Production of human chorionic gonadotrophin by a hepatoblastoma resulting in precocious puberty

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SUMMARY A two year old boy presented with precocious puberty associated with hepatoblastoma. Serum concentrations of β human chorionic gonadotrophin and α -fetoprotein were raised. An aggressive chemotherapeutic regimen resulted in useful palliation and interesting changes in the β human chorionic gonadotrophin and α -fetoprotein concentrations. In contrast to a previous report, the ultrastructure of the tumour showed frequent Golgi apparatus but no other electron dense membrane bound vesicles.

Hepatoblastoma is an embryonal tumour which can be associated with various non-metastatic syndromes. α -fetoprotein or, rarely, human chorionic gonadotrophin may be produced by the tumour and may be used as a tumour marker. Ectopic gonadotrophin production from this source is a rare cause of precocious puberty in boys.

Case report

PRESENTING FEATURES

A boy aged 28 months presented with a four month history of rapid skeletal growth, increasing penile size, pubic hair, and deepening of the voice. Examination showed him to be on the 90th percentile for height and weight and to have oily skin, a deep voice, pubic hair (stage II), and genital development (stage IV).¹ However, both testes were small (Prader Beads 3 ml). There was a large, firm, irregular hepatic mass extending down to the level of the umbilicus.

MANAGEMENT

Liver imaging using both ultrasound and radionuclide scanning showed a mass 8 cm in diameter within the right lobe of the liver. At laparotomy the tumour was found to extend across into the left lobe of the liver and was considered inoperable. Needle biopsy samples of the tumour were taken. There was no evidence on clinical examination, chest radiograph, and bone scan or at laparotomy for the spread of the tumour beyond the liver.

LABORATORY INVESTIGATIONS

Results of laboratory investigations were as follows: haemoglobin concentration 8.8 g/dl; erythrocyte sedimentation rate 38 mm in the first hour; serum bilirubin and liver transaminase values normal; plasma alkaline phosphatase >2000 IU/l; serum β human chorionic gonadotrophin concentration 197 IU/l (normal <5 IU/l); α -fetoprotein concentration 404×10^3 KU/l (normal <5 KU/l); plasma testosterone 49 nmol/l (normal for adult male <30 nmol/l); plasma oestradiol 520 pmol/l (adult males <160 pmol/l); basal plasma follicle stimulating hormone concentration 2 IU/l with no rise on luteinising hormone releasing hormone stimulation; basal luteinising hormone concentration 41 IU/l (owing to a cross reactivity with β human chorionic gonadotrophin).

PATHOLOGY

Light microscopy showed a vascular tumour arranged in a trabecular/sinusoidal pattern with numerous foci of haemopoiesis in the sinusoidal channels. The predominant tumour cell was large and polygonal and resembled fetal hepatocytes, but a few smaller, oval to polygonal cells with less cytoplasm resembling embryonal hepatocytes were also present (Fig. 1a). A mesenchymal stromal component to the tumour was not identified. Electron microscopy confirmed the foci of haemopoiesis. The large polygonal tumour cells had complex folded and interdigitated plasma membranes (Fig. 1b). Desmosomes were not seen but large numbers of microfilaments were prominent beneath the plasma membranes. Mitochondria were numerous and usually round. Abnormal circular and septal cristae

Fig. 1 (a) Tumour cells of two types are present. There are large cells with abundant cytoplasm, circular mitochondria widely dispersed among vesicular smooth endoplasmic reticulum, and a small nucleus (bottom right). Other tumour cells are smaller but have a relatively larger nucleus and greater numbers of mitochondria within the more electron dense cytoplasm. (uranyl acetate and lead citrate $\times 3200$)
 (b) There is pronounced complexity and infolding of the plasma membranes of the tumour cells. The cell top left has formed a large intracytoplasmic vacuole into which project several microvilli. (uranyl acetate and lead citrate $\times 8000$)
 (c) Portions of an infolded nucleus are seen top right and top left, a small membrane bound peroxisome $0.42 \mu\text{m}$ diameter is present centre, and several sets of Golgi apparatus (arrows) surround the peroxisomes. There are numerous microfilaments and microtubules also present within the cytoplasm. (uranyl acetate and lead citrate. $\times 26\,000$)

were often seen with them. Well developed profiles of both rough and smooth endoplasmic reticulum were present and ribosomes were also free within the cytosol. The Golgi apparatus was usually a prominent feature and also multiple in many cells (Fig. 1c). Peroxisomes were also present, but secretory granules were not identified. The nucleus was oval with a small nucleolus and a finely dispersed euchromatin pattern.

TREATMENT AND PROGRESS

A chemotherapeutic protocol was undertaken including vincristine, adriamycin, cyclophosphamide and 5 fluorouracil in six week cycles. There was an initial rapid fall in serum α -fetoprotein but no change in serum human chorionic gonadotrophin concentration and no change in the clinical signs of virilisation. Subsequently, despite treatment, the serum α -fetoprotein concentration rose (Fig. 2). Serial ultrasound scans showed no appreciable reduction in tumour size to correspond with the early fall in serum α -fetoprotein concentration.

Treatment was well tolerated and the child remained active and in good health for 10 months from diagnosis. Subsequently, there was clinical evidence of local tumour growth with further hepatomegaly and jaundice. Chemotherapy was withdrawn and the child died 13 months after presentation.

Fig. 2 Differential response of serum tumour markers to chemotherapy in a case of hepatoblastoma.

Discussion

Precocious puberty due to a virilising hepatoblastoma is a rare but well documented occurrence.²⁻⁸ Cases have been confined to boys, generally below three years of age, who have usually presented with accelerated skeletal growth and virilisation. Hepatic enlargement at presentation has been invariable. Most authors report little or no increase in testicular size; biopsy samples, when taken, have usually shown interstitial cell hyperplasia but no spermatogenesis, which suggests testicular stimulation by a gonadotrophin with only interstitial cell stimulating activity. The circulating gonadotrophin which was originally detected by bioassay in early reports has subsequently been identified as human chorionic gonadotrophin using a radioimmunoassay specific for the β chain.^{4,8} Human chorionic gonadotrophin has also been isolated from tumour cells cultured *in vitro*.⁴ Human chorionic gonadotrophin stimulates the testicular interstitial cells leading to androgen production and subsequent virilisation. Follicle stimulating hormone concentrations are unaltered—hence there is little increase in testicular size. The high circulating luteinising hormone concentrations are caused by cross reaction of human chorionic gonadotrophin in the luteinising hormone assay.

The raised plasma oestradiol concentration in this case and in previous reports^{3,6,8} was probably due to peripheral conversion of circulating androgens. Clinical evidence of feminisation has been restricted to gynecomastia in one case.²

Raised concentrations of circulating α -fetoprotein are not diagnostic of hepatoblastoma and are also found in hepatocellular carcinoma and some teratomas showing extra embryonal differentiation. Circulating α -fetoprotein concentrations offer a useful means of assessing response to treatment in some tumours. The differential response of human chorionic gonadotrophin and α -fetoprotein to chemotherapy in this case, together with a previous similar report,³ suggests either synthesis by separate cell lines or differential sensitivity to chemotherapy of metabolic pathways in the same cell.

Long term survival is dependent on removal of the tumour; without surgical resection the prognosis is measured in months, although occasional responses to irradiation⁹ or vincristine¹⁰ have been recorded. Our aggressive use of chemotherapy apparently controlled the growth of this inoperable tumour for about nine months. A biochemical "response" to chemotherapy was noted with serum α -fetoprotein concentration rapidly falling at the start of treatment. Circulating α -fetoprotein concentrations may therefore provide an index of

response to treatment in these tumours but must be interpreted cautiously since no similar fall in serum β human chorionic gonadotrophin concentration occurred in our patient. None the less, as treatment was well tolerated and maintained the child in excellent general health, the chemotherapeutic regimen appears to have produced useful palliation in a surgically inoperable case.

In the only published report on the ultrastructural appearances of a virilising hepatoblastoma secretory granules were found within the tumour cell cytoplasm.⁷ This is in contrast to our findings; tumour cells from our patient showed prominent and often multiple Golgi apparatus and, although peroxisomes and lysosomes were also present, there were no other membrane bound electron dense granules. As human chorionic gonadotrophin is a glycoprotein the presence of Golgi apparatus would be expected because this is required for addition of the carbohydrate side chains to the polypeptide. Conversely, secretory granules necessary for the storage of intermittently released cellular proteins would not be essential and, indeed, in our study were not present.

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