Originally misdiagnosed rhabdoid tumour of the kidney. A case report and differential diagnosis

Ivanda Franckeviča[1], Regina Kleina[2], Olga Voika[3]

[1]Children's Clinical University Hospital, Riga, Latvia
[2]Riga Eastern Clinical University Hospital, Riga, Latvia
[3]Faculty of Continuing Education, Riga Stradins University, Latvia

Rhabdoid tumour of the kidney (RTK) is considered to be one of the most aggressive neoplasms of early life. The histogenesis of RTK still remains a matter of controversy. Immunohistochemistry usually shows diffuse reactivity for vimentin, focal reactivity to the epithelial marker, variable expression of mesenchymal and neuroectodermal markers, and loss of INI1 protein staining. Expression of the Wilms' tumour protein (WT1) was described in the RTK cases. We would like to present a case of rhabdoid tumour of the kidney in Latvia, which caused diagnostic difficulties of a 27-month-old girl, and a short review of literature.

Key words: rhabdoid tumour of the kidney, Wilms' tumour, immunohistochemistry, WT1, INI1.

Introduction

Malignancies of the kidney represent approximately 6.3% of all tumours diagnosed in children below 15 years of age and 4.4% of malignant tumours in persons younger than 20 years. The most common type of renal cancer in childhood is Wilms' tumour (WT), representing 95% of all diagnoses [1]. Roughly, RTK comprises 2% of all paediatric renal tumours, and it is known to be one of the most aggressive neoplasms of early life [2]. Rhabdoid tumour of the kidney was recognized as a distinct tumour type in 1978, although initially it was classified as a possible rhabdomyosarcomatoid variant of WT [3]. The absence of muscular differentiation led to coin the term – rhabdoid tumour of the kidney – in 1981 [4]. The histogenesis of RTK remains controversial but its origin from primitive cells located in the renal medulla seems to be the most likely [5]. Various theories of RTK origin have been discussed in the literature, such as myogenous, neuroectodermal, histiocytic, epithelial, mesenchymal and mixed mesenchymal/epithelial ones. Microscopically, tumour cells typically display the cytological triad – vesicular chromatin, prominent cherry-red nucleoli and hyaline pink cytoplasmic inclusions [2]. Although RTK was historically included in the treatment protocols of the National Wilms' Tumour Study (NWTS) Group, this tumour is recognized as an entity separate from Wilms' tumour. In contrast to WT, RTK is characterized by the early onset of local and distant metastases, and resistance to chemotherapy. Whereas the overall survival rate for WT exceeds 85%, the survival rate for RTK is only 20-25% [6]. The incidence of malignant RTK in most countries has not been reported. According to the recent Society of Paediatric Oncology (SIOP) protocols, 107 cases of malignant RTK were identified from 1993 to 2005 [7]. No data on incidence of paediatric renal tumours, in particular rhabdoid tumour, have been reported in the Baltic States. Forty four primary renal tumours were diagnosed in Latvia at the Children's Clinical University Hospital from 1997 to 2010. The most common tumour type appeared to be nephroblastoma – 33 or 75% of cases. Rhabdoid tumour was diagnosed in two cases, comprising 4.54%. In the present paper the authors retrospectively analyze diagnostic difficulties as well as the results of immunohistochemical investigation obtained in one of two RTK cases.

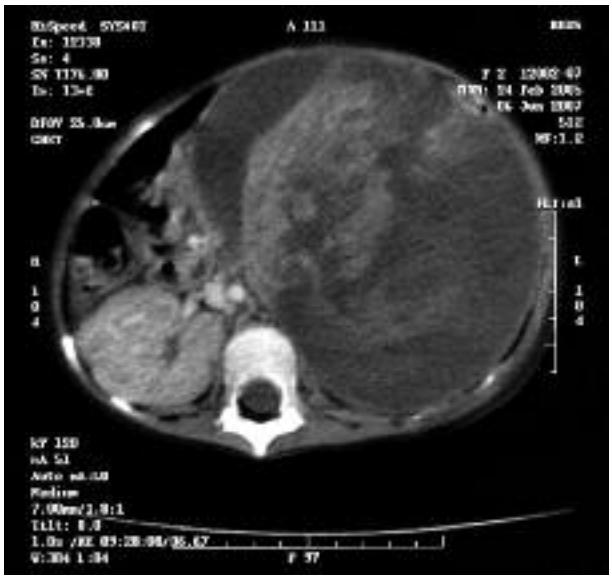

Fig. 1. Rhabdoid tumour of the kidney, CT showing a large tumour (right)

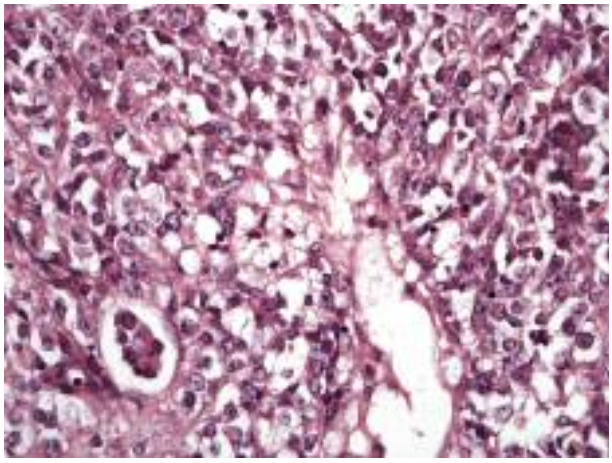

Fig. 2. Rhabdoid tumour of kidney, monotonous array of cells with abundant eosinophilic cytoplasm and spheroidal nuclei. HE, magnification 400×

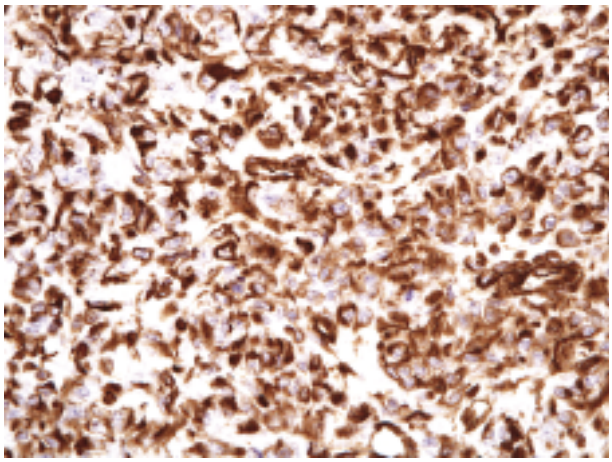

Fig. 3. Rhabdoid tumour of kidney, positive staining with vimentin in tumour cell cytoplasm. Magnification 400×

Material and methods

The nephrectomy specimen of primary RTK and lung metastasis samples were examined. The specimens were fixed in 10% neutral buffered formalin and embedded in Diawax (Diapath S.r.l, Bergamo, Italy). Four-micron-thick sections were stained with haematoxylin-eosin (HE). The formalin-fixed, paraffin-embedded tissues were cut on electrostatic slides (Histobond, Marienfeld, Germany) and investigated by immunohistochemistry using heat-induced epitope retrieval in Tris/EDTA buffer at pH 9.0 in microwave oven for 15 min at 97°C. We have determined epithelial membrane antigen (EMA), cytokeratin – AE1/AE3 (CK AE1/AE3), vimentin, Ki67, CD99, muscle-specific actin, S100, leukocyte common antigen (LCA), desmin, synaptophysin, neuron specific enolase (NSE), and CD34 (all antibodies DakoCytomation, Glostrup Denmark) using polymer conjugate system – EnVision. In addition, subsequent WT1 and INI1 protein expression in the primary tumour and metastases was investigated immunohistochemically. Clinical data were retrieved from the archive of the Children's Clinical University Hospital (Riga, Latvia). There is no ethical conflict in this report; the principles outlined in the Declaration of Helsinki were followed by the authors.

Results

A 27-month-old girl was admitted to the Children's Clinical University Hospital with anxiety, painful abdomen, recurrent vomiting, and fever of 38°C, persisting for five days. Computer tomography (CT) showed heterogeneous spherical retroperitoneal mass with sharp borders, measuring 17 cm × × 13.6 cm (Fig. 1). The patient received pre-operative chemotherapy according to the SIOP protocol and underwent nephrectomy. During the surgery, the tumour was found to infiltrate both the spleen and tissue around the aorta, spreading caudally to the small pelvis. The Department of Pathology received the renal tumour specimen of 17 cm × 10 cm × 13 cm. It was a soft and yellowish mass with areas of haemorrhages and extensive necrosis. Histologically the tumour appeared to grow in an arborising pattern with fibrovascular meshwork, providing alveolar-type architecture with small spaces lined by cells with vesicular nuclei, and prominent nucleoli (Fig. 2). Cytoplasmic inclusions were not prominent. Immunohistochemistry showed vimentin positivity (Fig. 3), and part of cells expressed CK AE1/AE3 and EMA. Muscle-specific actin, S100, CD99 and NSE were positive in rare cells. LCA, desmin, synaptophysin, and CD34 in tumour cells were negative. Ki67 often showed non-specific reaction of the cell membranes, the proliferation index was 17.41%.

Since WT1 and INI1 antibodies were not available at our department at that time, their expression was determined retrospectively. Although the growth pattern was a highly suggestive of malignant rhabdoid tumour, the panel decided in favour of Wilms' tumour blastemal type diagnosis. Apparently, diagnostic difficulties were due to extensive tumour necrosis and absence of cytoplasmic inclusions. The quality of immunohistochemical reactions was influenced by widespread necrosis. Chemotherapy was initiated according to the diagnosis of nephroblastoma, stage III, high risk. During the next 4 months, the patient received 4 courses of chemotherapy, and irradiation of the tumour bed and para-aortic lymph nodes. Four months later the initial diagnosis, multiple metastatic foci were detected in the liver (the largest measuring 1.4 cm) and in the right lung. Due to multiple metastases the resection of the middle lobe and the 7th lower lobe segment of the right lung was performed. The secondary lung tumour specimen showed a more solid growth pattern, being compared to the arborising variation detected in the primary malignancy. Necrosis, higher mitotic activity and typical dense eosinophilic cytoplasmic inclusions of malignant cells were present in metastases. The expression of immunohistochemical markers was similar in both primary and secondary rhabdoid tumours, except for the proliferation index of metastases, being 2.5 times higher: that can be explained by the increase of the tumour's malignant potential. The results of complete immunohistochemical investigation of primary and metastatic rhabdoid tumours are shown in Table I. The Panel of the Department of Pathology decided to change the initial diagnosis of nephroblastoma blastemal type to rhabdoid tumour. In the next two months, two ICE (ifosfamide, carboplatin, etoposide) and three irinotecan courses of chemotherapy were administered. While on chemotherapy, multiple metastases were detected in lungs. The patient has got pathological fractures of both the left tibia and the right fibula. Skeletal scintigraphy showed metastases in the 12th thoracic vertebra, in the proximal metaphysis of the right femur and right diaphysis of the tibia. Abdominal CT showed tumour recurrence within the nephrectomy bed, measuring 6 cm × 3 cm. Due to the extensive spreading process and tumour resistance to chemotherapy, the patient received palliative therapy and died 9 months after her first surgery.

Table I. Results of the immunohistochemical investigation in primary RTK and its metastasis

ANTIBODY	PRIMARY TUMOUR	METASTASIS
Vimentin	+	+
CK AE1/AE3	+/–	+
EMA	+/–	+/–
Actin (muscle specific)	R	–
S100	R	–
NSE	R	–
CD99	R	–
Desmin	–	–
Synaptophysin	–	–
LCA	–	–
Ki67	17.41%	43.07%
CD34	–	–
WT1	–	–
INI1	–	–

(+) – diffuse strong positivity; (+/–) – patchy positivity; R – rare cells positive; (–) – negative

Discussion

An accurate diagnosis of RTK is indeed a complicated issue in the practice of a paediatric pathologist. Although in most cases this diagnosis can be made solely on the basis of careful examination of light microscopic details, there is a sufficient opportunity to make an error. It should be mentioned that RTK may show an unexpected range of histological pattern variations, such as classical, sclerosing, epithelioid, spindled, lymphomatoid, vascular, pseudopapillary, and cystic, which may also contribute to diagnostic difficulties [6].

Moreover, growths originally diagnosed as rhabdoid tumour often prove to be other types of renal tumours [8, 9]. There was described a wide range of renal neoplasms mimicking RTK, representing a clinically and histogenetically diverse group that includes anaplastic WT, congenital mesoblastic nephroma, renal cell carcinoma, transitional cell carcinoma, collecting-duct carcinoma, oncocytoma, rhabdomyosarcoma, malignant neuroepithelial tumours, and lymphoma [8]. Cases of misdiagnosis of rhabdoid tumour are also mentioned in the literature. Vujanić *et al.* have reported 22 rhabdoid tumour cases diagnosed amongst 2392 renal tumours in children from the SIOP nephroblastoma files between 1971 and 1993. In this study, only 12 of the 22 cases were originally diagnosed as rhabdoid tumour by the referring pathologists. Other 10 cases were originally interpreted as clear cell sarcoma (4 cases), rhabdomyosarcoma (3 cases), undifferentiated carcinoma of the kidney (1 case) and blastemal Wilms' tumour (2 cases) [9]. The commonly described pseudorhabdoid lesion was of favourable histology WT with partial rhabdoid cytology. Conspicuous filamentous cytoplasmic inclusions or large nucleoli, typical findings in rhabdoid renal tumour, were the usual sources of diagnostic difficulties [8].

When analyzing the diagnostic difficulties in our RTK case, we need to take into account laboratory

Table II. Comparison of histological, immunohistochemical and molecular genetic features of blastemal type Wilms' tumour and rhabdoid tumour of the kidney

	Wilms' tumour	Rhabdoid tumour of the kidney
Histological features	small round to ovoid cells nodules or serpentine pattern high nuclear to cytoplasm ratio closely packed nuclei chromatin is often finely dispersed	poligonal or small round cells with vesicular nuclei sheets or trabecular pattern scattered hyaline eosinophilic cytoplasmic inclusions prominent nucleoli
Immunohistochemical features	vimentin and desmin reactivity, nuclear expression of WT1 INI1 immunostaining retained in the tumour nuclei	vimentin reactivity EMA and cytokeratins reactivity. Variable expression of mesenchymal and neuroectodermal markers INI1 immunostaining absent in the tumour nuclei
Molecular genetic features	inactivation of WT1 gene at chromosome 11p13 approximately 10% of cases	inactivation of the *hsNF5/INI1* tumour suppressor gene at chromosome 22q11.2

capability for immunohistochemical investigation, experience in both diagnosing RTK and interpretation of immunohistochemical data. In the 13-year period this was the second RTK case diagnosed in Latvia. The first one was identified 5 years prior to the present case. There were no diagnostic difficulties that case due to the characteristic classical cytology presentation of the tumour. Immunohistochemical differential diagnosis between WT and RTK can also be difficult owing to lack of a specific immunophenotype of WT. The blastemal component is typically reactive for vimentin, nuclear staining for WT1 is positive in blastemal areas in 70% to 100% of cases [10]. More mature areas of epithelial differentiation are reactive for cytokeratin. In comparison, RTK characteristically shows diffuse reactivity for vimentin, focal reactivity for at least one epithelial marker, and variable expression of mesenchymal and neuroectodermal markers [11], as can be seen in the present case in both the primary tumour and metastases. Biallelic inactivation of the hsNF5/INI1 tumour suppressor gene (resides on the long arm of chromosome 22) is the molecular hallmark of rhabdoid tumour. This leads to loss of INI1 protein expression, which may serve as a useful immunohistochemical marker in infants and young children [12].WT1 expression in the RTK cases may be possible. Focal positive staining of nuclei in one of two RTK cases was described by Charles *et al*. [13] but Ramani and Cowell reported nuclear WT1 immunoreactivity of three malignant rhabdoid tumours [14]. Likewise, expression of the WT1gene as detected by reverse-transcriptase polymerase chain reaction (RT-PCR) and parallel detection of

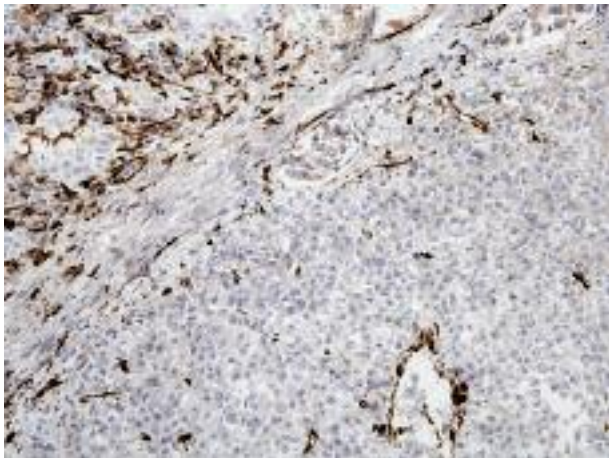

Fig. 4. Lung metastasis of RTK, negative nuclear staining with WT1 in tumour cells, non-specific cytoplasmic response in lungs. Magnification 200×

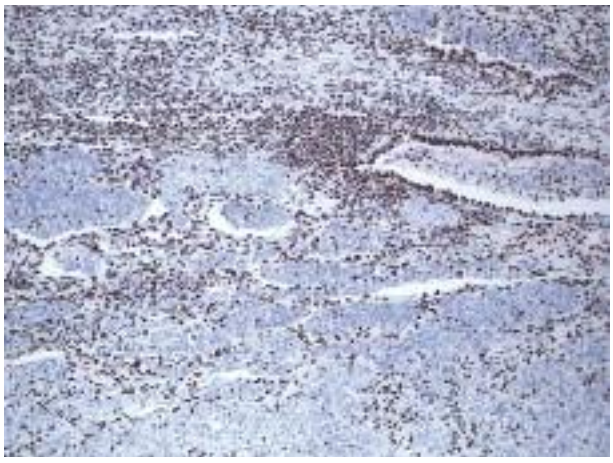

Fig. 5. Rhabdoid tumour of kidney, extensive loss of staining with INI1 (BAF-47) in tumour cells, whilst the nuclei of adjacent normal cells retain their pattern. Magnification 200×

WT1 protein by immunohistochemistry in some RTK cases was described [15]. Comparison of histological, immunohistochemical and molecular genetic features of blastemal type Wilms' tumour and rhabdoid tumour of the kidney is shown in Table II. In our case, immunohistochemical expression of WT1 was determined retrospectively and was negative not only in the primary tumour, but also in metastases (Fig. 4). It is evident that complete negative expression of WT1 in the case of differential diagnostic difficulties can help to detect RTK. However, in order to determine WT1 protein reactivity in RTK, it should be analyzed in larger series of rhabdoid tumour. To verify our final diagnosis of RTK retrospectively, INI1 protein expression in the primary tumour and metastases was immunohistochemically investigated. An extensive loss of the latter was found in tumour cells, whilst the nuclei of adjacent normal cells retain their pattern (Fig. 5). That finding is consistent with the literature data, supporting inactivation of *hsNF5/INI1* tumour suppressor gene on 22q11.2 in infants and young children [16], and detection of INI1 protein – the best and fastest ways to differentiate RTK from other tumours. In conclusion, it should be noted that due to rare occurrence of rhabdoid tumour, such as shown in our case, INI1 protein expression can be done in cooperation with larger centres of pathology.

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Address for correspondence

Ivanda Franckeviča MD
Department of Pathology
Children's Clinical University Hospital
Vienības gatve 45
Riga, Latvia LV-1004
phone: +371-67064459
fax: +371-67064473
e-mail: ivanda_katrina@navigator.lv