A CLINICOPATHOLOGIC AND IMAGISTIC REVIEW OF THREE CHILDREN WITH WILMS TUMOUR

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Abstract

Wilms tumour, also known as nephroblastoma, is the most common pediatric abdominal malignancy that occurs in early childhood with peak incidence between 2 and 4 years of age. The majority are unilateral, less than 5 % occurring bilaterally. The clinical presentation is typically with a painless left or right upper quadrant abdominal mass. In the following presentation we want to discuss the diagnostic clinicopathologic and imagistic workup of three male patients aged 1 to 2 years old with Wilms' tumor admitted in the Hematology Oncology Department of Pediatrics I Clinic, in Targu Mures in the second half of 2017

Key words: nephroblastoma, childhood, clinicopathologic

Introduction

Nephroblastoma is the second most common abdominal tumor in children. It represents approximately 6% of all pediatric cancers and accounts for more than 95% of all tumors of the kidney in the pediatric age group. Young children in the age range of 3 – 4 years are normally affected by this disorder (1). The majority of Wilms tumors are sporadic, however in a few of them, it occurs associated with syndromes including aniridia, hemihypertrophy or genitourinary malformations (cryptorchidism, hypospadias, horsshoe kidney) (2). Roughly 20% of all Wilms tumors carry WT1 mutation located on the chromosome 11p13, and most of these patients associate congenital anomalies and syndromes such as WAGR Syndrome, Denys Drash and Beckwith-Wiedemann (3,4,5). Normally, only one kidney is affected with Wilms tumor; however, in about 5% of the cases, both kidneys may have tumors. Most children with Wilms tumor present with increasing size of the abdomen or an asymptomatic abdominal mass that rarely crosses the midline, though it can extend inferiorly to the pelvis; also fever, vomiting, nausea, loss of appetite, microscopic hematuria and high blood pressure may be present (6,7). Once it's discovered a complete physical examination followed by a complete blood count, liver and kidney functions and specific tumor markers should be performed. Imaging studies include ultrasonography, CT and/or MRI, also radiographic examination of the chest is required to determine the presence of pulmonary metastases (8). Willms tumor must also be differentiated from a variety of malignant abdominal and pelvic tumors such as neuroblastoma, non-Hodgkin lymphoma, rhabdomyosarcoma, germ cell/teratoma, hepatoblastoma. Once the diagnosis is confirmed, accurate staging is imperative because appropriate therapy, as well as prognosis, is based on tumor stage (9). The histological type of the tumor has implications for therapy and prognosis: favorable histology refers to classic triphasic Wilms tumor composed of three elements: blastema, epithelia and stroma, unfavorable histology refers to the presence of anaplasia (8). Anaplasia is present in about 5% of Wilms tumors and is more common in older children, reaching a peak at approximately 5 years of age. Anaplasia can be focal or diffuse, with the focal subtype being somewhat more favorable (10). One of the main controversies in the treatment of children with unilateral Wilms tumor is whether or not to administer preoperative chemotherapy. The International Society of Pediatric Oncology (SIOP) recommends giving Vincristine and Dactinomycin chemotherapy before nephrectomy and classifies the pretreated renal tumors in low-risk tumors, intermediate-risk tumors (epithelial, stromal, mixed, focal anaplasia) and high-risk tumors (blastemal type, diffuse anaplasia, clear cell sarcoma, rhabdoid tumor) (11,12). The role of surgery in the therapy of Wilms tumor is very important because a well-performed procedure will accurately determine the stage of the disease and future therapy: Stage I the tumor is confined to the kidney and by definition, is excised completely with the capsular surface intact; Stage II the tumor is also confined to the kidney, but the capsule is penetrated or tumor is present in the perirenal soft tissue; Stage III tumor has post surgical residual non-hematogenous extension (lymph nodes); Stage IV tumor is characterized by hematogenous metastases (lungs, liver); and Stage V is characterized by bilateral renal involvement (8,13,14).

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Complete blood count	Case 1	Case 2	Case 3
Leukocytes (10^9/L)	19,6	8.48	9,65
Neutrophyls (10^9/L)	13,58	3,15	3,15
Erythrocytes (10^{12}/L)	3,9	4,6	4,1
Hemoglobin (g/dl)	10,7	11,7	11,1
Platelets (10^9/L)	67,7	176	231
Reticulocytes (‰)	23	19	12
Biochemical analysis			
Sedimentation rate (mm/h)	59	35	30
C- reactive protein (mg/L)	2	0.99	5
AST (U/L)	54	449	37,7
ALT (U/L)	7	706	15,5
Ureea (mg/dl)	18,96	28,31	31
Creatinine (mg/dl)	0,43	0,39	0,30
Glucose (mg/dl)	86	95	100
Serum Calcium (mmol/l)	2	1,98	2,06
Alkaline phosphatase (U/L)	106	246	368
Serum Total Proteins	4.02	11,56	16,12
Urinalysis	Microscopic hematuria	Microscopic hematuria	Hypostenuria

AST=Aspartate Aminotransferase, ALT=Alanine Aminotransferase
Table 1. Laboratory Findings of Case Reports

Tumoral markers and serology	Case 1	Case 2	Case 3
Vanillylmandelic acid (mg/24h urine)	2,58	1,18	2,46
Neuron Specific Enolase (ng/ml)	216,7	29,63	23,53
Serum Copper µg/dl	154,3	156,6	-
Ig G Anti EBV antibodies	Positive	Negative	Positive
Ig M Anti EBV antibodies	Negative	Negative	Negative
Anti HCV antibodies	Negative	Negative	Negative
Antigen HBs	Negative	Negative	Negative
Ig G Anti CMV antibodies	Negative	Positive	Negative
Ig M Anti CMV antibodies	Positive	Negative	Negative
Ig G Anti Toxoplasma antibodies	Negative	Negative	Negative
Ig M Anti Toxoplasma antibodies	Positive	Negative	Negative
HSV type 1, 2	Positive	Negative	Negative
HIV	Negative	Negative	Negative

EBV=Epstein Barr Virus, HCV=Hepatitis C Virus, HBV=Hepatitis B Virus, CMV=Cytomegalo Virus, HSV=Herpes Simplex Virus, HIV= Human Imunodeficiency Virus
Table 2. Laboratory Findings of Case Reports

The patency of the (inferior vena cava) IVC should be established prior to the resection; if it is not patent, preoperative chemotherapy should be administered (15). The chemotherapy guidelines proposed for stage I and II tumors with favorable histology, Vincristine and Dactinomycine, for stage III and IV tumors with favorable histology – Vincristine, Dactinomycine and Doxorubicine plus radiotherapy (3). For tumors with unfavorable histology, Vincristine, Dactinomycine, Doxorubicine and Cyclophosphamide is administered together with radiotherapy (3,16). The prognosis for patients with Wilms tumor is quite good, compared to the prognosis for most types of cancer. The patients who have the best prognosis are usually those who have a small-sized tumor, a favorable cell type, have less than two years old and have an early stage of cancer that has not spread (17). Long-term survival approaches 90% in localized disease (13,18).

Case series

The following presentation takes into consideration the overall clinical, pathological and imagistic characteristics for the diagnosis of Wilms tumor.

Case 1: First is a 2 year old male patient diagnosed in July 2017. The onset of the disease was one week before admission with poor appetite, followed by abdominal pain and vomiting. From the emergency room he receives symptomatic treatment at home, but the general condition worsens, associating fever above 38oC so the mother returns to the emergency room. Here an abdominal ultrasound reveals an 8 cm inhomogeneous tumor with calcifications in the left renal parenchyma. The suspicion of Wilms tumor is raised for which he is hospitalized in the Hematology-Oncology Compartment. Clinical examination and anamnesis at admission reveal no personal history of illnesses before this age, poor general state, normal colored skin, normal colored pharynx and tonsils, bilateral painless submandibular lymph nodes. Palpable large, firm mass in the left abdominal flank, with increased sensitivity of this area, liver in normal limits, spleen difficult to asses due to the abdominal tumor, poor appetite, slow intestinal transit (stools once every three days), bilateral cryptorchidia, dysuria, weight: 14kg. Over the course of admission, another abdominal ultrasound is performed for a much detailed description of the characteristics of the tumour and the findings were: liver 88.5/48mm, homogeneous echostructure, increased echogenicity, spleen within normal range, right kidney with normal size for age, left kidney occupied by a 118/78.6mm inhomogeneous, well defined tumor, with Doppler signal accentuated at the periphery, left kidney with disorganized structure and grade 2 hydronephrosis. A contrast CT scan is performed on the thorax, abdomen and pelvis showing absence of suspected lung nodules and no pathological lymph nodes on the mediastinal or axillaries level with minimal left pleural effusion. Abdomen CT scan revealed an inhomogeneous density mass with approximately 88/93/124mm, with areas of necrosis, with compressive effect on jejune and descending colon, without images of left renal vein thrombosis and IVC involvement, sub hepatic, perisplenic free fluid and in Douglas recess, retroperitoneal lymph nodes up to 8 mm (Figure 1). Laboratory tests as seen in Table 1 and Table 2 performed also for the differential diagnosis, confirmed the diagnosis of Wilms tumor, thus cytoreductive treatment is initiated with Vincristine and Dactinomycine D (4 weeks). The abdominal ultrasound 20 days after initiation of cytoreduction reveals a reduction in tumor size at 107/68mm. During this period of time a series of investigations were performed in order to establish the loco-regional invasion and possible secondary determinations of the tumor: cardiology examination with ultrasound parameters, neuropsychiatry examination and ophthalmologic exam within normal limits. To complete the set of laboratory tests a bone marrow exam was performed that did not show tumor invasion. One month after diagnosis, left nephrectomy is performed followed by tumor biopsy and the histopathology examination reveals a triphasic Nephroblastoma with predominance of the mesenchymal component (85%), the blastematic component below 66% (intermediate risk). The examined tumor tissue also presents extensive areas of necrosis (<50%) and the tumor infiltrates the fibrous pseudo capsule and tears up the renal capsule without infiltration of the basin and kidney hilum. There is no angio-lymphatic invasion. Afterwards the patient followed treatment according the Nephroblastoma SIOP stage I protocol for low/ intermediate risk with Dactinomycine, Vincristine and Epirubicin.

Case 2: Second case is a 1 year old male patient diagnosed in July 2017. The onset of the disease is about 3 weeks prior to admission, with persistent fever (2 weeks), poor appetite and altered general condition, for which he receives antipyretic treatment. Pediatric reevaluation discovers hepatic cytolysis, Ig M EBV positive and abdominal ultrasound reveals a tumor in the left kidney. He is admitted at Hematology-Oncology Department of Pediatrics I, Targu Mures, where investigations continue. Anamnesis reveals he was born prematurely at 35 gestational weeks through c-section, SGA (small for gestational age) weighing 1920g, subsequently hospitalized for transient neonatal hypoglycemia. Clinical assessment at admission reveals: influenced general condition, pale skin, capillary refill time ~ 3 sec, bilateral submandibular lymph nodes, painless, laterocervical and inguinal palpable lymph nodes, symmetrical bilateral vesicular murmur, no rallies, rhythmic heartbeats. Distended abdomen, apparently painless at palpation, umbilical hernia, liver at about 2 cm below right costal rib, palpable spleen, present intestinal transit, normally conformed external genitalia, weight 10 kg. The abdominal ultrasound reveals hepatomegaly with liver of 86/41mm, spleen with normal size for age, right kidney with normal size for age, left kidney occupied by a 99/46mm tumor, presenting fine septa to the upper pole, not exceeding the renal capsule, with present Doppler signal. Also a CT scan of the thorax, abdomen and pelvis is performed showing a well defined parenchymal tumor developed in the left kidney, native homogenous, discreetly inhomogeneous post contrast, with iodophylia slightly pronounced at the tumor capsule, with fine septa, other abdominal, thorax and pelvis structures with normal appearance (Figure 2).

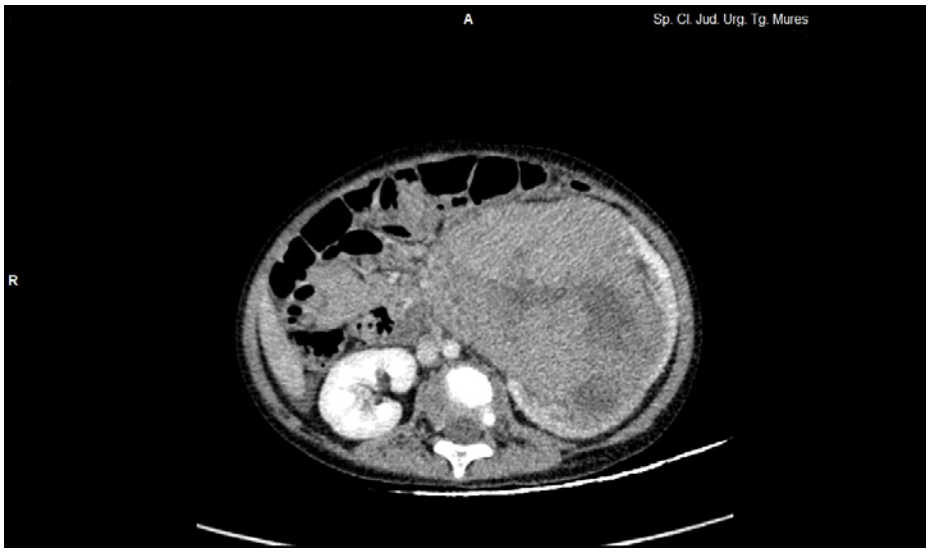

Fig. 1. (Case 1): Enhanced axial CT section of the abdomen demonstrates a very large inhomogeneous density mass arising from the left kidney displacing the remaining renal parenchyma, with areas of necrosis and compressive effect on jejune and descending colon. No involvement of the renal vein or IVC.

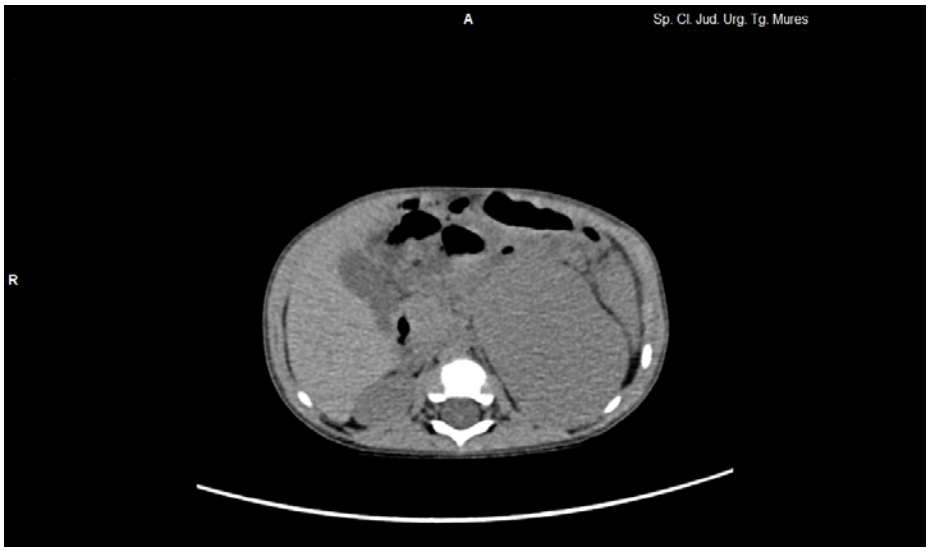

Fig. 2. (Case 2): Unenhanced axial CT section of the abdomen demonstrates a well defined native homogenous parenchymal tumor developed in the left kidney, without involvement of the renal vein or IVC.

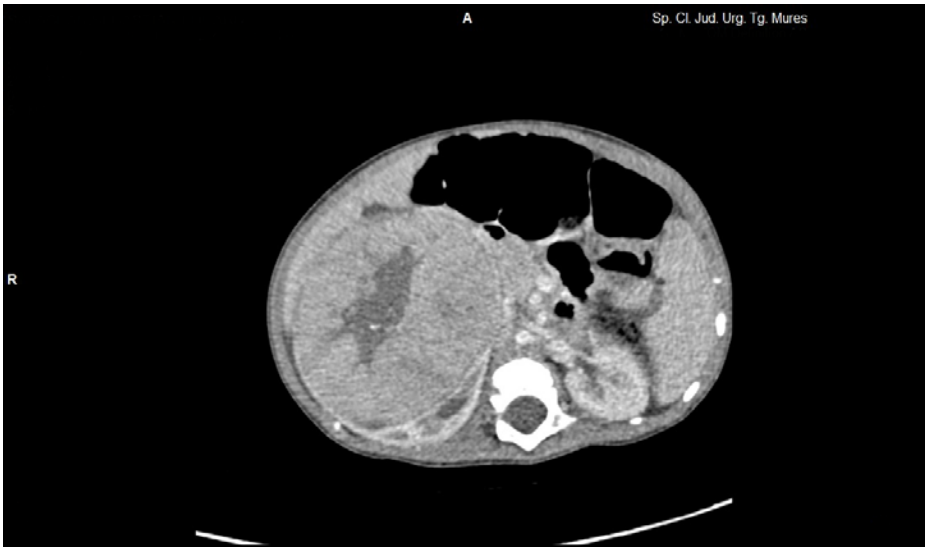

Fig. 3. (Case 3): Enhanced axial CT section of the abdomen confirms the presence of a right kidney tumor with central necrosis and hemorrhagic areas, exerting a compressive effect on IVC but still permeable.

Laboratory tests as seen in Table 1 and Table 2 performed also for the differential diagnosis, confirmed the diagnosis of Wilms tumor, so chemotherapy is initiated according to the SIOP 93-01 protocol, stage I, cytoreductive phase. Abdominal ultrasound 10 days after initiation of cytoreduction reveals a reduction in size of tumor at 91/44mm. Investigations were performed in order to establish the regional invasion and possible secondary determinations of the tumor: cardiology examination with ultrasound parameters, ophthalmologic exam within normal limits, neuropsychiatric examination diagnosed a mild hypotonia, also bone marrow exam was performed that did not show tumor invasion. After 4 weeks from the diagnosis left nephrectomy is performed, the total weight of the tumor and left kidney being 77g. The histopathology result classifies the tumor as a high-risk, stage I monophasic Nephroblastoma with more than 66% blastematic component. The tumor does not infiltrate the fibrous capsule, renal capsule and kidney. No angio-lymphatic invasion or tumor necrosis is observed. The surgery is followed by chemotherapy treatment (high grade stage I, no radiotherapy) with Etoposide and Carboplatin alternately once every three weeks with Epirubicinum and Ifosfamidum.

Case 3: The third case is a 1 year old patient diagnosed in October 2017. The onset of the disease is characteristically with an asymptomatic abdominal mass discovered by the parents the previous day. The patient is admitted to the Pediatric Hematology-Oncology Department of the Pediatrics I Clinic in Targu Mures for further investigations. Personal history reveals he was born prematurely at 34 weeks of gestation through Caesarean section (for pelvic presentation) with birth weight: 2560g. Physical examination on admission reveals a good general state, pale skin, dolichocephalism, anterior fontanel of 1.5/1cm, facial dysmorphism with micrognathia and viciously inserted dentition, no palpable lymph nodes, rickets rosary on thorax with flared bases, rhythmic heartbeats. Abnormal, globular abdomen, sensitive on the right abdominal flank, palpable tumor on the right abdominal flank with the lower edge to the right iliac fossa, liver hardly accessible due to the formation, non-palpable spleen, capricious consumption, intestinal transit present, normal external genitalia, weight 9.5kg. During hospitalization the abdominal ultrasound revealed a rounded-oval shape tumor of 98/98mm, exceeding the median line with a maximum diameter of 103 mm, with peripheral Doppler signal present. The renal structure of 38/18 mm is visualized at the upper pole, 7 mm pylon; the tumor exerts a compressive effect on large vessels, also retroperitoneal lymph nodes of 11mm are seen. Abdominal CT scan confirmed the presence of a right kidney tumor with dimensions of 95/88/93mm, with central necrosis and hemorrhagic areas, exerting a compressive effect on IVC but still permeable (Figure 3). Laboratory tests as seen in Table 1 and Table 2 performed also for the differential diagnosis, confirmed the diagnosis of Wilms tumor. Chemotherapy is initiated according to the SIOP 93-01 protocol for nephroblastoma, cytoreductive phase (Dactinomycine + Vincristin). In order to establish the regional invasion and possible secondary determinations of the tumor cardiologic examination was performed with normal ultrasound parameters, ophthalmologic exam within normal limits, neuropsychiatric examination was normal, also bone marrow exam was performed that did not show tumor invasion. Thoracic X-ray and cranial CT scan were negative.

Cytogenetic and molecular biology examination showed no variation in the number of copies at the level of the examined regions and no methylation defects have been revealed at the level of the examined regions at 11p15 level. At 4 weeks after diagnosis the repeated abdominal CT shows a reduction in tumor size (83/76/82mm) with the persistence of compressive effect on IVC, with bilateral nephrogram present. Afterwards total right nephrectomy is performed + tumor excision (total weight 234g), tumor biopsy and mesenteric ganglion biopsy and appendectomy. The histopathology examination confirms the diagnosis of the Wilms tumor (triphasic nephroblastoma with predominance in relatively equal proportions of the epithelial and blastematic component, with reduced mesenchymal component, associated with focal anaplasia), the tumor tissue infiltrates the capsule, but does not extend to the kidney itself or to the hilum. The mesenteric lymph node and appendix examined with the histological structure preserved. In the absence of secondary determinations, treatment is initiated according to the SIOP 93-01 Protocol for Nephroblastoma stage I.

Once the chemotherapy will be complete, all three patients will be followed for recurrence with chest CT scans and chest X-rays and with abdominal ultrasound, every 3 months for the first 3 years and then every 6 months for the next 2 years, blood tests and urinalyses will also be performed at each visit..

Discussions

Wilms tumor diagnosis includes a thorough history and clinical examination to identify possible genetic syndromes, genitourinary malformations, and genetic risk factors, and requires corroboration with paraclinical, imagistic and histological examination. Wilms tumor often becomes quite large before it is noticed, most of the times it's discovered by the parent or doctor during a physical examination. It is important to note that having a risk factor such as genetic predisposition, birth anomalies/defects or congenital anomalies does not mean that one will have the condition. But a risk factor increases the chances of having Wilms tumor compared to an individual without the risk factors (19). Therefore clinical examination is very important to establish these risk factors. In the presentation above one of the patients had criptorchydia, and case number 3 had dolichocephalism, anterior facial dysmorphism with micrognathia and viciously inserted dentition therefore Beckwith-Widemann syndrome was suspected but the genetic tests were negative. In the diagnostic work-up our clinic follows the main diagnostic tests used in detection of Wilms tumor, including physical exam with evaluation of family history, blood analysis such as complete blood count, creatinine levels, blood urea tests, urine analysis, abdominal ultrasound, abdomen CT scan, chest x-rays and bone scans if the tumor has metastasized. Definite diagnosis can only be made by surgical resection and biopsy followed by pathologist examination and staging. The imagistic workup includes abdominal ultrasonography that determines whether the mass is cystic or solid and whether the renal vein or vena cava is involved and abdominal CT or MRI that determines the extent of the tumor and spread to regional lymph nodes, the contralateral kidney, or liver (20). The ultrasound of the first case describes an inhomogeneous, well defined left kidney tumor and grade 2 hydronephrosis. The ultrasound of the second case describes hepatomegaly and a left kidney tumor not exceeding the renal capsule. And the ultrasound of the third case describes a rounded-oval shape right kidney tumor exerting a compressive effect on large vessels. Although many of the features seen on CT/MRI can also be identified on ultrasound, they are required to adequately stage the disease, and are established in protocols for Wilms tumour staging in North America and Europe (20). The abdominal CT examination of the first case revealed an inhomogeneous density mass with areas of necrosis, without images of left renal vein thrombosis and IVC involvement. The abdominal CT exam of the second case revealed a well defined parenchymal tumor developed in the left kidney, native homogenous and discreetly inhomogeneous post contrast. And the abdominal CT scan of the third case revealed the presence of a right kidney tumor with central necrosis, exerting a compressive effect on IVC. Diagnosis of Wilms tumor is typically made presumptively based on the results of the imaging studies, so nephrectomy rather than biopsy is done in most patients at the time of diagnosis. Biopsy is not done because of the risk of peritoneal contamination by tumor cells, which would spread the cancer and thus change the stage from a lower to a higher one requiring more intensive therapy. During surgery, loco-regional lymph nodes are sampled for pathologic and surgical staging (21). Because appropriate therapy, as well as prognosis, is based on tumor stage, accurate staging of patients with Wilms tumor at the time of diagnosis is very important. Classic Wilms tumor has a triphasic appearance, (stromal, epithelial, blastemal) however all three elements are not required to have a diagnosis of Wilms tumor (22). Case 1 presented has the best prognosis out of all, because of the classic triphasic composition, unlike case 2 that has a monophasic type with more than 66% blastematic component, and case 3 that has a triphasic nephroblastoma associated with focal anaplasia. Because case no 3 has focal anaplasia and genetic anomalies a cytogenetic analysis of his DNA was performed in order to establish genetically determined anomalies such as Beckwith-Wiedemann syndrome located at the level of the chromosome 11p15 and no methylation defects have been revealed.

As of 2004, there are significant differences between the treatment protocols American practice favors surgery followed by chemotherapy, European oncologists use preoperative chemotherapy and stage the tumor at the time of surgery rather than at the point of initial imaging studies. The International Society of Pediatric Oncology (SIOP) recommends giving Vincristine and Dactinomycin chemotherapy before nephrectomy for localized renal tumors. Following this protocol all three cases received preoperative chemotherapy, surgery and postoperative chemotherapy. Approximately 80-90% of children with a diagnosis of Wilms tumor survive with current multimodality therapy. Patients who have tumors with

favorable histology have an overall survival rate of at least 80% at 4 years after the initial diagnosis, even in patients with stage IV disease (10).

Conclusions

Any abdominal mass in a child must be considered malignant until diagnostic imaging such as ultrasonography or CT and laboratory findings define its true nature. Ultrasound is a very useful and cheap examination used to localise the kidney tumor and also distinguish from other causes of renal masses. Abdominal CT scan is the investigation of choice required to adequately stage the disease. Abdominal ultrasound is also used as a good parameter for evaluating the reduction in tumor size after performing cytoreduction. Histological examination of the tumor is the most important determinant of diagnosis and prognosis and can classify the tumors as having a favorable histology or an unfavorable histology, which is associated with a worse prognosis. The outcome is also reflected by the stage of the tumor at the time of diagnosis. Accurate staging is essential for the determination of the need for radiotherapy and the administration of appropriate chemotherapy regimen. Pretreatment with chemotherapy contributes to the reduction of the tumor, making it easier to remove, preventing the rupture of a large tumor into the peritoneal cavity. Wilms tumor has a very high cure rate, particularly when detected as a localized tumor

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