

In adults, the most commonly seen renal tumour is renal cell carcinoma. Wilms' tumour is the most commonly seen primary embryonic tumour of the kidney, which develops from totipotent cells of the metanephric blastema. In adults, it is more aggressive and shows a worse therapeutic response. There is no standard therapy for adult patients with Wilms' tumour. Histology of the primary tumour and the diffuseness, i.e. the stage of the disease, guide the adjuvant therapy. For this kind of patient, there are two different working groups of the "Society of Paediatric Oncology" (SIOP) in Europe" and "The National Wilms' tumour Study" (NWTs) in North America. They recommend either primary nephrectomy (NWTs) or preoperative chemotherapy (SIOP) for Wilms' tumour treatment. Vincristine, dactinomycin and doxorubicin constitute the backbone of many combinations for the treatment of Wilms' tumour. For this tumour, for which the therapeutic strategies were established for paediatric patient groups, the therapy based on clinical characteristics and stage was discussed by reviewing the literature.

Key words: adult Wilms' tumour, chemotherapy, relapse.

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A case report of adult Wilms' tumour

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Introduction

In adults, the most commonly seen renal tumour is renal cell carcinoma (RCC) [1]. Wilms' tumour (WT) is the most commonly seen primary malignant renal tumour in children [1, 2]. It is rarely seen in adults; its incidence is 8 per million in children [3], whereas its annual incidence is lower than 0.2 per million in adults. Clinically, it may be mistaken for other causal factors of renal masses, RCC being the most common. Approximately 3% of WTs were reported in adults [1, 4].

WT is a malignant embryonic tumour of the kidney that develops from totipotent cells of the metanephric blastema [4, 5]. It results from the abnormal proliferation of the metanephric blastema, without being differentiated into glomerules and tubules [6]. In WT, mature glandular structures observed in renal tumours are not observed. The co-occurrence of blastema, stroma and epithelium facilitates the diagnosis. Unlike renal cell cancer, WT is characterised by an embryonic appearance of the epithelial structures [5]. Although the ratio of three components is variable, the predominant blastemal component has a more aggressive clinical presentation [7].

Two histopathological groups are described. Classical nephroblastoma contains blastemal, epithelial and stromal components, occasionally with the predominance of one or two components and occasionally with equal rates of each component (triphasic). In the anaplastic type, tumour cells contain irregular mitotic forms, hyperchromasia and large increased nucleus (4–8%), and it may be categorised as focal or disseminated. This classification has a prognostic importance, by forming the risk groups and by modelling our therapy. Anaplasia may account for the increased resistance to chemotherapy [8]. Furthermore, anaplasia is associated with increased risk of recurrence [7].

Although Wilms' tumour seen in the adults has histologically similar characteristics compared to that observed in children, it has a more aggressive course and it shows a worse therapeutic response [2, 9]. Generally, in the case of WT, poor prognostic factors include loss of chromosome 16q, 1p heterozygosity, high telomerase activity, anaploidy and the presence of vascular epidermal growth factor. Metastases are most commonly seen in the lungs, in the pleura, in the tumour bed and in the liver. Hepatic involvement is worse than pulmonary involvement [10, 11]. The percentage of metastasis is 29% and 10% in adults and in children, respectively [6]. We planned to discuss the therapy of a patient with this tumour, which is rarely seen in adults, on which there are no large studies and for which the therapeutic strategies are developed for paediatric groups, according to the clinical characteristics and the stage, by reviewing the literature.

Case description

A 31-year-old female patient described a right lateral pain for the previous 3 years. Abdominal US performed for this purpose revealed a hyperechogen-

ic solid mass, which had heterogeneous internal structures with lobulated contours, and vascular structures were observed in a Doppler examination. It was located in the right kidney, with the largest of its dimensions measured to be approximately 143 mm × 104 mm; at first, renal cell carcinoma was considered. Abdominopelvic magnetic resonance imaging (MRI) showed a giant mass with the largest dimension of 14 cm × 12 cm × 8 cm, which destroyed renal parenchyma at the middle-lower pole level of the right kidney, and retrocaval soft tissue mass (metastatic lymphadenopathy). In thoracic computed tomography (CT), both lungs had lesions consistent with metastasis. At the Department of Urology, the patient underwent right radical nephrectomy + adrenalectomy. Its pathology was reported to be "Triphasic Type Wilms' Tumour (Epithelial + Stromal + Blastemal) that does not contain anaplasia". Two pericaval metastatic lymph nodes and eight pericaval reactionary lymph nodules were observed, but there was no necrosis in the tumour. Renal capsule, perinephritic adipose tissue and sinuses were infiltrated, adrenal was intact and lymphovascular tumour invasion was observed. Immunohistochemical analysis showed a result of WT-1 focal (+), CD56 (-), CD57 (-) and cytokeratin 7 (-). The margins of the urethra surgery performed using immunohistochemical method were intact. Thoracic CT obtained following the surgery showed nodular disseminated soft tissue masses with generally subpleural localisation, of which the largest had a diameter of approximately 27 mm, in both lungs and a hypodense area with a diameter of approximately 13 mm and with regular margins in the right lobe of the liver. The International Society of Paediatric Oncology-9 (SIOP-9) protocol (dactinomycine, vincristine, doxorubicin) was initiated to be administered to the patient. At the 5th week of the therapy, the patient complained of numbness and pain in both arms but more severely in the right arm. In her EMG, the examination of the upper and lower extremities showed polyneuropathy in which motor nerves were affected. Vincristine was discontinued after the dose given at the 7th week. After the 9th week of the therapy, when the control CT was compared to the pre-treatment period, a marked regression was observed in the size of the lesion in the right lobe of the liver and in both lungs, and a soft tissue mass (recurrence?) with a necrotic ovoid central part that reached a diameter of approximately 32 mm × 20 mm was detected in the operation lodge of the right nephrectomy. The patient was re-consulted to the department of urology for resurgery. Surgical intervention was not considered. Therefore, the patient was given 10 × 300 cGy : 3000 cGy external radiotherapy on the tumour area and on the lymphatics. The chemotherapy was continued after the radiotherapy. In the MRI performed after the radiotherapy, it was seen that a soft tissue lesion of approximately 2 cm previously seen in the operation lodge was not present in the new examination, but massive lesions reaching 2 cm in size in the right ovarian lateral lodge and 4 cm × 2 cm in the right lower quadrant were first considered as consistent with recurrence. Thoracic CT showed subcarinal, prevascular carinal lymphadenopathies in the mediastinum, and metastatic lesions with parenchymal localisation were also detected. Upon this

result, the therapy of the patient was discontinued at the 24th week. High-dose CT and stem cell transplantation were considered. The patient was given a protocol consisting of ifosphamide, carboplatin and etoposide. High-dose chemotherapy and stem cell transplantation treatments were applied to the patient in another centre, and the patient remains alive.

Discussion

Adult WT is rarely observed case that is interesting for physicians interested in oncology. In the literature for this tumour, which is rarely seen in the adults, Mitry et al. detected WT in 143 cases among 76,625 adults with primary renal tumours (0.19%) [12]. In SIOP 93-01, 30 of 962 patients showed adult WT [1]. Mean age varied between 17.5 and 30 years in various studies. Its incidence is slightly higher in women, with a F/M ratio of 1.00/0.92 [13]. Renal cell carcinoma consists of an older population compared to adult WT and, while RCC is predominant in men, WT predominates in women [14].

Clinical signs seen in adult patients with WT are different from those observed in children with WT. As seen in our patient, in adult WT, the most commonly seen sign is lateral pain. In some cases, weight loss and sudden decrease of performance status may accompany it. Furthermore, haematuria and, as signs of advanced stage disease, lassitude, fever and weight loss may be observed [5]. In children, the majority of cases are asymptomatic and the most commonly seen sign is painless abdominal distension [1, 4]. The diagnosis of adult WT does not have a pathognomonic finding that would allow us to radiologically differentiate it from other renal cancers. However, in adults, WT is larger and is defined with haemorrhage and necrotic areas [4]. Contrary to the larger and palpable mass observed in WT, the tumour is smaller and less palpable in RCC [14].

The metastasis rate at the time of diagnosis in adults was 1/3 of the patients in SIOP [1]. In a study performed on 17 adult patients, 5/17 were metastatic at the time of diagnosis [2]. In a study performed by Kioumehri *et al.* on 32 patients, 28% were metastatic and the most commonly seen sites of metastasis were lungs and liver [14]. Paediatric and adult patients are different in terms of the rates of metastasis, the rates being 29% in adults and 10% in children, and the most commonly seen sites of metastasis are lungs, liver, bone, skin, bladder, colon, brain and contralateral kidney [6].

In adult patients with WT there is no standard therapy [15]. Adjuvant therapy is guided by the histology of the primary tumour and the diffuseness, i.e. the stage of the disease [16]. For this group of patients, there are two different therapeutic modalities, which are called SIOP in Europe and The National Wilms' Tumour Study (NWTs) in North America. Accordingly, the general therapeutic modality consists of well-defined risk groups, chemotherapy and, in some cases, radiotherapy that followed primary radical nephrectomy based on the stage of the disease [1]. Nephrectomy alone may provide a cure in children aged below two years with stage 1, positive histological type and a tumour

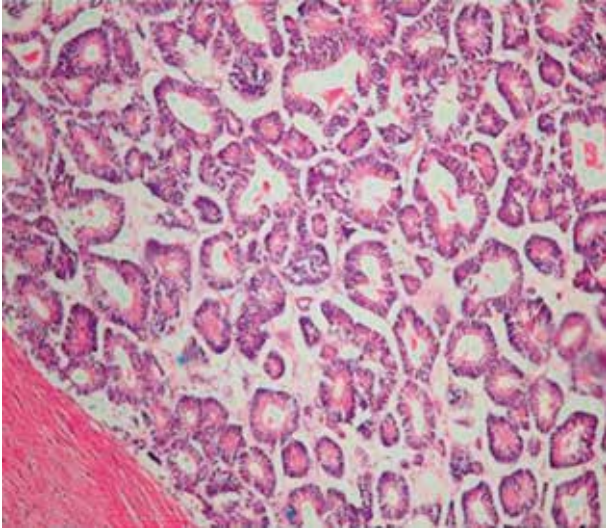


Fig. 1. Epithelial component, haematoxylin and eosin staining. Original magnification 100×

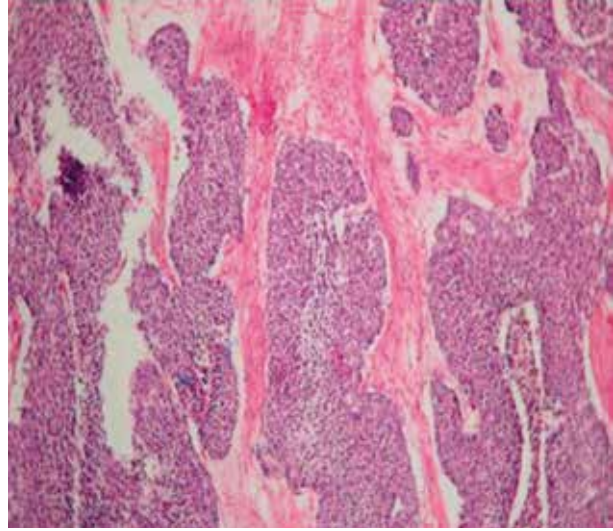


Fig. 2. Blastemal component, haematoxylin and eosin staining. Original magnification 100×

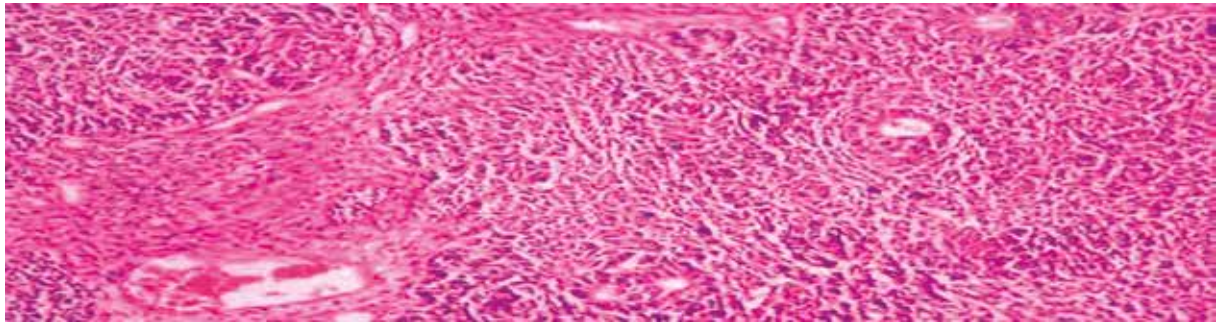


Fig. 3. Epithelial-blastemal-stromal component, haematoxylin and eosin staining. Original magnification 100×

weight below 550 grams in the paediatric series. Other than this group of patients, chemotherapy should be given for adult patients with WT. Vincristine, dactinomycin and doxorubicin constitute the backbone of many combinations for the treatment of WT [17].

Pre-operative therapies were tried in SIOP; 4 of 30 patients, all of whom were metastatic, were given pre-operative therapy, and three patients showed response to chemotherapy [1]. In NWTSG-5, stage 1–2 patients with favourable histology received vincristine-actinomycin (VA) without radiotherapy for 18 weeks, and in SIOP 93-01, stage 1 patients received VA for four preoperative weeks and for four post-operative weeks without radiotherapy, stage 2 patients received VA for four preoperative weeks and Vincristine-Doxorubicin-Actinomycin (VDA) for 27 post-operative weeks, and only the node-positive group received radiotherapy. While NWTSG recommended VDA and radiotherapy for 24 weeks for stage 3-4 patients with favourable histology, SIOP93-01 recommended VA for four preoperative weeks, VDA for 27 post-operative weeks and radiotherapy for stage 3 patients, VA for six preoperative weeks, VCA for 27 post-operative weeks and radiotherapy, whereas, if no complete response was observed at the end of nine weeks, ifosfamide, carboplatin, etoposide and

doxorubicin (ICED) therapy for 34 weeks was recommended [18].

When the survival rates obtained with these therapies are considered, what we have achieved looks most promising. When the first experiences of NWTSG obtained on 31 patients with adult WT, treated with multimodal therapy between 1968 and 1979, were published, 3-year survival rates were 74% in the paediatric patients vs. 24% in adult patients [2, 15]. During 4-year follow-up, for these 30 patients with adult WT who were treated using paediatric therapies in SIOP 93-01 between 1994 and 2001, disease-free survival and overall survival were found to be 57% and 83%, respectively. These investigators concluded that the prognosis was better when the patients were treated according to paediatric protocols [1]. Nevertheless, the prognosis was poorer in the patients with adult WT compared to paediatric patients, even when the comparison was made according to stage [2, 4, 15, 16]. The presence of anaplasia is an important prognostic factor. In a study, the mortality rate was 44% for 25 anaplastic patients and 7.1% for 364 patients without anaplasia [19]. Prognosis was poor in the patients with unfavourable histology and those with stage IV disease (haematogenous metastasis) despite the administration of multimodal therapies [15]. In

stage 4 patients with favourable histology, the addition of cyclophosphamide to VDA did not improve the results. In the anaplastic patients, the poor results remained despite the administration of conventional therapies such as VDA. For Stage 1 anaplastic patients, more aggressive regimens combined with doxorubicin were used. In Stage 4 diffuse anaplastic patients, the survival was extremely poor, with 4-year EFS less than 35%. Carboplatin, topotecan and irinotecan are currently being studied [17].

In adult WT, complete cure rates are also different from those observed in paediatric patients, and progression during the therapy is more common especially in patients with metastatic disease at the time of diagnosis. The complete cure rate is more than 85% in the paediatric group [1, 13], whereas 12 of 34 patients with adult WT described by Dawson et al. exhibited complete remission [6, 15]. In SIOP-93-01, 24 of 30 patients had complete remission. When six patients who showed progression under the treatment were considered, all patients were metastatic at baseline and two had anaplasia. Median survival of these patients was 14.4 months [1]. For the patients with recurrences, encouraging results were recently obtained. Accordingly, longer remissions are achieved using high-dose chemotherapy, radiotherapy, allogenic bone marrow transplantation or combination therapies with cisplatin and etoposide. Salvage therapy is successful in patients with a longer remission time, initial therapy with VA and low grade tumour. In the case of relapse, reuse of the original agents or the agents such as ifosfamide-carboplatin-etoposide improve overall survival [17]. Complete cure could not be achieved because the patient was in the metastatic phase at the time of diagnosis and was unable to receive the optimal treatment due to the presence of symptomatic neuropathy. The therapies that would be given after the recurrence are in the phase of development and therefore, have no large literature support. We planned to give to the patient a salvage regimen followed by high-dose chemotherapy and stem cell transplantation.

Doses given to the paediatric patient population have a poor tolerance in adults and severe associated toxicities have been reported [15]. In these patients, the main acute toxicity was vincristine-related neuropathy. In the SIOP study, 43% of the patients showed grade 3–4 neurotoxicity. In one patient, the therapy was discontinued at the end of the 6th week, whereas in other patients the dose was reduced or delayed. Consistent with the literature, the most commonly seen acute toxicity, neurotoxicity, was detected in our patient and the dose had to be discontinued before a dose reduction for this severe symptomatic toxicity.

In conclusion, in adult patients who present with renal mass and lateral pain, the likelihood of adult WT should be considered. WT in adults has a poorer prognosis compared to WT in children, and it creates difficulties for oncologists due to the availability of therapy protocols only for paediatric patients and the lack of randomised studies with high numbers of patients, but the results are incrementally improving.

Authors declare no conflict of interest.

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