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Malignant Teratoma Undifferentiated (MTU) Metastasising Solely as Differentiated Teratoma: Implications for the Aetiology of Residual Differentiated Disease Following Successful Chemotherapy

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FOLLOWING SUCCESSFUL chemotherapy for metastatic teratoma, up to 15% of patients demonstrate residual disease which should then be surgically excised. Differentiated teratoma is found in approximately 40–45% of these patients [1]. We report the first case of undifferentiated teratoma metastasising solely as differentiated teratoma in a patient who had received no treatment following orchidectomy, and discuss the implications for the aetiology of residual differentiated disease.

A 40-year-old patient underwent a right inguinal orchidectomy. Histology revealed undifferentiated tumour with yolk sac elements classified as malignant teratoma undifferentiated (MTU). Postoperatively, staging diagnosed stage I disease and he was placed on a surveillance programme with no chemotherapy.

Eighteen months into surveillance, an abdominal computed tomography (CT) scan demonstrated enlarged para aortic nodes, 2 cm in diameter, anterior to the left psoas at the level of the renal hilum. These had not been present on the postoperative staging scan. Chest CT scan and serum markers were normal. The nodes were radiologically unchanged 2 months later and so were excised for definitive diagnosis.

Histology of the nodes demonstrated multilocular structures surrounded by muscle, lined by intestinal epithelium with goblet cells and argentaffin cells, and ciliated epithelium. The features were consistent with deposits of mature teratoma showing enhanced differentiation, with no evidence of malignancy or atypia.

The patient was unwilling to accept further surveillance. As he had demonstrated metastatic disease (although differentiated) and a complete para aortic node dissection had not been performed, he received three cycles of bleomycin, etoposide and cisplatinum chemotherapy. He remains well and disease-free 3.5 years later.

Mature teratoma has been reported up to 7 years following complete remission, induced by chemotherapy and surgery [2, 3], and may subsequently undergo malignant transformation [4]. A number of hypotheses have been proposed to explain the finding of metastatic differentiated teratoma.

Therapy-induced differentiation

This is also reported in other tumours, including neuroblastoma, ovarian teratomas and cystadenocarcinomas. *In vitro* exposure of germ cell lines to agents, including retinoic acid, methotrexate and interferon-β, may induce differentiation, and in some instances the exact route of differentation is dependent on either concentration of the agent or growth characteristics of the cell line. However, recent animal and clinical evidence does not support this *in vivo* [5].

Spontaneous differentiation

Pugh and Cameron [6] described patients with differentiated testicular teratoma subsequently developing metastatic disease. This may represent either sampling failure of the primary tumour, or spontaneous differentiation of the primary lesion.

Metastasis of mature teratoma

Anecdotal reports of mature teratoma in both primary tumour and metastases appear. Synchronous spontaneous differentiation may have occurred or the primary may have contained atypical elements, with metastatic potential [7]. Smithers [8] described differentiated metastases in patients, but details of prior treatment are not clear. Snyder [9] reported a pulmonary deposit of mature teratoma from a patient with MTU and metastatic testicular trophoblastic (MTT), although other metastases had been irradiated or resected.

Overgrowth of chemo- or radio-insensitive mature teratoma

Here, differentiated elements are thought to be resistant to chemotherapy and radiotherapy and may even increase in size during systemic therapy, the so called "growing teratoma" syndrome [10]. This is supported by animal data demonstrating that therapy destroys metastatic malignant clones, leaving residual mature elements which have co-metastasised.

This case confirms that purely differentiated teratoma can metastasise from tumour within the testis. Mature elements in residual disease, resected following chemotherapy, may thus represent chemoresistant metastasised differentiated clones, and need not be due to any differentiating effect of chemotherapy. Metastatic differentiated disease should always be considered in either spontaneous regression or unexplained progression of metastatic disease.

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Pregnancy During Alpha-interferon Therapy in Patients with Advanced Hodgkin's Disease

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TREATMENT OF malignancy during pregnancy is very limited because of the teratogenic potential of antineoplastic drugs. Much of the published data concerns pregnancy in patients with chronic myelogenous leukaemia, hairy cell leukaemia and thrombocythemia [1], and, using a computer-assisted medical literature search programme (Cancerlit-CancerCD 1984–1994), we found reports on only 11 pregnant patients treated with alpha-interferon (IFNα) [2, 3] and no reports on use of such therapy in pregnant patients with Hodgkin's disease.

Here we report a case of pregnancy in a woman aged 30 years with advanced and heavily pretreated Hodgkin's lymphoma. In 1983, she was diagnosed elsewhere with mixed cellular Hodgkin's disease, stage IVB (liver–pericardium). Nine cycles of MOP (no procarbazine) were administered, achieving a complete response (CR). In 1987, while off therapy, she became pregnant for the first time and delivered a normal male infant. The disease recurred in 1988, and the patient underwent three cycles of MOPP–ABVD, after which she was lost to follow-up for 2 years. When she came back in relapse, three cycles of ProMACE-CytaBOM achieved no response.

The patient was first seen in our Department on January 1991 for axillary and neck nodal progressive disease. Treatment consisted of mantle field radiation therapy up to 4200 cGy and IFNα 3 000 000 U 3 times a week. After 10 months, local progression was detected in cervical nodes and more radiotherapy (3060 cGy) was administered. Systemic treatment with IFNα continued. As amenorrhoea never occurred, after 6 months of IFNα therapy, while in partial response and on treatment, the patient became pregnant on June 1992. She did not discontinue IFNα therapy until October 1992. The pregnancy was uncomplicated and in March 1993 she delivered a 3.200 kg male infant; placental examination was normal. The baby developed normally and is now 2 years old. The patient is alive but with progressive disease.

IFNα has been shown to be neither mutagenic *in vitro* nor teratogenic in animals [1], but it may have abortifacient effects in Rhesus monkeys when administered at doses significantly greater than those used in human standard therapy. IFNα inhibits cell proliferation probably through its effects on protein synthesis, RNA degradation and modulation of the immune system, rather than by inhibition of DNA synthesis [4, 5]. Most agents commonly used to treat chronic myelogenous leukaemia and Hodgkin's disease can inhibit DNA synthesis, and, therefore, have the potential to cause miscarriage, intra-uterine growth retardation and congenital malformation. None of the reported twelve infants born to IFNα-treated pregnant mothers have had congenital malformations (Table 1).

Some drugs used in treating malignancies (chronic myelogenous leukaemia), such as busulphan and hydroxyurea, inhibit DNA synthesis with potential teratogenic effects, particularly during the first trimester. Indeed, three of the 23 infants born to women who were treated with busulphan during pregnancy had congenital malformation [1]. IFNα lacks inhibition of DNA synthesis and to date, has been shown to be safe for use during pregnancy. Further data are needed to confirm the role of IFNα in the treatment of malignancy during pregnancy.

Table 1. Malignancies treated with IFNα during pregnancy

Mother's disease	Infants
Chronic myelogenous leukaemia	6
Thrombocythemia	3
Hairy cell leukaemia	2
Hodgkin's disease	1

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