Case Report

Alpha-fetoprotein surge following high-dose chemotherapy in germ cell tumours

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In patients with non-seminomatous germ cell tumours (NSGCTs) who receive chemotherapy and have residual disease, a persistently elevated serum marker level after induction chemotherapy indicates active and progressive disease. High-dose chemotherapy (HDCT) is the standard treatment for patients with relapsed NSGCT. We present a case of a patient with residual disease from NSGCT who showed an increase in serum alpha-fetoprotein levels after HDCT, mimicking progression. Resection of the mass did not show viable cells in the tumour specimen, thus suggesting that the elevated level of the marker was expression of hepatic reconstitution after drug-induced liver damage. HDCT is increasingly used in cases of relapsed NSGCT, and the possibility of treatment-induced alpha-fetoprotein elevation must be taken into account in patient management.

Keywords: Germ cell tumour, Residual mass, Progressive disease, High-dose chemotherapy, Alpha-fetoprotein levels

Introduction

Germ cell tumours are rare neoplasms accounting for less than 1% of all malignancies and are most frequently diagnosed in men in the third decade of life.[1] Mortality has declined markedly since cisplatin was introduced as the basis of chemotherapy in the mid-1970s.[1] In the *cisplatin* era, the 10-year survival rate of patients with metastatic non-seminomatous germ cell tumours (NSGCTs) treated with this drug increased significantly from 76% during the period 1977–1986 to 88% in the period 1987–1996.[2] This improvement resulted mainly from an increase in the survival of patients with poor prognosis and indicates more effective management of NSGCT over time. High-dose chemotherapy (HDCT) with haematopoietic progenitor cell support has led to an approximately 15% improvement in survival of these patients compared to historical data.[3–6] Moreover, in cisplatin-refractory disease, early tandem HDCT represents the recommended option but is potentially curative in only one-third of these patients.[7] In NSGCT patients with poor prognosis who receive primary or salvage chemotherapy and show residual disease with negative serum alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (beta-HCG), radical resection of all residual lesions is mandatory.[8,9] Persistent elevation of serum tumour markers, especially if levels begin to rise even further, is usually expression of progressive disease that requires further chemotherapy, thus delaying surgery. We report the case of an NSGCT patient showing liver toxicity and AFP surge after HDCT to outline the possibility of liver damage as the cause of increased AFP levels.

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Case Report

A 25-year-old male was admitted to hospital with severe chest pain and persistent cough. A chest-X-ray revealed a large mass in the anterior mediastinum, confirmed by CT scan (Fig. 1A). A biopsy was performed and mediastinal NSGCT was diagnosed. Histology was not further characterized due to the paucity of bioptic material and necrotic areas. No other sites of disease were detected at whole body CT scan. Laboratory tests revealed elevated serum beta-HCG (13 mUI/ml) and carcinoembryonic antigen (15 mg/dl). The patient underwent induction chemotherapy with cisplatin 20 mg/m^2 and etoposide 100 mg/m^2 administered on days 1–5, and bleomycin 30 IU on days 2, 9, and 16 (PEB), at 3-week intervals. Marker negativization was observed after the first course of PEB and a CT scan showed a radiological partial remission after the third treatment course (Fig. 1B). Four weeks after the end of PEB, the patient received cisplatin 20 mg/m^2 and etoposide

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100 mg/m^2 on days 1–5 followed by granulocyte-macrophage colony-stimulating factor 5 μg/kg/day to mobilize peripheral blood progenitor cells. Fourteen days after mobilization, 2.7×10^6 CD34$^+$ cells/kg b.w. were collected by a single leukapheresis and 4 weeks later the patient received a single course of HDCT with carboplatin AUC 20, etoposide 1800 mg/m^2 and cyclophosphamide 6400 mg/m^2 divided into four doses given on days 1, 2, 3, and 4. Peripheral blood progenitor cells were reinfused on day 7, followed by granulocyte colony-stimulating factor 5 μg/kg/day until haematopoietic reconstitution. Post-transplant neutropenia <500/μl and thrombocytopenia <20 000/μl lasted 9 and 7 days, respectively. Persistent grade-3 neutropenia was observed for the following 6 weeks. Severe stomatitis was reported for 9 days. On the seventh day after the start of HDCT, the patient showed serum aspartate aminotransferase (AST) 923 U/l and alanine aminotransferase (ALT) 909 U/l, progressively reducing until normalization was reached at +20 days. Although no change in tumour dimension was observed in the CT scan performed 3 weeks after HDCT (Fig. 1C), an increase in AFP (101 ng/ml) was seen at +28 days. For these reasons, surgical resection of the residual mass was postponed. AFP levels normalized after +106 days (Fig. 2) and surgical resection was performed shortly afterwards, the resected residua consisting of fibrosis and necrosis. Five years have passed since the induction chemotherapy and the patient is still disease-free.

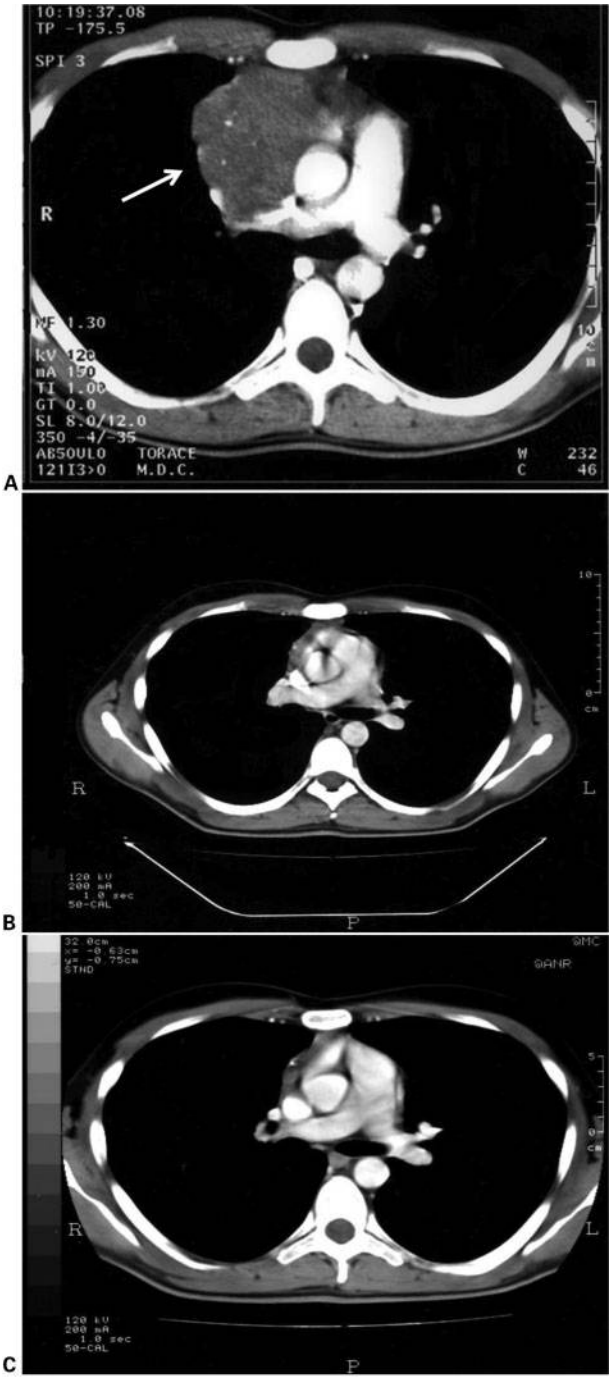

Figure 1 Patient with mediastinal germ cell tumour with alpha-fetoprotein elevation after high-dose chemotherapy. (A) Chest CT scan upon hospital admission revealed a large tumour mass in the anterior mediastinum. (B) After three courses of induction chemotherapy, a chest CT scan showed a substantial reduction in the tumour mass. (C) After high-dose chemotherapy, chest CT scan showed no further modification in tumour size.

Discussion

In patients with poor prognosis NSGCT and post-chemotherapy residual masses, surgical resection is indicated only if serum AFP and beta-HCG levels are within the normal range. A persistently elevated serum marker level after induction chemotherapy is suggestive of progressive disease and salvage therapy is thus contraindicated.[10] Conversely, a small number of studies reported that some patients with persistently elevated serum tumour markers after chemotherapy had locoregional disease and were amenable to surgical resection.[11,12] It thus appears important to clarify which patients with high serum tumour markers could benefit from surgical resection, although as yet no clear clinical or pathological variables have been found to identify such candidates.

Vuky and co-workers[11] reported their single-centre experience of post-chemotherapy surgery in patients with mediastinal NSGCT, highlighting the role of surgery in patients with elevated serum tumour markers. Of the 13 patients who had abnormally elevated markers before surgical resection, three with elevated AFP alone showed long-term survival. Resected residual masses consisted of mature teratoma, necrosis or viable malignant cells. Another study retrospectively reviewed 18 patients with mediastinal NSGCT who were selected for surgical resection in spite of elevated tumour markers after chemotherapy.[12] In this series, only eight patients remained disease-free; all had elevated AFP (median 70, range 26.6–830) but normal beta-HCG pre-resection, and all

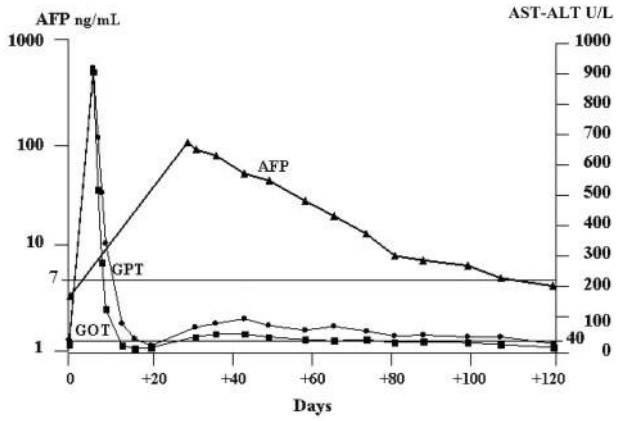

Figure 2 Elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) followed by increase in alpha-fetoprotein after high-dose chemotherapy.

resected specimens showed necrosis or mature teratoma. Small microscopic areas of tumour in residual masses missed by the pathologist or slow tumour marker decrease prior to resection were indicated as possible explanations for the high AFP value. In both case series, all but one of the patients with elevated presurgical AFP (<1000 ng/ml) and without viable malignant cells in bioptic specimens showed long-term survival.

In our patient whose serum AFP levels were continuously negative before and during treatment, elevation of transaminases and AFP may have been the expression of hepatic reconstitution after drug-induced liver damage.[13,14] In fact, most chemotherapeutic drugs administered to patients with germ cell tumours, e.g. cisplatin, etoposide, and cyclophosphamide, can induce hepatotoxicity.[14] When administered at high doses, liver injury occurs in around 20–50% of cases.[8]

Post-chemotherapy resection notwithstanding elevated AFP levels should only be considered in NSGCT patients selected on the basis of their clinical conditions, potential radical resectability, and radiological situation. Serum AFP >1000 ng/ml and its possible correlation with drug-induced liver toxicity must therefore be taken into account in each individual. Concanavalin A is a lectin that permits the separation of AFP molecular variants on the basis of their carbohydrate moiety. In a prospective study by Mora and co-workers, the concanavalin A affinity assay was used to discriminate between germinal or hepatic origin of AFP in germ cell tumour patients during chemotherapy or follow-up.[15] This assay could thus help to distinguish between AFP produced by germ cell tumours or by liver injury, including chemotherapy-induced hepatic toxicity, and thus facilitate surgical decision making.[16]

In conclusion, increased AFP levels in NSGCT patients must be interpreted with caution when post-chemotherapy liver damage is present. HDCT is increasingly used in these patients and the possibility of treatment-induced false-positive serum AFP elevation must be borne in mind. Strict monitoring of AST/ALT and bilirubin levels after HDCT is recommended to better evaluate any increase in AFP values. In patients with AFP elevation after HDCT but no clinical–radiological evidence of progression, resection of residual masses can be considered.

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