that of patients with common Wilms' tumour, which shows a peak between the ages of 2 and 3 years. In our series, the average age was 2 years 1 months (and even lower, 1 year 7 months, if patient 9 who was almost 9 years old, was excluded).

This retrospective study does not provide an answer to the question of whether nephrectomy and/or tumorectomy is indicated before chemotherapy in suspected FRN in young children (<2 years of age) who have unilateral nephroblastoma with an average tumour volume >1000 cm^3, but the number of patients with FRN among all Wilms' tumour patients is small. Furthermore, in cases where the diagnosis is doubt, where there is insufficient response by echo-measurements and structural changes, in the ongoing study a fine

needle biopsy will be performed. This may result in surgery at an earlier stage and thereby promote optimal subsequent therapy.

CONCLUSION

FRN is a rare variant of Wilms' tumour and a bad responder to preoperative chemotherapy. Unilateral cases of FRN have generally a favourable outcome when treated by surgery. Despite the demonstrated effectiveness of preoperative chemotheraphy in nephroblastoma in general, with the nontrivial risks of possible overtreatment and undertreatment, the increased ambiguity of tumour stage and histological evaluation after treatment, suggests that the risks and potential benefits need to be carefully weighed for each patient before implementation, in case of children younger than 2 years of age with an unilateral nephroblastoma with a tumour volume of $>1000\,cm^3$.

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