Failure of normalisation of α fetoprotein concentration after successful treatment of teratoma

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Raised α fetoprotein concentrations may not always be diagnostic of active germ cell tumour

The development of successful treatment regimens for germ cell tumours has been one of the important advances in cancer chemotherapy. The effects of such treatment are monitored by measurement of serum concentrations of the tumour markers α fetoprotein and human chorionic gonadotrophin, as well as clinical and radiological assessment. The persistence of raised concentrations of α fetoprotein during or after treatment requires urgent investigation to delineate teratoma resistant to chemotherapy. We report on a patient with testicular teratoma who relapsed after initial chemotherapy in whom appreciably raised serum concentrations of α fetoprotein did not fall despite apparently successful salvage chemotherapy and surgery. An exhaustive search for a further residuum of disease was not fruitful. The finding of raised liver enzyme activities and hepatomegaly led to a liver biopsy, which showed alcoholic hepatitis. The patient decreased his alcohol intake, resulting in normalisation of his α fetoprotein concentration and liver enzyme activities.

Case report

A 37 year old man presented in May 1991 with testicular swelling and hepatomegaly. Orchiectomy was performed for an undifferentiated malignant teratoma that extended into the spermatic cord and blood vessels. Staging investigations showed para-aortic lymphadenopathy and a single lung metastasis. His concentration of human chorionic gonadotrophin was 1094 IU/l and of α fetoprotein 37 μ g/l. Imaging studies showed no signs of liver metastases. His hepatomegaly was attributed to his alcohol consumption of 28 units a week and was accompanied by raised liver enzyme activities and a raised erythrocyte mean cell volume. He received four cycles of combination chemotherapy

with carboplatin, etoposide and bleomycin, resulting in normalisation of tumour markers and resolution of his lung lesion and paraaortic lymphadenopathy.

Eight months later he developed acute left sided chest pain. Computed tomography of his chest showed metastases and mediastinal lymphadenopathy. The intrapulmonary lesions were shown by needle biopsy to be recurrent teratoma. He was treated with salvage chemotherapy with the POMBACE regimen (a mixture of cisplatin, vincristine, methotrexate, bleomycin, dactinomycin, cyclophosphamide, and etoposide.¹ At relapse his tumour markers were normal, but during chemotherapy his concentration of α fetoprotein rose rapidly, reaching a maximum of 1889 μ g/l. After two courses of POMBACE his α fetoprotein was still 1490 μ g/l and his lung lesions were unchanged in size.

Thoracotomy was performed for removal of residual disease: the resected specimens contained necrotic tissue only. His α fetoprotein concentration remained above 1000 μ g/l, and screening of sanctuary sites by computed tomography of his brain, abdomen, and chest and ultrasound examination of the contralateral testis showed no metastases. During his admission for thoracotomy his liver enzyme activities started to rise, with no accompanying change in liver span or clinical features to suggest acute hepatitis. His γ -glutamyltransferase concentration was 445 IU/l (normal range <40 IU/l) and the concentration of aspartate aminotransferase was 41 IU/l (<40 IU/l), but concentrations of both serum bilirubin and alkaline phosphatase were within the normal range. Serial computed tomography and ultrasound examinations of the liver showed diffuse enlargement only, with no evidence of metastases or hepatoma. The patient then admitted that his alcohol intake had risen before his thoracotomy to over 70 units a week. Serum ferritin concentrations were normal, and serological tests for hepatitis A, B, and C yielded negative results. A liver biopsy showed changes suggestive of alcoholic hepatitis. In retrospect, this diagnosis should have been considered at an earlier stage.

Over the next year the patient was able to reduce his alcohol intake to 4 units a week with a concomitant fall in his serum γ -glutamyltransferase and α fetoprotein concentrations (figure). Fourteen months after salvage chemotherapy and cessation of his excess alcohol intake, his α fetoprotein and γ -glutamyltransferase concentrations were within normal limits, and follow up computed tomography showed no evidence of recurrent teratoma.

Discussion

α Fetoprotein is an oncofetal antigen secreted by the fetal liver, yolk sac, and gastrointestinal tract and is normally cleared rapidly after birth. Serum concentrations are raised in the second and third trimesters of normal pregnancy, in 20-70% of patients with germ cell tumours,² and in 70% of patients with hepatoma.³ In both germ cell tumours and hepatoma the concentration of α fetoprotein correlates with tumour bulk. Serial measurements before, during, and after treatment of germ cell tumours are mandatory. Treatment

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Changes in concentrations of tumour markers and liver enzyme activities with time

Non-neoplastic disorders associated with raised α fetoprotein concentrations

Paediatric

Tyrosinaemia
Indian childhood cirrhosis
Neonatal hepatitis

Adult

Primary biliary cirrhosis
Extrahepatic biliary obstruction
Alcoholic hepatitis
Chronic active hepatitis
Drug induced hepatitis
Viral hepatitis

should lead to a fall in α fetoprotein concentration consistent with its known half life of five days. If this fails to occur chemotherapy resistance is suggested and urgent further investigation is needed, together with a reappraisal of treatment. A rising or persistently raised concentration of α fetoprotein on its own, in the presence of normal results of clinical and radiological investigations, is conventionally indicative of relapse⁴.

Although measurement of α fetoprotein is valuable in the management of germ cell tumours, several situations exist in which raised concentrations of α fetoprotein may not be due to a new or recurrent malignancy (box). The development of a radioimmunoassay for α fetoprotein to replace less sensitive assays that used countercurrent immunoelectrophoresis has led to the observation that serum α fetoprotein concentrations may be marginally raised in some normal healthy people, including a subset of individuals with a familial predisposition, expressed in an autosomal dominant fashion.⁵ Raised α fetoprotein concentrations may be associated with living in certain environments, such as the Ivory Coast and savanna regions of Africa, possibly because of increased exposure to hepatotoxins.⁶

Production of α fetoprotein is also increased in association with hepatic parenchymal inflammation, hepatic necrosis, and hepatic regeneration. The greater the changes the higher the concentration of α fetoprotein, which may reach 300 000 $\mu\text{g/l}$ in fulminant hepatic necrosis. In our patient increased production of α fetoprotein was due to alcoholic hepatitis, which subsided only once his alcohol intake was appreciably reduced. Although raised α fetoprotein concentrations secondary to chemotherapy regimens containing methotrexate have been observed, no reports of this effect of methotrexate have been published. α Fetoprotein concentrations are raised as a result of excessive alcohol intake but only in the presence of hepatitis. No correlation has been shown between raised liver enzyme activities and α fetoprotein concentrations without histological changes in the liver.

As this case illustrates, the major problem with using α fetoprotein concentration is its heterogeneity, which causes poor assay sensitivity and specificity. Clearly,

identification of the different "species" of α fetoprotein in various benign and malignant conditions would be extremely useful clinically. In our patient the results of such assays would have shown that the failure of his serum α fetoprotein concentration to decline after chemotherapy was due to increased hepatic synthesis of α fetoprotein secondary to alcoholic hepatitis.

α Fetoprotein is a very large protein and has several surface epitopes.⁷ The different molecular forms of α fetoprotein in benign liver disease, hepatoma, germ cell tumours, and hepatic metastases from colorectal neoplasms can be differentiated by their lectin binding properties⁸ or by monoclonal antibodies, which might offer a better prospect of establishing the source of a raised serum α fetoprotein concentration.¹⁰

The presence of persistently raised concentrations of α fetoprotein after chemotherapy for germ cell tumours necessitates urgent and thorough investigation to exclude residual disease. In a small proportion of patients inappropriately high concentrations may be familial or secondary to hepatic injury. Identification of different species of α fetoprotein in such patients by either the lectin binding ability or the surface epitopes of these species would prove extremely useful and may prevent further, inappropriate treatment being started.

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Cambodian health in transition

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As conflict and suffering in Bosnia, Chechnya, Rwanda, and Zaire continue to be at the forefront of world attention, some countries seem to be largely forgotten. It is timely to take stock of conditions in the small country of Cambodia as it struggles to take its place after a long period of isolation. Countless Cambodians and ethnic Vietnamese have died there this year and during the past 25 years, victims of senseless killing or preventable disease.

Early in 1975 one of us (PJK) led a relief team of 200 health workers, 190 of them Cambodians, taking medical care and food supplements to a million or so women and children who were refugees in besieged Phnom Penh. Later that year all expatriates were evicted from the country by the advancing forces of Pol Pot. On re-establishing contact in 1980 we found that only 12 of the original Cambodian team had survived. Their stories of suffering and killing, and of escape and survival, under the murderous regime that followed

are harrowing. Cambodia now has a fast growing population of around 9 million, a fifth of whom are children under 5 years old. Their health and safety are still precarious.

Background

The past 20 years of Cambodian history have been characterised by civil war and terrible brutality. In the early 1970s the country suffered intense bombing by the United States on its western border with Vietnam. The fall of Phnom Penh to the Khmer Rouge marked the beginning of four years of genocide under the rule of Pol Pot; the country was turned into a "killing field," with up to two million people dying as the result of violence, starvation, and disease. In 1979 the Vietnamese ended Pol Pot's rule and installed a hardline socialist regime. Over the next 10 years Cambodia suffered a vicious civil war as the government in Phnom Penh battled with guerrilla factions backed

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