

Risk Stratification and Consecutive Prognosis Progresses in Childhood Wilms Tumors. Two cases report

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Rezumat

Stratificarea riscului și progresele prognostice consecutive în tumorile Wilms la copii. Considerații pe două cazuri

Introducere: Considerată cea mai comună neoplazie a tractului urinar și totodată una din cele mai frecvente tumori maligne ale copilului, nefroblastomul sau tumora Wilms (TW) suscită un interes major datorită în special succeselor terapeutice în contrast cu diagnosticul adeseori întârziat, malignitatea și factorii de risc particulari. Sunt prezentate două observații ilustrative din experiența proprie.

Descrierea cazurilor: Observația 1, fetiță de 22 luni spitalizată în mod repetat pentru constipație habituală, tulburări de dezvoltare somatoponderală și modificări comportamentale. O ecografie inițială descoperă o formațiune hipocogenă de 21 mm Ø la nivelul polului superior al rinichiului drept, investigație neaprofundată datorită neglijenței părinților. La ultima internare CT confirmă prezența unei tumori solide de 23/25 mm fără depozite ganglionare sau la distanță, imagine sugestivă pentru diagnosticul de TW. Conform protocolului unității bolnava este supusă chimioterapiei standard și după 4 săptămâni se practică nefrectomie polară superioară. Examenul histologic certifică diagnosticul de nefroblastom trifazic. Postoperator chimioterapie după protocolul Societății Europene de Oncologie Pediatrică (SIOP). Supraviețuire fără probleme după 23 luni. Observația 2: de asemenea fetiță, de 3 ani, normal dezvoltată dar cu retard mental mediu (QI=40) se

internează pentru dureri abdominale difuze și constipație. US decelează o formațiune tumorală renală stângă de circa 6 cm Ø situată polar superior. La CT leziunea cu densitate parenchimatosa neomogenă măsoară 6,2/5,5/7,2 cm, apare dezvoltată din polul renal cu care este în contact larg posterolateral. Este formulat diagnosticul de TW și după chimioterapie preoperatorie se practică nefrectomie radicală stângă cu ligatură vasculară inițială. Anatomopatologic: nefroblastom cu anaplasie focală stadiul II cu risc crescut. Continuă chimioterapia conform protocolului SIOP regim high risk. Supraviețuire confortabilă la 24 luni.

Discuții: Ambele cazuri de sex feminin sub 3 ani având ca simptome constipația și tulburările de dezvoltare psihică, au fost descoperite prin US, diagnosticul fiind stabilit prin CT. Chimioterapia pre- și postoperatorie încadrând intervenții adaptate stadiului bolii, a condus la vindecări stabile de circa doi ani.

Concluzii: respectând protocelele europene (SIOP), chimioterapia preoperatorie sistematică este aplicabilă, bine tolerată și eficientă în observațiile autohtone de nefroblastom determinând o reducere notabilă a volumului și implicit a stadiului tumorii ca și o diminuare a riscului chirurgical.

Cuvinte cheie: nefroblastom, tumoră Wilms, nefrectomie, chimioterapie preoperatorie

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Abstract

Background: Even if Wilms' tumour is the commonest primary malignant neoplasia in children, it maintained a continuous interest due to actual therapeutic successes contrasting with the customary delayed diagnosis, malignancy and specific risk factors.

Patients and Methods: Two recent illustrative cases from our clinic are presented. The first one - a little girl of 22 months with repeated admissions for habitual constipation and psychomental disturbances revealed at abdominal ultrasonography a hypo-echoic mass at the superior pole of the right kidney. CT confirmed the presence of a solid homogeneous mass of 23/25 mm without node or distant metastases, suggestive for Wilms' tumour. Conforming to SIOP protocol she received chemotherapy and after 4 weeks a superior polar nephrectomy was performed. Pathology confirmed the diagnosis of triphasic nephroblastoma of intermediary risk. Postoperative chemotherapy according to the protocol SIOP assured the cure with a disease free period of 23 months. The second case - also a girl, of 3 years, is admitted for constipation, pain in the left flank and mental retard (QI=40). Ultrasonography determined a huge mass ($\varnothing \sim 6$ cm) situated at the superior pole of the left kidney. CT attested a non-homogeneous, encapsulated tumour image of 6.2/5.4/7.2 cm in large posterolateral contact with the renal parenchyma out of which it appears to be developed. The diagnosis of WT is strongly suggested and after chemotherapy a radical left nephrectomy with initial vessels ligation was performed. Pathology: stage IIb nephroblastoma with focal epithelial anaplasia. After surgery she continued the chemotherapy (HR regime), was cured and excepting a medullar aplasia is in a good health after 24 months.

Discussions: Our both cases were girls under 3 years, presenting nonspecific features: constipation and psychic troubles, the tumour being incidentally discovered by the abdominal ultrasonography. CT established the diagnosis. Conventional chemotherapy framing adapted to the tumour's stage and surgery conducted to a stable cure of about two years in both cases.

Conclusions: Conforming to the SIOP protocols preoperative chemotherapy was applicable, well-tolerated and efficacious for two recent cases presented in our clinic, determining the shrinkage of tumour volume and stage and consecutive reduction of the surgical risks.

Key words: nephroblastoma, Wilms' tumor, nephrectomy, chemotherapy

Background

Nephroblastoma (Wilms' tumour) is the most common renal tumour in childhood, representing approximately 6 – 7 percent of all paediatric cancers, with an incidence of 10 cases per million children less than 15 years of age per year and continues to arouse interest by remarkable actual therapeutic successes, consecutive to the multidisciplinary approach. The conjugated efforts of the oncologists, surgeons, pathologists, radiologists and other specialists lead at present to a more than 90 percent cure rate of these "terrible" lesions (1,2). The National Wilms Tumour Society (NWTs) in USA and the

Société Internationale d'Oncologie Pédiatrique (SIOP) in Europe, are two reputed cancer research cooperative groups, devoting their efforts to enhance the quality of the screening, precocious diagnosis and therapeutic protocols, but also of the fundamental studies about genetics, immunology and molecular pathogeny of these tumours (3,4,5,6).

In lack of an organized national programme of screening and a standardized therapy in our country, few publications underlined the clinical peculiarities and diagnosis hesitations, illustrated also by our two own cases (7,8,9,10,11).

Case report

The first one subjected NA, a one year and 10 months old female child, observed also one year ago in our clinic for "habitual constipation", who is readmitted for difficult bowel evacuation (just one or two time a week) and 2nd degree rectal prolapse. In the previous hospital stay a 21 mm \varnothing hypoechoic mass at the superior pole of the right kidney was discovered but not explored because of parents' heedlessness. Physical examination revealed a 2nd degree distrophy (IP=0,71), pallor, muscular hypotrophy, 2nd degree left parasternal systolic soufflé and confirmed the constipation and the prolapse (secondary?). The little girl also presented rare convulsions, agitation and episodes of aggressiveness. Laboratory tests determined a hypochromic microcitary anaemia, but the liver and kidney function tests were normal. Abdominal ultrasonography has shown increased dimensions of the previously described mass (25 mm \varnothing), in a context of disorganization of the renal architecture (Fig. 1). CT scan showed the existence of a well-limited, homogenous tumoural mass with parenchymal density measuring 23/25 mm, situated at the superior kidney pole. Left kidney was normal. Bilateral simultaneous renal secretion and excretion was present. There were no adenopathies, ascites or secondary deposits (Fig. 2). These investigations are highly suggestive for the diagnosis of a Wilms' tumor stage II with moderate risk,

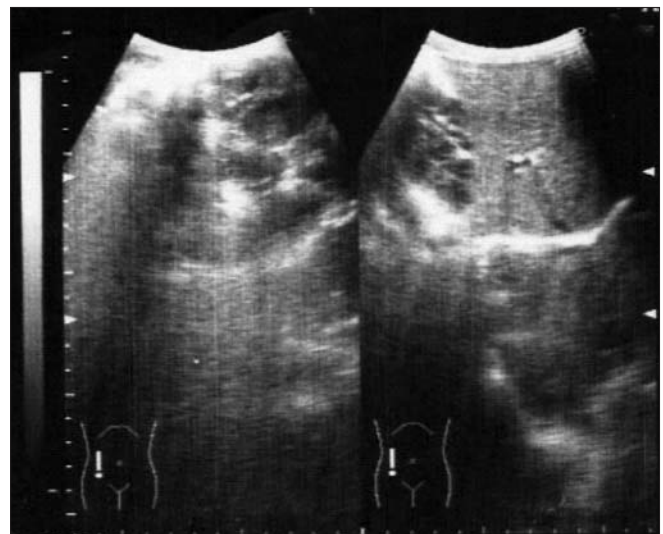


Figure 1. "Tumour" of the superior pole of the right kidney



Figure 2. Stage I right kidney nephroblastoma

therefore even in the lack of the histologic assessment, a preoperative chemotherapy according to the SIOP protocol was initiated with reduced doses owing to the deficiency in weight – only 9 kg – of the child (actinomycin 45 mg/kgc and vincristine 1.5 mg/m²).

4 weeks later, through transrectal laparotomy a standard superior polar nephrectomy with normal tissue margins was performed. The ideal removal of the lesion confirmed the encapsulated character of the tumour, weighting 15 g and the absence of adhesions, extensions or metastases. (Fig. 3)

Microscopy: triphasic nephroblastoma with predominant tumour necrosis (> 50%) Stage II (Fig. 4). The same medicamentary combination is administrated postoperatively and a complete cure, verified by the annual follow-up, was obtained.

The second case: DA, also a girl of 3 years old, with normal stature-weight development but with a significant familial context of neoplasia, is admitted for painful left flank sensitivity, constipation (just one time every three days), mental and language deficiency (IQ=40). Ultrasonography determined a round, well limited mass, with heterogenous echotexture, of about 6 cm Ø situated at the level of the superior pole of the left kidney, suggestive (after the experience with the previous case) for the diagnosis of nephroblastoma (Fig. 5).

Abdominal CT scan showed an ovoid tumour, well framed by a “typical solid formation’s capsule”, with unequal parenchymal density measuring 6.2/5.4/7.2 cm (in cranial-caudal axis). It was situated on the postero-lateral aspect of the left kidney, having large contact with the renal parenchyma out of which it seemed to have developed, impinging and deforming this and other abdominal structures.

Both kidneys’ main functions were normal. There were no pathological changes of the contralateral kidney or of other viscera or nodes. (Fig. 6) Routine chest x-ray did not detect any metastasis. Laboratory tests: leukocytosis with neutrophilia, increased LDH.

With a presumptive diagnostic of high-risk stage II nephroblastoma (also without pathological confirmation) pre-operative chemotherapy was indicated, the little girl undergoing the same protocol as in the previous case. During the course of treatment she presented digestive intolerance and neutropenia.

After 7 weeks, a radical left nephrectomy with initial vascular ligation through subcostal approach was performed in



Figure 3. Superior polar nephrectomy. Operative specimen

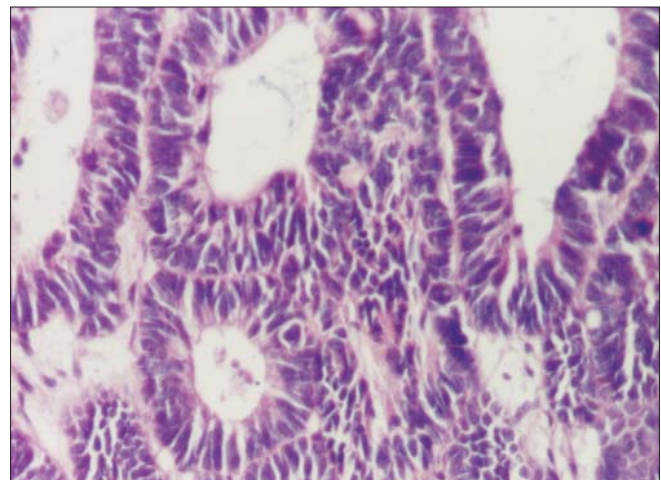


Figure 4. Triphasic nephroblastoma with predominant tumoral necrosis (HE x 100)

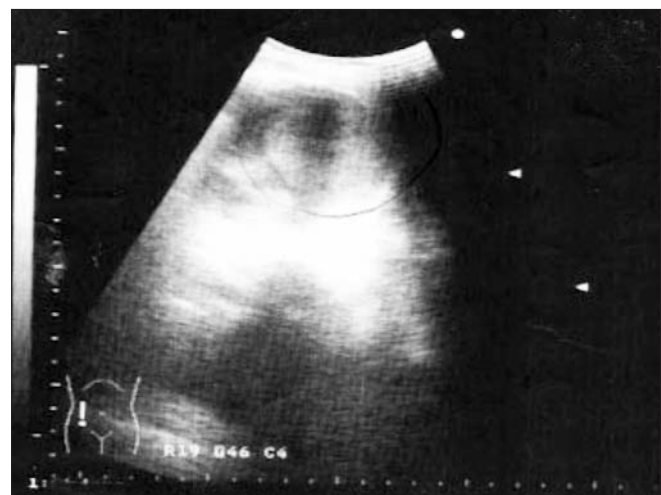


Figure 5. Renal echography: image of left Wilms’ tumor

favourable anatomical conditions, in lack of adhesions or infiltrations of the adjacent structures. (Fig. 7) The absence of lymph node, peritoneal or visceral secondary deposits was



Figure 6. CT: Image of left nephroblastoma

intraoperatively confirmed. Histology: nephroblastoma with epithelial predominance and focal anaplasia (Fig. 8). Postoperatively the patient received VP16 150 mg/m² and carboplatin 200 mg/m² alternating with cyclophosphamide 450 mg/m² and doxorubicin 50 mg/m² (SIOP high-risk protocol). The development of medullar aplasia imposed the interruption of chemotherapy and administration of packed red blood cells. Finally, stable cure confirmed at 24 months follow up was obtained.

Discussions

Described by Wilms in 1899, nephroblastoma is a “bizarre” malignant neoplasia with triphasic development from the embryonal, pluripotent, precursory kidney cells: undifferentiated metanephric blastema, fibroblast-like and epithelial stromal elements. The tumours are usually sporadic, familial cases representing only 1 percent of records. In the majority of cases WT occurred between 6 months and 5 years of age and the sex distribution is equal among boys and girls. Both our little patients were girls enrolling in the period of peek age incidence. Anaplastic forms are present in 5 percent of cases (2,10).

Twelve-fifteen percent of cases presented genitourinary congenital anomalies (horseshoe kidney, hypospadias, testicular ectopy), aniridia (isolated or associated with urinary malformations and mental retardation comprising WARD syndrome), congenital hemihypertrophy, Beckwith-Wiedeman syndrome (diffuse macroglosia, gigantism), Denys-Drash syndrome (diffuse mesangial sclerosis, pseudohermaphroditism), trisomy 18, hamartomas etc (12).

WTs are produced by disturbances of the genes responsible for the development of the kidney and the urinary tract. Karyotype analysis successively identified the tumour suppressor gene Wilms’ tumour 1 (WT1) located on the chromosome 11p13 and more recently a second Wilms tumour gene (WT2) which maps to an imprinted region of chromosome 11p15 or independently imprinted domains IGF2 or KIP2. However, only 2/3 of WT cases present detectable genes (13,14).

Pathology: the tumour is commonly huge (reaching even 1000 g), well circumscribed (pseudocapsule from obliterated parenchyma) and with firm consistence.

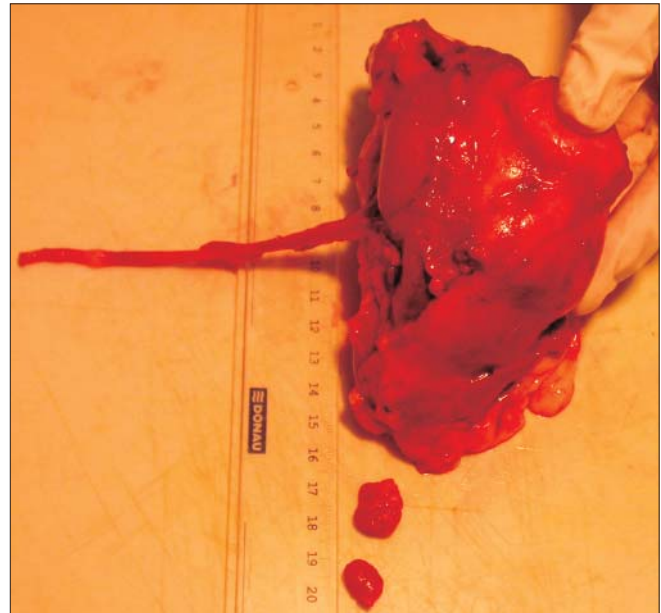


Figure 7. Radical right nephroureterectomy
Operative specimen

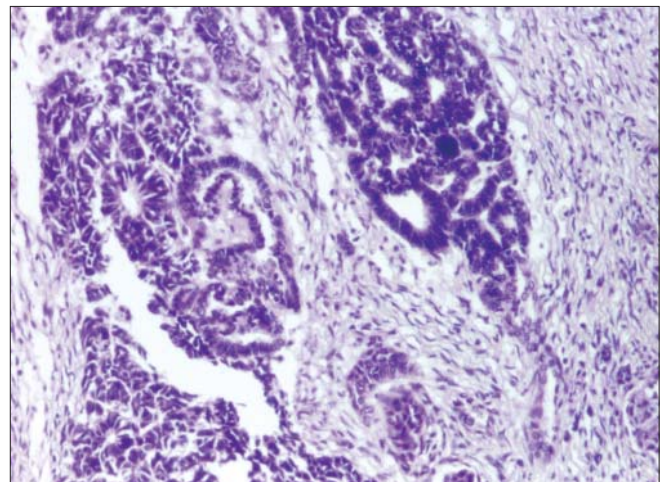


Figure 8. Nephroblastoma with epithelial predominance and focal anaplasia (HE x 200)

Cut section: lobulated gray-white tissue replacing the usual renal parenchyma variegated with zones of necrosis, haemorrhage, cystic degeneration and fibrosis. The tumour extends into the renal vein, rarely in the ureter and bladder. Local invasion is also rare, but the tumour spreads through the lymphatic and vascular routes to the regional nodes (15%), pancreas, liver etc.

Microscopically, WT reproduces the kidney differentiation in embryogenesis, being characterized as a “triphasic” neoplasia with blastemal, stromal and epithelial components. A typical lesion is composed of metanephric blastema clusters separated by mesenchyme. They present an arrangement of oval or little polygonal cells with hyperchromic nuclei and scanty cytoplasm. Variable epithelial differentiation may be encountered (obs 1). Focal anaplastic (obs 2) or diffuse variants

contain hyperchromic nuclei with pleomorphism, greater dimensions and abnormally mitotic figures; the latter have an unfavourable prognostic (14,15).

Clinical presentation is dominated by the presence of an asymptomatic flank mass discovered by the caregivers or the paediatrician on a routine visit. This failed in both our cases (however a “vigorous” palpation must be avoided). Sometimes the child presents discomfort or vague abdominal pains. Behaviour troubles, apathy, indisposition, irritability or aggressiveness were present in both our patients. To these, we must add and mention micro or macroscopic haematuria, fever, digestive complaints – anorexia, vomits, constipation (“warning sign” in both our cases), hypertension (renin producing cells) or varicocele, cough and pleurodynia. There are cases debuting with acute abdominal pain phenomena (tumour rupture or torsion) or acute renal failure. Prolonged asymptomatic evolution leads to delays of the medical consultation and diagnosis in advanced stages (2,10).

Current explorations include also the study of chromosomes 11p13, 11p15 (allele duplication) or of the WT1 gene.

Imaging methods included chest X-ray in order to reveal if the tumour has spread in the thorax, ultrasonography for initial exploration and monitoring after therapy. Abdominal CT scan and especially MRI establish the tumoral origin, displaying lymphadenopathies, bilateral forms, secondary liver deposits and vascular or adjacent structure invasion. PET can detect occult metastases or recurrences. (16)

Biopsy/FNAC is controversial but intraoperative biopsies are mandatory. Finally, an accurate staging is fundamental for an adequate therapy.

Recent multidisciplinary modern treatment of childhood WT including surgery, chemotherapy and irradiation, represents, by means of its objective successes (with more than 90% overall survival rate) a modern paradigm of cancer disease management. (17,18)

The outline of a new risk stratification concept which is currently used to assign patients with WT to a specific protocol-based therapy also contributed to these progresses. Therefore, adding to tumour stage and histological subtype, the traditional prognostic factors in WT, are new elements such as patient’s age, tumour size, response to therapy (failures, recurrences) and identification of risk factors (adverse or toxic effects) and also a different approach of the prognostic significance of the genetic and epigenetic predispositions and biologic markers, specifically the LOH of chromosomes 1p and 16q, AND ploidy etc. Also, the stratification of therapy equals to the translation of the risk assessment from histological to genetic or even molecular level for each case, obtaining a maximum of immediate efficiency with lesser therapy. (19)

Hence, the Children Oncology Group (COG) organized a national database of histological and cytogenetic studies, surgical and imaging reports from which an expert group elaborated a stratification protocol of the cases with WT, divided in 4 risk groups named ARENO3B2 (followed by suchlike) which allow an optimal, individualized therapeutic option (20).

Surgery with safe and complete resection is the key element

in achieving the cure of nephroblastoma. Indications for surgical extirpation include tumours confined to the kidney, extended beyond the kidney but not crossing the midline, and those with or without vascular extension, primarily with low risk and low or intermediary lesions (21).

According to the NWTS protocol, after an accurate staging, the initial step in the treatment of WT is radical nephrectomy eventually completed by regional or periaortic lymph node dissection (21,22). In the SIOP practice, which we also adopted, chemotherapy preceded the laparotomy, biopsy and excision (23).

Partial nephrectomies under chemotherapy can be considered in cases of solitary kidney, bilateral WT, kidney failure or small size polar lesions. Emergency or subtotal bilateral nephrectomies and reductive or extended excision of the adjacent viscera or metastases can be practiced out of necessity in various circumstances (haemorrhages, torsions, huge lesions, recurrences etc). Since the SIOP protocol provide adjuvant therapy in all WT cases, laparoscopic nephrectomy can be a feasible and safe procedure in selected groups of children (24).

Chemotherapy proved an incontestable value and efficiency in the management of WT with crucial contribution to the prognostic improvement of these lesions in the last three decades, aiding to a global cure rate of more than 90% of cases. The chemotherapy used most often to treat WT include actinomycin D, vincristine and doxorubicin as prime line agents, accompanied by cyclophosphamide, ifosphamide, carboplatin and etoposide in cases with unsatisfactory response or recurrences, administrated in different modalities, combinations or time intervals depending on clinical stage, risk and prognostic factors, histological and biological profile. The drugs can be administered before surgery (SIOP) pursuing tumoral volume shrinkage, the reduction of the capsular and tumoral intrusion risk during operation and the lowering of local recurrences and number of metastases. (25)

A favourable therapeutic answer constituted a valuable prognostic indicator. The postoperative chemotherapy use (NWTS) allows an exact evaluation of the tumor together with its pathology and also the study of the molecular biology.

Finally, WT have a high sensibility to ionizing radiation, which is a major component of the therapy of these lesions in advanced cases, recurrences or cases with unfavourable histology (26).

Conclusions

The real successes of the modern multimodal treatment of WT led in the last decades to the tripling of the percentage of real stable cures (from 30% to over 90 percent), allowing a prolonged normal existence for the majority of these patients. A superior “stratification” of the genetic, biologic, morphological and clinical risk factors with the object of an individualized therapy - especially of the antitumoral medication - gives way to an optimistic perspective regarding the therapeutic standards of these tumours.

Author contribution

Diaconescu Smaranda - conceived the study, imaging diagnosis, Olaru Claudia - preparation and drafting the manuscript, Mihăilă Doina - pathology, Aprodu Gabriel Sandu - performed surgery, Miron Ingrith – chemotherapy, cases follow up.

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