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Primitive small round cell tumour of the adrenal gland presenting with fever of unknown origin and t(12;22)(q13;q12) cytogenetic finding

K Y Lam, C Y Lo, T W H Shek, E S K Ma, W Y Au, G C F Chan

Abstract
This report describes a left adrenal tumour in a 16 year old Chinese girl who presented with fever of unknown origin. The histological and ultrastructural features of the adrenal tumour were those of a primitive small round cell tumour with neuroendocrine differentiation. Cytogenetic analysis of cultured tumour cells showed a reciprocal translocation t(12;22)(q13;q12). This is the first example of such a tumour being reported in the adrenal gland. The adrenal tumour was also the cause of the fever, which subsided after the removal of the tumour.

Keywords: adrenal; cytogenetic; primitive tumour; pyrexia of unknown origin

Tumours that arise from the adrenal medulla show either neuroendocrine or neural differentiation. These include phaeochromocytoma, ganglioneuroma, ganglioneuroblastoma, neuroblastoma, neurilemmoma, malignant peripheral nerve sheath tumour, malignant melanoma, primitive neuroectodermal tumour (PNET), and tumours with mixed differentiation. In this report, we describe a primitive adrenal medulla tumour with unique clinicopathological and cytogenetic features.

Case report
PATIENT
A 16 year old Chinese girl, previously in good health, was admitted because of prolonged intermittent fever. Physical examination was unremarkable. Laboratory studies revealed anaemia (haemoglobin concentration, 78 g/litre), mild leucocytosis (white blood cell count, 11.9 × 10^9/litre), and a raised erythrocyte sedimentation rate (> 140 mm/hr). The concentration of C3 was 2700 mg/litre (range, 600–1300) and the C reactive protein concentration was 260 mg/litre (normal, < 10 mg/litre). However, immunoglobulin concentrations were within the normal range. Renal and liver functions were normal except for increased concentrations of alkaline phosphatase (674 U/litre; normal range, 36 – 117) and γ glutamyl transferase (215 U/litre; normal range, 11–49). Screening for hepatitis virus was negative. Bone marrow aspiration and repeated culturing of blood, urine, and bronchoalveolar lavage showed no evidence of bacterial growth. Screening of blood for malaria, rickettsia, and brucella was negative. There was no clinical or laboratory evidence of collagen vascular disease. During her hospitalisation, the patient suffered from a high swinging temperature; a maximum temperature of 41°C was recorded. Subsequent abdominal ultrasonography revealed a left suprarenal heterogeneous lesion that was confirmed by computed tomography (CT) and magnetic resonance imaging to be a heterogeneous left adrenal mass with a maximum dimension of 6.2 cm (fig 1). Hormonal investigations (24 hour urinary catecholamine values, serum cortisol, and overnight dexamethasone suppression test) were within the normal ranges. Fine needle aspiration of the adrenal mass was performed under CT scan, and revealed features consistent with a malignant tumour. Total adrenalectomy was performed. There was no definite evidence of invasion into the adjacent soft tissue, enlarged lymph nodes, or distant metastases.

The postoperative recovery was uneventful and the swinging fever that had persisted on and off for more than two months duration subsided immediately after surgery. Standard staging of the disease, including a CT scan of the thorax and bone scintigraphy, did not reveal metastatic disease. Adjuvant local radiotherapy and systemic chemotherapy were administered. However, the patient had lung metastases two years after surgery, which was confirmed by biopsy.

Methods
Fresh tissue samples (1 mm³) of the resected adrenal gland were taken. They were (1) fixed in 2.5% buffered glutaraldehyde and then processed for ultrastructural examination under a transmission electron microscope and (2) put into culture medium for cytogenetic studies. Cytogenetic studies were performed...
on short term overnight synchronised and non-synchronised cultures of marrow cells. These cells were supplemented by a direct harvest and analysed in accordance with standard protocol.  

Fresh frozen tumour tissues were also analysed for the chimaeric transcripts that encode fusion products found commonly in PNET and clear cell sarcoma. These gene fusion products were identified by the reverse transcription polymerase chain reaction (RT-PCR) using cDNA that was derived from tumour tissue RNA as a template. PCR products were identified by gel electrophoresis using ethidium bromide stained gels. The sequence of the primer used and the experimental conditions of the RT-PCR were as described previously. The presence of amplifiable RNA was confirmed by RT-PCR using primers specific to β actin (a ubiquitously expressed gene in human tissues). Primers specific to the EWS and ATFI genes were used to test for the presence of the gene fusion transcript commonly found in clear cell sarcoma. The DTC-1A clear cell sarcoma cell line, which produced approximately 950 bp of PCR product, was used as control. Primers specific to EWS, FLI1, or ERG were used to detect the presence of gene fusion transcripts commonly noted in PNET. Two PNET control cell lines known to have a t(11;22) translocation were used as positive controls in these studies. The PCR products were Southern blotted on to a nylon membrane and probed with an internal end labelled oligonucleotide specific to EWS, FLI1, and ERG.

Immunohistochemistry was conducted on 5 μm thick sections from representative paraffin wax embedded blocks using the avidin-biotin–peroxide complex method. Antibodies to the following antigens were used: vimentin, neuron specific enolase (NSE), synaptophysin, chromogranin, desmin, smooth muscle actin, myoglobin, myosin, leucocyte common antigen (LCA), Mak-6, CAM 5.2, cytokeratin 7, cytokeratin 20, HMB-45, CD34, and CD99.

**Results**

**GROSS PATHOLOGY**
The resected left adrenal gland weighed 180 g. The contour of the adrenal gland was distorted by a medullary tumour measuring

8 × 7.5 × 4.0 cm. The cut surface of the mass showed white fleshy tumour tissue with multiple areas of haemorrhage and necrosis virtually replacing the whole adrenal gland.

**HISTOLOGICAL FEATURES**
The adrenal tumour was composed of sheets of uniform small and medium oval cells with scanty cytoplasm and irregular nuclei with fine chromatin (fig 2). Mitotic counts were approximately 1/10 high power fields. In some foci, multinucleated tumour giant cells were noted. Rosettes or rosette-like structures were not present. The tumour cells were embedded in a vascular stroma in which haemorrhage and haemosiderin deposits were frequently found. Extensive areas of necrosis with perivascular preservation of viable tumour cells forming a peritheliomatous pattern were also seen.

**IMMUNOHISTOCHEMICAL FINDINGS**
Immunohistochemical studies revealed that the primary tumour cells were positive for vimentin but negative for CD99, neuroendocrine markers (NSE, chromogranin, and synaptophysin), cytokeratins (Mak-6, CAM 5.2, cytokeratin 7, and cytokeratin 20), S-100, HMB-45, muscle markers (actin, desmin, myosin, and myoglobin), CD31, CD34, and LCA. The tumour cells from the metastatic lesion in the lung were positive for CD99.

**ELECTRON MICROSCOPY**
Ultrastructural examination showed closely opposed cells that were uniform and primitive.
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