

Extrarenal Wilms' Tumour of the Ovary

A case report

Khalil A. Albiroty,¹ Amal Al Sabahi,¹ Saud Al Shabibi,² Zakyia I. Al'Ajmi,³ Karima Al Hinaï,¹ *Nawal Al-Mashaikhi¹

ABSTRACT: Wilms' tumour (nephroblastoma) is the most common abdominal malignancy in children. Extrarenal Wilms' tumour is rare, with limited reports in the literature. We report a two-year-old girl who presented to a tertiary care hospital in Muscat, Oman, in 2019 with an abdominal mass. The patient was diagnosed with unilateral ovarian Wilms' tumour (initially diagnosed by closed biopsy and confirmed later by histopathology study of the excised tumour). This report highlights the unusual location and presentation of Wilms' tumour and presents the medical challenge in both the initial clinical impression and pathological diagnosis. Furthermore, this report details the therapeutic plan and shows the good outcome achieved by using the classic renal Wilms' tumour therapy protocols.

Keywords: Wilms' Tumor; Ovary; Pediatrics; Case Report; Oman.

WILMS' TUMOUR (NEPHROBLASTOMA), IS the most frequently occurring abdominal malignancy of childhood and comprises more than two-thirds of the paediatric renal masses in the first five years of life.¹ Extrarenal Wilms' tumour (ERWT) is rare, but there have been a few reports.^{1–3} The estimated incident rate of ERWT is almost 0.5–1% of all cases of Wilms' tumour.^{2–4} Common reported location of Wilms' tumour outside the kidney include the retroperitoneum, inguinal canal, scrotum and vagina.⁴ Misdiagnosis for other common retroperitoneal masses of that region is not uncommon.¹

Case Report

A two-year-old girl was admitted to a tertiary care hospital in Muscat, Oman, in 2019 for evaluation of an abdominal mass with a history of two months of poor appetite, night sweats, fever and undocumented weight loss. The initial abdominal and chest computed tomography (CT) revealed a large well-defined heterogeneous soft tissue mass occupying most of the abdominal cavity. The mass measured 13.5 × 10.5 cm with few specks of calcification. It encased most of intra-abdominal vessels, including the upper abdominal aorta and renal arteries; the anterior wall of the inferior *vena cava* was not well demarcated, likely obstructed by the mass. The kidneys were displaced posteriorly with moderate obstructive hydronephrosis with reduced enhancement. The bowel loops were displaced laterally. There was moderate right pleural effusion and small effusion on the left without pulmonary metastasis or nodules [Figure 1].

The patient was admitted to the paediatric intensive care unit with severe respiratory distress and a high suspicion of bacterial ascites. The patient was treated with broad-spectrum antimicrobials. Ultrasound-guided emergent stents were inserted bilaterally in the lower pole of each kidney and a core biopsy was taken from the periphery of the mass. Basic laboratory screening tests showed hypercalcaemia (serum calcium = 3.8 mmol/L); therefore, intravenous furosemide and maximum hydration therapy were initiated.

Tissue histopathology showed a malignant blue round cell tumour with positive immunohistochemical staining for WT1 and cluster of differentiation (CD)99 and focally positive for AE1/AE3. The tumour cells were negative for leukocyte common antigen, CD3, CD20, terminal deoxynucleotidyl transferase, B-cell lymphoma-2, NB84, synaptophysin, chromogranin, neuron-specific enolase, myogenic differentiation 1 and desmin. The histopathology slides were sent abroad for a further expert opinion [Figure 2].

Based on radiological findings and histopathology reports, the initial clinical impression was of a peripheral neuroectodermal tumour (PNET) or desmoplastic small round cell tumour; Wilms' tumour seemed less likely. As the patient's condition was critical, and so as not to delay treatment while waiting for the histopathology expert's opinion, the first cycle of chemotherapy based on Ewing/PNET (VDC/IE)-COG AEWS1031 protocol-regimen A was started.

After one cycle of chemotherapy, the expert's histopathology report found a poorly differentiated malignant neoplasm consisting mainly of the rounded cells with limited amounts of amphophilic cytoplasm

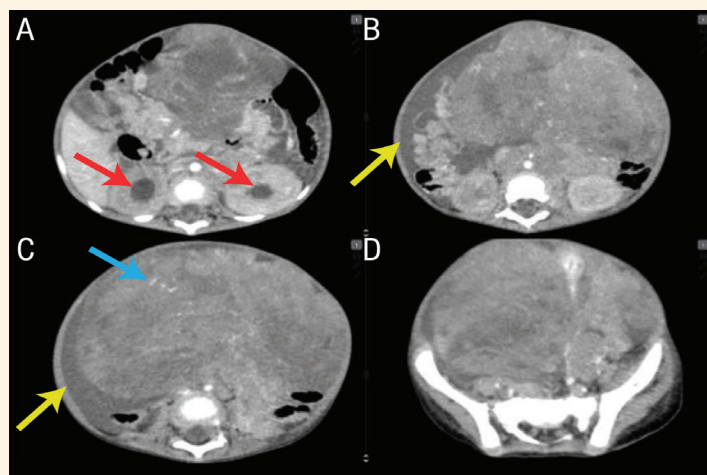


Figure 1: Axial images of contrast enhanced computed tomography of the abdomen of a two-year-old girl showing a large intra-abdominal soft tissue mass with heterogenous enhancement (**B, C and D**) and intra-lesional enlarged blood vessels (blue arrow). It surrounded major abdominal vessels. There was secondary (**A, B and C**) obstructive bilateral hydronephrosis (red arrows) with reduced renal parenchymal enhancement denoting long-standing obstruction nephropathy. Ascites is also present (yellow arrows).

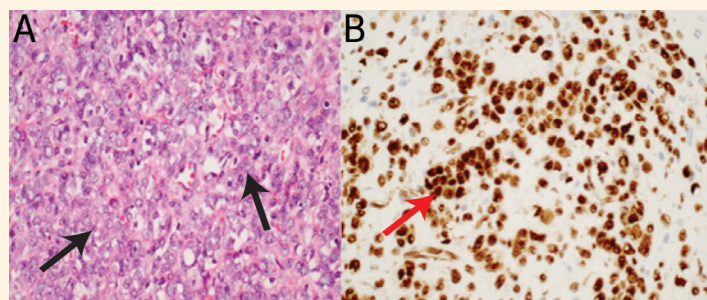


Figure 2: **A:** Haematoxylin and eosin of the excised tumour at $\times 40$ magnification showing sheets of small to medium-sized undifferentiated cells with hyperchromatic nuclei and scant eosinophilic cytoplasm (black arrows). **B:** Immunohistochemical staining showing of the tumour cells showing diffuse nuclear positivity for WT1 (red arrow).

and irregular vesicular nuclei. The neoplastic cells showed diffuse nuclear positivity for WT1 as well as multifocal striking positivity CD99. This appearance is reflective of Wilms' tumour (blastemal-predominant).

In light of the final histopathology report, the treatment protocol was changed to high-risk Wilms' tumour AREN0321-UFH; the patient received 13 cycles of chemotherapy as per the protocol. The treatment was interrupted multiple different times due to prolonged neutropaenia for a total of one month.

Post-week 13 of chemotherapy, the patient's abdomen and chest CT assessment showed interval resolution of pleural effusion. There was a regression of lower abdominal mass, measuring $5 \times 4.5 \times 3.4$ cm with specks of calcification. The abdominal mass was anterior to iliac vessels and the bowel displaced away from the tumour with no vascular or bowel encasement. The small extension around the left renal hilum also regressed in size. This lesion abutted the renal vessels but with no encasement or invasion. The kidneys were normal with no focal lesions, with mild residual dilation of collecting systems as was

seen before the chemotherapy [Figure 3]. After this CT scan, she underwent debulking surgery. During surgery, it was found that the tumour originated from the left ovary as a continuation of the left fallopian tube adherent; there was minimal invasion to the sigmoid colon and the dome of the bladder wall. Also, the right ovary looked pathological. The left ovary was excised with salpingectomy and appendectomy and biopsies from the right ovary and the tissue around the tumour were taken; removal of all enlarged lymph nodes was performed and full inspection was done for all suspected tissues. Abdominal CT assessment post-surgery showed interval resection of the lower abdominal mass and no apparent tumour residual.

Tumour and tissue biopsies' histopathology of the left ovary and fallopian tube revealed a residual of small round blue cell tumour constituting approximately 7% of the examined sample, in a background of chemotherapy-related changes. These residual tumour cells were positive for WT1, CD99 and focally for epithelial membrane antigen (EMA). The immunophenotypical features were consistent

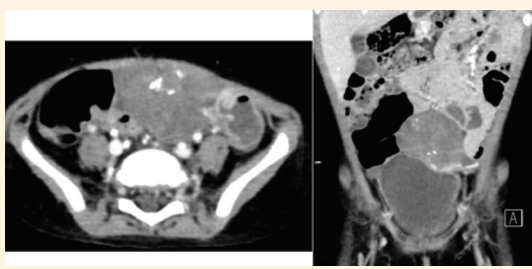


Figure 3: Follow-up abdomen computed tomography scans showing a reduction in size and consequent mass effect on the kidneys.

with extrarenal (ovarian) Wilms' tumour, mixed type (pre-treated, intermediate risk). There was no evidence of anaplasia in the residual tumour. The percentage of necrosis was 93% of the whole examined tissue. Few defects were seen in the ovarian capsule; these showed chemotherapy-related changes but no viable residual tumour. All resection margins were free of viable tumour. There was no evidence of vascular invasion and no teratomatous elements were present. The right ovary had chemotherapy-related changes and had no tumour-related findings.

Eventually, the patient completed the chemotherapy plan and received whole abdomen radiotherapy (12 Gy in 8 fractions) as per the protocol. The end of the treatment assessment showed a normal chest CT scan with no evidence of tumour residual or disease recurrence.

Currently, the patient is being regularly followed-up for tumour surveillance. As of her second-year post-therapy follow-up, she was doing well without any concerns. The patient's parent provided informed consent for publication of this report.

Discussion

ERWT (nephroblastoma) is defined when the tumour meets two criteria: it is a (1) histologically confirmed nephroblastoma and is in an (2) extrarenal location. ERWT is rare in adults and children with few reported cases.⁵

ERWT develops in the retroperitoneum in males and in the inguinal area in females. In reference to the literature, there is no specific manifestation of ERWT.⁵ In a discussion of 34 cases of extra-renal Wilm's tumour, Coopes *et al.* highlight that stage I contributed to 30%, II to 10%, III to 57% and IV to 3% of all cases.⁶ In the current case, the tumour was located in the unilateral ovary, which is not a commonly observed location for ERWT. In addition, it presented in an advanced stage with the presentation of ascites and pleural effusion. Currently, there are a total of 11 reported cases with unilateral ovarian extrarenal Wilms tumour.⁷

Turashvili *et al.*'s reported cases of primary ovarian Wilms' tumour showed that the mean age was 22 years (range: 1–56 years). Moreover, the most frequent clinical symptom at presentation was abdominal pain ($n = 8$). The median tumour size was 13 cm (range: 2.5–18 cm) and all tumours were unilateral. Only four out of 11 reported cases of ovarian Wilms' tumour were treated with chemotherapy. No recurrences were reported in any of the eleven patients.⁷ The current case falls within the reported age range (2 years old) and tumour size range (13.5 cm). She also presented with abdominal pain and a unilateral ovarian mass and was treated with high-risk Wilms' tumour chemotherapy protocol.

The exact embryonic origin of ERWT is unclear.^{1,4} There are conflicting reasonable hypotheses that it originates from ectopic metanephric blastema or from primitive mesodermal tissue. The most popular theory is based on the Connheim's cell rest theory, which explains that persistent embryonal cells are likely to undergo malignant transformation at any point in time.⁴

It is well known that ERWT does not exhibit characteristic radiological features.⁵ This was the case with the current patient; it is therefore important to not rely solely on radiological reports when determining a treatment plan for an obscure abdominal mass in a child. A histopathological diagnosis is encouraged at the very least with ultrasound-guided biopsy. Accurate diagnosis and then appropriate therapy should be based on the histology report after tumour removal. It is important to emphasise the significance of having a second opinion with other experts if there is any doubt in the histopathological findings, thereby allowing for the most effective and appropriate therapy. Therapy should not be initiated without a thorough histopathology report, with exceptions when there are clinical emergencies. In the current case, the most related therapy was used based on the provisional histopathology report until the final and accurate histopathology report was received.

According to Shojaeian *et al.*, out of 87 reported childhood ERWT cases, favorable histology was observed in most cases. This made the prognosis better in ERWT compared to the classic Wilms' tumour with the same stage and histology.² In the current case, the predominant component was the blastemal type, which has a poor prognosis and allows the patient to be put on a high-risk protocol.

In the present case, molecular studies were not done due to cost limitations and the unavailability of specialised laboratories providing such services; the immunohistochemical studies aided in reaching a diagnosis. In this case, ETV4 was negative making

a CIC-related sarcoma unlikely. PHOX2b, which is very specific test for neuroblastoma, was negative in the current case. Importantly, this case was negative for desmin and EMA; this eliminates the likelihood of a desmoplastic tumour. CD99 is a very non-specific marker with much antigen cross-reactivity; in Ewing sarcoma, this would be expected to be strong and diffuse unlike the weak patchy positivity in this case. Hence, the absence of other markers and positive findings for WT1 confirms the diagnosis of Wilms' tumour.

The treatment plan was informed by the renal Wilms' tumour protocol (chemotherapy and radical surgery plus radiotherapy, if indicated).^{2,5,6} The therapeutic steps, following surgical excision, depend on both the tumour stage and the histological finding.² In the current case, total excision of the ovary was necessary as it was invaded by the tumour; full inspection of any suspected tissue and removal of any enlarged lymph nodes were performed. The total excision of the ovary with removal of all enlarged lymph nodes were being supported by the Children Oncology Group (COG) chemotherapy plan, followed by adjuvant chemotherapy and focal radiotherapy to the abdomen. The latter treatment approach was adopted in the current case due to the patient's history of ascites, the closed biopsy finding at the diagnostic phase and the blastemal type of histological component finding.

The chemotherapy-radiotherapy modality of treatment may cause injury to the hypothalamic-pituitary gonadal axis and impair gonadal function, especially if used for abdominal radiation.⁸ However, the radiation risk is dependent on treatment volume, total dose, fractionation schedule and age at treatment. It was found that a radiation dose higher than 18 Gy does result in effects ranging from altered pubertal timing to complete ovarian failure.⁸ The current case required, as per COG protocol, 12 Gy focal abdominal radiations. Permanent ovarian failure occurs mainly in childhood cancer patients who are treated with radiation doses greater than 20 Gy. An ovarian transposition to a region that is lateral or medial to the planned radiation volume was found to be useful as this may preserve ovarian function in young females.⁸

For therapy outcome, the two-year event-free survival of the reported ERWT cases was almost 85% and the mortality rate was 5%, which are similar to renal Wilms' tumour outcomes.² The current patient completed her second year of regular follow-up with a good outcome and no active issue or consequence.

Conclusion

Though ERWT can be difficult to diagnose preoperatively, it should be considered in as a differential diagnosis when a patient presents with any asymptomatic abdominal mass. Furthermore, as there is neither a typical clinical presentation nor specific radiological findings, the diagnosis should be based on a pathology report from the excised tumour. The recommended therapy plan for ERWT is similar to that of renal Wilms' tumour therapy plan.

AUTHORS' CONTRIBUTION

KAA, AS and NM drafted the manuscript. SS provided the radiological images and handled the radiological aspects of the manuscript. ZIA provided the histopathology images and handled the histopathological aspects in the manuscript. KH reviewed the manuscript and provided critical feedback. NM revised and edited the manuscript. All authors approved the final version of the manuscript.

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