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SHORT COMMUNICATION

A case of mixed adult Wilms' tumour and angiosarcoma responsive to carboplatin, etoposide and vincristine (CEO)

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Abstract Here we report an unusual case of mixed Wilms' tumour and angiosarcoma in a 38-year-old female patient who presented with haematuria and right lower back pain. A computed tomographic (CT) scan confirmed a massive renal tumour associated with extensive retroperitoneal lymph node involvement, bony metastases and a right hip fracture. She was initially managed with palliative nephrectomy, which was followed by rapid postoperative deterioration. Histopathology revealed differentiated adult Wilms' tumour with renal angiosarcoma, whereas the pathology of the para-aortic lymph node and bone metastasis revealed angiosarcoma only. In view of her cachexia and cytopaenia, emergency chemotherapy was initiated using a modified regimen of carboplatin, etoposide and vincristine (CEO) in preference to the more traditional but less well-tolerated VAC (vincristine, actinomycin D, cyclophosphamide). Four cycles of this protocol yielded a dramatic response on re-staging CT scan. This case suggests that highly angiogenic tumours such as angiosarcoma may be effectively palliated using agents usually reserved for refractory Wilms' tumour, and supports the view that adult Wilms' tumour is more sensitive to such agents.

Keywords Adult Wilm's tumour · Angiosarcoma · Drug therapy

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Introduction

Wilms' tumor is the most common renal tumour in children, but is rare in adults. With respect to treatment, there are only a few small series of adult Wilms' patients treated with different protocols [1–5], with the result that no standard treatment for adult Wilms' tumour is established [6]. Although the tumour stage of adult Wilms' tumour tends to be higher than childhood Wilms', it has still been traditionally considered a curable disease if treated with radical nephrectomy followed by chemotherapy [7]. Yet despite this widespread belief, the prognosis of stage IV disease has proven to be dismal in adult Wilms' patients treated with VAC-type paediatric protocols [8]. Frequent VAC resistance has given rise to suggestions that platinum/etoposide combinations be used [9]. Here we report an instructive case of mixed Wilms' tumour and angiosarcoma.

Case report

A 38-year-old female with good past health and negative family history presented with haematuria, right loin discomfort and diffuse bone pain. Blood tests showed anaemia, thrombocytopaenia and elevated serum lactate dehydrogenase (LDH). A computed tomographic (CT) scan

revealed a 13 cm tumour arising from the upper pole of the right kidney, associated with extensive retroperitoneal lymph node involvement, bony metastases and a right hip fracture (Fig. 1a). Positron emission tomography (PET) confirmed increased fluorodeoxyglucose (^{18}FDG) metabolism in all of the above sites (Fig. 1b). The provisional diagnosis was metastatic renal cell carcinoma, and management was initiated with palliative nephrectomy.

Histopathology of the resected specimen showed nodular tumour with extensive haemorrhagic necrosis. Solid blastematous elements were seen admixed with small crowded tubules, and there were foci of coagulative necrosis as well as mitotic activity. The appearances were judged to be those of differentiated Wilms' tumour (Fig. 2a). Adjacent infiltrative nodules of a sarcomatoid tumour were also present, in which the spindle cells formed anastomosing vascular channels, and displayed moderate nuclear pleomorphism. Immunohistochemical studies showed the atypical spindle cells were positive for CD31 and negative for CD34, cytokeratin, S100 and actin. The morphology and immunophenotype of the spindle cell component was that of angiosarcoma. The pathological diagnosis therefore was of a mixed adult Wilms tumour and angiosarcoma. However, pathology of the para-aortic lymph node metastasis and bone metastasis revealed angiosarcoma only (Fig. 2b).

The immediate postoperative course was complicated by a precipitous decline in platelet count (10×10^9/l), rising LDH from 890 to 2,407 U/l, development of a massive pleural effusion with mediastinal shift, and spinal cord compression at multiple levels causing incontinence and paraparesis (Fig. 3a). Blood tests showed worsening thrombocytopenia (3×10^9/L), prolonged clotting time and increased D-dimer, consistent with disseminated intravascular coagulation. The patient was transferred to intensive care for ventilator support, where ultrasound-guided

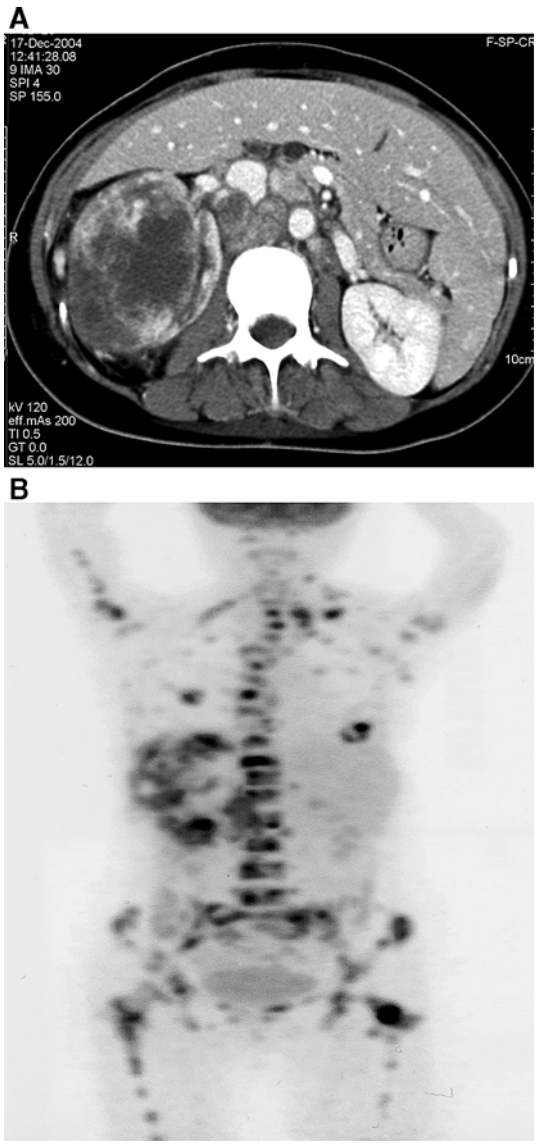

Fig. 1 Imaging studies on presentation. **a** Abdominal CT scan showing the 13 cm tumour arising from the upper pole of the right kidney, associated with extensive retroperitoneal lymph node involvement. **b** ^{18}FDG-PET scan showing massive right renal tumour associated with disseminated bone metastases, nodal metastases, and left hip fracture

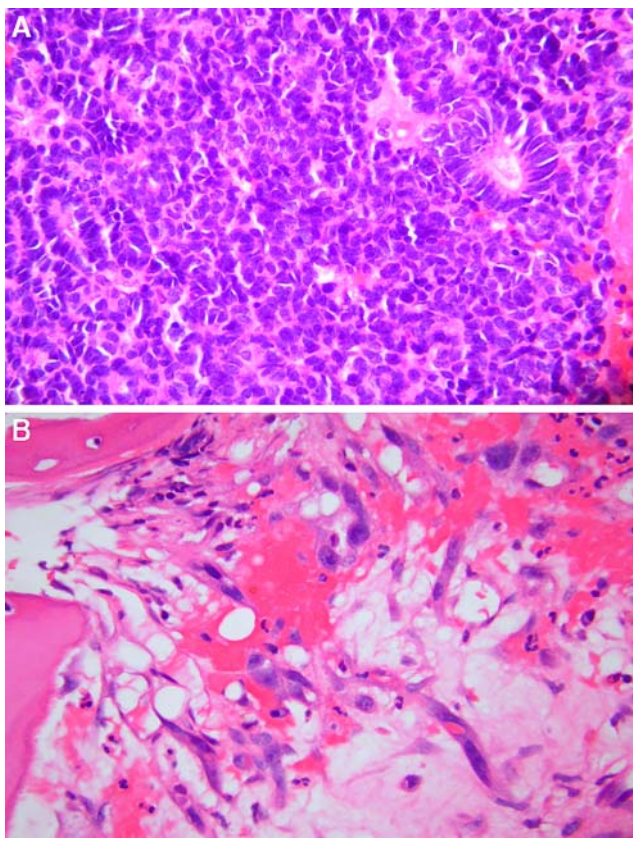

Fig. 2 Histopathologic studies. **a** Right kidney tumour, showing primary adult Wilms' tumour. **b** Bone marrow metastasis, showing pure angiosarcoma

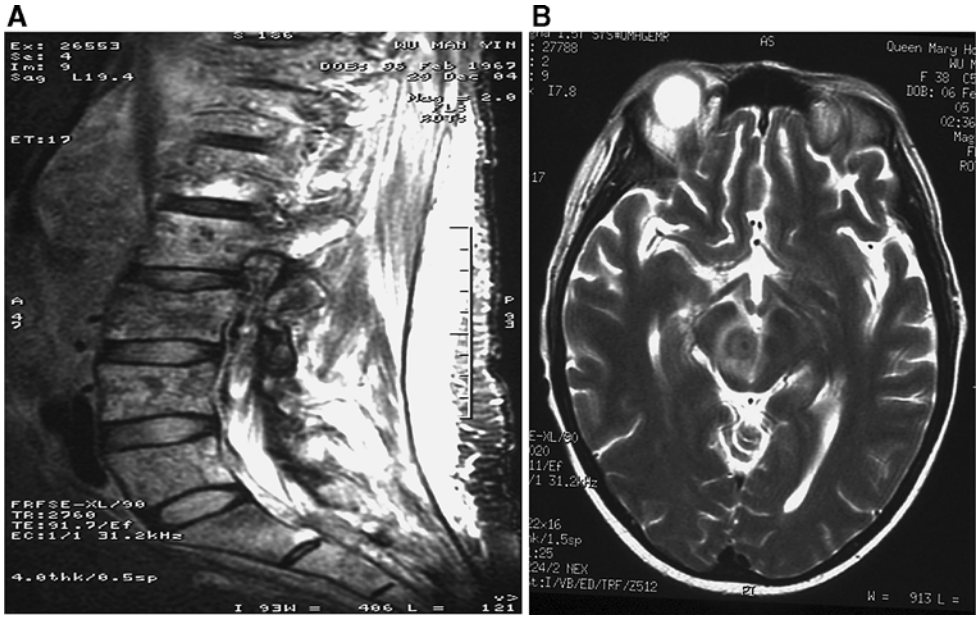

Fig. 3 Metastatic complications. **a** MRI scan of the spine, showing compression at multiple spinal levels. **b** MRI scan of the brain, showing highly vascular brainstem metastases

pleural tapping revealed heavily-bloodstained pleural fluid which was duly aspirated to dryness under CT guidance.

Emergency chemotherapy using carboplatin, etoposide and vincristine (CEO) was associated with rapid clinical improvement. Concurrent irradiation to the spinal cord led to a partial response of the compressive lesions as judged by magnetic resonance imaging (MRI), with neurologic stabilization. Four cycles of CEO with platelet support were administered; a re-staging CT scan confirmed marked treatment response in kidney and all metastatic sites, consistent with a declining trend of serum LDH (Table 1). Over 3 months, the degree of clinical improvement justified fixation of the right hip by hemi-arthroplasty. High-dose chemotherapy for the presumed diagnosis of chemosensitive mixed adult Wilms' tumour and angiosarcoma was then considered; within a few days of the hip operation, however, the patient complained of diplopia, and cranial MRI confirmed haemorrhagic brain metastases (Fig. 3b). She was treated with cranial irradiation and two further courses of palliative chemotherapy (paclitaxel and carboplatin), but succumbed to a brainstem haemorrhage within a month of the relapse.

Table 1 Time-course of serum LDH before and during CEO chemotherapy

Timing	Serum LDH level
On admission	2,407
After CEO cycle 1	1,745
After CEO cycle 2	835
After CEO cycle 3	550

Discussion

To our knowledge the present case is the first report of mixed adult Wilms' tumour and angiosarcoma. Interestingly, the adult Wilms' tumour component was present only in the kidney, but the angiosarcomatous component was disseminated in lymph nodes and bone marrow. The histological origin of the tumour remains debatable, as staining for Wilms' tumour 1(WT1) protein was not done; hence, rather than being a synchronous tumour arising from a germline abnormality, the angiosarcomatous component could have arisen via differentiation from the Wilms' tumour. An earlier report from Taiwan described concomitant renal cell carcinoma and angiosarcoma complicated by microangiopathy in a patient with von Hippel–Lindau (VHL) disease [10]. The *VHL* gene locus is on chromosome 3p, and this same genetic region is also deleted in both hereditary and sporadic renal cell carcinoma [11, 12] in contrast, the (paediatric, *WT1*) Wilms' tumour locus is on chromosome 11p13 [13], while adult Wilms' has been linked to isochromosome 7q [14]. Of note, WT1 overexpression is frequently associated with vascular tumours [15], and VHL manifests not only with renal tumours but also with cerebellar haemangioblastomatosis—reminiscent of the fatal brainstem lesions in the present patient. Although we were unable to obtain a cytogenetic analysis in this patient, the unusual clinical features of the case suggest a morphologic overlap unified by an underlying genetic lesion responsible for renal tumours, coagulopathy, and brainstem metastases [16, 17]. Moreover, though our case is a mixed adult Wilm's tumour, its clinical course typifies that of adult Wilms' tumour, insofar as prompt systemic therapy was needed post-operatively [18].

The response of adult Wilms' tumour to paediatric Wilms' protocols remains controversial area. Despite previous disappointing results [8], Kalapurakal et al. [19] showed that adult Wilms tumor with favorable histologic type can achieve impressive 82% 5-year overall survival when treated with paediatric protocols, in which vincristine, dactinomycin, cyclophosphamide, with or without doxorubicin and local radiotherapy were employed. Conversely, in patients with high-risk paediatric Wilms' tumour, carboplatin and etoposide are more frequently used. Carboplatin and etoposide has recently been shown to be a potential promising regimen in the treatment of relapsed or refractory Wilms tumour. The response rate in children with relapsed and poor-risk Wilms' tumor was >80% in one study [20].

Carboplatin, etoposide and vincristine (CEO) have all been reported to be effective single agents for adult Wilms' tumour [21] but have not previously been used together. In the present case, CEO chemotherapy demonstrated impressive cytoreductive efficacy as reflected by the rapid decline in serum LDH and the clinical and radiological response; this also illustrates that LDH may be a useful marker to monitor response in patients with this rare cancer entity [22]. Although further studies are needed, the gratifying systemic response of this aggressive case supports the notion that this rare disease entity has a favourable response to platinum/etoposide-containing chemotherapy.

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