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Hemihypertrophy, Bilateral Wilms' Tumours and Clear-cell Adenocarcinoma of the Uterine Cervix in a Young Girl

Jean-Phillippe Stalens and Jacques Ninane

THE ASSOCIATION of congenital hemihypertrophy with tumours of embryonal origin like nephroblastomastosis and Wilms' tumours or with adrenocortical tumours is well known [1, 2]. We report another association in a young girl who had hemihypertrophy and developed Wilms' tumour of both kidneys and clear-cell adenocarcinoma of the uterine cervix.

This 4-year-old Caucasian girl was the offspring of a normal pregnancy with no recorded drug exposure. She was referred to us for left hemihypertrophy first diagnosed at the age of 6 months.

A screening ultrasonography of the kidneys revealed a right mass measuring 21 mm in diameter which was confirmed by CAT scan. The child then underwent a right radical nephrectomy. Pathological examination showed a classical Wilms' tumour. Postoperative chemotherapy (vincristine 1.5 mg/m^2 and D actinomycin 0.75 mg/m^2 at intervals of 3 weeks for 6 months) was given and the child was then closely followed-up by chest X-ray and renal ultrasonography. 54 months after surgery, she had one episode of macroscopic haematuria. Renal ultrasonography revealed a solid tumour of the upper pole of the left kidney. Chest X-ray, liver ultrasonography and bone nuclear scan were normal. Pre-operative chemotherapy combining vincristine and D actinomycin was administered during 4 weeks. The tumour shrank dramatically in size and the child underwent tumorectomy. Examination of pathological specimen revealed a classical triphasic nephroblastoma. Karyotype of the resected tumour showed monosomy 22. Post-operative chemotherapy combined vincristine, D actinomycin and epiadriamycin for a total of 27 weeks. The patient remained free of symptoms for 25 months. She then presented with vaginal bleeding. Ultrasonography and CAT scan of the pelvis revealed a mass developing from the cervix and measuring 3.5 cm in diameter. There was no abnormal node in the pelvis. Resection of the cervical tumour was then performed by the vagina. Pathological examination showed a clear-cell adenocarcinoma of the cervix. The child then underwent conisation with extended lymph node resection but there was no residual tumour and the removed nodes were normal.

The patient has been closely followed-up. There is no evidence of disease 14 months after the last operation.

The association of hemihypertrophy with nephroblastomatosis and Wilms' tumour is well recognised but not with clear-cell adenocarcinoma. Hemihypertrophy is congenital and since nephroblastomatosis, Wilms' tumour [3] and clear-cell adenocarcinoma of the cervix [4] have embryonal origins, one might imagine a common origin to explain their association. It is of interest to note that there was no history of maternal ingestion of stilbestrol or related oestrogens during pregnancy. Furthermore, karyotype on the second Wilms' tumour showed monosomy 22. This chromosome abnormality has never been described in Wilms' tumour. It would have been interesting to have the karyotype of the other Wilms' tumour and of the clear-cell adenocarcinoma and the molecular genetics on these three tumours since several studies indicate the involvement of two distinct regions of chromosome 11p (11p13 and 11p15) [5, 6] and of one locus of chromosome 16q [7] in the development of Wilms' tumours.

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Triple Malignant Neoplasms in a Patient with Adult T-Cell Leukaemia

Nobutaka Imamura and Atsushi Kuramoto

WE HAVE previously reported multiple primary neoplasms in patients with adult T-cell leukaemia (ATL) [1]. We here report a patient who developed four malignancies including ATL.

In 1984, the patient underwent a gastrectomy for gastric cancer (tubular adenocarcinoma). In 1985 a colonectomy was performed for colon cancer (well-differentiated adenocarcinoma). He was subsequently investigated for leukocytosis (white blood cell count 23 800/μl). By two-colour fluorescence, monoclonal proliferation of CD4$^+$, CD29$^+$, CD45RA$^-$ leu-

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kaemic cells, a typical phenotype of ATL as reported previously [2], was observed in addition to the existence of $CD38^+$ PCA-1 positive plasma cells which coexpressed cytoplasmic immunoglobin (Ig) G, λ.

Monoclonal increment of Ig G, λ (4570 mg/dl) was detected by immunoelectrophoresis. Both IgM and IgA were suppressed. Absence of NK activity as well as low number of NK cells [3] were found. Anti-HTLV-I (human T-cell leukaemia virus-I) antibody was identified by passive agglutination, immunofluorescence and enzyme-linked immunosorbent assay testing [4]. In bone marrow, numerous myeloma cells were found in addition to ATL cells, indicating the co-existence of multiple myeloma. The ATL cells showed gene rearrangement for the T-cell receptors TcRβ and TcRγ. The ATL cells overexpressed HRAS p21 and p53 suppressor oncogene products, which suggests the existence of point mutations [5], as well as *myc* and PCNA (proliferating cell nuclear antigen, p36kD). The patient died from bacterial meningitis associated with central nervous system invasion of ATL cells.

We identified ATL-derived factor (ADF) [6] in the cytoplasm of both the gastric and colon adenocarcinomas, and invading ATL cells by indirect immunofluoroscopy and immunohistochemistry [7]. We also identified *ras* p21 products in these neoplasms, using anti-p21 *ras* monoclonal antibody.

The observations in this rare case suggest a possible association between ATL cells and premalignant cells, through ADF or other unknown factors in the activation of *ras* oncogenes. Subsequent suppression of host immune defence mechanisms in ATL permits the emergence of the secondary neoplasms [8]. Recent reviews by Hunter [9] and Sawyers *et al.* [10] are consistent with this hypothesis. ATL patients and/or HTLV-1 carriers should be carefully examined for their possibility of developing malignant neoplasms. The association of point mutation on *ras* oncogene and p53 suppressor oncogene remains to be elucidated [5].

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Treatment of Advanced Neuroblastoma

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EVANS *et al.* [1] make some interesting comments about treatment of high-risk neuroblastoma in general and our and the Royal Marsden's papers on consolidation therapy in particular. We would like to answer these.

The main purpose was to describe toxicity, not to claim improved efficacy. We wished to highlight the fact that significant toxicity may result from the use of multiple drugs as consolidation therapy with autologous marrow rescue. From our review of the literature on consolidation therapy, we concluded that a 40% 2 year event-free survival could be achieved with multiple or single agents and could not convince ourselves that more agents resulted in better survival. In this we agree with Corbett *et al.* [2]. With this background, and despite our encouraging results, any benefit of additional chemotherapy during consolidation will be shown only by carrying out randomised studies of single- vs. multiple-agent consolidation therapy in a group who have received uniform, preconsolidation induction therapy.

There are a number of potential reasons for the discrepancy in progression-free survival rates between the two studies. We did say that there is "uncertainty about the relative contributions to survival of induction and consolidation regimens" and pointed out that our study did not attempt to address this issue. However, readers will not be misinterpreting our paper if they inferred that we suspect differences in induction therapy might be critical in influencing overall outcome. The relative importance of altering the induction schedule, in particular increasing dose intensity with the rapid schedule of chemotherapy at 10-day intervals, will be shown in the randomised European Neuroblastoma Study Group 5 study in which the two arms consist of induction therapy with the same drugs at the same dose but different dose intensity.

Any difference in survival between the two studies cannot be due to purging of the marrow by one group rather than the other. Both papers state that unpurged marrow was used. The only obvious handling difference was that we used refrigerated unmanipulated marrow whilst the Royal Marsden Group used cryopreserved marrow. If this difference in handling (rather than chance, consolidation or induction therapy) resulted in differences in survival, we need to develop a rationale for the mechanism and investigate it. We think it is an unlikely explanation.

The assessment of outcome would have been more obvious if we had not included 1 patient with stage 3 disease. We did so

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