

Late recurrence in children with Wilms' tumor

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SUMMARY: Büyükpamukçu M, Köksal Y, Varan A, Atahan L, Çağlar M, Akyüz C, Kutluk T, Büyükpamukçu N. Late recurrence in children with Wilms' tumor Turk J Pediatr 2007; 49: 226-230.

We aimed in this study to evaluate the clinical and radiological features of the late recurrence of Wilms' tumor in children.

Among 553 children diagnosed with Wilms' tumor between 1972 and 2004, four cases were determined to be late recurrences. Clinical, histopathological parameters, treatment details, and outcomes of the patients were evaluated retrospectively.

The ages of the patients at the time of diagnosis were 2, 5, 5, and 9 years and the male/female ratio was 1/3. Two patients had stage II disease and two had stage IV characteristics. Histopathological examination showed favorable histology in all of the patients. Initial treatment was surgery and chemotherapy, which included vincristine and actinomycin-D. Abdominal radiotherapy was performed in two patients. Recurrence times were 36, 41, 51, and 96 months. Local recurrence and lung metastasis were detected in two patients, local recurrence in one, and lung nodules in the fourth patient. At the time of relapse, the chemotherapy protocols were as follows: vincristine, actinomycin-D, adriamycin, and cyclophosphamide in two patients; vincristine, actinomycin-D, and epirubicin in one patient; and vincristine, actinomycin-D, and adriamycin in the last patient. In the cases with late local recurrence, one patient had a local spillage and one patient had regional lymph node involvement. Although the other patient had local spillage, regional lymph node involvement, and renal artery invasion, isolated lung recurrence was observed. Only one patient had progressive disease and is still under treatment, whereas the other patients died with disease.

Major recurrence sites were both local and the lungs. All of the patients had regional features including spillage, regional lymph node involvement, and vascular or capsular involvement. Late recurrence in patients with Wilms' tumor is a poor prognostic factor and should be treated with an intensified regimen.

Key words: Wilms' tumor, late recurrence, follow-up.

Wilms' tumor (WT) is the most common malignant renal tumor in children. In developed countries, with surgery, chemotherapy and in selected cases radiotherapy, cure rates of over 90% are obtained in cases with localized disease and favorable histology¹. However, a small group of WT patients continue to suffer relapses. In developing countries, it has been reported that 20% of patients had relapse^{2,3}. The relapses mostly occur within the first two years. Late recurrence of WT is

an extremely rare entity and its pathogenesis is poorly understood^{4,5}. Herein, we describe four patients with WT who had a recurrence after two years.

Case Reports

Case 1

A five-year-old girl was admitted to our hospital with abdominal mass and fever in October 1991. On physical examination, there was a huge mass in her right abdomen. WT was

diagnosed with tru-cut biopsy. Due to its enormous mass, pre-operative chemotherapy including vincristine and actinomycin-D as well as preoperative radiotherapy were administered. Subsequently, the mass was excised totally. Histopathological examination showed favorable histology. The primary investigations revealed that it was stage II. She was treated with vincristine and actinomycin-D for one year.

Forty-one months after diagnosis, a routine follow-up chest X-ray showed the presence of masses in both lungs. Abdominal ultrasound (US) and computed tomography (CT) were normal. Radiotherapy was performed (whole lung 12Gy and the metastases 20Gy) followed by metastasectomies. She commenced chemotherapy for 18 months with vincristine, actinomycin-D and epirubicin. However, 11.5 years after the first diagnosis (91 months after the first relapse), she was admitted to our hospital with pain in her right lumbar region. On physical examination, a 6-cm mass was observed in the abdomen. Abdominal US and CT revealed a giant mass surrounding the aorta, and tru-cut biopsy confirmed WT of blastemic type. Chemotherapy including vincristine, actinomycin-D, carboplatin and etoposide was started. After two cycles of chemotherapy, the mass was stable. Surgery was performed, but the mass could not be excised because it surrounded the aorta. The patient had progressive disease and has been under treatment for 30 months since the second relapse.

Case 2

In April 1991, a two-year-old boy was admitted to a local hospital with complaints of an abdominal mass and hematuria for one month. On physical examination, there was an abdominal mass which abdominal US revealed was on the right kidney. Chest X-ray showed a coin lesion in the right middle lobe. The abdominal mass was totally excised with nephrectomy. During surgery, renal hilar lymph node involvement was also observed. WT without anaplasia was diagnosed on histopathological examination. The primary investigations revealed it to be stage IV. Chemotherapy including vincristine and actinomycin-D and abdominal radiotherapy were administered. However, after the first cycle of chemotherapy, he was lost to follow-up.

Ninety-six months after diagnosis, he was admitted to our hospital with respiratory distress. The patient had had no complaint, treatment or presentation at another hospital until the second admittance. There was a 16-cm mass in the right abdomen and hepatomegaly on physical examination. Abdominal US revealed a giant mass in the right abdomen. Chest X-ray and CT showed a mass in the left hemithorax and invasion of the diaphragm. He was given chemotherapy including vincristine, actinomycin-D, cyclophosphamide and adriamycin. After induction therapy, lung radiotherapy was performed. In March 2000, he was in complete remission. However, a 3-cm mass was detected in the left lung in June 2000. It was removed and histopathological examination showed mixed type WT. The chemotherapy that followed included carboplatin, etoposide and ifosfamide. After he had complete remission of the disease, in January 2001, he was admitted to our hospital with focal seizures. Cranial CT revealed a 5-cm mass. The mass was excised gross totally. Whole brain radiotherapy was performed. Subsequently, thoracic, abdominal and intracranial masses were detected and he died of disease.

Case 3

In March 1999, a five-year-old girl was admitted to a local hospital due to abdominal mass. On physical examination, there was an 8-cm mass in her left abdomen. Abdominal US and CT revealed a mass of the left kidney. Chest X-ray and CT were normal. The mass was totally excised. She referred to our hospital for treatment. The primary investigations revealed that she had stage II disease. Histopathology showed mixed type WT and she was treated with vincristine and actinomycin-D for six months. Thirty-six months after diagnosis, a mass was found during a routine follow-up. Abdominal US and CT revealed a 10-cm mass in the operation region. The mass was removed sub-totally. Radiotherapy to the abdomen and chemotherapy including vincristine, actinomycin-D and adriamycin were administered. However, progression developed at the seventh month of therapy and she died of disease shortly thereafter.

Case 4

In December 1976, a nine-year-old girl was admitted to our hospital with an abdominal mass and pain for 10 days. On physical

examination, there was a left abdominal mass and hepatosplenomegaly. Intravenous pyelography showed the left kidney was not functioning. Chest X-ray was normal. The mass was excised during an operation in which local spillage, para-aortic lymph node involvement and invasion of the renal artery were observed. Hepatobiliary scintigraphy revealed hepatosplenomegaly and liver metastases. The primary investigations revealed that the patient had stage IV characteristics. On histopathological examination, WT without anaplasia was diagnosed. She was treated with radiotherapy and chemotherapy including vincristine and actinomycin-D for 18 months. Fifty-one months after diagnosis, chest X-ray showed the presence of a mass in the left lung, and chemotherapy including vincristine, actinomycin-D, adriamycin and cyclophosphamide was administered. Lung radiotherapy was also performed. She did not have any response to the treatment and died with disease (Table I).

Discussion

Wilms' tumor is highly sensitive to chemotherapy and radiation, and refinements in surgery, chemotherapy and radiotherapy have led to cure rates that exceed 90%¹. Despite modern multimodal treatment, approximately 16% of patients with favorable histology disease and 41% of patients with unfavorable histology

experience relapse³. The relapse usually occurs within the first two years following treatment. Late recurrence of WT is extremely rare and its pathogenesis is poorly understood^{4,5}. The rate of recurrence of non-metastasizing WT later than 24 months was reported to be 1.4-3.9%⁶.

In our series, only four of 553 patients had a recurrence later than 24 months. Of those four, only one patient was given pre-operative chemotherapy after tru-cut biopsy. Local spillage was determined in two patients (Cases 1 and 4). In Case 1, tru-cut biopsy was performed for diagnosis. Local spillage in Case 4 occurred during the operation. Cases 2 and 4 had regional lymph node involvement. Invasion of the renal artery was found in only one patient (Case 4). Two patients had stage II (Cases 1 and 3), and two patients were stage IV (Cases 2 and 4), and they all had favorable histology. Therapies in Cases 1, 2, and 4 included abdominal radiotherapy.

In the National Wilms' Tumor Study (NWTS)-2 and NWTS-3, prognostic factors for children with recurrent WT were investigated⁷. In these studies, the rate of late relapse, in which the interval between nephrectomy and date of relapse was higher than 12 months, was 35% in WT with relapse. Kim et al.⁴ reviewed the late recurrence of WT and reported that late lung recurrence was seen in six of 18 patients in the entire English literature. Late recurrences in the primary region were observed in six

Table I. Clinical Summary of the Patients

Patients	1	2	3	4
Age	5	2	5	9
Gender	F	M	F	F
Clinico-radiological features	Right renal mass Lung metastases	Right renal mass Liver metastases	Left renal mass	Left renal mass
Pathologic examination	FH	FH	FH	FH
Stage	II	IV	II	IV
Treatment	Surgery Act-D+VCR Abdomen RT	Surgery Act-D+VCR Abdomen RT	Surgery Act-D+VCR	Surgery Act-D+VCR Abdomen RT
Relapse time (months)	41 132	96	36	51
Relapse localization	Lung Local	Local+lung	Local	Lung
Follow-up	Alive	Dead	Dead	Dead

F: Female. M: Male. FH: Favorable histology. Act-D: Actinomycin-D. VCR: Vincristine. RT: Radiotherapy.

patients. Interestingly, three patients had metachronous bilateral WT, and one patient developed a tumor in the contralateral kidney. They explained that nephroblastomatosis might be a link between teratogenic/genetic dispositions and overt WT⁴.

In our patients, relapse times were 36, 41, 51, and 96 months. Recurrence sites of these patients were primary region in one case (Case 3), lung in two patients (Cases 1 and 4) and both primary region and lung in one case (Case 2). Interestingly, in Case 1, first late recurrence occurred in both lungs at the 41st month of diagnosis. However, the second late recurrence occurred in the primary region at the 132nd month of the diagnosis.

The pathogenesis of late recurrence or metastasis in WT is not well known. Possible mechanisms may include escape from immune vigilance, cell dependency on growth factors, scarce vascularization in some areas of the tumor, and the silent persistence of the nephrogenic rest. The complexity of the metastatic process is notable and there is convincing evidence of the role of oncogenes and suppressor genes in regulating metastatic growth⁸⁻¹². In WT, after surgery, microscopic deposits, which escape from the treatment modalities including chemotherapy and radiotherapy, may persist in the primary region for an extended period. Later, they may acquire biological activity^{4,5}. If incomplete resection is performed, the particular biological activity of the residual cells may be another possible explanation for the late recurrence¹¹.

Gibson et al.¹³ reported a case of WT with relapse 13 years after the original diagnosis. Their patient did not have cytogenetics available at original diagnosis, but at relapse she was found to have a 1q abnormality, which may have predisposed her to an increased risk of relapse.

The role of radiation therapy in the pathogenesis of late tumor recurrences has been suggested. However, late recurrence cannot be precisely linked to radiation alone, because some patients did not receive irradiation or the sites of the recurrence such as lungs were outside the field of irradiation⁴. Radiation therapy may cause a delay in the biological activity of the cells, which escape from the host's immunological surveillance system.

In our cases, all of the patients except Case 3 underwent abdominal radiotherapy. Local recurrence was determined in Cases 1, 2, and 3. Cases 1, 2 and 4 had late lung recurrences. Interestingly, in Cases 1 and 2, both lung and local late recurrence was observed. In cases with late local recurrence, two patients had a local spillage (Case 1 and 4) and two patients (Cases 2 and 3) had regional lymph node involvement. Although Case 4 had local spillage, regional lymph node involvement and renal artery invasion, no late local recurrence was observed. We believe that the regional features and radiation therapy may cause a delay in the biological activity of the cells, which in turn may play a role in the late local recurrence. Distant late metastases are related to the hematogenous spread of persistent tumor cells, which escape from a host's immunological surveillance system and treatment modalities.

Grundy et al.⁷ reported that prognosis of patients with late recurrence was better than those with intermediate and early recurrences. However, only one of our patients is in partial remission.

In conclusion, the pathogenesis of late recurrence in WT may be due to the silent persistence of the nephrogenic rest or to residual tumor cells in the initial surgery area which escape from a host's immunological surveillance system and the treatment modalities including chemotherapy and radiotherapy. How and why these cells acquire the biological activity such a long time after diagnosis is not well known. As seen in our cases involving WT, regional features such as spillage, regional lymph node involvement, and vascular or capsular invasion must be evaluated carefully. These patients may have a risk for late recurrence and should be followed up accordingly.

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